Imaging Brain Structure and Function

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CSE/EE 577
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Why image the brain?

- What's wrong? (Medical diagnosis)
- How does it work? (Neuroscience)
- To aid intervention (Medical treatment, Engineering)

Why is the brain hard to image?

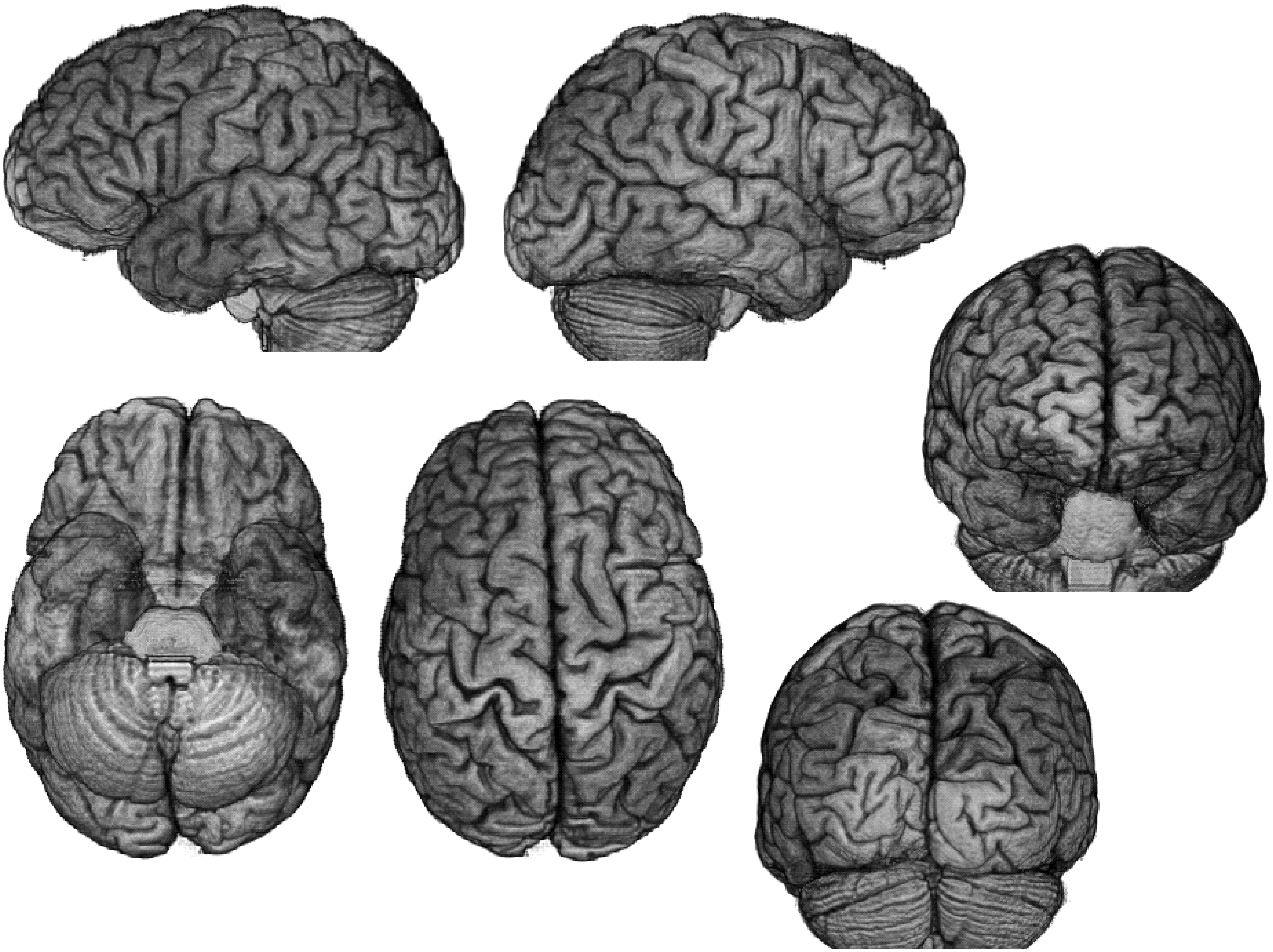
- Different soft tissues (gray matter, white matter) give low contrast to xrays
- Cerebral anatomy is 3D complex and variable
- Much of the organization of the brain is still poorly understood.
- Neurophysiological processes must be imaged indirectly through their coupled vascular and metabolic effects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

Digital image paradigm: “image” as an abstract concept

- Images are matrices of values of a physical or physiological parameter, extended over an anatomic space.
- The parameter is not derived “directly” from hardware sensors, but by post-acquisition computation.
- Digital "images” are often an element in further workflow.

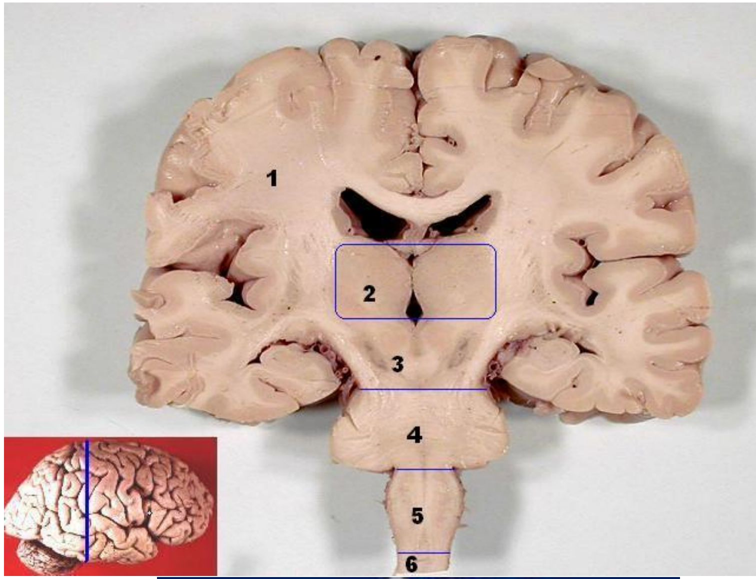
Outline

- The brain
- Brain imaging modalities
- Standard anatomical space
- Image processing



The brain is an *organ*

Blood, blood vessels, connective tissue (meninges), etc.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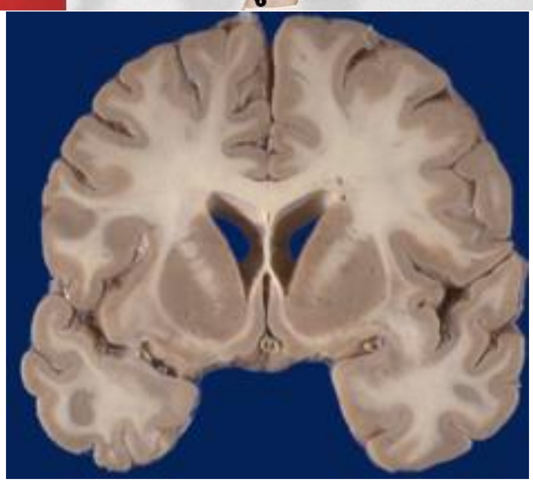
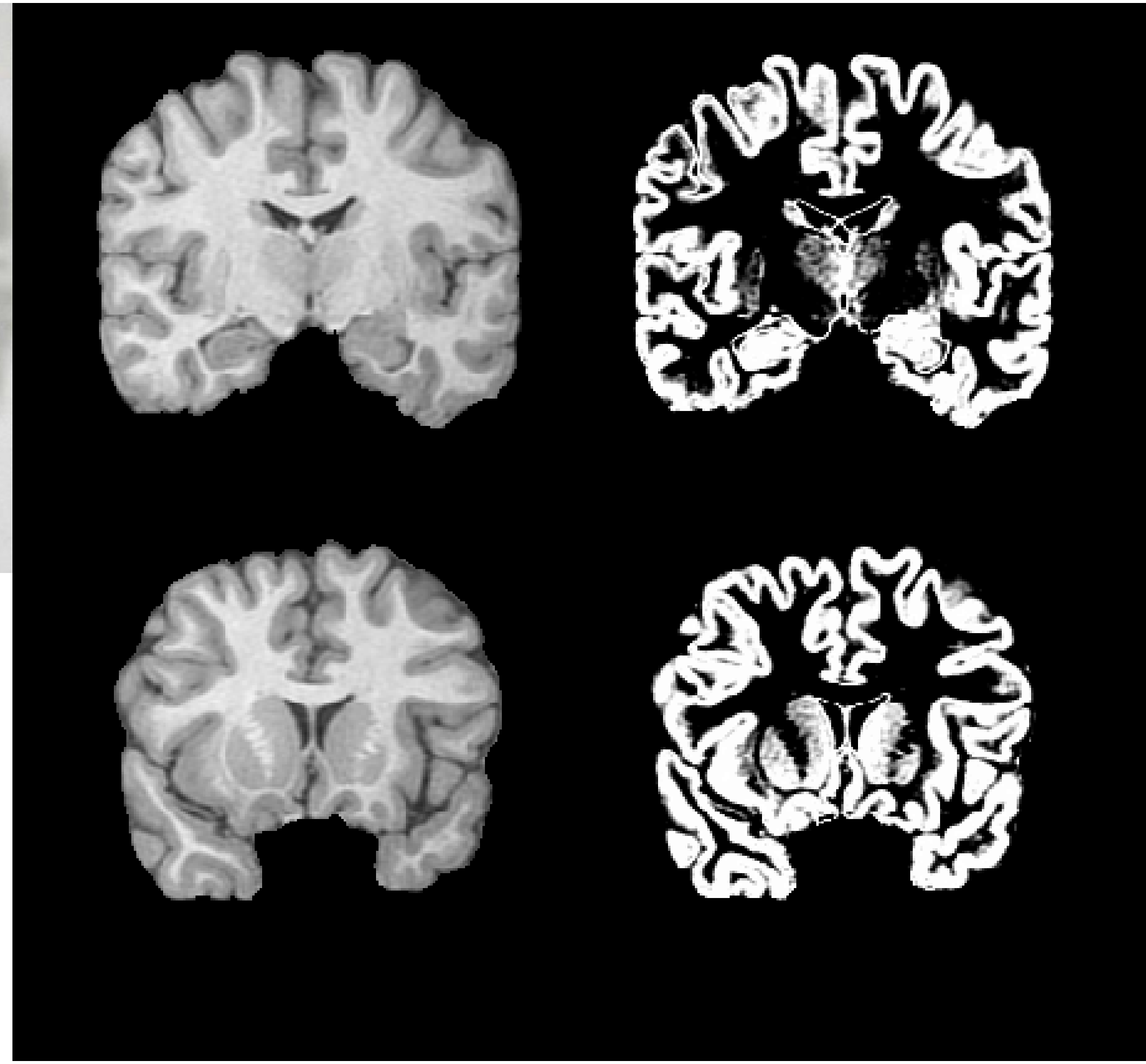
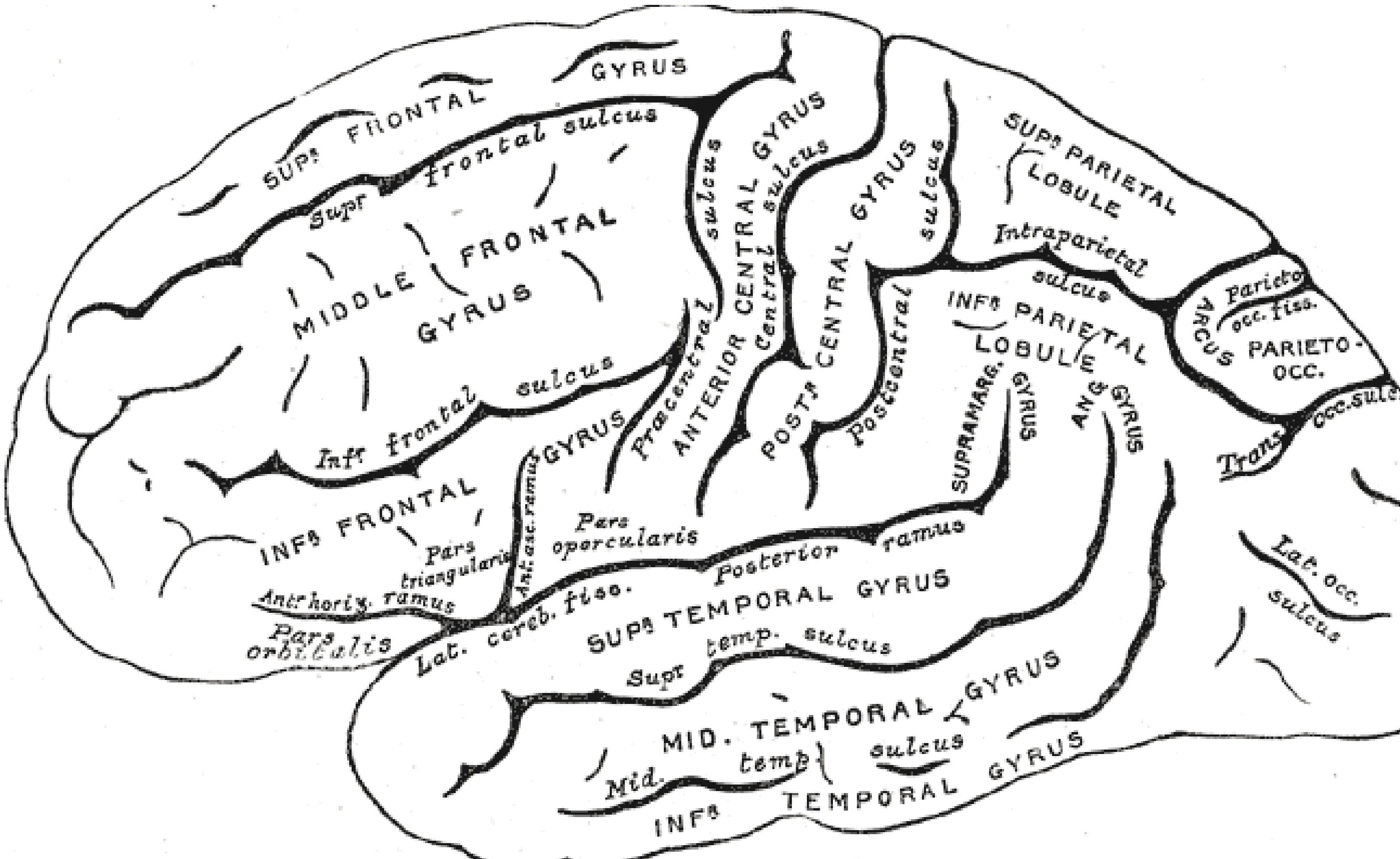
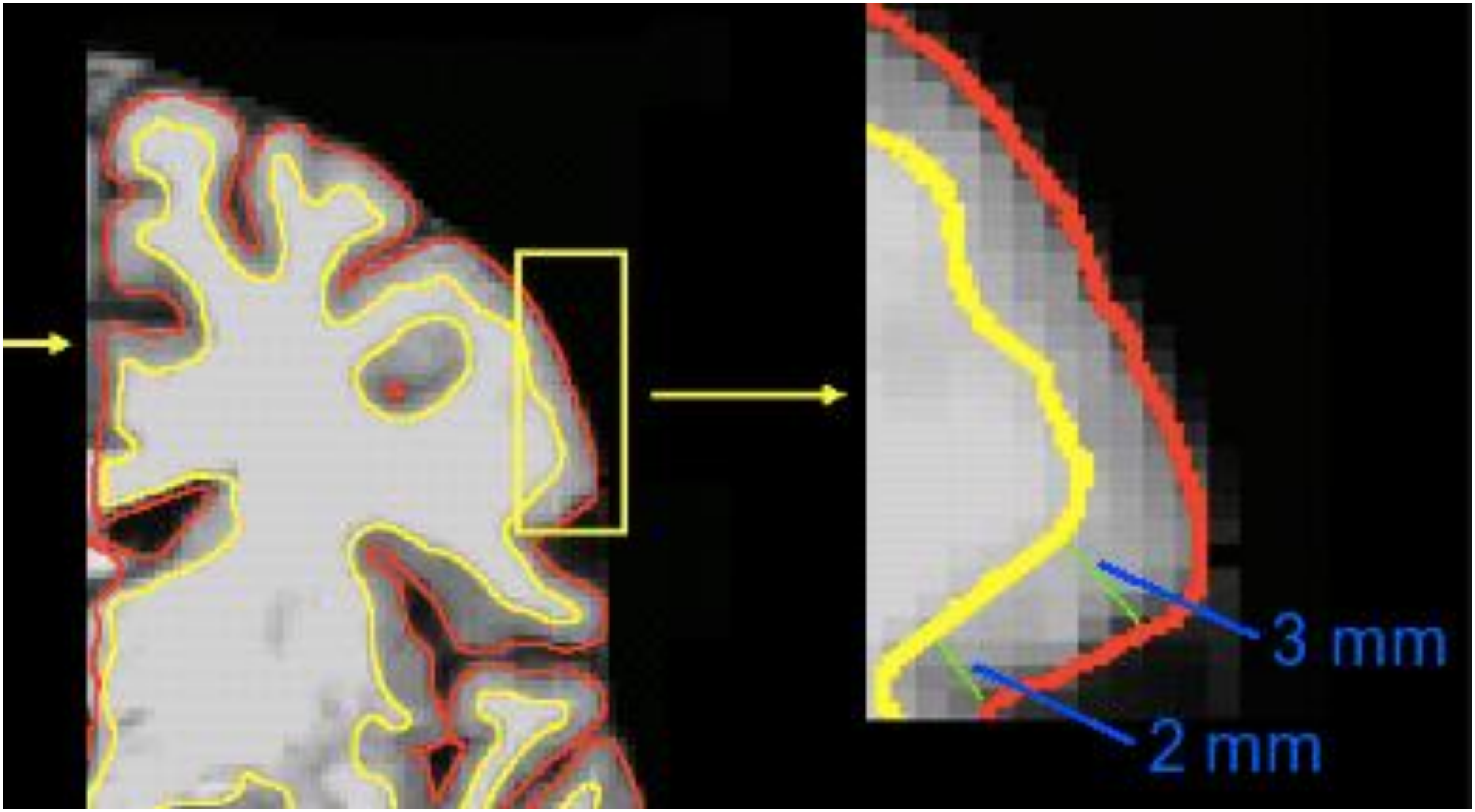




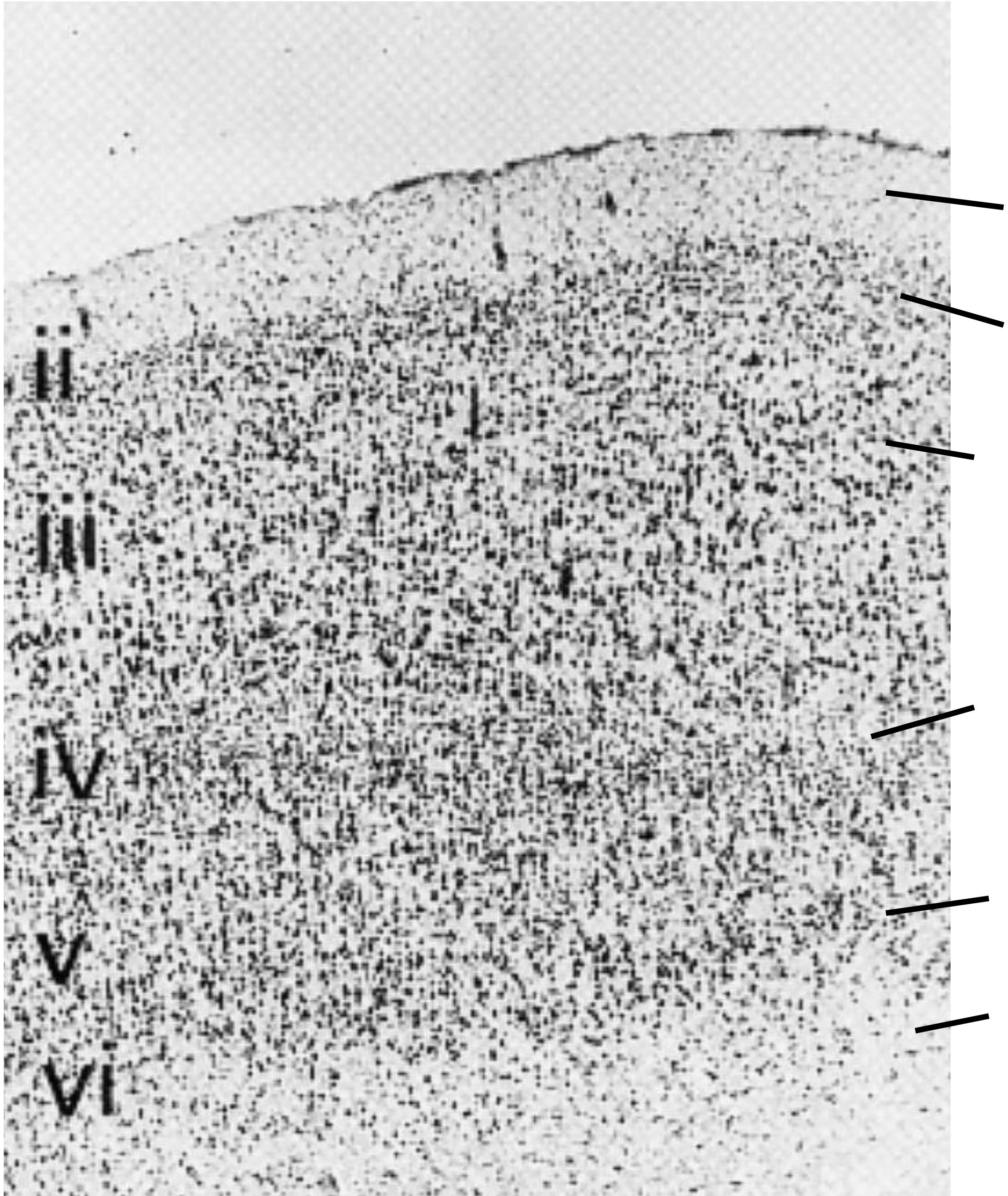
Sulci and Gyri of the Cerebral Cortex



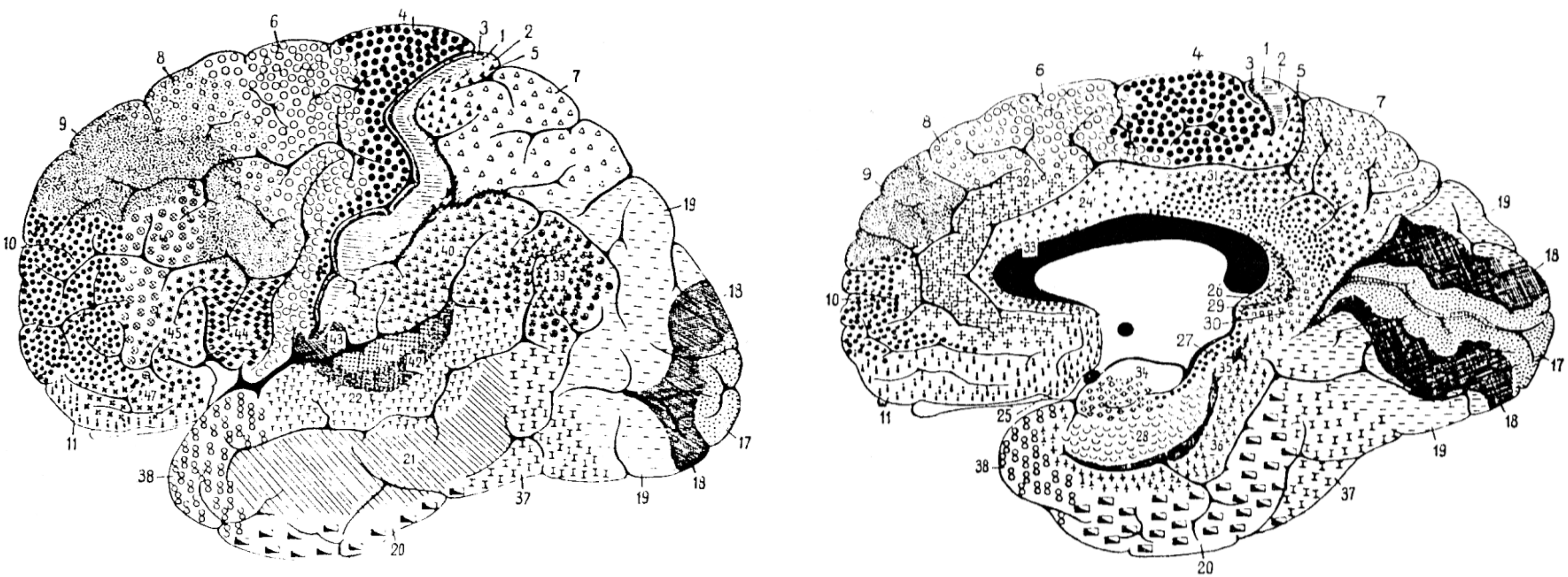
Gray matter, white matter

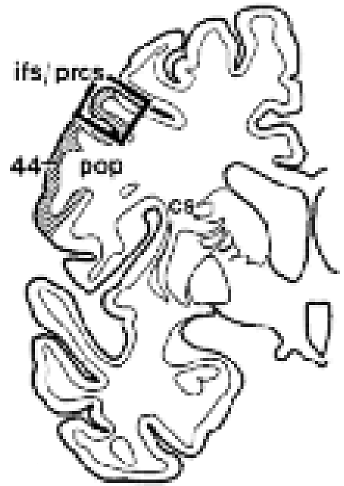


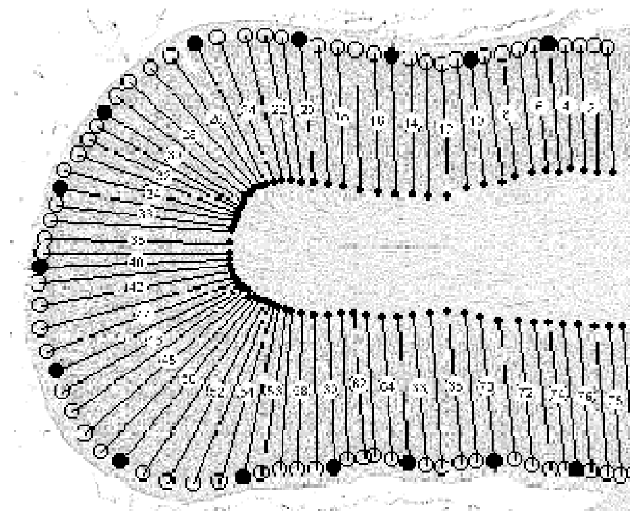
Cerebral cortex

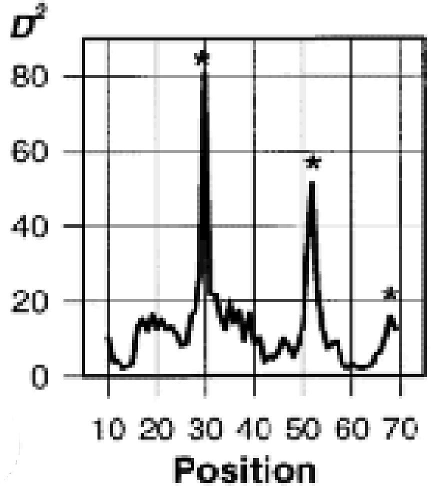

ii
iii
iv
v
vi
I Molecular layer
II External granular layer
III External pyramidal layer
IV Internal granular
V Internal pyramidal
VI Multiform layer

