Statistical Challenges for Neuroimaging Data Analysis
Lecture 1. Introduction

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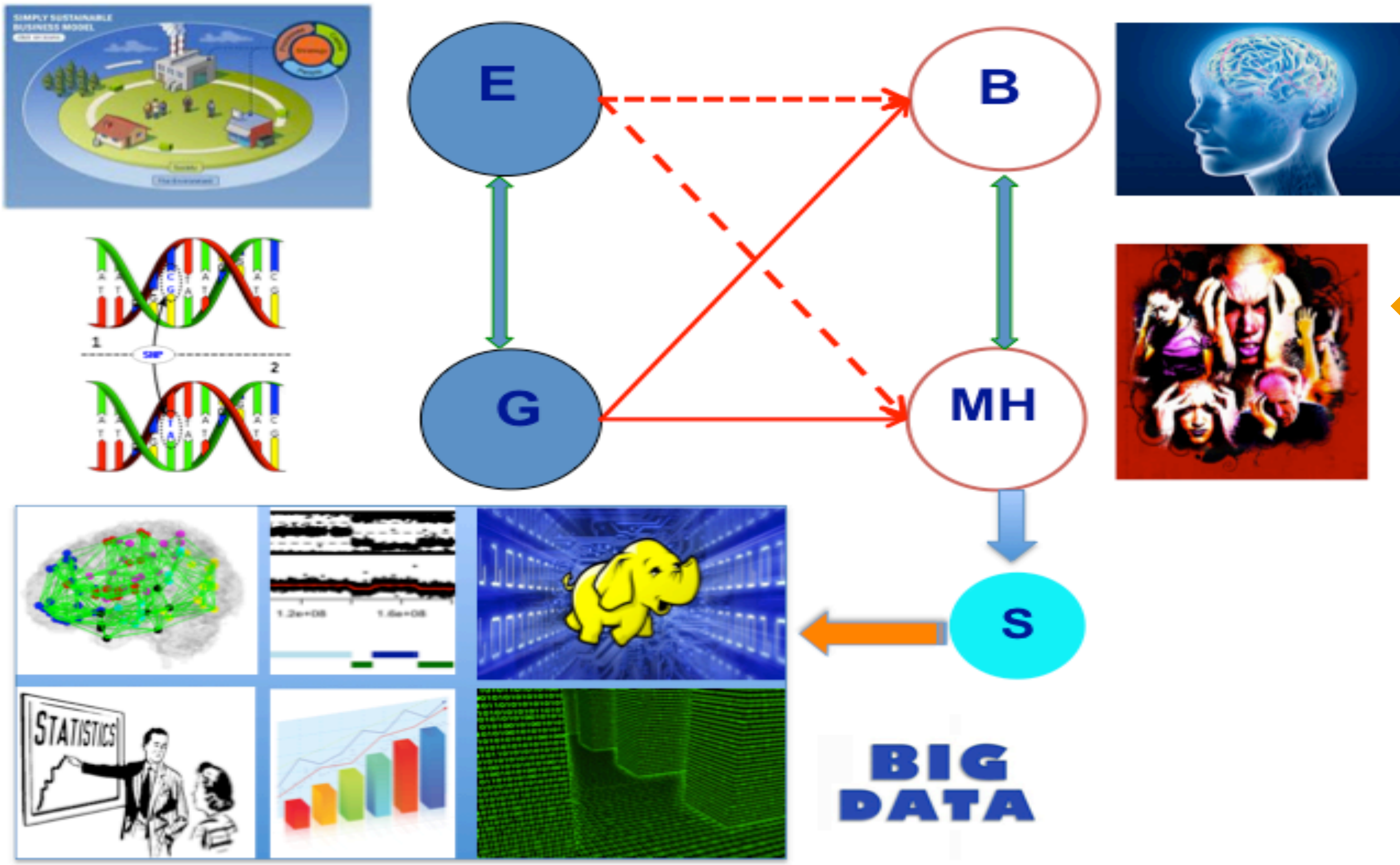
UNIVERSITY OF ALBERTA

"uplifting the whole people"

— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908

Big Data in Medical Science



Brain development

Brain tumor

Psychiatry

Neurology

Common Goal: Detect potential genes for inherited phenotypes

Reading Materials

1. Paul Suetens (2009). *Fundamentals of Medical Imaging*. Second edition. Cambridge University
2. Fass, L. (2008). Imaging and cancer: a review. Molecular Oncology. 115-152.
3. Ganguly, D., Chakraborty, S., Balitanas, M. and Kim, T. (2010). Medical Imaging: A Review. Communications in Computer and Information Science, 78, 504-516.
4. Lei (2012). *Statistics of Medical Imaging*. CRC press.

Acknowledgement: Some pictures were copied from multiple resources including Suetens (2009), Fass (2008), Dr. Niethammer, Drs. Lindquist, Rowe, Huettel, Wiki, gustaf@cb.uu.se, FSL, etc.

Part 1. Imaging Science

Imaging Science

From Wikipedia, the free encyclopedia

Imaging Science

is a multidisciplinary field concerned with the generation, collection, duplication, analysis, modification, and visualization of images.

As an evolving field, it includes research and researchers from

Physics, Mathematics, Statistics, Electrical Engineering, Computer Vision, Computer Science and Perceptual Psychology.

Three key components

- **Image acquisition:** studies the physical mechanisms and mathematical models and algorithms by which imaging devices generate image observations.

- **Image interpretation/application:** is to see, monitor, and interpret the targeted world/patterns being imaged.

- **Image processing:** is any linear or nonlinear operator that operates on the images and produces targeted patterns.

What is image?

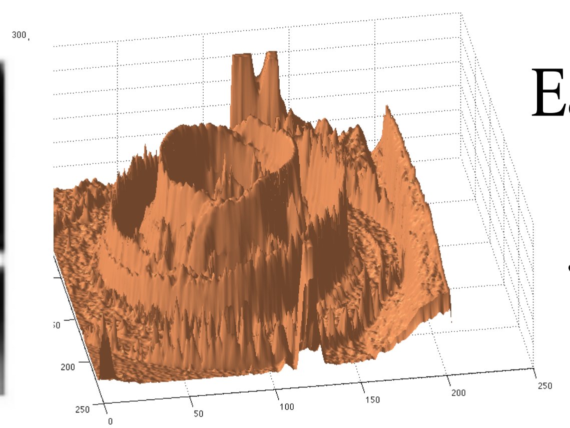
(i) In computer science an image is an exact replica of the contents of a storage device (a hard disk drive or CD-ROM for example) stored on a second storage device.
(ii) is an optically formed duplicate or other reproduction of an object formed by a lens or mirror.



What is image?

- *Mathematics. Image is the point or set of points in the range corresponding to a designated point in the domain of a given function.*
- As $\tilde{x} \in \Omega \subseteq R^k \; f(\tilde{x}) \in M \subseteq R^m \quad f : \Omega \to M \subseteq R^m$

Ω is a compact set.



Additional Conditions:

Each component of $f(\tilde{x})$ is nonnegative.

$$\int_\Omega \| f(\tilde{x}) \|^k \, d\tilde{x} < \infty \quad \text{for some } k>0$$

Digitized Images

Digitized Images $f : \Omega_0 \rightarrow \{0, 1, \cdots, M_0\}$

- **Sampling (grid points):** $\Omega_0 \in \Omega$
  - **An ordered array or a triangular array or etc;**
  - **A set of small cells of the same shape and size (pixels, voxels).**
  - **Sometime, it involves interpolation.**

- **Sampling Rate ensure that all the relevant information contained in the image is largely retained by sampling.**

- **Quantization: is a process of assigning the function value at each sampling point to one of the finite set of integers.**

Sampling Arrangements

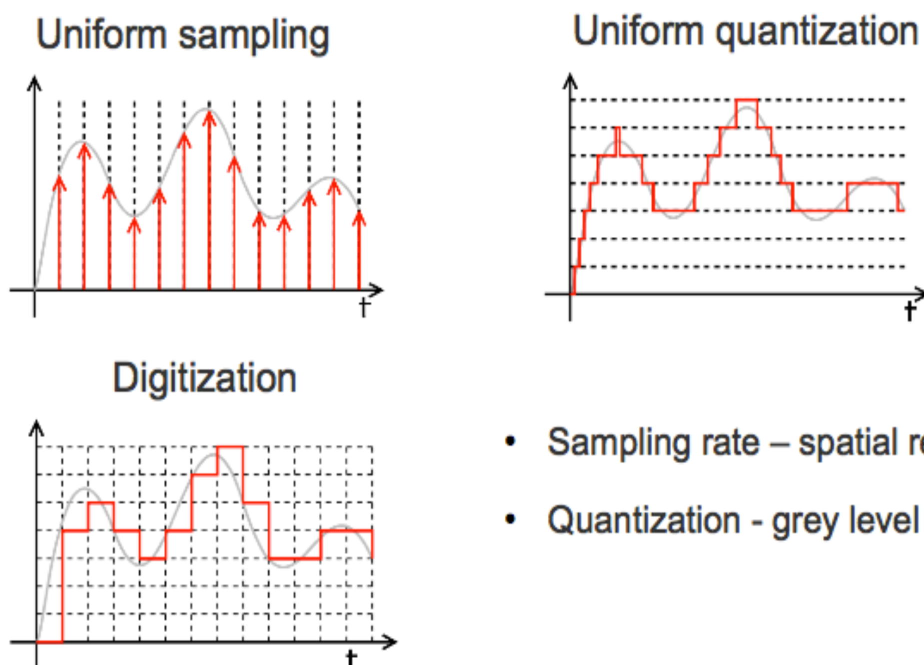
Uniform sampling Square grid, Rectangular grid, Hexagonal grid

•Non-uniform sampling Closer where it is necessary, eye.

•Image size 128*128, 256*256, 512*512,

•The sampling is normally determined by the sensor arrangement

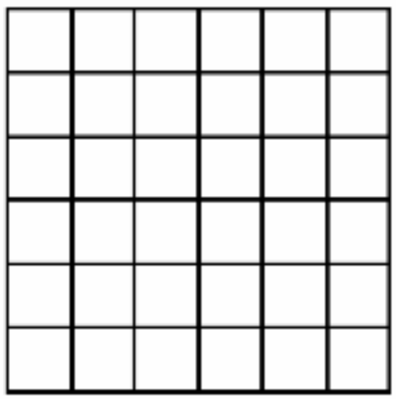
Digitization



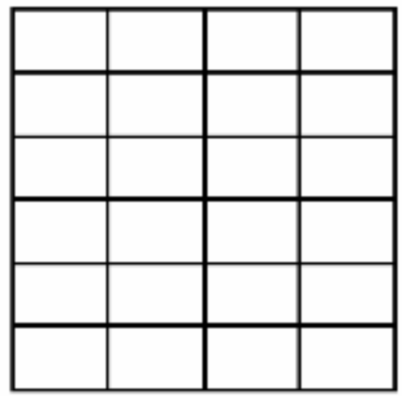
- Sampling rate – spatial resolution
- Quantization - grey level resolution

Images from Wikimedia Commons

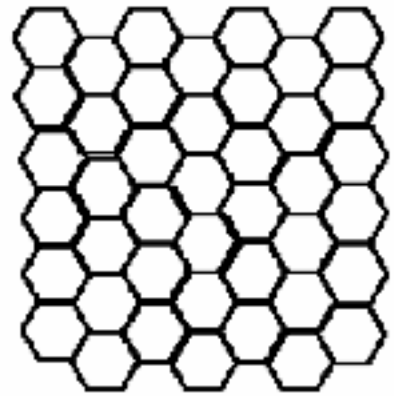
Representation and Connectivity 2D



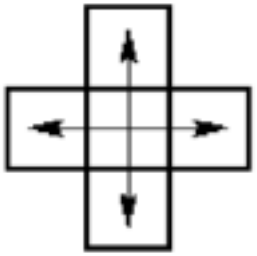
Square



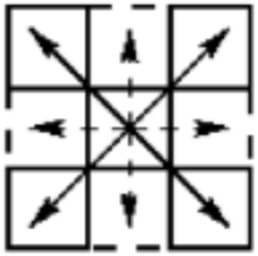
Rectangular



Hexagonal



4 connectedness



8 connectedness

6 connectedness

General Digital Image

$$f(x,y,z,t,s):\Omega \rightarrow \{0,1,\cdots,M_0\}$$

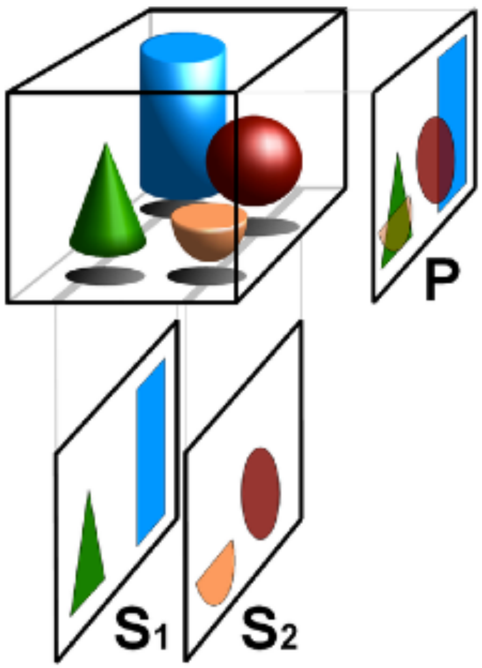
- Spatial parameters

  (x,y,z)
- Time parameters

  t
- Spectral parameters

  s
- A limited range of values

  M_0



- Spatial resolution
- Temporal resolution
- Spectral resolution

  Range of wave-length

  Number of color
- Gray scale resolution

The spectral resolution of a frequency spectrum is a measure of its ability to resolve features in the electromagnetic spectrum.

Part 2. Image acquisition

Imaging Devices

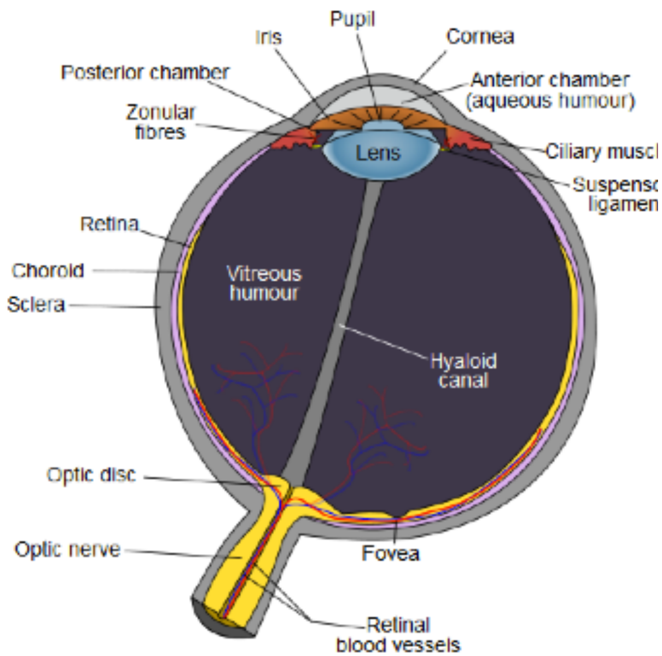


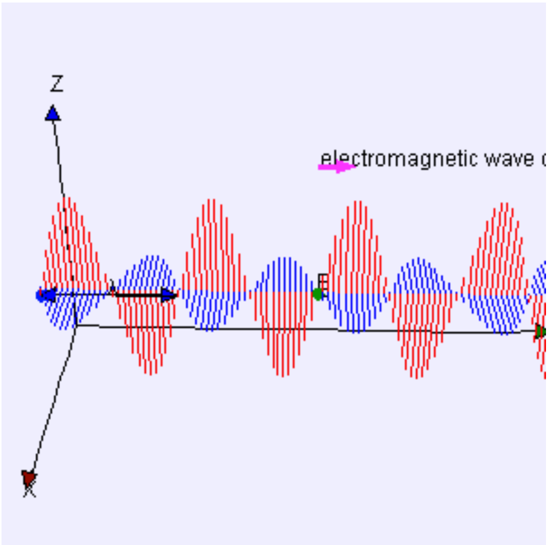
Figure 5.13 PET scanner. A movable table shifts the patient through the circular hole in the gantry. The external design is similar to that of a CT scanner and to some extent to that of an MRI scanner. (Courtesy of the Department of Nuclear Medicine.)

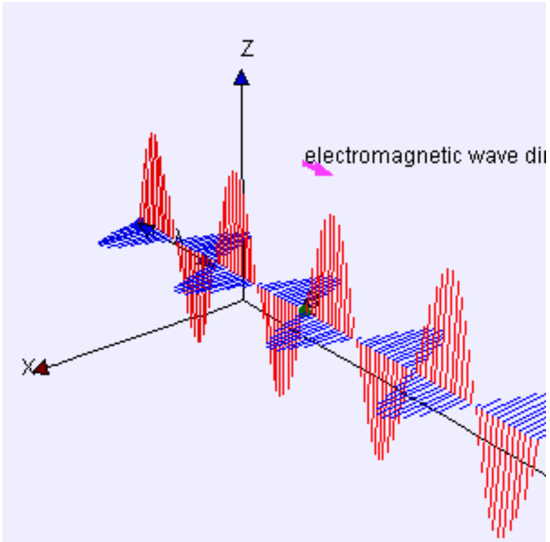
Targets

- Electromagnetic waves (most technologies)
- Sound (ultrasound)
- Particles (electron microscopy)
- Mechanical contact forces (scanning probe microscopy)

Electromagnetic Waves

Electromagnetic radiation (**EM radiation** or **EMR**) is a form of energy emitted and absorbed by charged particles, which exhibits wave-like behavior as it travels through space. EMR has both electric and magnetic field components, which stand in a fixed ratio of intensity to each other, and which oscillate in phase perpendicular to each other and perpendicular to the direction of energy and wave propagation.





