

Statistical Challenges for Neuroimaging Data Analysis

Lecture 1. Introduction

WNAR 2018 @ Edmonton
Linglong Kong
lkong@ualberta.ca



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.

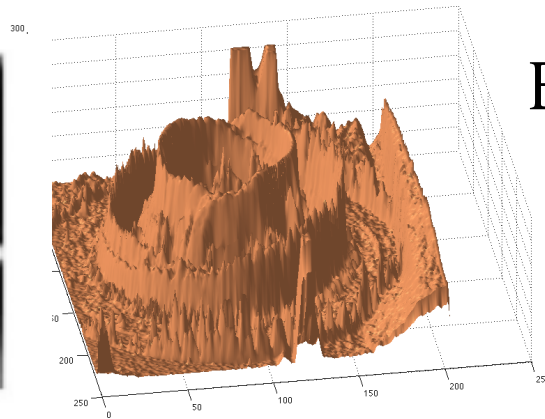
- **As** $\tilde{x} \in \Omega \subseteq R^k$ $f(\tilde{x}) \in M \subseteq R^m$ $f : \Omega \rightarrow M \subseteq R^m$

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 $f : \Omega_0 \rightarrow \{0, 1, \dots, M_0\}$

- **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.

Part 2. Image acquisition

Imaging Devices

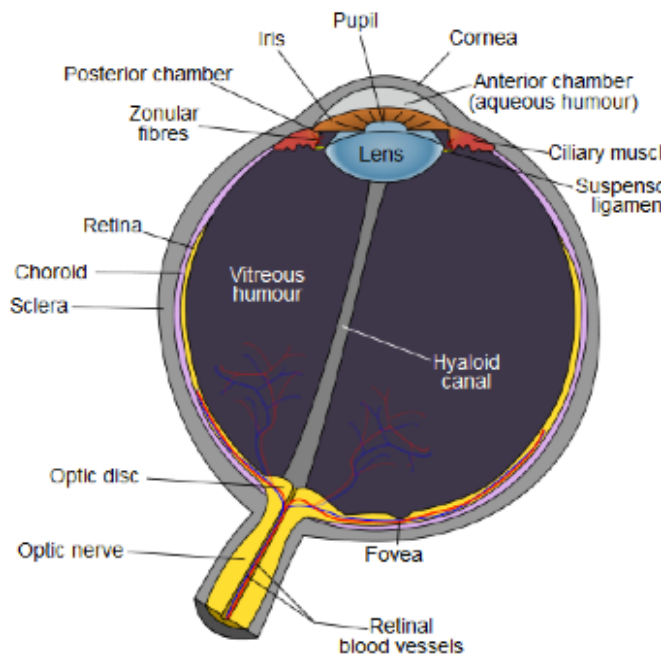


Figure 5.13 PET scanner. A movable table shifts the patient through the circular hole in the gantry. The external design is similar to that of a CT scanner and to some extent to that of an MRI scanner. (Courtesy of the Department of Nuclear Medicine.)

Targets

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

Electromagnetic Waves

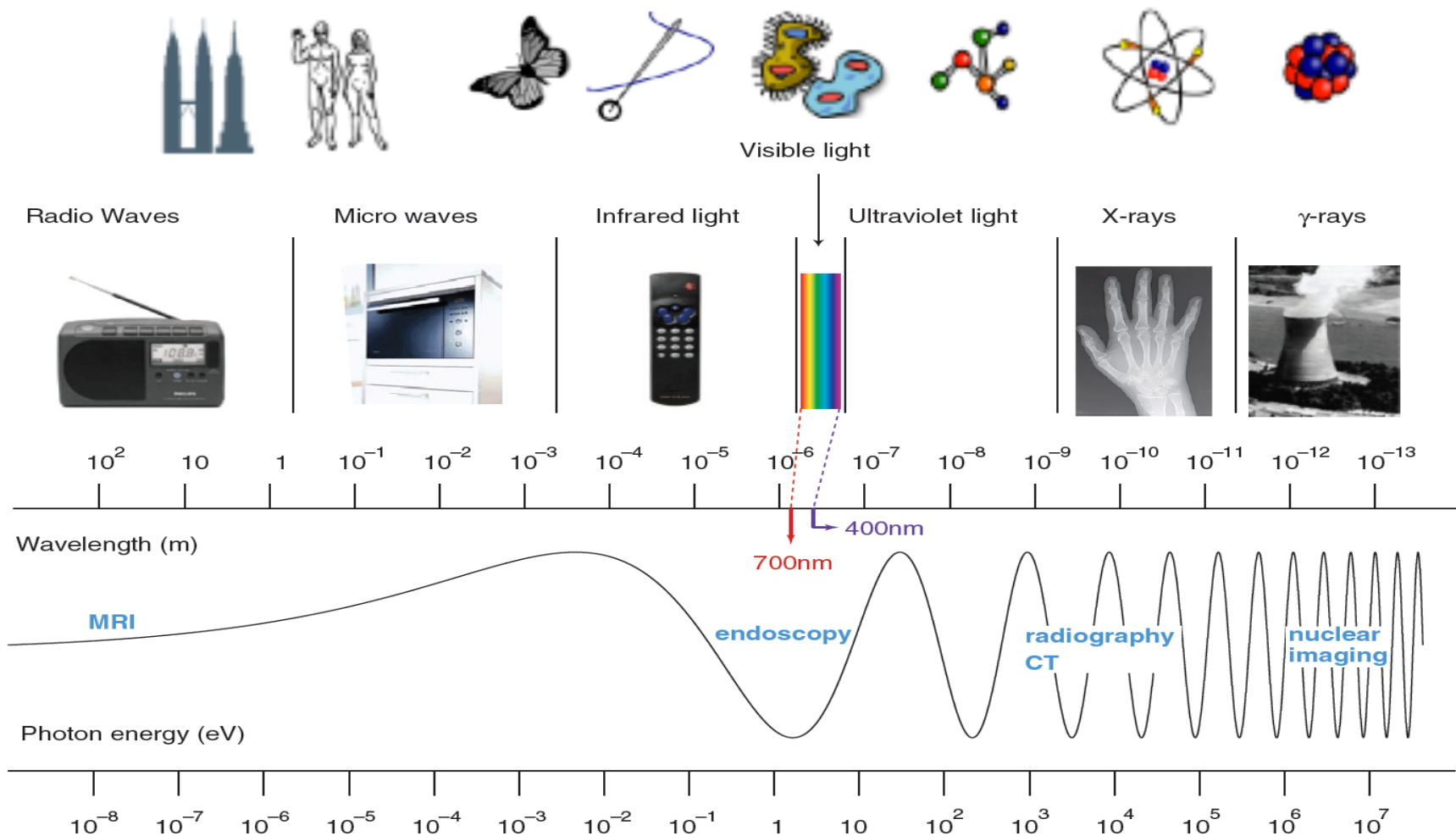


Figure 2.1 The electromagnetic spectrum.

Electromagnetic Imaging

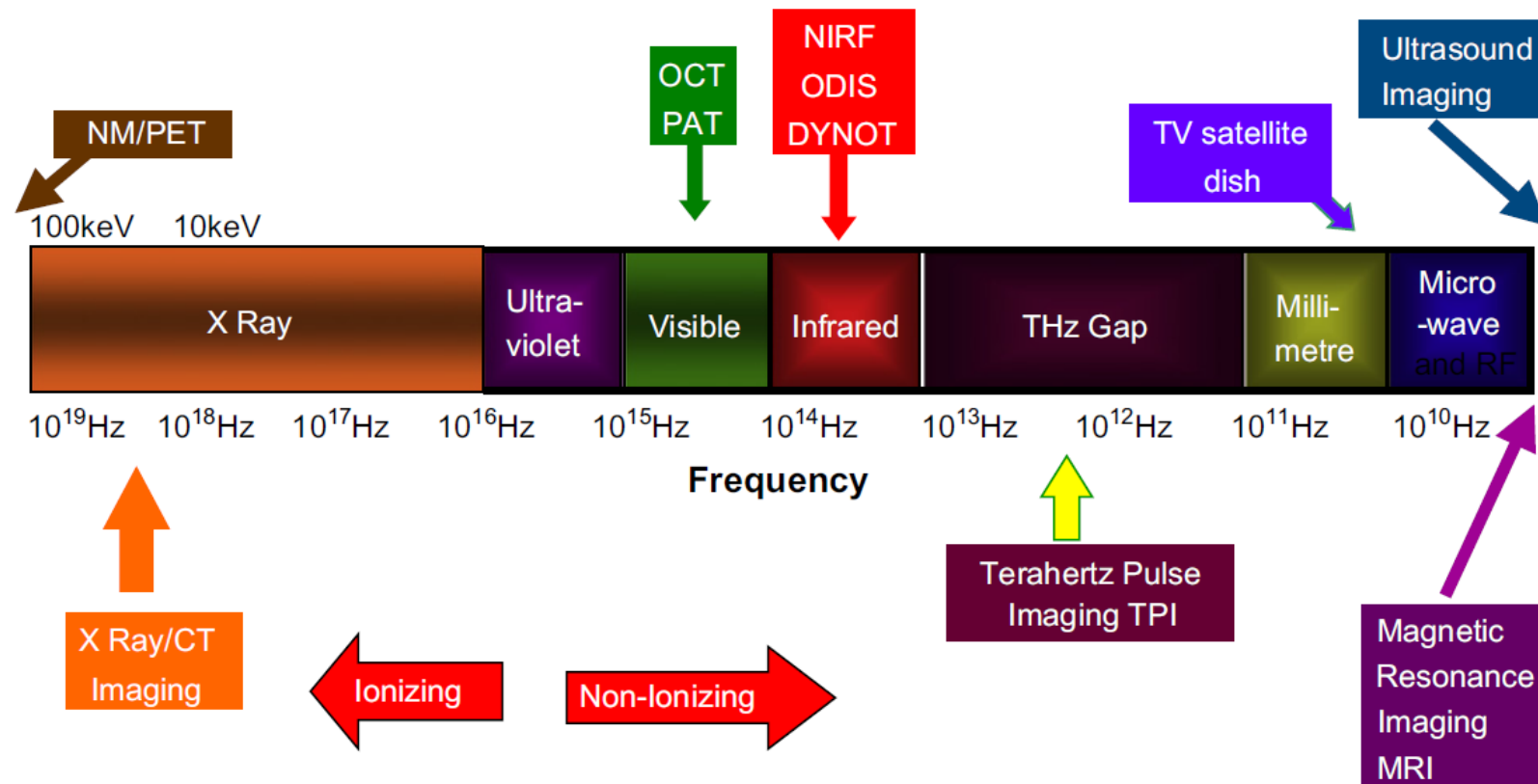


Figure 4 – Frequency spectrum of electromagnetic radiation imaging technologies.