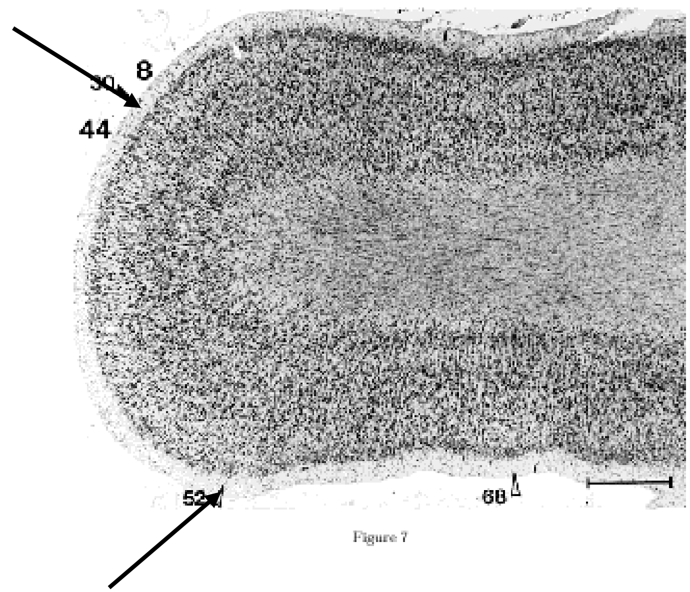
Brodmann's cytoarchitectonic map (1909)





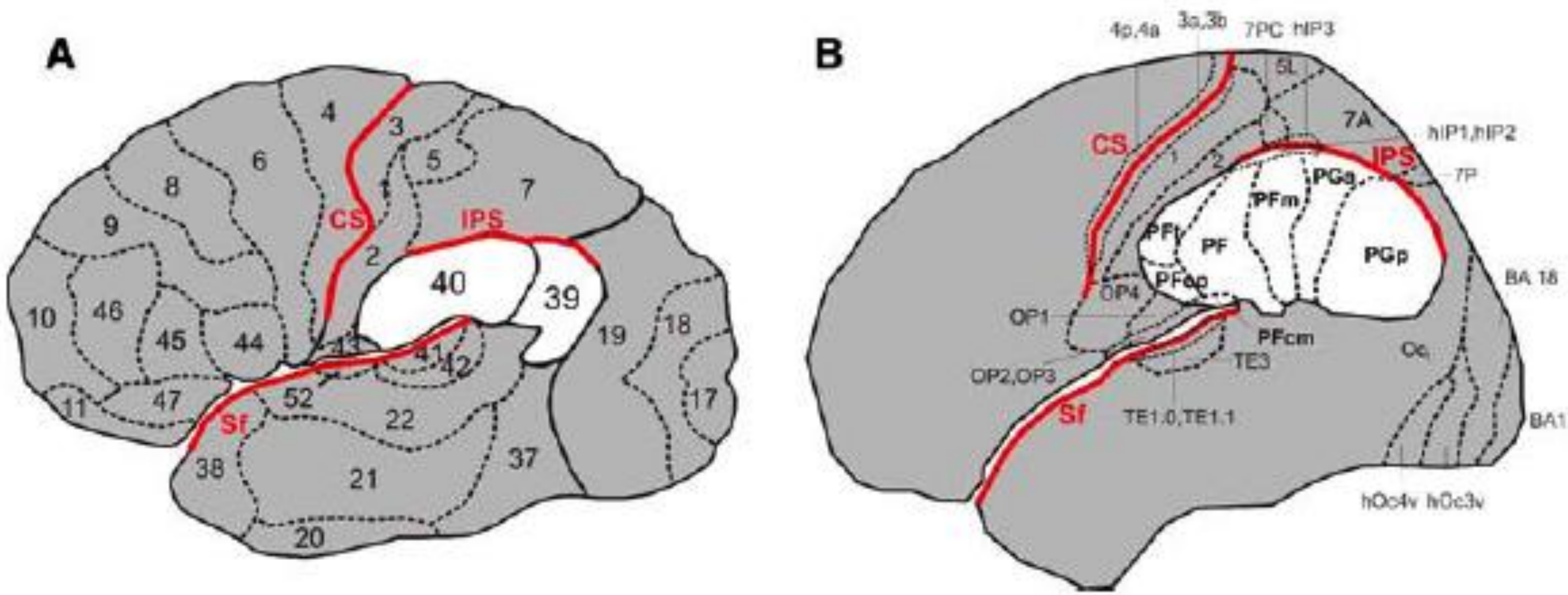






From Amunts et al

Julich cytoarchitectonic map (2009)



Outline

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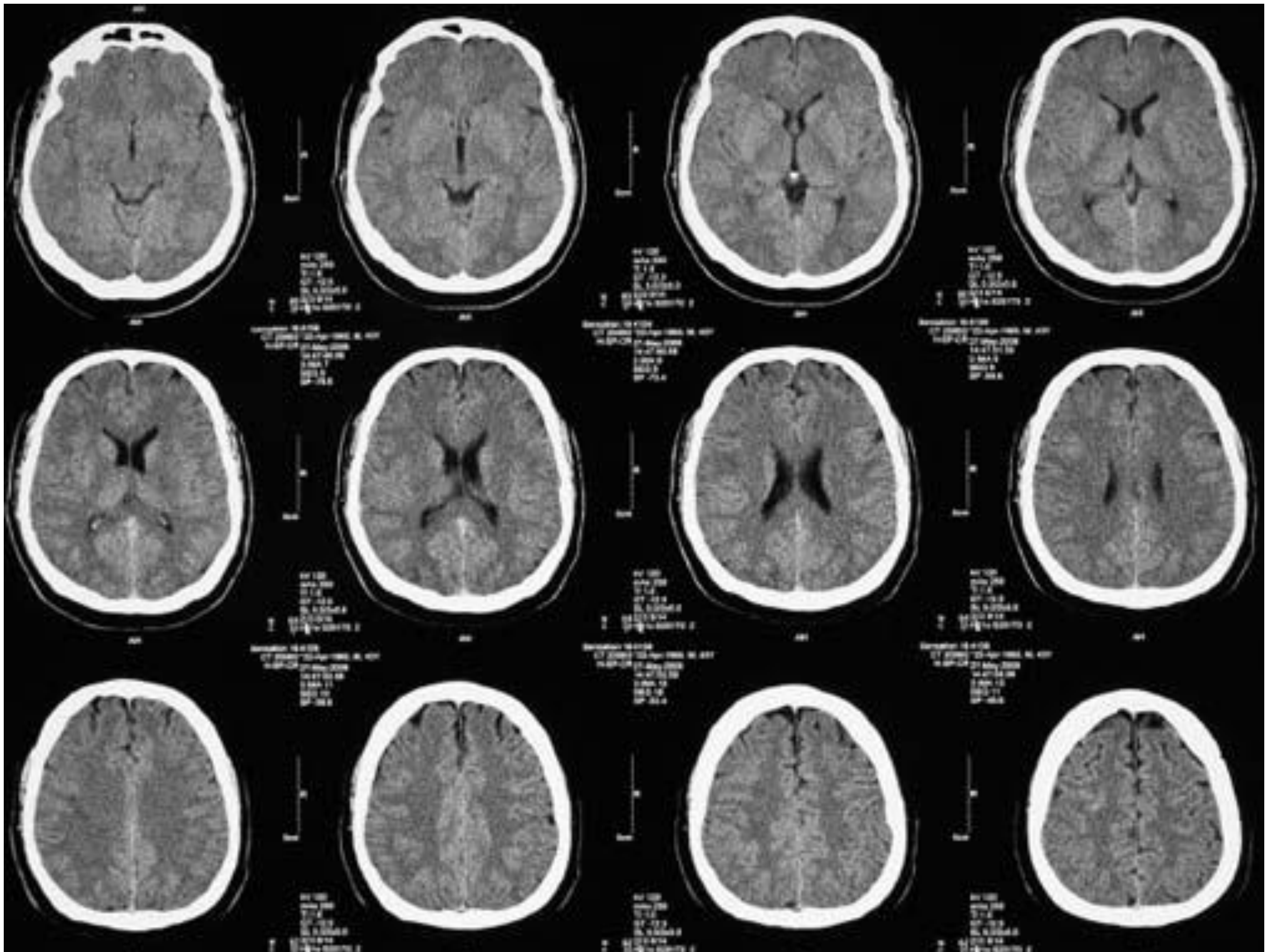
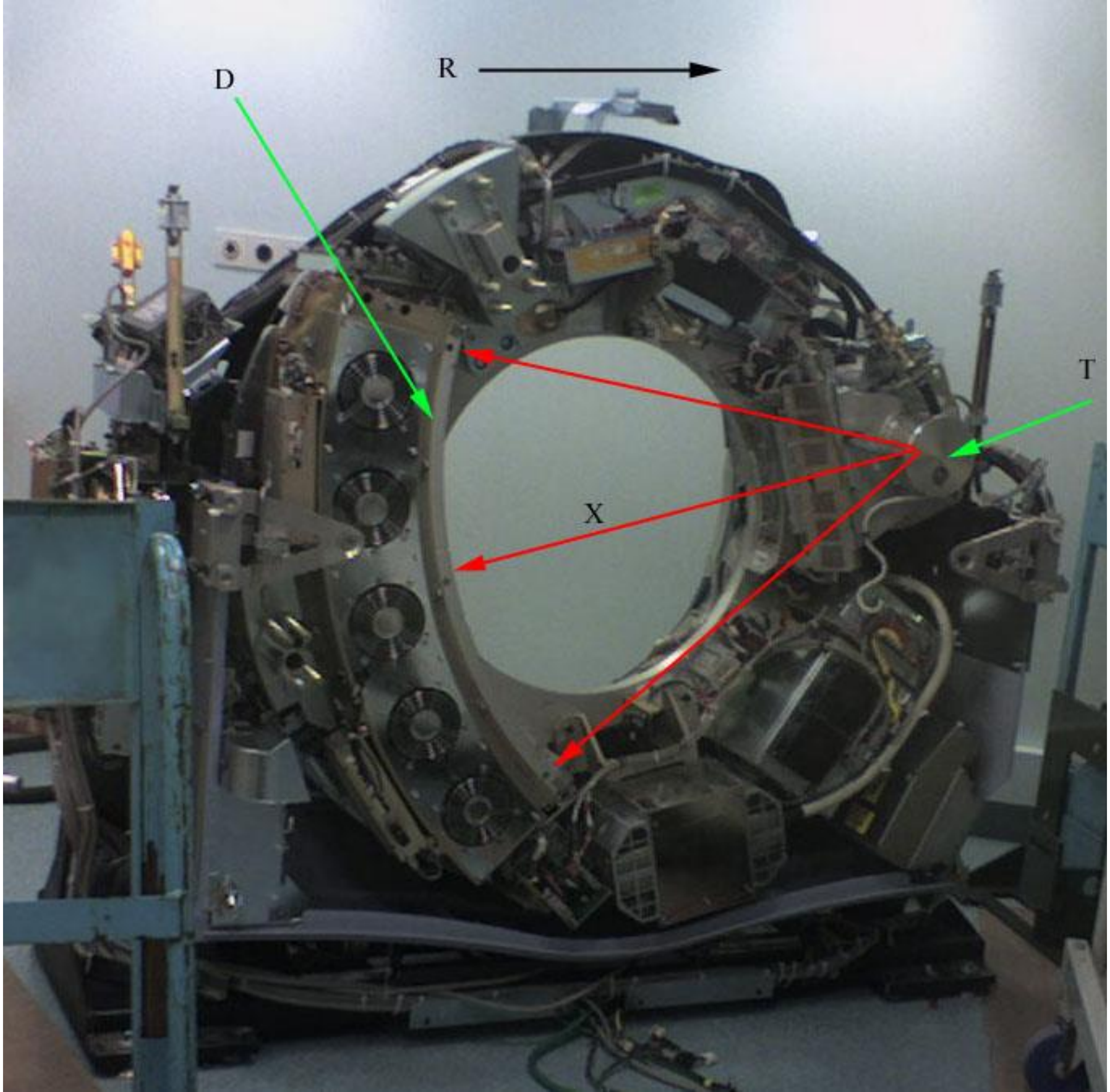
- Brain imaging modalities
- Standard anatomical space
- Image processing

Imaging Modality

- Categorized by the physical method by which an imaging procedure is performed
  - the source of energy and the type of sensors
- A taxonomy of medical brain imaging modalities:
  - Ionizing radiation
    - External ionizing radiation (**X-rays**)
    - Internal ionizing radiation (**nuclear medicine**)
  - Nonionizing radiation
    - Radiofrequency energy (**magnetic resonance imaging** [MRI])
    - Ultrasound
    - Visible light optical imaging

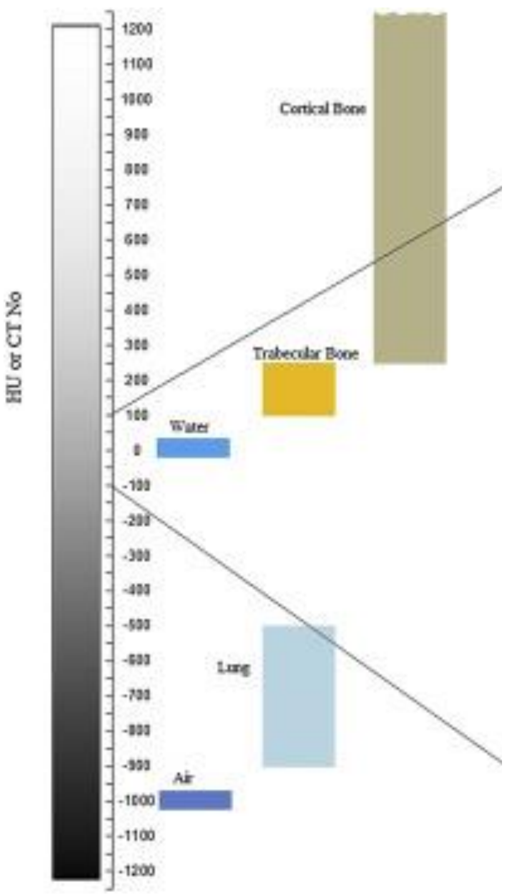
Xray Computed Tomography



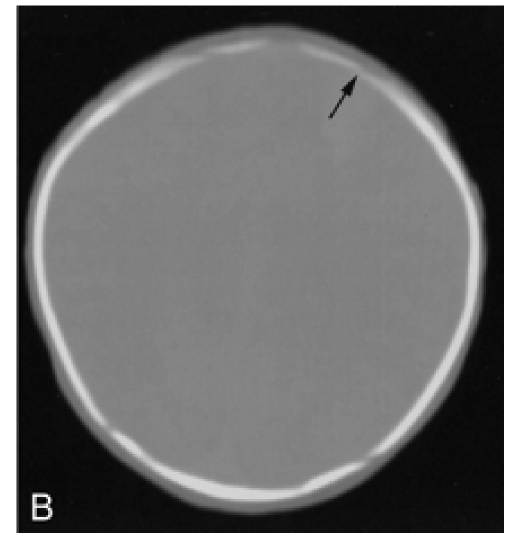

D
R
T
X

CT gives maps of radiodensity

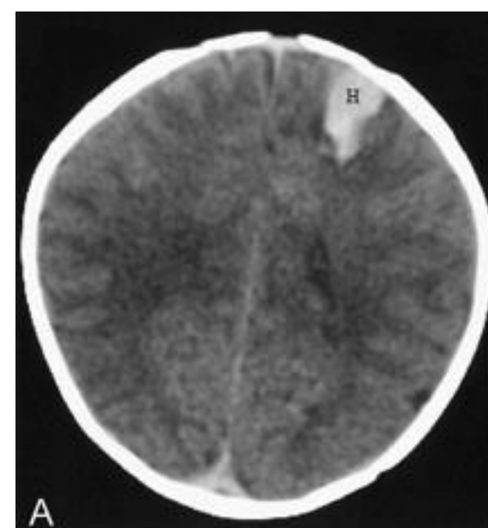
"Hounsfield Number"



