Imaging Brain Structure and Function

Thomas J. Grabowski, Jr., MD
Professor, Radiology and Neurology (joint)
Director, UW Integrated Brain Imaging Center
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Integrated Brain Imaging Center
University of Washington Department of Radiology

Partnered with Philips 3T Achieva research scanner
An initiative of UW Radiology to promote UW neuroscience

MR-based imaging
Cognitive Neuroscience
Medicine
Why image the brain?

- What’s wrong? (Medicine)
- How does it work? (Neuroscience)
- Can function be modified? (Rehabilitation, Engineering)
Sulci and Gyri of the Cerebral Cortex
Cerebral cortex

- The largest gray matter structure
- 50% of the cerebral volume!
- 28 billion neurons, 10 trillion synapses
- Probably confers the capacity for information processing and storage
Cerebral cortex has a radial plan

Cortical minicolumns are polyclones of a small number of progenitors

Deeper layers form first, later neurons climb past them

Migration along radial glia

Asymmetric division of progenitors in the germinal matrix
In theory, metabolic mapping techniques can resolve cortical processes at the level of cortical columns.

2-deoxyglucose: visual stim in cats
From Amunts et al
Brodmann’s cytoarchitectonic map (1909)
Julisch cytoarchitectonic map (2009)
Why is the brain hard to image?

• Differentiated (gray, white) soft tissues give low contrast to x-rays
• Cerebral anatomy is 3D complex and variable
• Cerebral functional zones are defined by microscopic features that can’t be imaged directly
• Neurophysiological processes must also be imaged indirectly through vascular and metabolic processes
• Much of the organization of the brain is still poorly understood.
Antiquity (i.e. pre-1975)

The pneumo-encephalogram
Talairach Space
Positron Emission Tomography (PET)

An imaging technique in which images of brain physiological parameters are inferred from the biodistribution of positron-emitting radiopharmaceuticals
Positron emission
PET detectors
[\textsuperscript{18}F]Fluorodeoxyglucose PET
PET

- Physiologically distributed signal
- Unmatched sensitivity
- A medical procedure with ionizing radiation
- Requires radionuclide source (cyclotron) and radiochemistry facilities
- Tracers exist for tissue metabolism (18F-FDG), blood flow (15O-water), DNA synthesis (18F-FLT), and a number of others.
Digital image paradigm

- Images are considered to be matrices of values of a physical or physiological parameter, gridded over an anatomic space.
- The parameter is not derived “directly” from hardware sensors, but reflects post acquisition processing.
- Thus "image” becomes an abstract concept, and an element in further workflow.
Xray Computed Tomography
Tissue vs. Bone Windows

Hounsfield Number
Computed tomography

- First tomographic anatomic imaging technique
- Modest soft tissue contrast
- Contrast agent (iodinated) already existed
- Good sensitivity to pathology, esp. blood
- Good resolution of bony structures
- Rapid (good throughput, low sensitivity to motion)

- Finds uses as a first-line emergency technique
- Integrated with PET for attenuation correction and anatomic image fusion
- Used very extensively in body imaging
Intracerebral hypertensive hemorrhage
Magnetic Resonance Imaging (MRI)
MRI

- Water has a natural frequency
- More precisely, its hydrogen nuclei have a quantum mechanical property called *spin angular momentum*
- The spin states of hydrogen nuclei diverge in energy level in the presence of a magnetic field (Zeeman splitting)
- Water protons absorb or give off energy to move between these energy levels, at the natural frequency, the Larmor frequency, which is a function of the magnetic field strength.
Wasserstiefel
Roman Signer
1986
Over time, the water protons align with the uniform magnetic field. This is called “longitudinal magnetization.”

The time constant of this aligning process is called ‘T1’. The asymptotic magnetization is related to the proton density of the tissue.

\[ M = M_0 \left(1 - e^{-t/T_1}\right) \]
Excitation

• Radiofrequency energy at the Larmor frequency transfers to the water protons of the system.

• This does two things:
  – Introduces a transverse component to the magnetization
  – Synchronizes the precession of the protons

• When the pulse of RF input stops, the system (water in the magnet) will radiate radiofrequency energy for a little while
In a magnetic field, protons precess at a natural frequency. Energy can go in or out of this system *only* at this frequency.
Relaxation: T1, T2, T2*

• With time (described by T1) the excited dipoles will relax back into alignment with the field.

• Before that happens, the precession will get out of phase (described by T2) and no more signal will be available.

• But even before that, local imperfections in the field will probably cause even faster dephasing (described by T2*).
T1 relaxation occurs at different rates in different tissues

- T1 relaxation is slowest in a homogeneous sample of water (e.g. in CSF)
- T1 relaxation is faster in lipid-rich white matter than in gray matter
- Differential relaxation is the key to tissue contrast in MRI
When a second RF pulse occurs before T1 relaxation finishes ...

