CEREBRAL BLOOD FLOW AND METABOLISM

Part 3 - 2016
Neuroimaging Techniques

Structural
- Magnetic resonance imaging (MRI)
- Computed tomography (CT)
- Ultrasound

Functional
- Functional MRI
- Positron emission tomography (PET)
- Single photon emission computed tomography (SPECT)
- Electroencephalography (EEG)
- Magnetoencephalography (MEG)
Cerebral Angiography

Cerebral angiography is a procedure that uses a special dye (contrast material) and x-rays to see how blood flows through the brain.

Cerebral angiogram: obtained using an iodine based contrast medium.
The cerebral angiogram of an 87-year-old man with acute onset left hemiplegia.

A: preoperatively, middle cerebral artery occlusion (no collateral supply)

B: after intra-arterial thrombolysis. One segment has recanalized with restoration of blood flow to the superior division, but a persistent occlusion in the inferior division.

short arrow: right internal carotid artery
long arrow: middle cerebral artery
arrowhead: anterior cerebral artery
The cerebral angiogram of a 67-year-old woman presenting with acute onset unresponsiveness and quadriparesis.

A: occlusion at the mid-basilar level with absent flow to the distal basilar artery as well as the distal branches of the basilar artery

B: post-thrombolysis, complete recanalization of the basilar artery

short arrow: left vertebral artery
long arrow: basilar artery
arrowhead: posterior inferior cerebellar arteries
white arrow: posterior cerebral arteries
white arrowhead: superior cerebellar arteries
Computed Tomography

Tomography

~ Imaging in sections, or slices

Computed

~ Computerized algorithms: geometric processing used to reconstruct an image
Computed Tomography

**Uses X-rays**
- Dense tissue, like bone, blocks x-rays.
- Gray matter weakens (attenuates) the x-rays.
- Fluid attenuates even less

A computerized algorithm (filtered back projection) **reconstructs** an image of each slice.
CT Image Formation
CT Image Formation

Reconstruction matrix

\[
\begin{align*}
    a_{11} + a_{12} + a_{13} + a_{14} + a_{15} &= 2 \\
    a_{11} + a_{22} + a_{23} + a_{24} + a_{25} &= 2 \\
    a_{31} + a_{32} + a_{33} + a_{34} + a_{35} &= 2 \\
    a_{41} + a_{42} + a_{43} + a_{44} + a_{45} &= 2 \\
    a_{51} + a_{52} + a_{53} + a_{54} + a_{55} &= 2 \\
    a_{11} + a_{22} + a_{33} + a_{44} + a_{55} &= 6 \\
    a_{15} + a_{25} + a_{35} + a_{45} + a_{55} &= 2 
\end{align*}
\]
CT Image Reconstruction – 6 Slices
CT Image Reconstruction – 12 Slices
CT Image Reconstruction – Final Image
Perfusion CT

- Perfusion computed tomography (CT) allows rapid qualitative and quantitative evaluation of cerebral perfusion by generating maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT).

- The examination is based on the indicator dilution theory: iv. administration of contrast medium → the X-ray density of the brain temporarily increases. Mathematical algorithms: parameters denoting cerebral perfusion are calculated and represented in the form of color-coded parameter images.

Stroke: border of damage
Computed tomography angiography (CTA) is a computed tomography technique used to visualize arterial and venous vessels throughout the body.

Precise anatomical images available (to determine vessel diameter, the surrounding soft tissue structures and bony parts)
CT Angiography

Benefits

- Examination of blood vessels in many key areas (eg. brain, kidneys, lungs)
- Displays the anatomical detail of blood vessels more precisely than other techniques (MRI or ultrasound)

Risks

- Risk of an allergic reaction (contrast material containing iodine)
- Contrast material can harm kidney (kidney disease or diabetes)
- Associated with a significant dose of ionizing radiation
Perfusion-CT demonstrates mixed infarct and penumbra in the left side, whereas CT-angiography relates it to an occlusion (arrow).

After intravenous thrombolysis: recanalization of the left sylvian artery. Follow-up perfusion CT shows an almost complete resolution of the penumbra.
Modern imaging methods

SPECT, PET, nMRI
History of Nuclear Medicine

- Starts with the invention of the X-ray
- 1946: radioactive iodine was used to treat a patient’s thyroid cancer
- 1950’s: radioactive nucleotides were being used to treat hyperthyroidism
- Soon after: snapshot images of form and structure or organs (liver, spleen, brain, gastrointestinal track, ect.)
- 1980’s: nuclear medicine cameras and imaging computers allowed for the instillation of over 100 different procedures

Nuclear medicine became an integral part of patient care, and an important diagnostic and therapeutic specialty.
Single Photon-Emitted Computed Tomography (SPECT)

- Tomographic imaging technique using gamma rays. It is very similar to conventional nuclear imaging using a gamma camera (however, it is able to provide true 3D information).