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

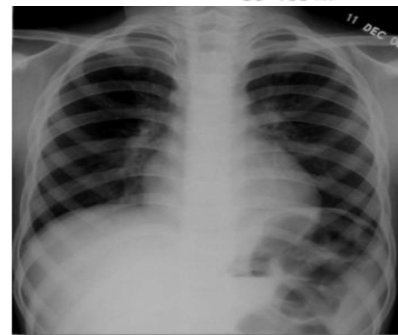
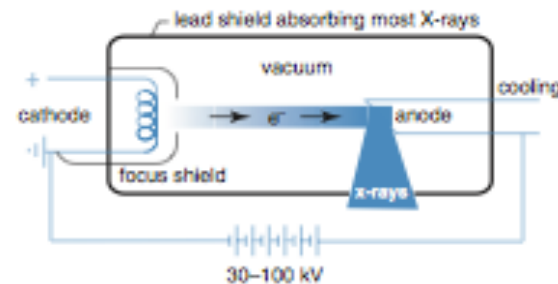
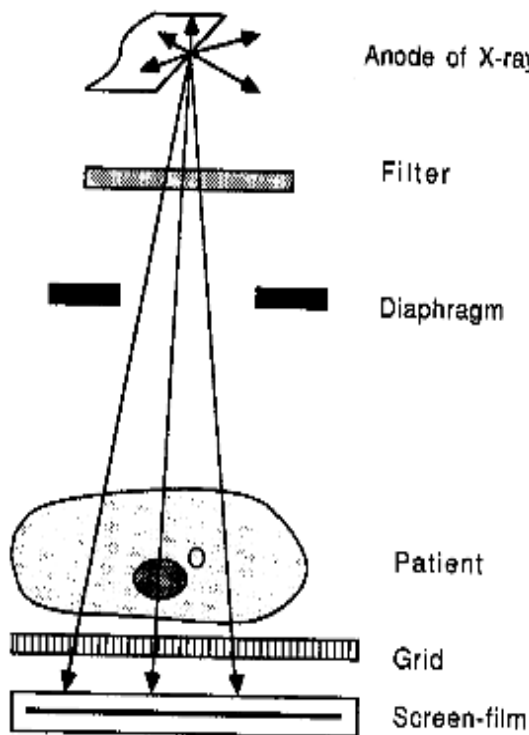
From Wikipedia, the free encyclopedia

- 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).



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.

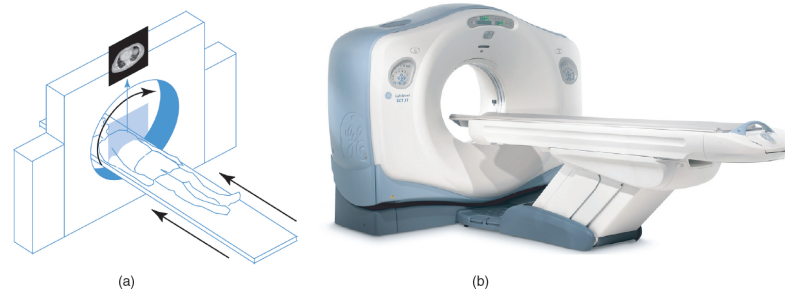
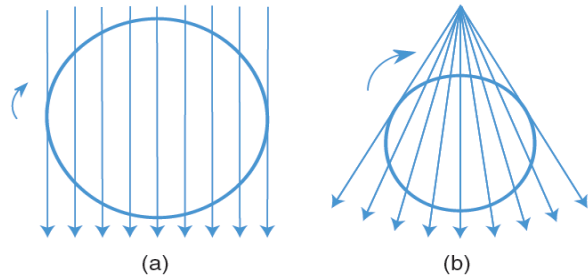


Figure 3.1 (a) Schematic representation, and (b) photograph of a CT scanner (Courtesy of GE Healthcare)

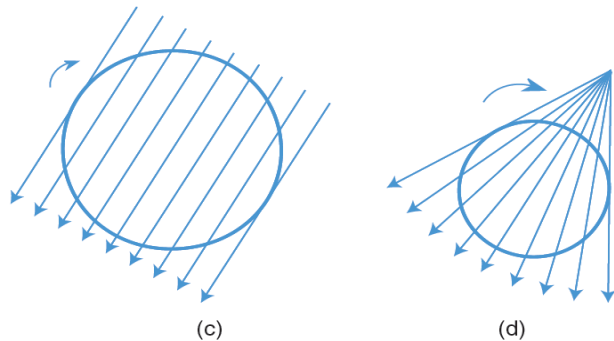
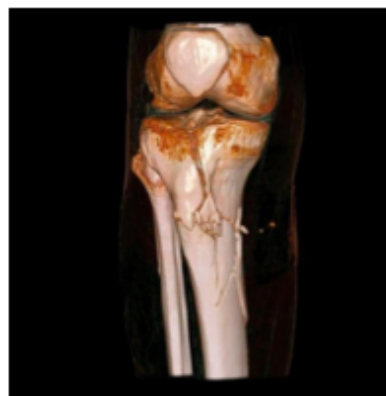
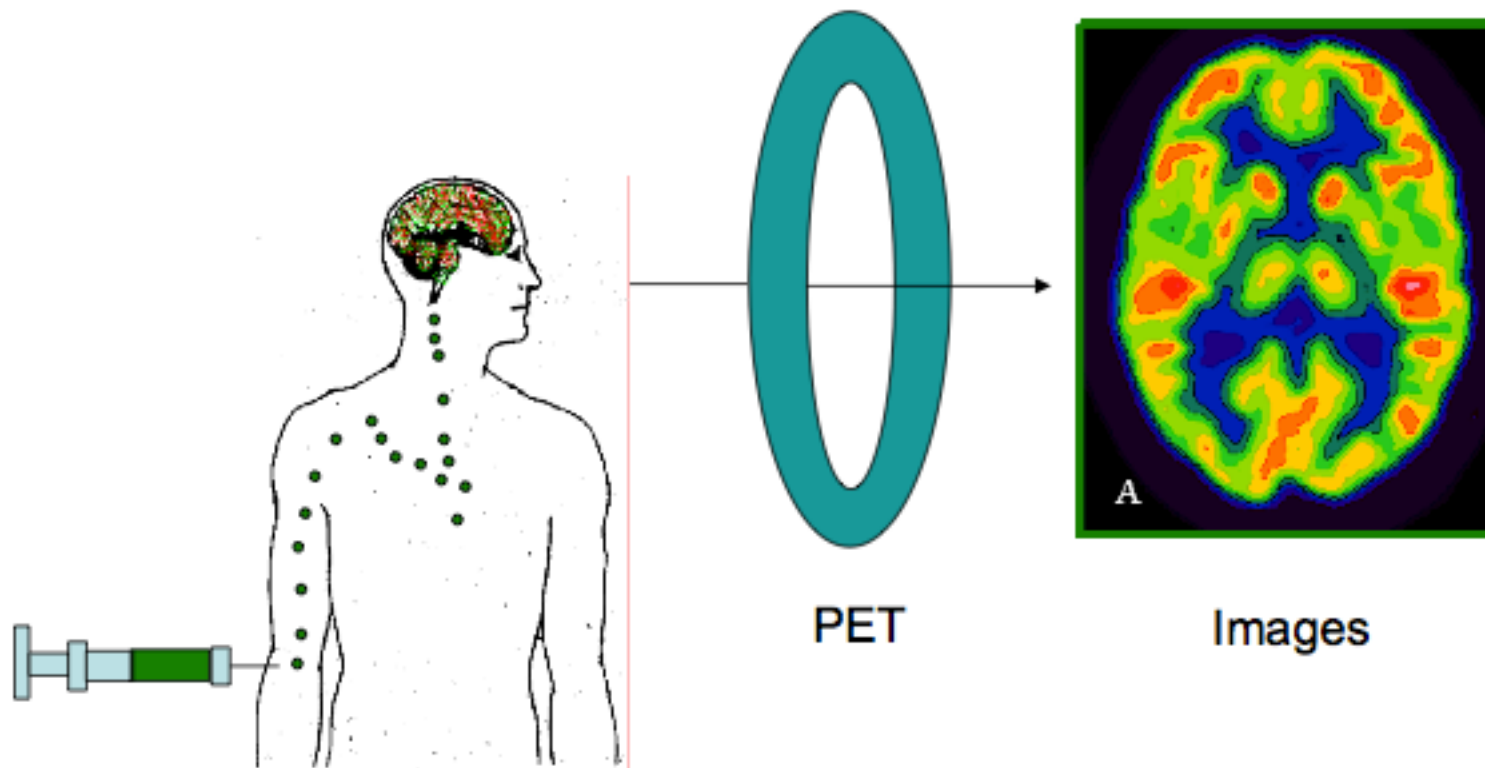


Figure 3.2 Basic scanning procedure in CT. A set of lines is scanned covering the entire field of view: (a) parallel-beam geometry and (b) fan-beam geometry. This process is repeated for a large number of angles (c and d).