• If it occurs after T1 relaxation is complete, it has identical results to the first pulse
• If it occurs after T2 relaxation is complete but before T1 relaxation is complete, it will excite a smaller response (partially saturated)
• Thus repeated pulses with TR < T1 will result in differential saturation of signal in GM, WM, CSF.
• Thus in brain T1-weighted signal is WM > GM > CSF
Together, the values of TR and TE emphasize different tissue parameters.

- **T1**
  - TR = 300 msec
  - TE = 20 msec

- **T2**
  - TR = 3000 msec
  - TE = 120 msec

- **PD**
  - TR = 3000 msec
  - TE = 20 msec

A **short** TR and **short** TE emphasizes T1 contrast.

A **long** TR and **long** TE emphasizes T2 contrast.

A **long** TR and **short** TE emphasizes proton density contrast.
FLAIR: FLuid-Attenuated Inversion Recovery
– T2 weighting with black spinal fluid
The MRI signal is rich

- Proton density
- Relaxation times (T1, T2)
- Magnetic field distortion (T2*)
- Flow
- Diffusion
- Chemical shift
- Magnetization transfer
- ....
Magnetic resonance angiography
“MRA”
The economy of MRI

- The currency of MRI is signal, i.e. the sum of the longitudinal magnetization of the protons in the field of view.
- This is a fixed budget, that can be used more or less efficiently, and can be spent to obtain some combination of:
  - Better spatial resolution
  - Better signal to noise ratio (SNR)
  - Reduced imaging time
- There are always trade-offs!
- Advances in MRI are often in the form of a smarter pulse sequence.
Efficient pulse sequences

• Maximize the amount of time spent listening for the signal
• Maximize the number of protons in the sample that are being put to work at any one time
• Optimize the relationship between TR and TE to maximize signal
• We use two efficient sequences extensively: MP-RAGE and EPI GRE fMRI
Cortical thickness
Diffusion Tensor Imaging
Diffusion

Random "walk" of the water molecular also known as "Brownian motion"

Isotropic Diffusion

Anisotropic Diffusion

Ellipsoid = Probability of Diffusion Distribution
Diffusion eigenvectors

Diagonalization of this tensor provides three eigenvectors ($ev_1$, $ev_2$ and $ev_3$) with three corresponding eigenvalues ($\lambda_1$, $\lambda_2$ and $\lambda_3$)

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix} = E^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} E$$
Diffusion Tensor Images
Diffusion imaging

• Parameters neurologists are used to seeing
  – Diffusion-weighted image
  – Apparent diffusion coefficient - ADC

• Parameters neuroscientists are used to seeing
  – Diffusion fractional anisotropy – FA
    
    A measure of how constrained water is to diffuse in only certain directions

  – Diffusion principal eigenvector
    
    The axis along which water diffuses most freely
Diffusion imaging

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DTI Tract Tracing
In vivo Connectivity-based Cortex Parcellation

Preprocess DWI

Model Diffusivity

Segment T1
FS Destrieux Atlas

Targets: all ROIs

Cortico-subcortical boundary

Seed:
Lh-supramarginal + Lh-angula

Compute and cluster tractograms

Rosalia Tungaraza
Caspers/Zilles parcellation IPL
Histology, N=10
MNI standard space

IBIC/Tungaraza parcellation IPL
HARDI MRI, N=19
MNI standard space
Functional Magnetic Resonance Imaging (fMRI)
Activation of the anterior temporal lobes during listening to discourse.
Physiological basis of fMRI

Neural processes are imaged *indirectly*, through parameters related to metabolic substrate delivery.
Neurovascular coupling

Synaptic electrochemical activity

*DEPENDS ON*

Maintenance of membrane potentials

*WHICH DEPENDS ON*

Metabolism of glucose

*WHICH DEPENDS ON*

Substrate delivery via blood flow
The hemodynamic response

- A version of functional hyperemia
- Excitatory neurotransmission produces nitric oxide and PGE2
  - Via stimulation of NMDA receptors on neurons
  - Via stimulation of metabotropic receptors on astrocytes
  - Coupled Ca++ influx activates nitric acid synthase and phospholipase A2
  - Diffusion of NO and PGE2 dilates surrounding arterioles
Basis of fMRI signal

- Neural Activity
- Metabolism
- Blood Flow
- dHb
- T_2^*
- MR Signal

Hemodynamic Response Function (HRF)

Blood Oxygenation Dependent Signal

“BOLD”
Three fMRI paradigms

• Activation paradigm
  – Signal model: predicted BOLD timecourse

• Functional connectivity paradigm
  – Signal model: correlated signal timecourses

• Information paradigm
  – Signal model: patterns of signal across voxels
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HRF sums linearly over trials

