Imaging Brain Structure and Function

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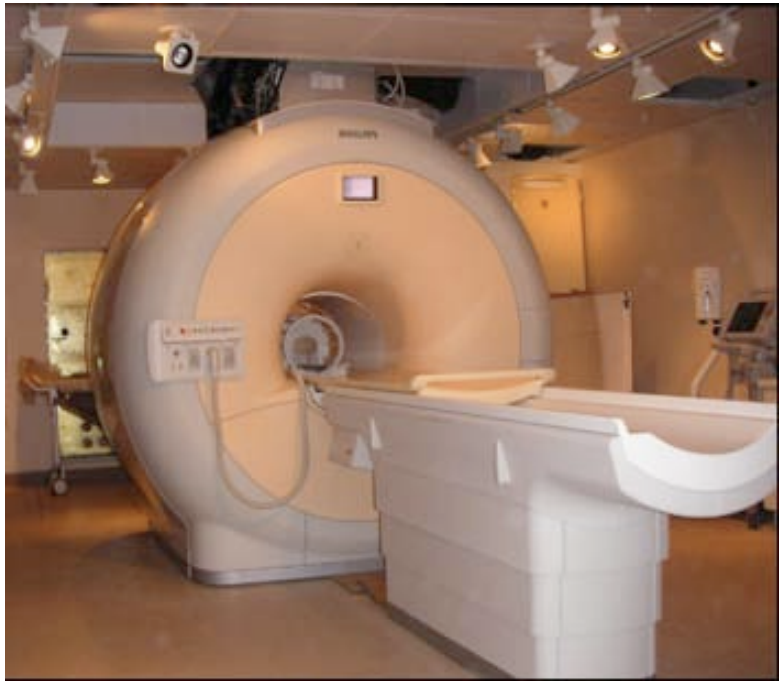
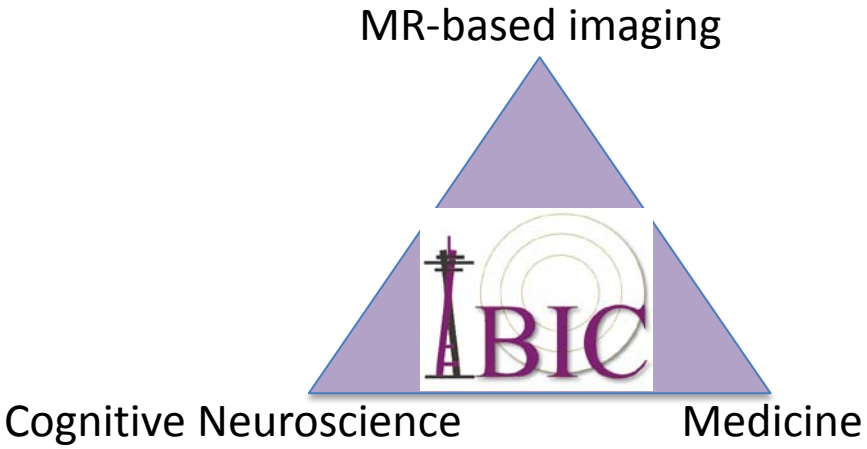
CSE/EE 577
October 31, 2011

Integrated Brain Imaging Center

University of Washington Department of Radiology

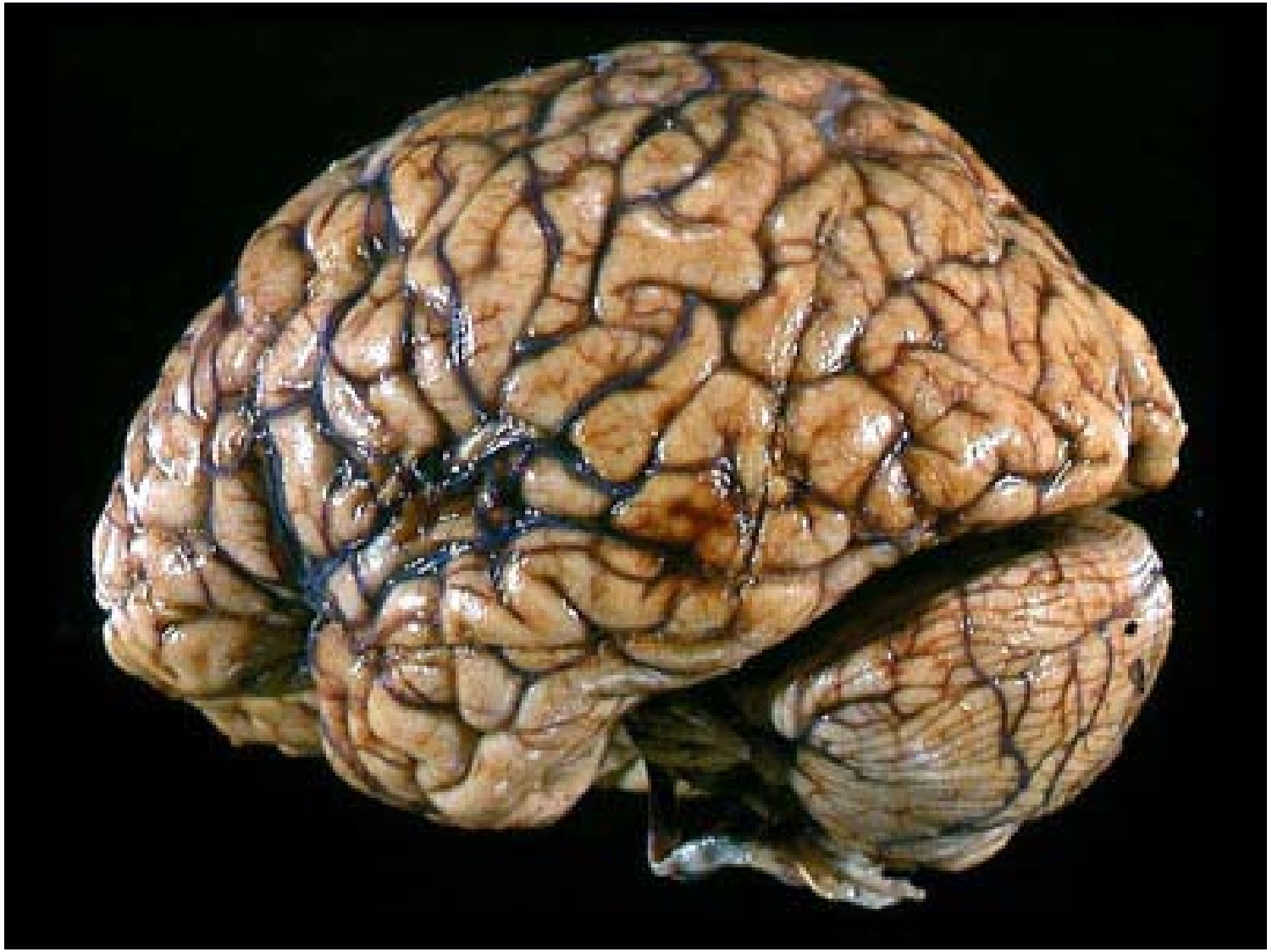
Partnered with Philips 3T Achieva research scanner
An initiative of UW Radiology to promote UW neuroscience

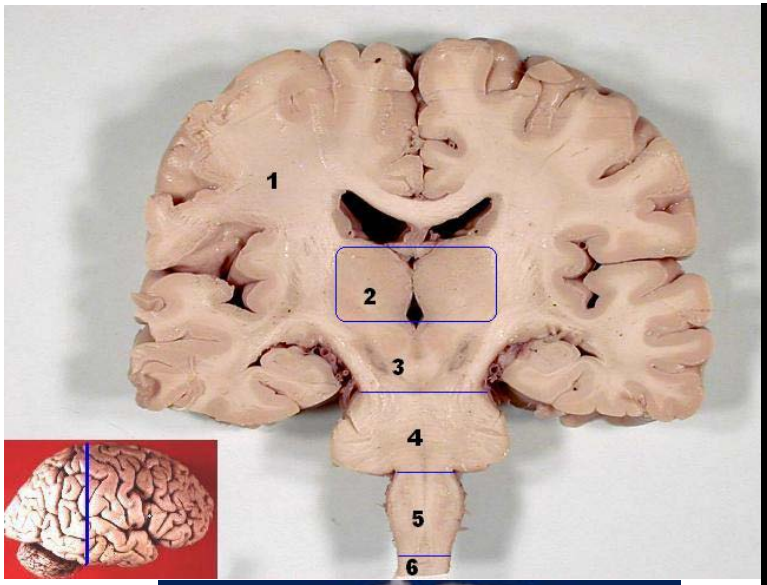




Why image the brain?

- What's wrong? (Medicine)
- How does it work? (Neuroscience)
- Can function be modified?
  (Rehabilitation, Engineering)

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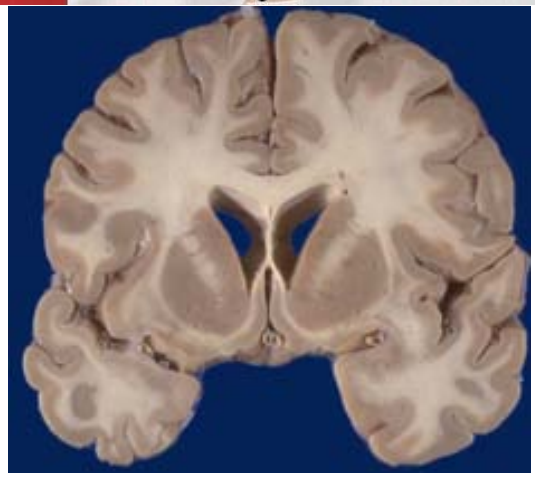
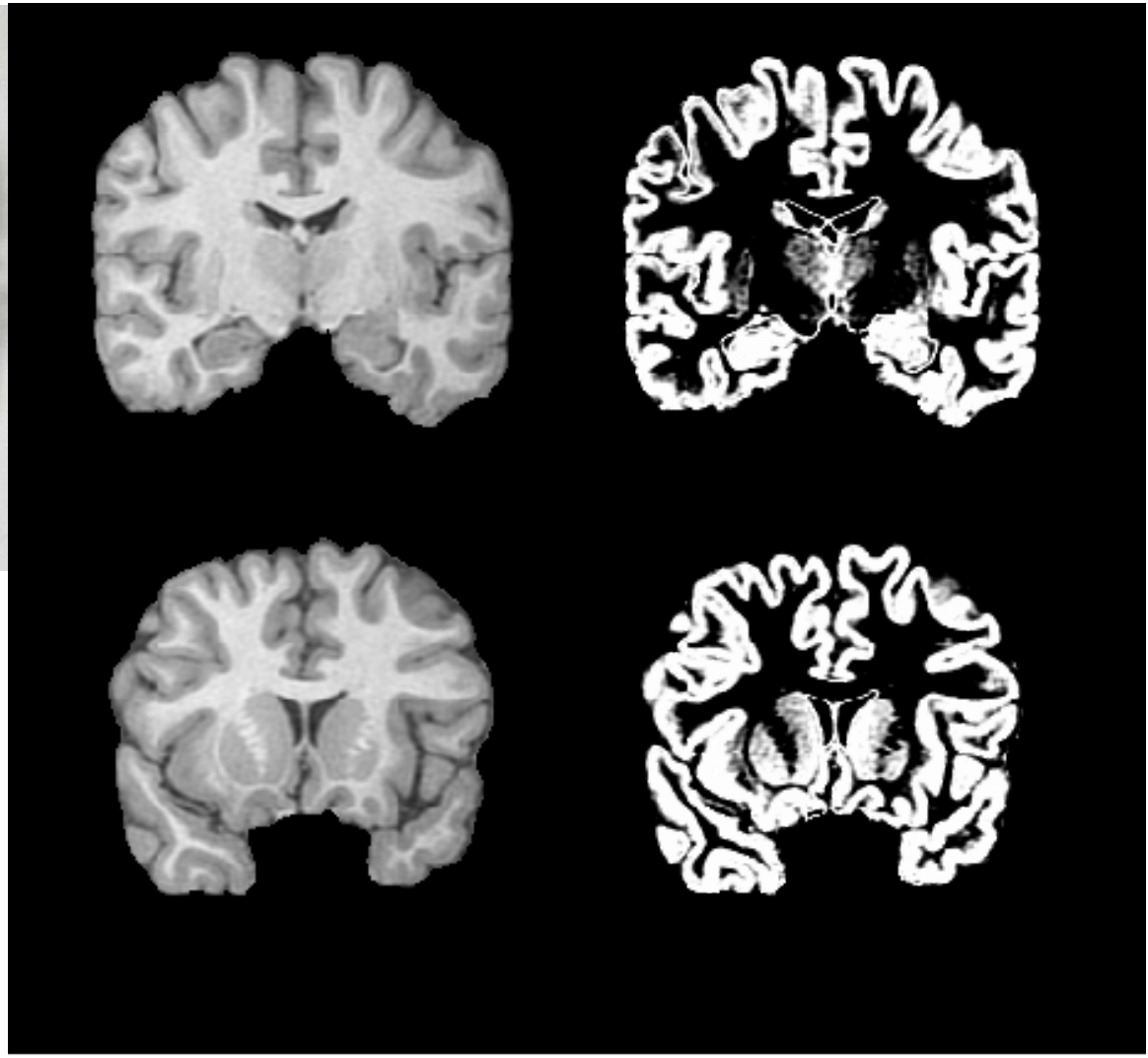
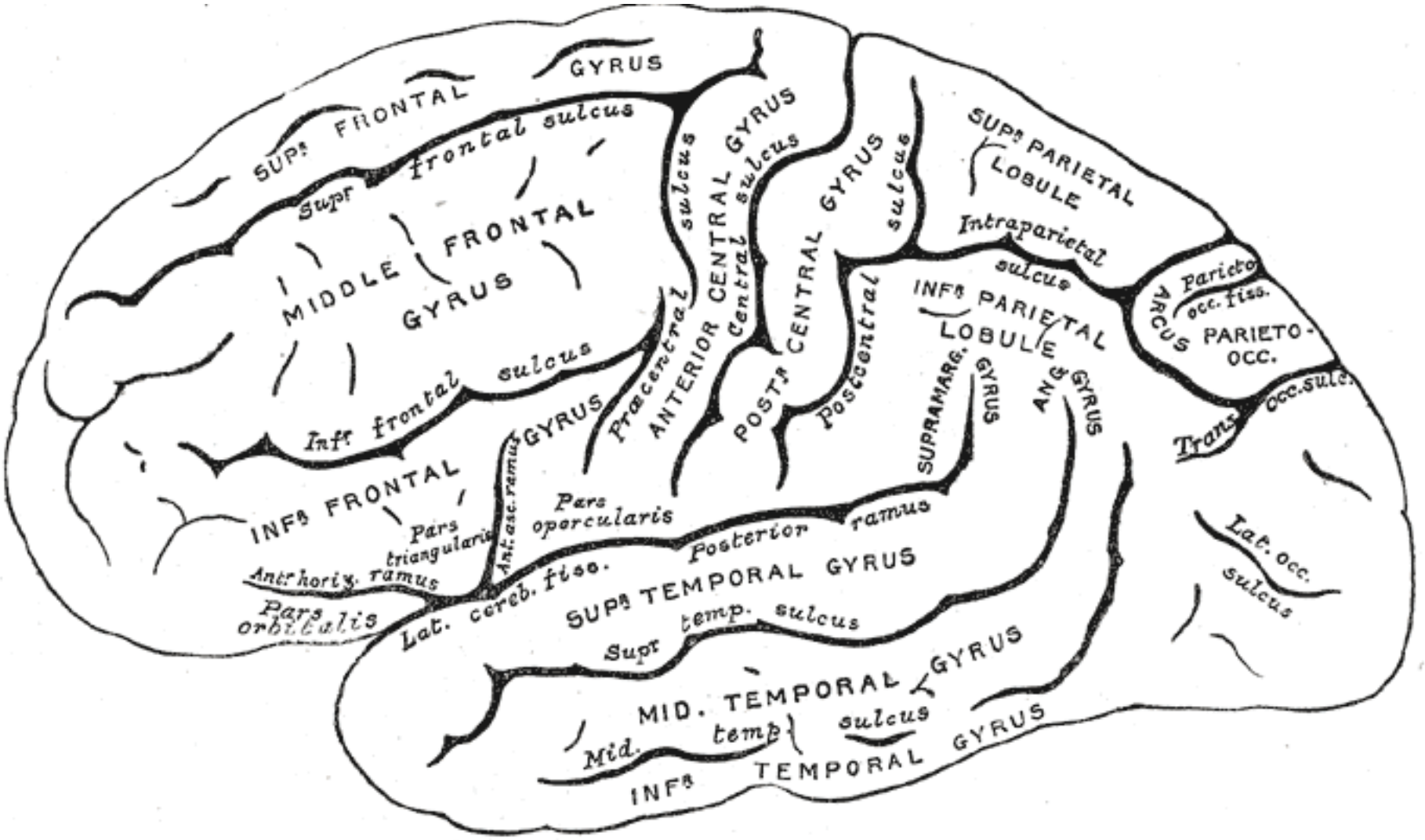




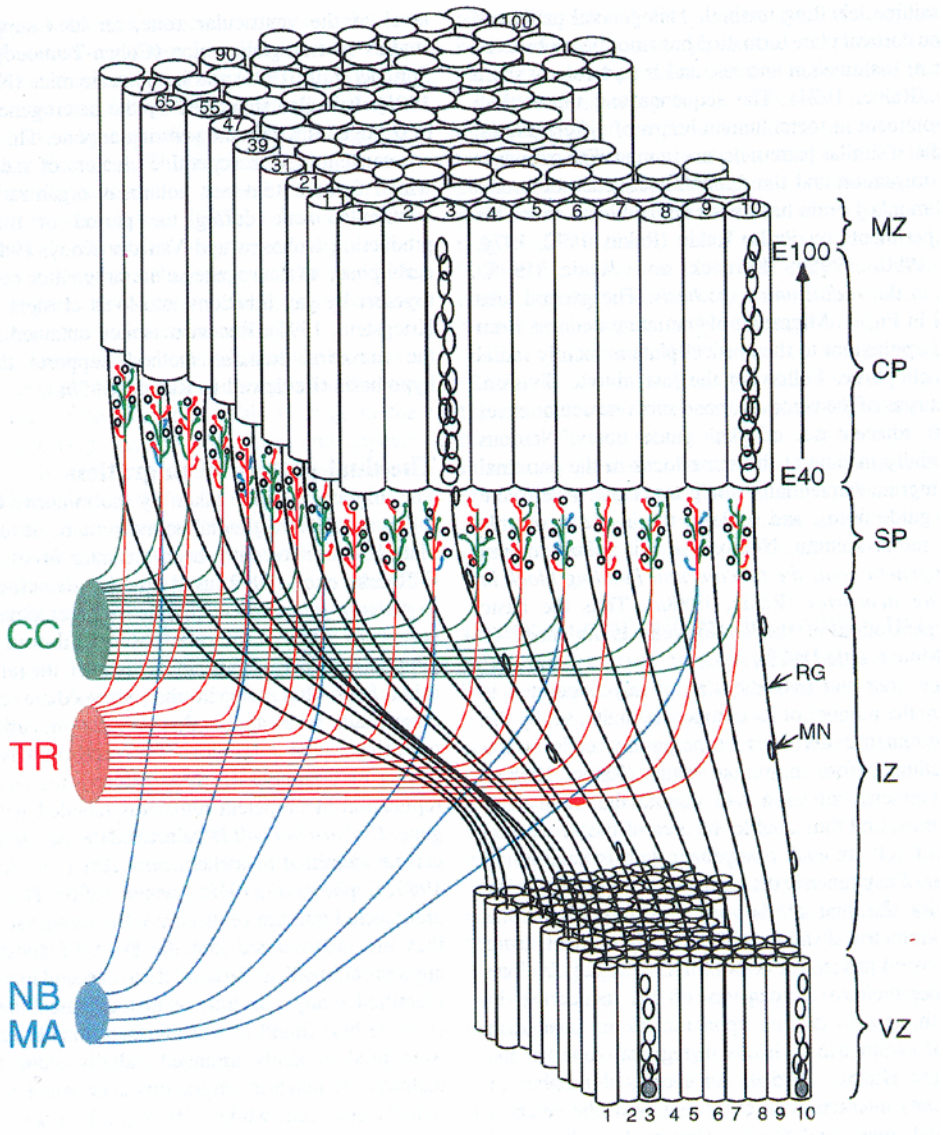
Sulci and Gyri of the Cerebral Cortex



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

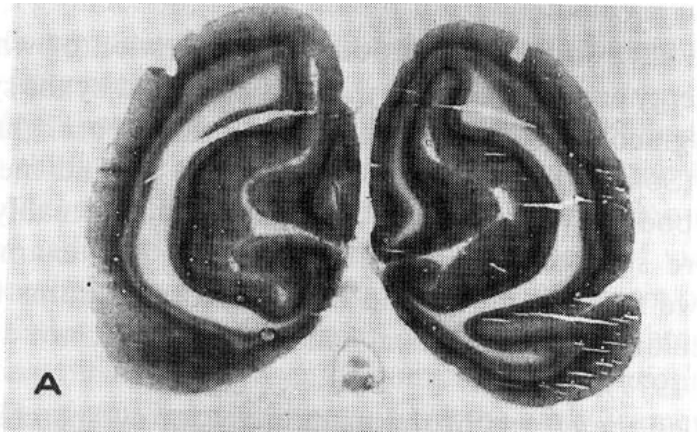
Deeper layers form first, later neurons climb past them

Migration along radial glia

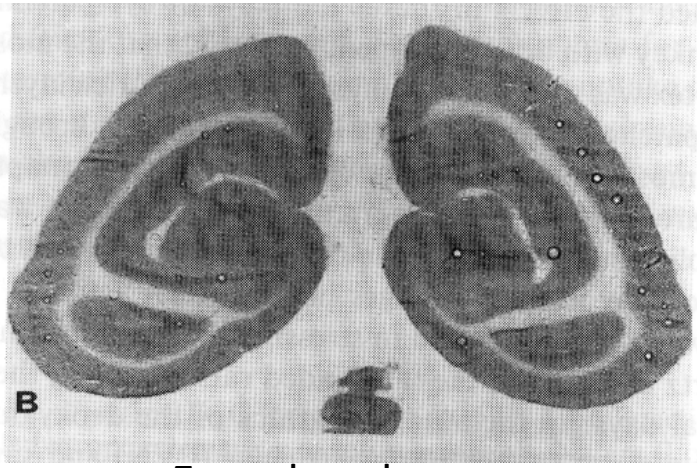
Asymmetric division of progenitors in the germinal matrix

In theory, metabolic mapping techniques can resolve cortical processes at the level of cortical columns.