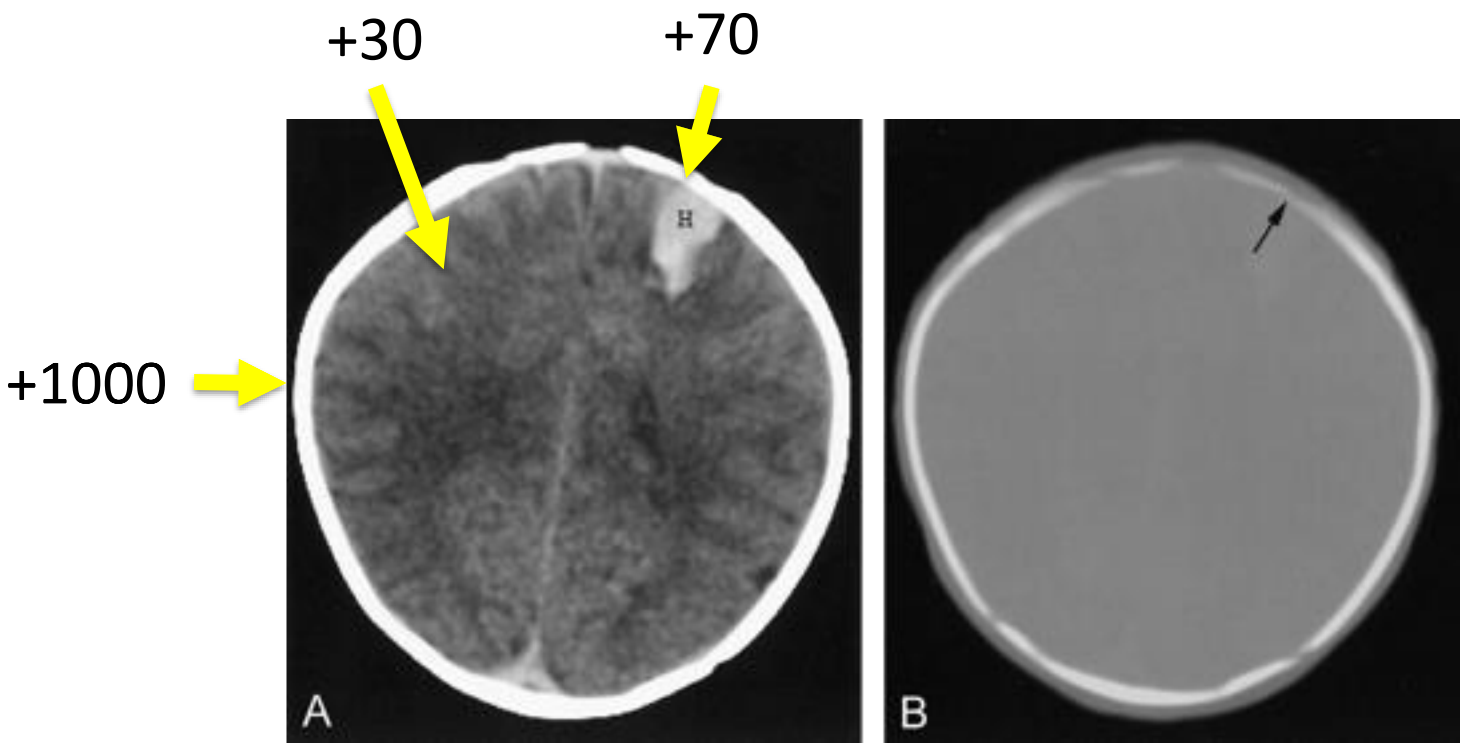
Bone Window



Tissue Window

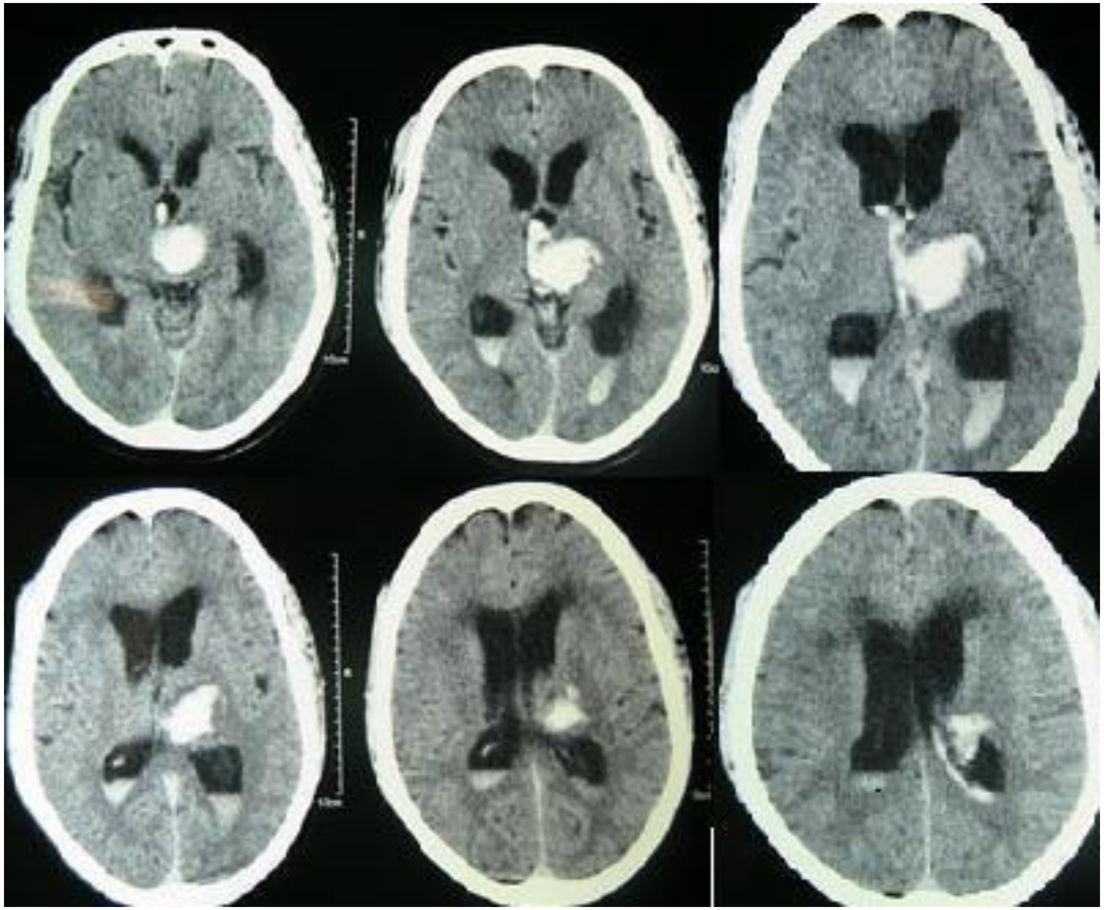


Tissue vs. Bone Windows



Hounsfield Number – radiodensity

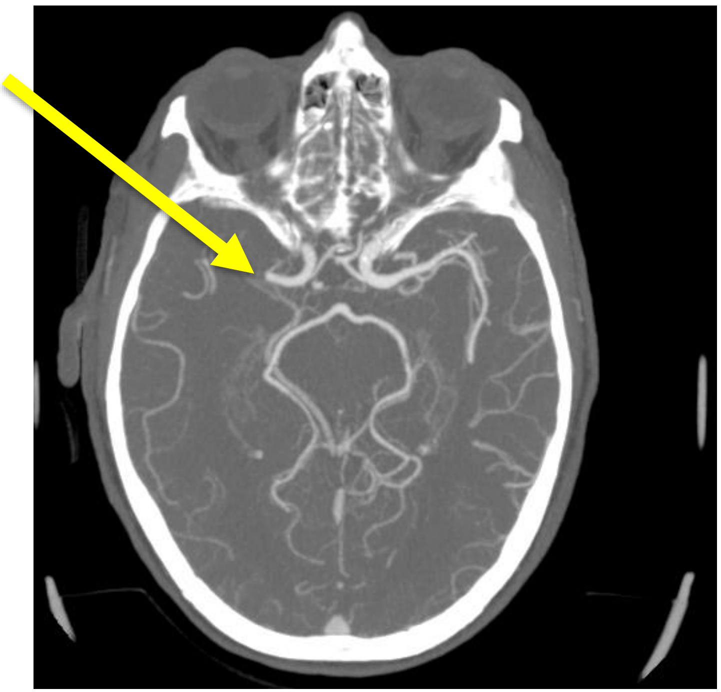
Intracerebral hypertensive hemorrhage



CT angiography

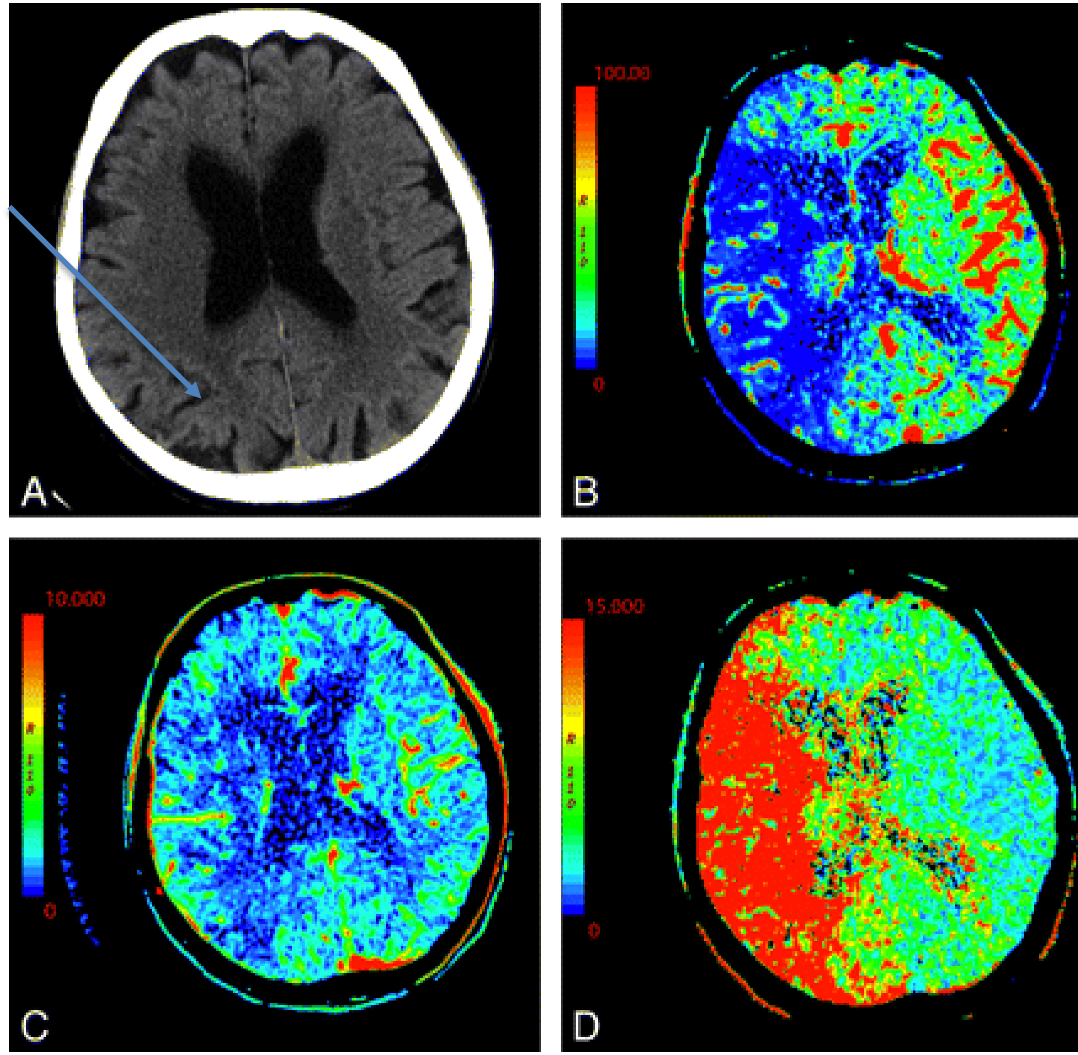
CT in Acute Stroke

CT Angiogram:
R Middle Cerebral Artery Occlusion



Non contrast CT

Blood flow



Blood volume

Transit time

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
- Fast (good throughput, low sensitivity to motion)

- Most “available”
- Finds uses as a first-line emergency technique
- Integrated with PET for attentuation correction and anatomic image fusion
- Used extensively in body imaging (organs in motion)

Artifacts

Artifacts

- Beam hardening – affects skull base, spinal column, vicinity of implanted metal

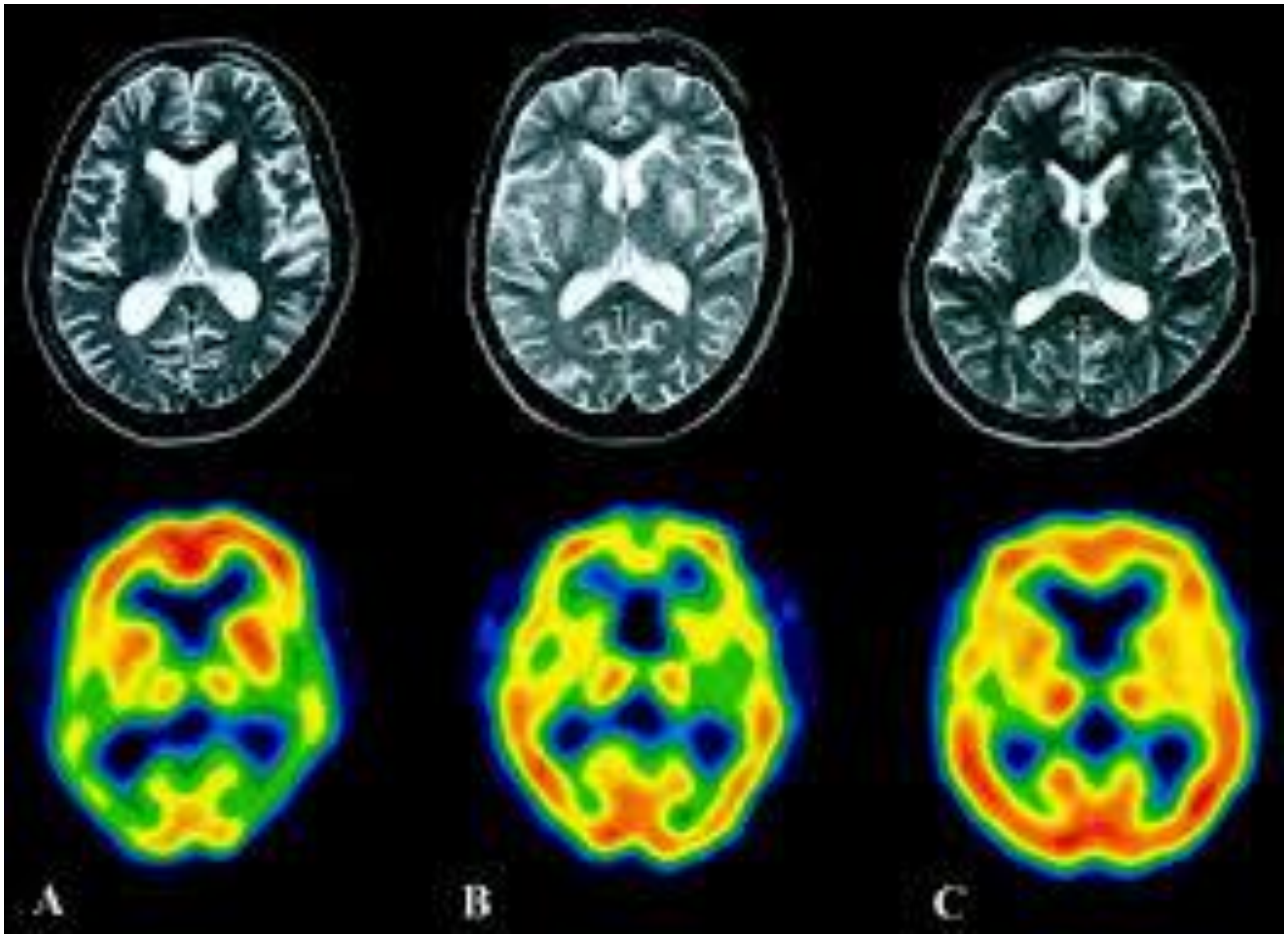
Other issues

- Ionizing radiation exposure
- Contrast agent can cause renal damage
- Poor visualization of soft tissue per se

Nuclear Medicine brain scans

Images of brain physiological parameters are inferred from the biodistribution of radiopharmaceuticals

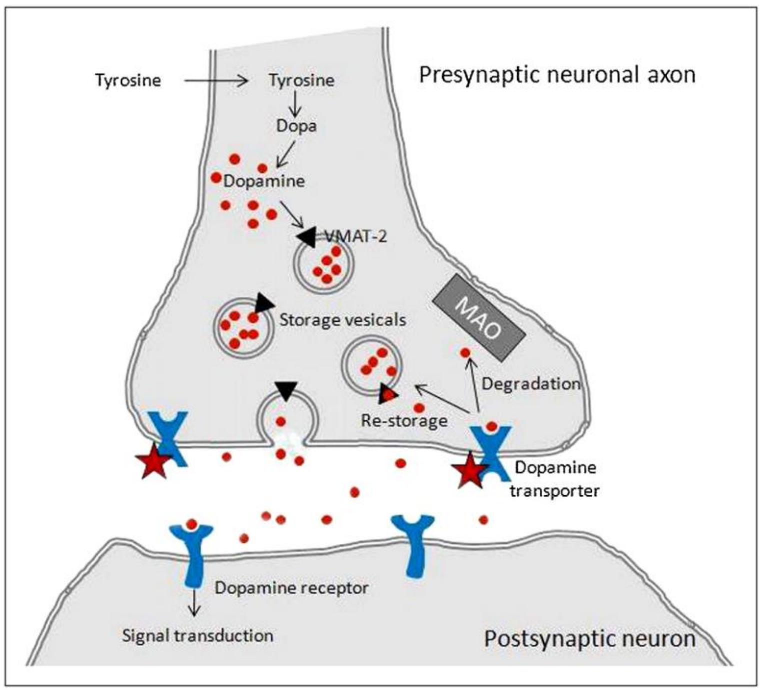
Blood Flow SPECT
[^{99}Tc]-HMPAO

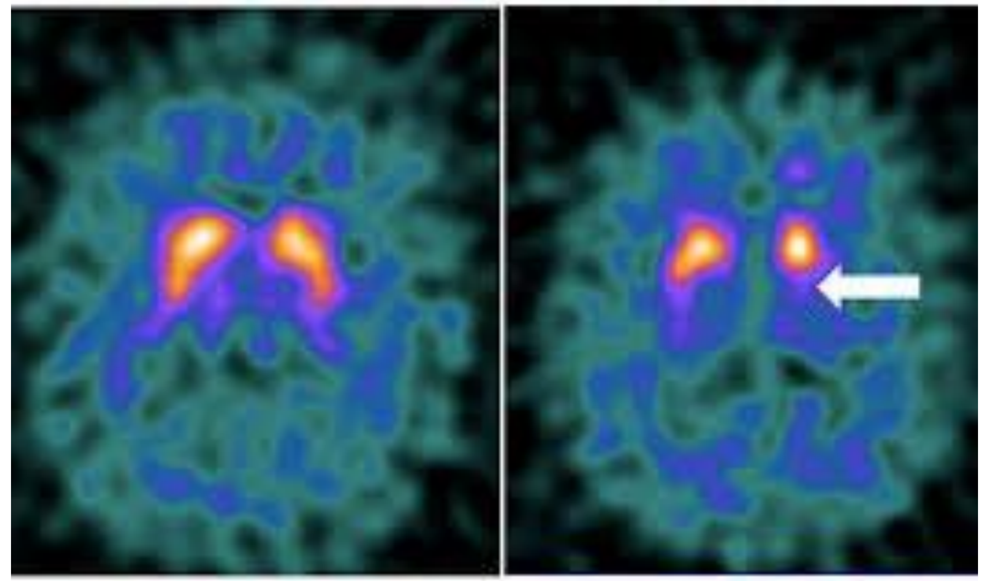


DaTscan™ CII

Ioflupane I123 Injection

See the Difference

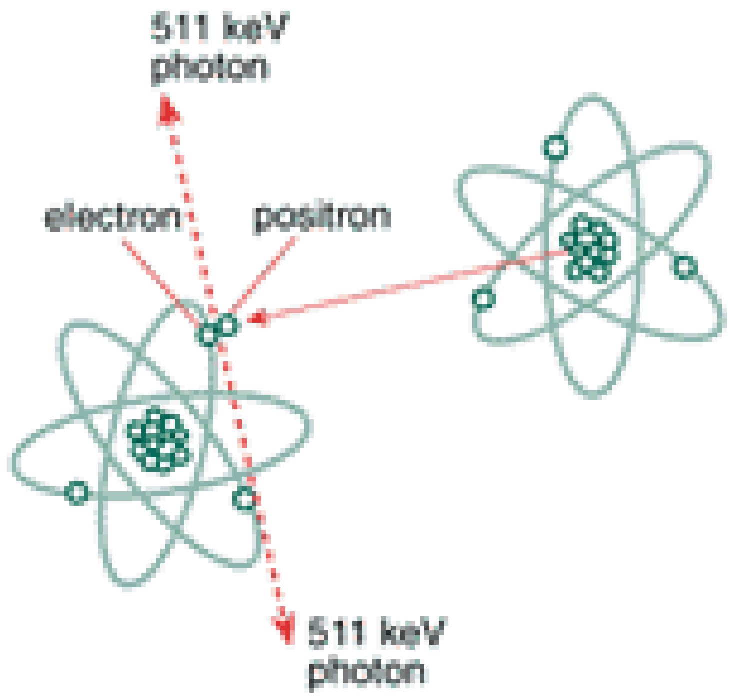




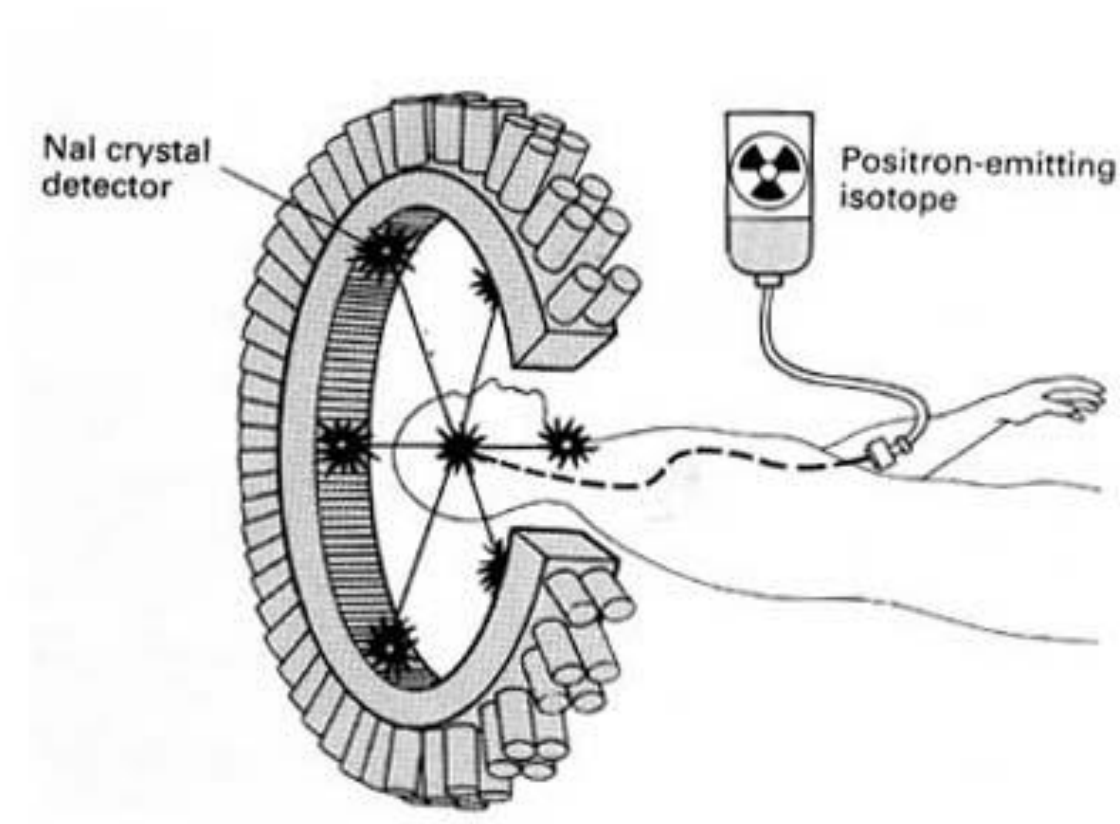
Normal
Essential tremor
Drug-induced parkinsonism

Parkinson disease

Positron emission



PET detectors



Functional Imaging

Imaging the brain *at work*

Neural processes are imaged through parameters related to metabolic substrate delivery

Glucose analogs as radiotracers

Neurovascular coupling

Synaptic electrochemical activity

DEPENDS ON

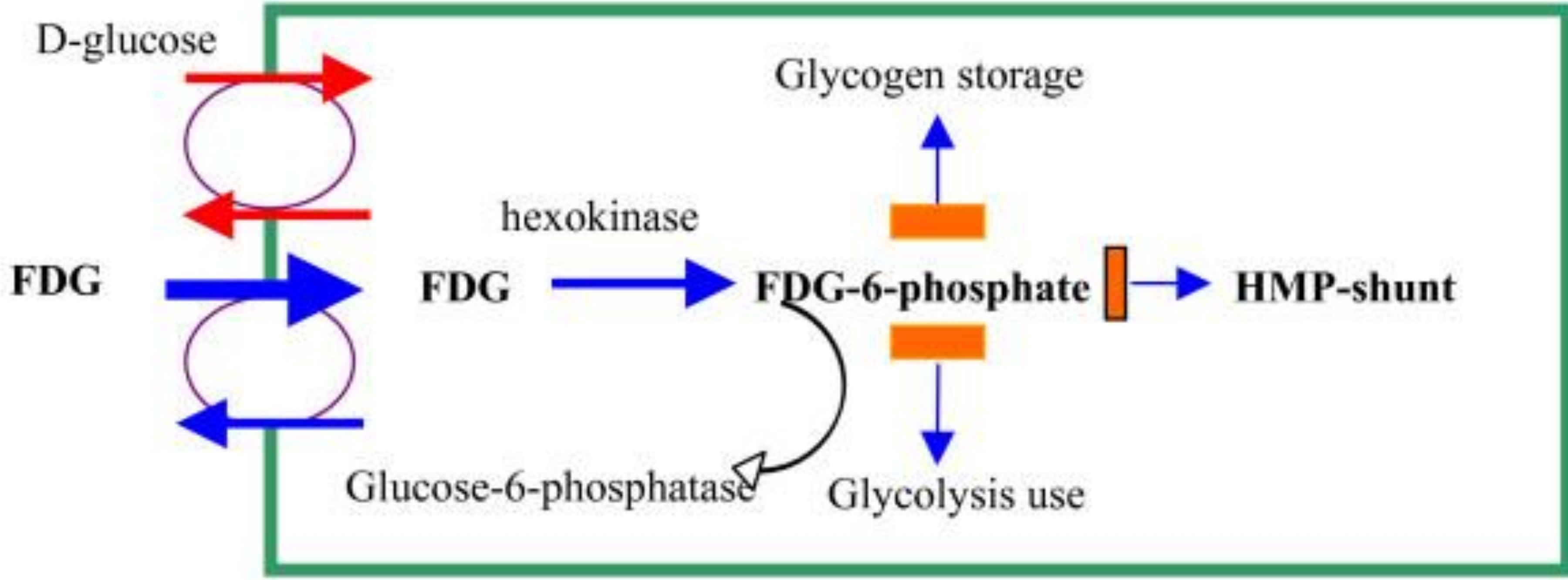
Maintenance of membrane potentials

WHICH DEPENDS ON

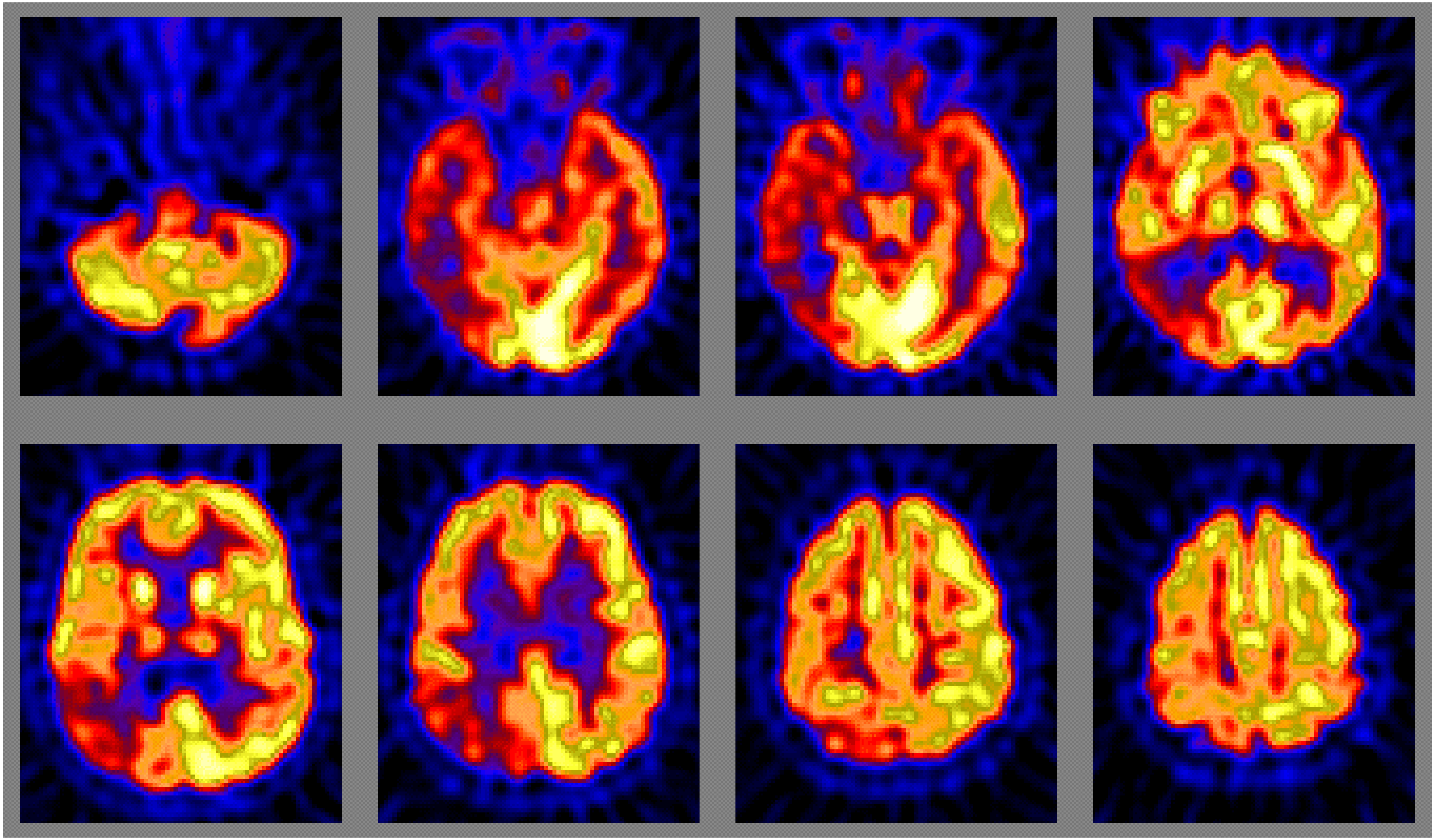
Metabolism of glucose

WHICH DEPENDS ON

Substrate delivery via blood flow


D-glucose
Glycogen storage
hexokinase
FDG
FDG
FDG-6-phosphate
HMP-shunt
Glucose-6-phosphatase
Glycolysis use