Electromagnetic Waves

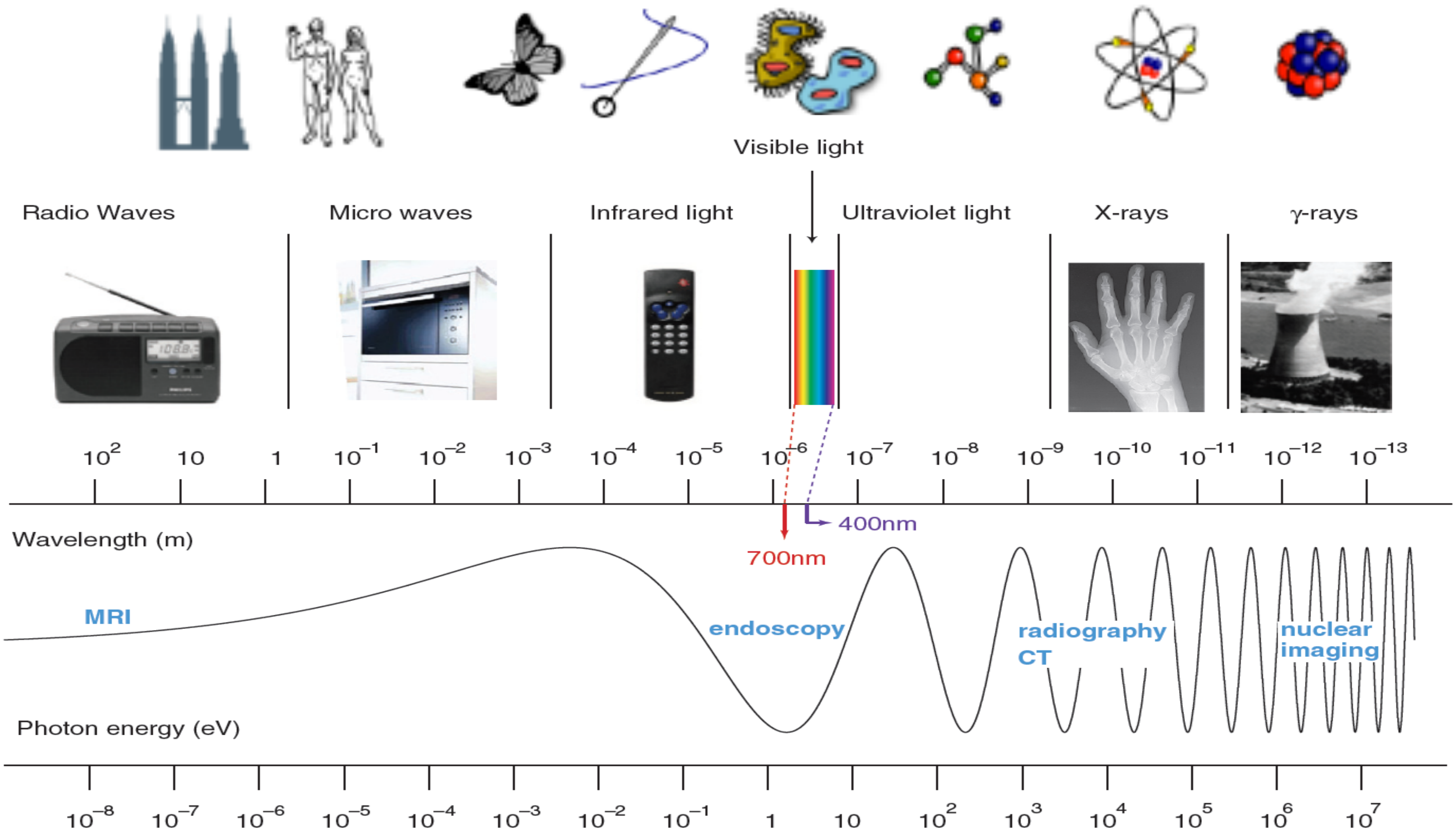


Figure 2.1 The electromagnetic spectrum.

nm (nanometer, E-9m)

Electromagnetic Imaging

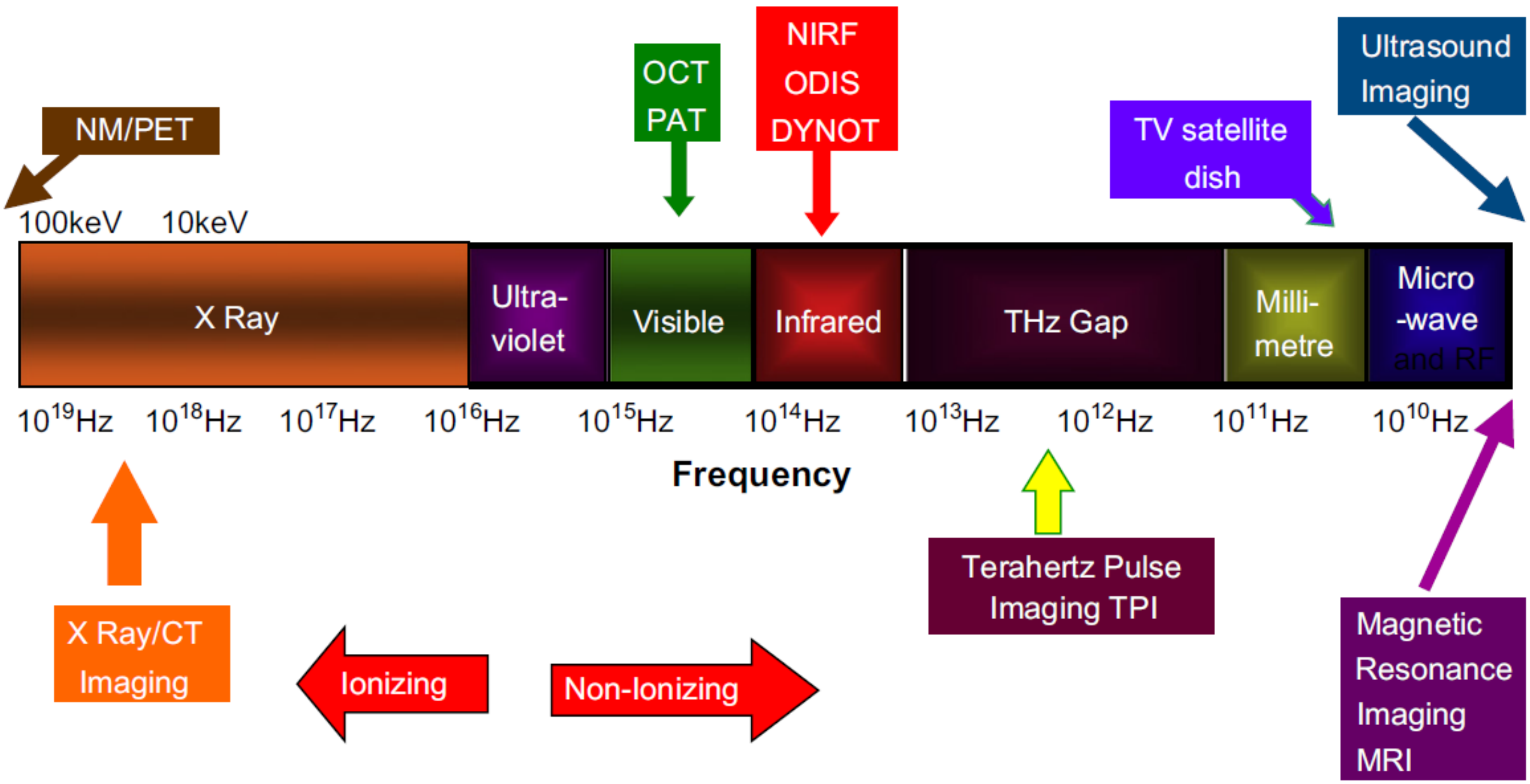


Figure 4 – Frequency spectrum of electromagnetic radiation imaging technologies.

Electromagnetic Imaging

- Radio range: radio astronomy, MRI
- Microwave range: RADAR
- Visible range: Standard camera, light microscopy
- X-ray range: CT, micro-CT
- Gamma range: Gamma camera

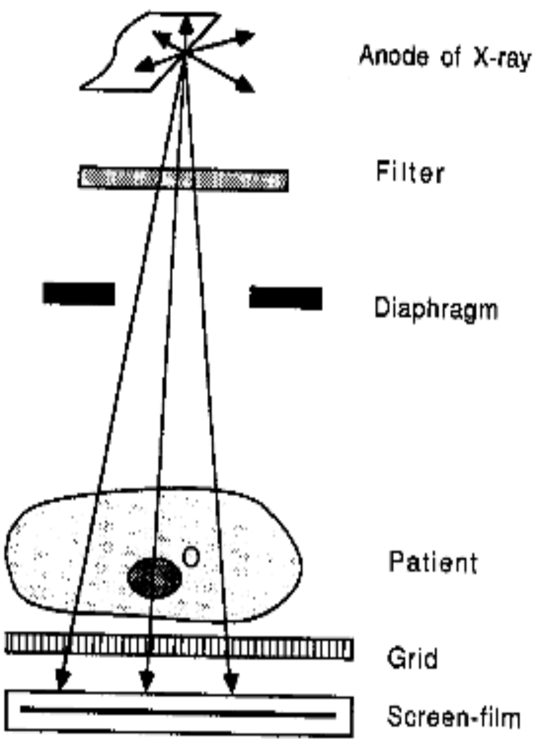
Medical imaging

From Wikipedia, the free encyclopedia

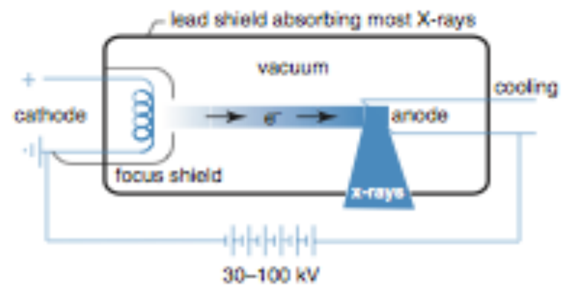
- Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology).
- 2010, 5 billion medical imaging studies were done worldwide.
- Radiation exposure from medical imaging in 2006 made up about 50% of total ionizing radiation exposure in the United States.

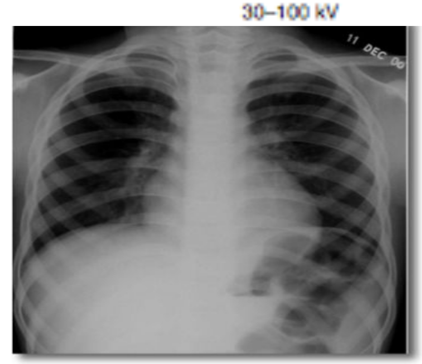
X-rays

X-rays are ionizing waves consisting of photons traveling at the speed of light with energy E=hf



- X-rays produced by a tube.
- Filtered to removed undesired energy.
- Restriction to illuminate organ of interest.
- Grid removes scattered radiation.
- Recording of image on electronic plate (or film).





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— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908

Computed Tomography (CT)

Computed Tomography (3D X-rays) is an imaging method employing tomography created by computer. Digital geometry processing is used to generate a 3D image of the inside of an object from a large series of 2D X-ray images taken around a single axis of rotation.

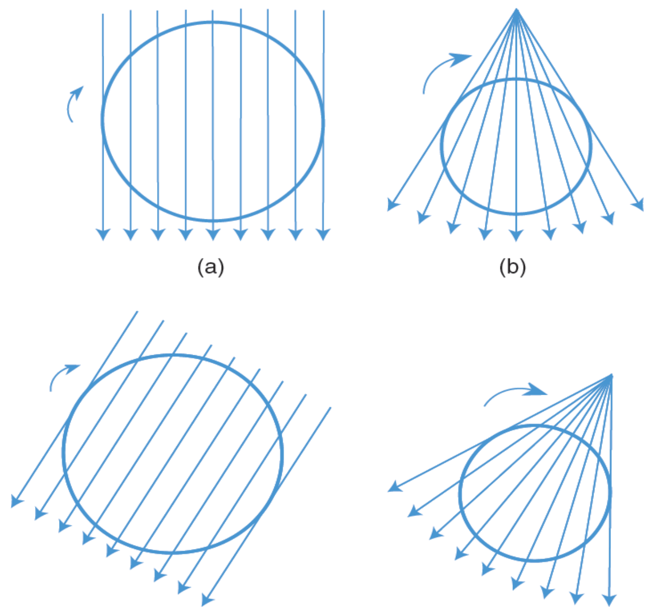


Figure 3.2 Basic scanning procedure in CT. A set of lines is scanned covering the entire field of view: **(a)** parallel-beam geometry and **(b)** fan-beam geometry. This process is repeated for a large number of angles (**c** and **d**).

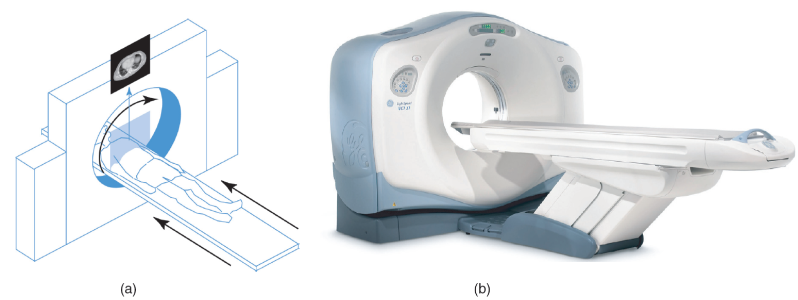
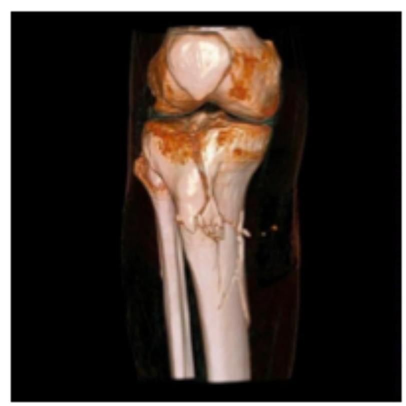
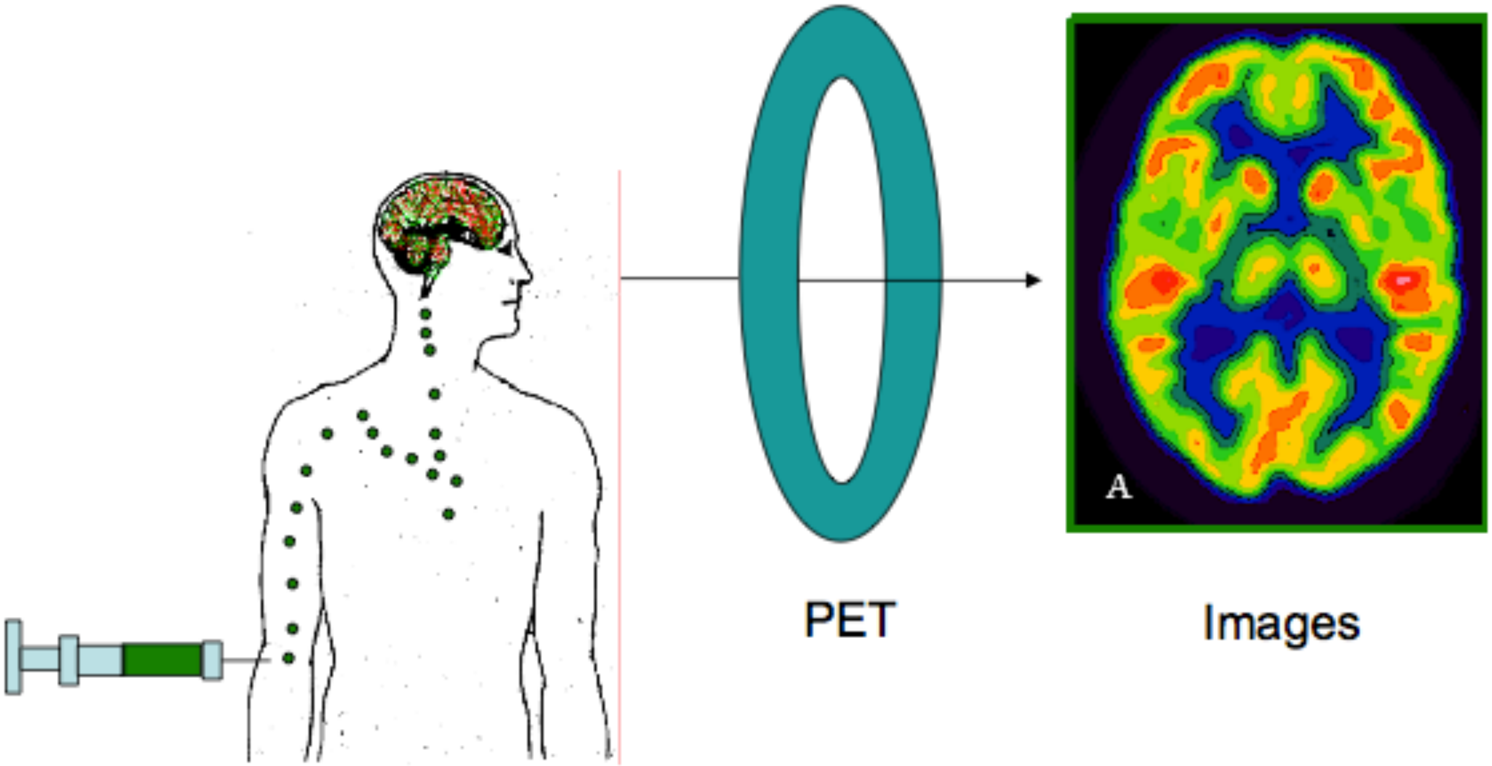


Figure 3.1 **(a)** Schematic representation, and **(b)** photograph of a CT scanner. (Courtesy of GE Healthcare.)



SPECT and PET

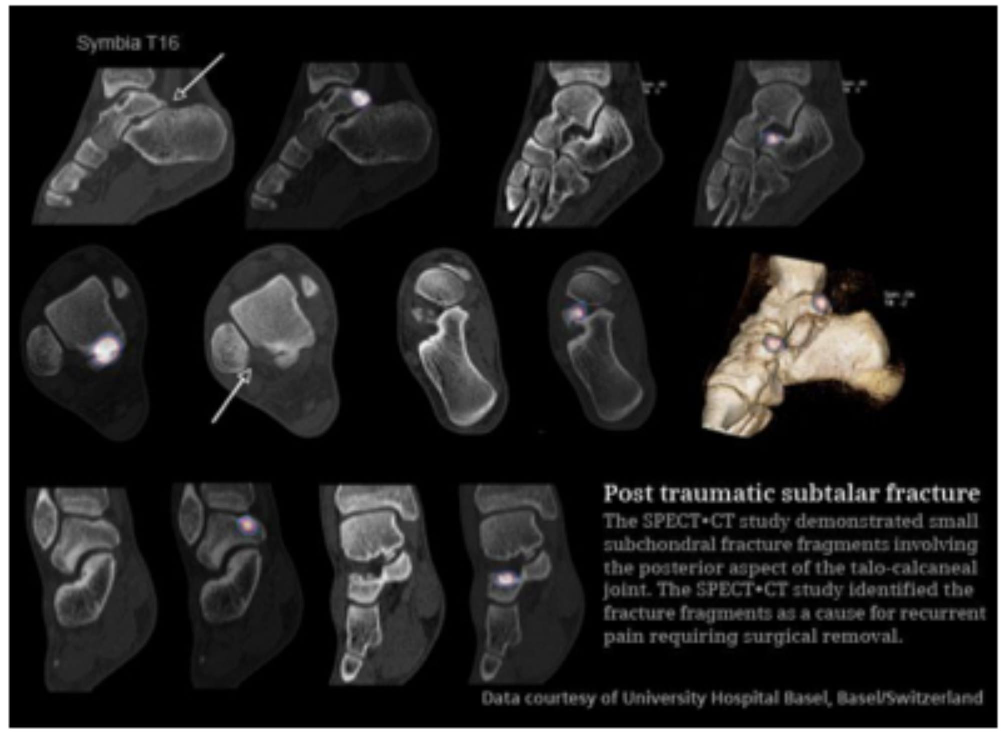


SPECT

SPECT=Single-Photon Emission Computed Tomography
is a nuclear medicine tomographic imaging technique using gamma rays for measuring the blood flow to the brain.

Radio-labeled chemical (ECD or HMPAO) is quickly injected at time of seizure onset to detect the region of increased blood flow, which is associated with seizure activity.

By comparing the intraictal scan (imaged during seizure) and the interictal scan(imaged without seizure), the regions of activation in the brain are detected to locate the seizure origin.

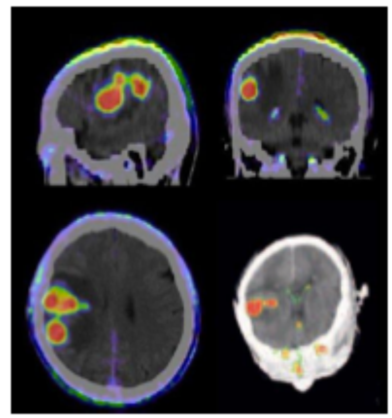


http://www.youtube.com/watch?v=I6V6VLxQIkY

PET

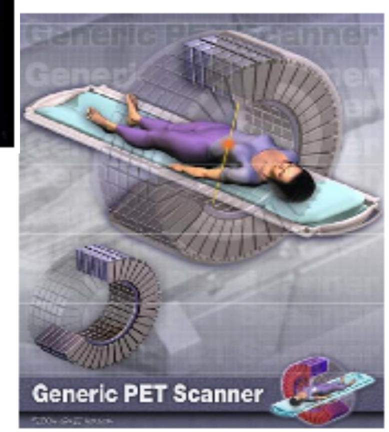
PET=Positron Emission Tomography **is a functional imaging technique to extensively study the relationship between energy consumption and neuronal activity. It uses positron-emitting radioactive tracers that are attached to molecules that enter biological pathways of interest.**

FDG: Fluorodeoxyglucose (similar to Glucose).



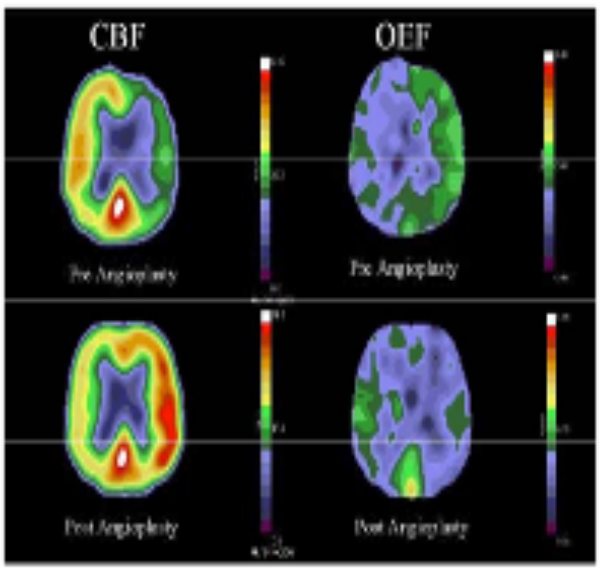
Brain uses glucose as major source of energy. normal brain picks up FDG in a large amount.

In epilepsy, the brain cell (neuron) does not function right or the neurons are lost due to a variety of reasons.



FDG-PET scan detects the regions of brain where the Glucose uptake is low (hypo-metabolism), which is often associated with the site of seizure origin.