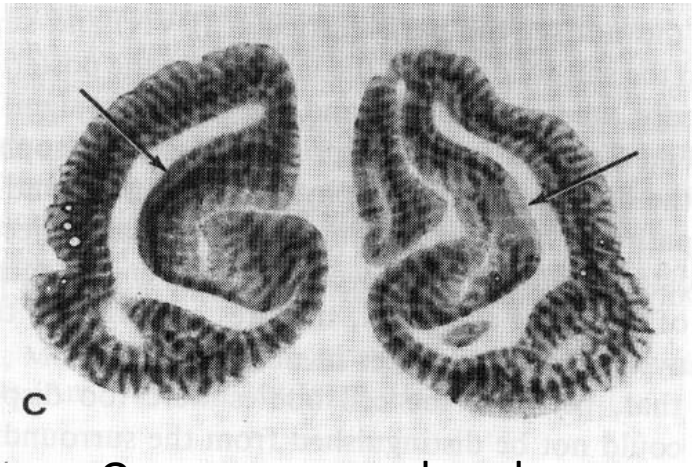
2-deoxyglucose: visual stim in cats



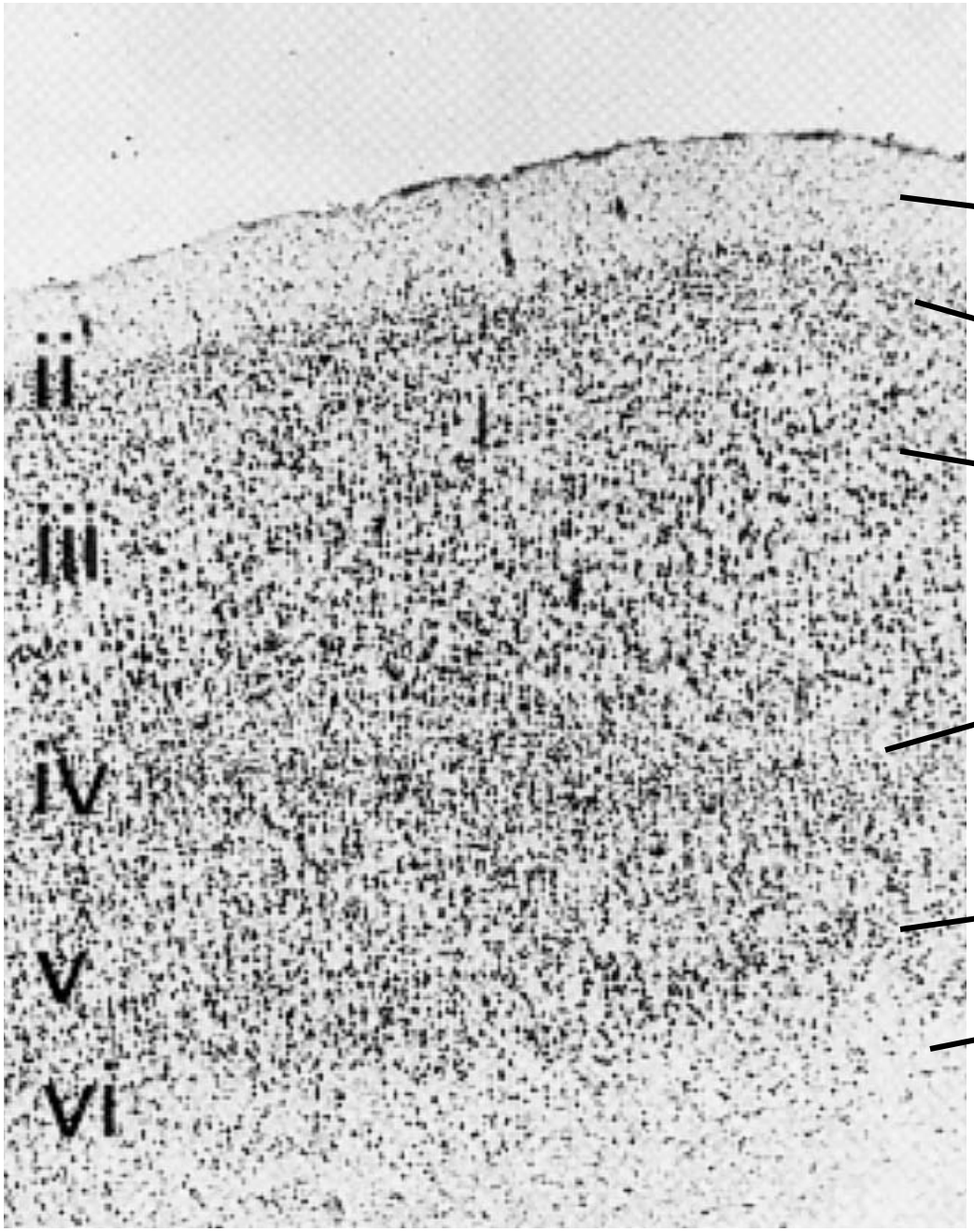
Eyes open



Eyes closed



One open, one closed



I Molecular layer

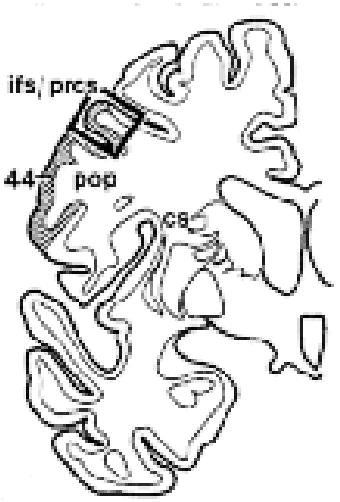
II External granular layer

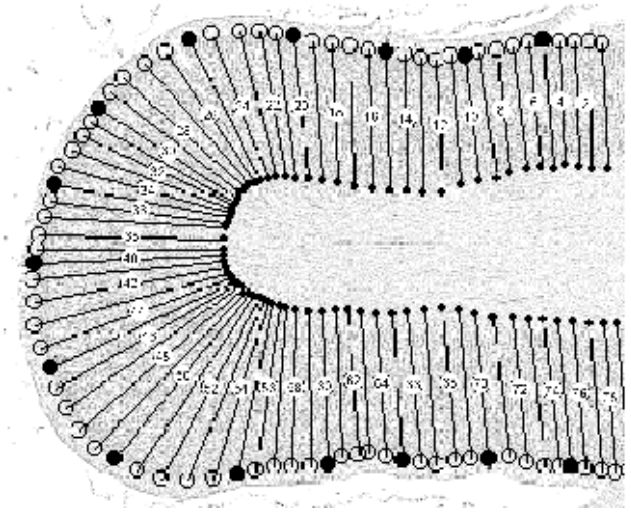
III External pyramidal layer

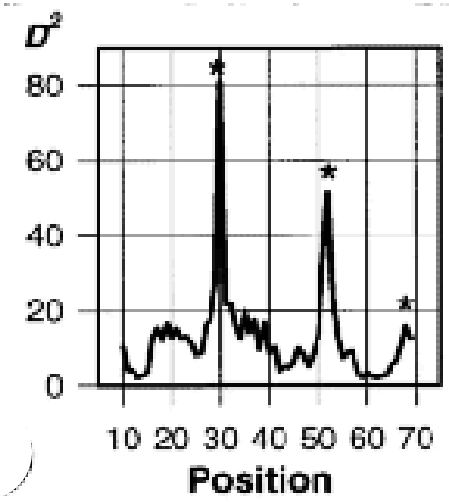
IV Internal granular

V Internal pyramidal

VI Multiform layer







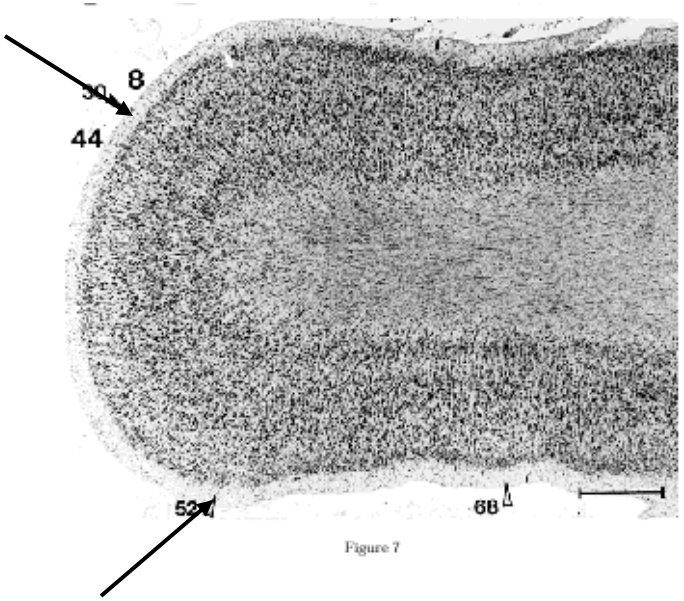
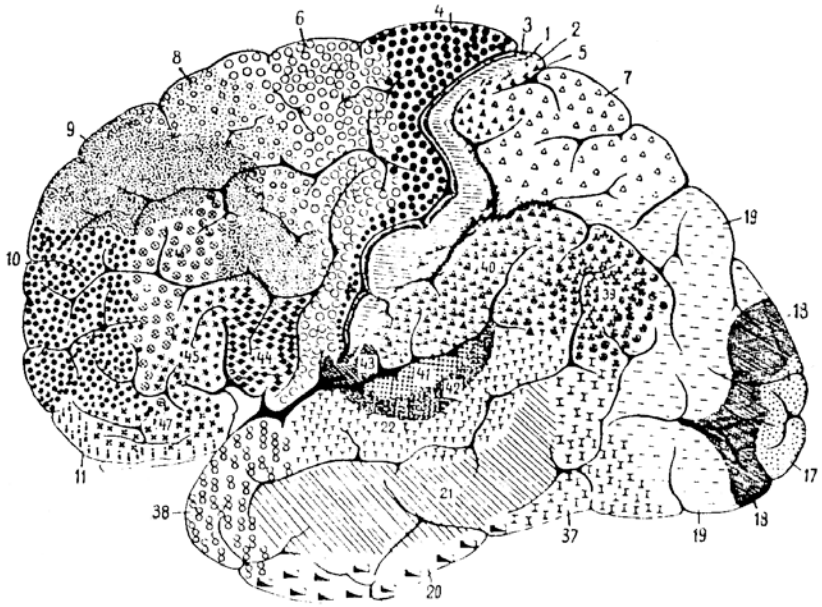
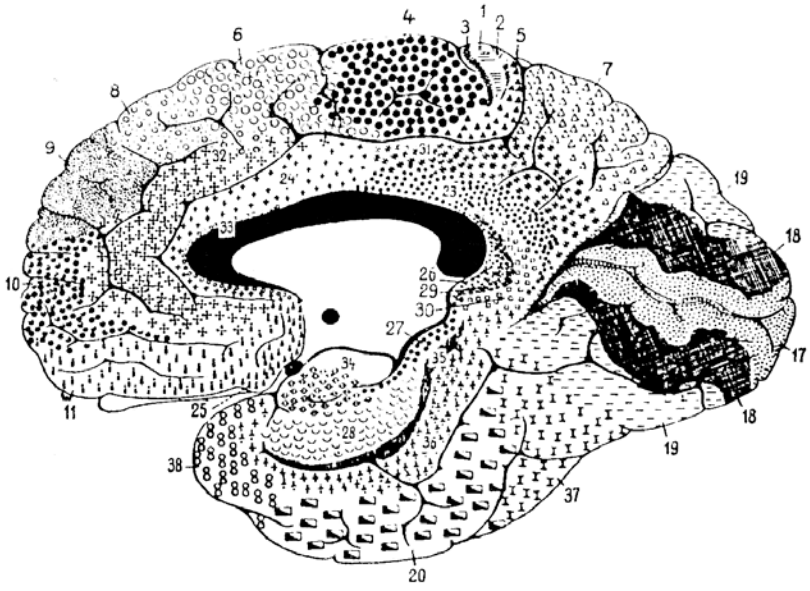


Figure 7

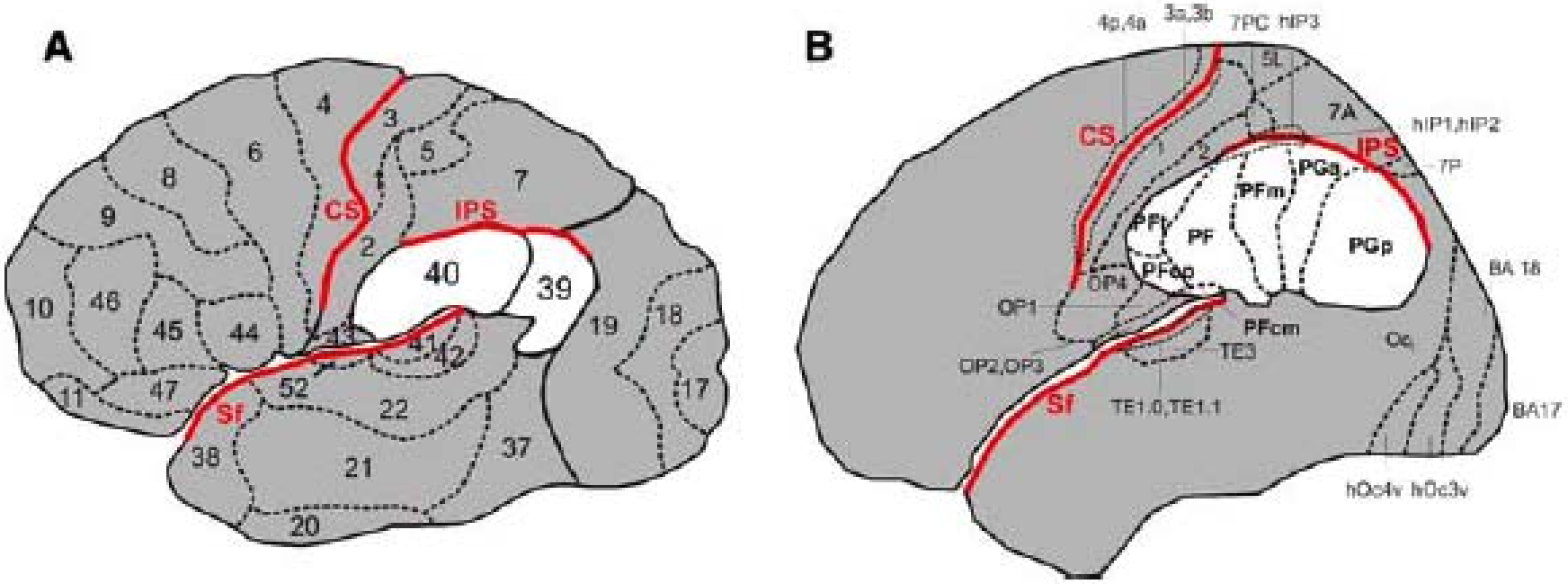
From Amunts et al

Brodmann's cytoarchitectonic map (1909)





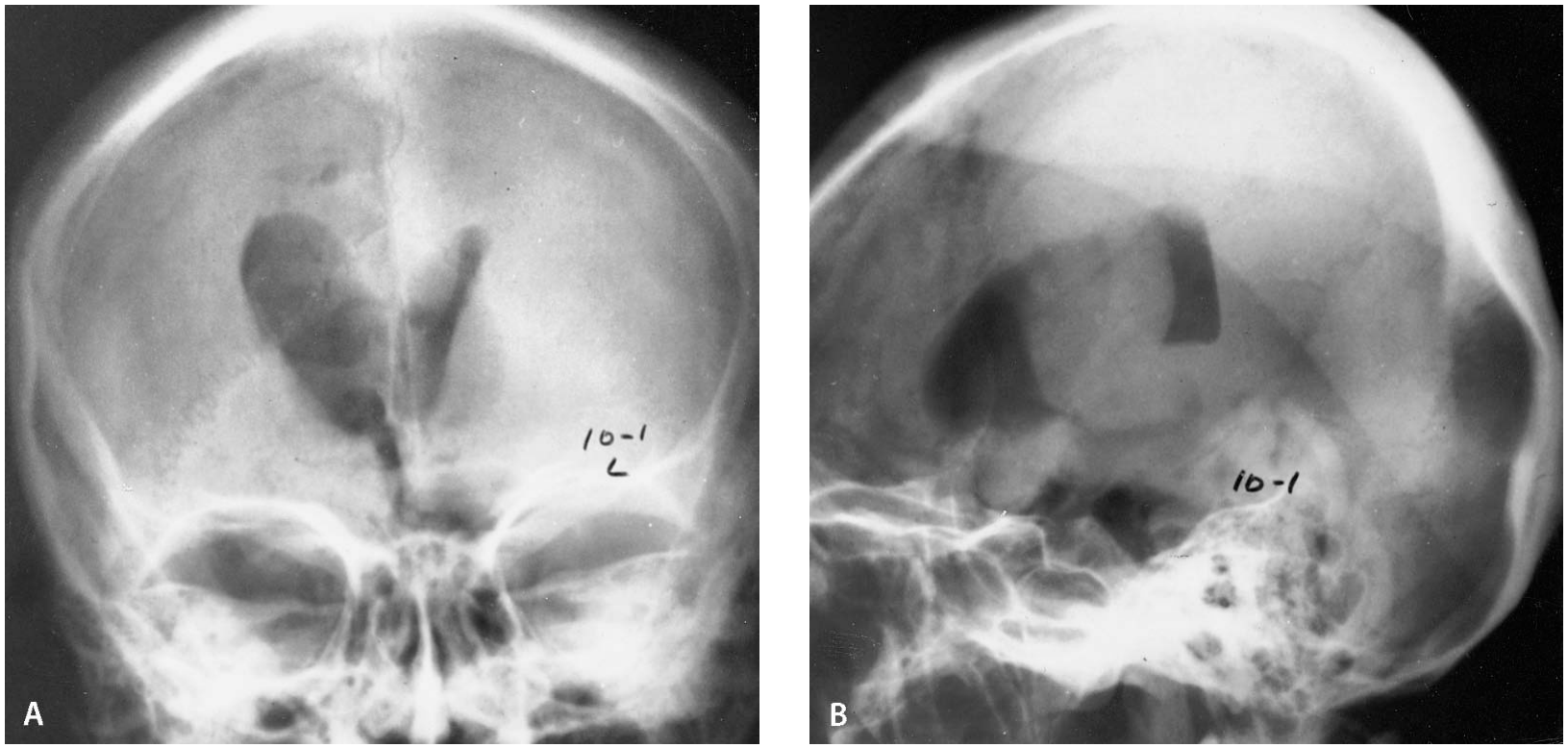
Julisch cytoarchitectonic map (2009)



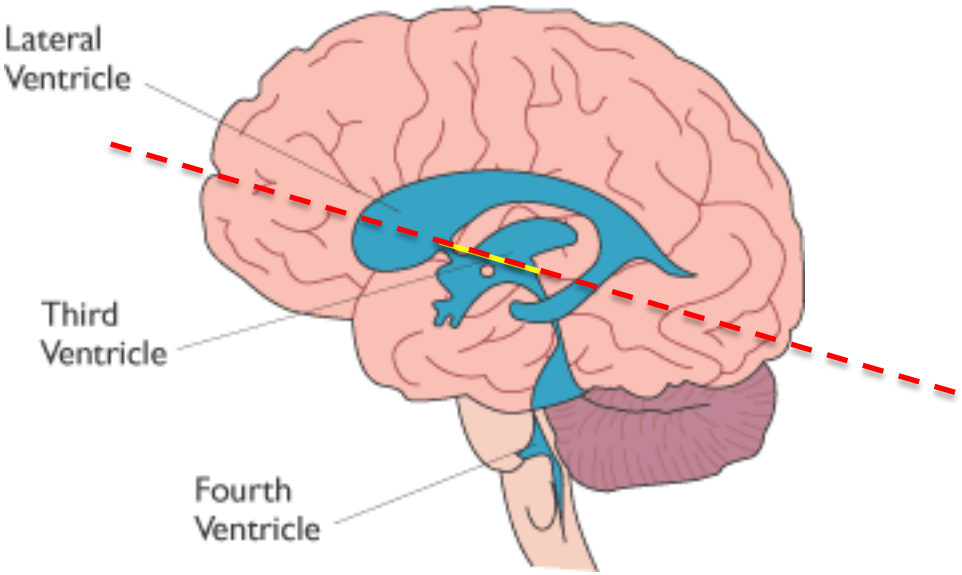
Why is the brain hard to image?

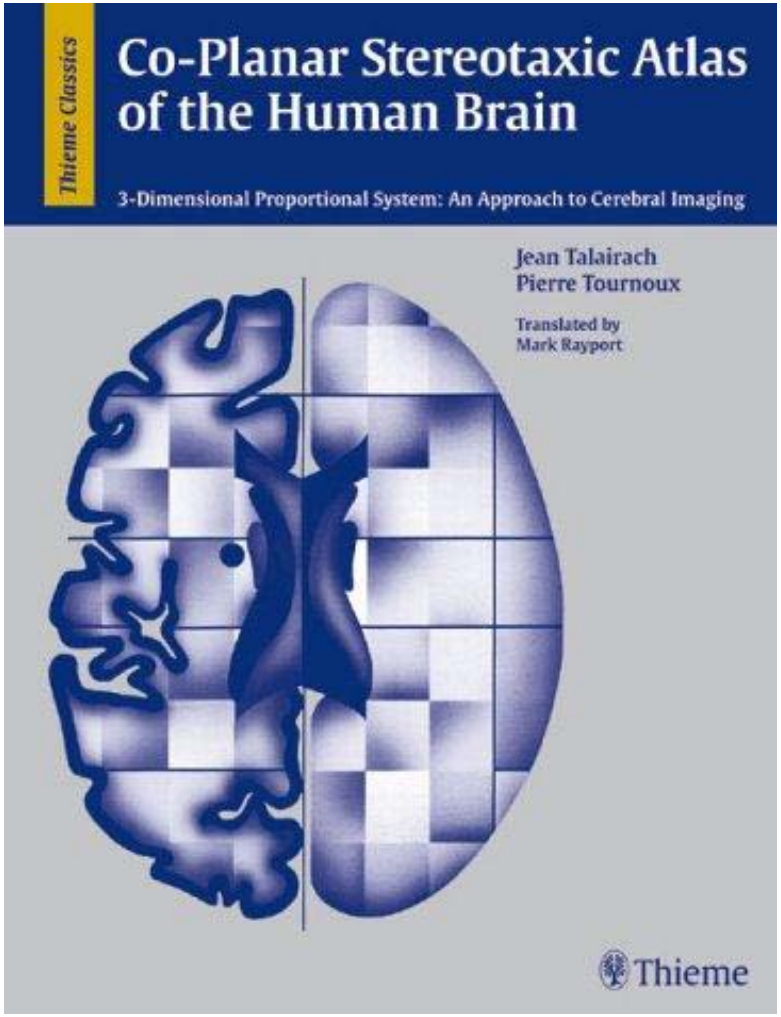
- Differentiated (gray, white) soft tissues give low contrast to xrays
- Cerebral anatomy is 3D complex and variable
- Cerebral functional zones are defined by microscopic features that can’t be imaged directly
- Neurophysiological processes must also be imaged indirectly through vascular and metabolic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

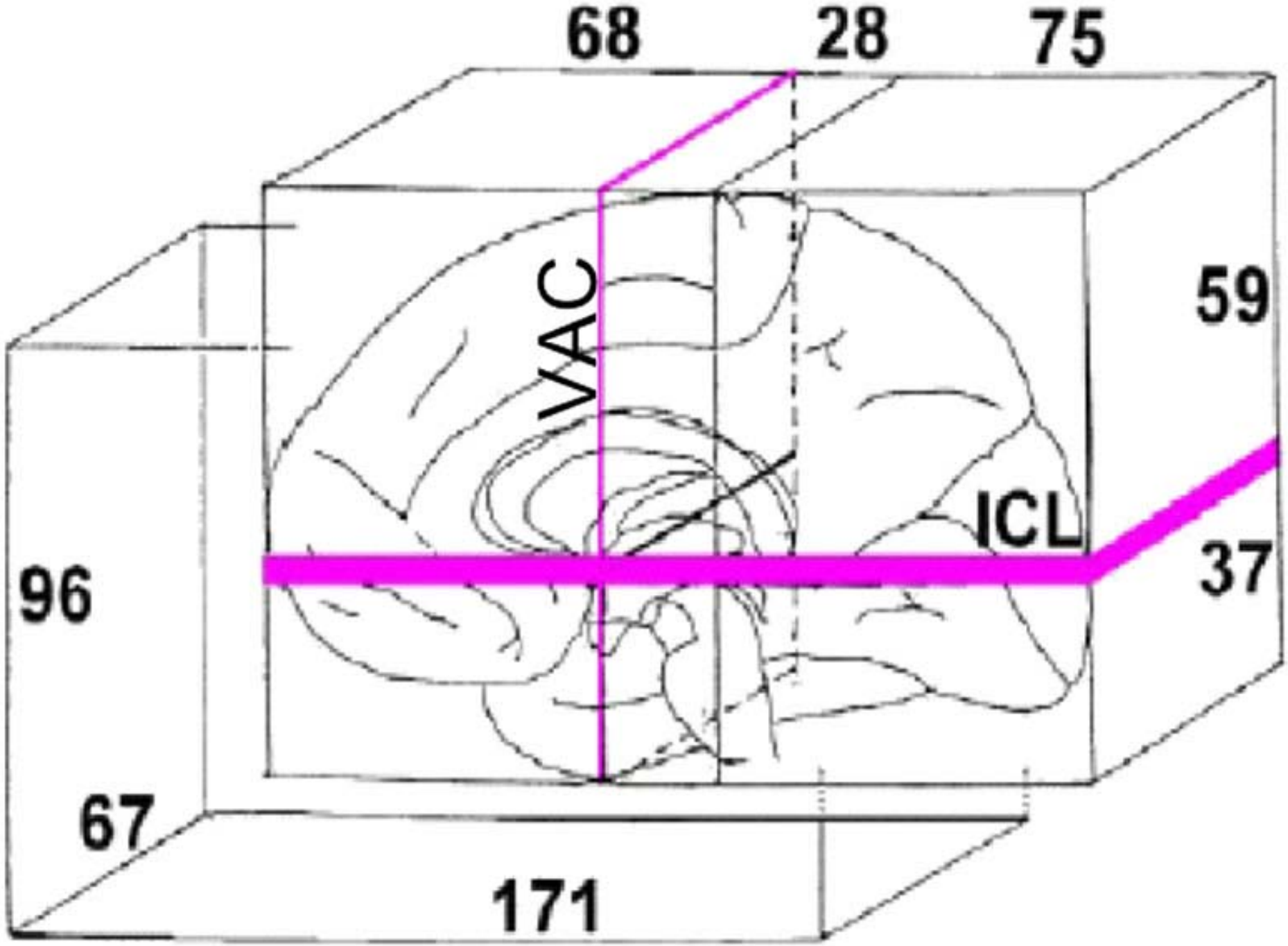
Antiquity (i.e. pre-1975)



The pneumo-encephalogram


Lateral
Ventricle
Third
Ventricle
Fourth
Ventricle


Thieme Classics
Co-Planar Stereotaxic Atlas of the Human Brain
3-Dimensional Proportional System: An Approach to Cerebral Imaging
Jean Talairach
Pierre Tournoux
Translated by
Mark Rayport
Thieme


68
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VAC
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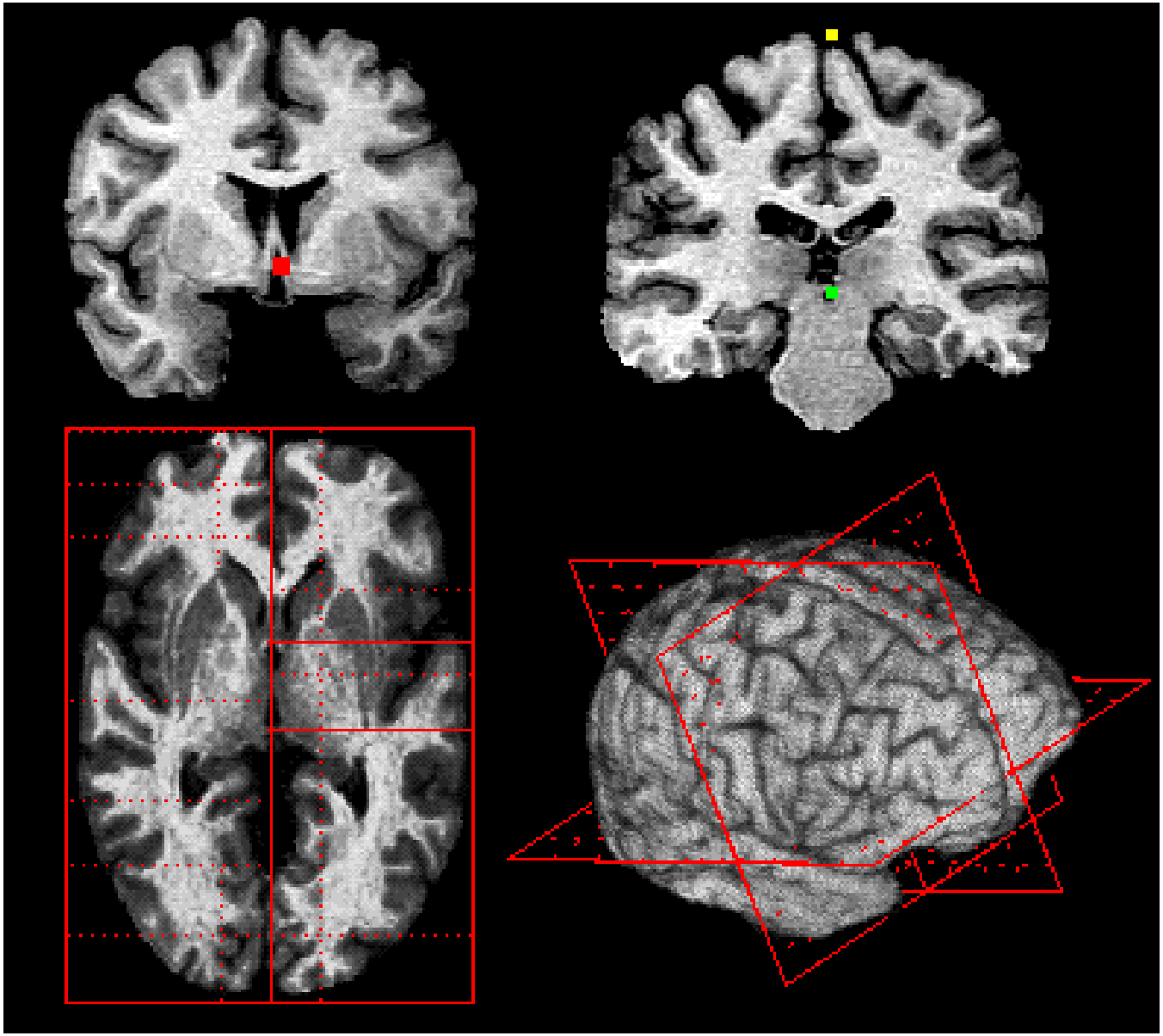
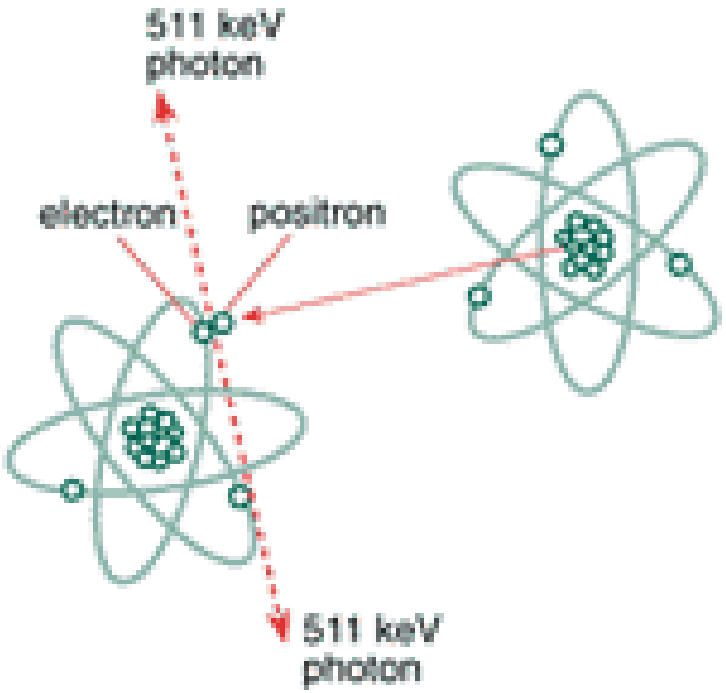
Talairach Space