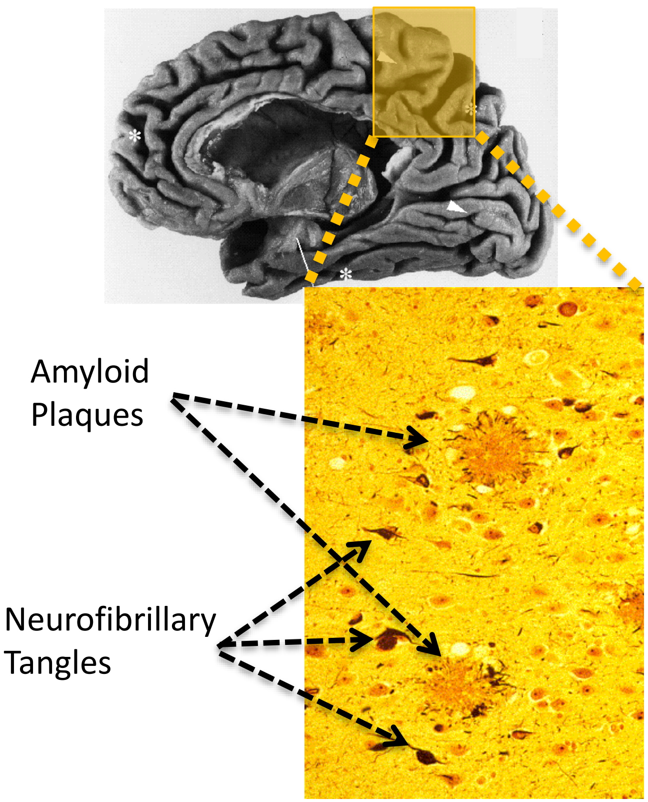
[^{18}F]Fluorodeoxyglucose PET

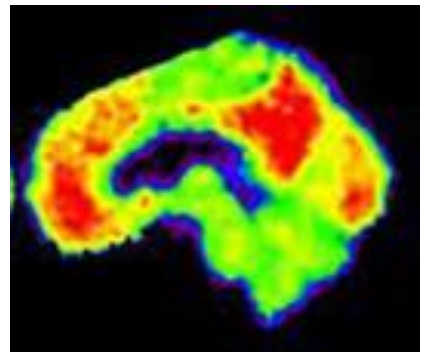


PET

- Physiologically distributed signal
- Unrivaled 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), Alzheimer disease proteins, and more.

BRAIN IMAGING OF ALZHEIMER'S DISEASE

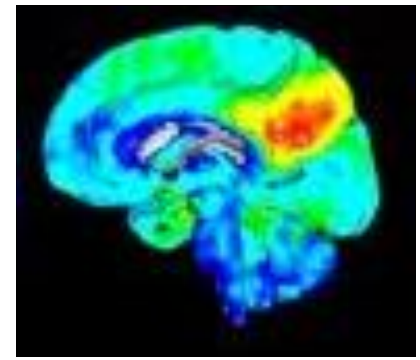




AMYLOID PET SCAN

Detects amyloid plaques
Stereotypical distribution
Leads symptoms by 15 years
Doesn't change over time

Use: to certify diagnosis
Spinal fluid is an alternative.



TAU PET SCAN

Detects tau tangles
Variable distribution
Correlates well with symptoms
Tracks advance of disease

Use: to delineate disease impact
To track treatment

Artifacts

- Artifacts
  - Off-target tracer binding
- Other issues
  - – Ionizing radiation exposure
  - – Requires radionuclide source (cyclotron) and radiochemistry facilities
  - – Poor visualization of anatomy
  - – Inherently low resolution compared to CT, MRI

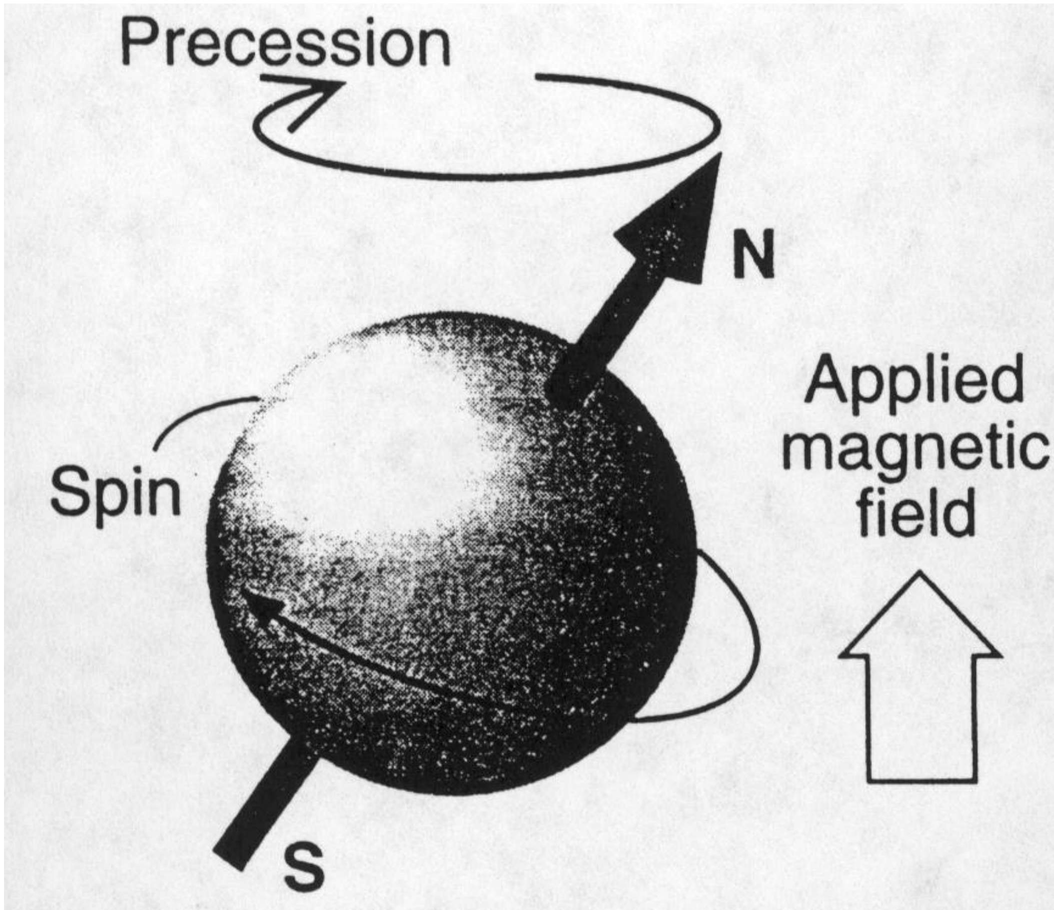
Magnetic Resonance Imaging (MRI)

Wassersteifel
Roman Signer
1986

MRI

- Water molecules have a natural frequency at which they can accept and radiate energy
- The hydrogen nuclei of water have a quantum mechanical property called *spin angular momentum*
- The spin states (ground, excited) of H nuclei diverge in energy level in the presence of a magnetic field
- Water protons absorb or give off quanta of energy to move between these energy levels
- The natural radiofrequency at which this occurs is a function of the magnetic field strength (Larmor freq).

In a magnetic field, protons precess at a natural frequency.
Energy can go in or out of this system *only* at this frequency.



Excitation

- Radiofrequency energy at the Larmor frequency transfers to the water protons of the system.
- This does two things:
  - Synchronizes the precession of the protons
  - Introduces a transverse component to the magnetization (which one can detect and measure)
- When the pulse of RF input stops, the system (water in the magnet) will radiate radiofrequency energy for a little while, at the Larmor frequency

Relaxation: T1, T2, T2*

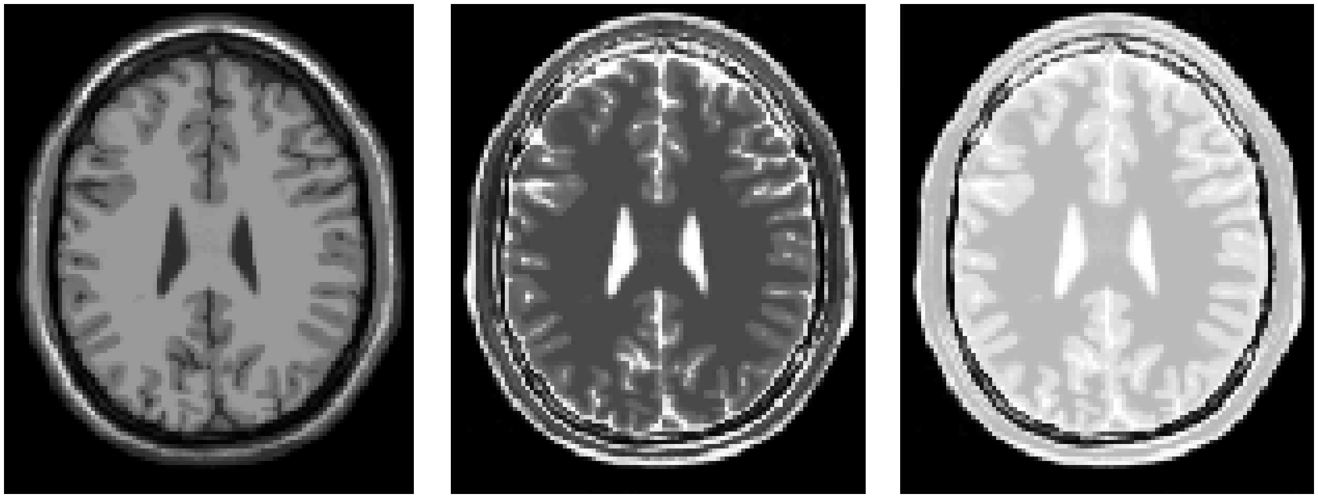
- With time (described by T1) the excited dipoles will relax back into alignment with the field.
- Before that happens, their precession will get out of phase (described by T2) and no more signal will be available.
- But even before that, local imperfections in the field will probably cause even faster 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

Together, the values of TR and TE emphasize different tissue parameters.

T1	T2	PD



T1	T2	PD
TR = 300 msec TE = 20 msec	TR = 3000 msec TE = 120 msec	TR = 3000 msec TE = 20 msec

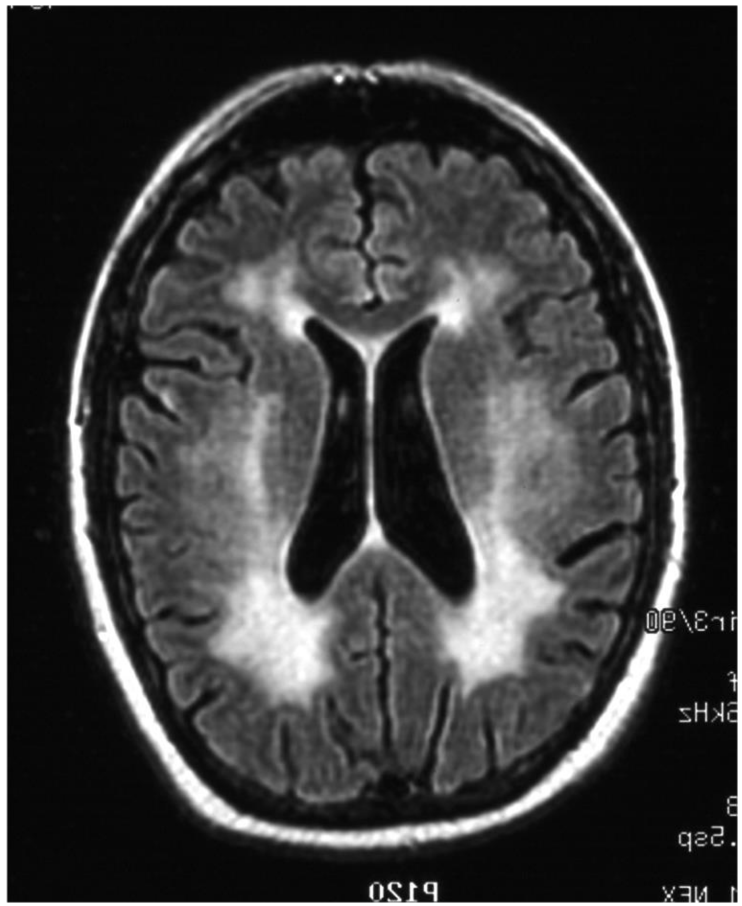
A **short** TR and **short** TE emphasizes T1 contrast.

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
- ……

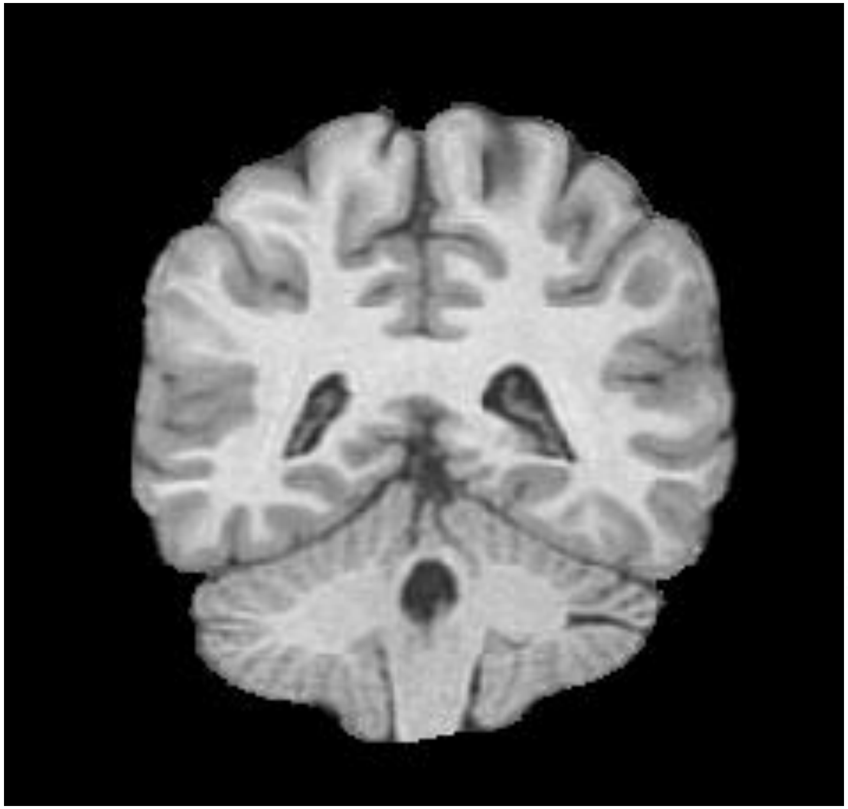
Magnetic resonance angiography "MRA"

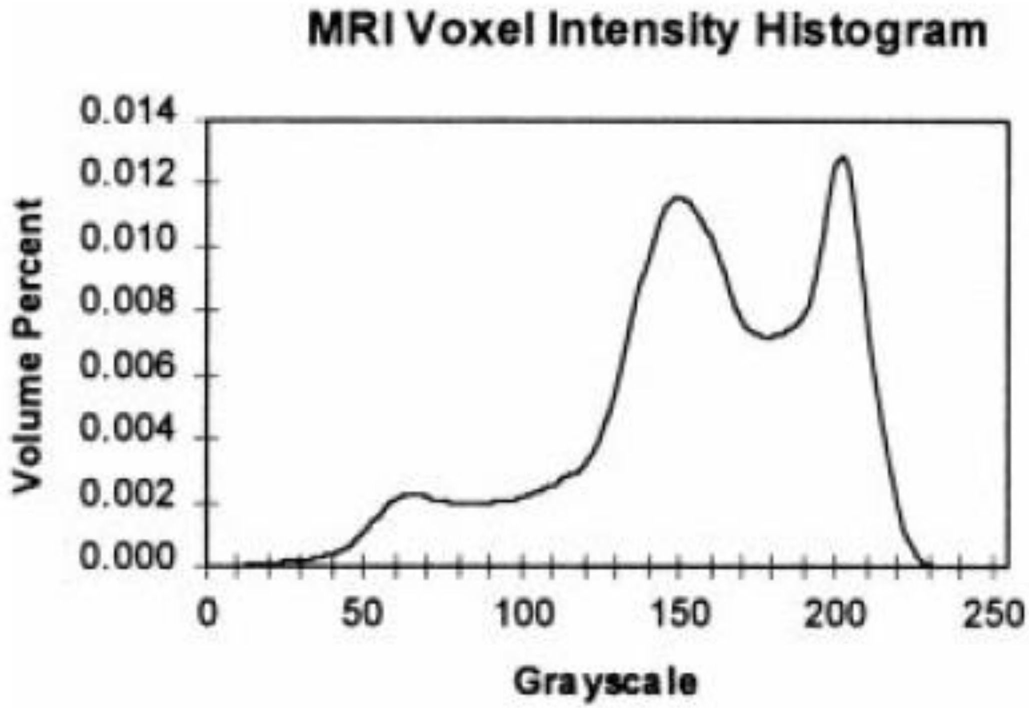
The “economy” of MRI

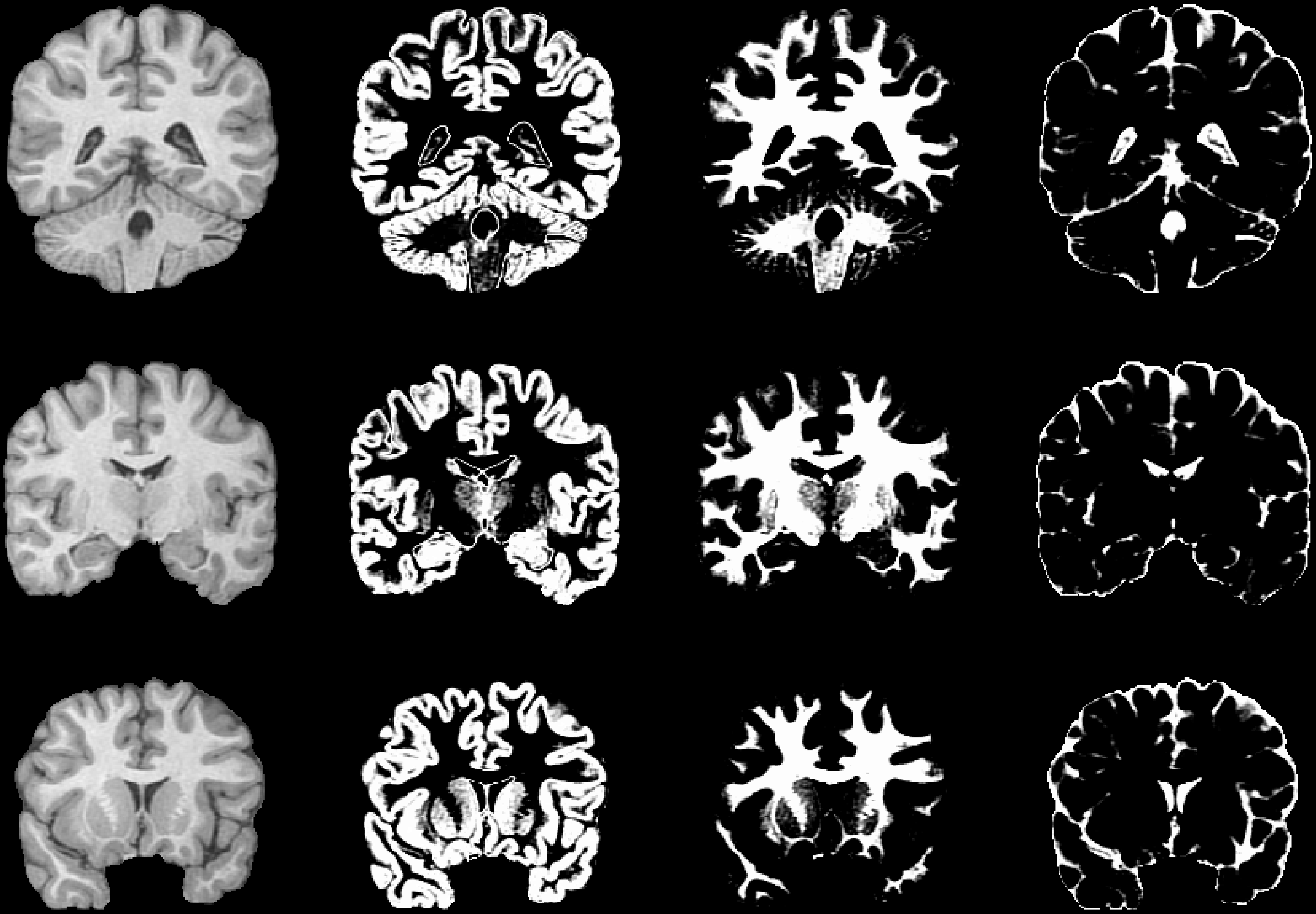
- In MRI, signal is the sum of the longitudinal magnetization of the protons in the field of view
- This is a like fixed budget, to be spent to obtain some combination of:
  - Better spatial resolution
  - Better signal to noise ratio (SNR)
  - Reduced imaging time
- There are always trade-offs!
- Some pulse sequences are more “economical” than others
- Advances in MRI are often in the form of a smarter pulse sequence, i.e. software-driven