SPECT and PET



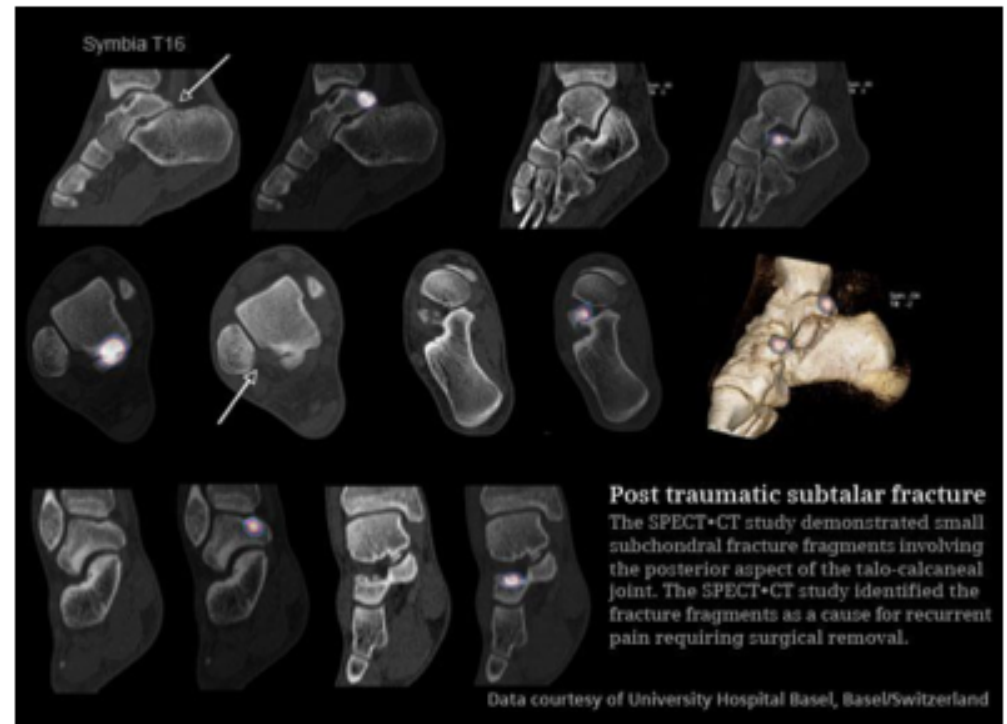
SPECT

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=l6V6VLxQIkY>

PET

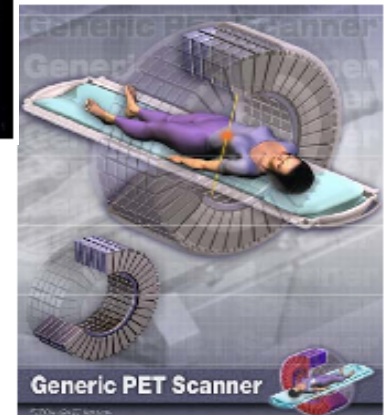
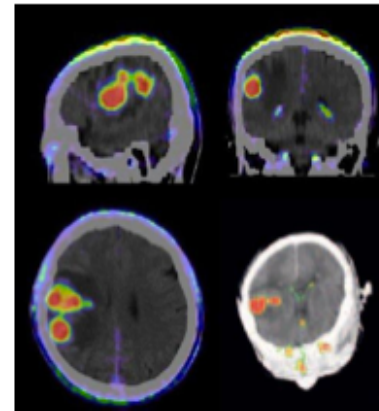
PET=Positron Emission Tomography is a functional imaging technique to extensively study the relationship between energy consumption and neuronal activity. It uses positron-emitting radioactive tracers that are attached to molecules that enter biological pathways of interest.

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 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

Fetus at 14 weeks

Fetus at 29 weeks

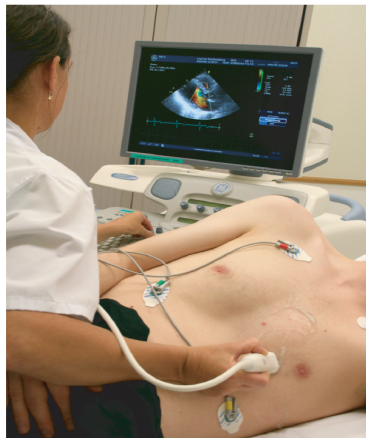
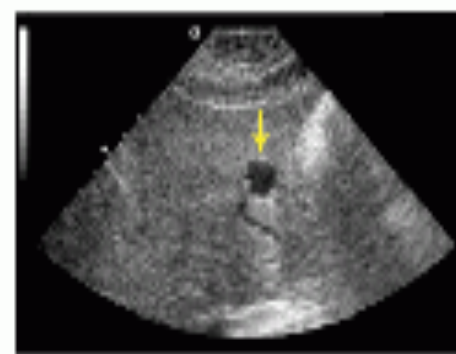
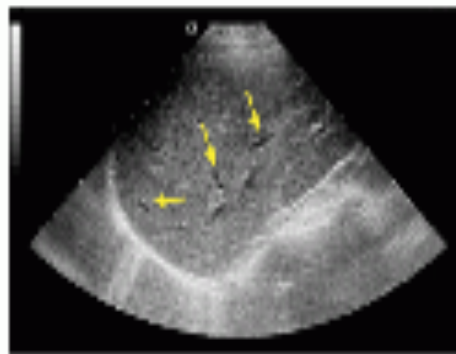


Figure 6.34 Example of a commercial echocardiographic scanner. (Courtesy of the Department of Cardiology.)



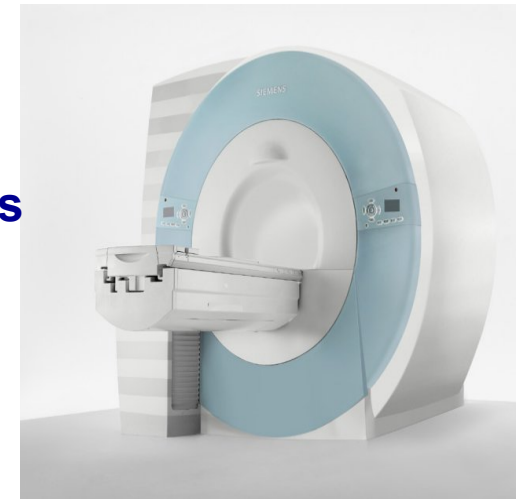
2D transducer: general appearance



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>

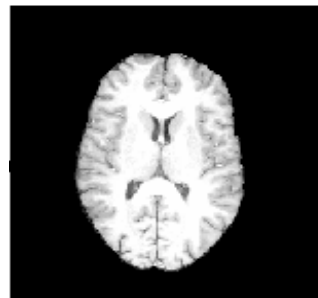
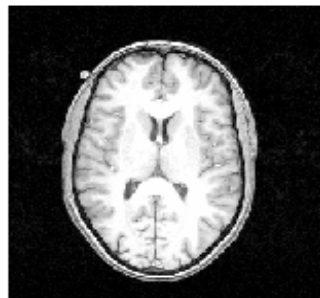
Magnetic Resonance Imaging

- 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.

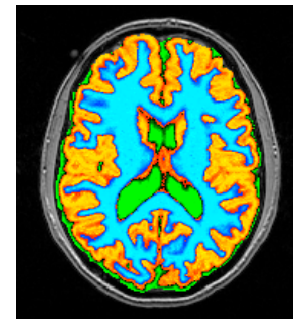
<http://www.youtube.com/watch?v=XwUn64d5Ddk&feature=related>

Magnetic Resonance Imaging

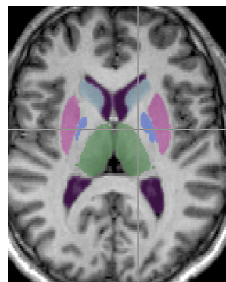
Basic stages in the structural analysis pipeline:



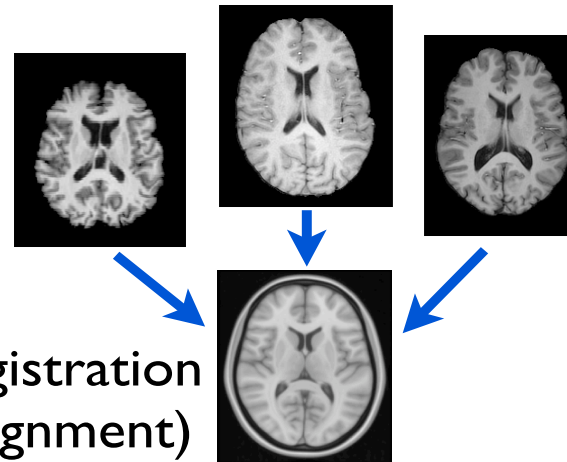
Brain Extraction



Segmentation
(tissue-type)



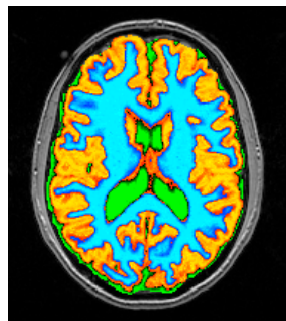
Segmentation
(structure)