PET measures and tracers



Reduced Cerebral Blood Flow (CBF) and elevated compensatory Oxygen Extraction (OEF) before and after carotid artery angioplasty (stroke risk)

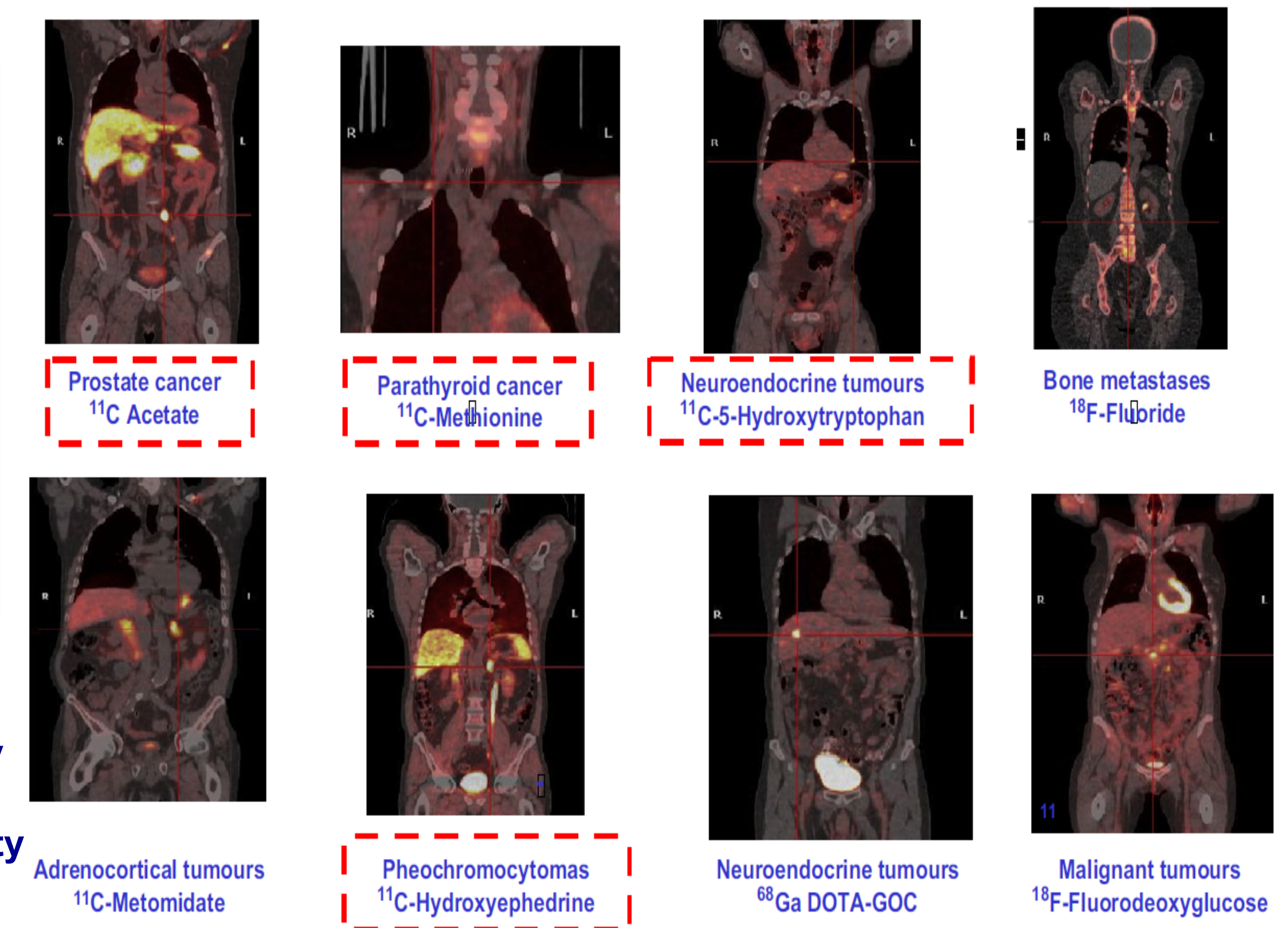


Figure 13 – Examples of PET tracers in oncology where endogenous substances are framed (courtesy of Imanet Uppsala).

PET and SPECT

PET and SPECT scan is different from CT, MRI or Ultrasound, which detect structure changes and anatomy, can provide physiological and molecular information of brain.

PET and SPECT are clinically indicated for pre-surgical localization of seizure origin. They are covered by most insurance providers.

They provide valuable seizure localization information in addition to MRI scan, EEG and clinical assessment to the surgeons.

Ultrasound imaging

Ultrasound imaging involves exposing part of the body to high-frequency sound waves to produce pictures of the inside of the body.

- Because ultrasound images are captured in real-time, they can show the structure and movement of the body's Internal organs, as well as blood flowing through blood vessels.

- When a sound wave strikes an object, it bounces back, or echoes. By measuring these echo waves it is possible to determine how far away the object is and its size, shape, and consistency (whether the object is solid, filled with fluid, or both).

- In medicine, ultrasound is used to detect changes in appearance of organs, tissues, and vessels or detect abnormal masses, such as tumors.

Ultrasound imaging of fetus

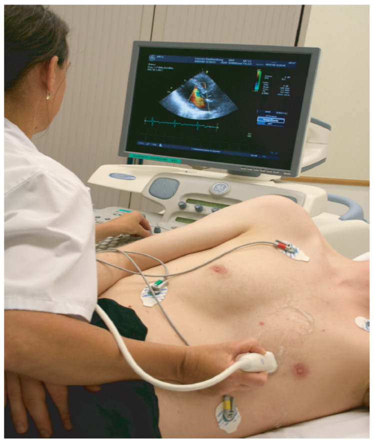
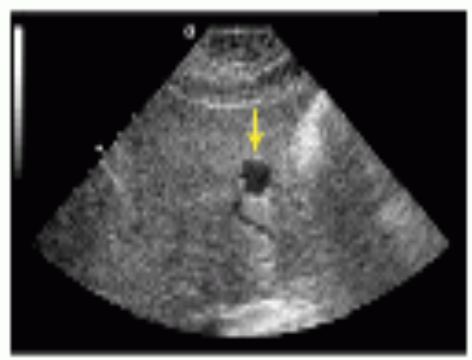


Figure 6.34 Example of a commercial echocardiographic scanner. (Courtesy of the Department of Cardiology.)

Fetus at 14 weeks

Fetus at 29 weeks

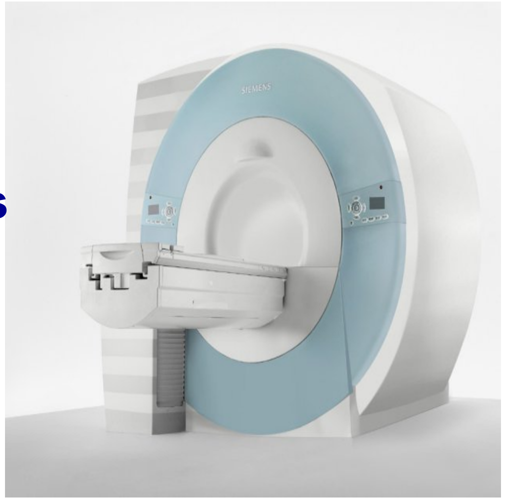
2D transducer: general appearance



Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is to visualize detailed internal structures. The good contrast is provided between the different soft tissues of the body make it useful in brain, muscles, heart, and cancer.
No ionizing radiation.

It uses a powerful magnetic field to align the magnetization of some atoms in the body, then uses radio frequency fields to systematically alter the alignment of this magnetization. This causes the nuclei to produce a rotating magnetic field detectable by the scanner.



Paul Lauterbur and Peter Mansfield were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging".

https://www.youtube.com/watch?v=N3VJHjALUEo

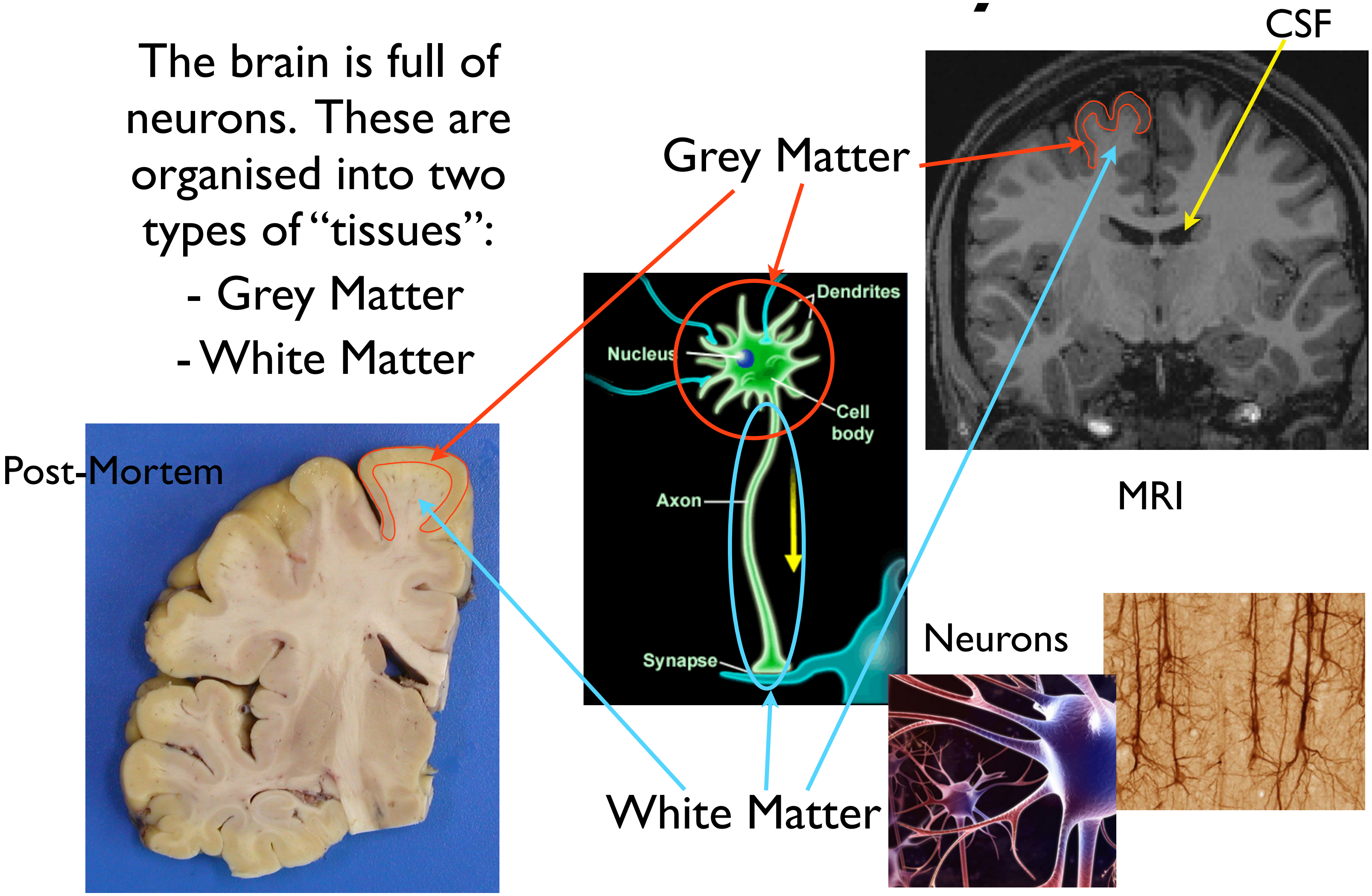
Magnetic Resonance Imaging

- The subject is placed into the MR scanner.
- The nuclei of ^1H atoms align with the magnetic field.
- Within a slice of the brain, a radio frequency pulse is used to tip over the aligned nuclei.
- Once the pulse has been removed, the nuclei strive to return to their original aligned positions and thereby induce a current in a receiver coil.
- A signal is created.

Magnetic Resonance Imaging

The brain is full of neurons. These are organised into two types of "tissues":

- Grey Matter
- White Matter

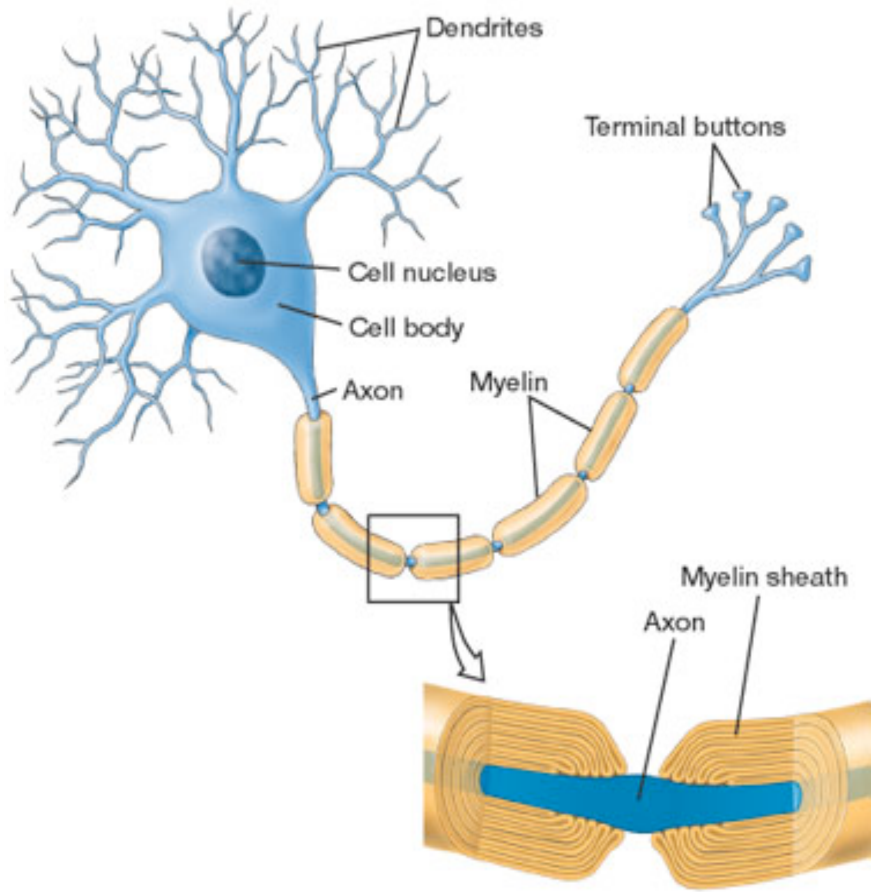


Magnetic Resonance Imaging

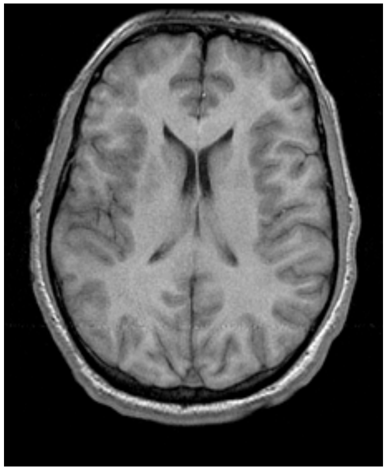
Neurons are densely connected and have *many* dendrites

Axons conduct electrical signals and are surrounded by *myelin*

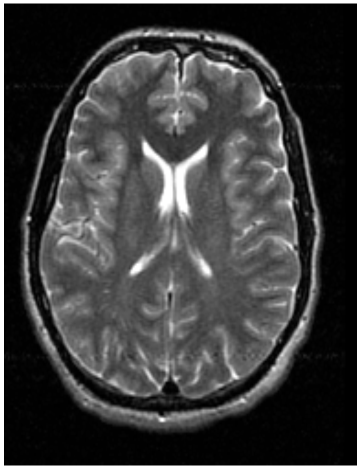
Myelin is a major factor in determining the MR signal and contrast



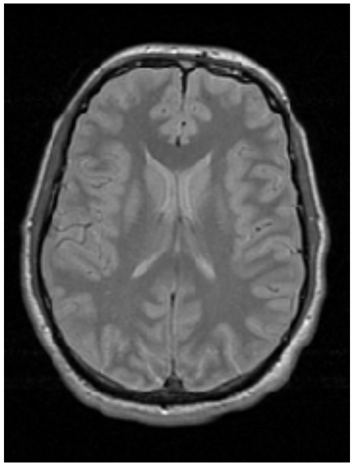
Magnetic Resonance Imaging



T_1-weighted



T_2-weighted



Proton Density

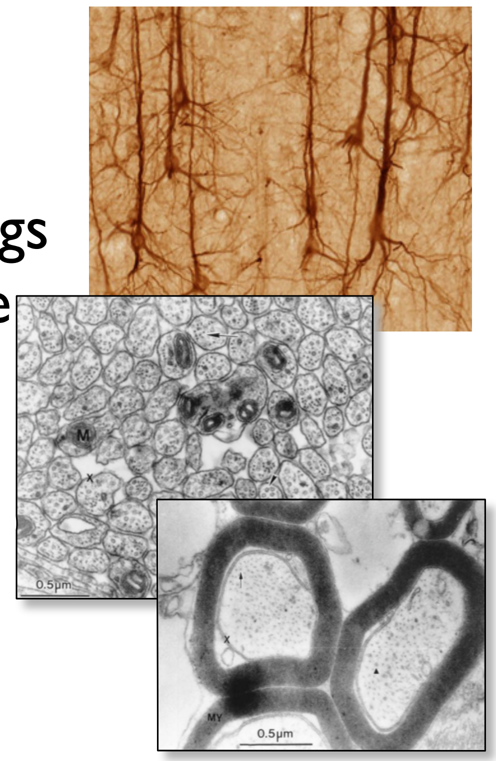
- Images gross brain anatomy
- Time depends on SNR & resolution (typ. 5-15 mins)
- Many different (and good) varieties of sequences to acquire these images

Magnetic Resonance Imaging

- 3 main quantities involved here:
  - Density of **water** & fat (proton density)
  - T_1 relaxation time
  - T_2 relaxation time

- Relaxation times depend on *many* things (*e.g.* molecular tumbling speed) but are sensitive to micro-environment and hence "tissue type"

- Intensity is usually a complicated weighting of different factors

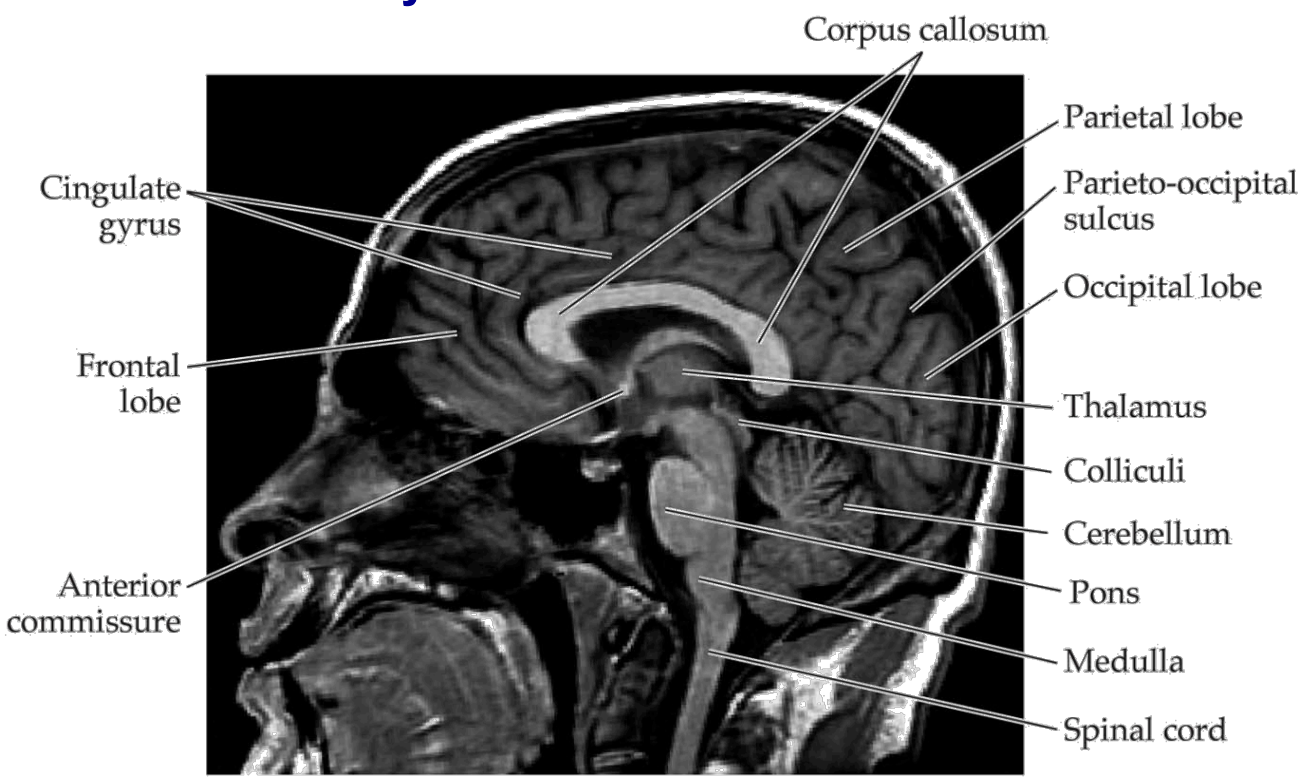


Magnetic Resonance Imaging

- Does *not* measure tissue type (GM/WM/CSF) directly
- It is not quantitative
- T_1 and T_2 values vary within GM and WM
  (but this can be interesting!)
- Partial volume average of signals
- Does not distinguish bone from air
- Contrast can be poor/variable in subcortical regions
- Single sequence does not show all pathologies
- Artefacts and noise

Magnetic Resonance Imaging

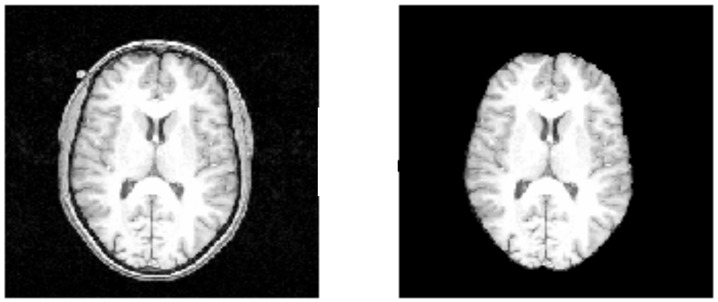
MRI studies brain anatomy.