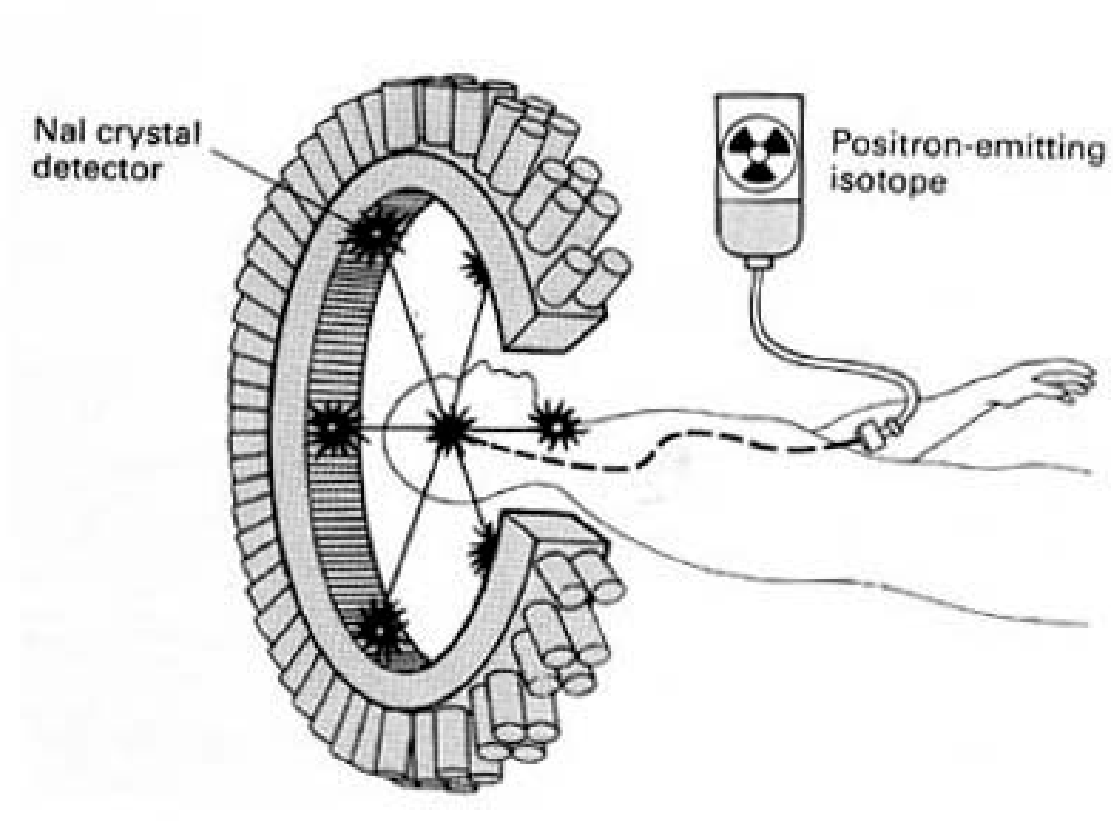
Positron Emission Tomography (PET)

An imaging technique in which images of brain physiological parameters are inferred from the biodistribution of positron-emitting radiopharmaceuticals

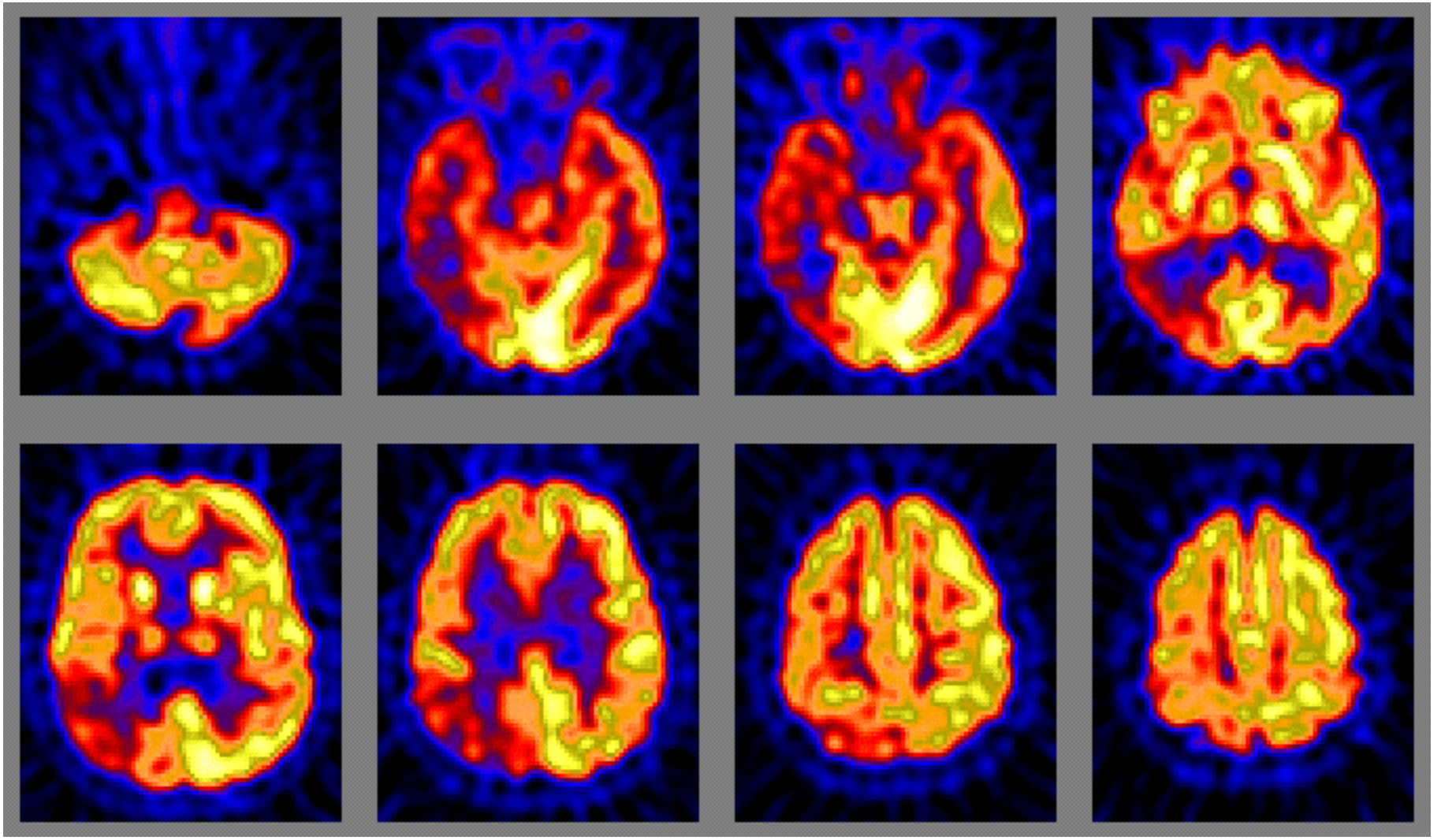
Positron emission

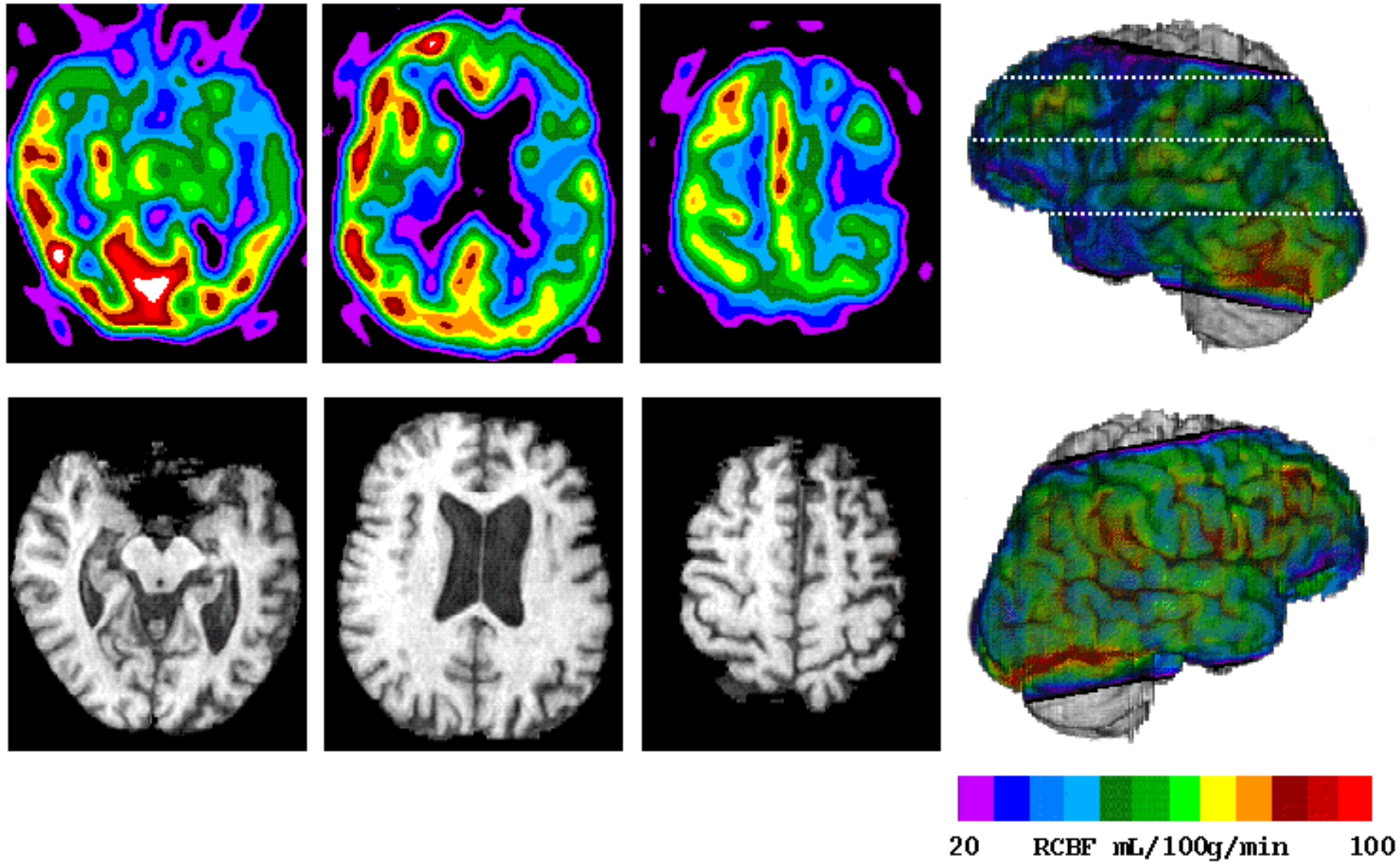


PET detectors



[^{18}F]Fluorodeoxyglucose PET




20 RCBF mL/100g/min 100

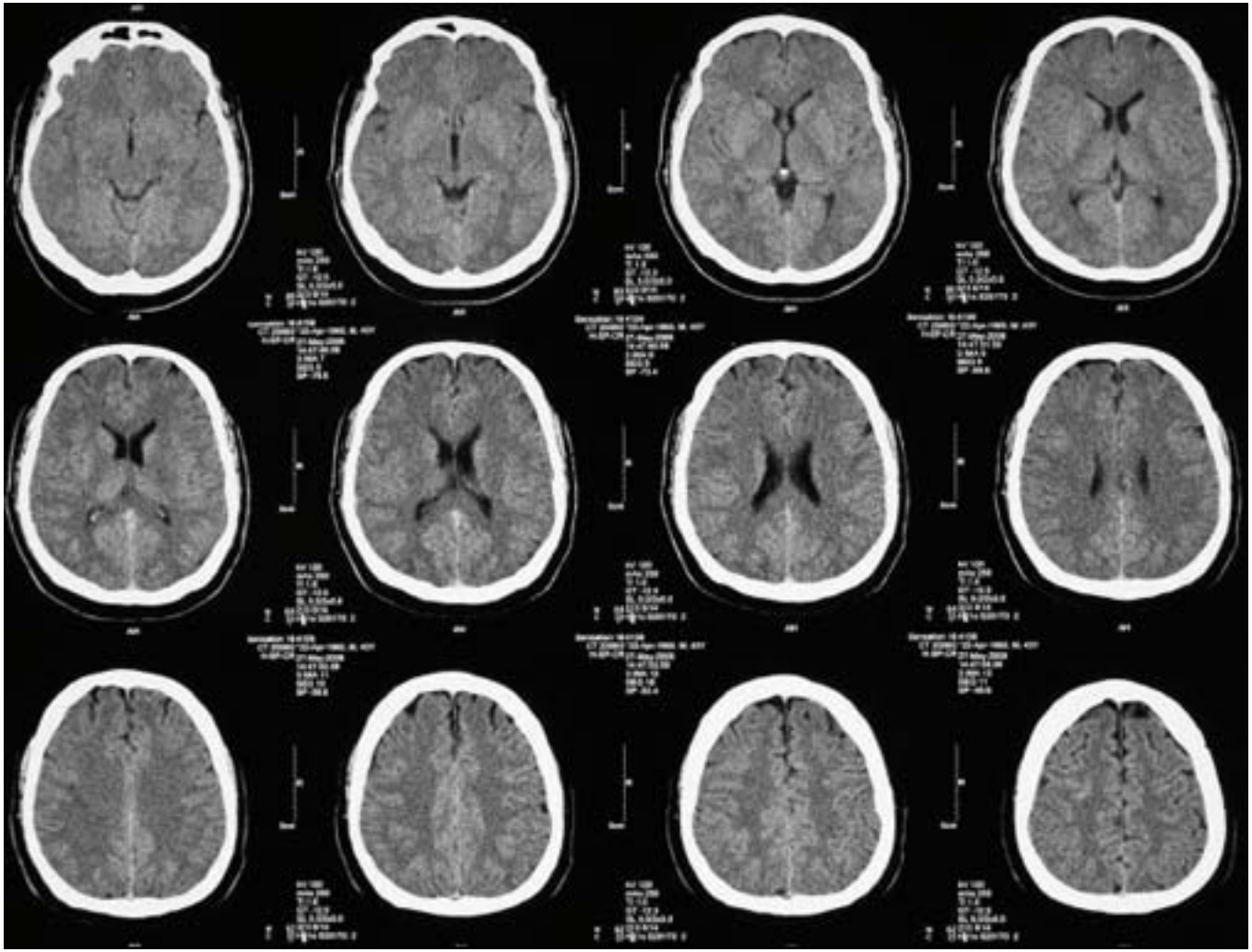
PET

- 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.

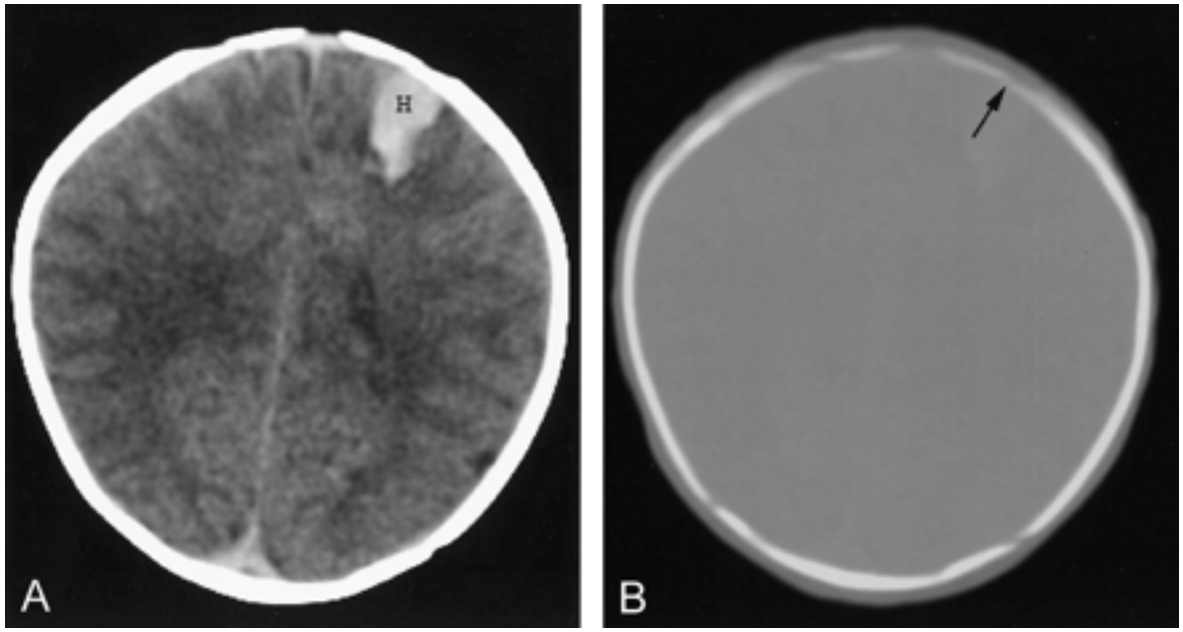
Digital image paradigm

- 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



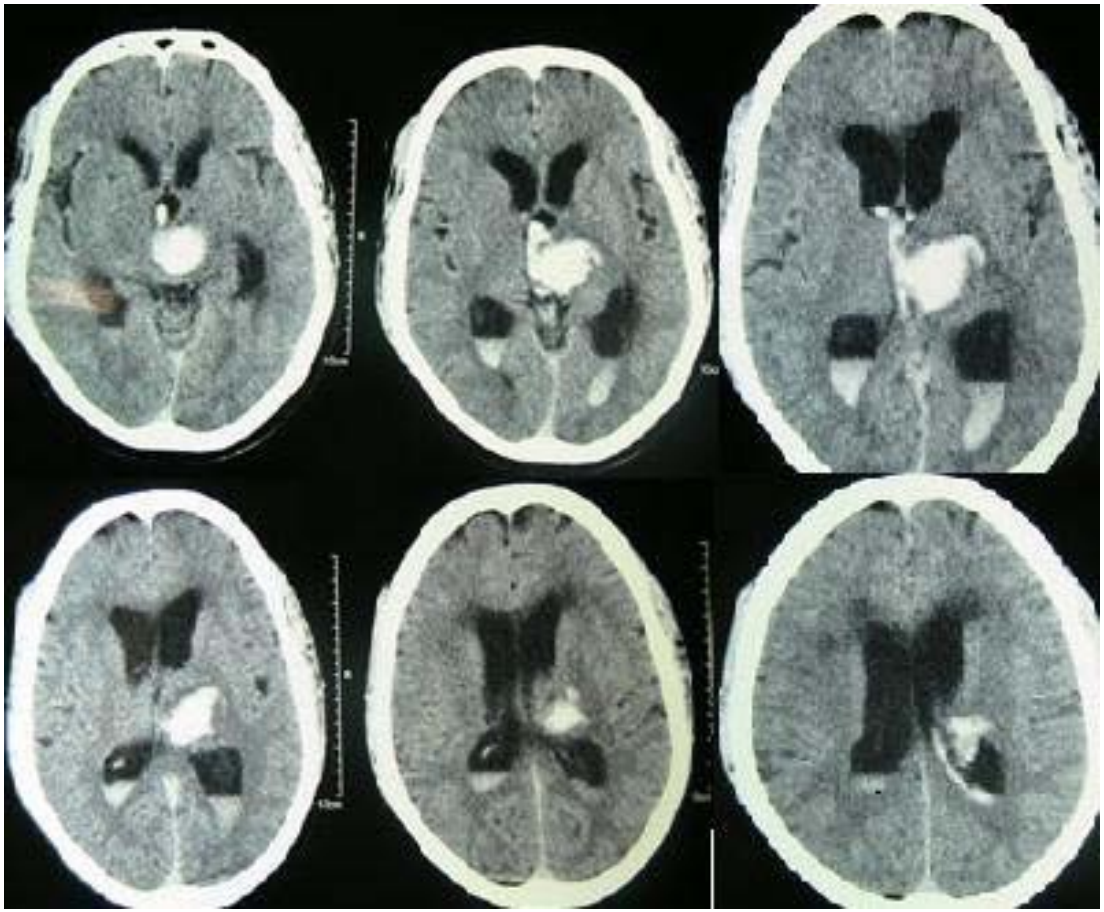
Hounsfield Number

Computed tomography

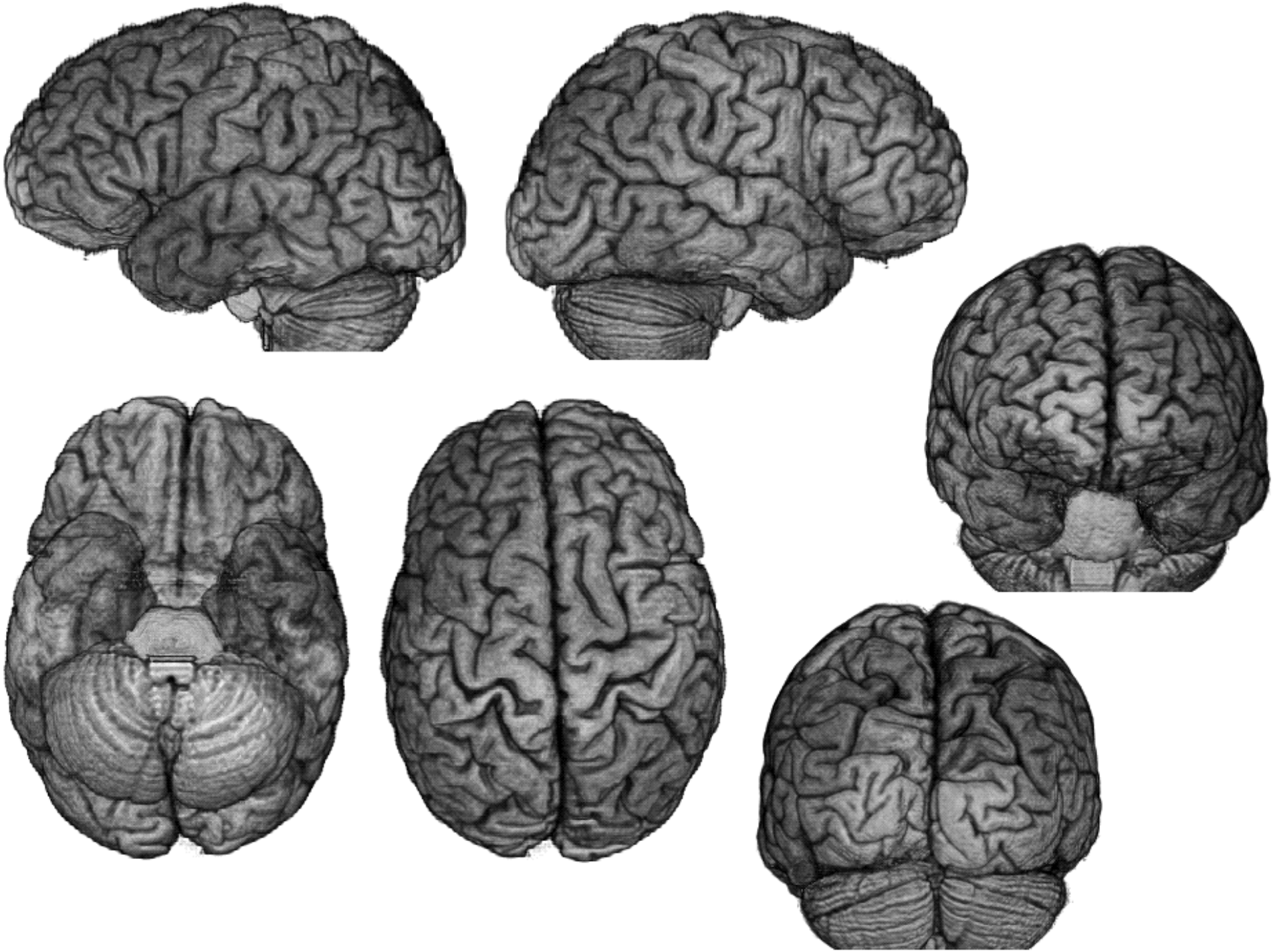
- First tomographic anatomic imaging technique
- Modest soft tissue contrast
- Contrast agent (iodinated) already existed
- Good sensitivity to pathology, esp. blood
- Good resolution of bony structures
- Rapid (good throughput, low sensitivity to motion)