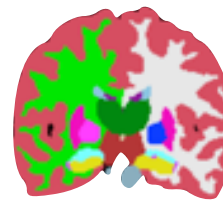
Registration
(alignment)

Magnetic Resonance Imaging

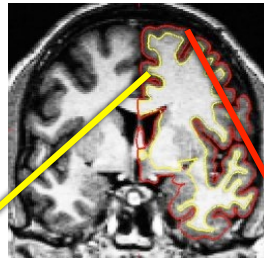
- Quantify tissue volumes and structure shape/size



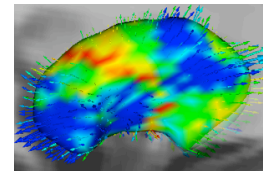
Tissue types:
GM / WM / CSF



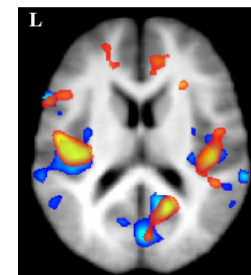
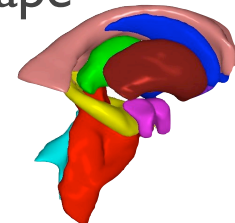
Sub-cortical
structure &
shape



Cortical
surfaces &
thickness



Local GM
changes



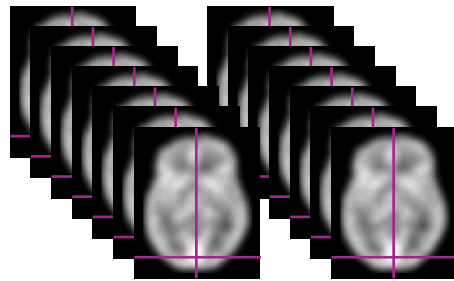
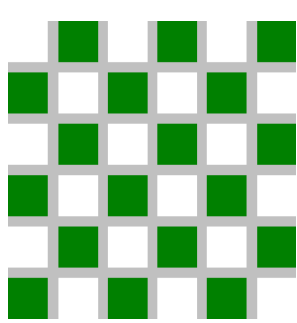
Magnetic Resonance Imaging

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

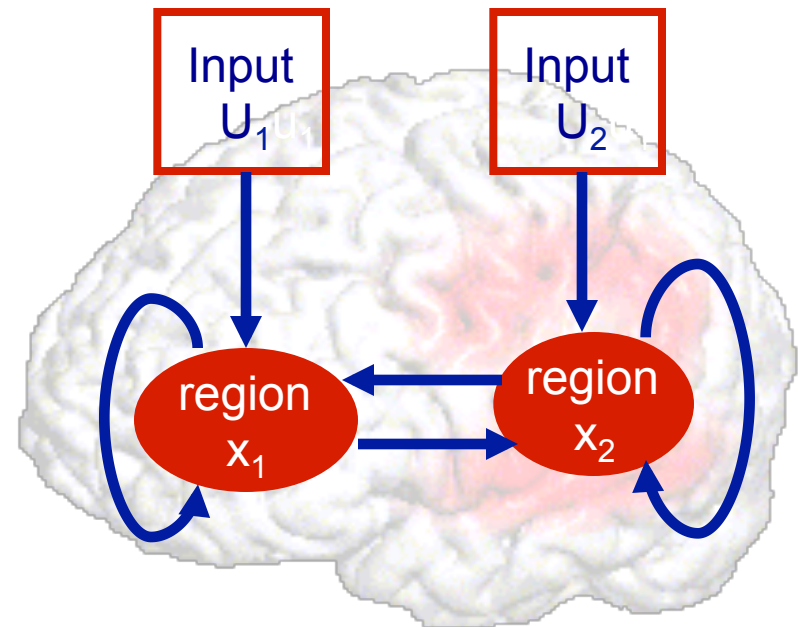
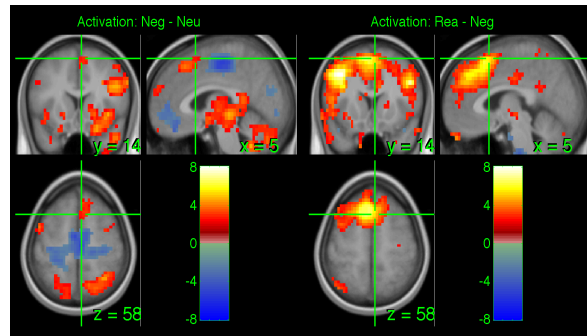
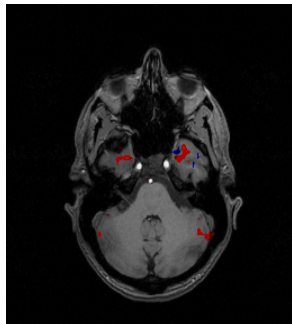
- | | |
|---|----------------------------------|
| • Susceptibility-Weighted Imaging (SWI) | <u>Sensitive to:</u> |
| • Quantitative Susceptibility Imaging (QSI) | iron
(and myelin) |
| • Magnetization Transfer (MT) | chemical species/
environment |
| • MR Spectroscopy (MRS) | |
| • Angiograms & Venograms | arteries & veins |
| • Quantitative T_1 and T_2 maps (relaxometry) | tissue μ structure |
| • Myelin maps | myelin |
| • B_0 map (fieldmap) | fields |
| • B_1 map (RF) | within head |

Functional MRI (fMRI)

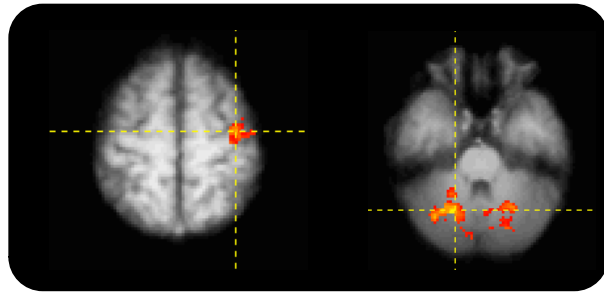
Functional MRI measures the hemodynamic response (change in blood flow) related to neural activity in the brain or spinal cord of humans or other animals. Since the early 1990s, fMRI has come to dominate the brain mapping field due to low invasiveness, absence of radiation exposure, and relatively wide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



group 1 group 2



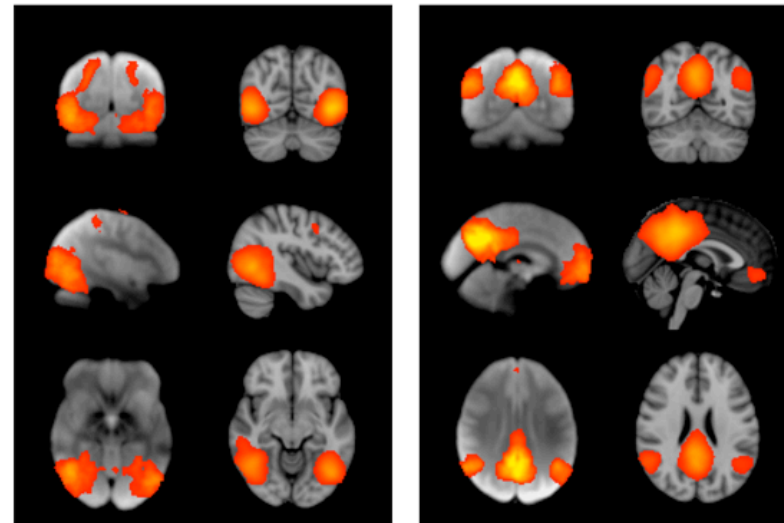
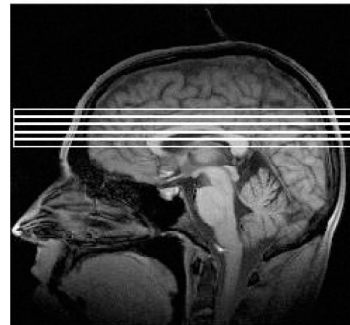
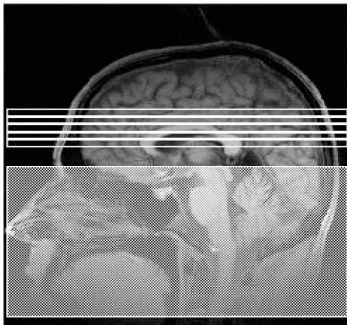
Functional MRI (fMRI)