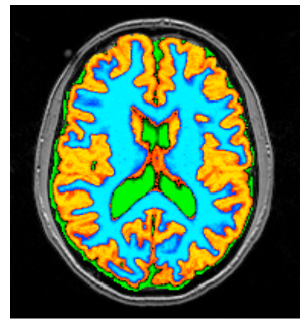
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 6.19

Magnetic Resonance Imaging

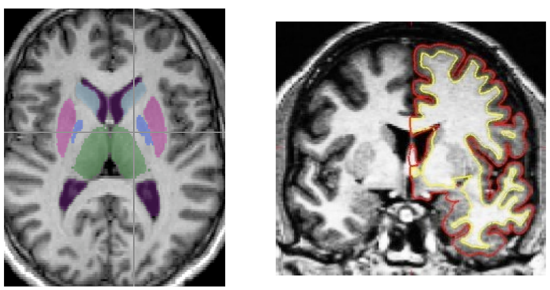
Basic stages in the structural analysis pipeline:



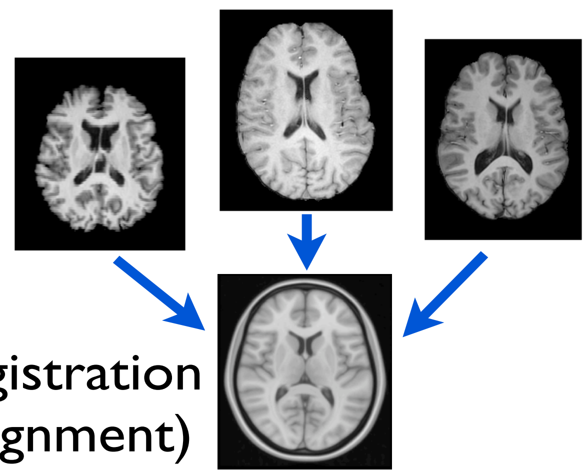
Brain Extraction



Segmentation (tissue-type)



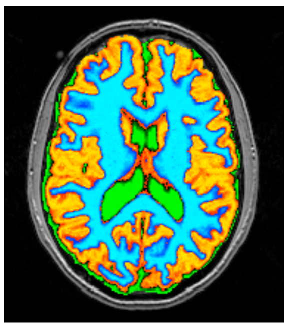
Segmentation (structure)



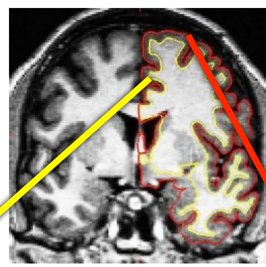
Registration (alignment)

Magnetic Resonance Imaging

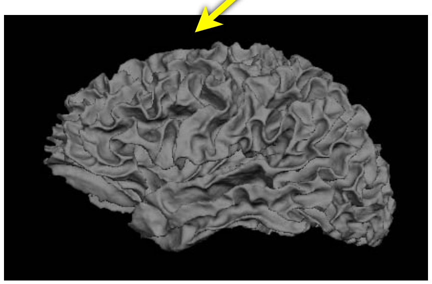
- Quantify tissue volumes and structure shape/size

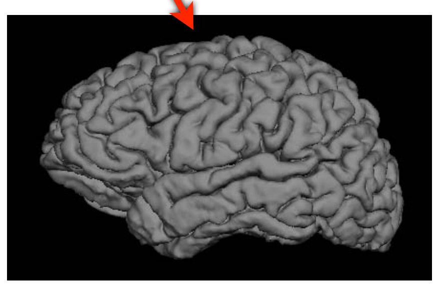


Tissue types:
GM / WM / CSF

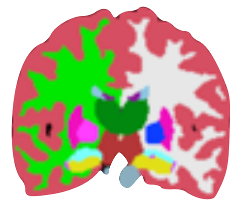


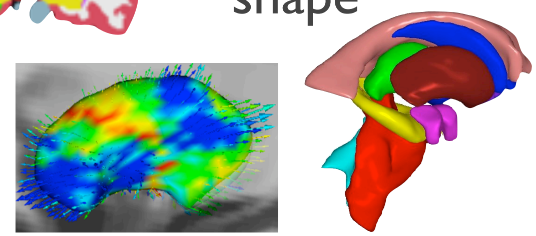
Cortical
surfaces &
thickness



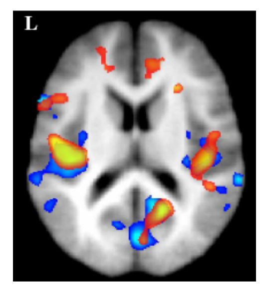


Sub-cortical
structure &
shape

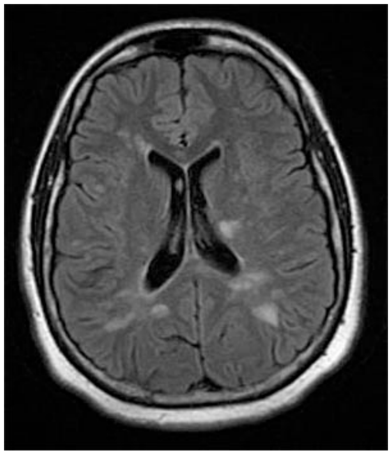




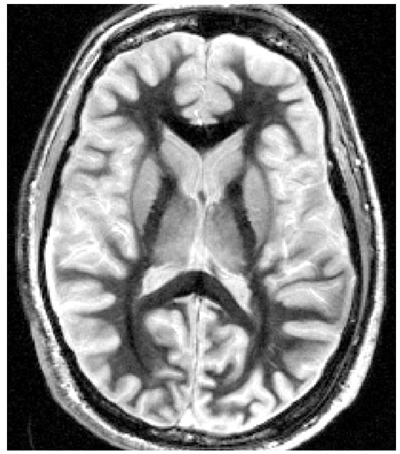
Local GM
changes



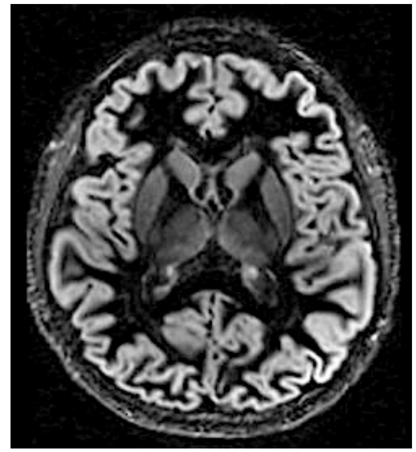
Magnetic Resonance Imaging



FLAIR



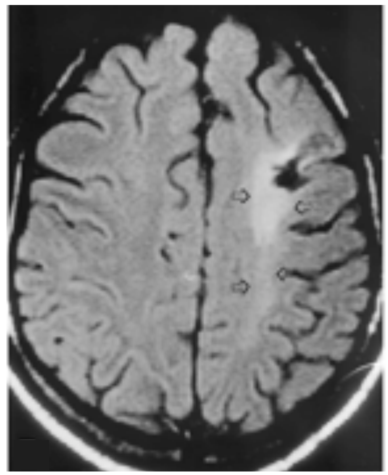
WM nulled



Double Inversion Recovery (DIR)

- By changing timing and signals (RF/gradients) of MR sequence can *null* certain "tissues" or flows
- Useful for highlighting lesions/pathologies
- Also can give better sub-cortical contrast
  - e.g. Brainstem; Globus Pallidus internal/external

Magnetic Resonance Imaging



SWI / QSI MT Veno/Angio-grams

- By sensitising the sequence to different properties can detect other features of tissue:
  - SWI/QSI: S=susceptibility; magnetic field changes due to iron content (primarily) and myelin/WM
  - MT: Magnetisation Transfer; bound/free water
  - Veno/Angio-grams: flow/blood iron/contrast agent

Magnetic Resonance Imaging

Many other types of structural MRI, for example...

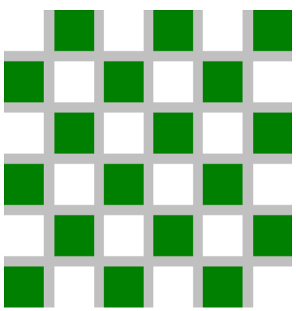
Sensitive to:

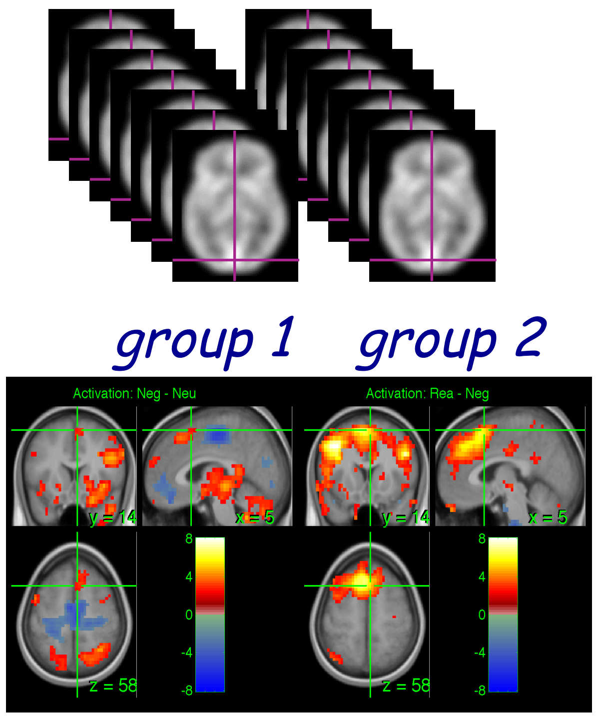
- Susceptibility-Weighted Imaging (SWI) — iron
  - Quantitative Susceptibility Imaging (QSI) — (and myelin)
- Magnetization Transfer (MT) — chemical species/
- MR Spectroscopy (MRS) — environment
- Angiograms & Venograms — arteries & veins
- Quantitative T_1 and T_2 maps (relaxometry) — tissue μstructure
- Myelin maps — myelin
- B_0 map (fieldmap) — fields
- B_1 map (RF) — within head

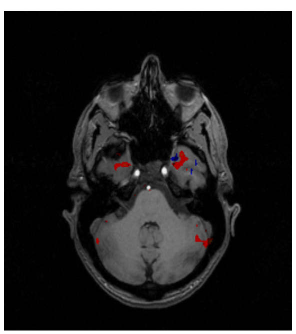
http://www.youtube.com/watch?v=XwUn64d5Ddk&feature=related

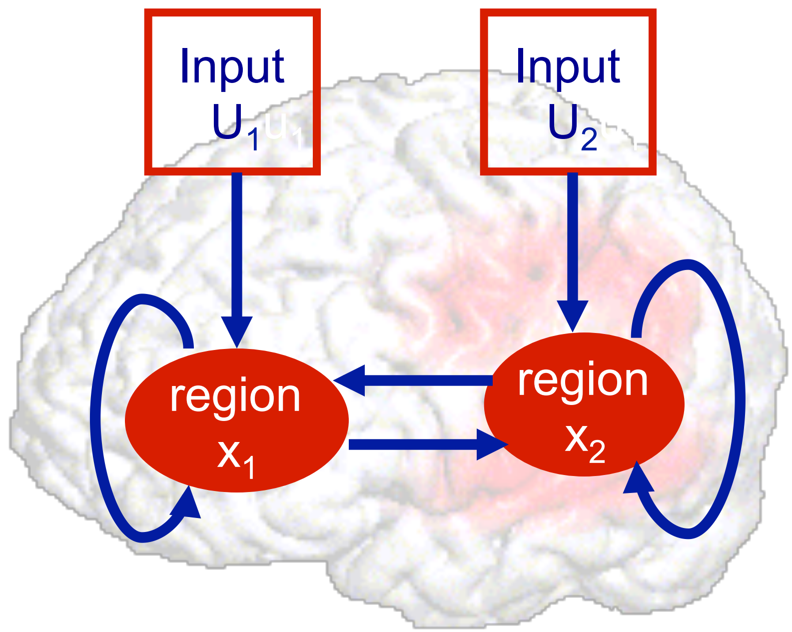
Functional MRI (fMRI)

Functional MRI measures the hemodynamic response (change in blood flow) related to neural activity in the brain or spinal cord of humans or other animals. Since the early 1990s, fMRI has come to dominate the brain mapping field due to low invasiveness, absence of radiation exposure, and relatively wide availability.

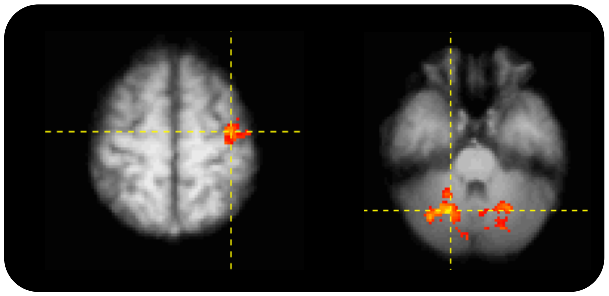




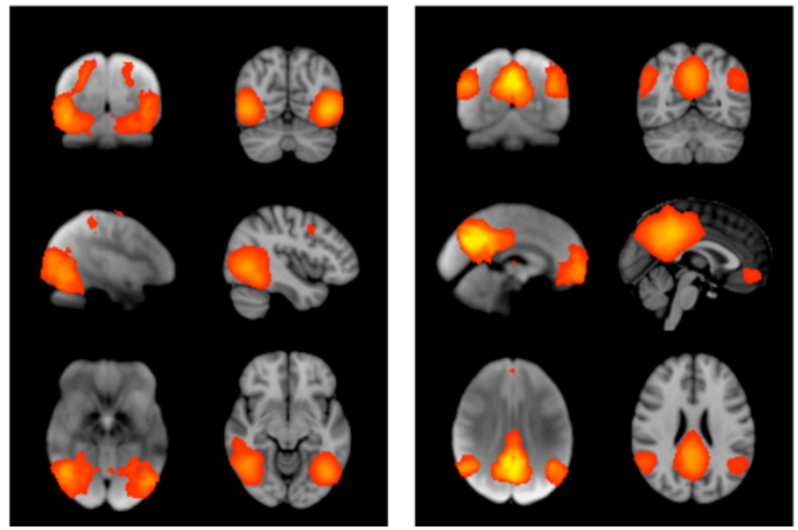




Functional MRI (fMRI)

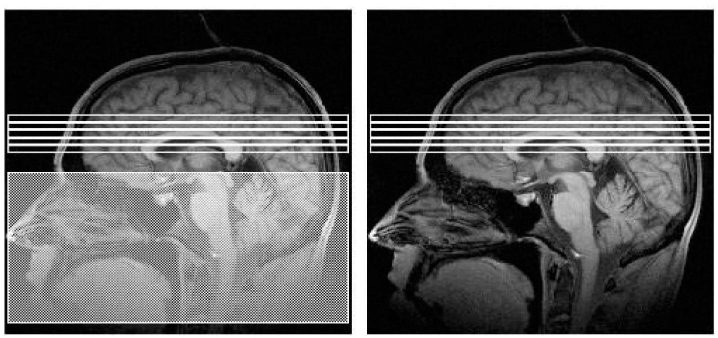


Task FMRI



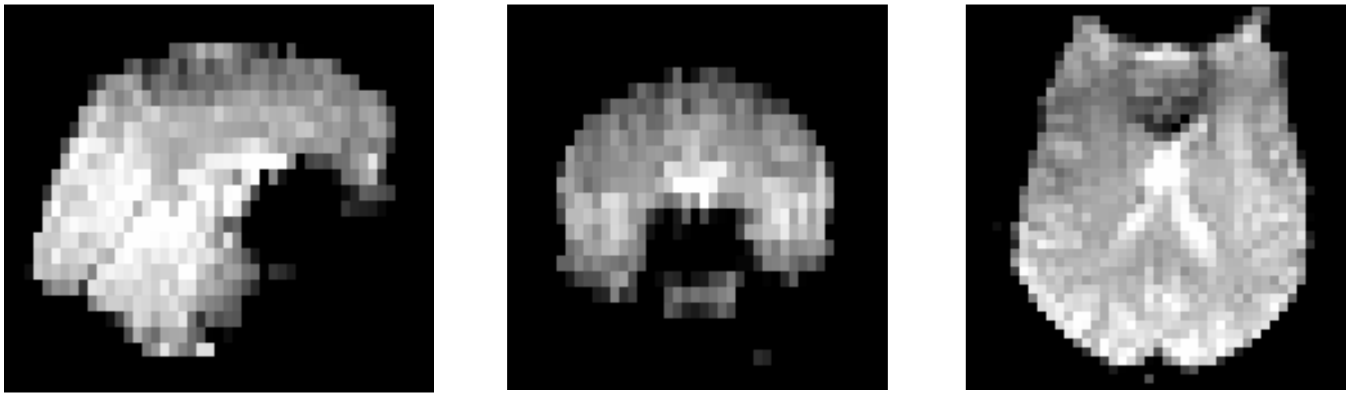
Resting-State FMRI
& Connectivity

Tag *Control*



ASL

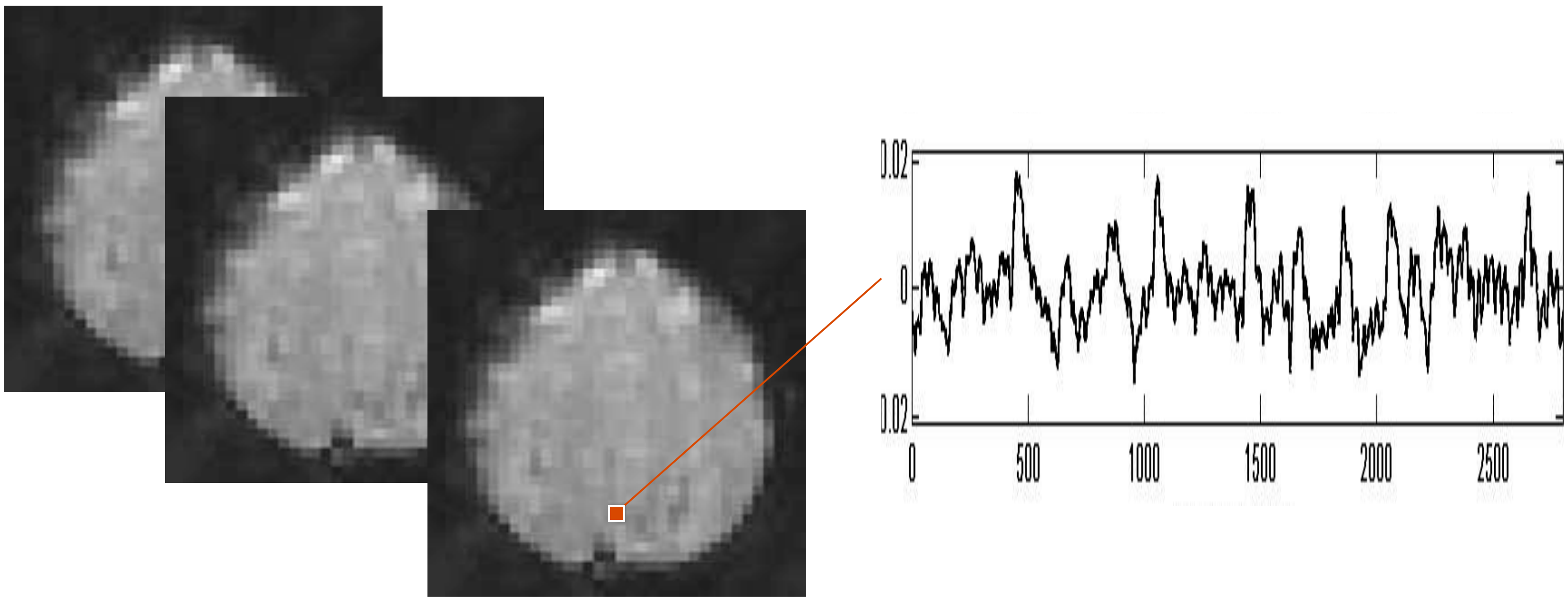
Functional MRI (fMRI)



- A sequence of low resolution T_2*-weighted volumes are taken during the FMRI experiment
- Optimised for BOLD sensitivity and speed
- Take one volume every 1-3 seconds
- Often take around 200 volumes (10 minutes)
- An FMRI volume is shown here in *orthogonal* view

Functional MRI (fMRI)

fMRI studies brain function.