- Finds uses as a first-line emergency technique
- Integrated with PET for attentuation correction and anatomic image fusion
- Used very extensively in body imaging

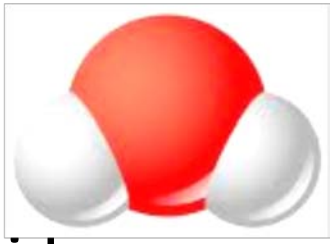
Intracerebral hypertensive hemorrhage



Magnetic Resonance Imaging (MRI)



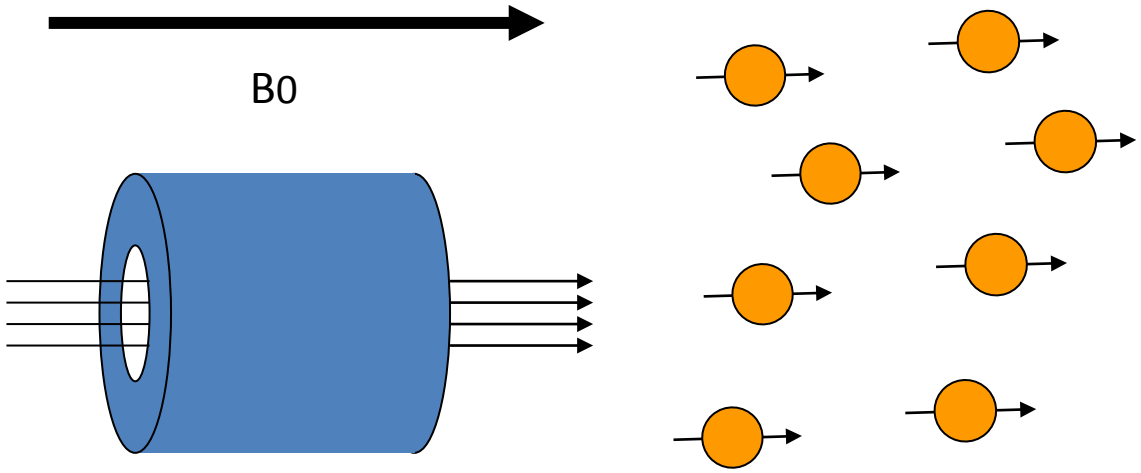
MRI



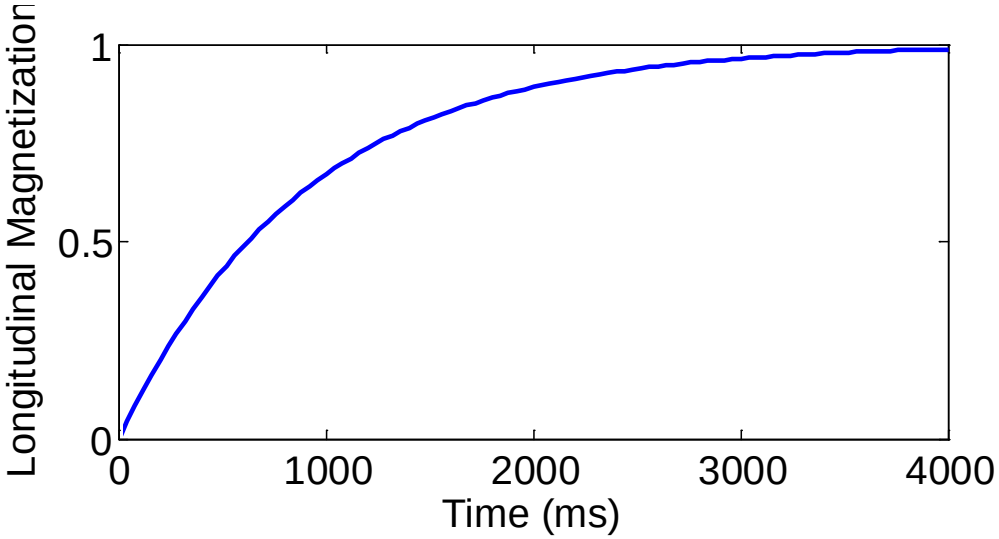
- Water has a natural frequency
- More precisely, its hydrogen nuclei have a quantum mechanical property called *spin angular momentum*
- The spin states of hydrogen nuclei diverge in energy level in the presence of a magnetic field (Zeeman splitting)
- Water protons absorb or give off energy to move between these energy levels, at the natural frequency, the Larmor frequency, which is a function of the magnetic field strength.

Wassersteifel
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.

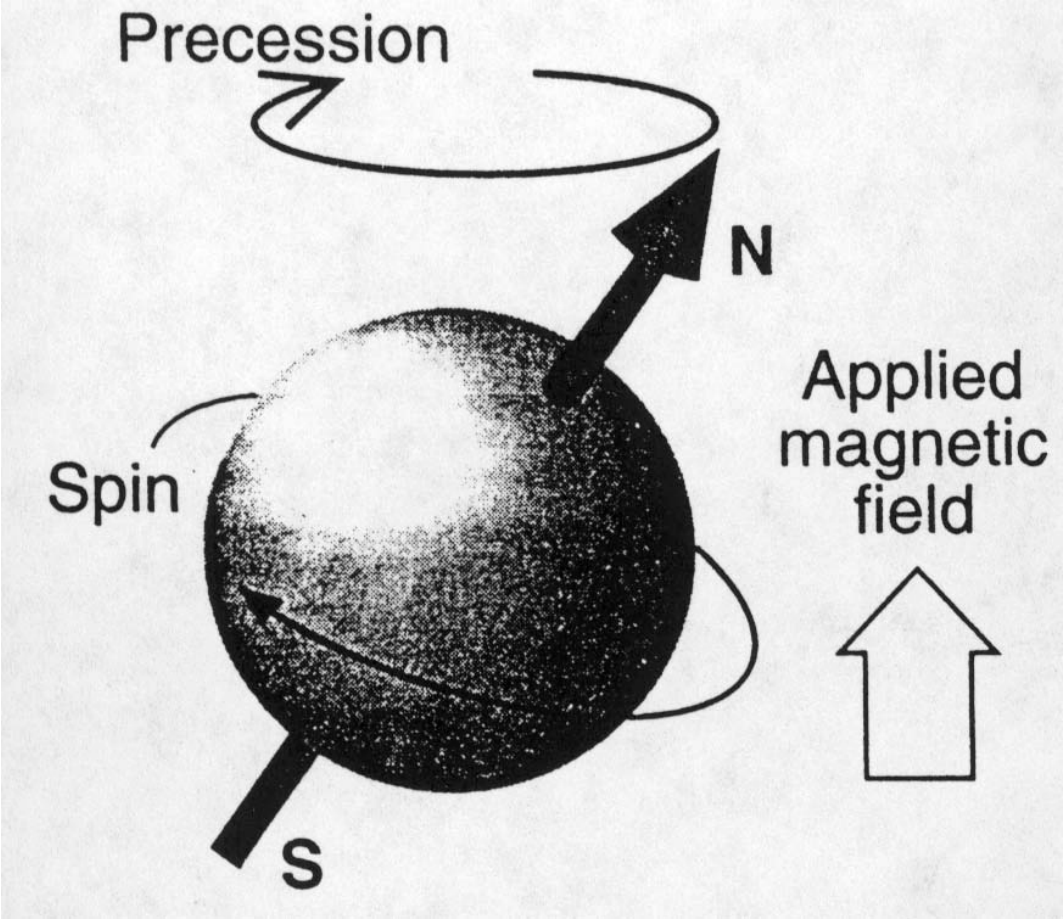


$$M = M_0\left(1 - e^{-t/T_1}\right)$$

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*).

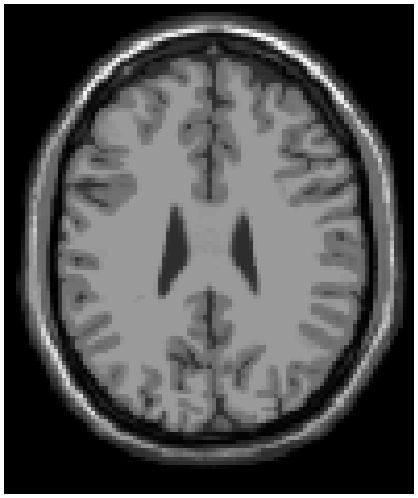
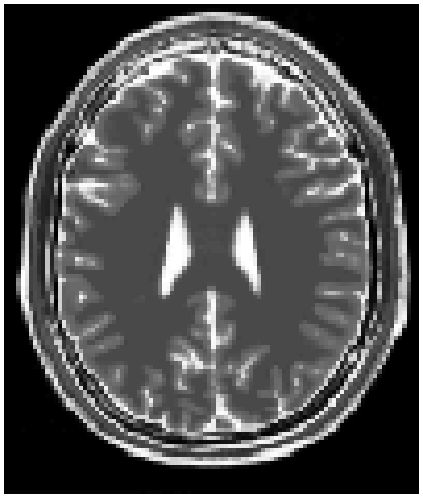
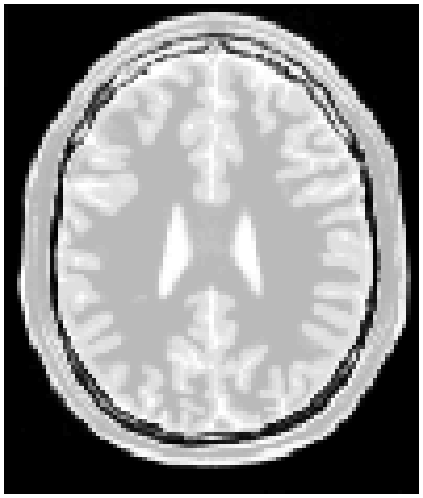
T1 relaxation occurs at different rates in different tissues

- 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	T2	PD
		
TR = 300 msec TE = 20 msec	TR = 3000 msec TE = 120 msec	TR = 3000 msec TE = 20 msec

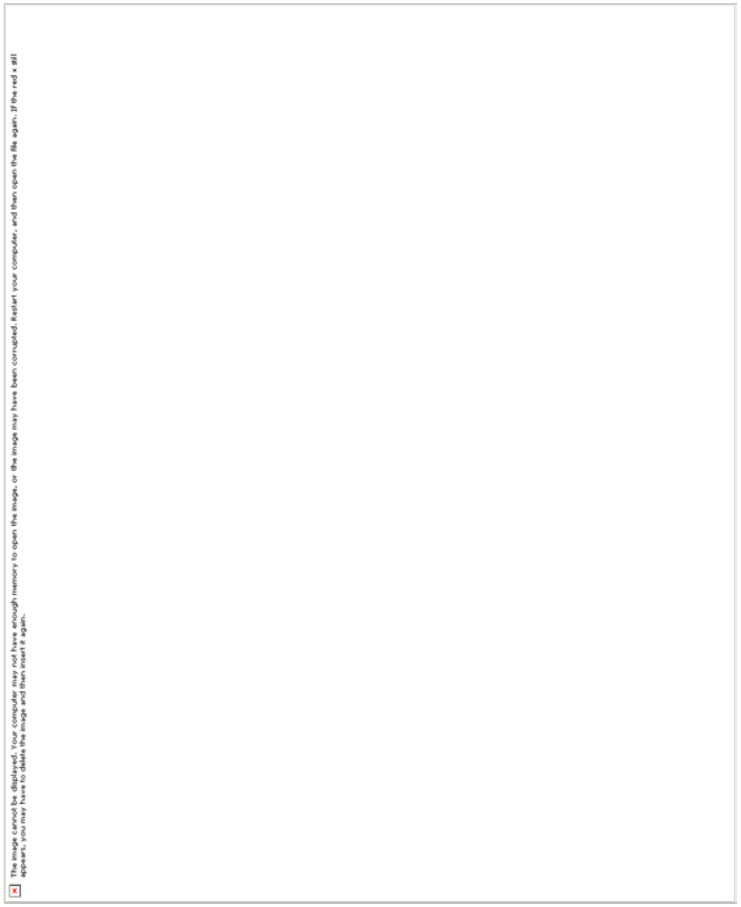
A **short** TR and **short** TE emphasizes T1 contrast.

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

A **long** TR and **short** TE emphasizes proton density contrast.

FLAIR : FLuid-Attenuated Inversion Recovery

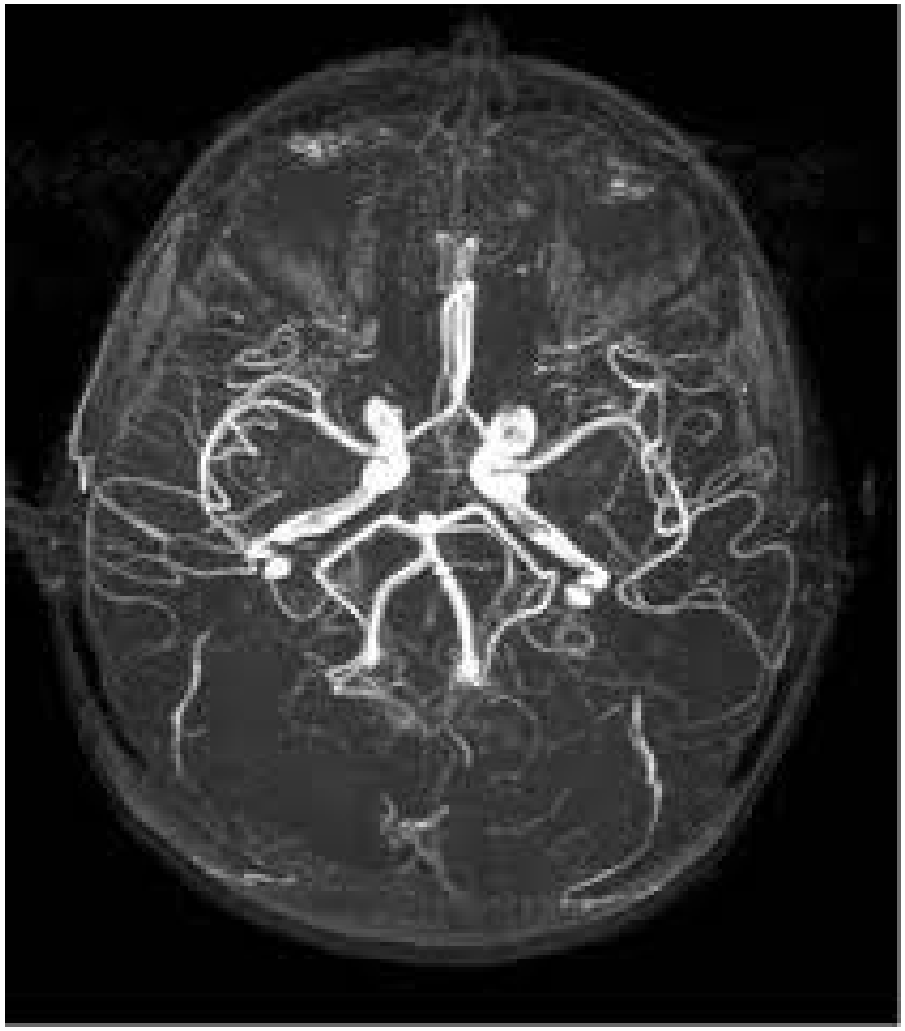
– T2 weighting with black spinal fluid



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"

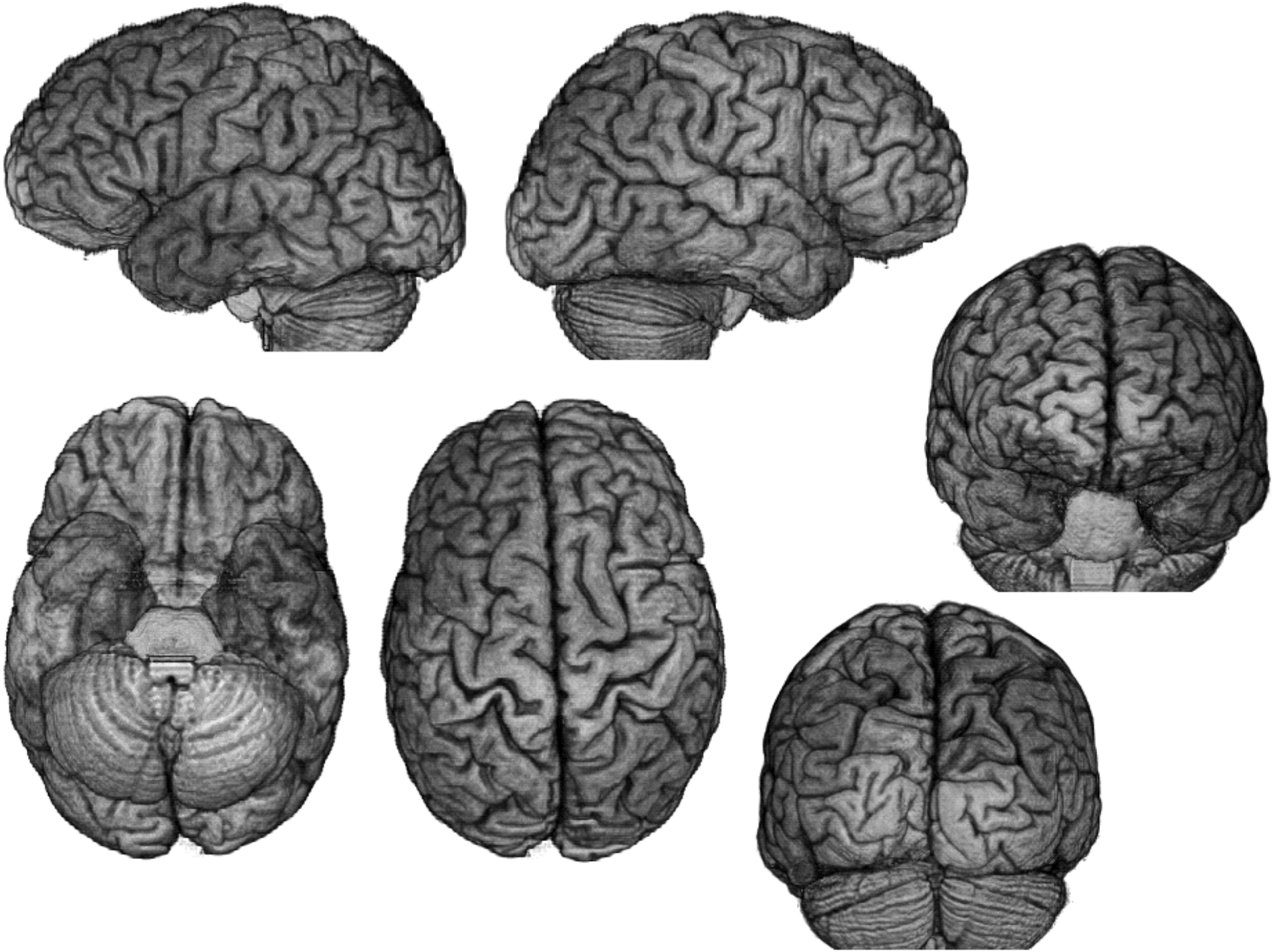


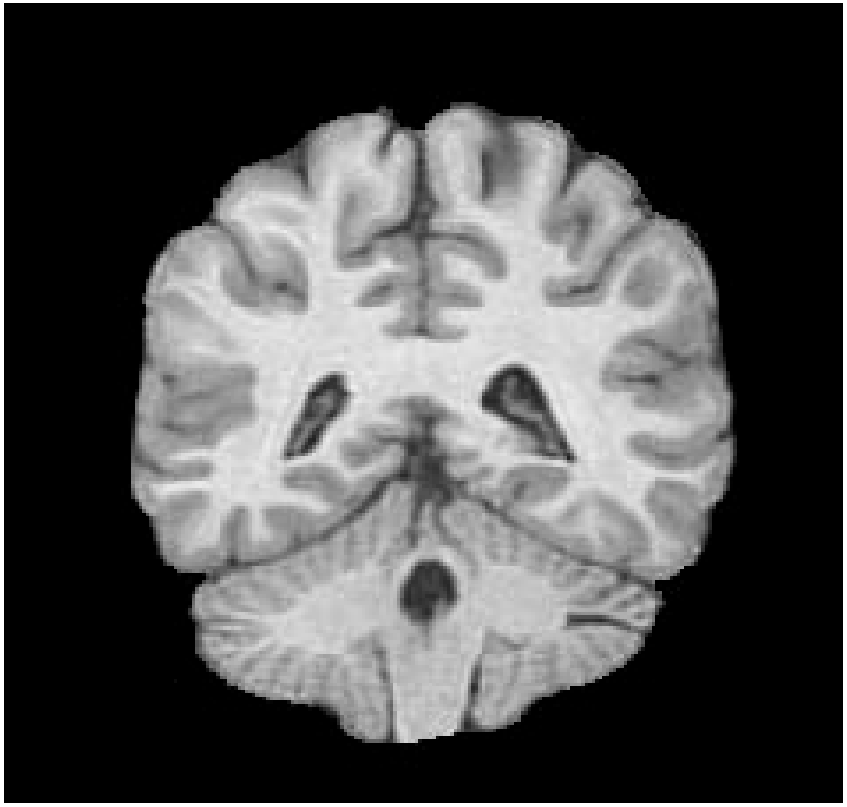
The economy of MRI

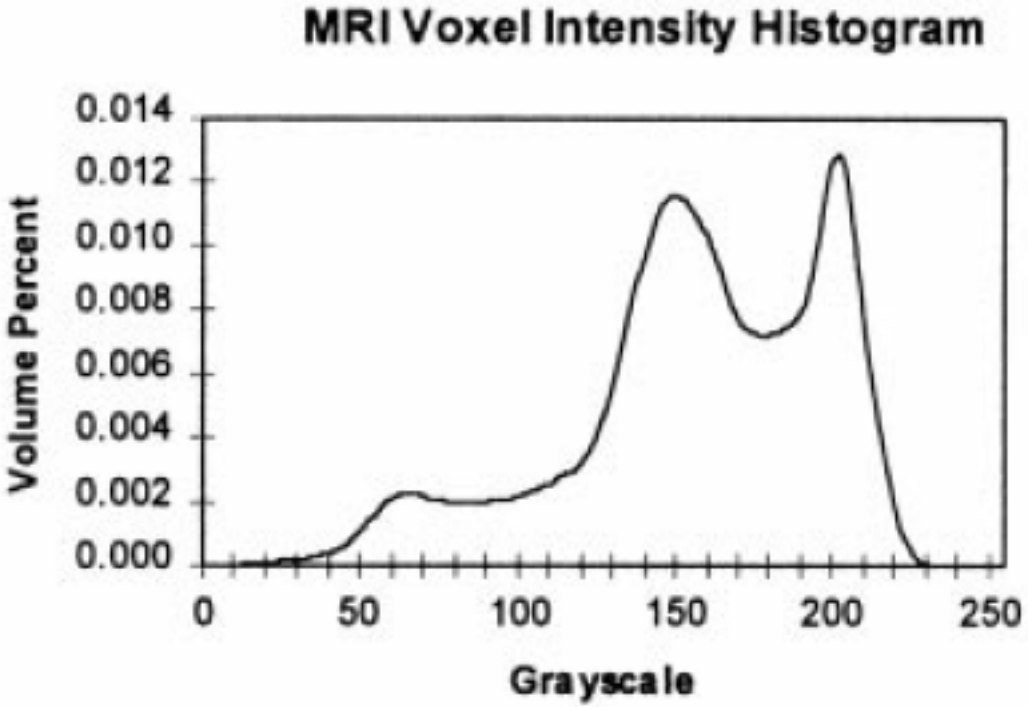
- The currency of MRI is signal, i.e. the sum of the longitudinal magnetization of the protons in the field of view
- This is a fixed budget, that can be used more or less efficiently, and can be spent to obtain some combination of:
  - Better spatial resolution
  - Better signal to noise ratio (SNR)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