Task FMRI

Tag

Control

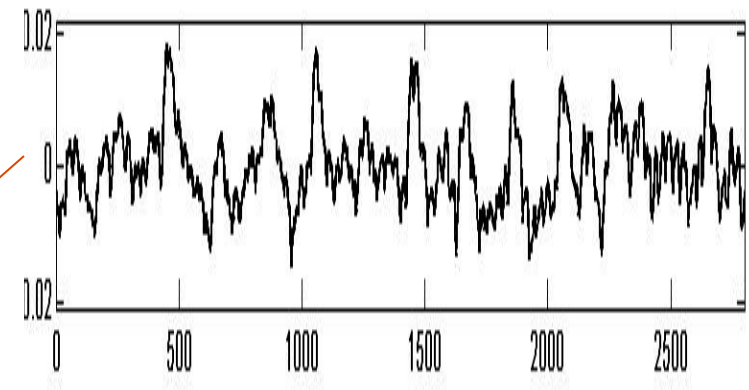
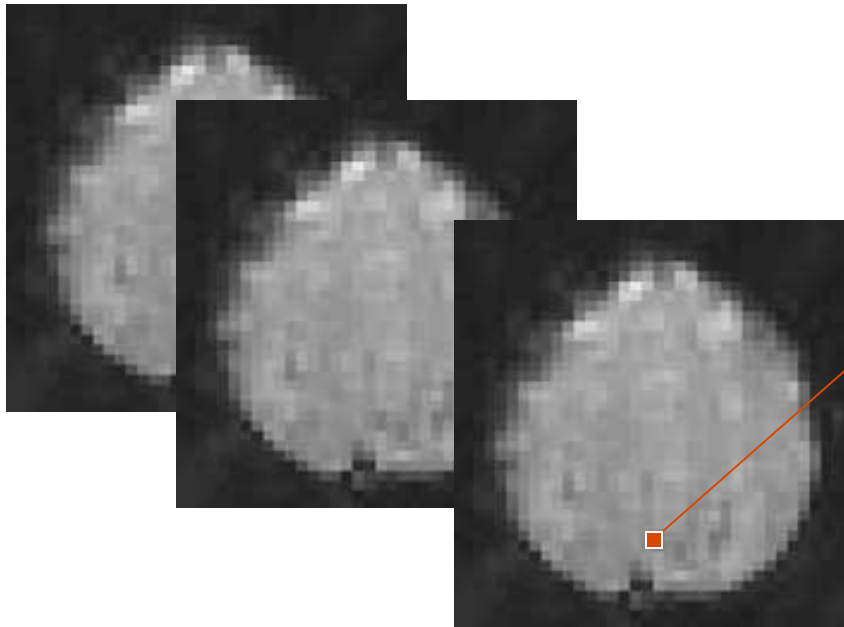


Resting-State FMRI
& Connectivity

ASL Arterial Spin Labeling

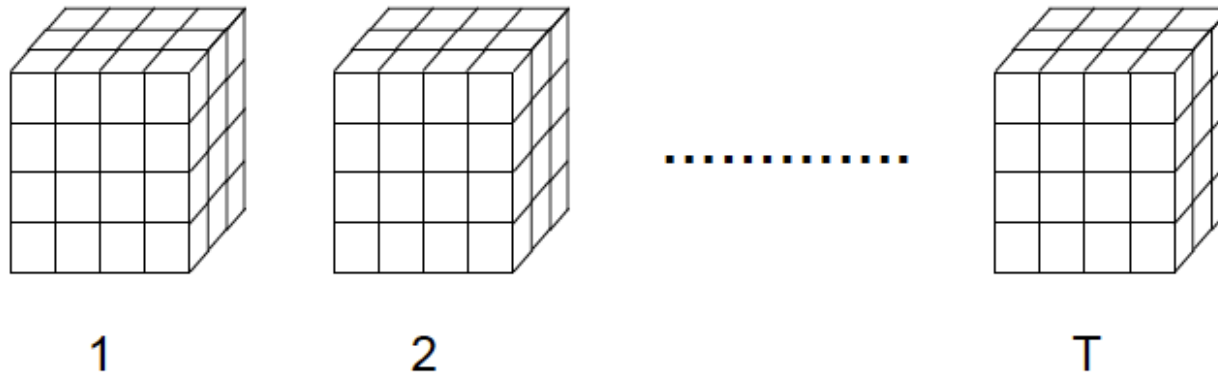
Functional MRI (fMRI)

fMRI studies brain function.



Functional MRI (fMRI)

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



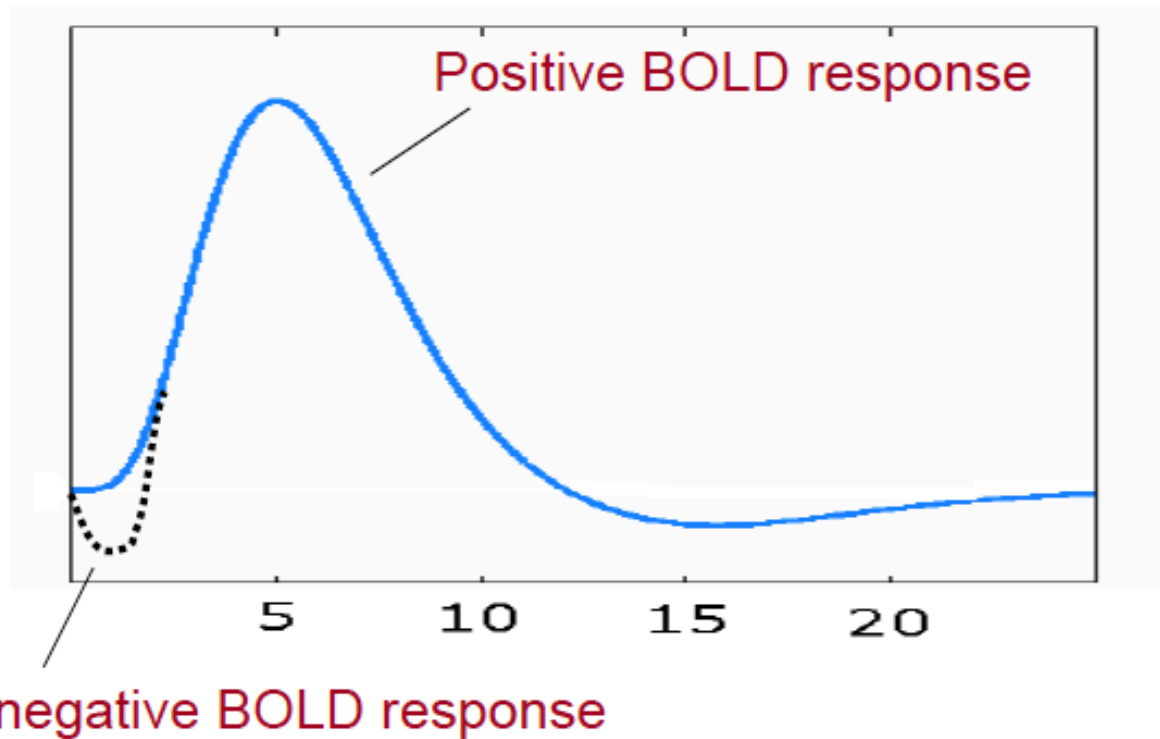
- During the course of an experiment several hundred images are acquired (~ one every 2s).

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.

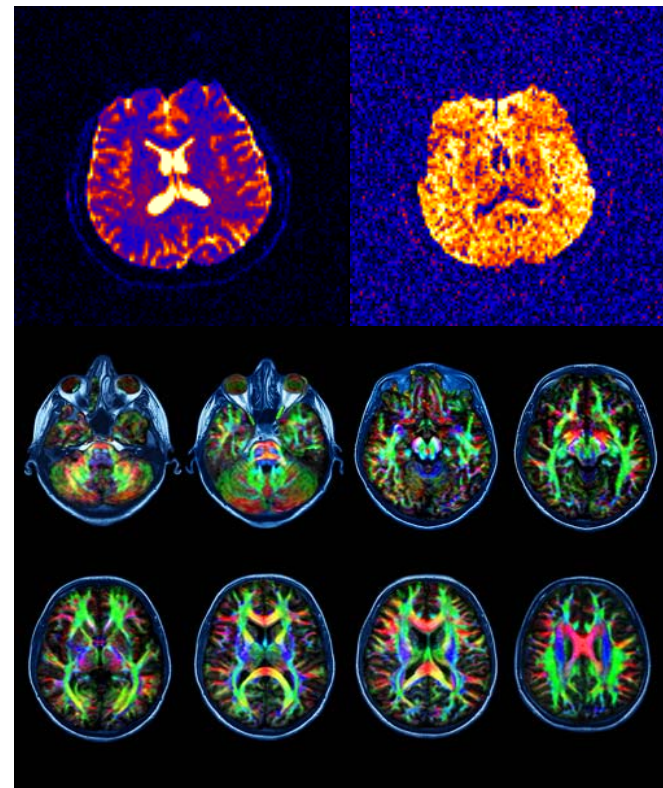
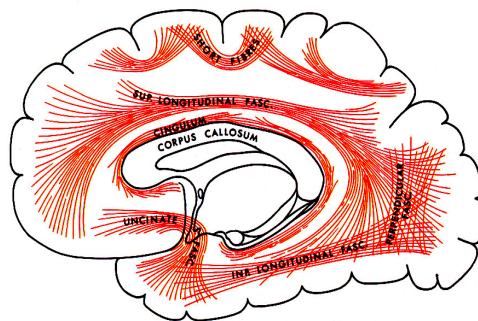
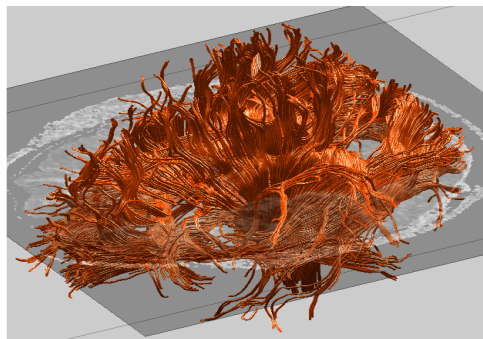
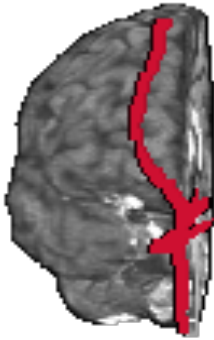
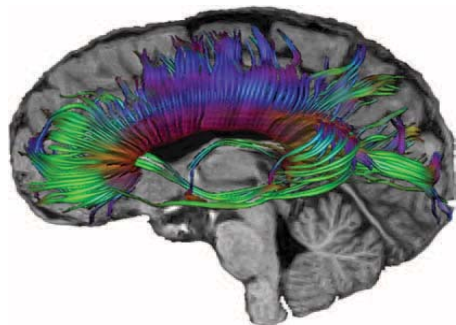
BOLD fMRI

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



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 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.