A. Dale and R. Buckner
Hum Brain Mapp 5:329
1997
Blocked Design (aka Block Design)

• Brain is placed in experimental and control states for discrete blocks of time
  – Typically 15-60 seconds
  – Usually operationalized as repeated performance
• Has historical roots in the design of $[^{15}\text{O}]$water PET activation experiments
• Remains widely used because of fundamental advantages of simplicity and efficiency
Event-related design

• A study design in which the events of interest are not grouped, but presented or elicited individually.
• The HRFs of events of interest are modeled explicitly.
• Despite lower design efficiency, there are compelling advantages to er-FMRI
  – Some task situations are not block-able
  – Post hoc selective trial averaging
  – Decorrelation of effects and artifacts
  – Estimation of the BOLD response function
Event-Related Design

Time, seconds

MRI signal
What is “Efficiency”? 

• Design Efficiency is related to the power to detect a response. It is also called “detection power.”

• Detection efficiency is related to the amount of informative variance per unit of time in the evoked BOLD curves.
• The key advantage of er-fMRI is **experimental flexibility**.
• Event-related design allows the analysis to be sensitive to performance differences across trials.
• This advantage derives from
  – preserving correspondence of images to events \textit{AND}
  – the independence of the effects evoked by each event.
Activation of hippocampus during successful memory encoding and retrieval
fMRI Data Post-Processing

Image Acquisition
- Motion correction
- Anatomic alignment
- Intensity normalization

Physiologic data acquisition
- Stimulus recording
  - Convolution w/ HRF (EV)

General linear model
  - Multiple linear regression
    - Test statistics
      - Thresholding/inference
        - Interpretation
fMRI time series

MR signal

\( t \)
fMRI signal reflects multiple simultaneous effects

• Task
• Physiologic fluctuations
  – Cardiac pulsatility
  – Respiratory effects
  – CSF flow/pulsation
• Head motion/spin history
• Slow drifts
• Thermal noise
Statistical analysis

- Problem: at each voxel, estimate the task effect in the presence of other effects
- Technique: multiple linear regression supported by the general linear model:

\[ Y = \beta_1 X_1 + \beta_2 X_2 + \ldots + \varepsilon \]

- The task effect is estimated by regression coefficient (\(\beta\)) and tested with a \(t\) statistic
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Finger tapping
Fourier transform

Resting State Paradigm

Biswal et al., 1997

Box car GLM

REST

BOLD

Signal Intensity

Finger tapping

Resting

Fourier transform

BOLD
Default Mode Network

Relevance to adaptive behavior

Deactivation DMN  Activation DAN

Relevance to disease

Raichle & Mintun, 2007
Summary: functional connectivity paradigm

• BOLD fluctuations formerly thought to be “noise” are correlated across distant sites.
• Analysis of functional connectivity “at rest” identifies consistent “intrinsic networks”
• Functional connectivity is grounded in anatomic connectivity
• Intrinsic networks may reflect a fundamental level of large-scale physiologic organization
Three fMRI paradigms

- **Activation paradigm**
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Multivoxel pattern analysis
Pattern recognition fMRI
Information-based fMRI
Machine learning
Univariate vs. Pattern Analysis

Differences in the magnitude of response ('involvement')

- Local smoothing
  - Each voxel analyzed independently

Differences in information content

- Fine-grained distributed response pattern
  - Joint relationship among voxels/features

Figure adapted from Mur et al., 2009
Pattern analysis: Multidimensional space

- Dimension 1 (voxel 1)
- Dimension 2 (voxel 2)

- fMRI response pattern to a stimulus corresponds to a location in a multidimensional activation space
- Classifiers are trained to discriminate between response patterns to different stimulus categories, and tested on independent data
- Animals
- Tools

Linear classifier
Pattern analysis: Multidimensional space

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Kriegeskorte et al., 2008
Representational similarity/dis-similarity –

- Generates a continuous measure, per trial/item
- Enables a flexible analysis of the relationship of activity pattern to information.

Kriegeskorte 2009
• **Structure**
  – Parcellation/volumetry
  – Tissue segmentation/VBM
  – Cortical thickness*

• **Connectivity**
  – Tractography
  – WM integrity
  – Connectivity-based parcellation*

• **fMRI**
  – Activation fMRI
    • Block-design fMRI
    • Event-related fMRI
  – Functional connectivity fMRI*
    • Resting state
    • Task-related
  – Multivariate pattern analysis (MVPA) fMRI*
    • Classification
    • Representational similarity
Summing Up

• MRI approaches to brain structure and function continue to diversify and become more powerful, driven mostly by conceptual and software innovation.
• Multispectral/multimodal approaches are now common, clinically and in research.
• Imaging approaches are beginning to analyze brain activity in terms of actual systems structure (columns, fields, large scale systems)
• Most of the techniques have not (YET) found their way into clinical application