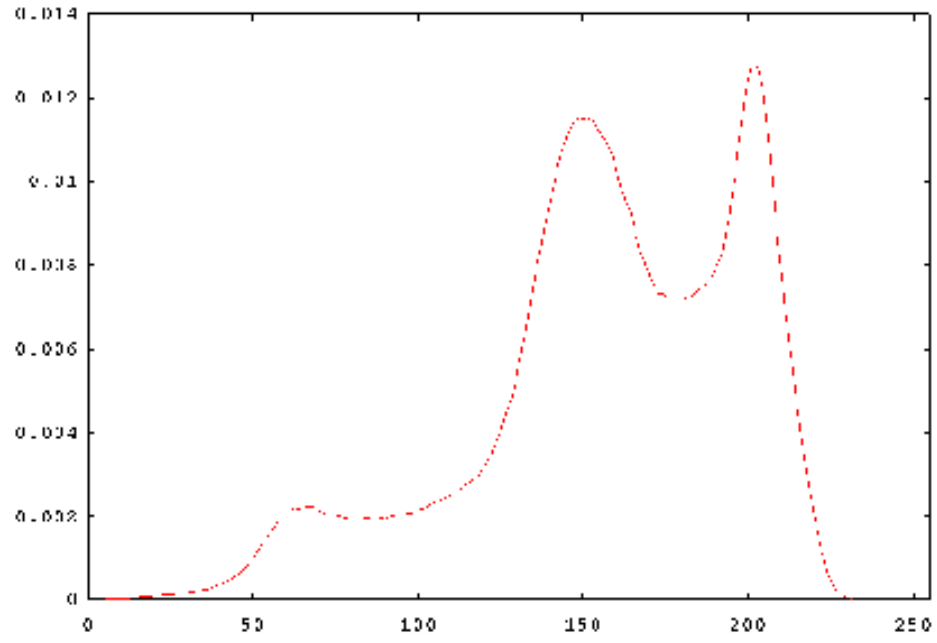
Efficient pulse sequences

- 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

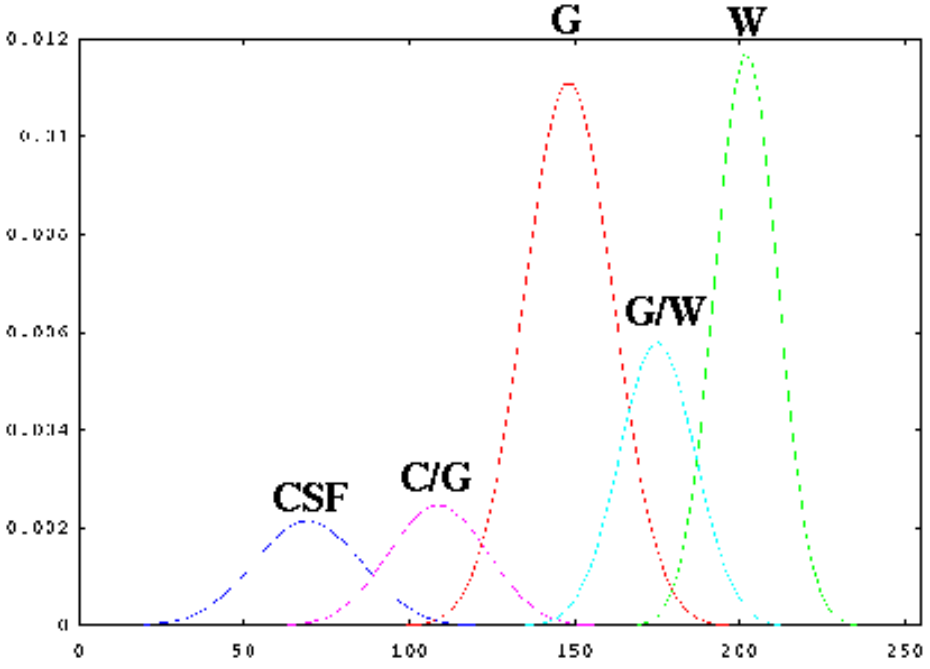




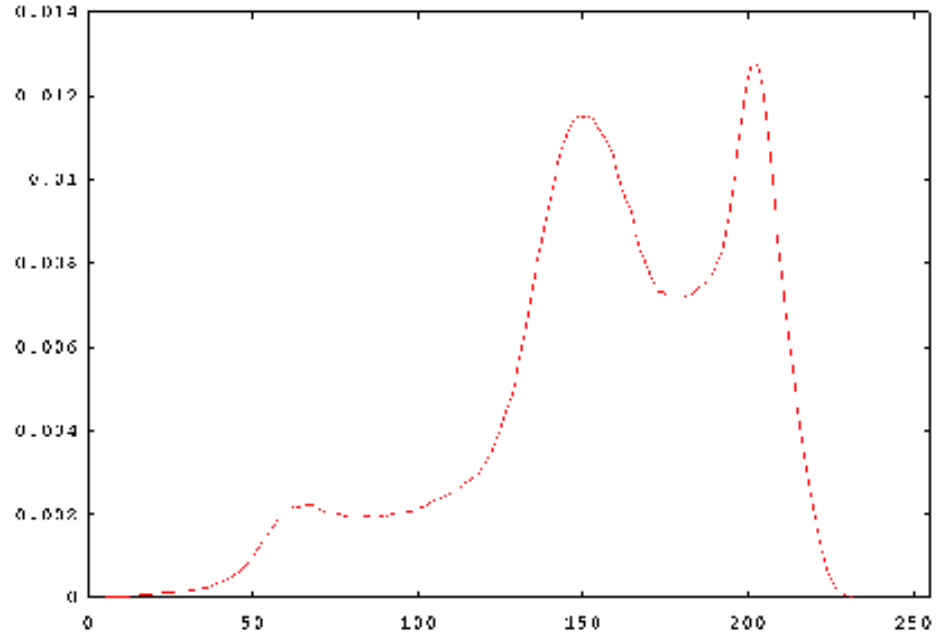

MRI Voxel Intensity Histogram
Volume Percent
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
50
100
150
200
250
Grayscale



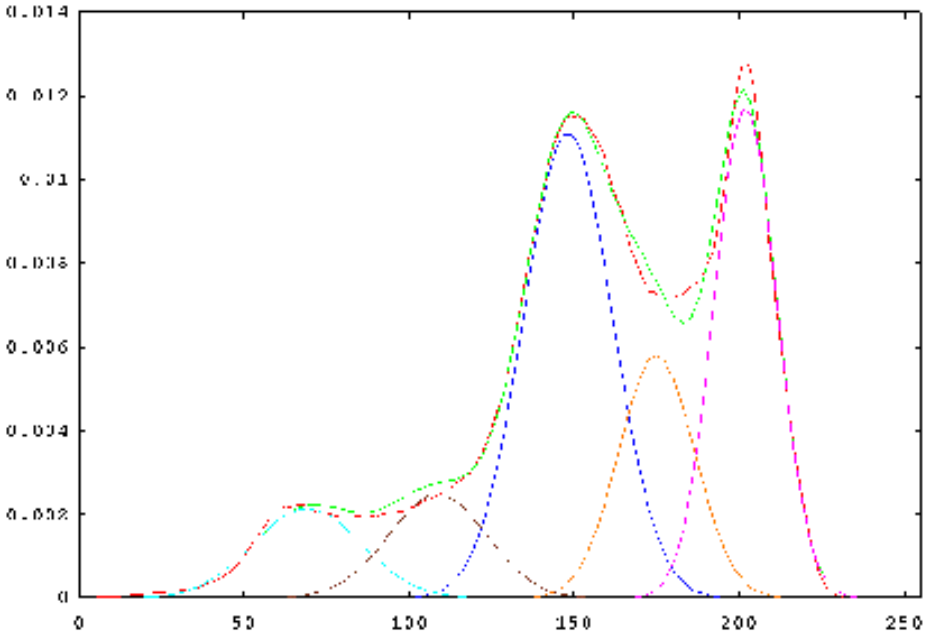
MRI pixel intensity histogram



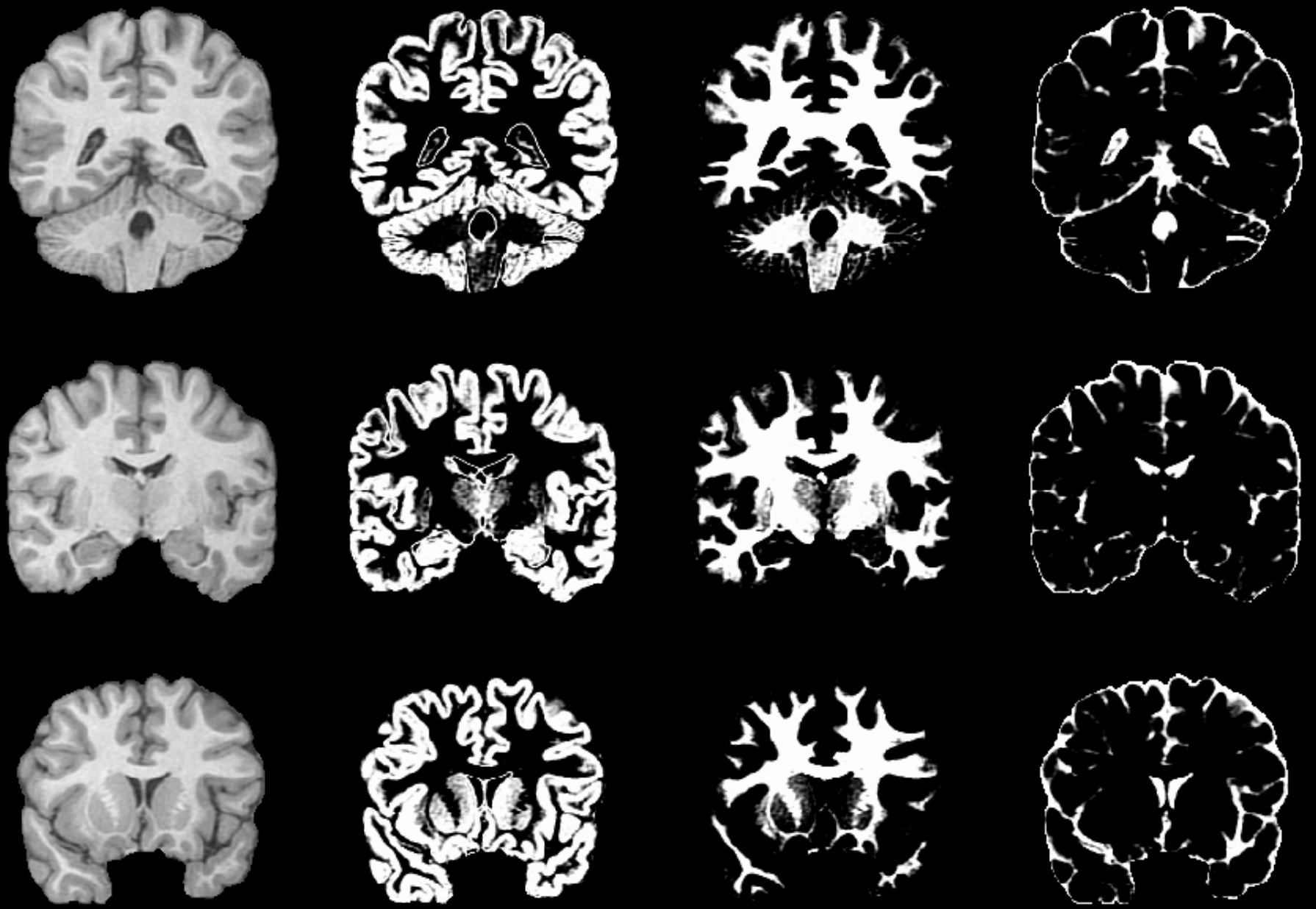
Model parameterization



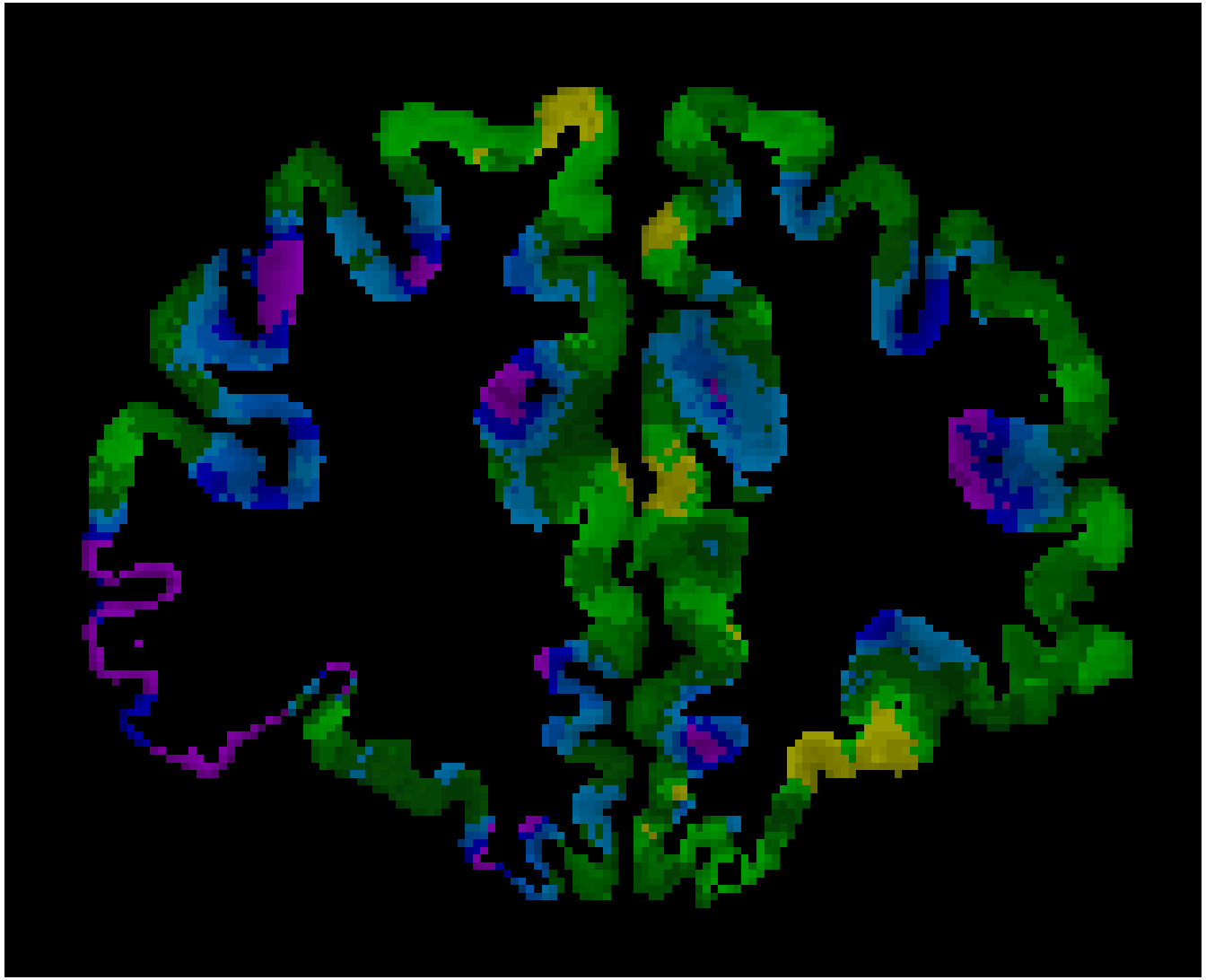
Modeled histogram (Σ 5 gaussians)



Model plotted with actual histogram

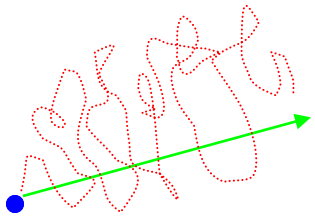


Cortical thickness

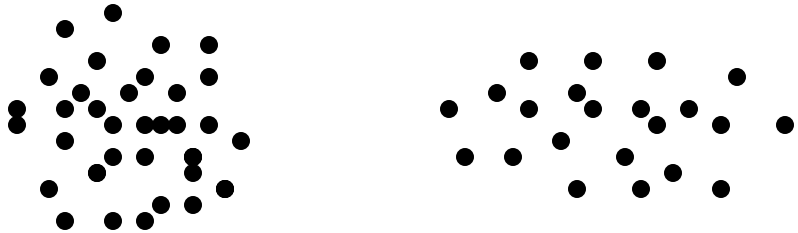


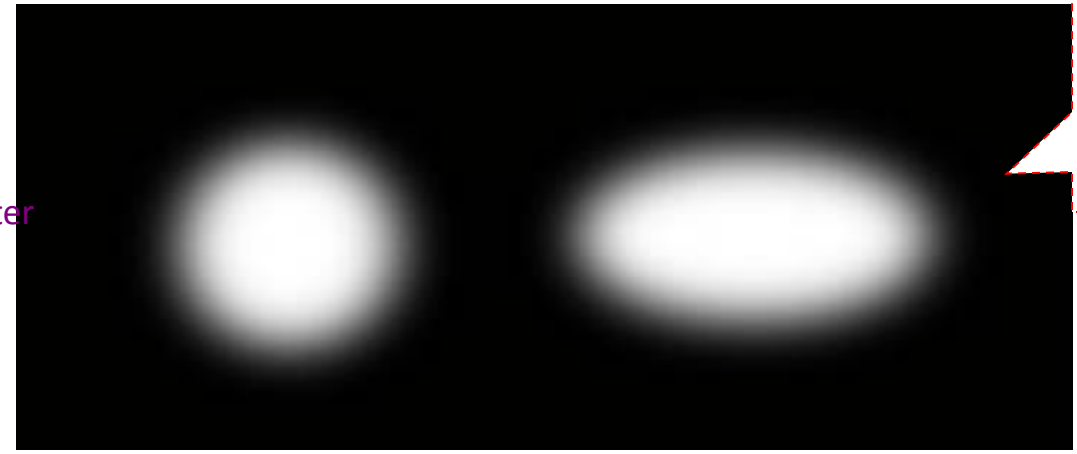
Diffusion Tensor Imaging

Diffusion



Random “walk” of the water molecular also known as “Brownian motion ”

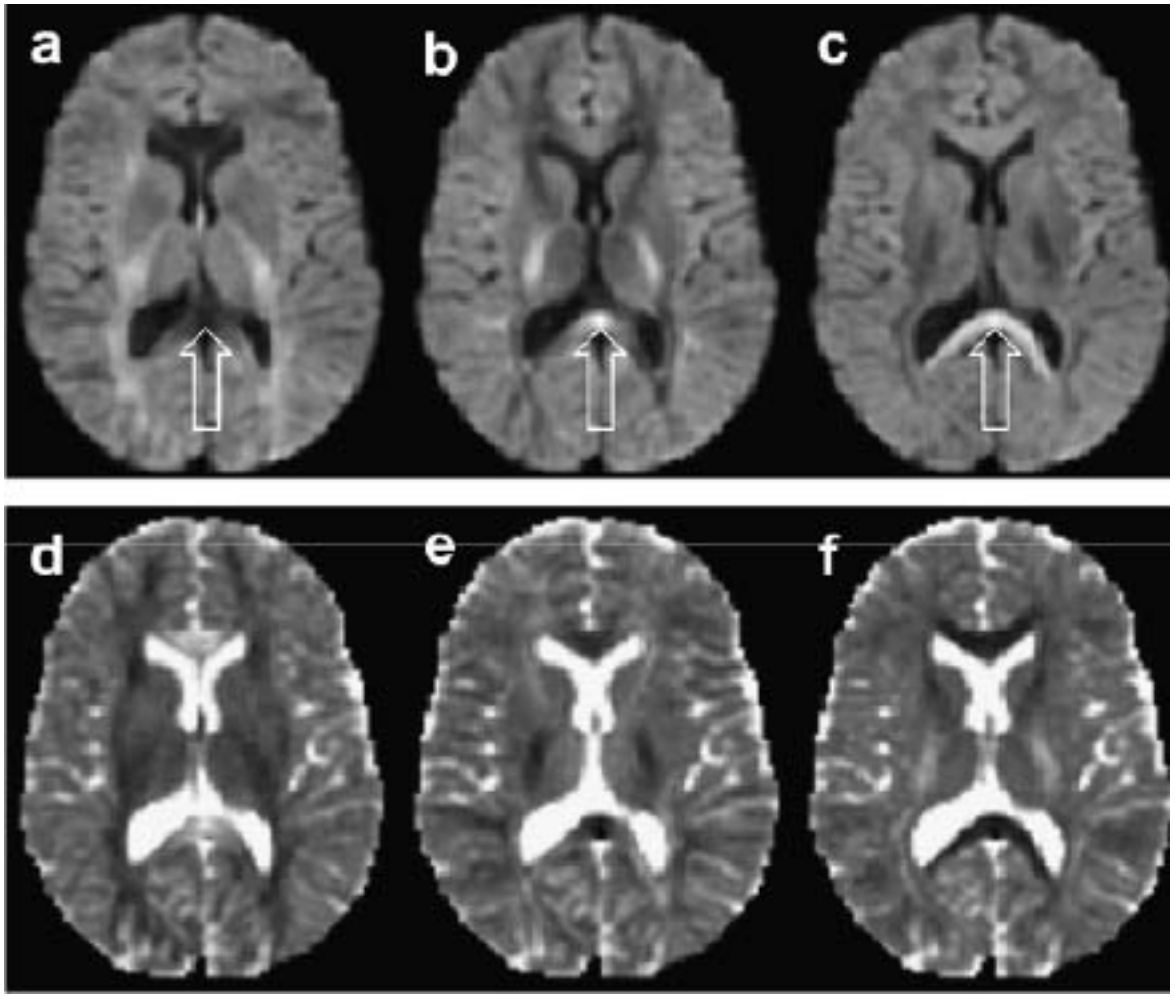




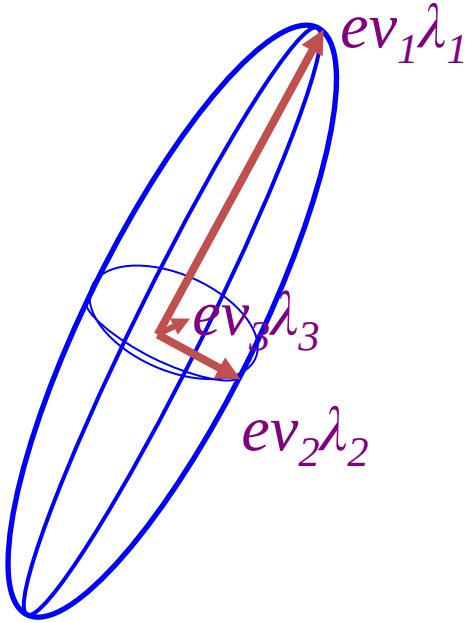
Ellipsoid = Probability of Diffusion Distribution

Isotropic Diffusion

Anisotropic Diffusion


a
b
c
d
e
f

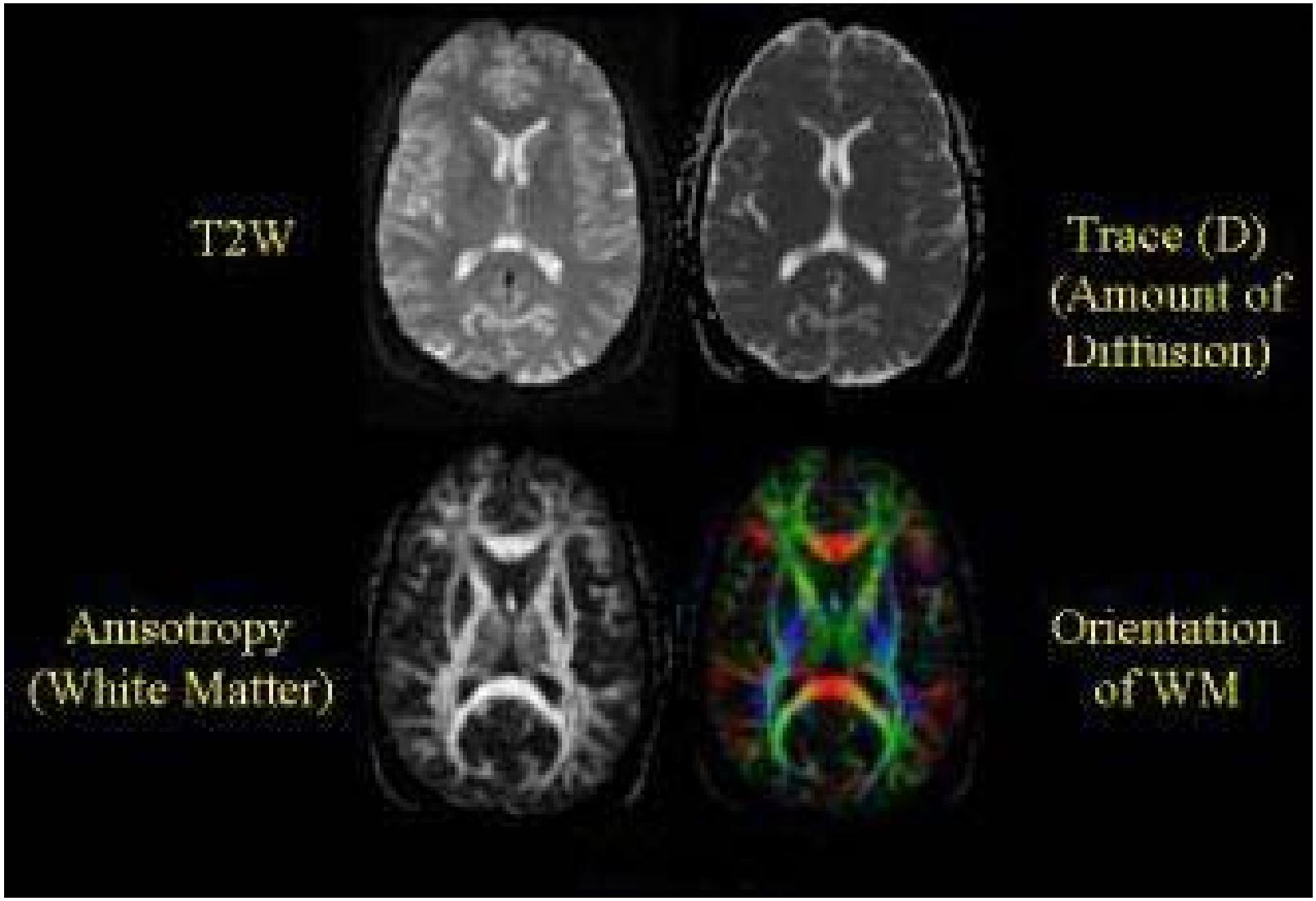
Diffusion eigenvectors



Diagonalization of this tensor provides three eigenvectors (ev_1, ev_2 and ev_3) with three corresponding eigenvalues (λ_1, λ_2 and λ_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