- The technique requires injection of a gamma-emitting radioisotope into the bloodstream of the patient, to be carried and bound to a place of interest in the body, which then allows the ligand concentration to be seen by a gamma-camera.
Gamma Camera

- Gamma camera (~scintigraphy) is a device used to image gamma radiation emitting radioisotopes.

Information on the position and intensity of incident gamma-ray is recorded by Flat Panel Display.

Back projection is performed from forward projection data into the space confined by collimators.
Gamma Camera - Components

- **Collimator: Lead (tungsten or platinum)**
  - Narrows a beam of particles or waves
  - Excludes erroneous gamma rays
  - Determines spatial resolution to detection efficiency ratio

- **NaI(Tl) crystals**
  - Convert the energy deposited by a high energy gamma ray into a large number of lower energy photons

- **Photomultiplier tubes**
  - Multiply the current produced by incident light by as much as 100 million times
  - Transform photons to electrical signals using photocathode
Image Reconstruction

Gamma rays are counted into matrix

- Filtering
  - Convolution Method (9 point smoothing)
  - Fourier Method

- Digital vs. Analog
  - Too few pixels
  - Too few bytes per pixel
Radioisotopes

- Simple soluble dissolved ion
- Also have chemical properties that allow it to be concentrated in ways of medical interest for disease detection
- However, most of the time in SPECT, a marker radioisotope (radioactive properties) has been attached to a special radioligand (chemical binding properties to certain types of tissues)
- Targeted for different tissues

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Activity</th>
<th>Half-life</th>
<th>Energies (KeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium-133</td>
<td>1uCi</td>
<td>10.7 years</td>
<td>81.0, 356.0</td>
</tr>
<tr>
<td>Cadmium-109</td>
<td>1uCi</td>
<td>453 days</td>
<td>88.0</td>
</tr>
<tr>
<td>Cobalt 57</td>
<td>1uCi</td>
<td>270 days</td>
<td>122.1</td>
</tr>
<tr>
<td>Cobalt 60</td>
<td>1uCi</td>
<td>5.27 years</td>
<td>1173.2, 1332.5</td>
</tr>
<tr>
<td>Europium-152</td>
<td>1uCi</td>
<td>13.5 years</td>
<td>121.8, 344.3, 1408.0</td>
</tr>
<tr>
<td>Manganese-54</td>
<td>1uCi</td>
<td>312 days</td>
<td>834.8</td>
</tr>
<tr>
<td>Sodium-22</td>
<td>1uCi</td>
<td>2.6 years</td>
<td>511.0, 1274.5</td>
</tr>
<tr>
<td>Zinc-65</td>
<td>1uCi</td>
<td>244 days</td>
<td>511.0, 1115.5</td>
</tr>
<tr>
<td>Technetium 99m</td>
<td>1uCi</td>
<td>6.01 hours</td>
<td>140</td>
</tr>
</tbody>
</table>
History of SPECT

- Edwards and Kuhl developed the MARK VI, the first Emission Computed Tomography (ECT) device.
  - consisted of several sodium iodide photon detectors
  - arranged in the rectangular shape around the head of the patient
- Tomomatic-32, first SPECT imaging device, was similar to the MARK VI but had 32 photon detectors.
- ECT was discredited due to unusable images.
- Gained acceptance once X-ray CT image reconstruction algorithms were applied to ECT to take into account for attenuation for scatter in the body.
## Technological Advances

### Problems:
- Long scan times
- Low resolution
- Attenuation

### Solutions:
- Triple headed cameras drastically reduce scan times
- Improved cameras and computers enhance resolution
- Visual Tracking Systems to monitor patient movement and correct images accordingly
- Attenuation Correction software
Benefits

- ECT produces 3-D images that relate an organ’s function
- Allows for better relay of extent of disease and reveals the course of the disease earlier
- Large amount of data on brain function
- Simple process with immediate results
- Much less expensive than MRI or PET

Risks

- Unlike MRI and X-ray, there is an injection
- Claustrophobia is a cause for concern
- Quality of image can be lessened by patient movement
Clinical Applications

- In the 70’s & 80’s, SPECT was largely replaced by CAT and MRI scans because they provided superior resolution.
- Recently, SPECT has returned to prominent use, especially in diagnosing cardiac and neurological abnormalities.
- While CAT and MRI scans only provide images of static brain anatomy, SPECT offers clues to brain function by tracing blood allocation.
SPECT Images of Common Neurological and Psychiatric Disorders

- Types of brain SPECT images:

  - **Surface Image:**
    - Full symmetrical activity across cortical surface

  - **Active Image:**
    - High activity in cerebellum and visual or occipital cortex