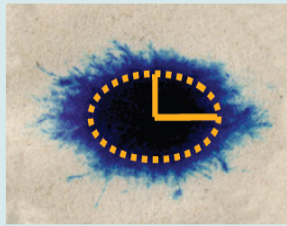
$$D = \begin{pmatrix} d_{1,1} & d_{2,1} & d_{3,1} \\ d_{2,1} & d_{2,2} & d_{3,2} \\ d_{3,1} & d_{3,2} & d_{3,3} \end{pmatrix} \geq 0$$

Diffusion Tensor MRI

Anisotropic Diffusion



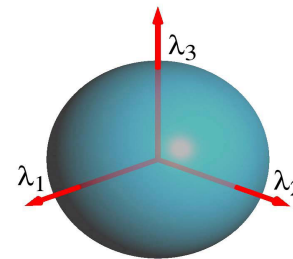
Kleenex



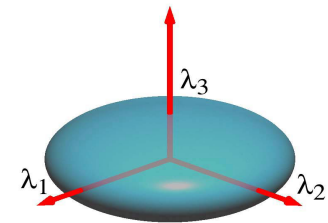
newspaper

Provided by
G. Kindlmann

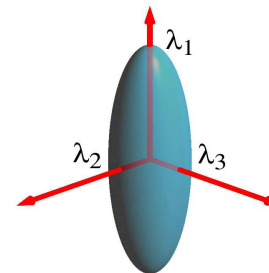
Diffusion Tensors



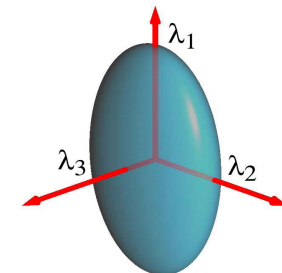
(a)



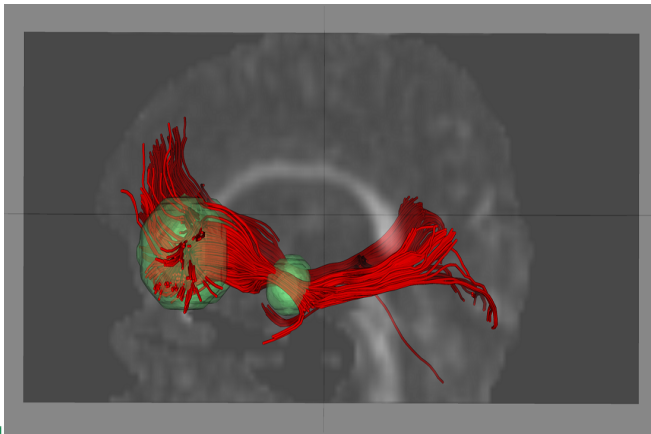
(b)



(c)

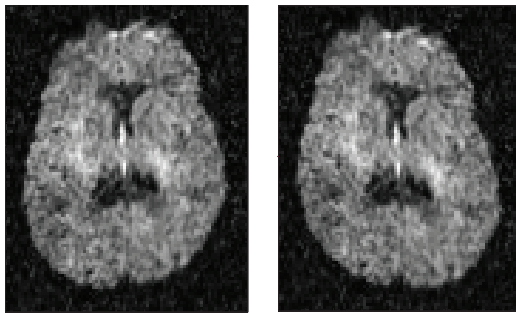


(d)

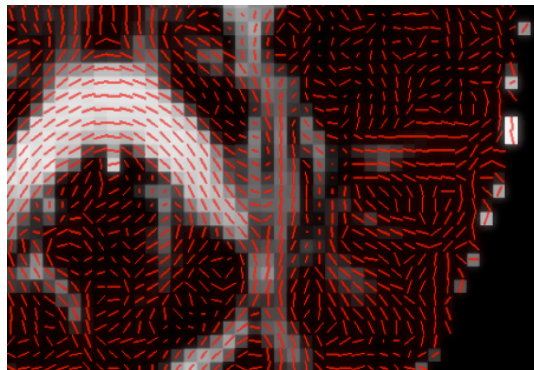


Diffusion Tensor MRI

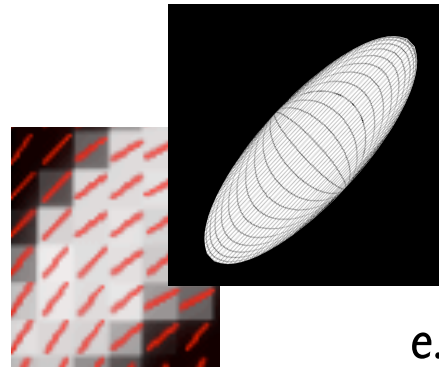
Basic stages in the diffusion analysis pipeline:



Eddy Current & Motion Correction

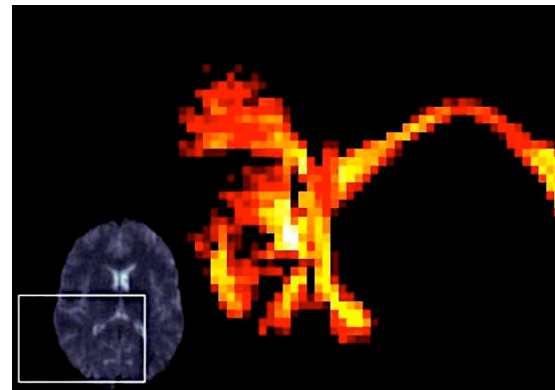


Fibre/
direction
modelling

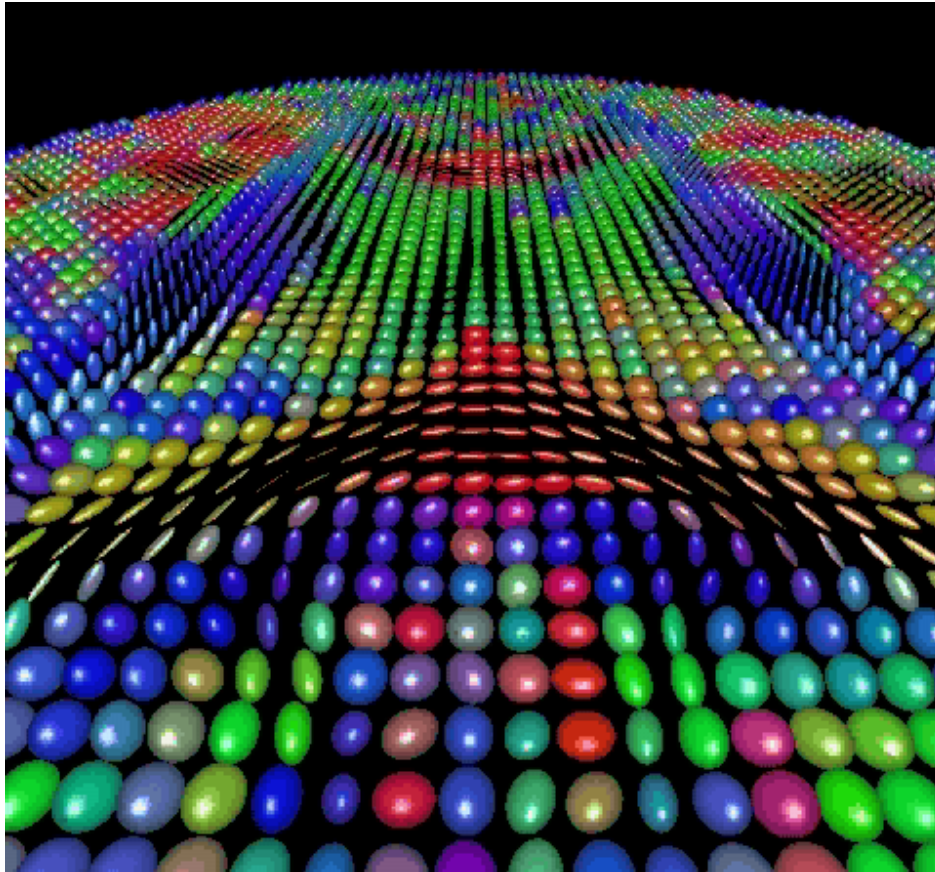


“Tensor”
Fitting
e.g. FA, MD

Probabilistic Tractography



Diffusion Tensor MRI

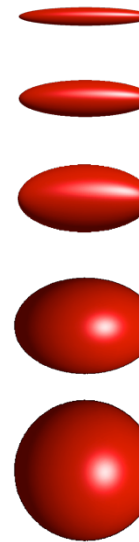


Splenium of the corpus callosum

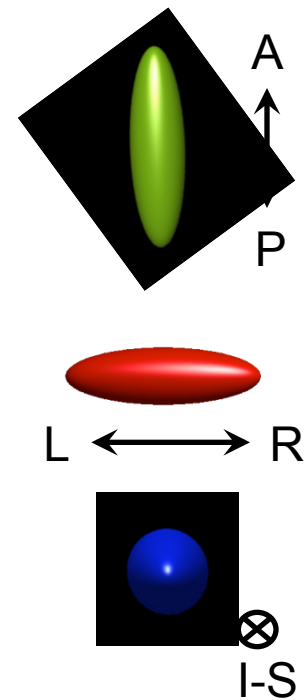
shape

colour

High anisotropy



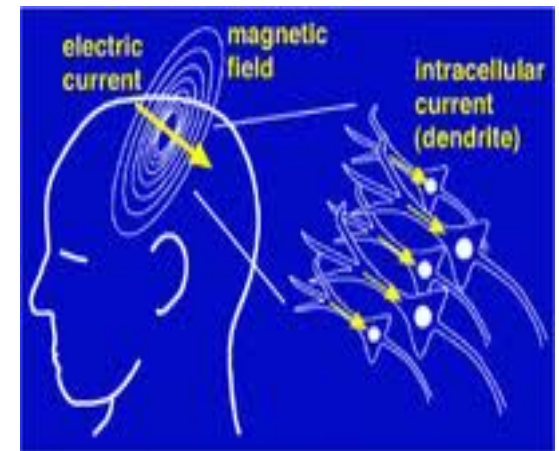
Low anisotropy



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)