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



Artifacts

Artifacts

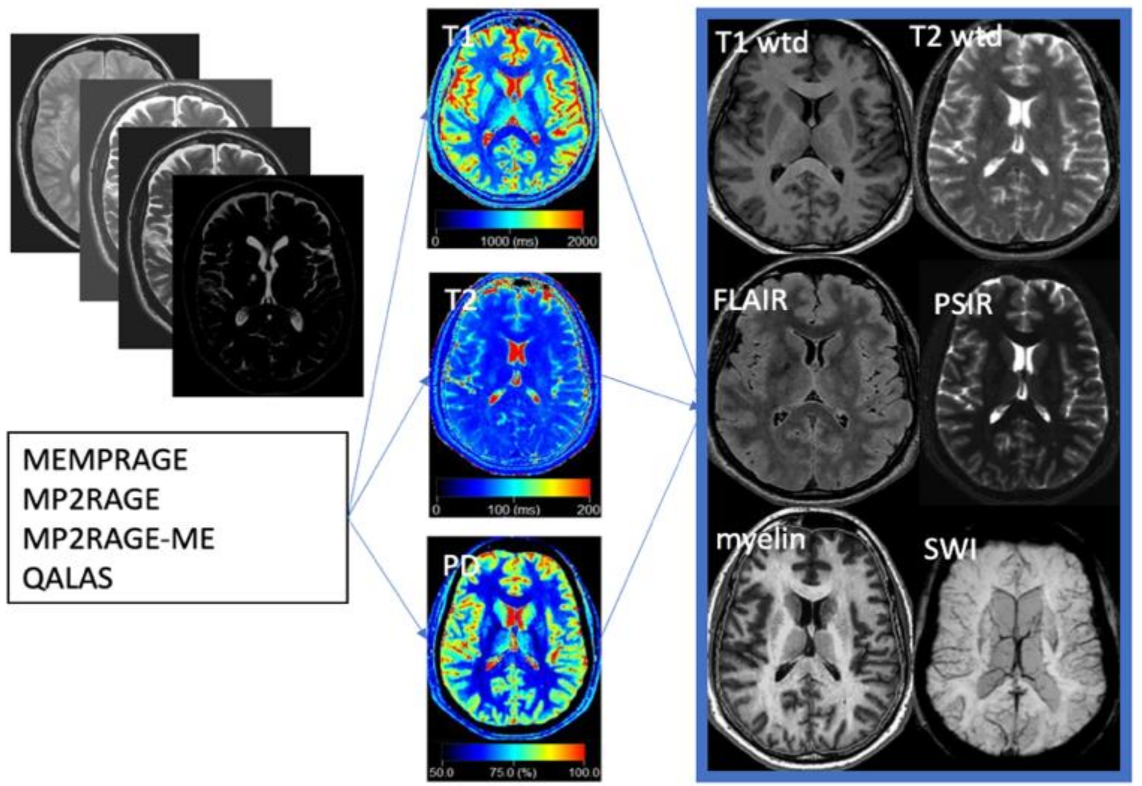
Motion degrades images

Flow (blood, CSF)

Other issues

- Signal doesn't have absolute meaning
  - "*T1-weighted* images"
- Complex interactions of signal sources
- Inherently low signal

MR relaxometry
MR fingerprinting



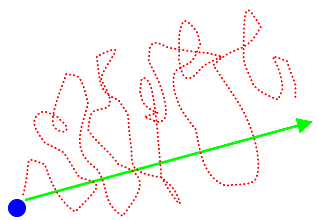
Rapid Relaxometry sequences
(~6-8 min)

Tissue-specific images of MRI parameters

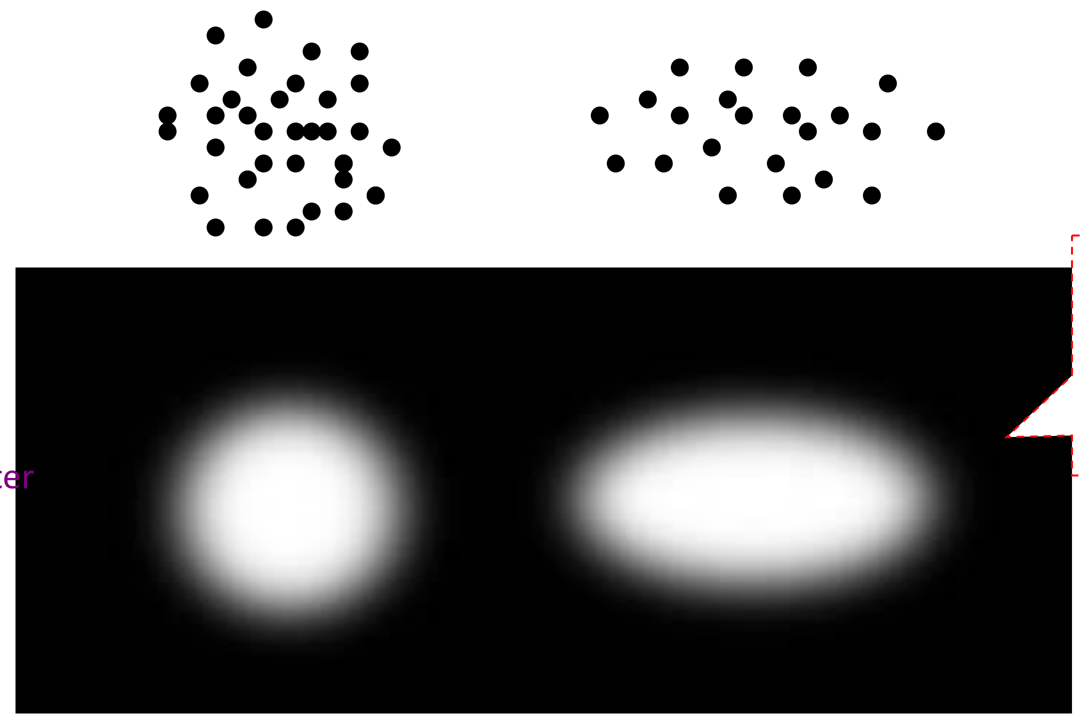
Synthesized parameter-weighted
Images for diagnostic evaluation
And for cross-site harmonization

Diffusion Imaging

Diffusion



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

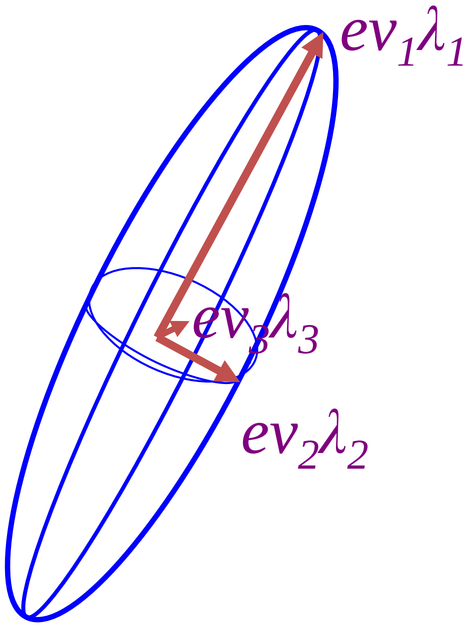


Ellipsoid = Probability of Diffusion Distribution

Isotropic Diffusion

Anisotropic Diffusion

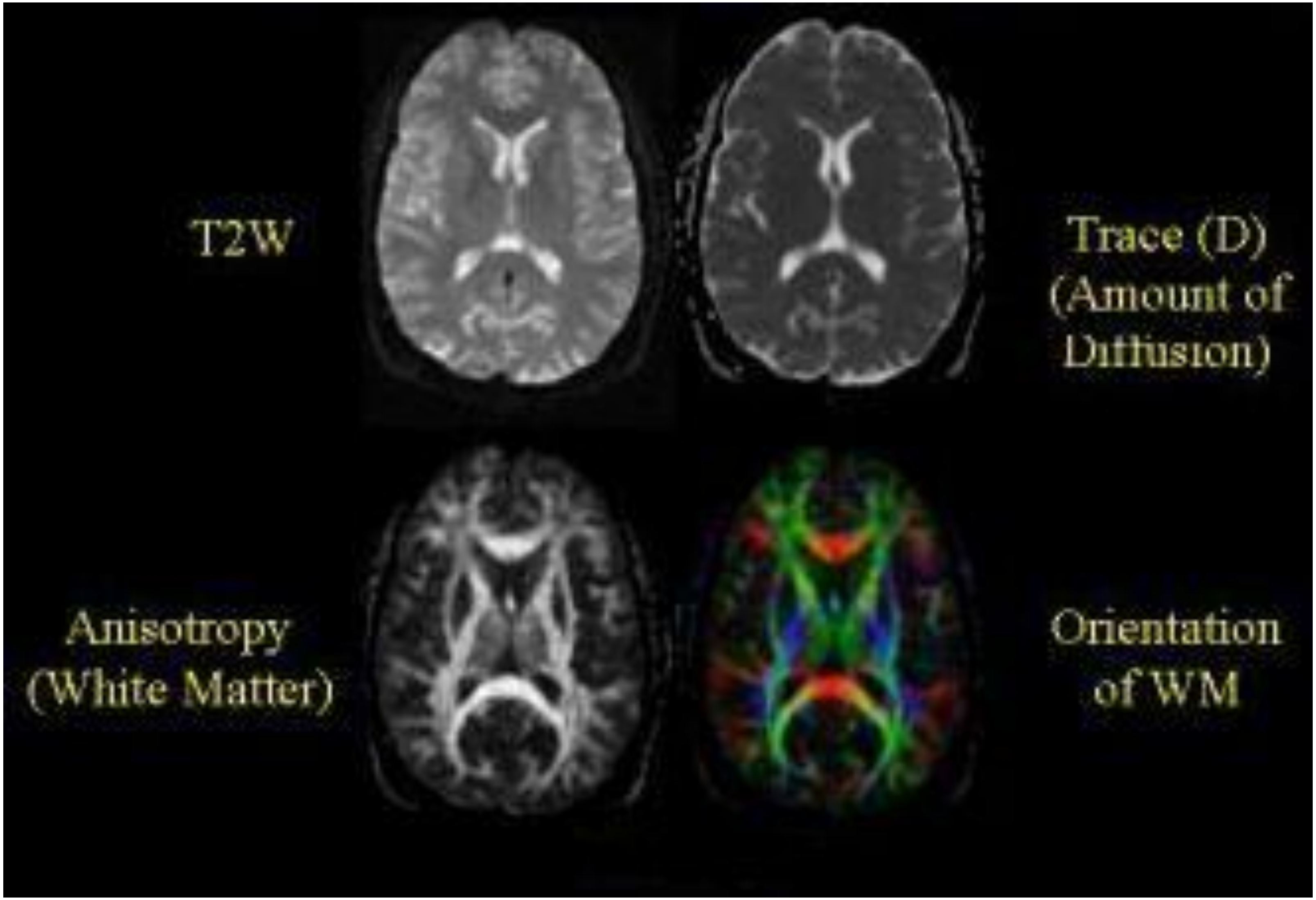
Diffusion eigenvectors



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



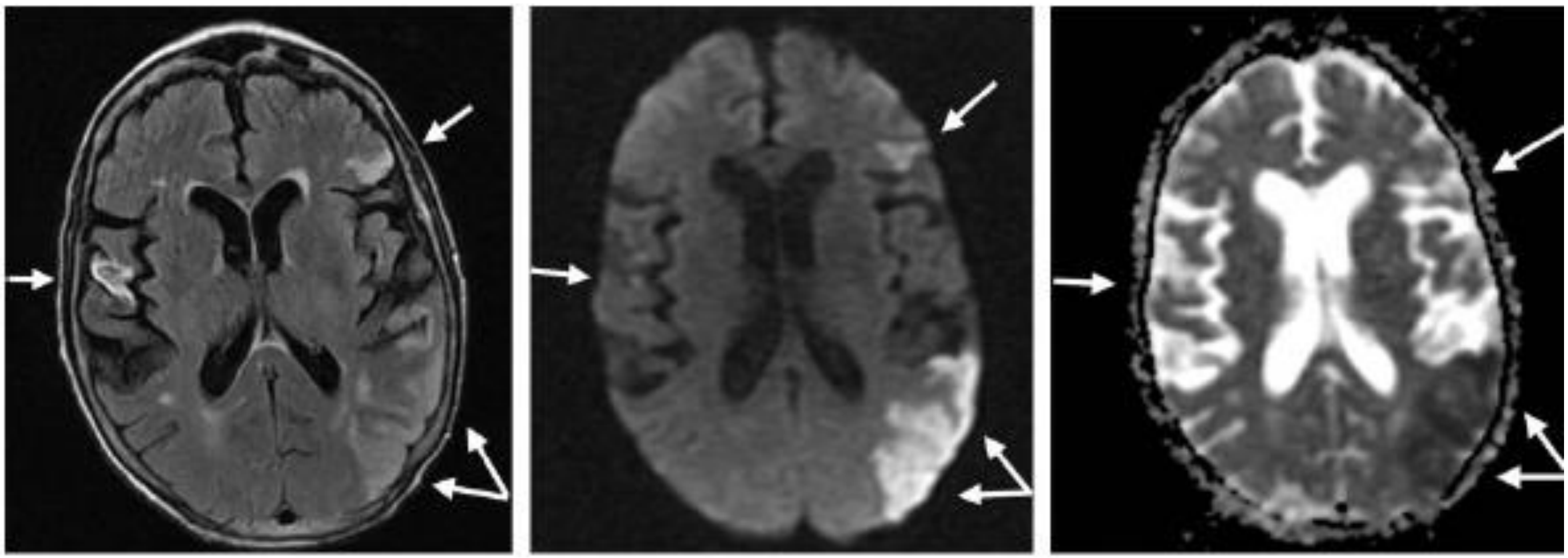
Diffusion imaging

- Parameters neurologists are used to seeing
  - Diffusion-weighted image
  - Apparent diffusion coefficient - ADC
- Parameters neuroscientists are used to seeing
  - Diffusion fractional anisotropy – FA

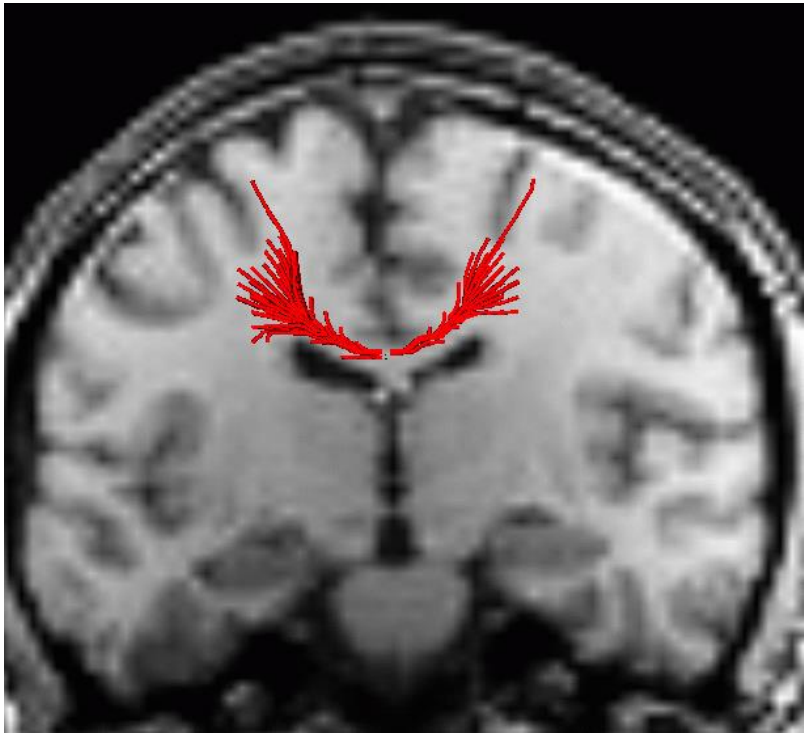
    A measure of how constrained water is to diffuse in only certain directions
  - Diffusion principal eigenvector

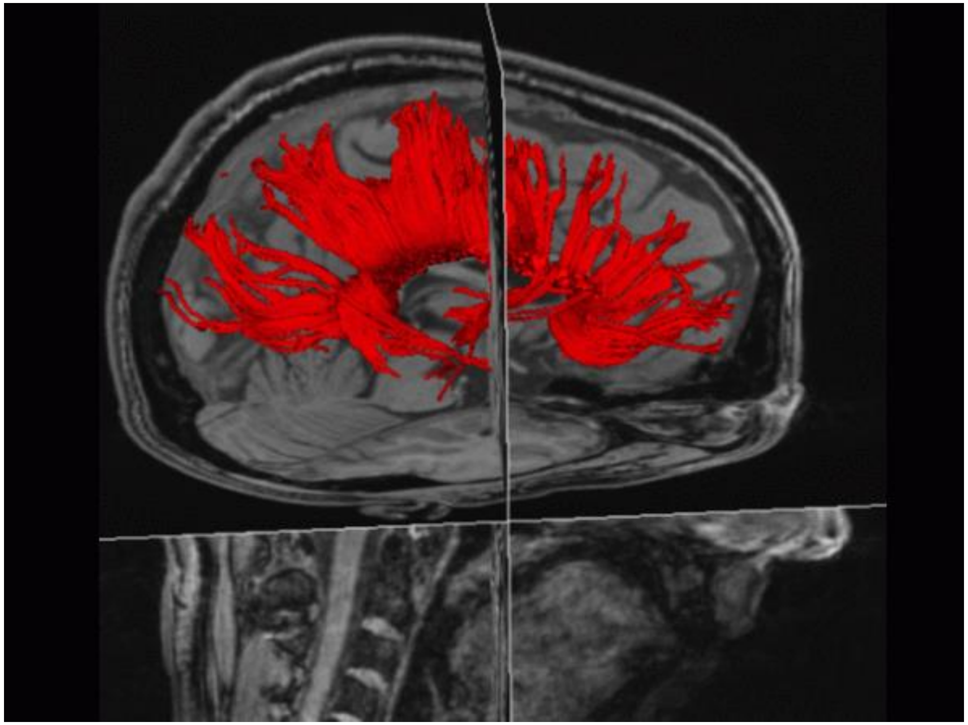
    The axis along which water diffuses most freely

Detecting acute stroke with diffusion MRI



DTI Tract Tracing



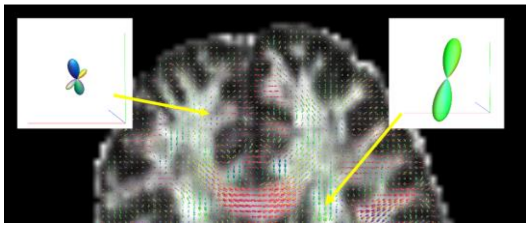


In vivo Connectivity-based Cortex Parcellation

Preprocess DWI

↓

Model Diffusivity



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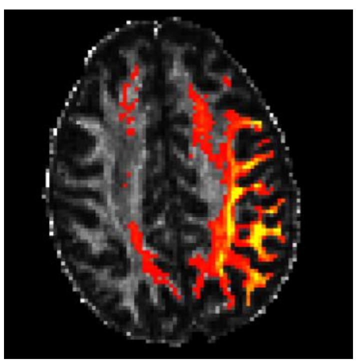
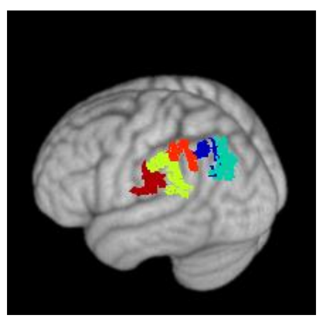
Compute and cluster tractograms





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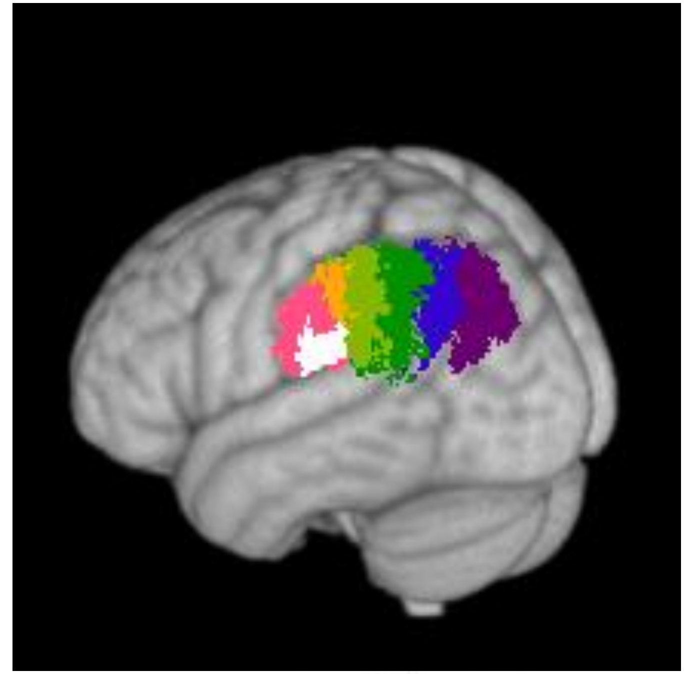
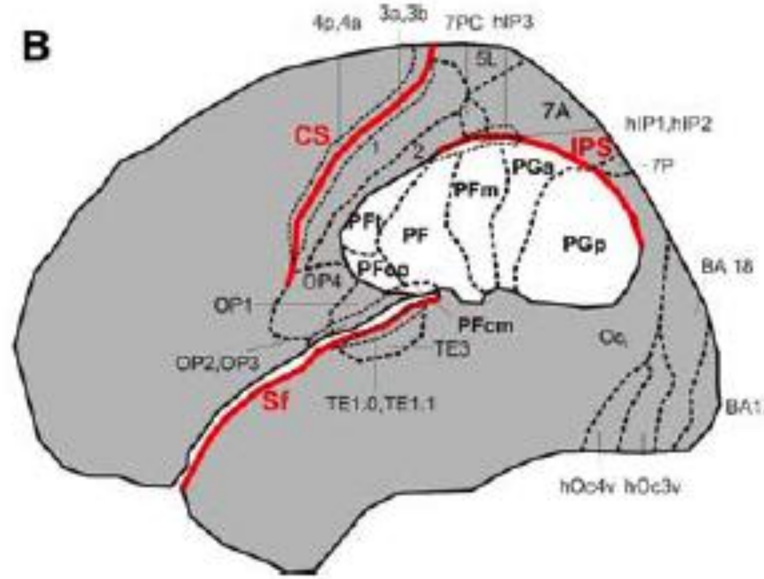




Functional Magnetic Resonance Imaging (fMRI)

Physiological basis of fMRI

Brain activity is imaged *indirectly*, through parameters related to metabolic substrate delivery.