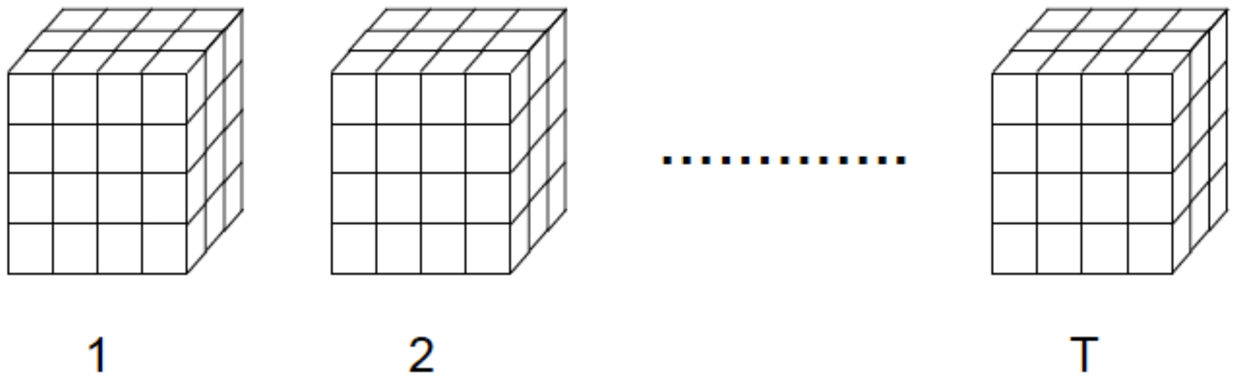


UNIVERSITY OF ALBERTA

"uplifting the whole people"
— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908

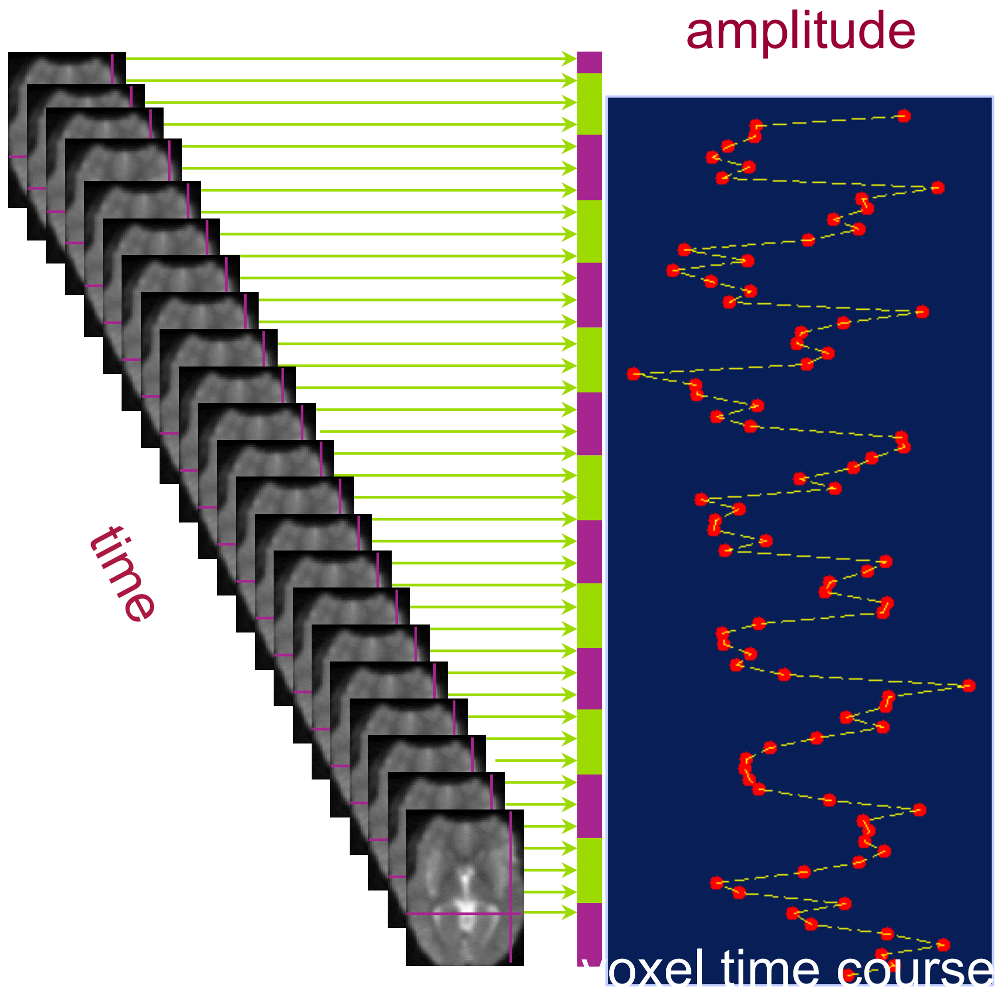
Functional MRI (fMRI)

- Each fMRI image consists of ~100,000 brain 'voxels' (cubic volumes that span the 3D space of the brain).



- During the course of an experiment several hundred images are acquired (~ one every 2*s*).

One voxel = One time series

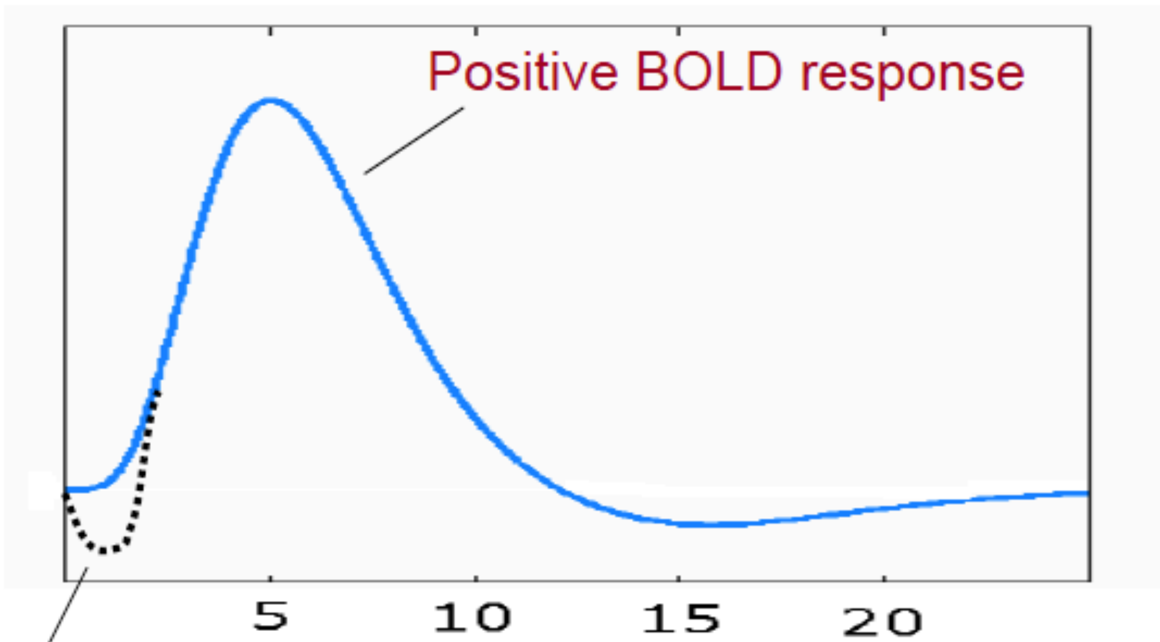


BOLD fMRI

- The most common approach towards fMRI uses the Blood Oxygenation Level Dependent (BOLD) contrast.
- BOLD fMRI allows us to measure the ratio of oxygenated to deoxygenated hemoglobin in the blood.
- It is important to note that BOLD fMRI doesn't measure neuronal activity directly, instead it measures the metabolic demands (oxygen consumption) of active neurons.

BOLD fMRI

The hemodynamic response function (HRF) represents changes in the fMRI signal triggered by neuronal activity.



Experimental Design

Block design

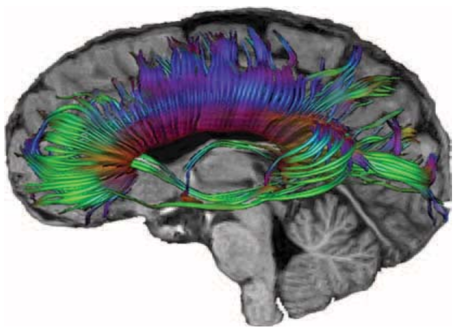
Each condition is presented for an extended period of time.

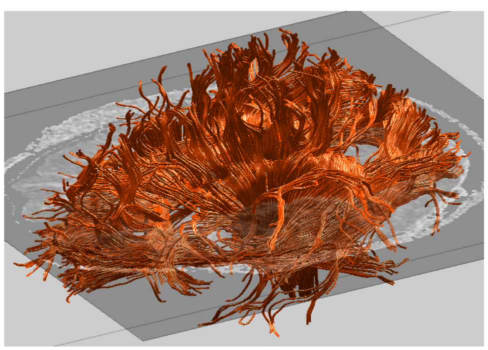
Event-related design

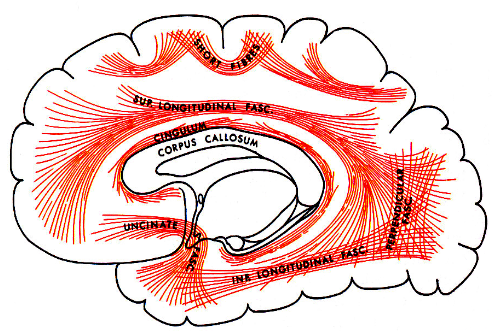
Each event is presented for a short duration.

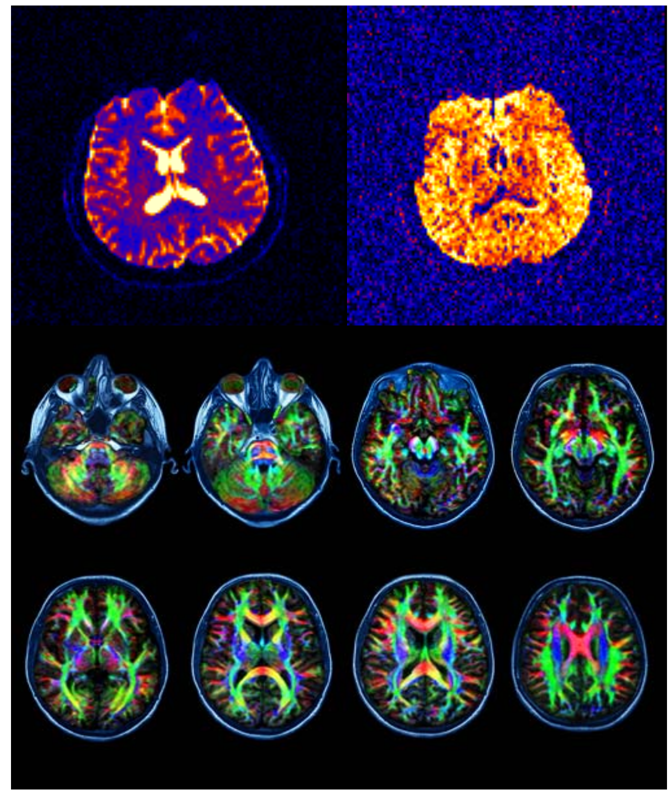
Diffusion Tensor MRI

Diffusion Tensor MRI can provide information about damage to parts of the nervous system and about white matter connections among brain regions.

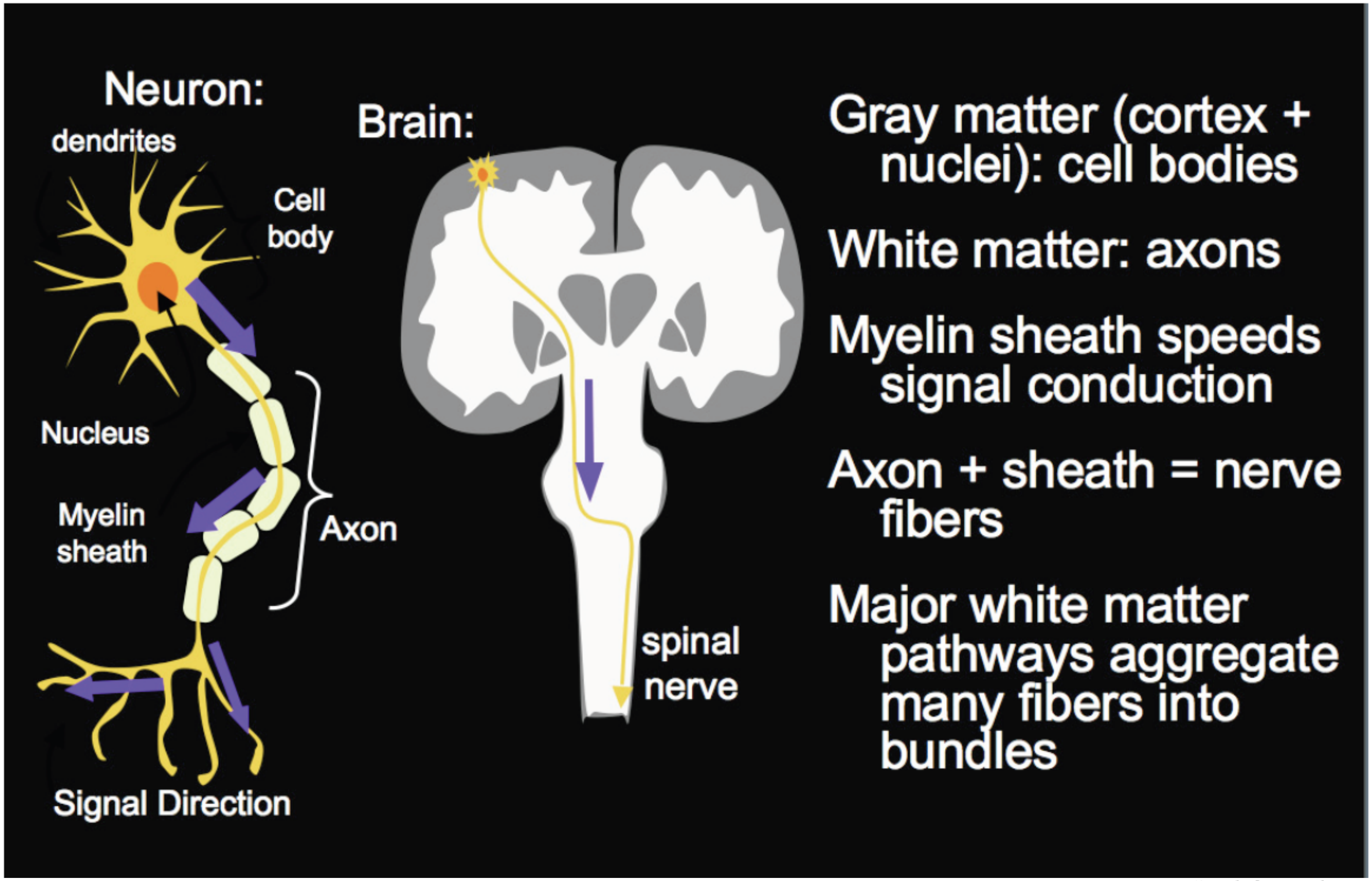




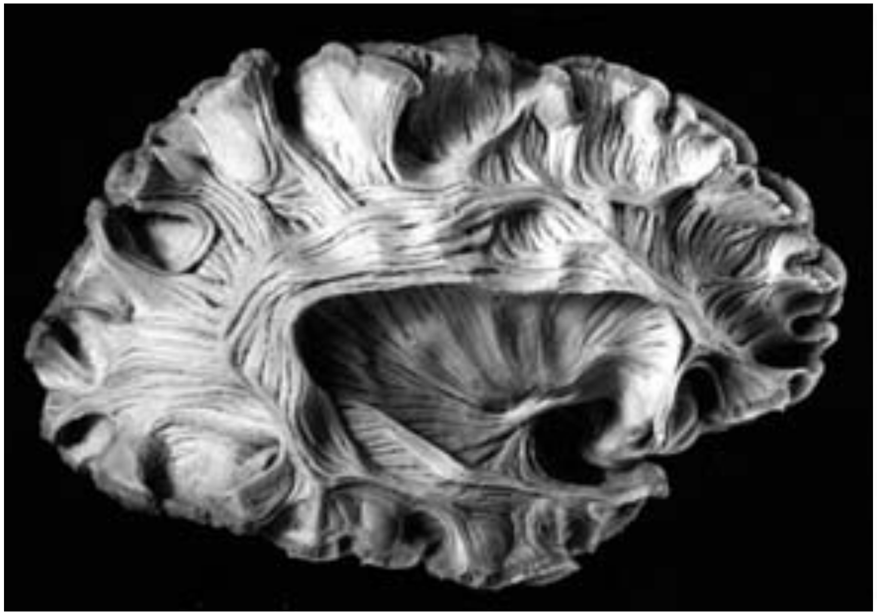




Diffusion Tensor MRI



Diffusion Tensor MRI



1 Short Arcuate Bundles
2 Superior Longitudinal Fasciculus
3 External Capsule
4 Inferior Occipitofrontal Fasciculus
5 Uncinate Fasciculus
6 Sagittal Striatum
7 Inferior Longitudinal Fasciculus

Diffusion Tensor MRI

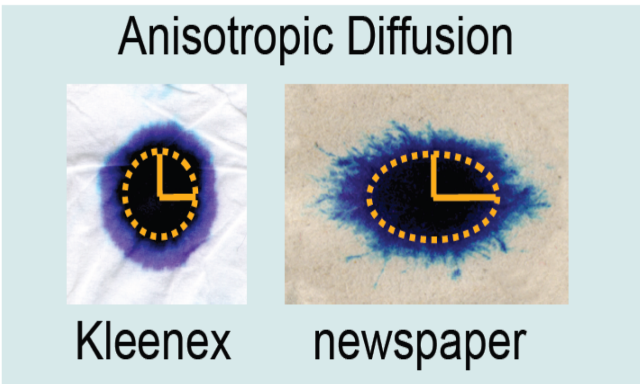
Diffusion Tensor Magnetic Resonance Images: an imaging modality developed in the past decade that allows measurement of fiber-tract trajectories *in vivo* in soft tissues, such as nerves, muscles, ligaments, and tendons.

Diffusion tensor (DT) images are used to map accurately the structure and orientation of fiber tracts in the white matter of the human brain in vivo.