Part 3. Neuroimaging Applications

Neuroimaging Applications

Structural MRI

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

Functional MRI (task)

Diffusion MRI

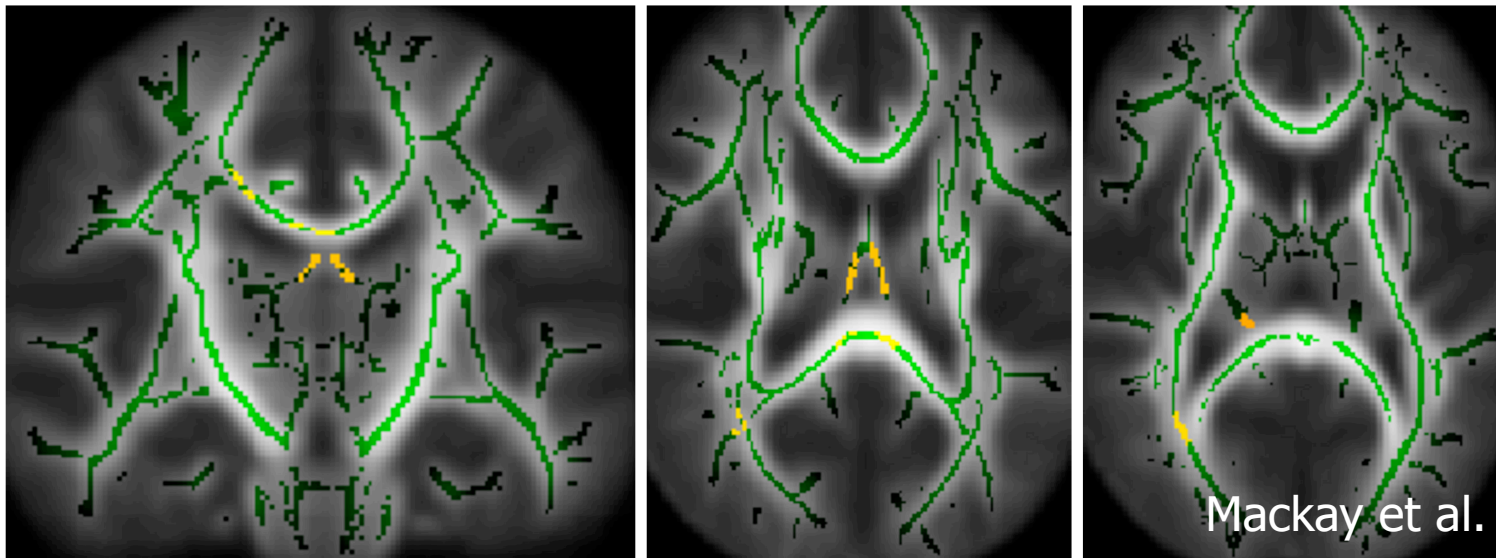
Functional MRI (resting)

Neuroimaging Applications

schizophrenia

Diffusion MRI

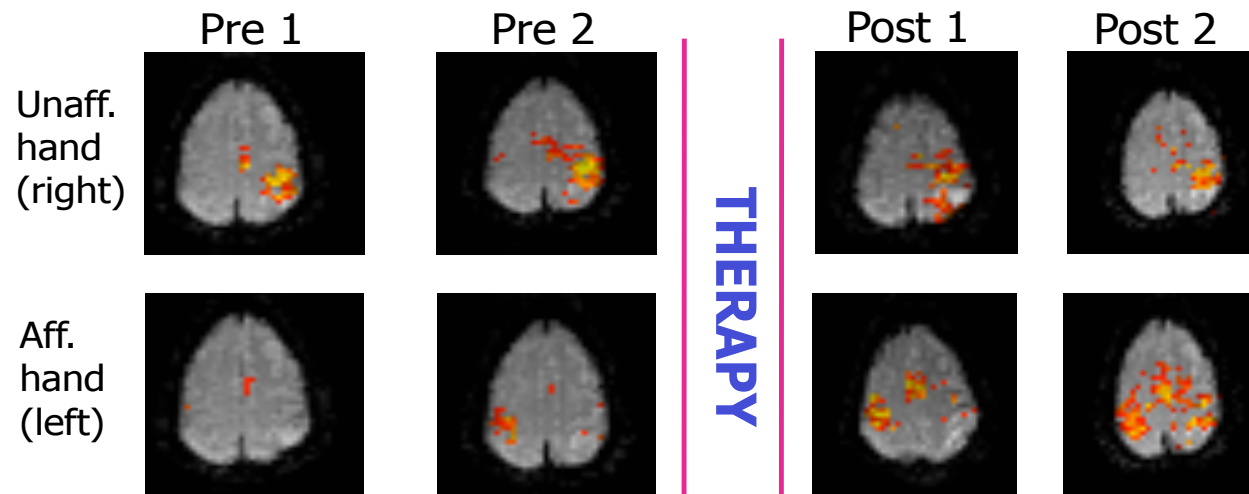
- White matter integrity - imaging tissue nature change
- Damage to brain connectivity - reduction in schizophrenia in corpus callosum, fornix, longitudinal fasciculus



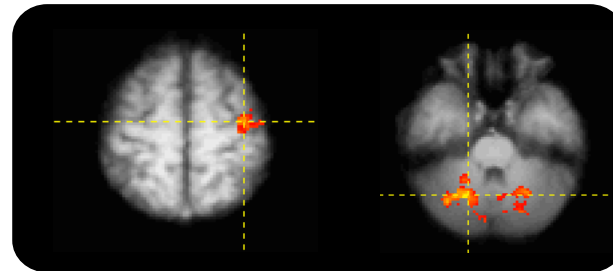
Neuroimaging Applications

stroke therapy

**Single
subject:
responder**



**Group:
Correlations
with
improvement**



**Functional
MRI (task)**

Johansen-Berg, et al.,
Brain 2002

Neuroimaging Applications

Altered **functional connectivity** in young, healthy carriers of APOE- ϵ 4

Distinct patterns of brain activity in young carriers of the *APOE*- ϵ 4 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}

^aUniversity Department of Psychiatry and ^bFunctional Magnetic Resonance Imaging of the Brain Centre, University of Oxford, Oxford OX3 9DU, United Kingdom; ^cLaboratory of Epidemiology, Neuroimaging, and Telemedicine, Istituto di Ricovero e Cura a Carattere Scientifico San Giovanni di Dio-Fatebenefratelli, Brescia 25125, Italy; ^dGlaxoSmithKline Research and Development, Clinical Imaging Centre, London W12 0NN, United Kingdom; and ^eDepartment 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)

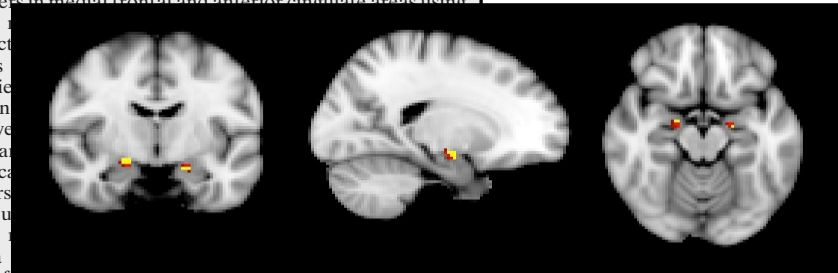
The *APOE* $\epsilon 4$ allele is a risk factor for late-life pathological changes that is also associated with anatomical and functional brain changes in middle-aged and elderly healthy subjects. We investigated structural and functional effects of the *APOE* polymorphism in 18 young healthy *APOE* $\epsilon 4$ -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 $\epsilon 4$ -carriers relative to noncarriers. The encoding task produced greater hippocampal activation in $\epsilon 4$ -carriers relative to noncarriers. Neither result could be explained by differences in memory performance, brain morphology, or resting cerebral blood flow. The *APOE* $\epsilon 4$ 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* $\epsilon 4$ -carriers compared with 8 noncarriers in medial frontal and anterior cingulate areas using a working memory task. Filbey et al. (19) also reported reduced activation in the same areas in 8 *APOE* $\epsilon 4$ -carriers compared with 8 noncarriers using a resting-state task. Both studies used a 10-minute task and found no differences in brain function between carriers and noncarriers.