Neurovascular coupling

Synaptic electrochemical activity

DEPENDS ON

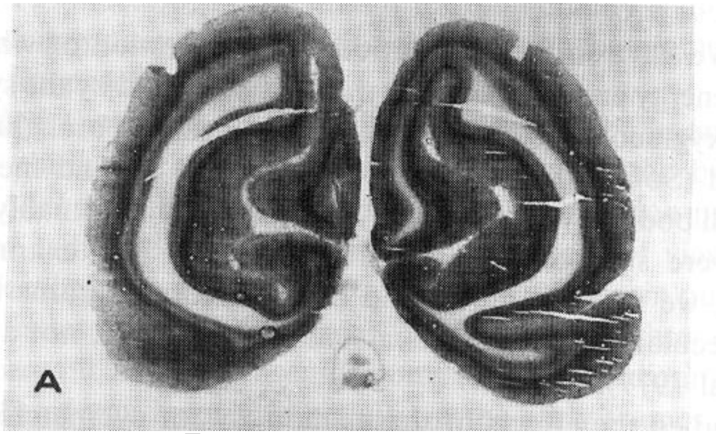
Maintenance of membrane potentials

WHICH DEPENDS ON

Metabolism of glucose

WHICH DEPENDS ON

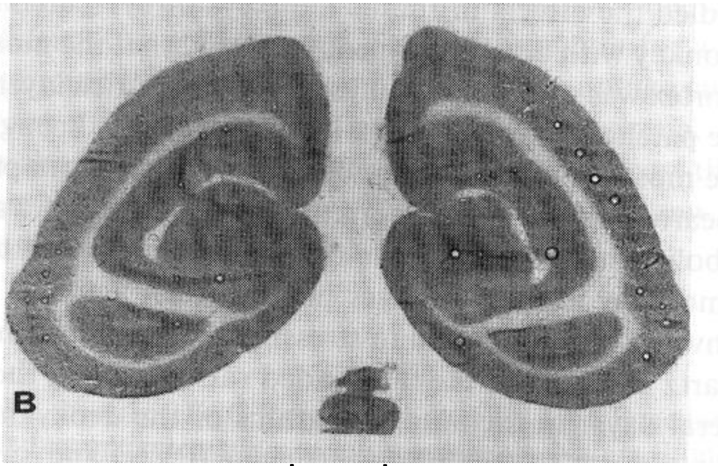
Substrate delivery via blood flow



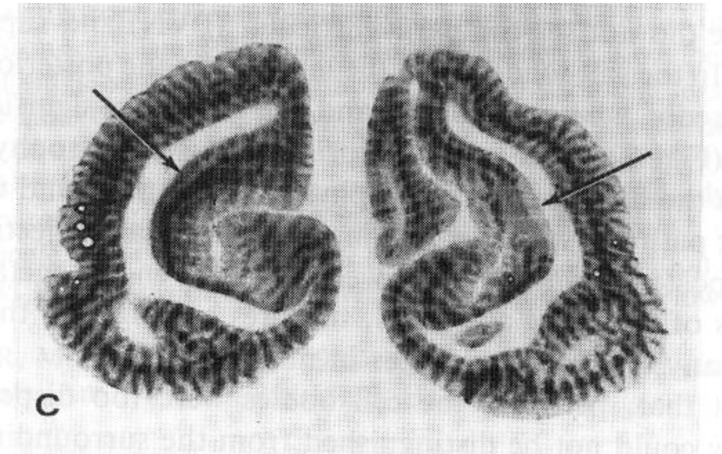
Eyes open

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

2-deoxyglucose: visual stim in cats

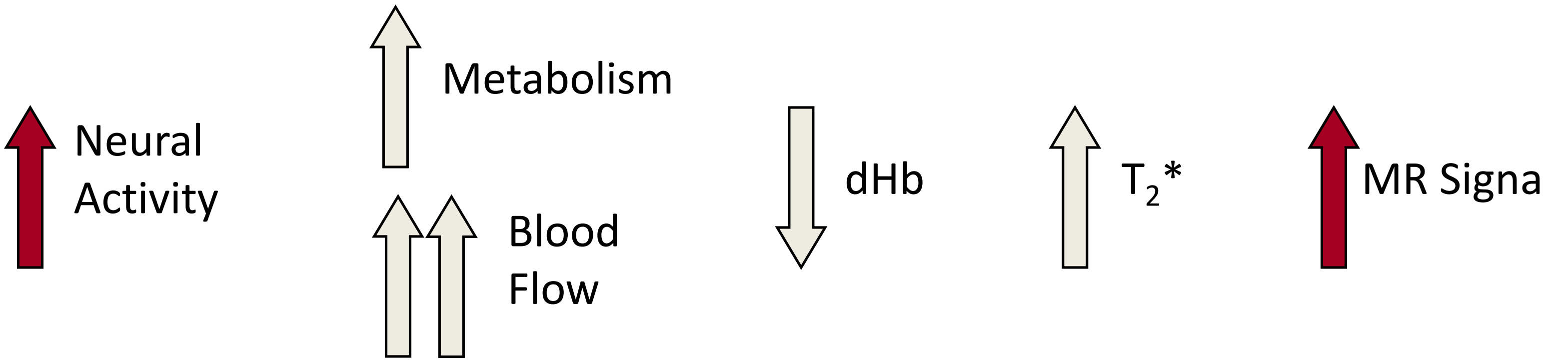


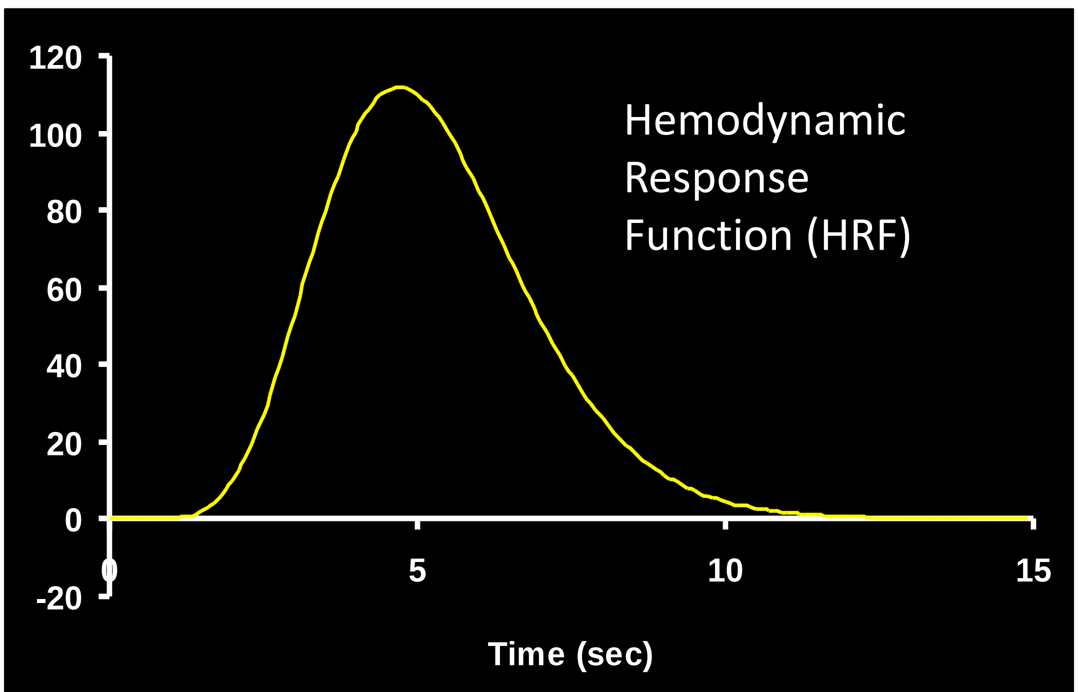
Eyes closed



One open, one closed

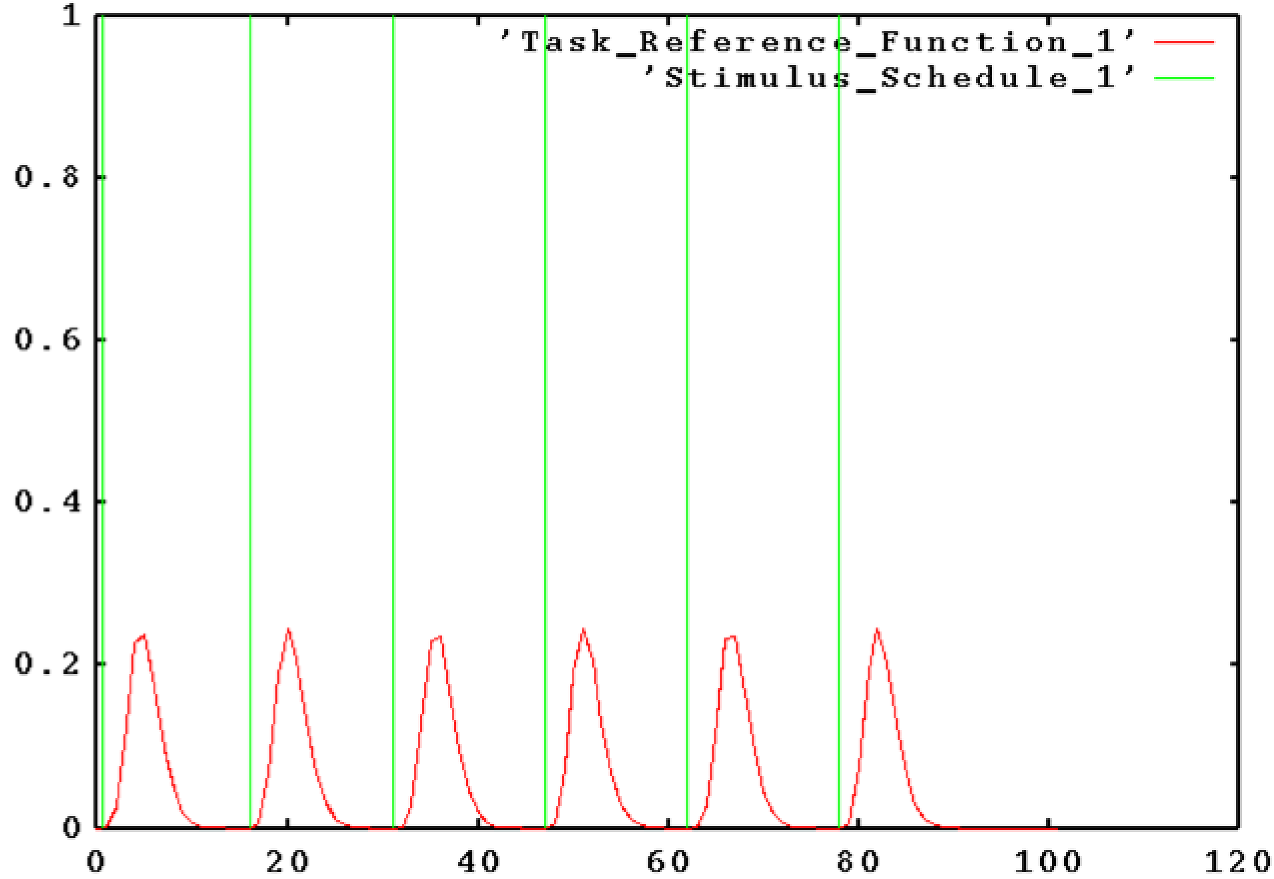
Basis of fMRI signal





Blood Oxygenation Dependent Signal

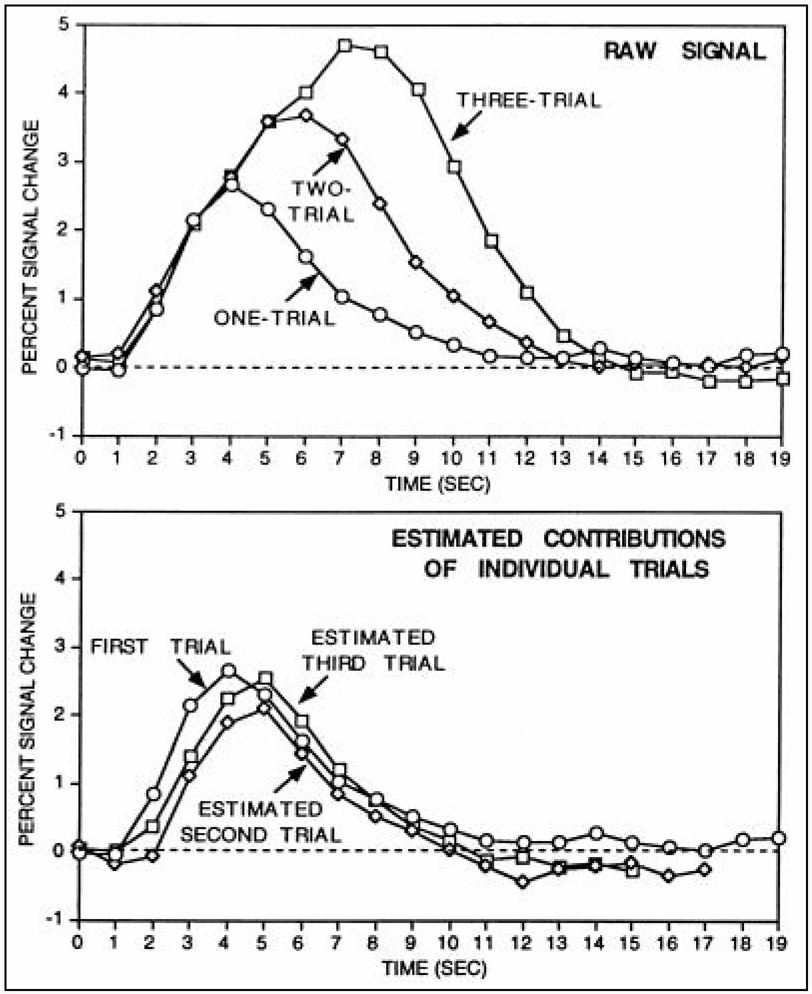
“BOLD”



MRI signal

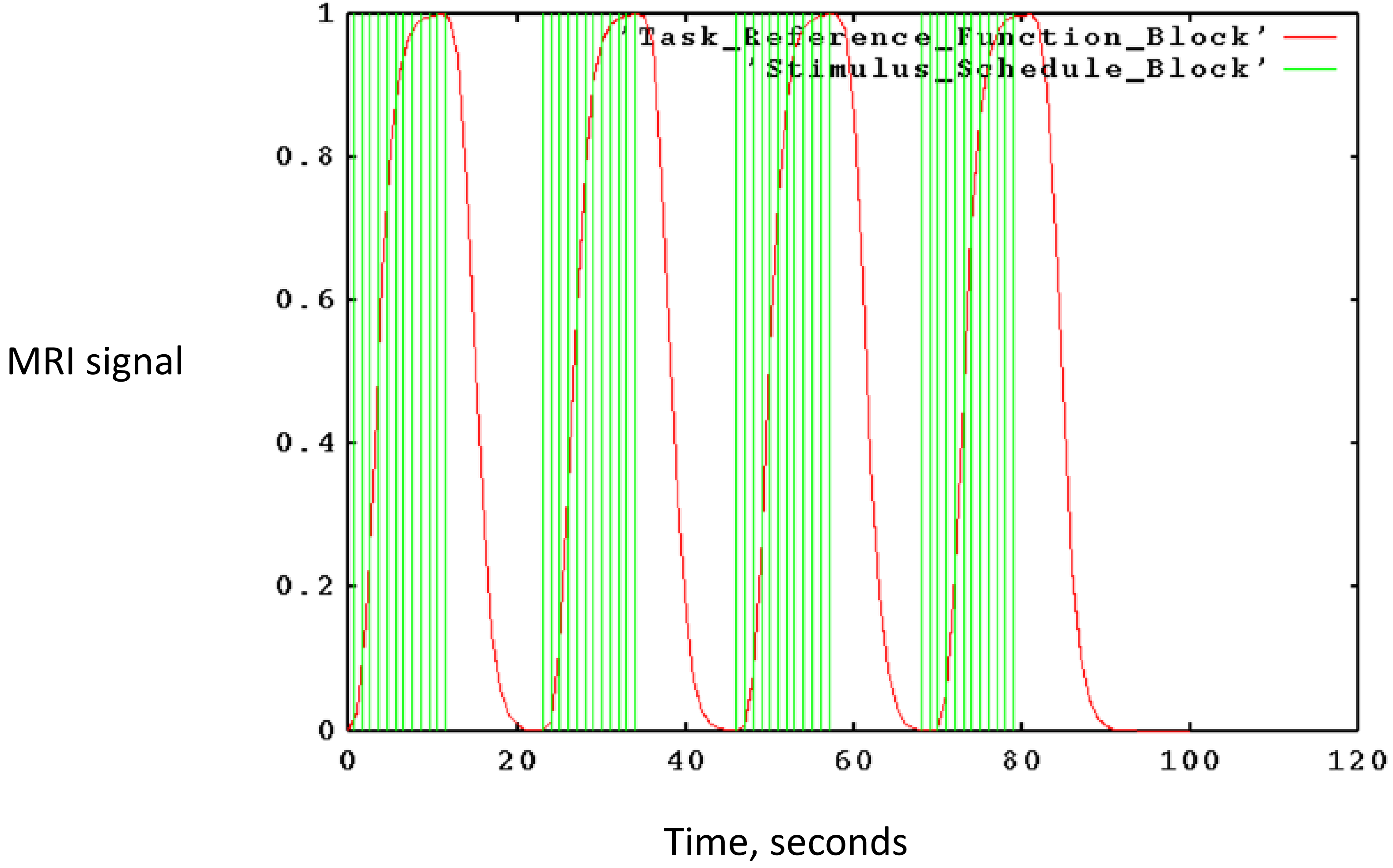
Time, seconds

HRF sums linearly over trials

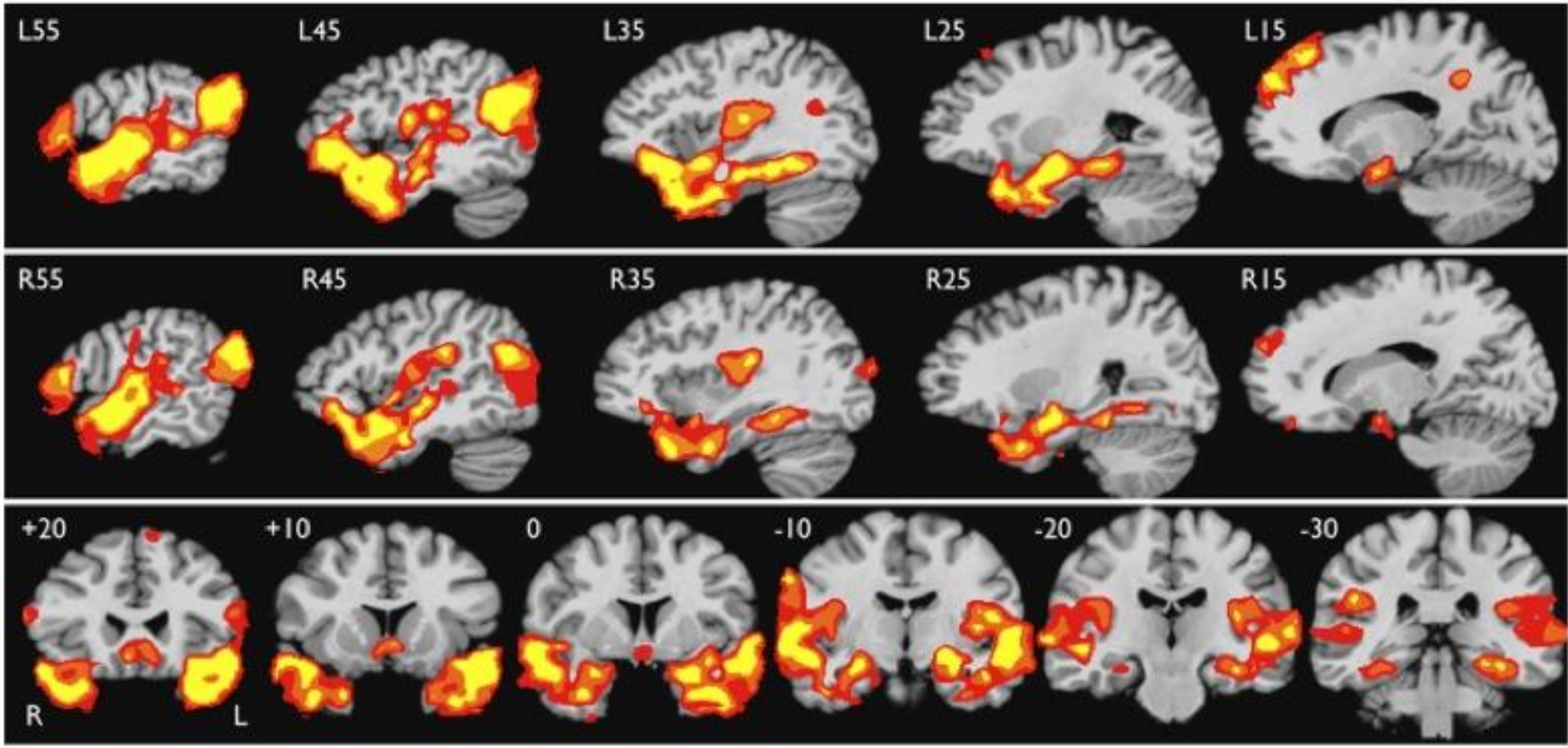


A. Dale and R. Buckner
Hum Brain Mapp 5:329
1997

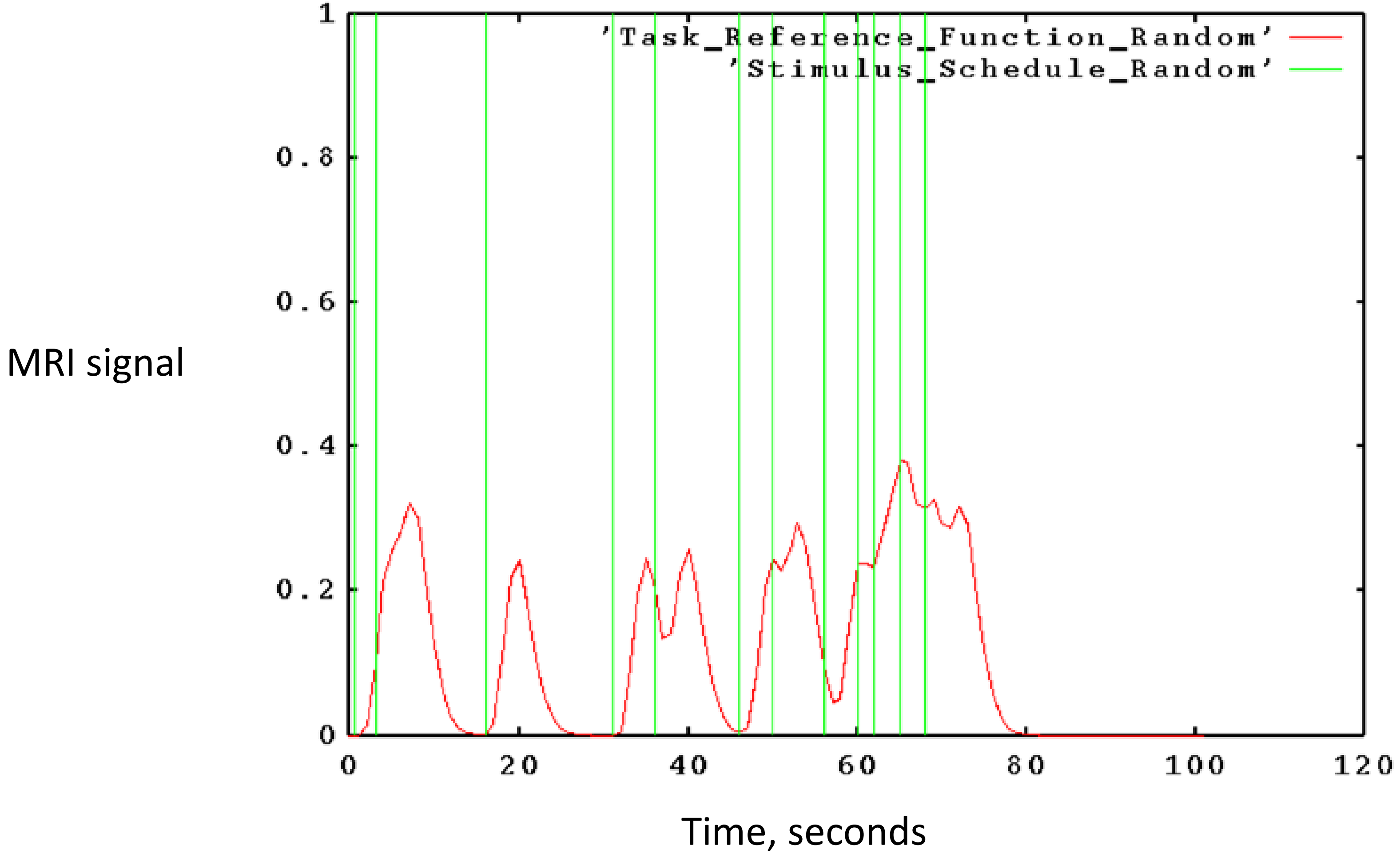
Block Design

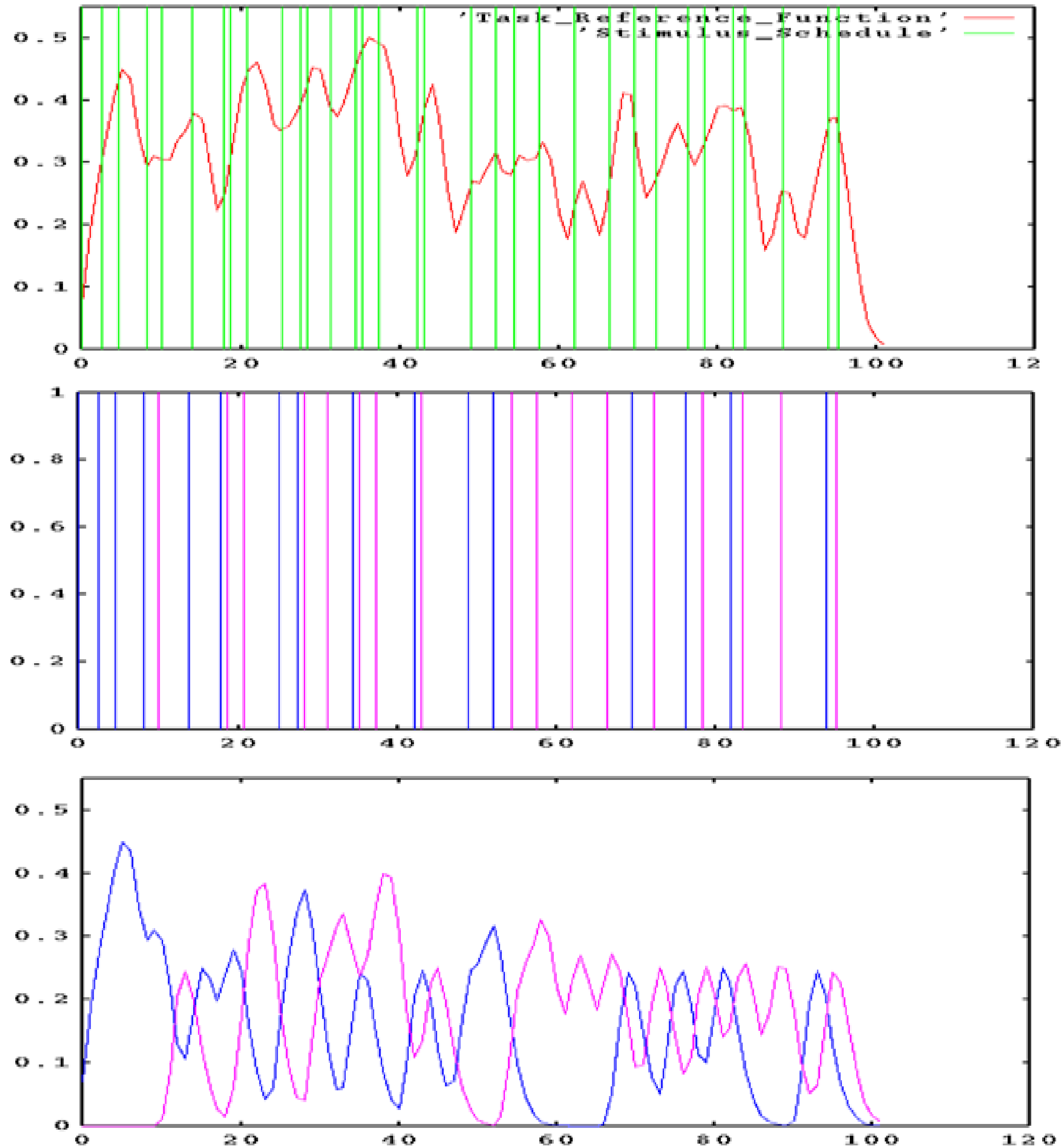


Activation of the anterior temporal lobes during listening to words.