Examiners look for too much/little activity in a certain area, or asymmetry in areas that should be symmetrical.
SPECT Images of Common Neurological and Psychiatric Disorders

Right Sided Stroke

Alzheimer’s Disease
pervasive hypoperfusion

Head Trauma

to left PFC - severe
aggression problems/violence

Depression
increased limbic activity (left) and decreased
prefrontal and temporal lobe activity
SPECT Images of Common Neurological and Psychiatric Disorders

- **Schizophrenia**
  Before (left) and after (right) medication

- **Attention deficit hyperactivity disorder**
  Normally (left) and while performing a concentration task (right)

- **Alcohol**
- **Marijuana**
- **Cocaine**
- **Heroin**
PET - nuclear medicine imaging technique that produces a 3D image or picture of functional processes in the body.

Detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (which is introduced into the body on a biologically active molecule).
PET Scan of the Brain

- Using **radionuclide** (FDG – Fluodeoxyglucose – $^{18}\text{F}$) that is like glucose, the PET scan will show how the tissues in the brain are functioning.
- Areas of less function **use less energy**, and areas with increased metabolic activity **use more energy**.
Radiopharmaceuticals

- **Radionuclide**
  - $^{11}$C half-life ~20 min
  - $^{13}$N 10 min
  - $^{15}$O 2 min
  - $^{18}$F 110 min

The half-life of $^{18}$F is long enough that radiotracers can be manufactured commercially at offsite locations and shipped to imaging centers.

- **Localization**
  - Biochemical metabolism within the cell

- **Adult Dose Range**
  - 5-15 mCi (185-555 MBq)

+ glucose, water, ammonia or other molecule = radiotracers
Indications in the CNS

- Evaluation of cerebrovascular disease
  - Strokes
  - Transient ischemic attacks (TIAs)

- Evaluation of epilepsy

- Evaluation of movement disorders
  - Huntington
  - Parkinson

- Evaluation of psychiatric disorders
  - Schizophrenia
  - Mood disorders
Indications in the CNS

- Evaluation of dementia
  - Alzheimer’s disease

- Evaluation of tumors
  - Evaluation of grade and extend of glioma
  - Evaluation of chemotherapy

- To locate the specific surgical site prior to surgical procedures of the brain

- To evaluate the brain after trauma to detect hematomata (blood clot), bleeding, and/or perfusion (blood and oxygen flow) of the brain tissue
Before the PET Examination

The patient must fast six hours prior to the appointment time except water!

In addition, patient should avoid any carbohydrates from his/her diet (e.g., bread, pasta, potatoes and rice) 24 hours prior to the appointment time, because carbohydrates taken before the test will reduce the effectiveness of it!
Brain 3D
One of the most exciting methodological advances for brain research has been in functional brain imaging; it enables the localization and characterization of neural activity in the living human brain.

Recently developed 3D-PET imaging techniques using $\text{H}_2^{15}\text{O}$ and $^{18}\text{F}-\text{FDG}$ make it possible to visualize the brain activity associated with cognitive processes.

We will visualize functional neuroanatomy of subjective feelings of sleepiness, visceral perception, itching, and emotion using $\text{H}_2^{15}\text{O}$.
During a seizure, the area responsible for the seizure will show up as an area of increased glucose use.

Between the seizures, PET shows a characteristic pattern of reduced need for glucose.
Epilepsy
Alzheimer’s Disease

PET scan of a healthy brain compared to a brain at an early stage of Alzheimer’s disease.

Diminished FDG uptake in the temporal lobes which are compatible with Alzheimer’s disease.
Parkinson’s disease

18F-AV-133 images of vesicular monoamine transporters acquired 90–120 minutes post injection in a normal elderly subject (left) and a patient with mild Parkinson’s disease (right) demonstrating a dramatic reduction in dopaminergic innervation to the striatum
Brain Tumor
Contraindications

- Patient too agitated, uncooperative, or claustrophobic to remain still for acquisition

- Because PET involves cellular metabolism, drugs and food ingestion, or lack thereof, bears specific consideration for each study
PET uses **beta-plus-emitting** radionuclides such as $^{11}$C, $^{13}$N, $^{15}$O, and $^{18}$F which annihilate into two 511-keV photons that travel in opposite directions.