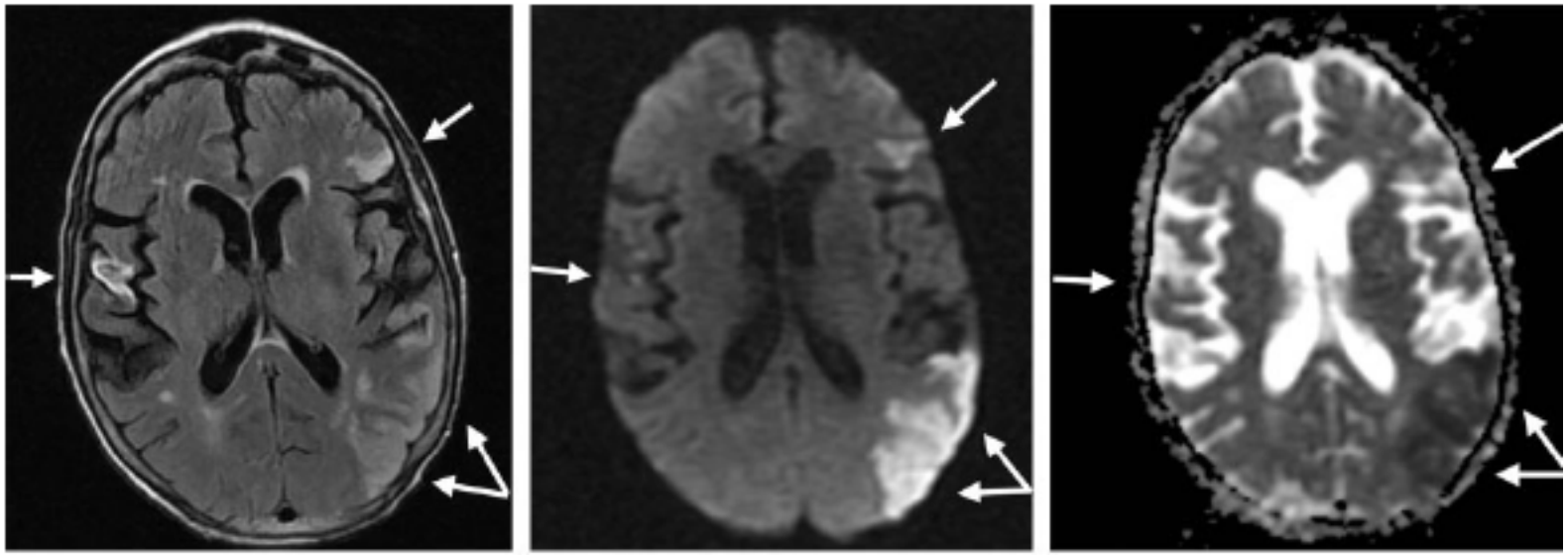


Diffusion imaging

- 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



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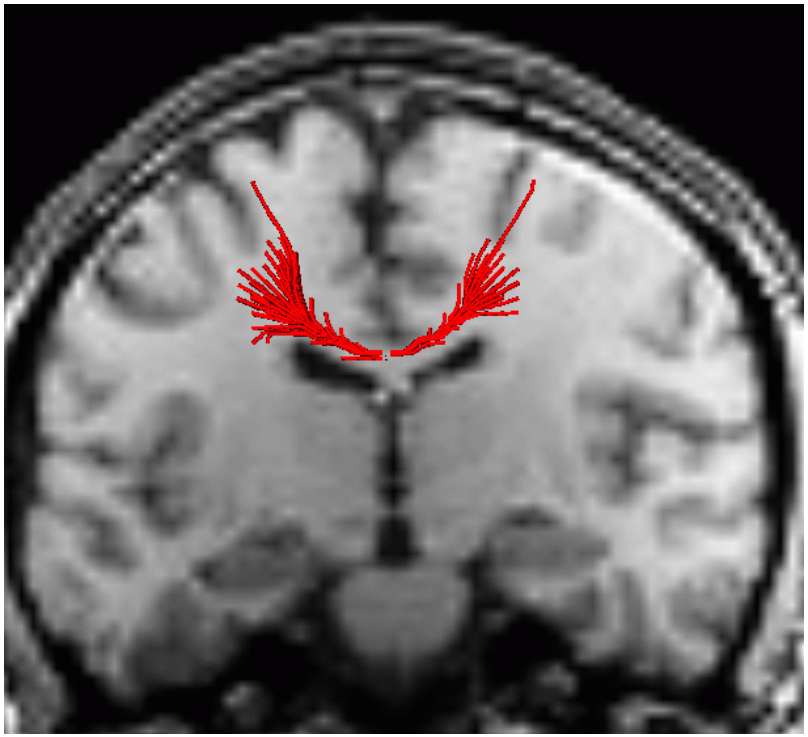
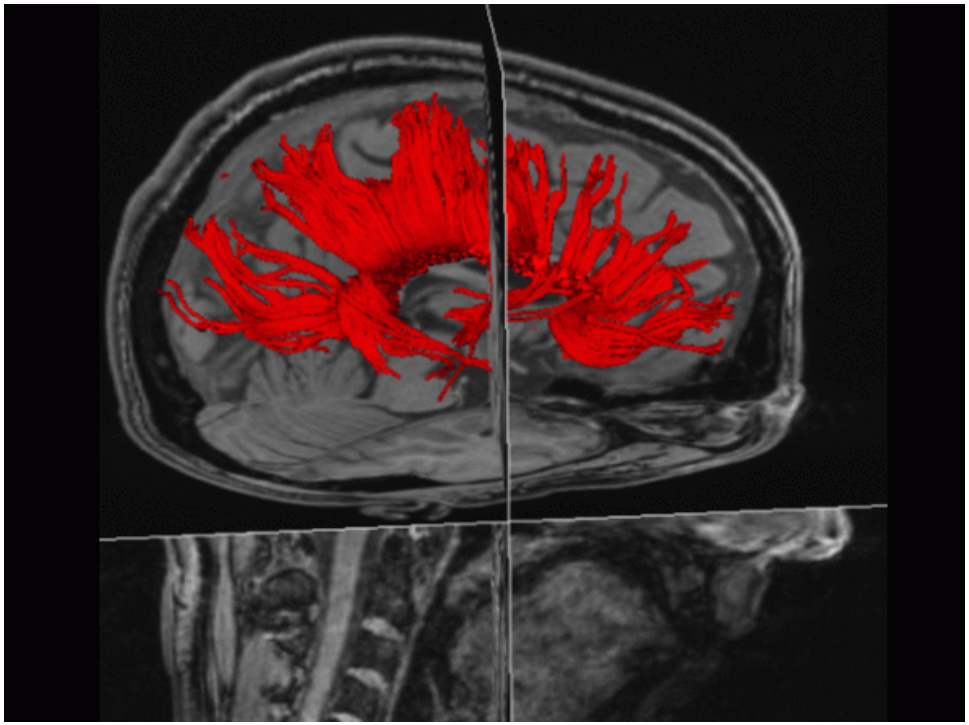
DTI Tract Tracing

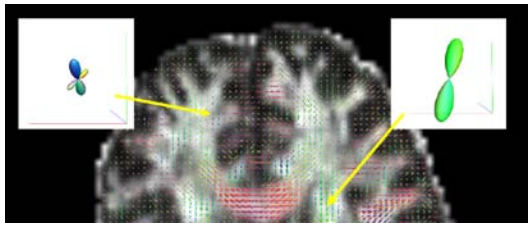




In vivo Connectivity-based Cortex Parcellation

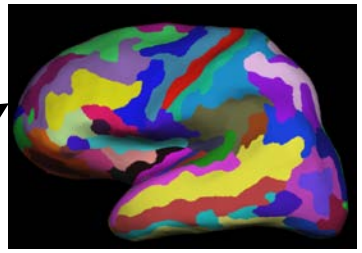
Preprocess DWI

Model Diffusivity

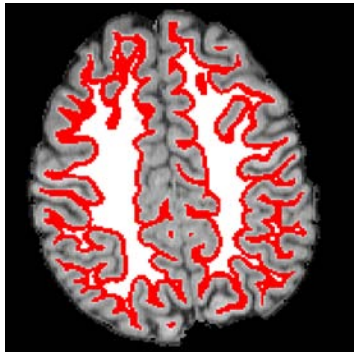


Segment T1

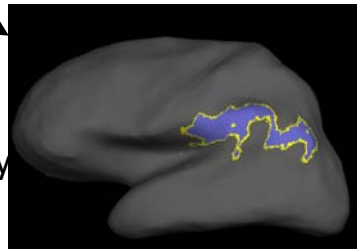
FS Destrieux Atlas



Targets: all ROIs

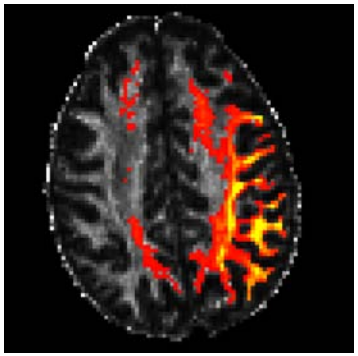


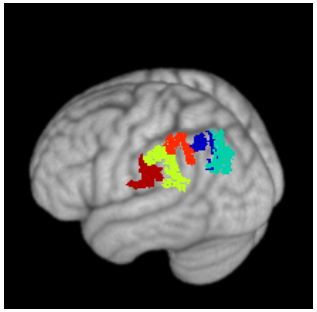
Cortico-subcortical boundary



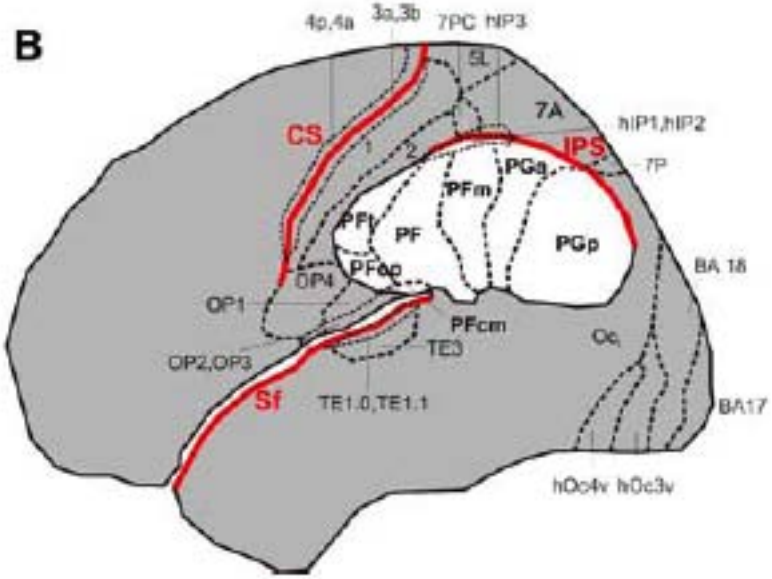
Seed:
lh-supramarginal + lh-angula

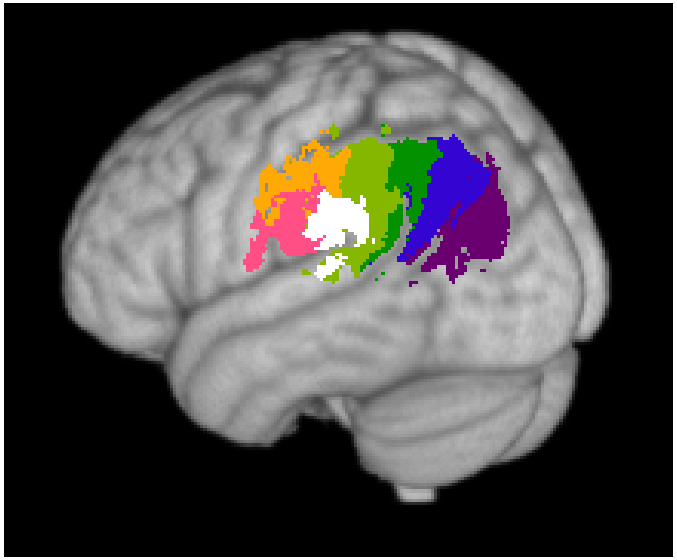
Compute and cluster tractograms



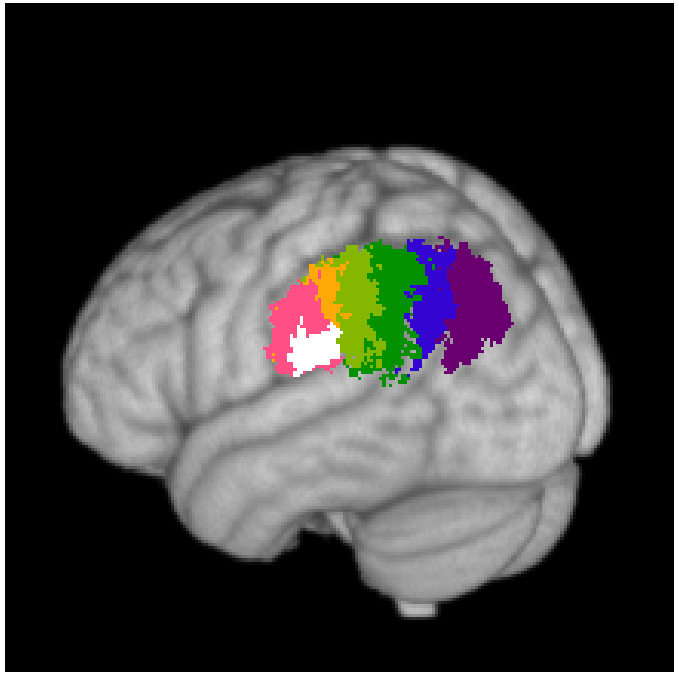


Rosalia Tungaraza





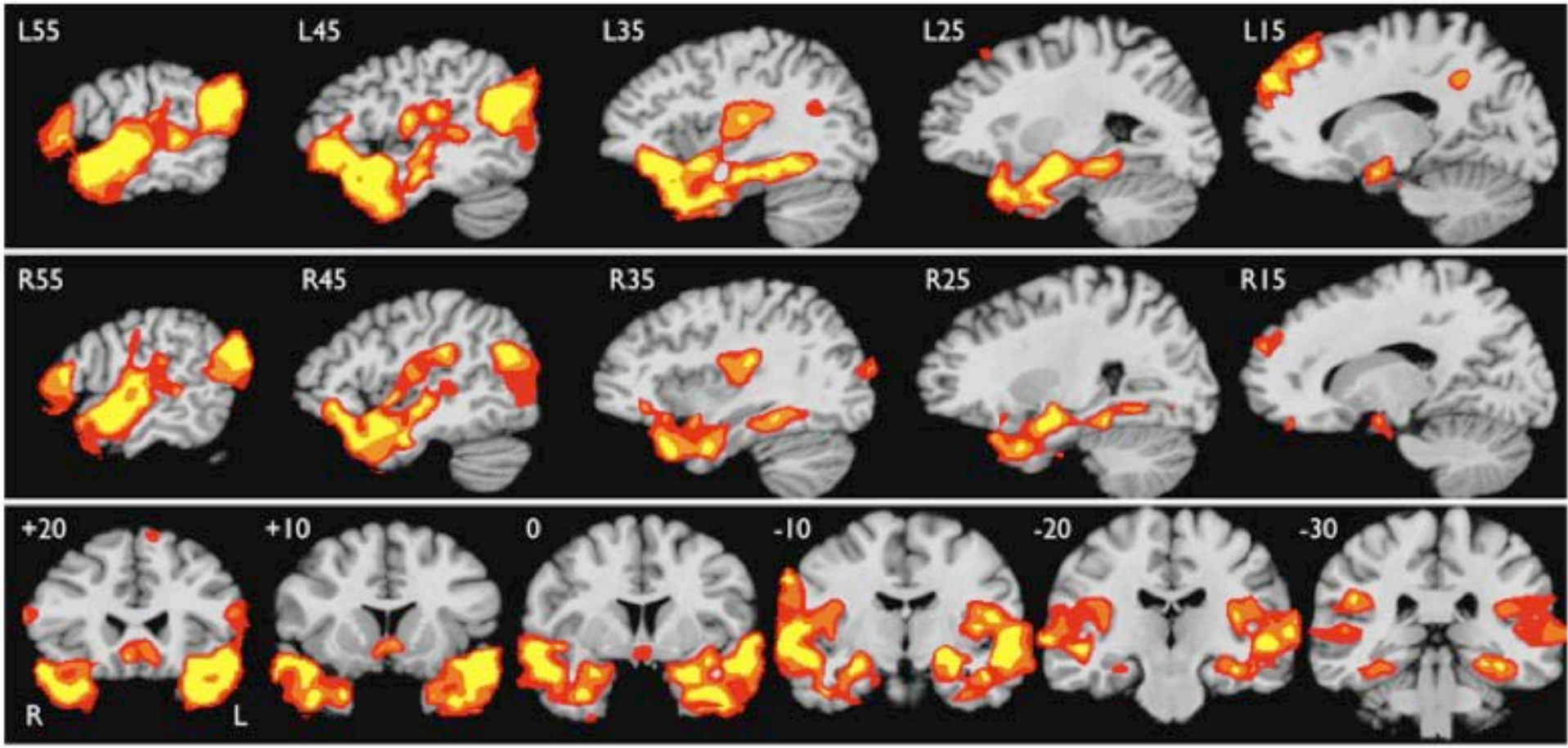
Caspers/Zilles parcellation IPL
Histology, N=10
MNI standard space



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 phopholipase A2
  - Diffusion of NO and PGE2 dilates surrounding arterioles

Basis of fMRI signal

Neural Activity

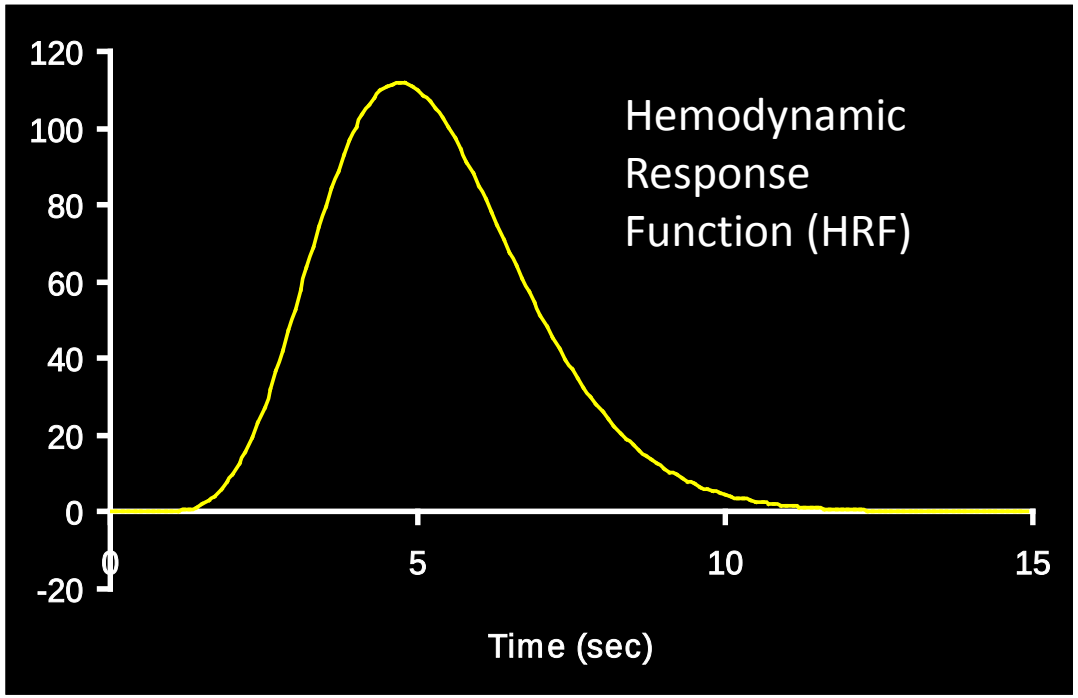
Metabolism

Blood Flow

dHb

T_2*

MR Signal



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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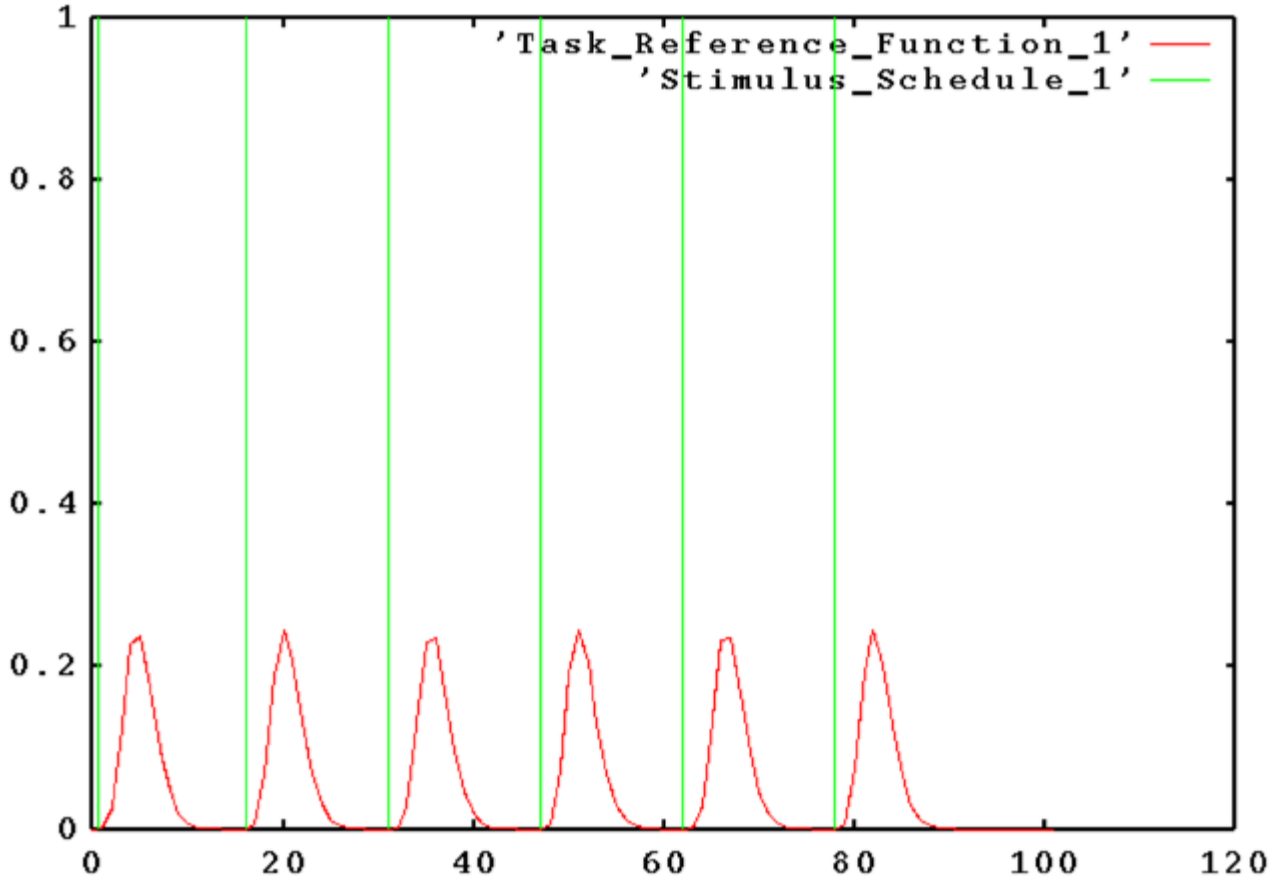
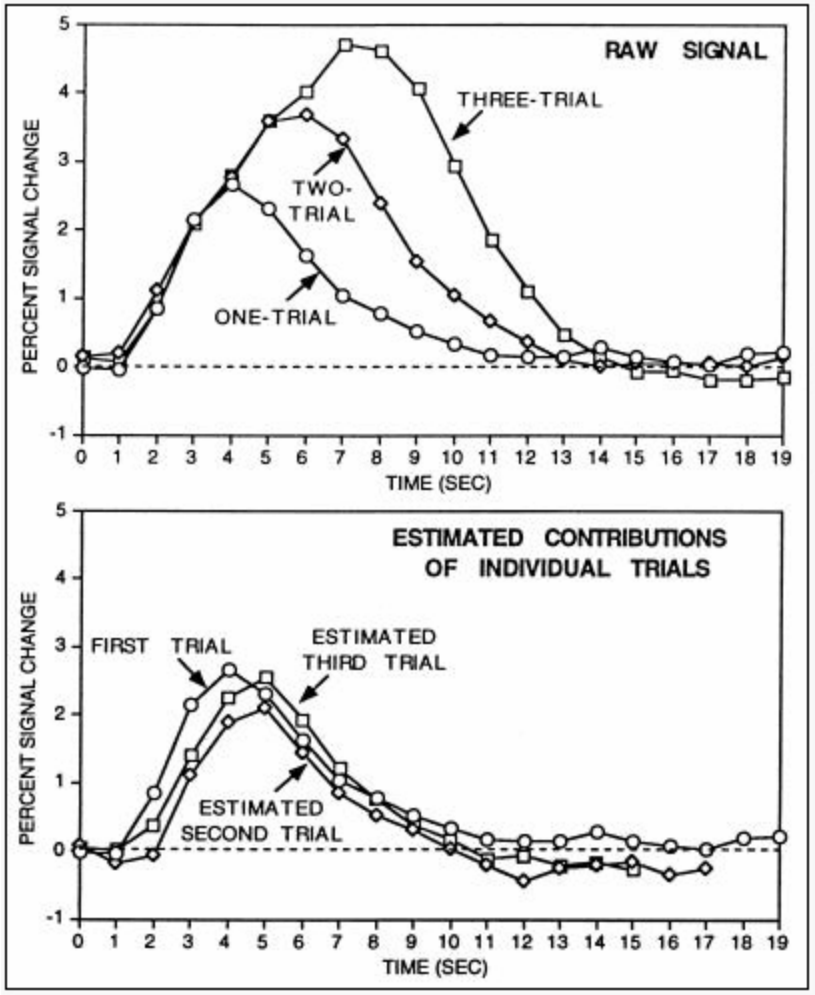
MRI signal