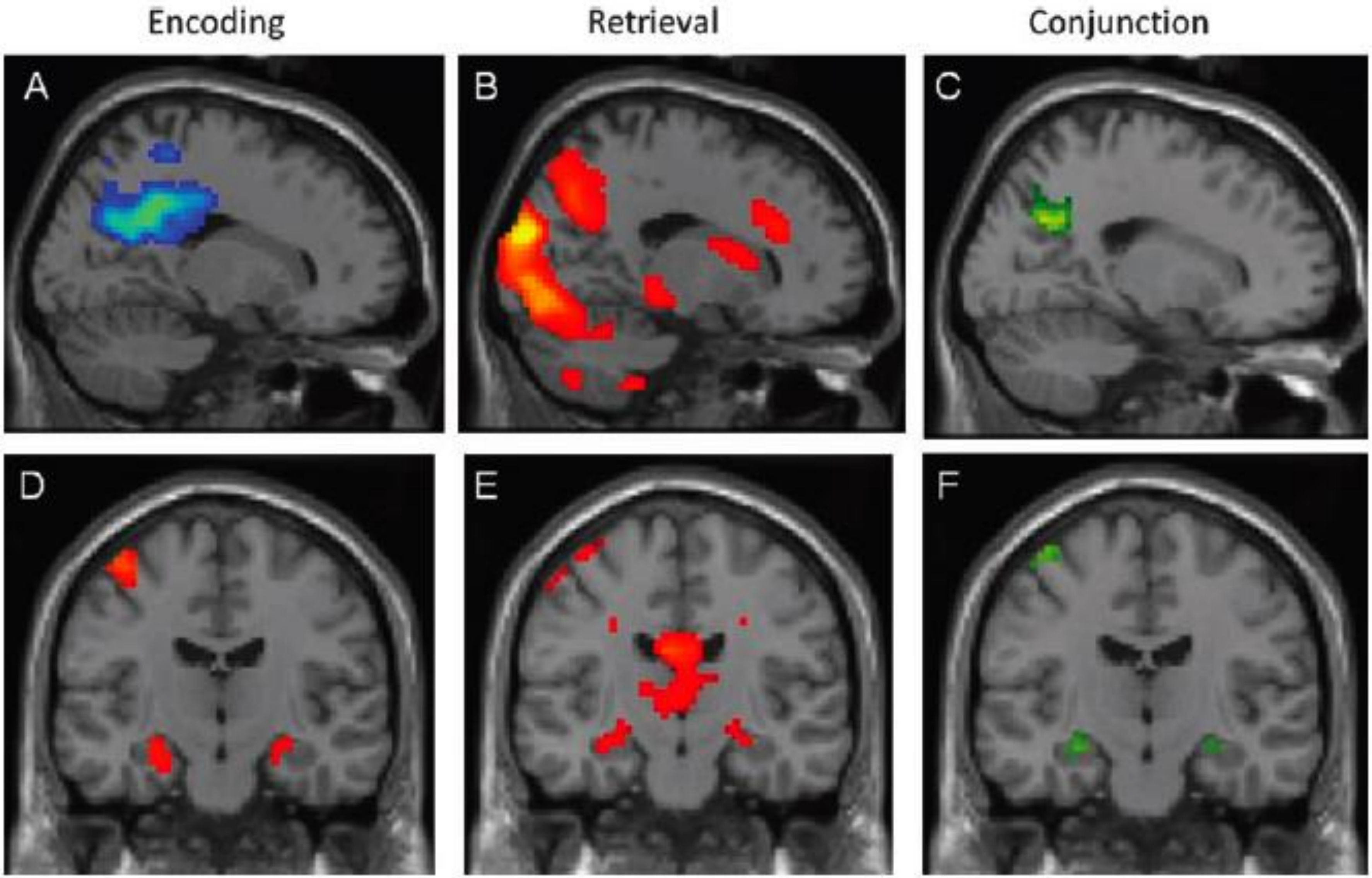
Event-Related Design





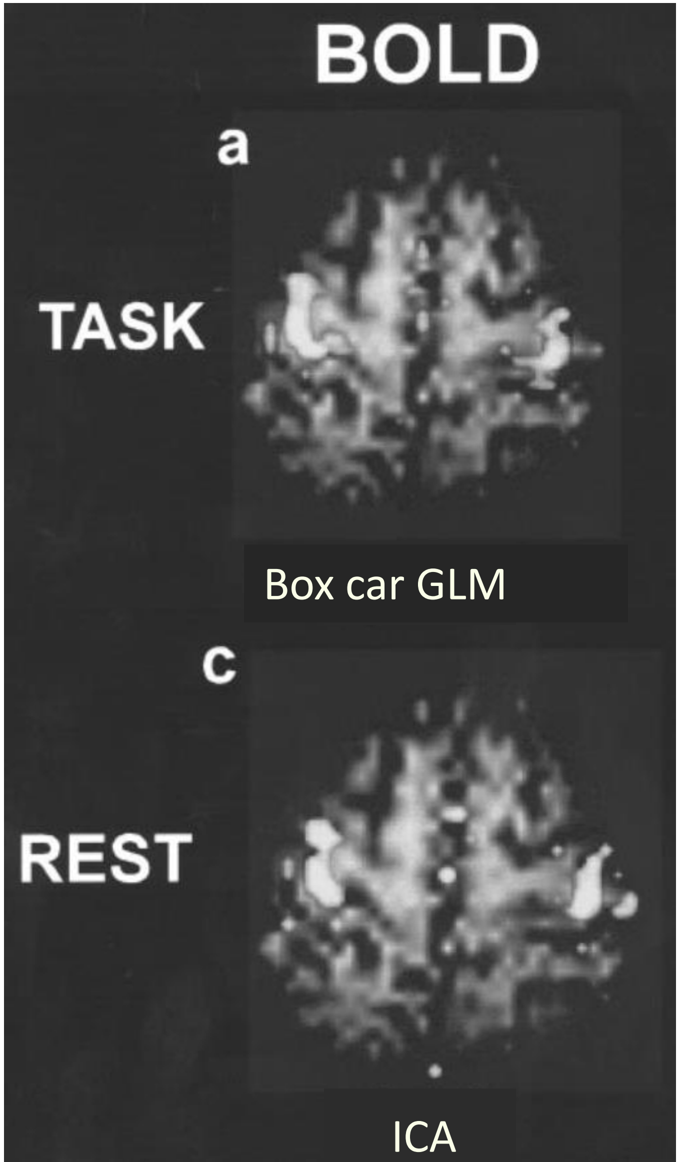
'Task_Reference_Function'
'Stimulus_Schedule'
0.5
0.4
0.3
0.2
0.1
0
20
40
60
80
100
12
1
0.8
0.6
0.4
0.2
0
20
40
60
80
100
120
0.5
0.4
0.3
0.2
0.1
0
20
40
60
80
100
120

Activation of hippocampus during successful memory encoding and retrieval



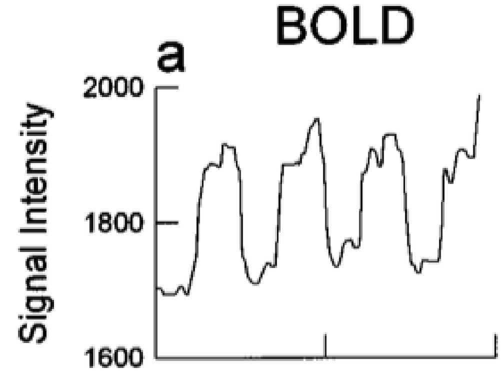
Two fMRI paradigms

- Activation paradigm
  - Signal model: predicted BOLD timecourse
- Functional connectivity paradigm
  - Signal model: correlated signal timecourses



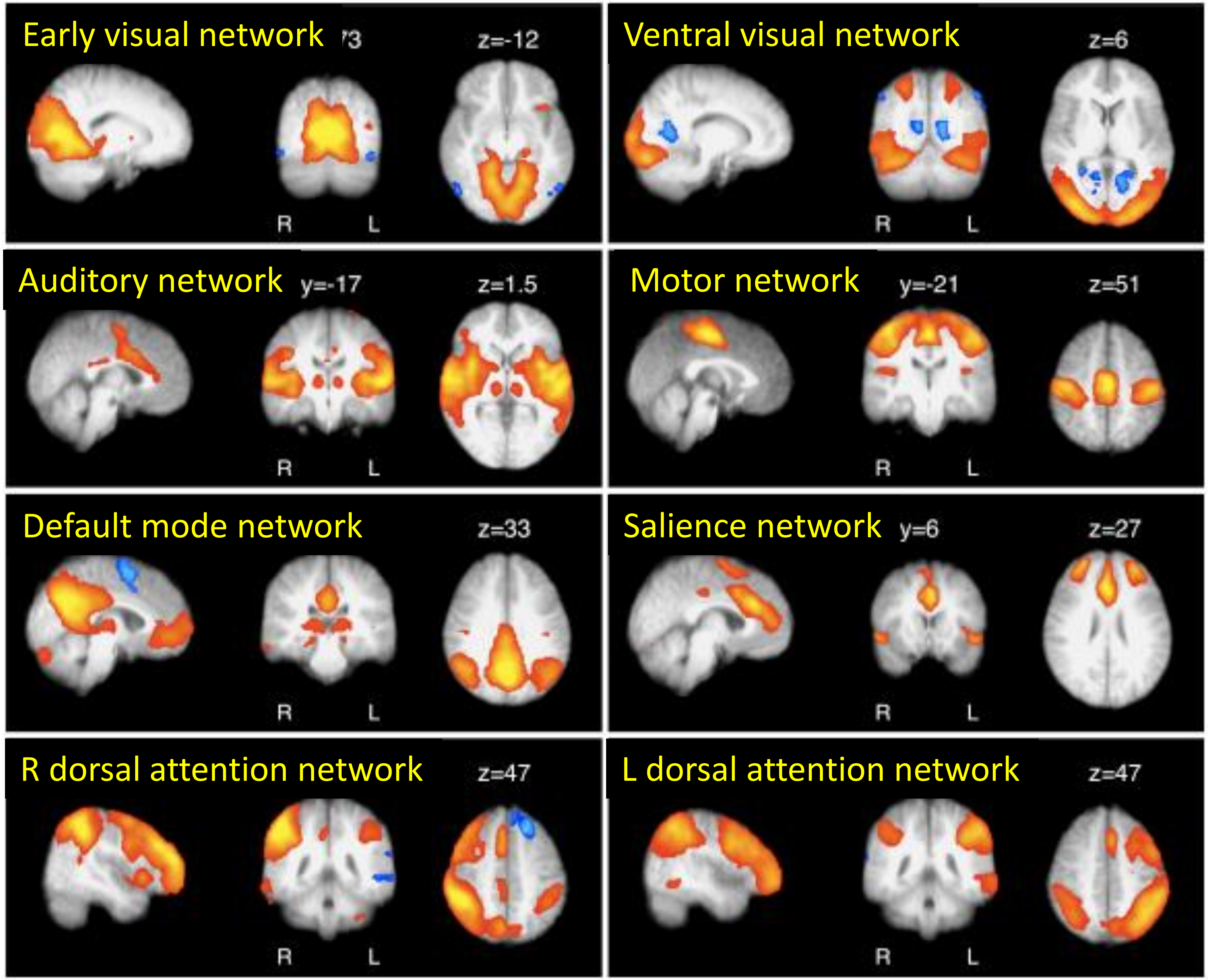
Biswal et al., 1997

Finger tapping



Resting

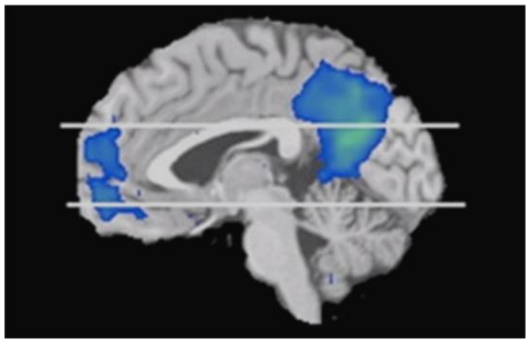
Fourier transform



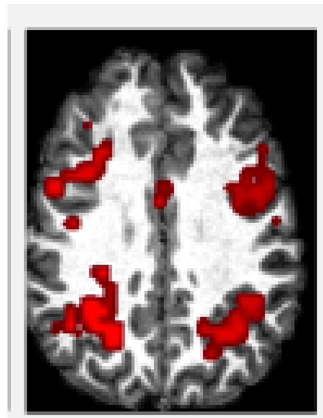
Damoiseaux et al 2006

"Default" Mode Network

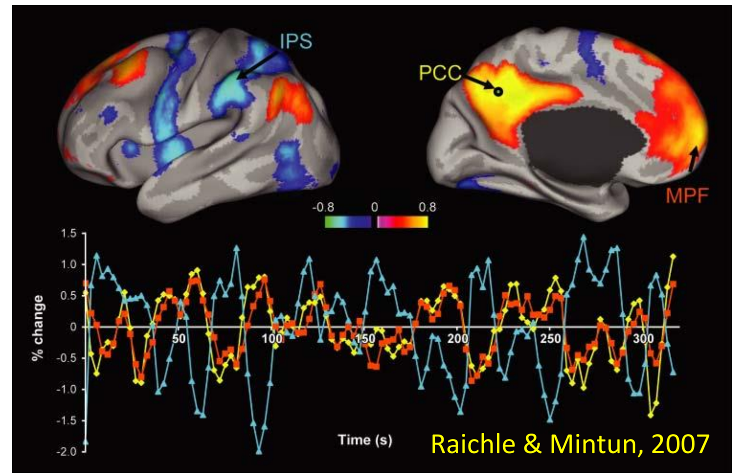
Relevance to adaptive behavior



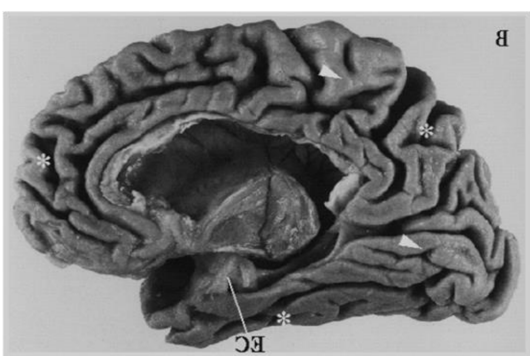
Deactivation DMN

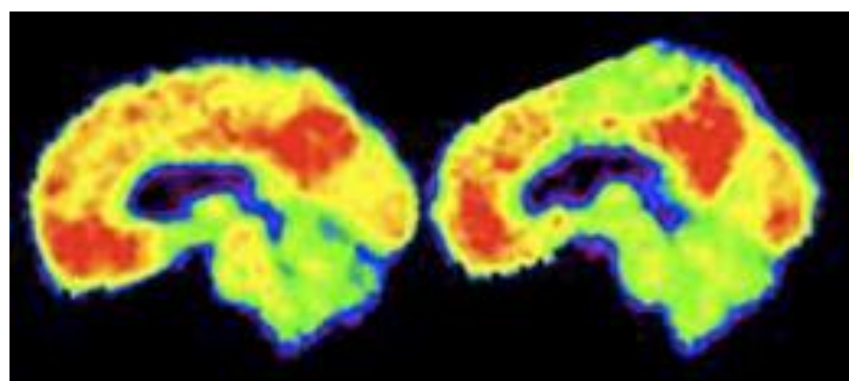


Activation DAN



Relevance to disease





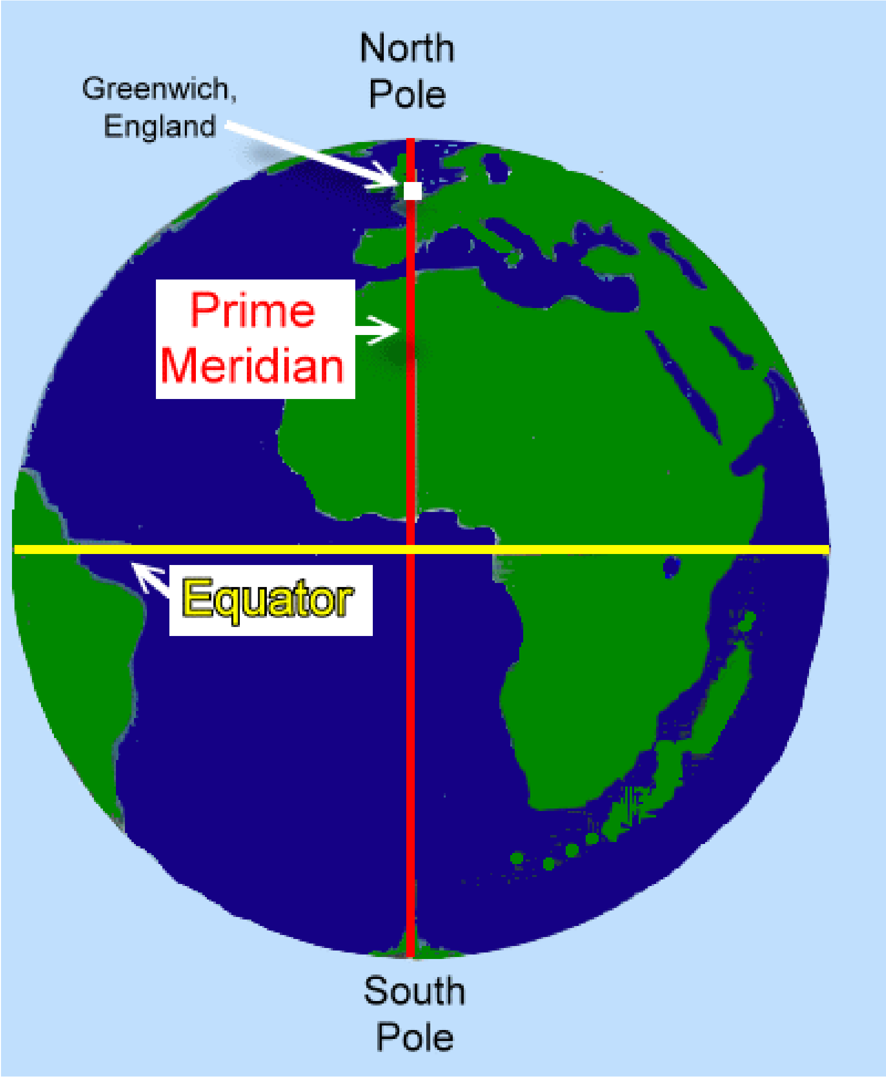
Summary: functional connectivity paradigm

- 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

Outline

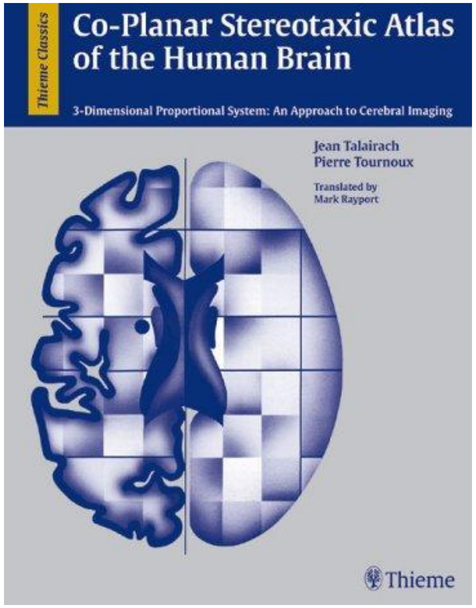
- The brain
- Brain imaging modalities
- Standard anatomical space
- Image processing