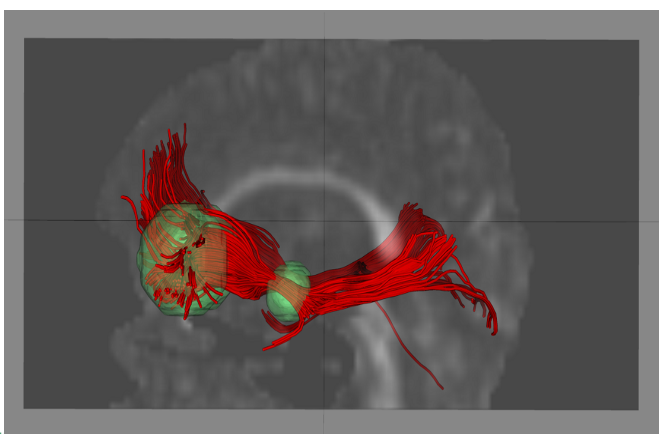
MRI can measure magnitude and direction of local water diffusion. The directional dependence of diffusion is characterized by a matrix of the effective diffusion of water.

$$D = \begin{pmatrix} d_{1,1} & d_{2,1} & d_{3,1} \\ d_{2,1} & d_{2,2} & d_{3,2} \\ d_{3,1} & d_{3,2} & d_{3,3} \end{pmatrix} \geq 0$$

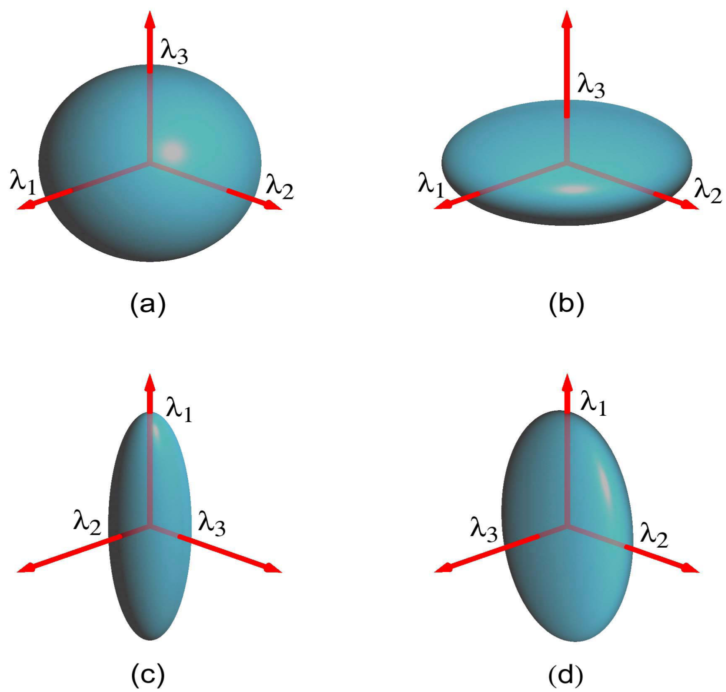
Diffusion Tensor MRI

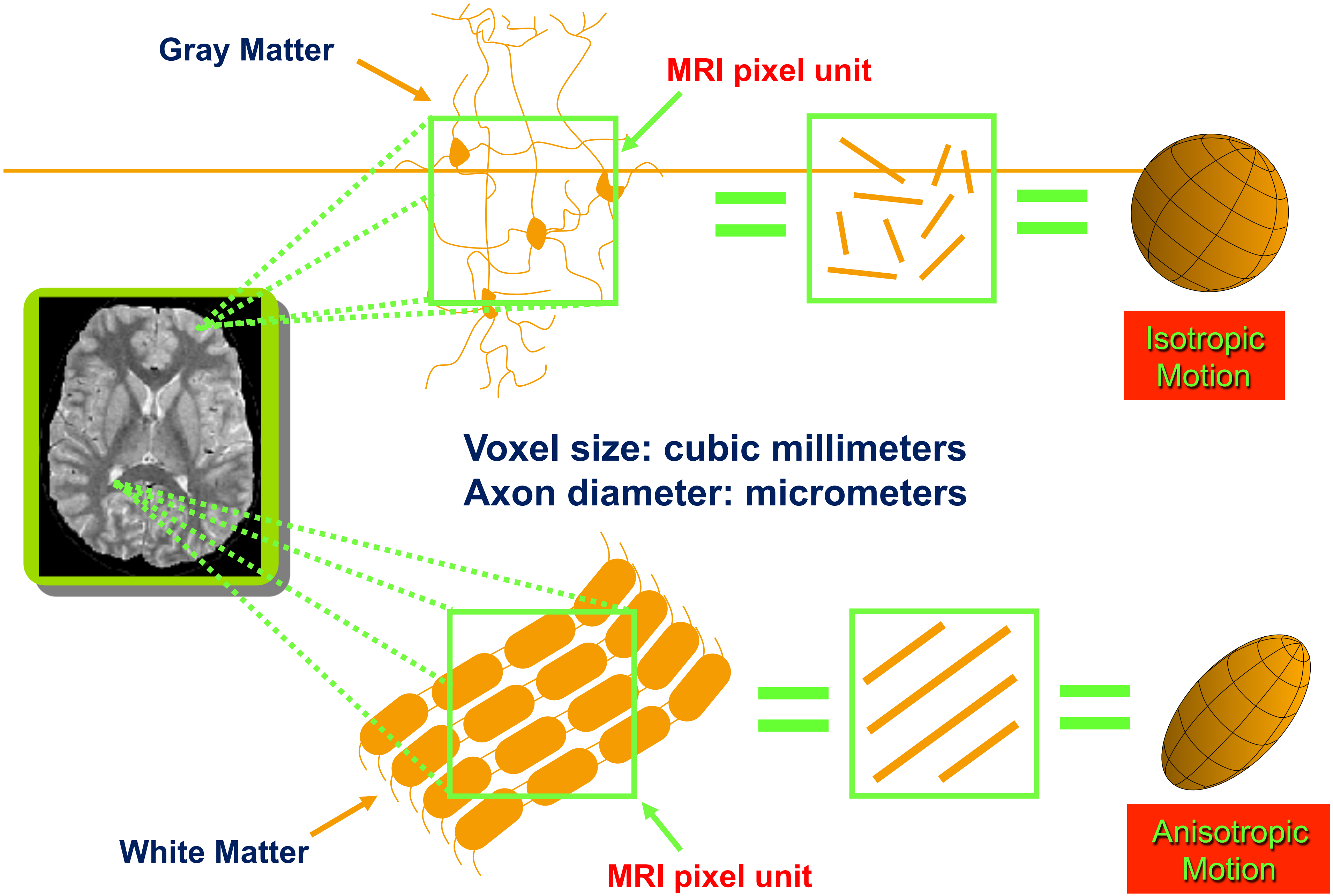


Provided by
G. Kindlmann

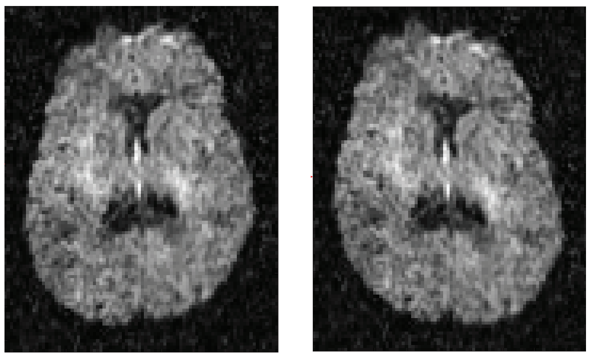


Diffusion Tensors

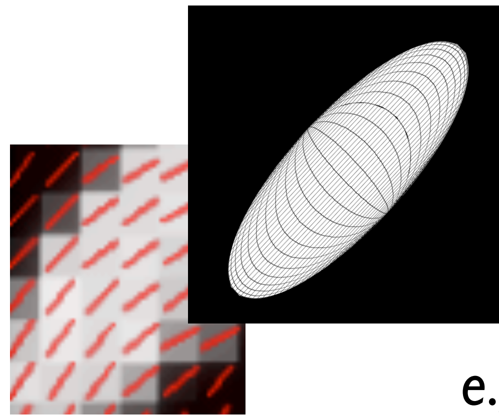



Gray Matter
MRI pixel unit
Isotropic Motion
Voxel size: cubic millimeters
Axon diameter: micrometers
White Matter
MRI pixel unit
Anisotropic Motion

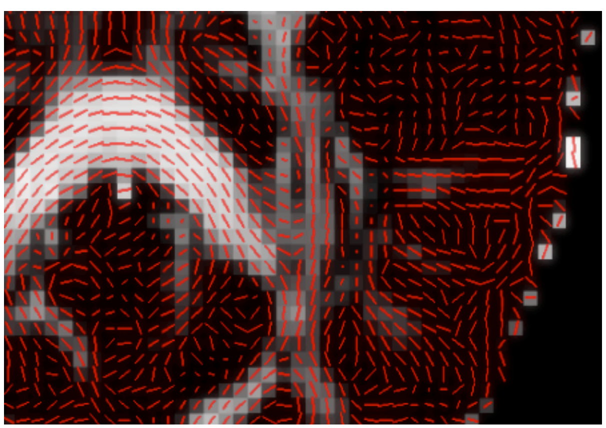
Basic stages in the diffusion analysis pipeline:



Eddy Current & Motion Correction

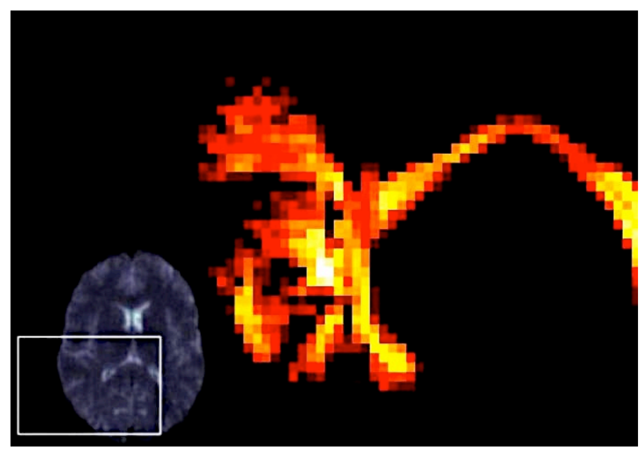


"Tensor"
Fitting
e.g. FA, MD

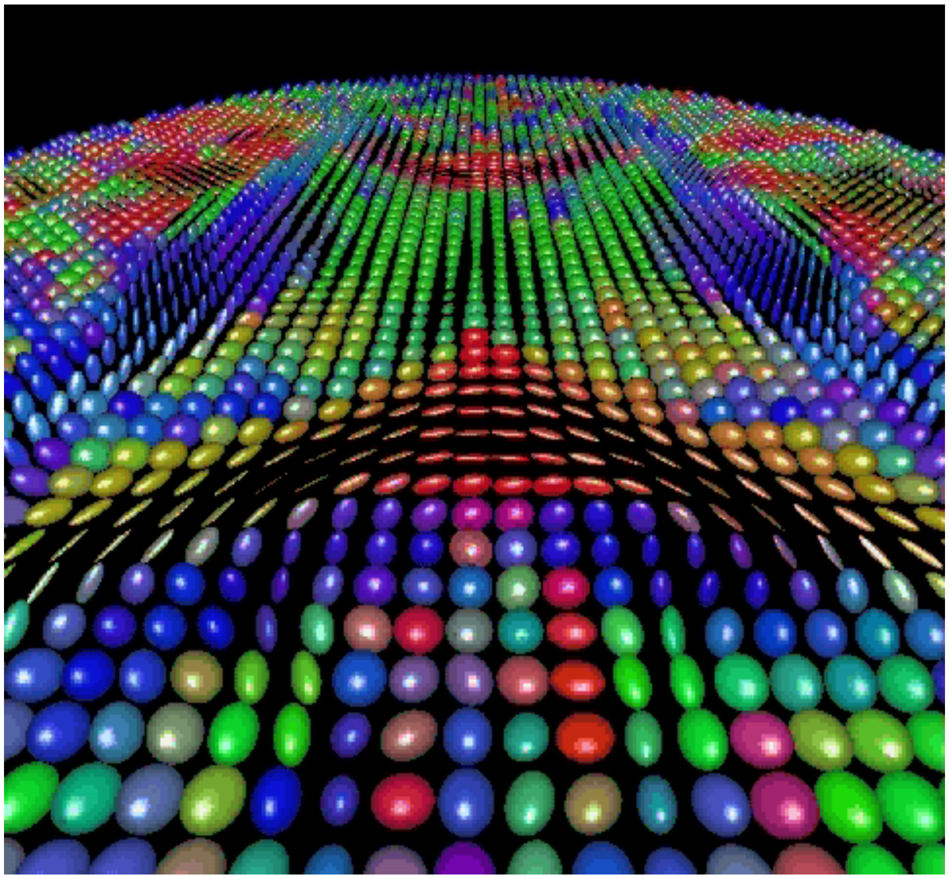


Fibre/
direction
modelling

Probabilistic Tractography



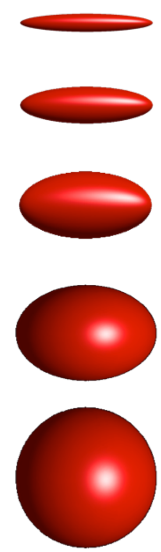
Diffusion Tensor MRI



Splenium of the corpus callosum

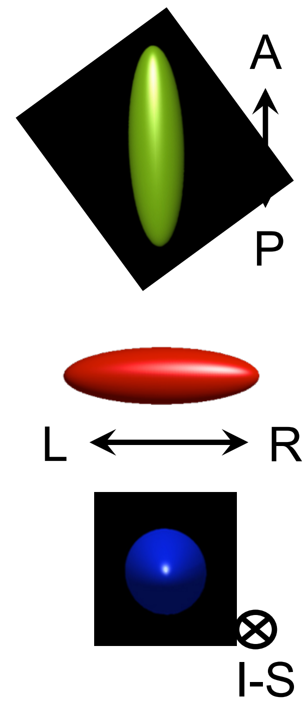
shape

High anisotropy



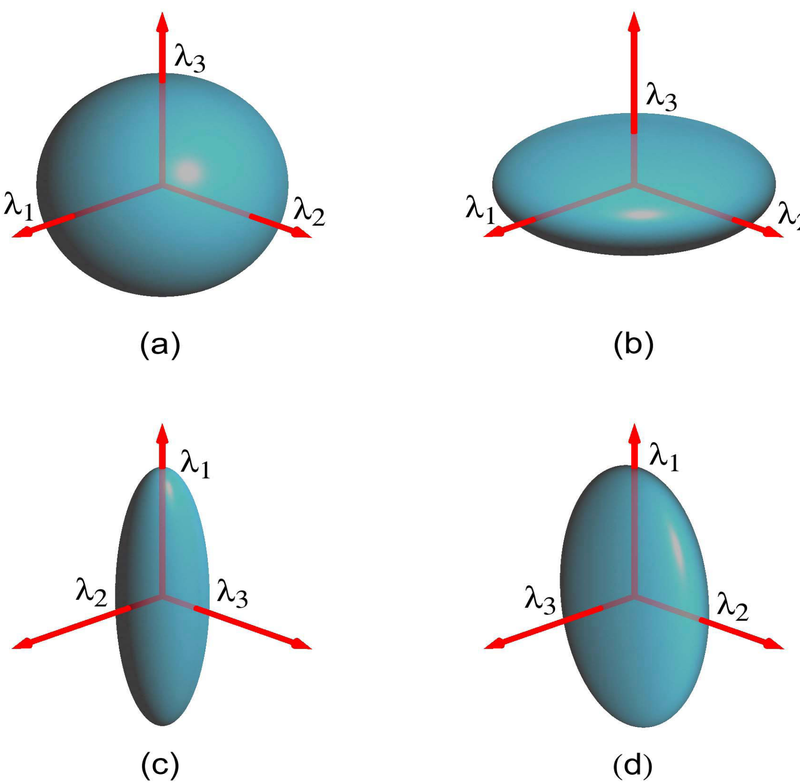
Low anisotropy

colour



1997

Diffusion Tensor MRI



Singular DT

(a) Isotropic

$$\lambda_1 = \lambda_2 = \lambda_3$$

(b) Discoid

$$\lambda_1 = \lambda_2 > \lambda_3$$

(c) Prolate (cigar)

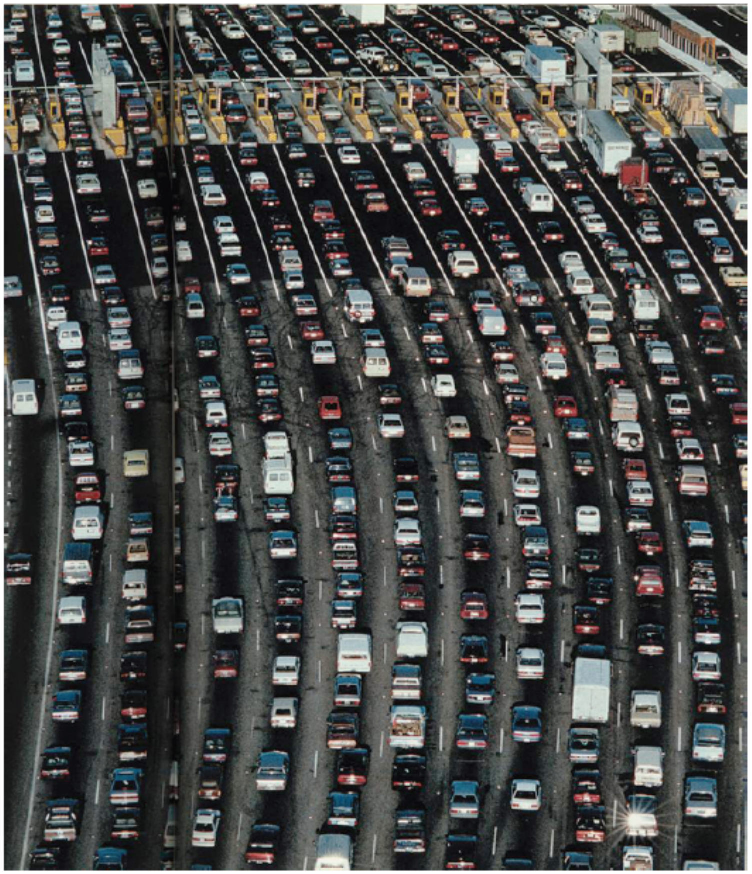
$$\lambda_1 > \lambda_2 = \lambda_3$$

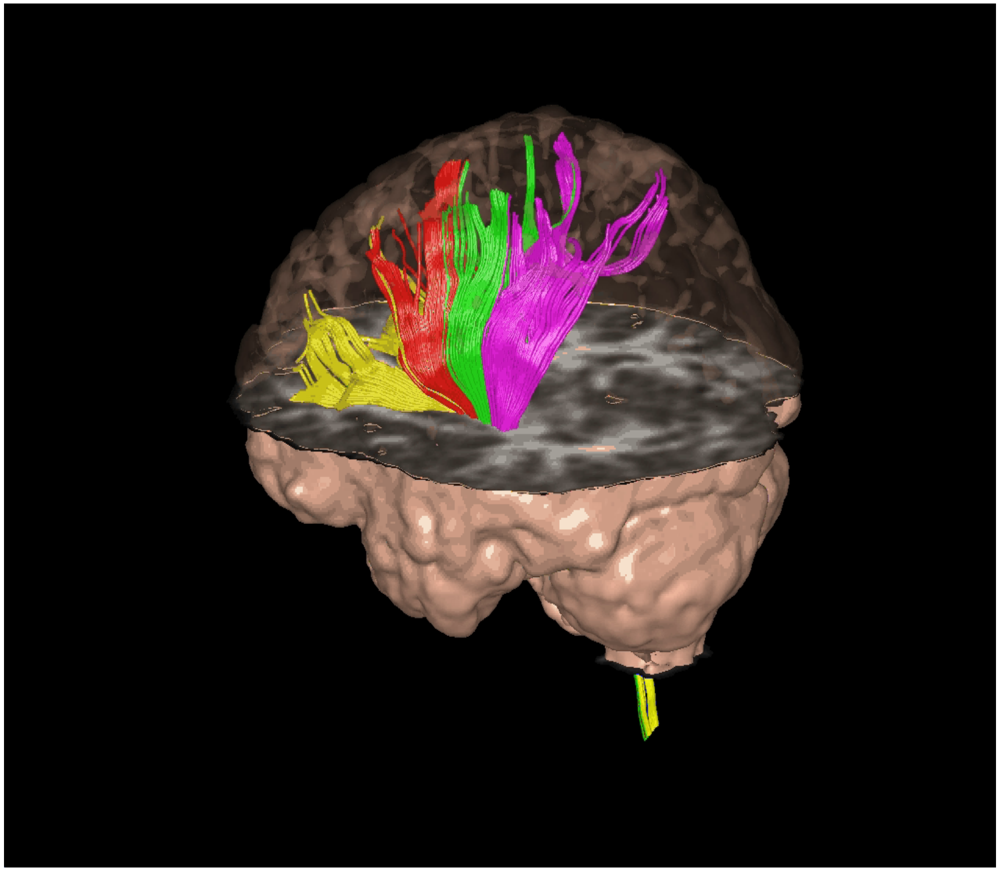
(d) Nonsingular

$$\lambda_1 > \lambda_2 > \lambda_3$$

$$D = \lambda_1 \vec{\eta}_1 \vec{\eta}_1^T + \lambda_2 \vec{\eta}_2 \vec{\eta}_2^T + \lambda_3 \vec{\eta}_3 \vec{\eta}_3^T$$