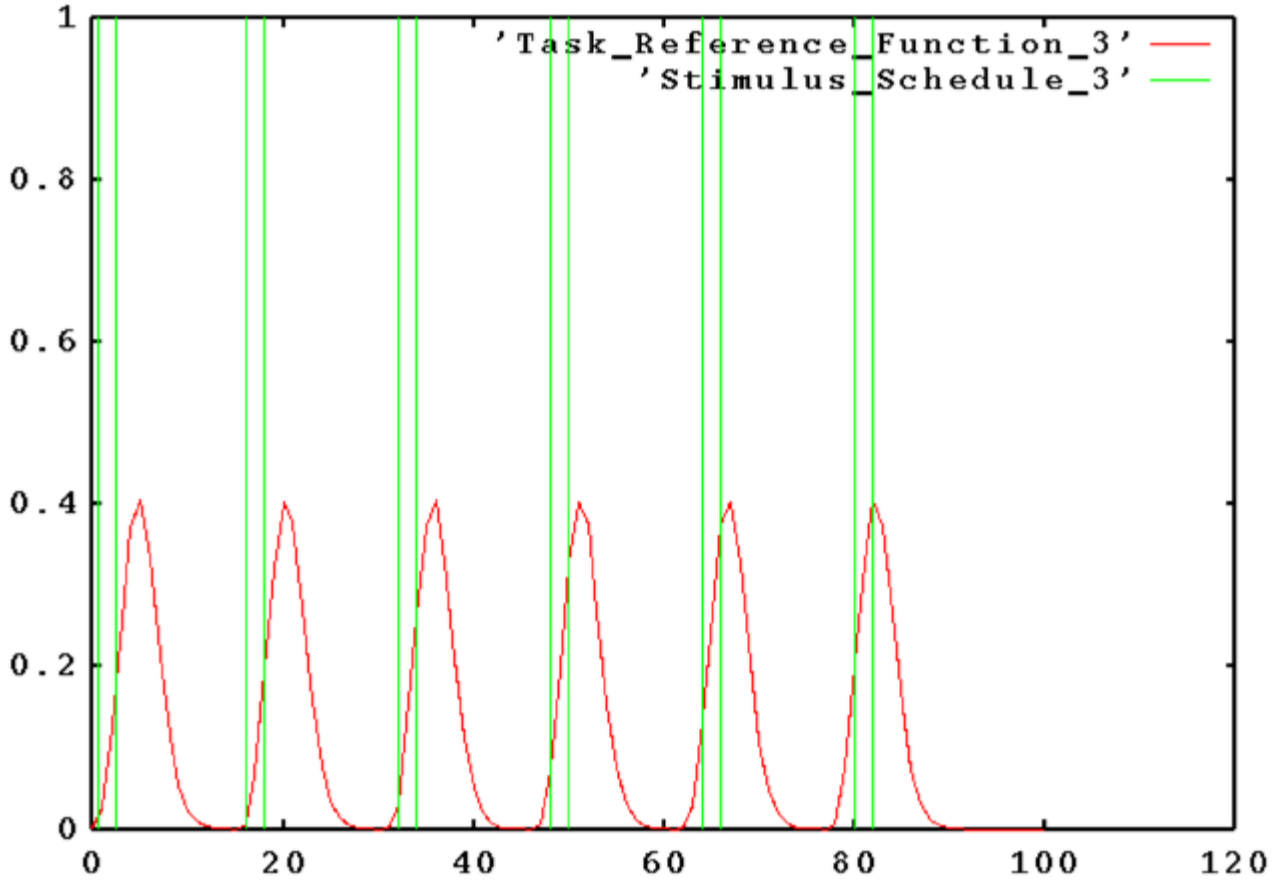
Time, seconds

HRF sums linearly over trials



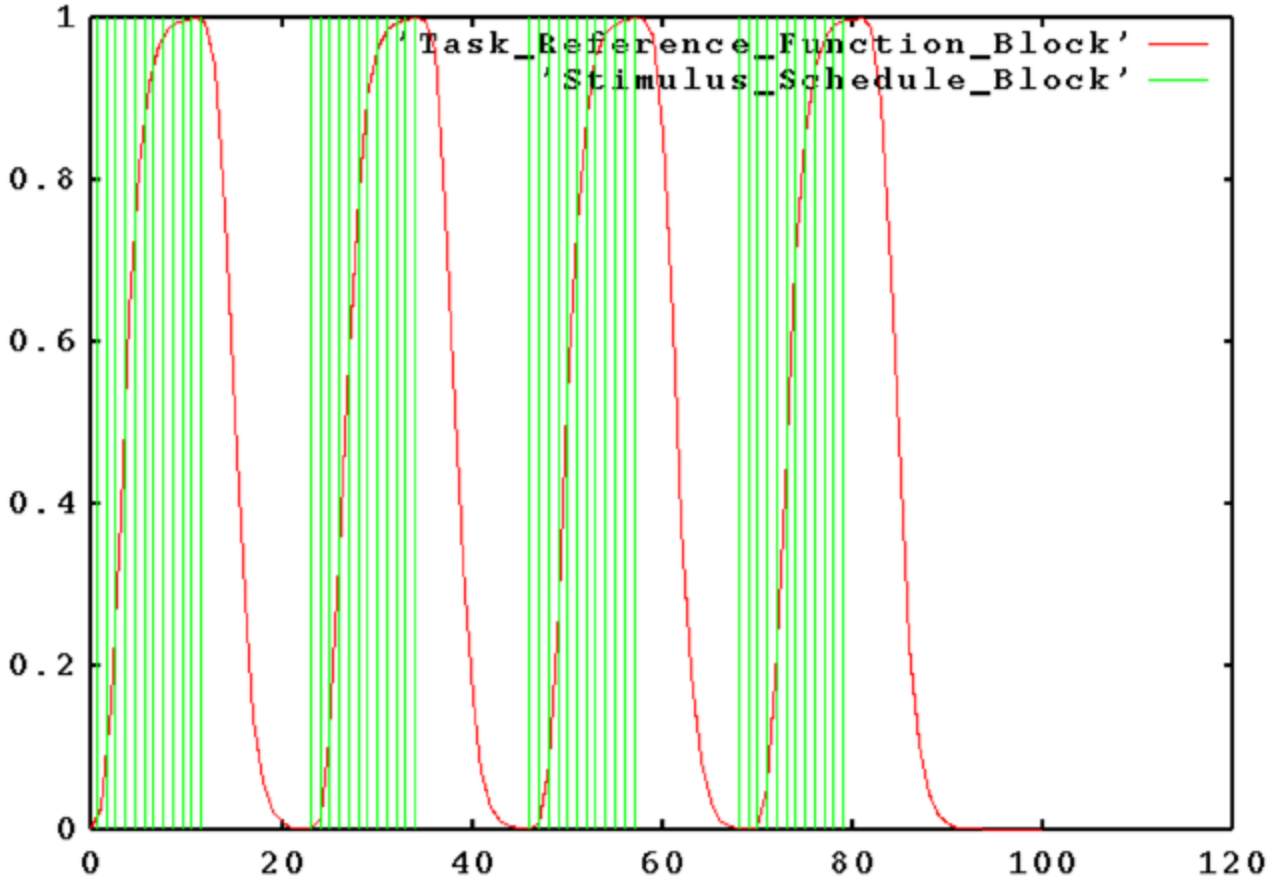
A. Dale and R. Buckner
Hum Brain Mapp 5:329
1997

MRI signal



Time, seconds

Block Design



Blocked Design (aka Block Design)

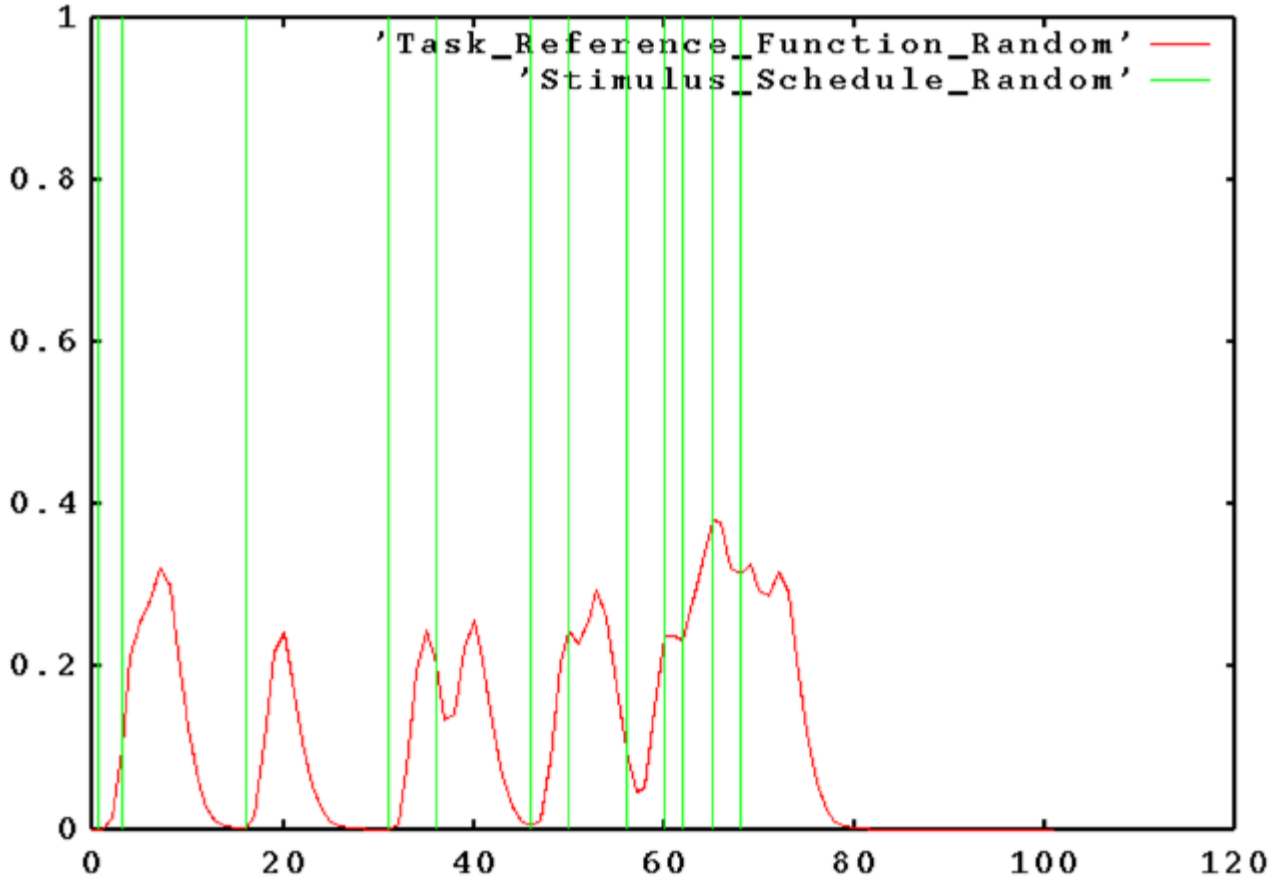
- Brain is placed in experimental and control states for discrete blocks of time
  - Typically 15-60 seconds
  - Usually operationalized as repeated performance
- Has historical roots in the design of [^{15}O]water PET activation experiments
- Remains widely used because of fundamental advantages of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

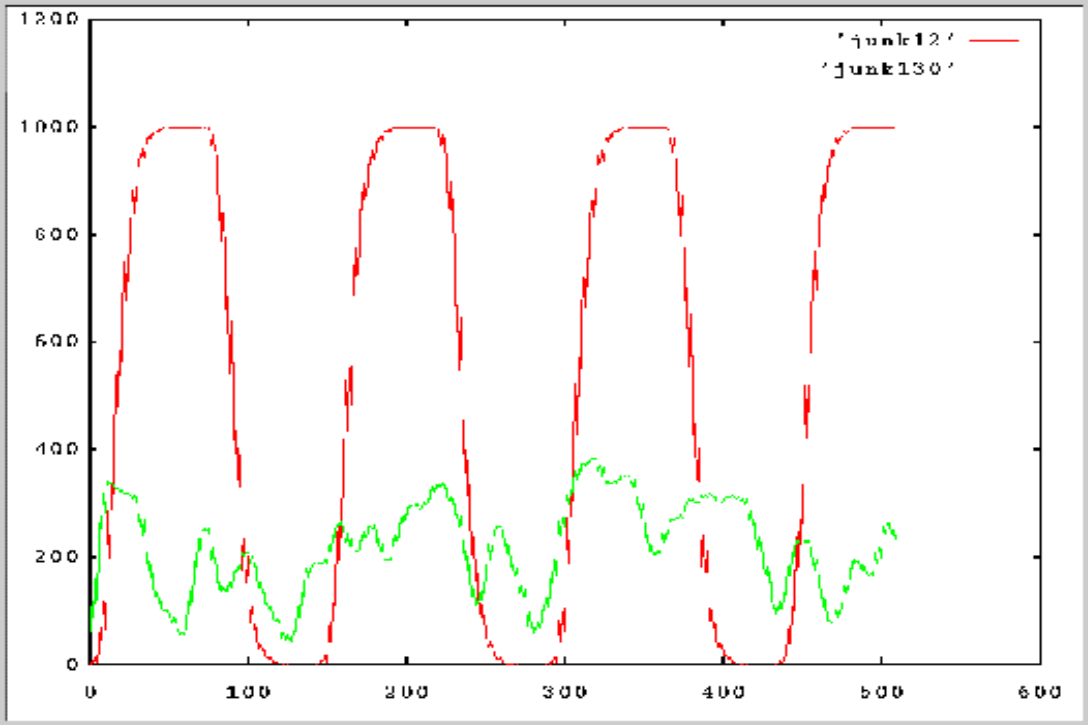
MRI signal

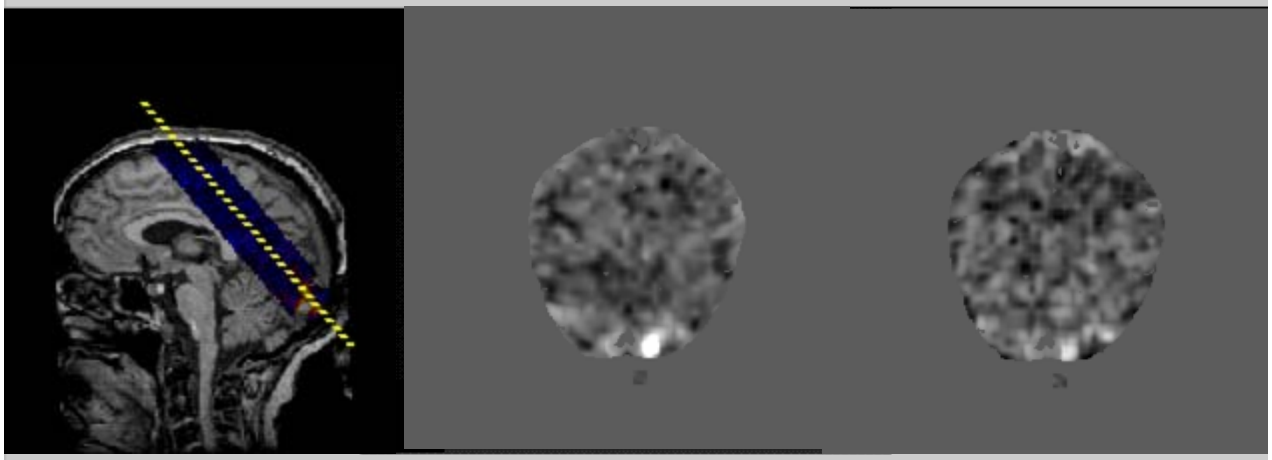


Time, seconds

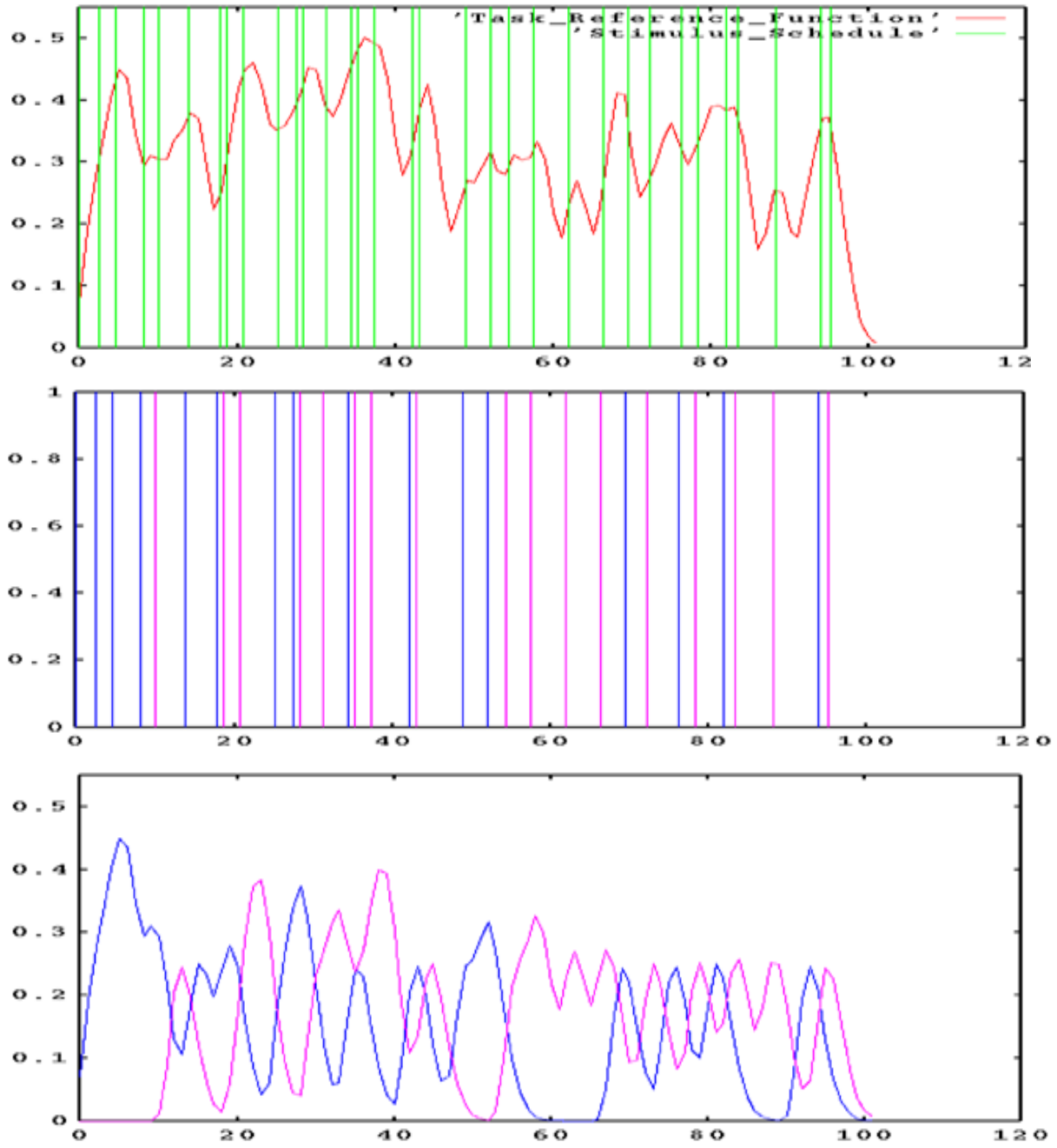
What is “Efficiency” ?

- 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.

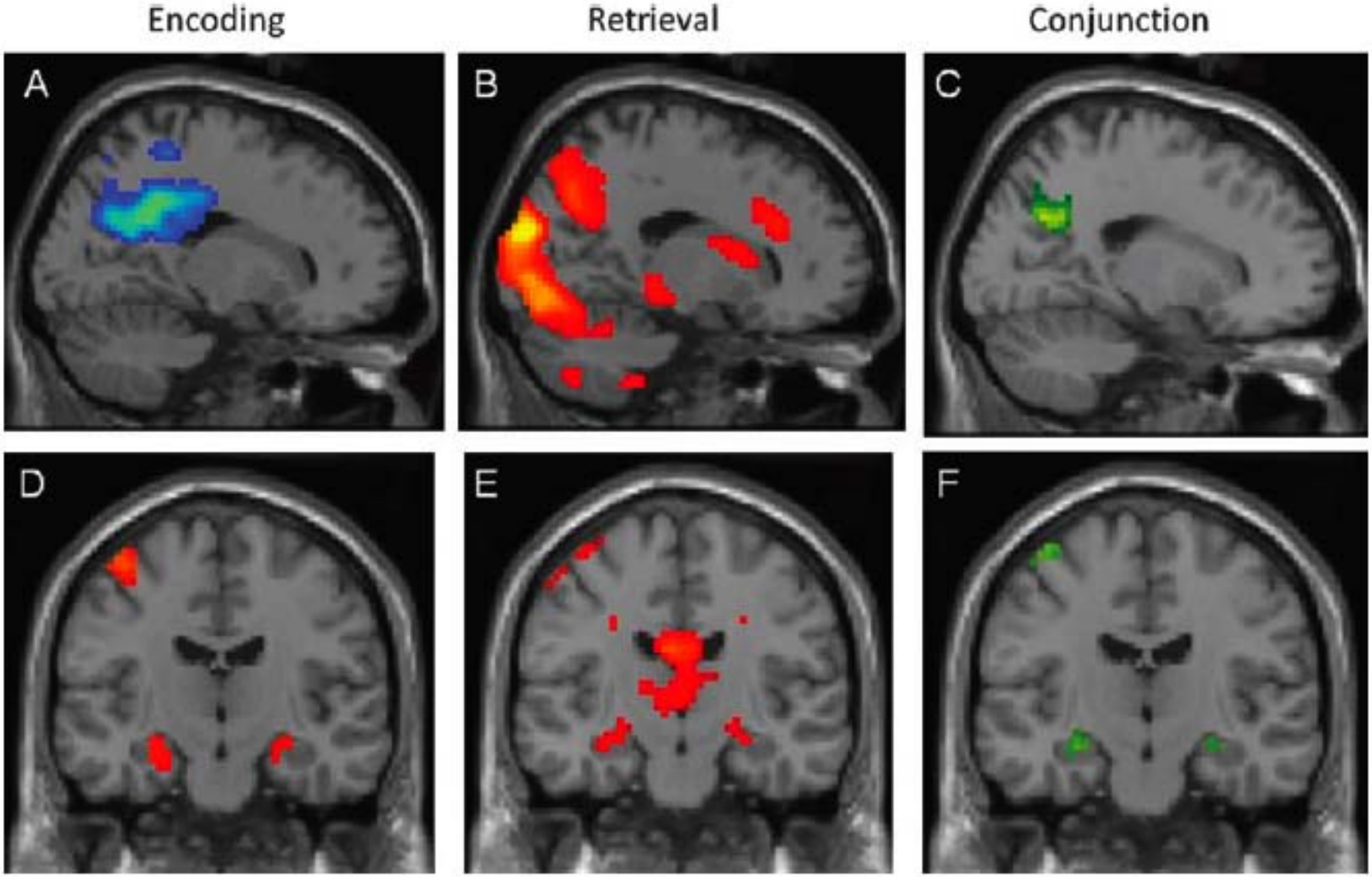

'junk12'
'junk130'
1200
1000
800
600
400
200
0
0
100
200
300
400
500
600



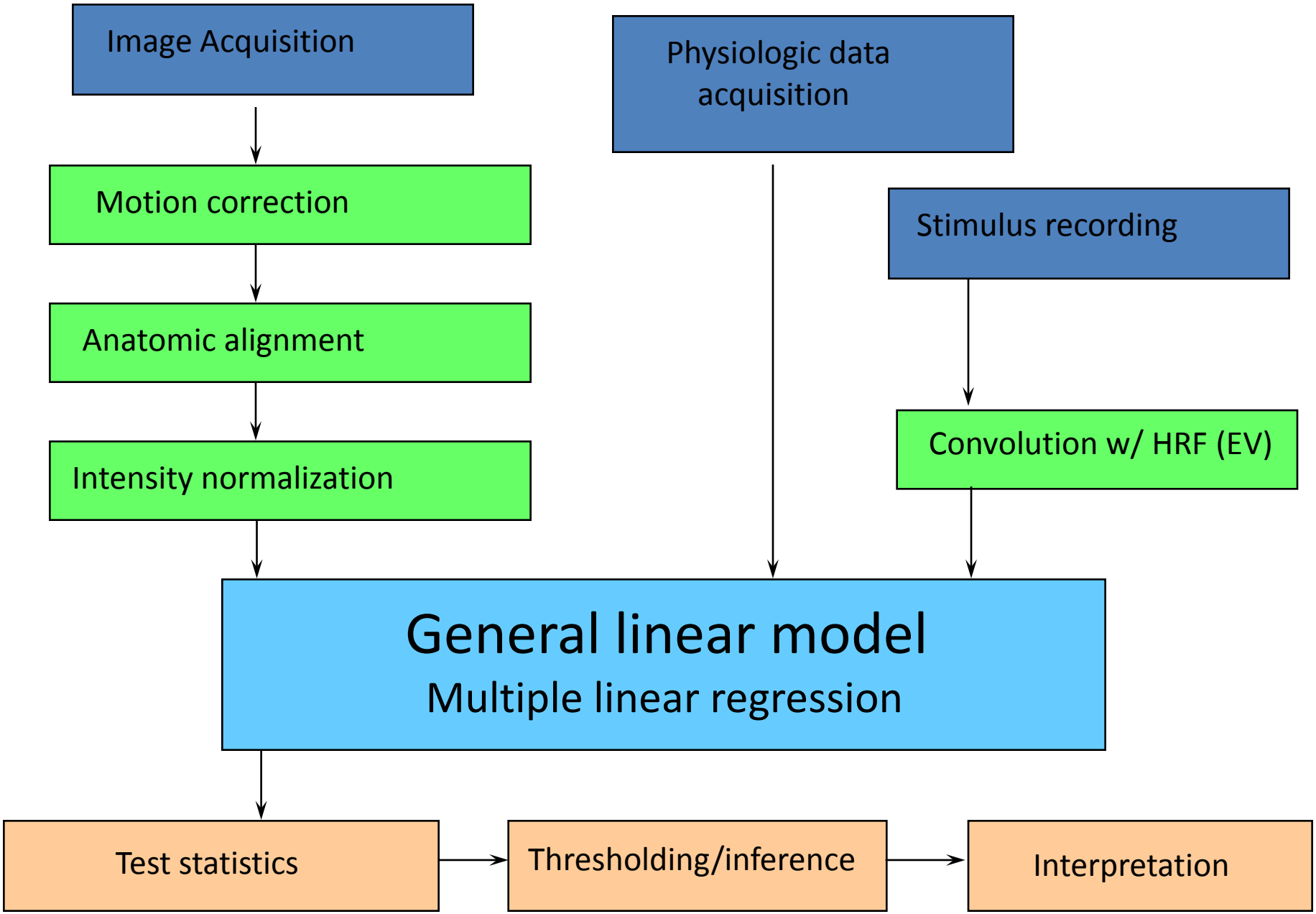
- The key advantage of er-fMRI is experimental flexibility.
- Event-related design allows the analysis to be sensitive to performance differences across trials.
- This advantage derives from
  - preserving correspondence of images to events
    AND
  - the independence of the effects evoked by each event.