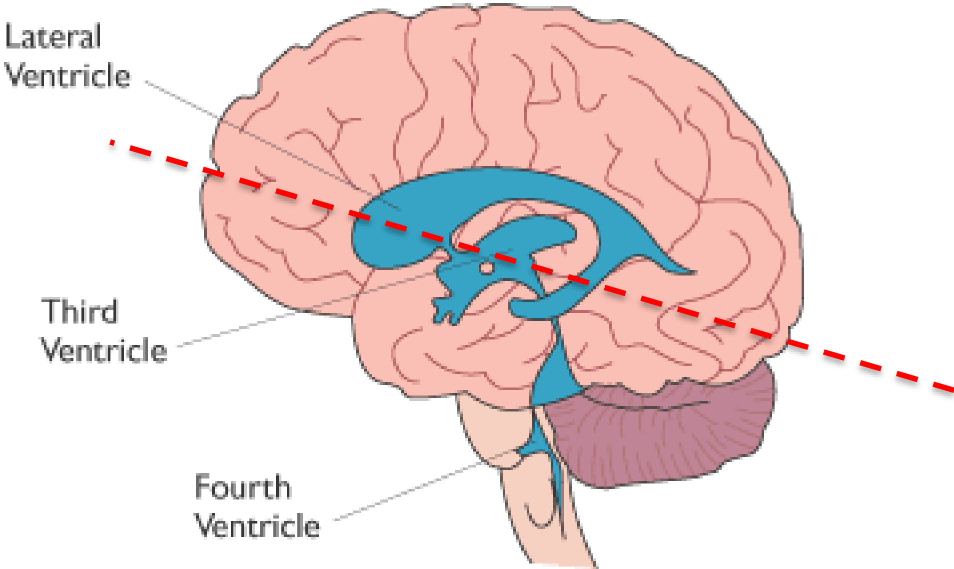
Anchoring standard space



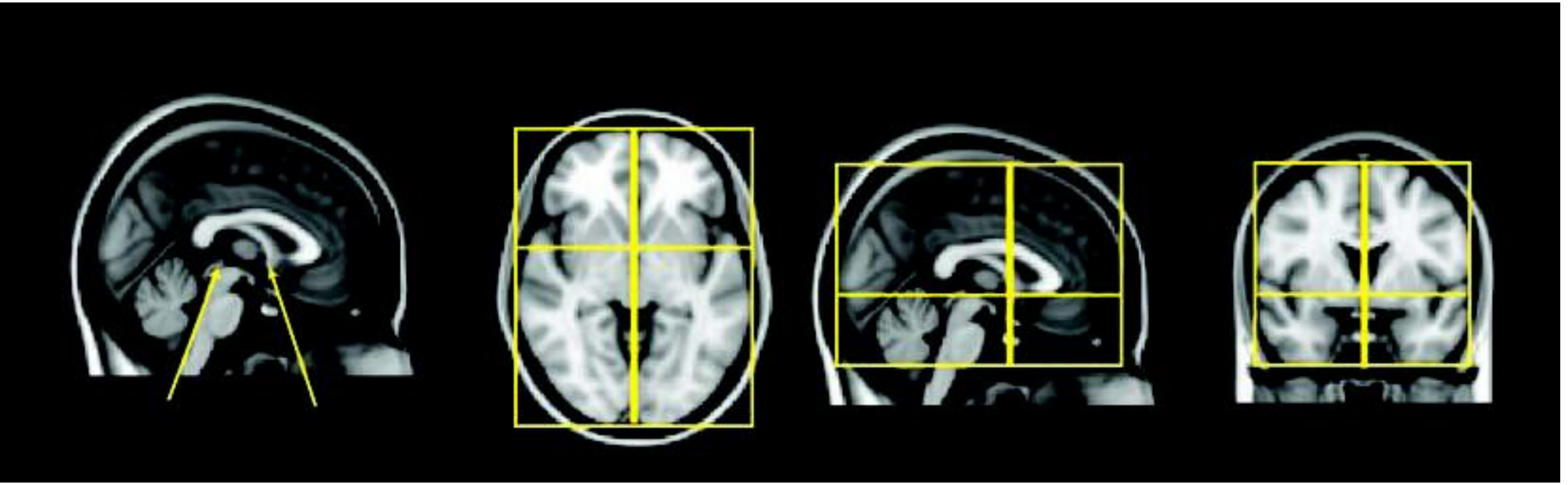
Anchoring standard space

The brain "equator" is the intercommisural line

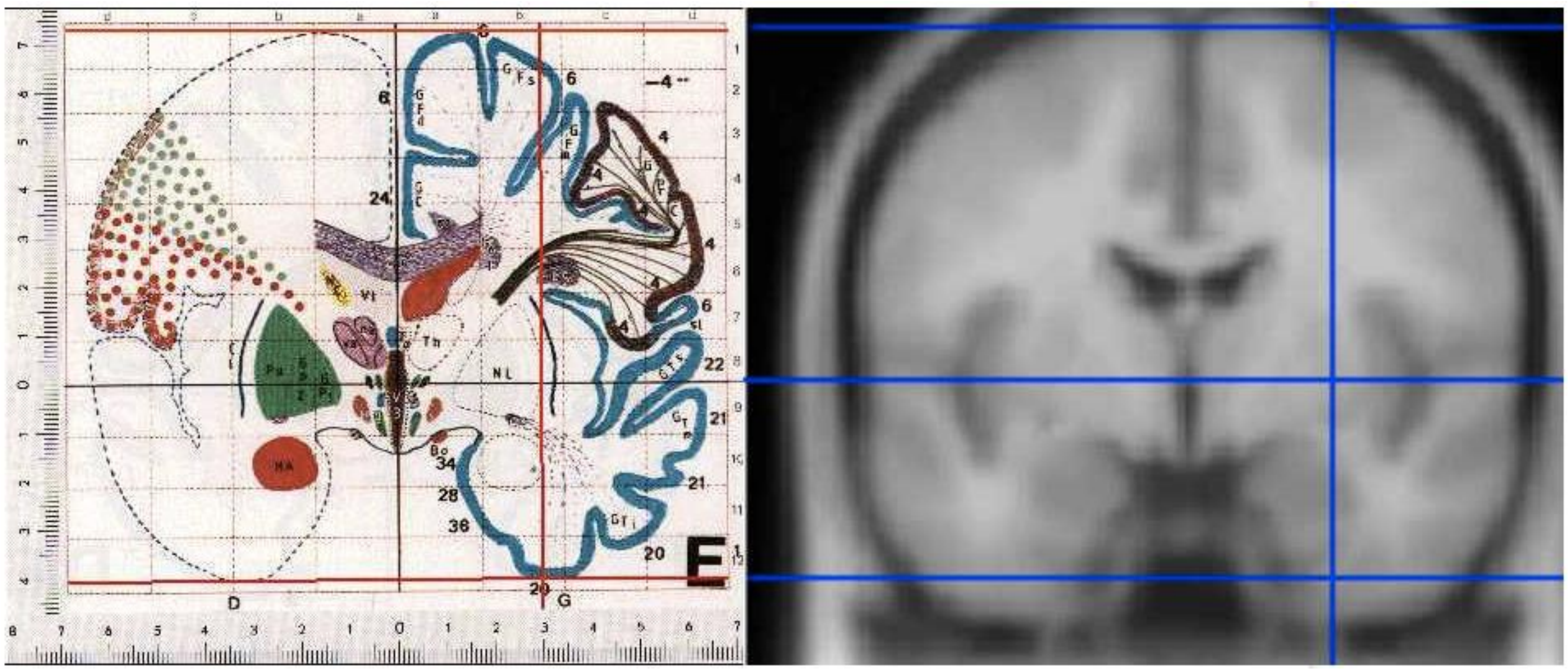


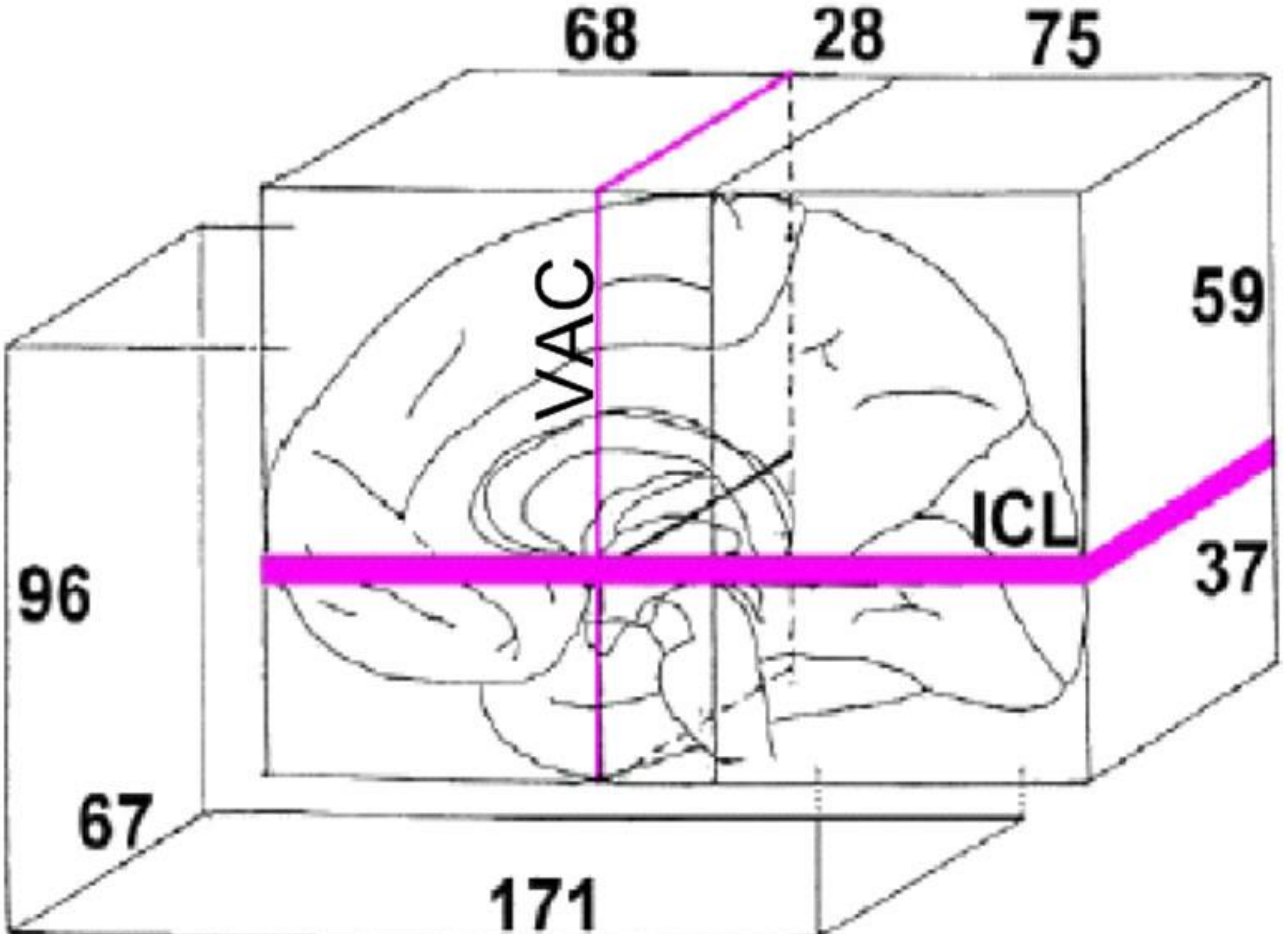


Talairach Space

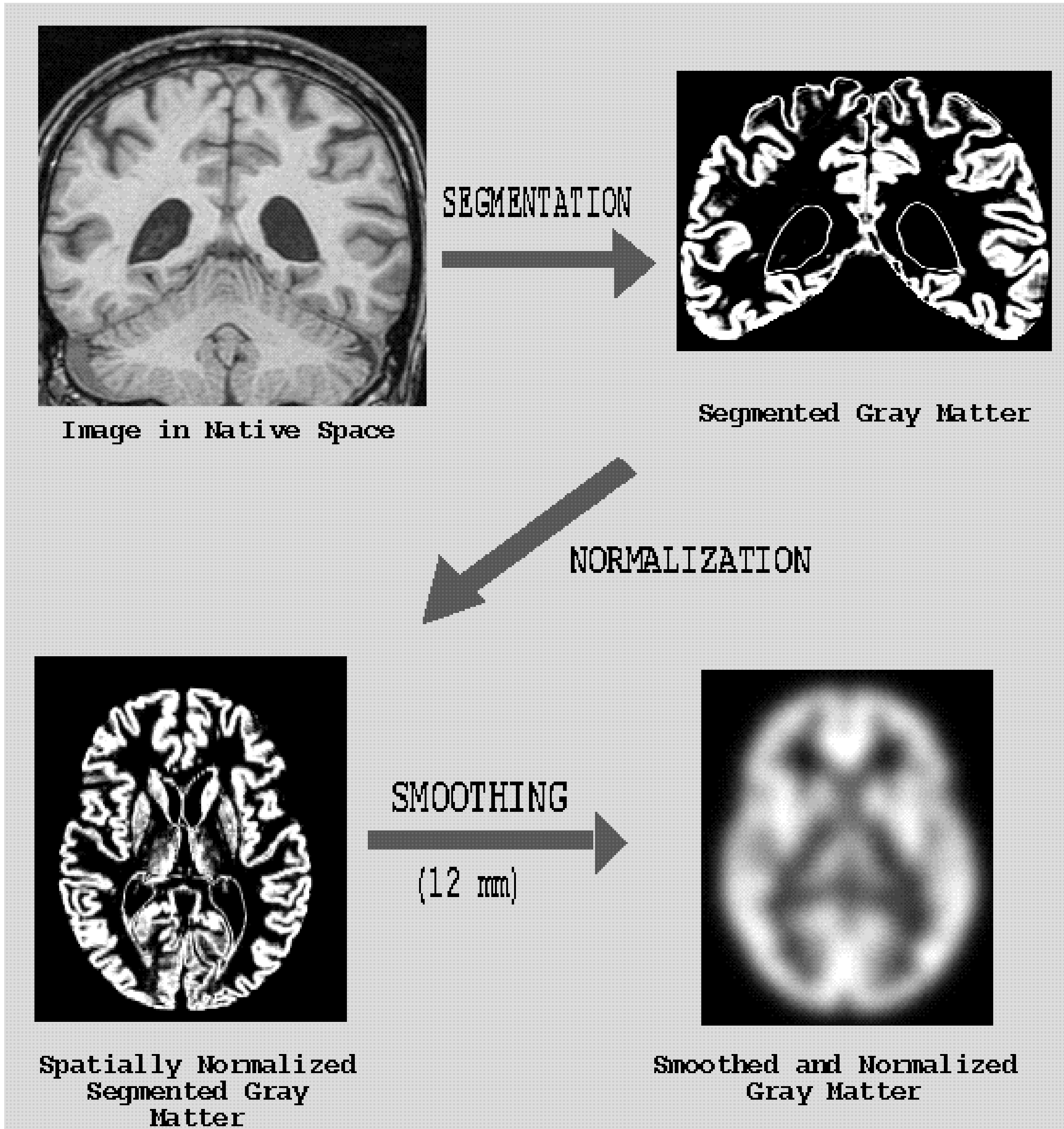


Talairach Space
Montreal Neurological Institute (MNI) space




68
28
75
VAC
59
ICL
37
96
67
171

Voxel-based morphometry



Limits on interpretation of spatial normalization

- Anatomic variability in Talairach space
  - 1.5 cm
- Irreducible cortical variability
  - This variability is itself variable
  - Cytoarchitecture adds another layer of variability
- Not always easy to assign results to one location
  - Local maximum of statistic field, vs center of mass
  - Extent-based statistics vs Magnitude-based statistics
- fMRI data are typically smoothed for SNR reasons

Outline

- The brain
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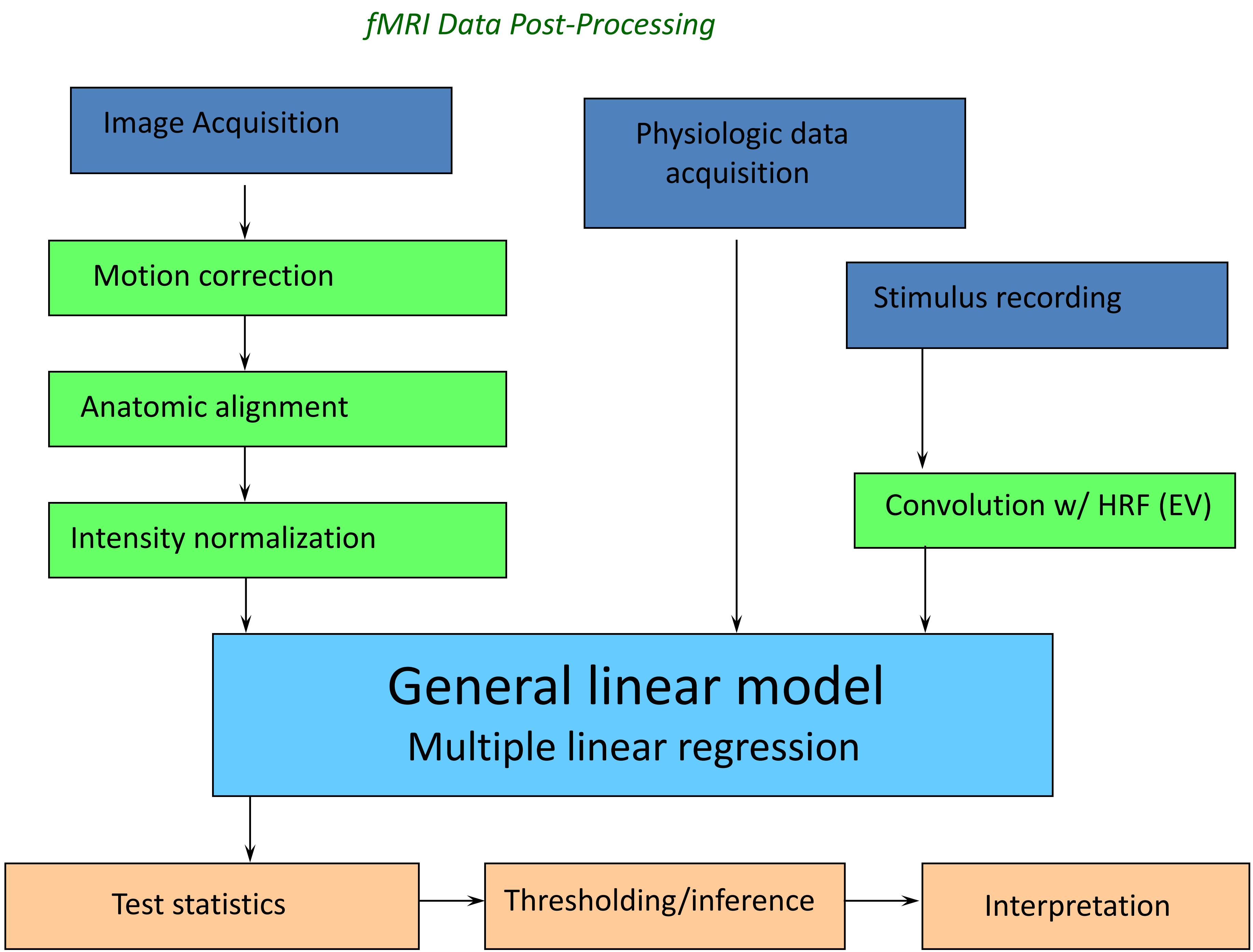
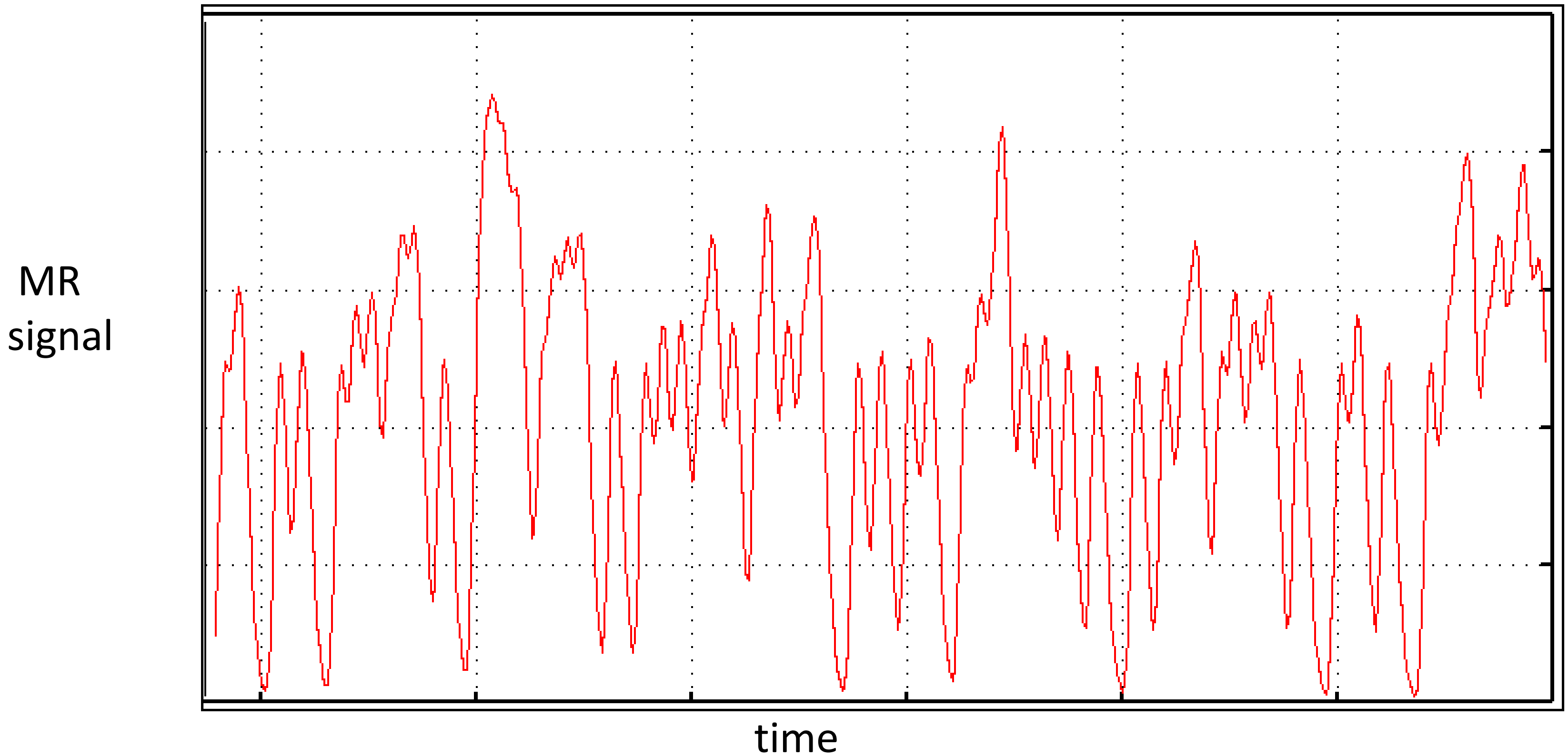

fMRI Data Post-Processing
Image Acquisition
Physiologic data acquisition
Motion correction
Stimulus recording
Anatomic alignment
Convolution w/ HRF (EV)
Intensity normalization
General linear model
Multiple linear regression
Test statistics
Thresholding/inference
Interpretation

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

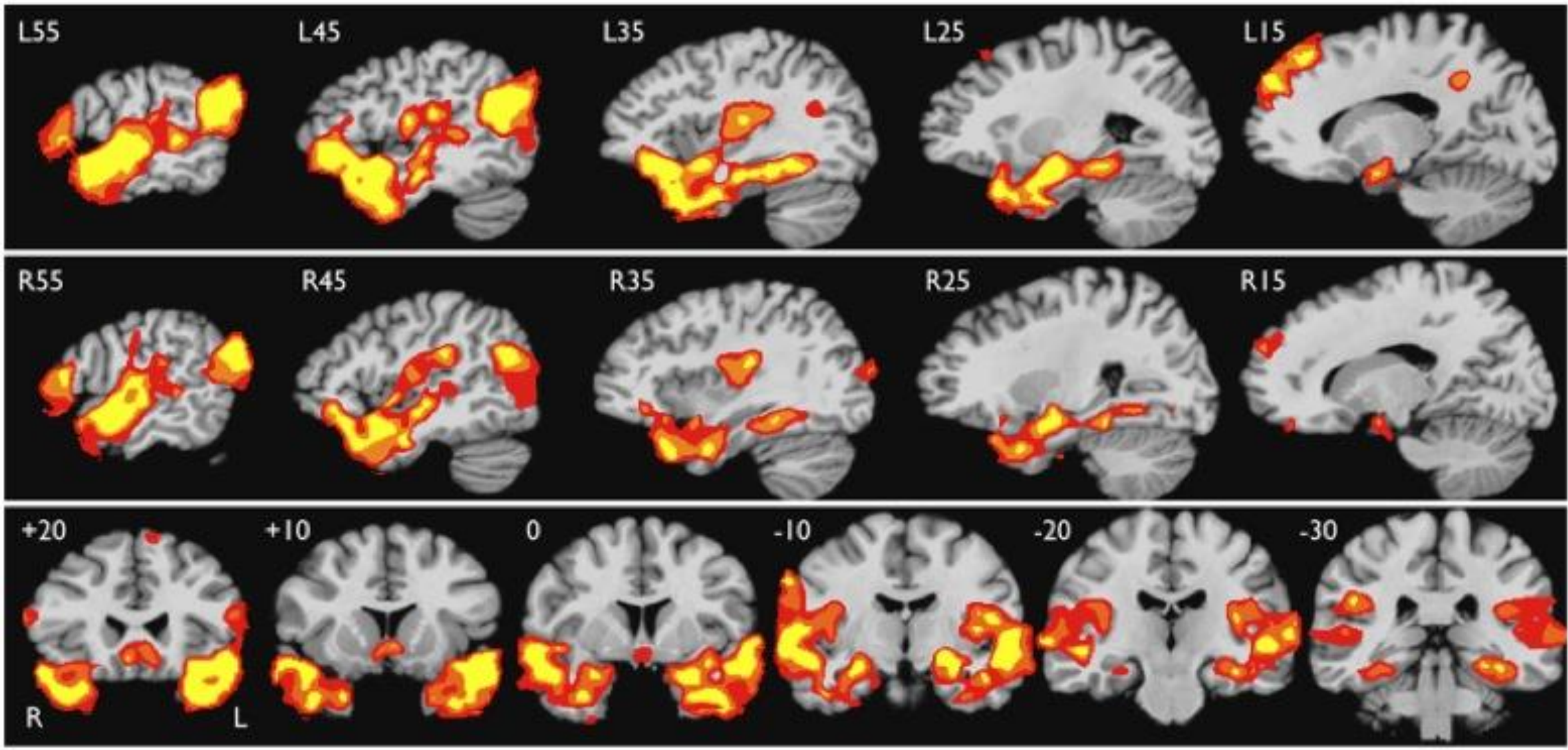
Statistical analysis

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

$$Y = \boldsymbol{\beta}_1 X_1 + \boldsymbol{\beta}_2 X_2 + \ldots + \varepsilon$$

  - The task effect is estimated by regression coefficient (β) and tested with a *t* statistic

Activation of the anterior temporal lobes during listening to words.



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 natural systems structure (columns, fields, large scale systems)
- Most of the techniques have not (YET) found their way into clinical application

Questions?