Here, we tested for associations between *APOE* $\epsilon 4$ -carrier status and structural and functional brain organization in a sample of 35 years old, healthy, right-handed individuals. We tested for associations between *APOE* $\epsilon 4$ -carrier status and spontaneous brain activity relative to a resting-state task. We tested for associations between *APOE* $\epsilon 4$ -carrier status and resting-state functional connectivity (RSFC) 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)



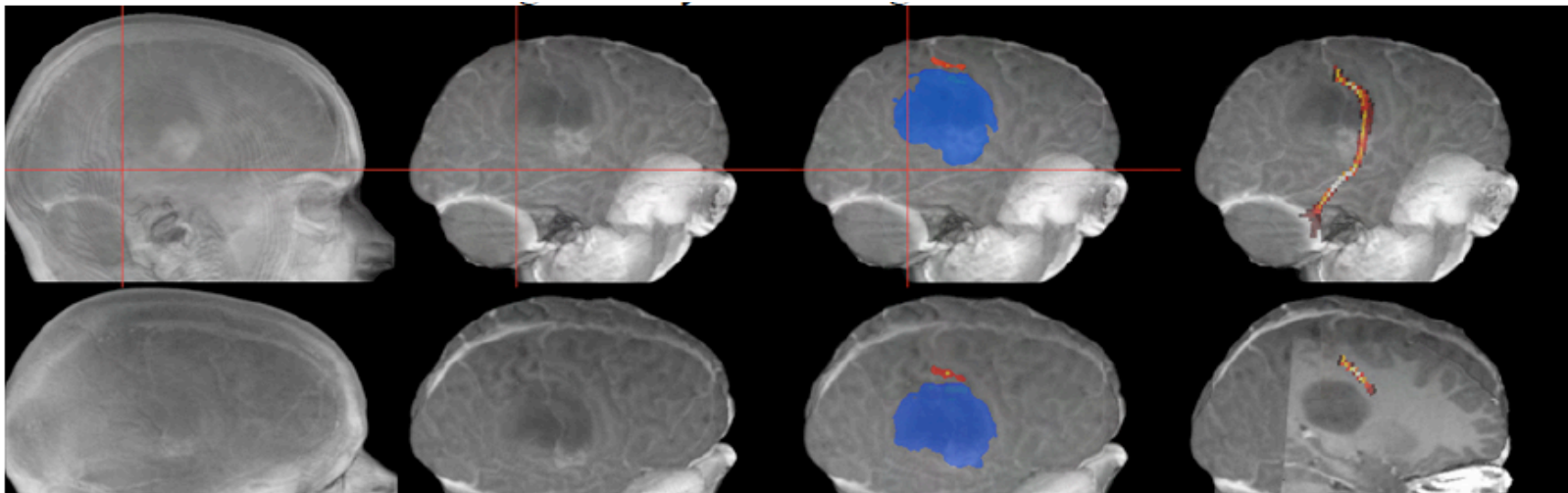
Neuroimaging Applications

Surgical planning

**Diffusion
MRI**

+

**Functional
MRI (task)**



(Bartsch et al., JMRI 2006)

Part 4. Image Processing

Image Processing

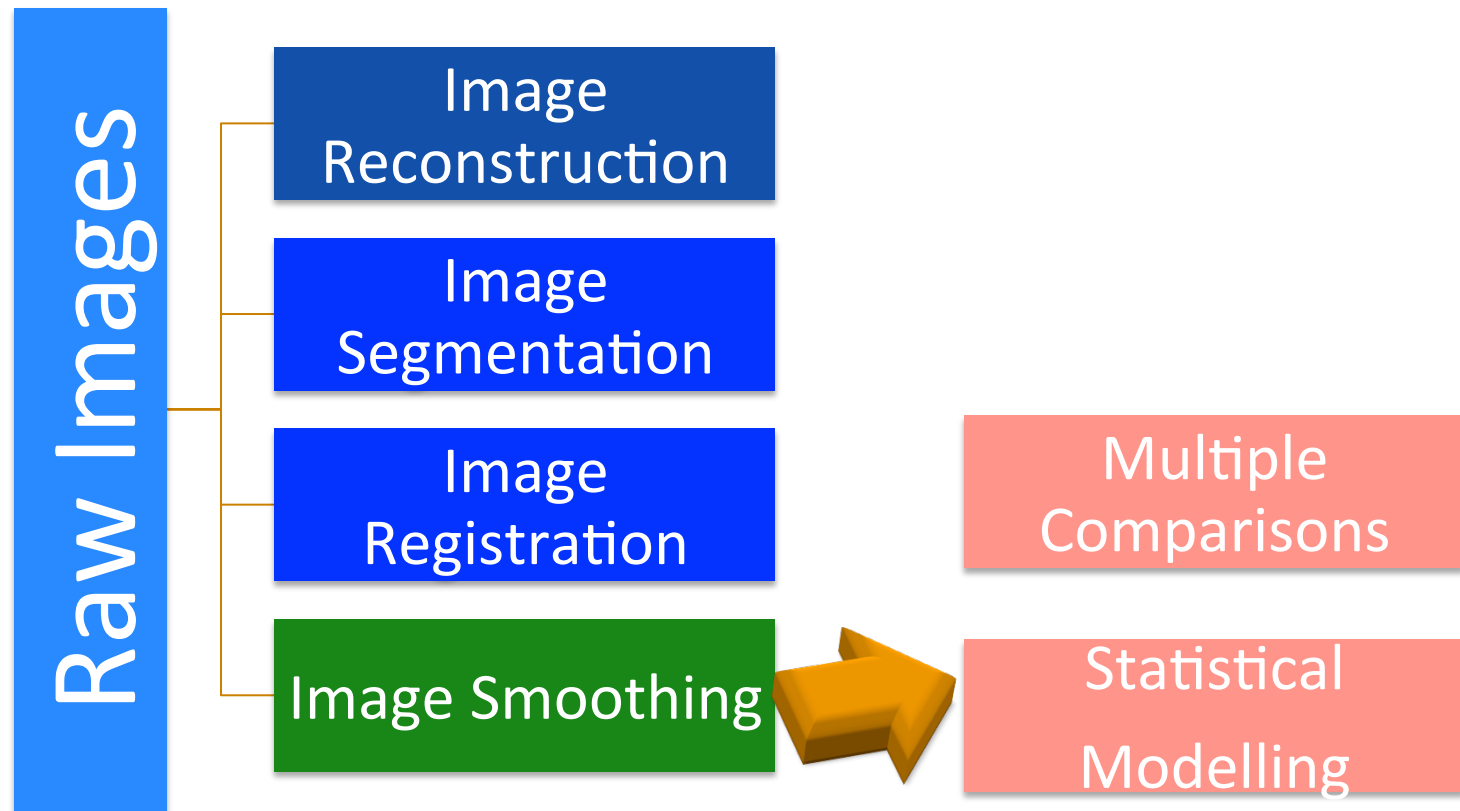
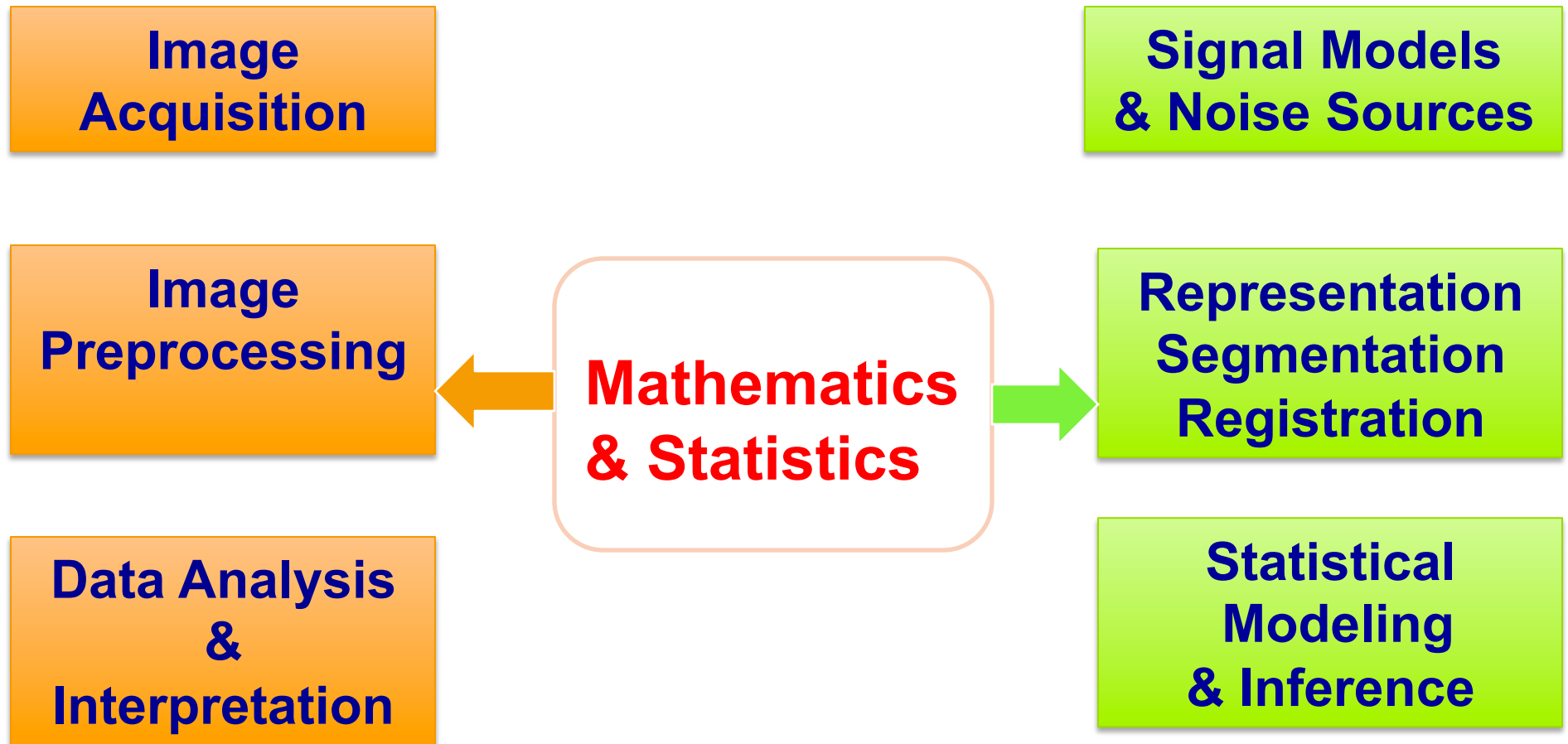


Image Processing



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)

FMRI 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