'Task_Reference_Function'
'Stimulus_Schedule'
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
12
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
120
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120

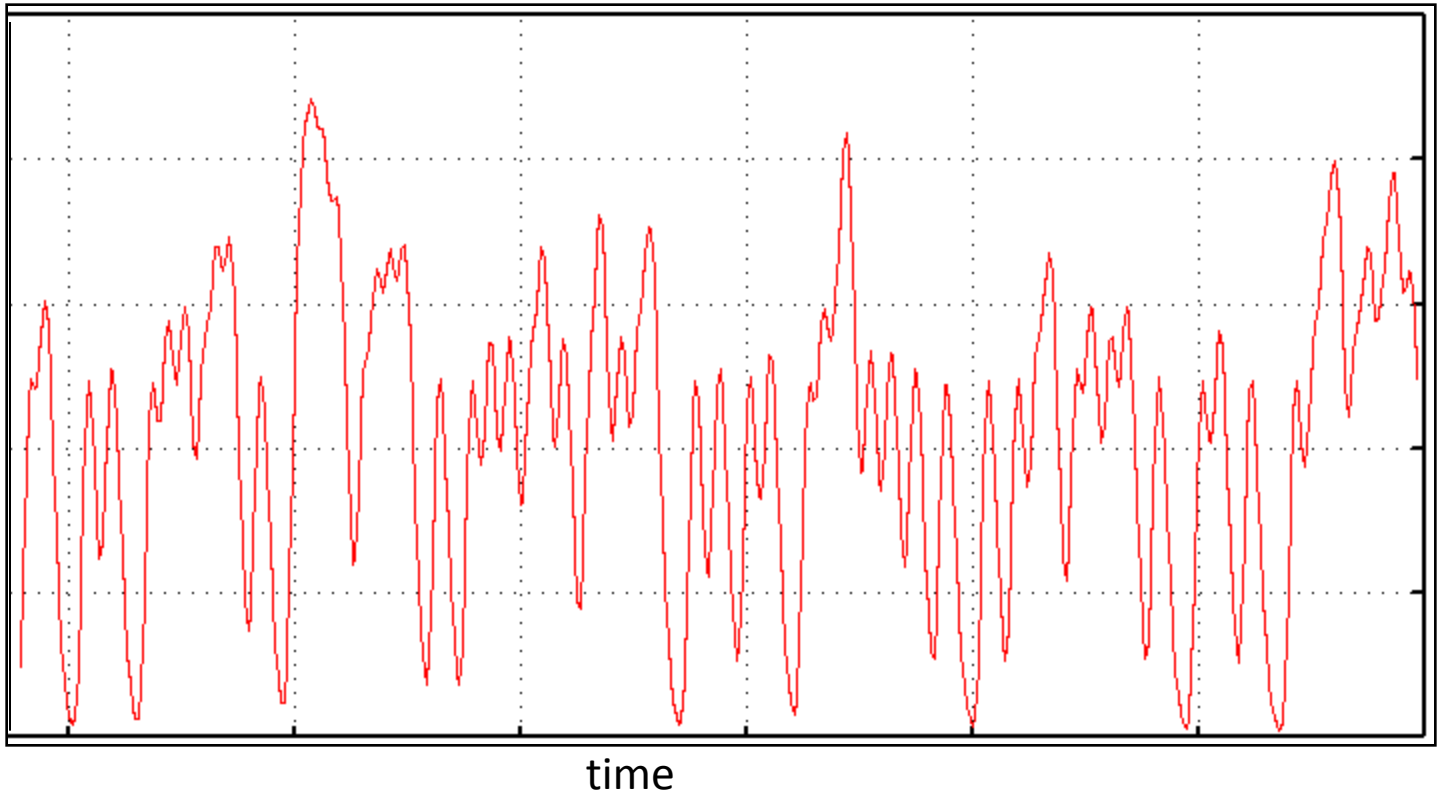
Activation of hippocampus during successful memory encoding and retrieval



fMRI Data Post-Processing



fMRI time series



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 (β) and tested with a *t* statistic

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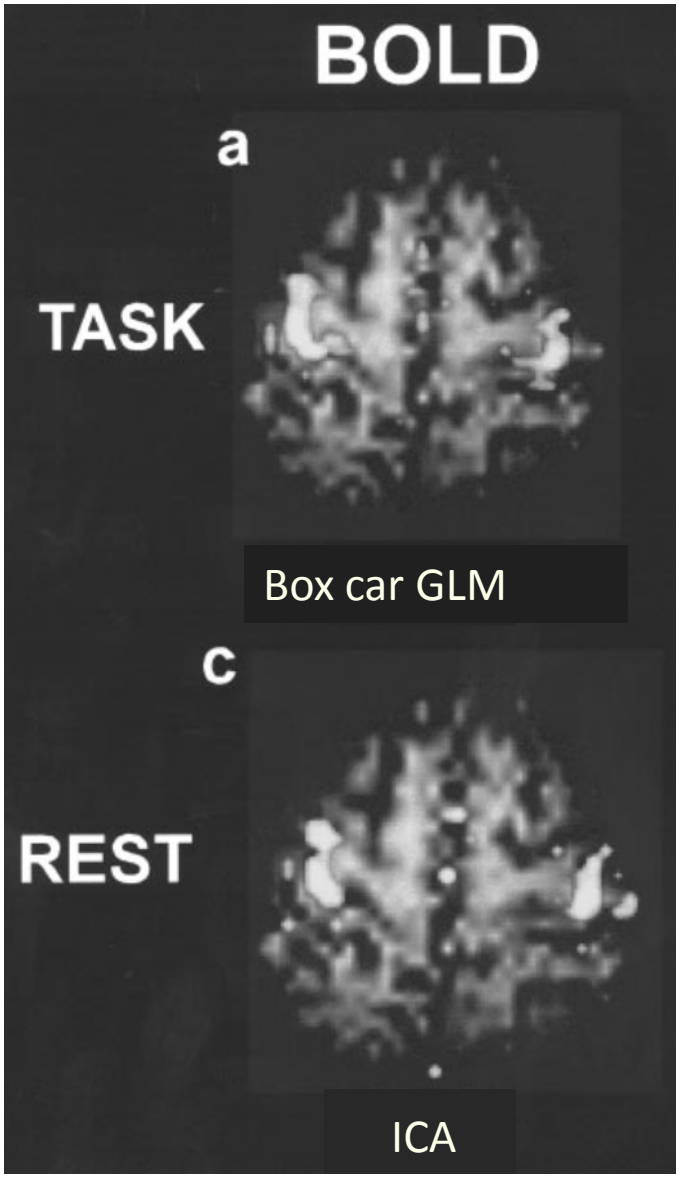
  - Signal model: correlated signal timecourses
- Information paradigm
  - Signal model: patterns of signal across voxels

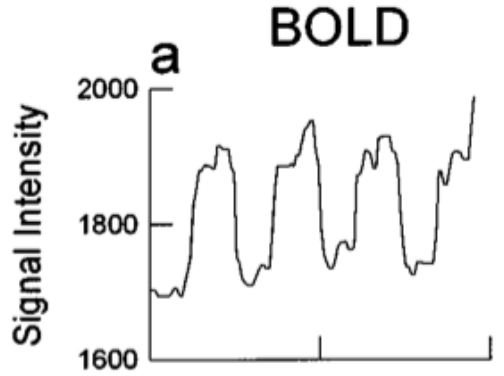


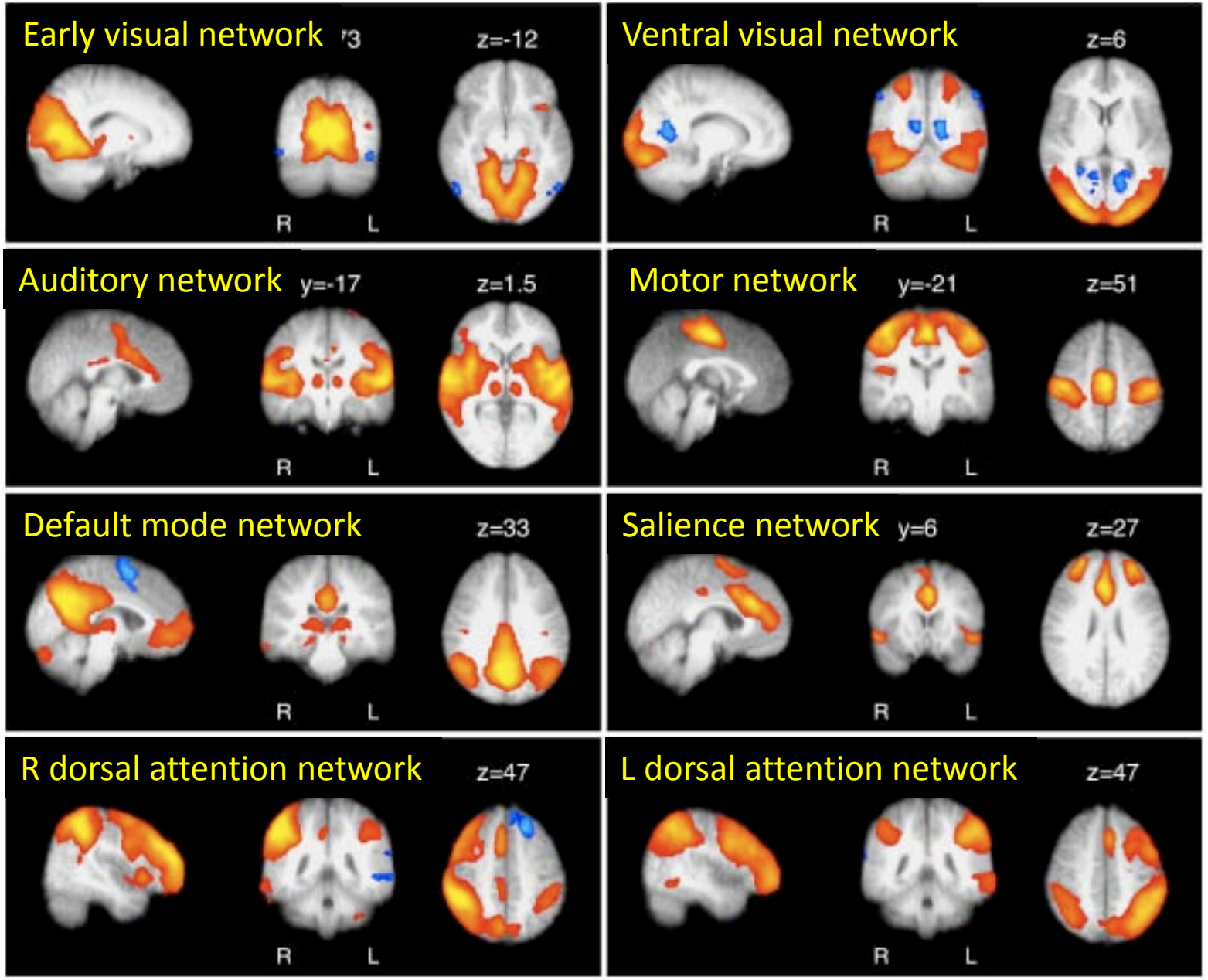
Biswal et al., 1997

Finger tapping

Resting

Fourier transform

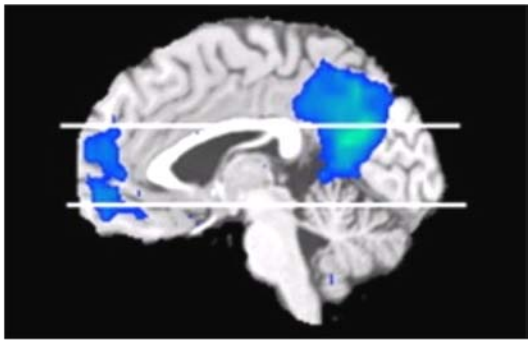




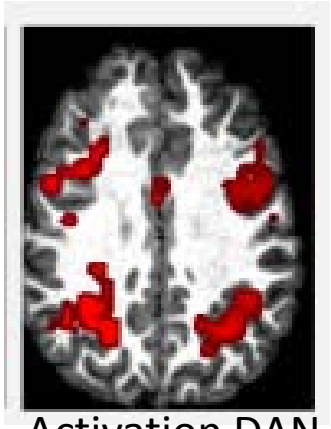
Damoiseaux et al 2006

Default Mode Network

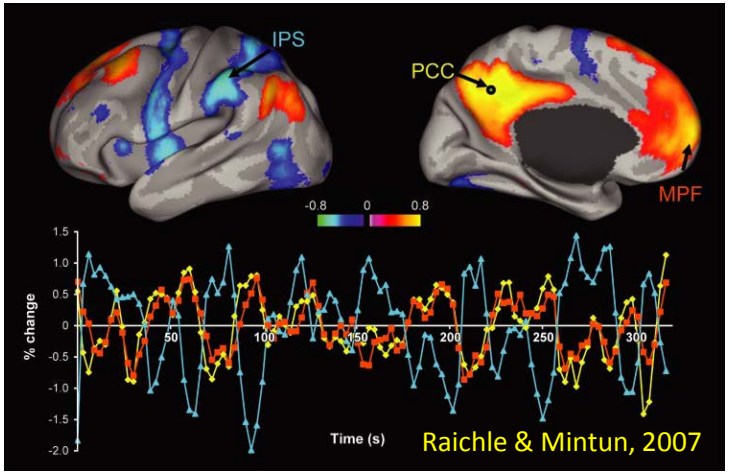
Relevance to adaptive behavior



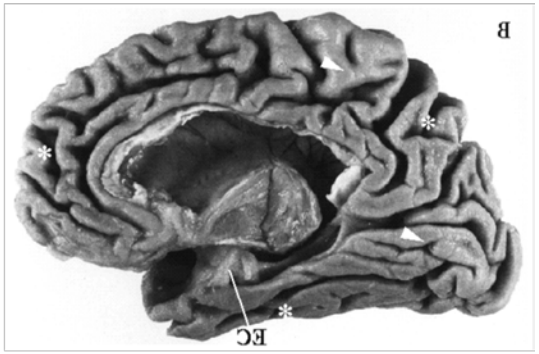
Deactivation DMN

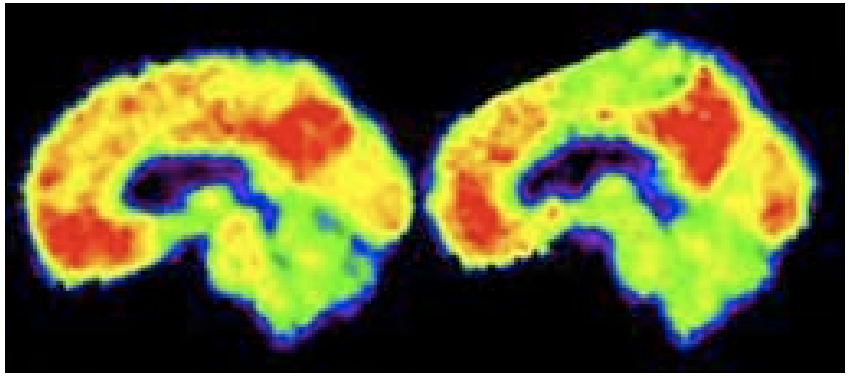


Activation DAN



Relevance to disease





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
  - Signal model: predicted BOLD timecourse
- Functional connectivity paradigm
  - Signal model: correlated signal timecourses
- Information paradigm
  - Signal model: patterns of signal across voxels

Multivoxel pattern analysis
Pattern recognition fMRI
Information-based fMRI
Machine learning

Univariate vs. Pattern Analysis

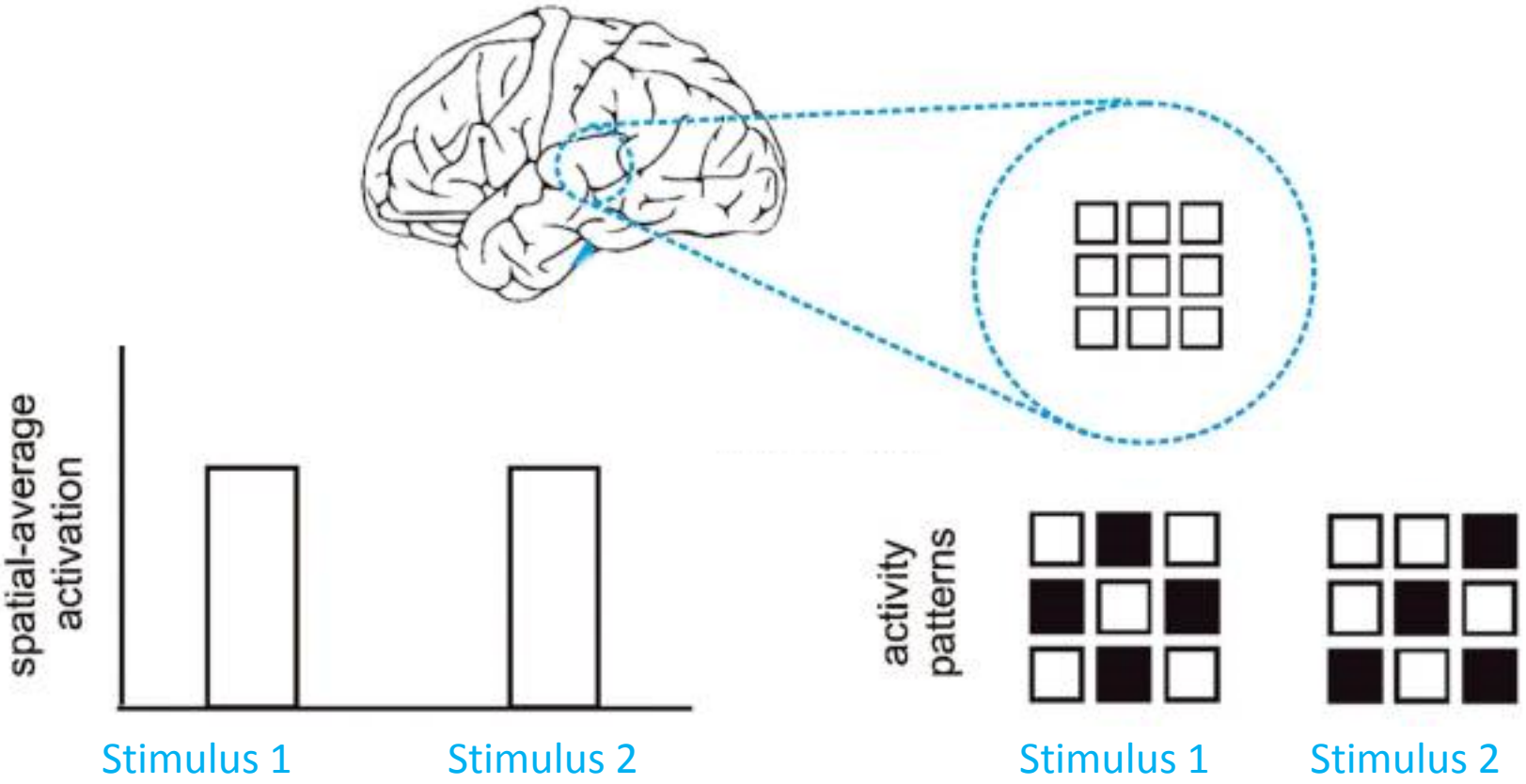
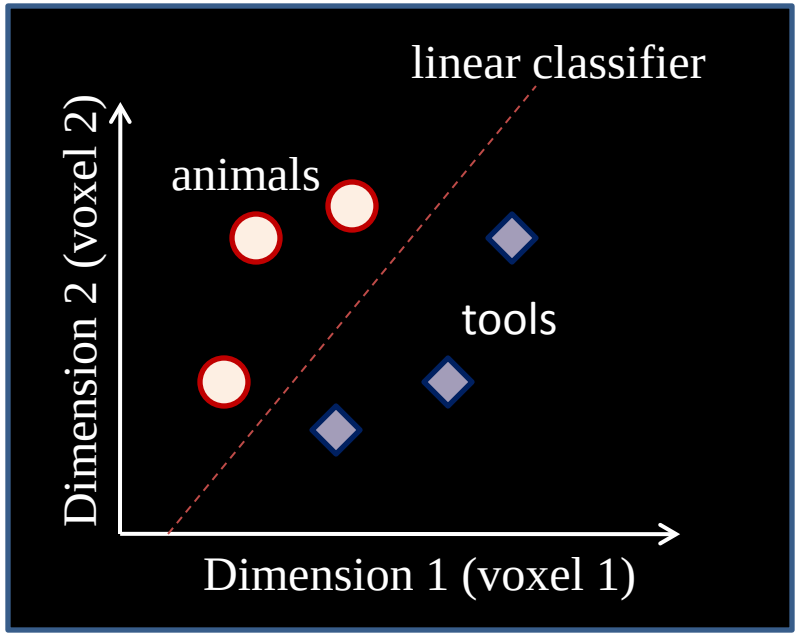
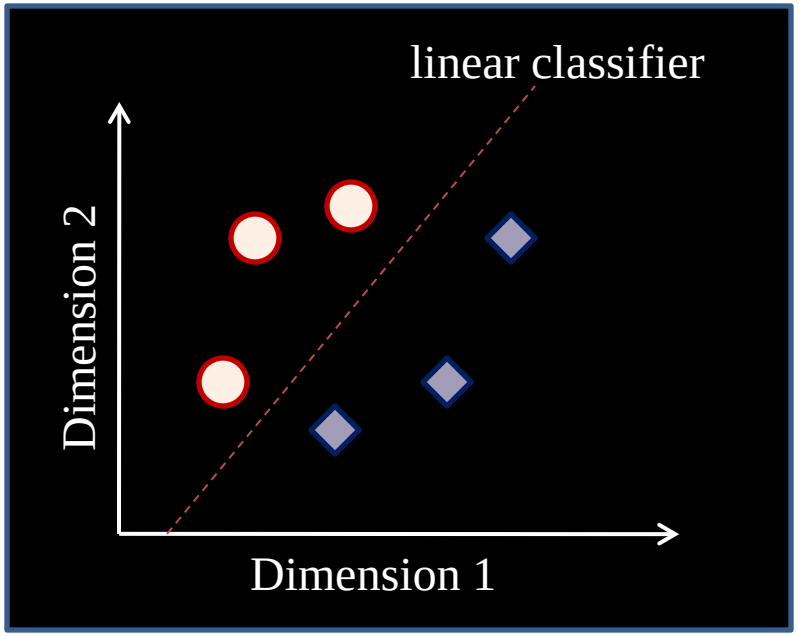


Figure adapted from Mur et al., 2009

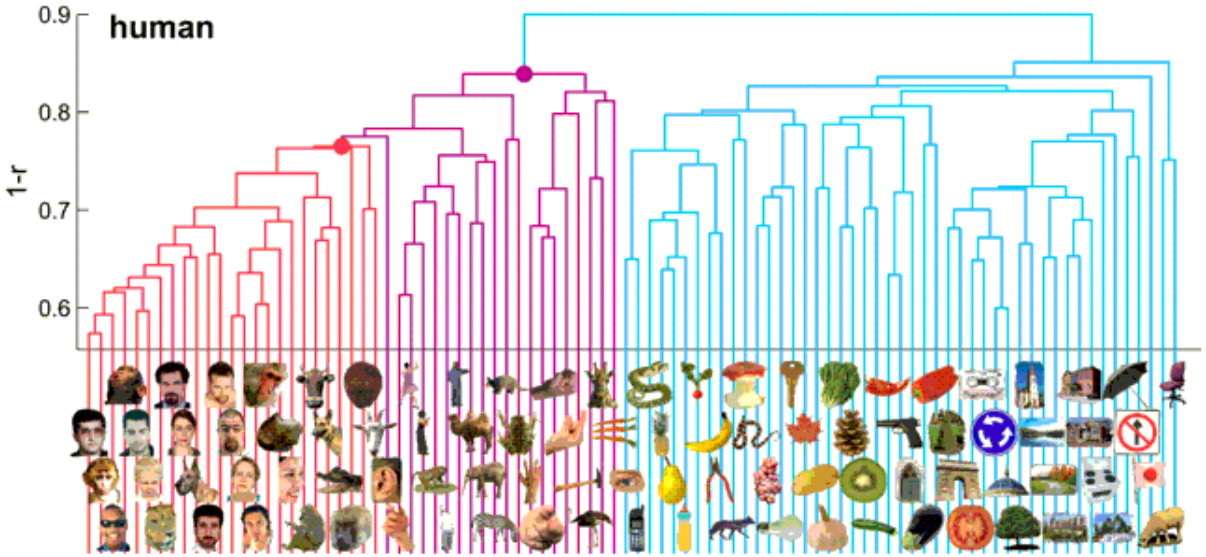
Pattern analysis: Multidimensional space

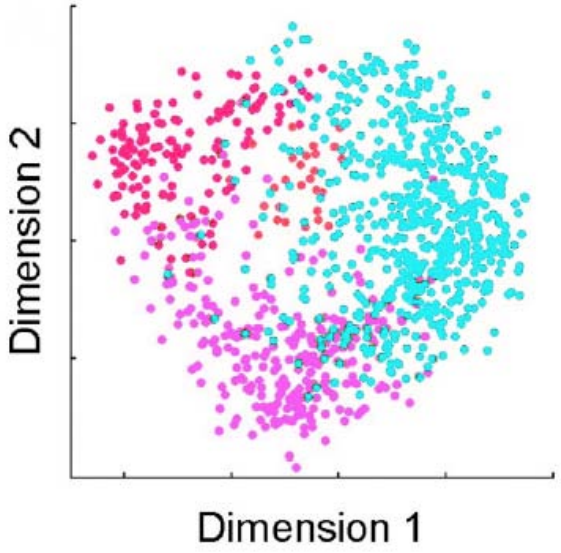


Pattern analysis: Multidimensional space

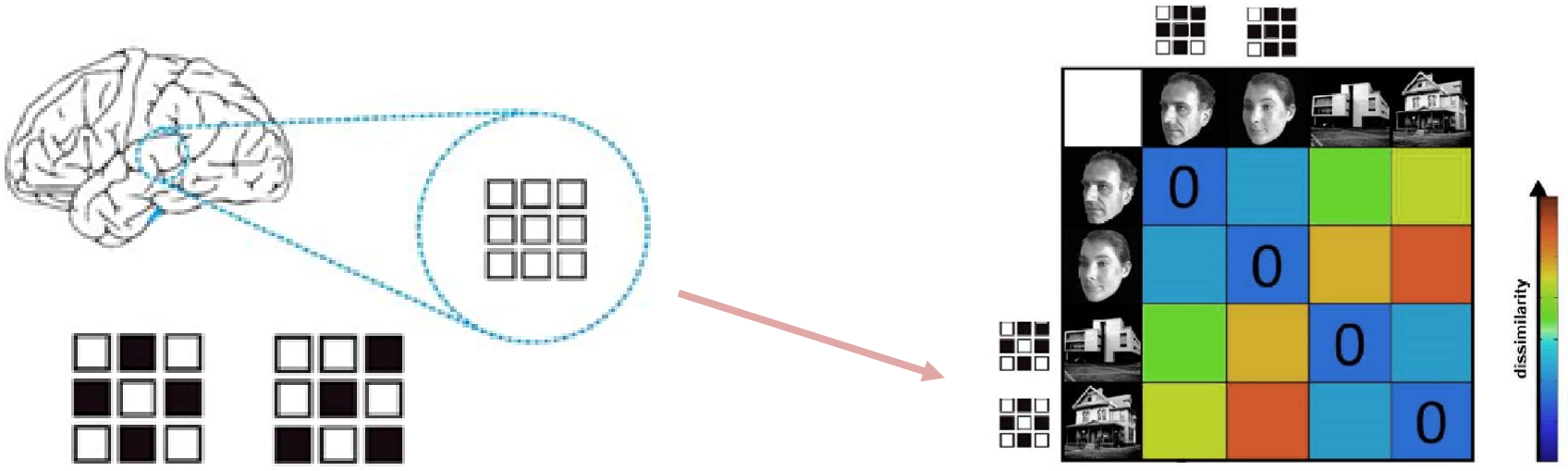


- fMRI response pattern to a stimulus corresponds to a location in a multidimensional activation space
- Classifiers are trained to discriminate between response patterns to different stimulus categories, and tested on independent data





Representational similarity/dis-similarity –



Kriegeskorte 2009

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

- 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 similiarity**

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