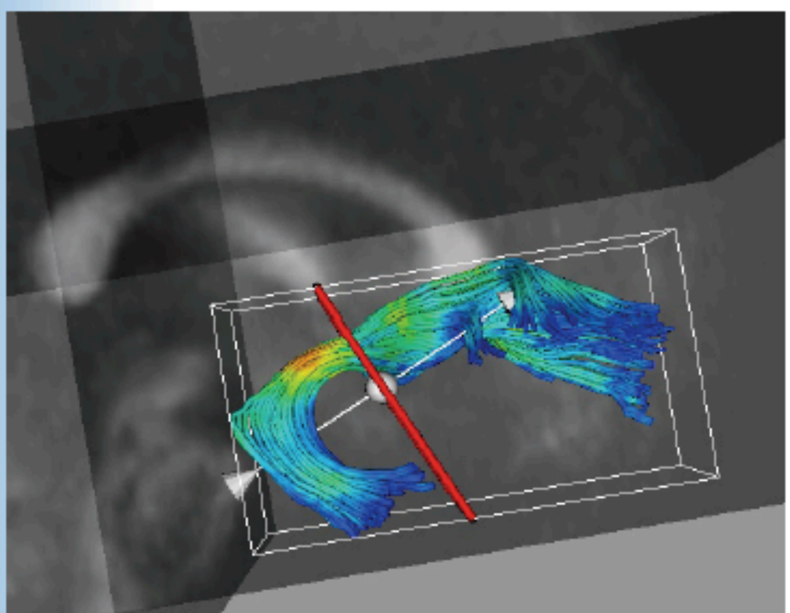
Diffusion Tensor MRI

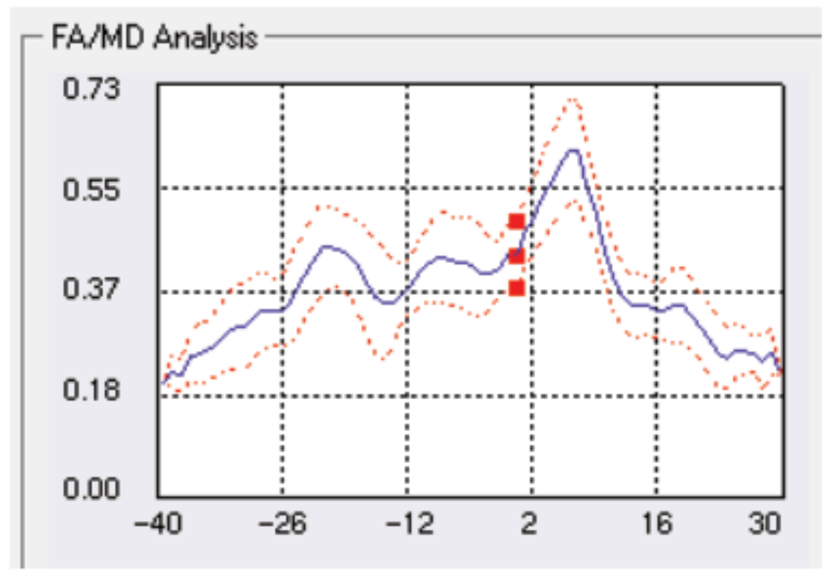




Quantitative Tractography

- Use fiber tracts as curvilinear regions
  1. Average within the whole tract
  2. Profiles of tensor scalars along tract



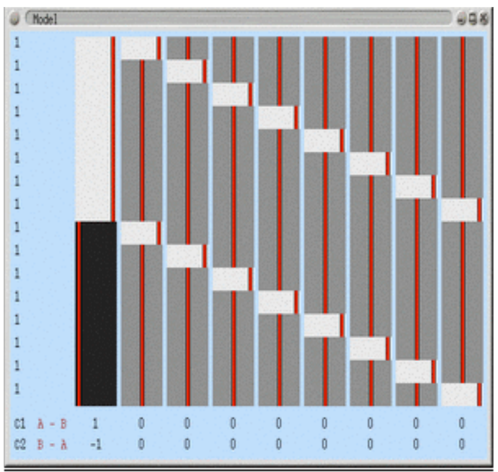


Diffusion Tensor MRI

Later stages in the diffusion analysis pipeline:

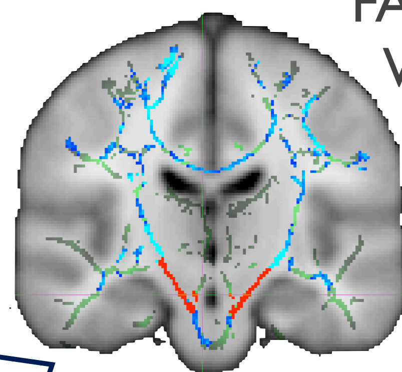
Statistics

(non-parametric)

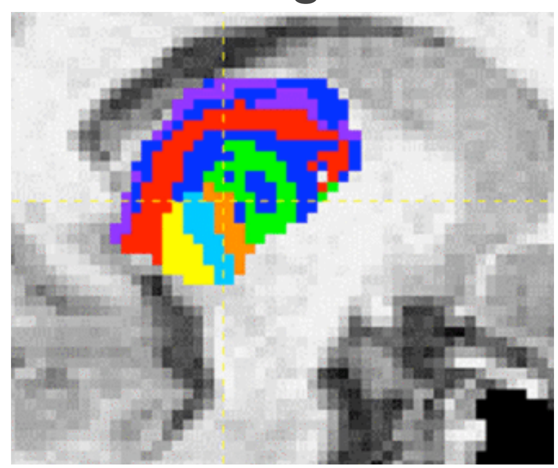


To investigate group-level changes/relations

FA changes in WM tracts



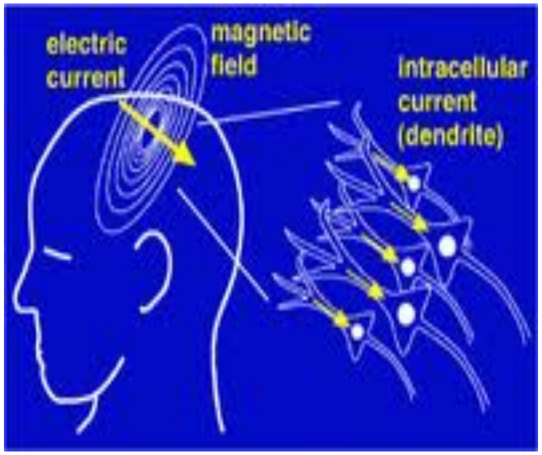
Tractography-based Segmentation



MEG/EEG

Magnetoencephalography (**MEG**) is a technique for mapping brain activity by recording magnetic fields produced by electrical currents in the brain using very sensitive magnetometers.

Electroencephalography (**EEG**) is the recording of electrical activity along the scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain.



Complementary techniques

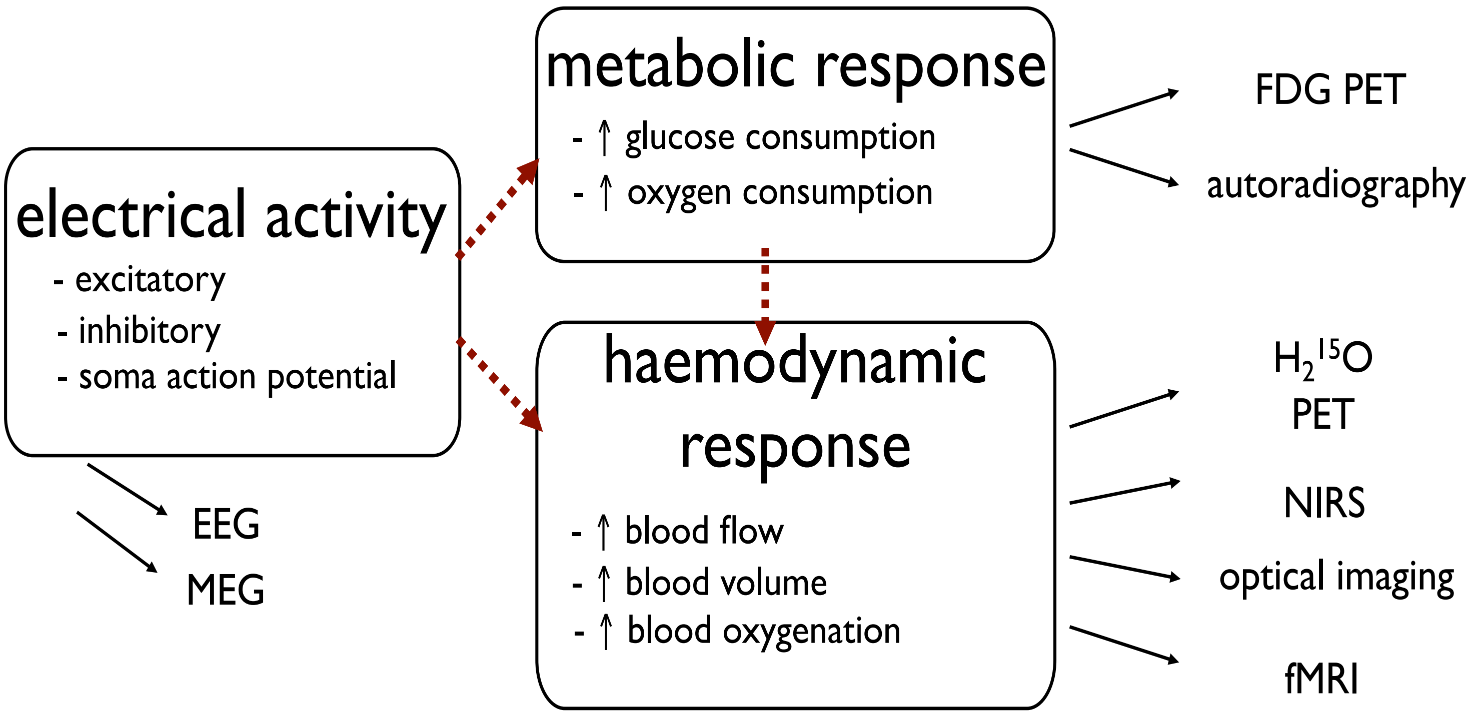
Structural MRI:
- CT (bones/membranes/vessels/tumours)
- Histology (microstructure)

Diffusion MRI:
- Tracer studies (individual fibres)
- Histology (myelin/axon dimensions/glia)

Functional MRI:
- PET/SPECT (metabolic/ligands/low res.)
- EEG/MEG (electrical activity/high temporal res.)
- NIRS (haemodynamics/high temporal res.)
- TMS/TDCS (alter regional brain function)
- Electrodes (single cells/cell groups)

Complementary techniques

Physiological Measures



Part 3. Neuroimaging Applications

Neuroimaging Applications

Structural MRI

- Variety of acquisitions
- Measurement basics
- Limitations & artefacts
- Analysis principles
- Acquisition tips

Functional MRI (task)

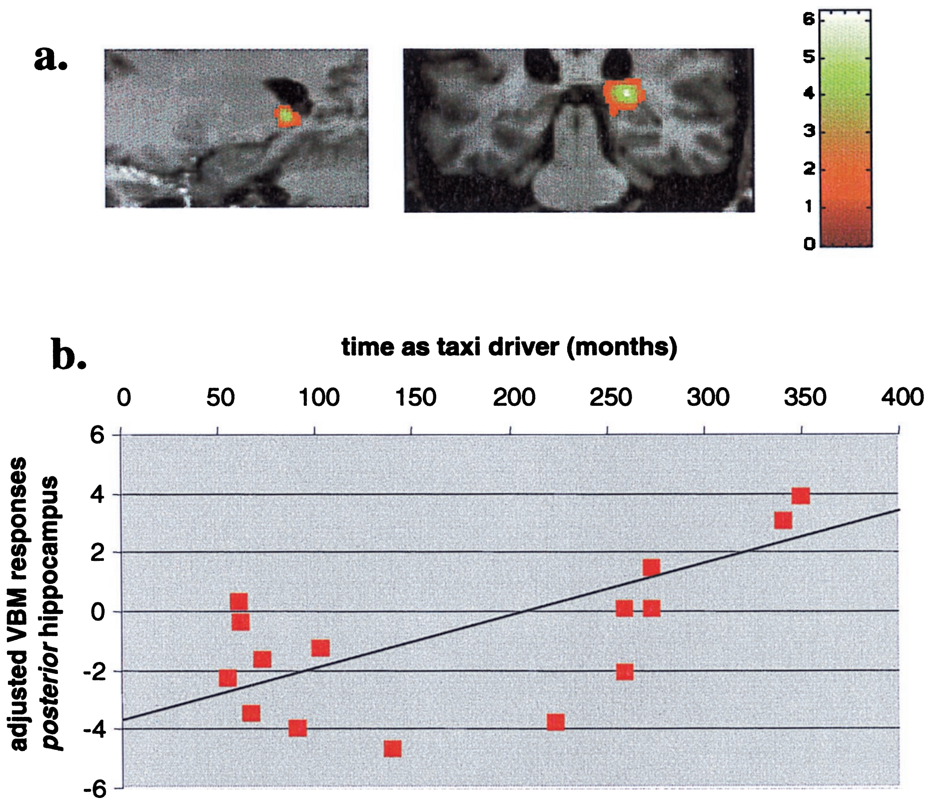
Diffusion MRI

Functional MRI (resting)

Image Applications

neuroscience

- Study of taxi drivers showing *structural plasticity*



Structural MRI

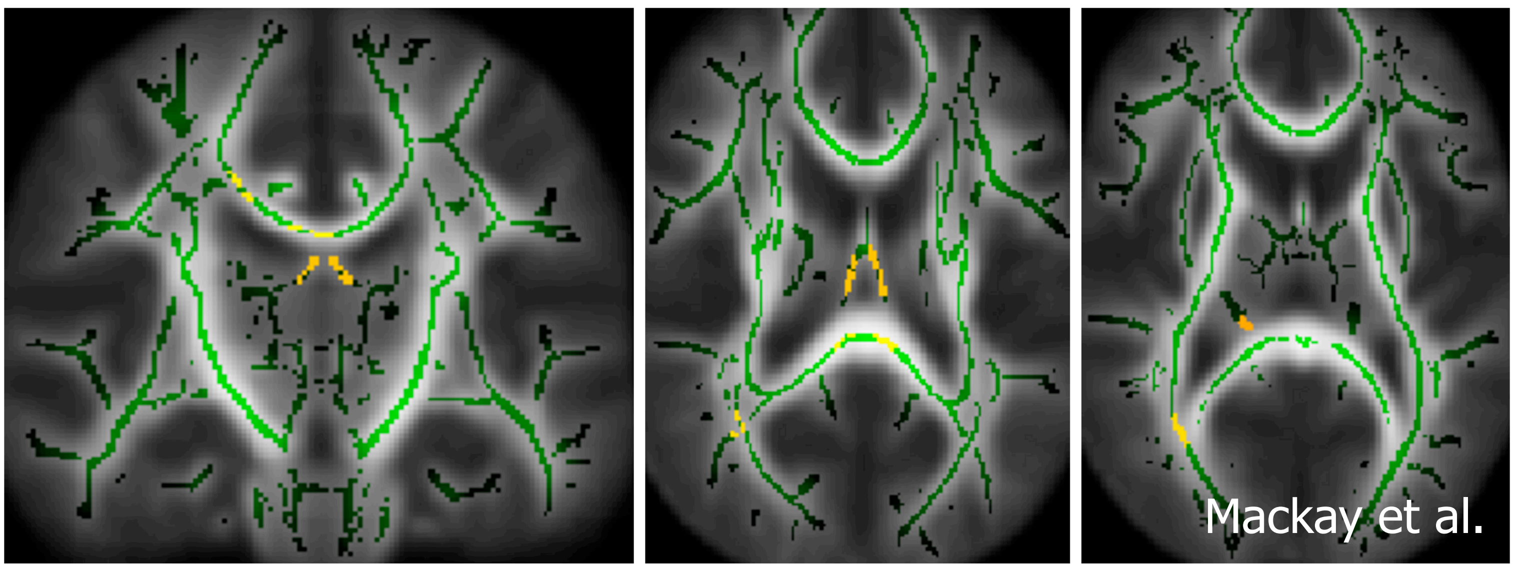
Maguire et al., PNAS, 2000

Neuroimaging Applications

schizophrenia

Diffusion MRI

- White matter integrity - imaging tissue nature change
- Damage to brain connectivity - reduction in schizophrenia in corpus callosum, fornix, longitudinal fasciculus



Neuroimaging Applications

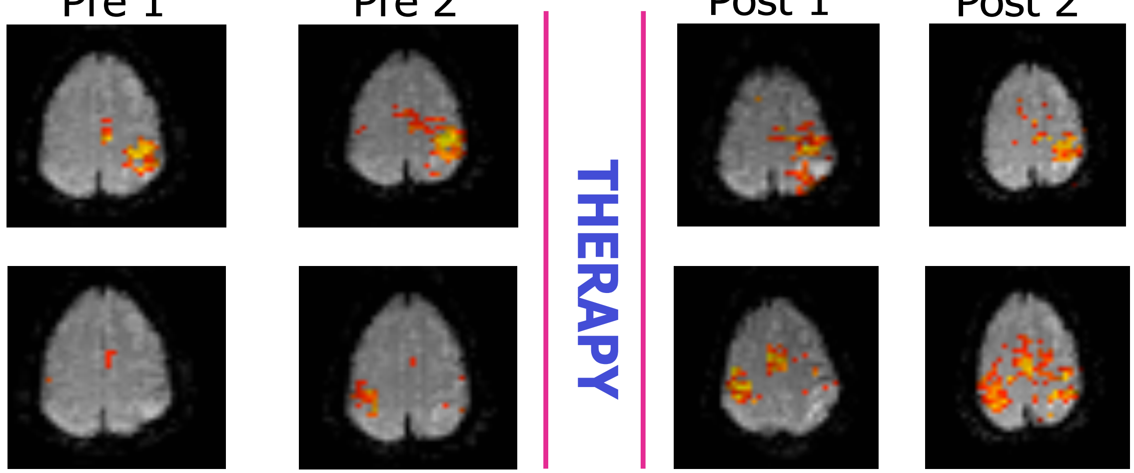
stroke therapy

Single subject: responder

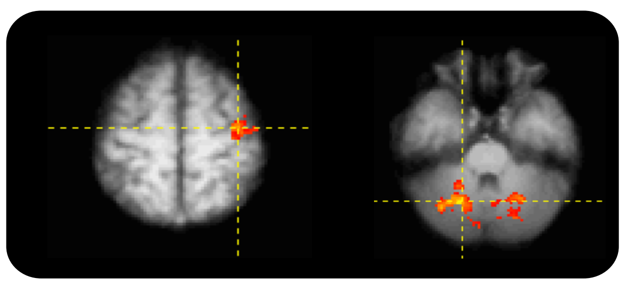
Pre 1 | Pre 2 | Post 1 | Post 2

Unaff. hand (right)

Aff. hand (left)



Group: Correlations with improvement



Functional MRI (task)

Johansen-Berg, et al., Brain 2002

Neuroimaging Applications

Altered **functional connectivity** in young, healthy carriers of APOE-ε4

PNAS PNAS PNAS PNAS

Distinct patterns of brain activity in young carriers of the *APOE*-ε4 allele

Nicola Filippini[a,b,c], Bradley J. MacIntosh[b], Morgan G. Hough[b], Guy M. Goodwin[a], Giovanni B. Frisoni[c], Stephen M. Smith[b], Paul M. Matthews[d,e], Christian F. Beckmann[b,e], and Clare E. Mackay[a,b,1]

[a]University Department of Psychiatry and [b]Functional Magnetic Resonance Imaging of the Brain Centre, University of Oxford, Oxford OX3 9DU, United Kingdom; [c]Laboratory of Epidemiology, Neuroimaging, and Telemedicine, Istituto di Ricovero e Cura a Carattere Scientifico San Giovanni di Dio-Fatebenefratelli, Brescia 25125, Italy; [d]GlaxoSmithKline Research and Development, Clinical Imaging Centre, London W12 0NN, United Kingdom; and [e]Department of Clinical Neuroscience, Imperial College, Hammersmith Campus London W12 0NN, United Kingdom

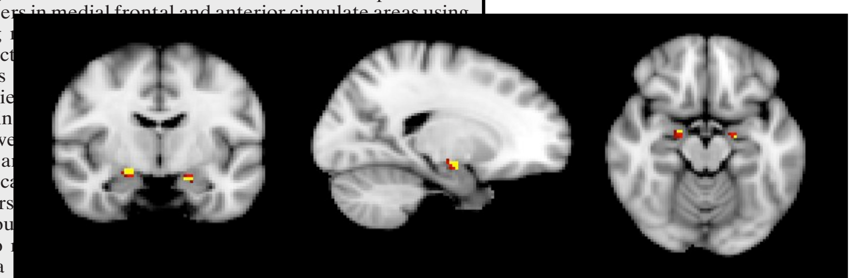
Edited by Robert W. Mahley, The J. David Gladstone Institutes, San Francisco, CA, and approved March 6, 2009 (received for review November 25, 2008)

The *APOE* ε4 allele is a risk factor for late-life pathological changes that is also associated with anatomical and functional brain changes in middle-aged and elderly healthy subjects. We investigated structural and functional effects of the *APOE* polymorphism in 18 young healthy *APOE* ε4-carriers and 18 matched noncarriers (age range: 20–35 years). Brain activity was studied both at rest and during an encoding memory paradigm using blood oxygen level-dependent fMRI. Resting fMRI revealed increased "default mode network" (involving retrosplenial, medial temporal, and medial-prefrontal cortical areas) coactivation in ε4-carriers relative to noncarriers. The encoding task produced greater hippocampal activation in ε4-carriers relative to noncarriers. Neither result could be explained by differences in memory performance, brain morphology, or resting cerebral blood flow. The *APOE* ε4 allele modulates brain function decades before any clinical or neurophysiological expression of neurodegenerative processes.

hippocampus | memory | neuroimaging | resting connectivity

fMRI studies have tested for early life associations of the *APOE* polymorphism with changes in brain function. Filbey et al. (18) reported greater activation in 8 *APOE* ε4-carriers compared with 8 noncarriers in medial frontal and anterior cingulate areas using
a working
reduced act
ε4-carriers
Both studie
ences brain
Here, we
structural a
APOE ε4-ca
to 35 years
spontaneou
relative to
showing a
frequency fluctuations (less than 0.1 Hz) are defined as "resting state networks" (RSNs), and they reflect intrinsic properties of functional brain organization (21). We were specifically inter-

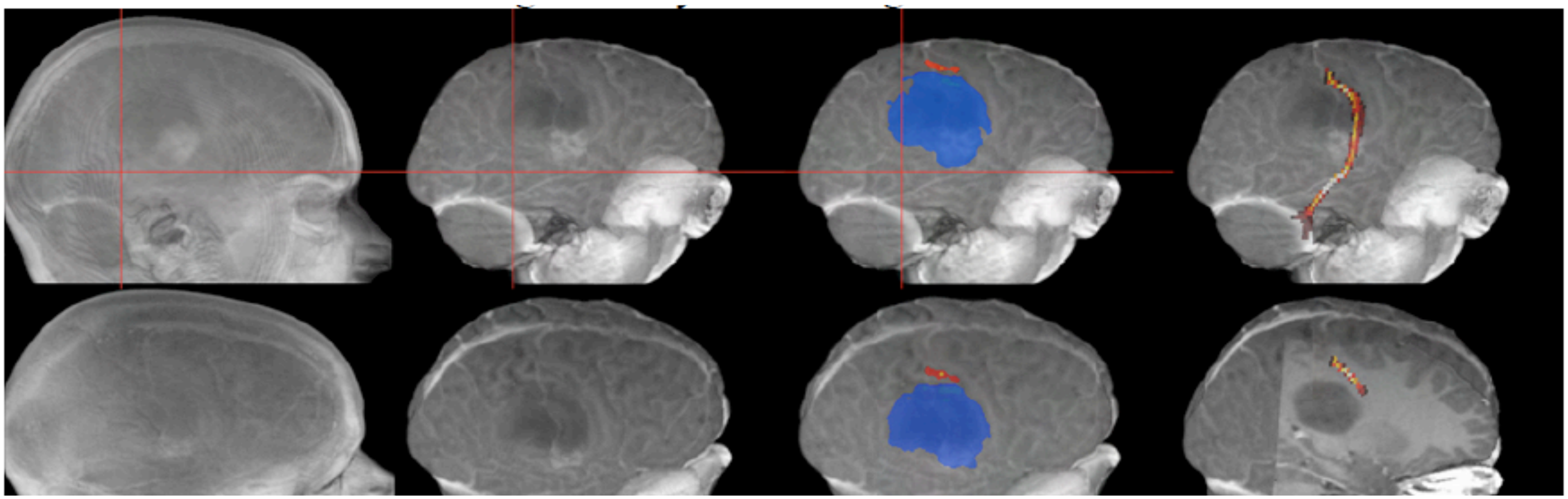
Functional MRI (resting)



Neuroimaging Applications

Surgical planning

Diffusion MRI + **Functional MRI (task)**



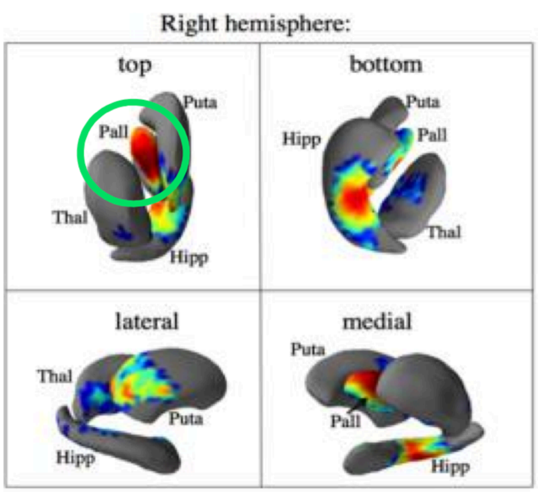
(Bartsch et al., JMRI 2006)

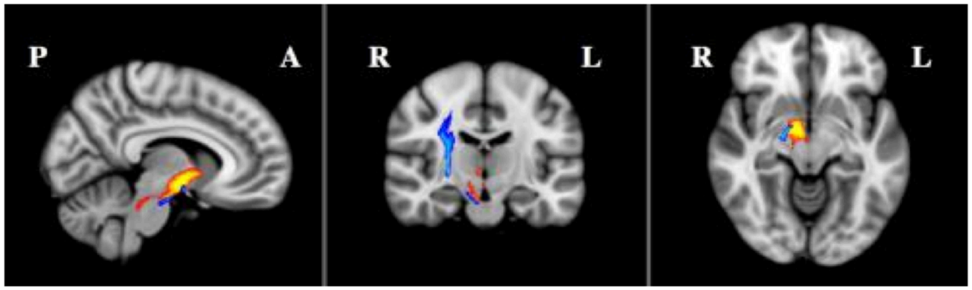
Neuroimaging Applications

Parkinson's Disease

Structural MRI + **Diffusion MRI**

Look at tracts connected to regions of structural change





Menke et al., Brain 2013

Part 4. Image Processing

Image Processing

Raw Images

- Image Reconstruction
- Image Segmentation
- Image Registration
- Image Smoothing

Multiple Comparisons

Statistical Modelling

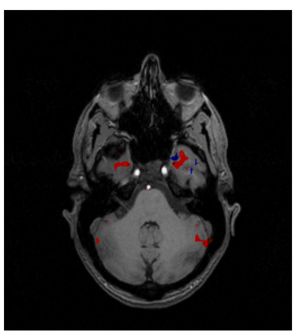


Image Processing

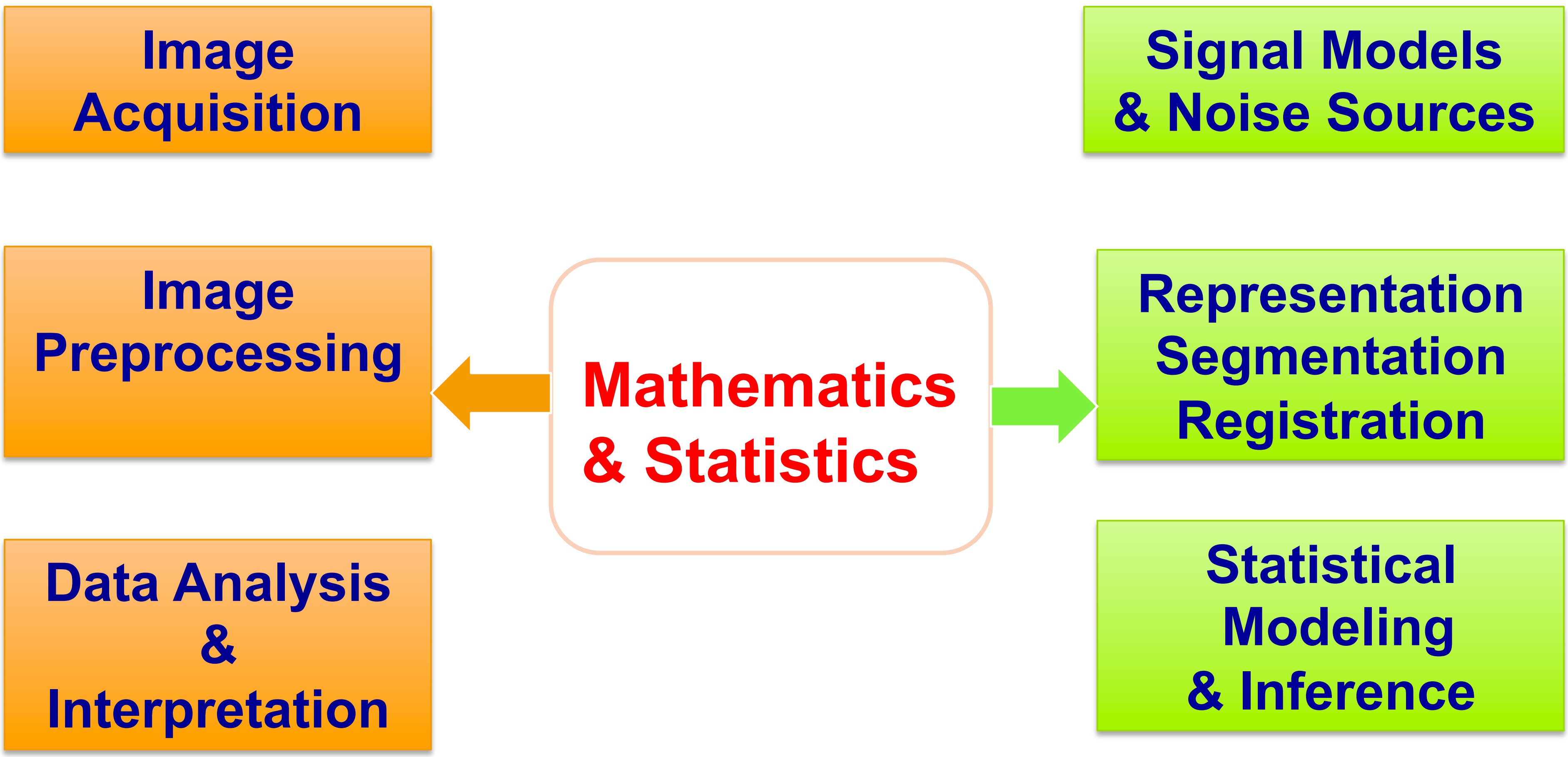
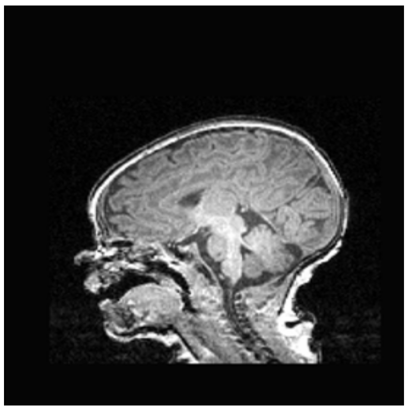
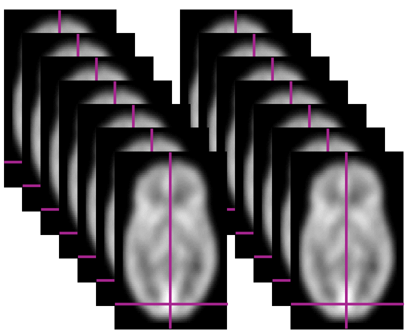


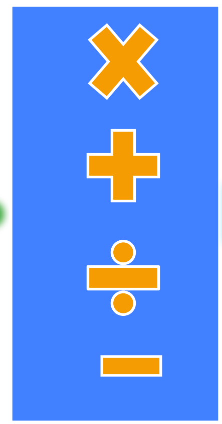
Image Processing

$$f$$

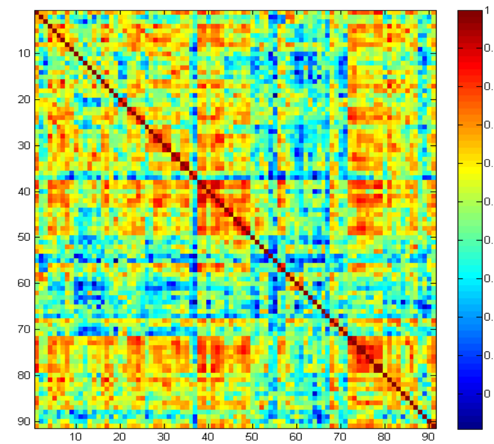


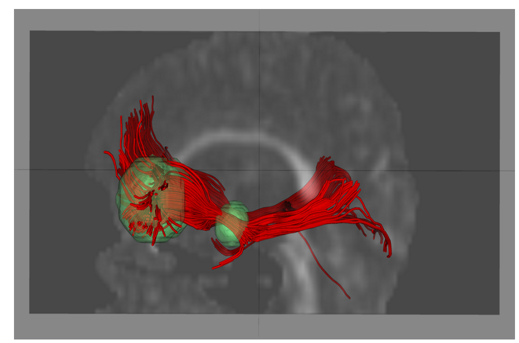


$$T$$

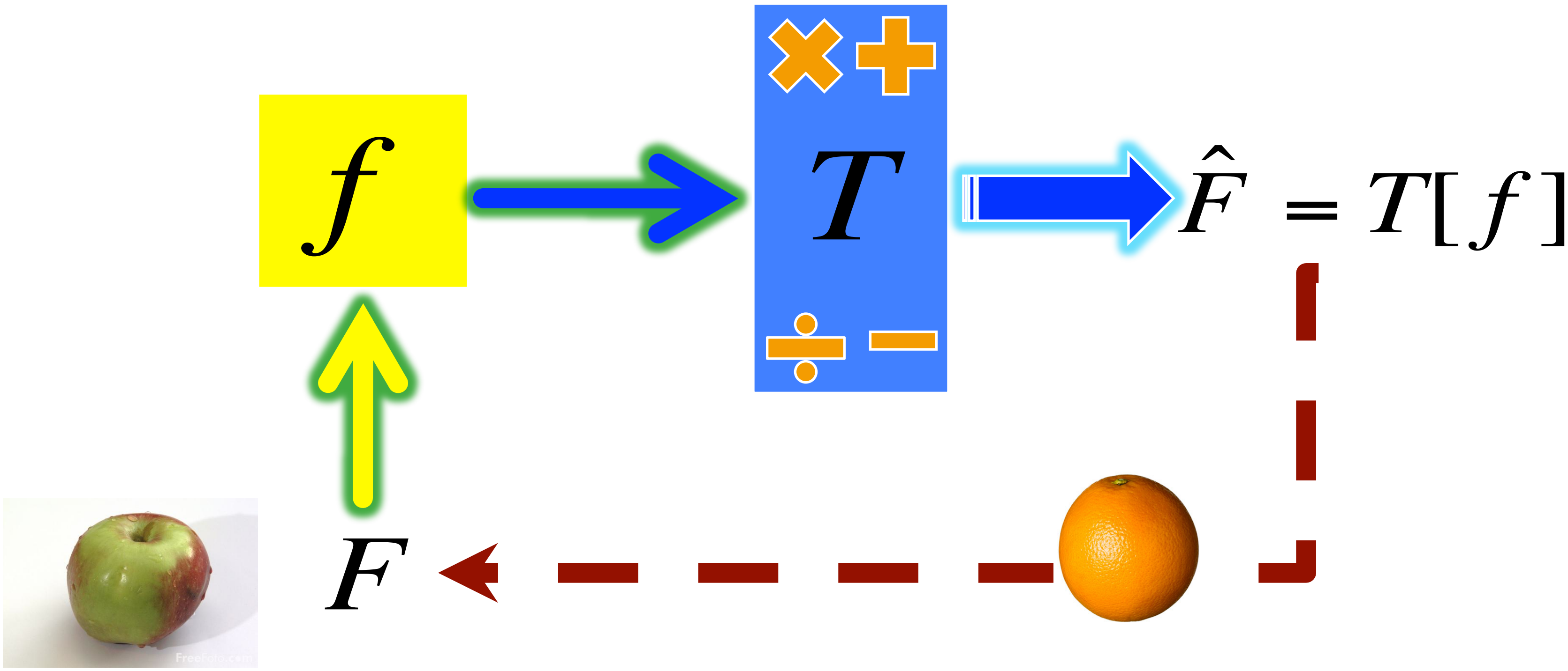


$$\hat{F} = T[f]$$





ill-posed inverse problems



Key Steps

- Image contrast enhancement
- Image deblurring
- Image Inpainting
- Image Denoising
- Image Representation
- Image Segmentation
- Image Registration

Part 5. Challenges and Strategies

Society

Society for Industrial and Applied Mathematics

IEEE Computer Society

IEEE Signal Processing Society

Organization for Human Brain Mapping

International Society for Magnetic Resonance in Medicine

Medical Image Computing and Computer Assisted Intervention

Conference

SIAM Conference on Imaging Science (IS)

Human Brain Mapping (HBM)

IEEE Conference on Computer Vision and Pattern Recognition (CVPR)

Medical Image Computing and Computer Assisted Intervention (MICCAI)

Information Processing in Medical Imaging (IPMI)

International Symposium on Biomedical Imaging (ISBI)

Neural Information Processing Systems Foundation (NIPS)

Publications

SIAM Journal on Imaging Sciences
IEEE Pattern Analysis and Machine Intelligence
NeuroImage
IEEE Transactions on Medical Image
IEEE Transactions on Signal Processing
IEEE Transactions on Image Processing
IEEE Transactions on Signal Processing Magazine
Medical Imaging Analysis
Human Brain Mapping

Annals of Applied Statistics
Biometrics
Biostatistics
Journal of American Statistical Association ACS

Data Sets

Public Data Sets:

- **1000 Functional Connectomes Project**
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)**
- **NIH MRI Study of Normal Brain Development**
- **National Database for Autism Research**
- **Human Connectome Project**
- **…**

Software

http://www.nitrc.org/

NITRC = The Source for Neuroimaging Tools and Resources

Statistical Parametric Mapping (SPM)

FMRIB Software Library (FSL)

Analysis of Functional NeuroImages (Afni)

3D Slicer

FreeSurfer

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Training

- Courses on Imaging Statistics and Statistical Computing
- Courses on pattern recognition and machine learning.
- Introductory Training Courses in ENAR and JSM
- Advanced Imaging Statistical Courses in HBM and MICCAI
- Applying Imaging Related Training Grants/CANSSI/PIMS
- Collaborating with Statisticians from other universities
- Attracting good students and scholars
- SAMSI Challenges in Computational Neuroscience (CCNS)
- BIRS/Banff Jan 31 – Feb 5, 2016

Part 6. Research Opportunities

Research Opportunities

- Imaging Sequence
  - Evaluation and Optimization, Statistical Methods in Diagnostic Medicine, Experimental Design
- Imaging Reconstruction
  - Variable Selection Problem, Matrix Decomposition, Optimization
- Imaging-signal Model
  - Parametric Models and Nonparametric Models
- Imaging Segmentation
  - Cluster Analysis, Markov Random Field, Partial, Differential Equation, Bayesian Methods
- Imaging Registration
  - Regression Methods, Infinite-dimensional Statistics

Research Opportunities

- Shape Analysis
  - Differential Geometry, Statistical Shape Theory, Nonparametric Methods
- Population Statistics
  - Regression Analysis, Longitudinal Data Analysis, Multivariate Data Analysis, Functional Data Analysis, Nonparametric Smoothing Methods
- Functional Data
  - Image-on-Image, Image-on-Scalar, Scalar-on-Image, Functional Smoothness, Spatial-temporal Covariance Operators, Large Subject Heterogeneity, Design-related Statistical Issues
- Network Statistics
  - Random Graph Models
- Imaging Genetics
  - High-dimensional Response and Covariate Problems, Multiple Comparison, Causal Inference