SPECT involves detection of **gamma rays** emitted singly from radionuclides such as $^{99m}$Tc, $^{123}$I, and $^{111}$In.
NMR = nuclear magnetic resonance

**nuclear**: properties of nuclei of atoms

**magnetic**: magnetic field required

**resonance**: interaction between magnetic field and radio frequency

NMR → MRI

Felix Block and Edward Purcell
- 1946: atomic nuclei absorb and re-emit radio frequency energy
- 1952: Nobel prize in physics

Source: Jody Culham’s web slides
History of fMRI

MRI
- 1973: Lauterbur suggests NMR could be used to form images
- 1977: clinical MRI scanner patented
- 1977: Mansfield proposes echo-planar imaging (EPI) to acquire images faster

fMRI
- 1990: Ogawa observes BOLD effect with T2*
  blood vessels became more visible as blood oxygen decreased
- 1991: Belliveau observes first functional images using a contrast agent
- 1992: Ogawa & Kwong publish first functional images using BOLD signal

Source: Jody Culham’s web slides
Some Terms to Know

**Longitudinal magnetization** $\sim B_0$ - is used to denote the main magnetic field

  objects placed within $B_0$ will gradually align to this field

  *(longitudinal relaxation)*

**$M_0$** – is used to denote the net magnetization of an object within $B_0$

  $M_0$ is ‘tipped’ out of alignment with $B_0$ to create the MR image – so $M_0$ is now measured as **transverse magnetization**

**RF pulse** – radio frequency pulse (not to be confused with ‘resonant frequency’)

to read $M_0$ it must be tipped out of alignment with $B_0$ – this is achieved by sending an RF pulse at certain resonant frequencies and gradients
**Some Terms to Know**

**Magnet** – the big magnet that we allocate the Tesla value to that creates $B_0$

**Gradient Coil** – smaller magnets that are used to tip the net magnetization of the subject ($M_0$) out of alignment with $B_0$. There are actually three gradient coils orthogonal to one another so that gradients can be applied in the x, y and z planes.

**RF coil** – *radio frequency coil* – these are typically receive only coils and are used to measure $M_0$ at some time after the RF pulses have been applied. Send/receive coils are also available.
Physics of Protons

- motion of electrically charged particles results in a magnetic force orthogonal to the direction of motion

- protons (nuclear constituent of atom) have a property of angular momentum known as spin

Angular momentum (spin) of a proton.
Protons Aligning within a Magnetic Field

- In "field free" space: protons are randomly oriented.
- Inside magnetic field: protons align with or orthogonal to the magnetic field ($B_0$).

- When placed in a magnetic field ($B_0$; e.g., our MRI machines), protons will either align with the magnetic field or orthogonal to it (process of reaching magnetic equilibrium).
- There is a small difference (10:1 million) in the number of protons in the low and high energy states – with more in the low state leading to a net magnetization ($M$).

Source: Mark Cohen’s, Robert Cox’s, Jody Culham’s web slides
Precession – the Spinning Top Analogy

What is actually aligned with the $B_0$ is the axis around which the proton precesses – the decay of precession (i.e., it is the rate of precession out of alignment with $B_0$ together with the proton density of the tissue concerned that is crucial in MRI)

Source: Cohen and Bookheimer article
Larmor Frequency

- the energy difference between the high (oriented with $B_0$) and low (oriented against $B_0$) energy protons is measurable and is expressed in the Larmor equation

Larmor equation

\[ f = \gamma B_0 \]
\[ \gamma = 42.58 \text{ MHz/T} \]

At 1.5T, $f = 63.76$ MHz
At 4T, $f = 170.3$ MHz
RF Excitation

- protons can flip between low and high energy states (i.e., flip between being aligned with or against $B_0$)

- to do so the energy transfer must be of a precise amount and must be facilitated by another force (e.g., other protons or molecules)

- in MRI, RF (radio frequency) pulses are used to excite the RF field – the Swing analogy – tipping the net magnetization out of alignment with $B_0$
Cox’s Swing Analogy

- Person sitting on swing at rest is “aligned” with externally imposed force field (gravity).

- To get the person up high, you could simply supply enough force to overcome gravity and lift him (and the swing) up.
  Analogous to forcing M over by turning on a huge static B1.

- The other way is to push back and forth with a tiny force, synchronously with the natural oscillations of the swing.
  Analogous to using tiny B1 to slow flip M over.
Excite Radio Frequency (RF) field

- **transmission coil**: apply magnetic field along $B_1$ (perpendicular to $B_0$) for ~3 ms
- oscillating field at Larmor frequency
- frequencies in range of radio transmissions
- $B_1$ is small: ~1/10,000 T
- tips M to transverse plane – spirals down
- analogies: guitar string (Noll), swing (Cox)
- final angle between $B_0$ and $B_1$ is the **flip angle**
Longitudinal relaxation and $T_1$

- temperature influences the number of collisions (and hence the rate at which protons flip between low and high energy states)

- so magnetic equilibrium ($M_0$), or the rate at which a body placed inside $B_0$ becomes magnetized depends on temperature – this is known as *longitudinal relaxation*

- the T1-weighted image (usually used for anatomical images) measures the rate at which the object placed in $B_0$ (the unsuspecting subject in our case) goes from a non-magnetized to a magnetized state – the longitudinal relaxation

- different types of molecules (and by extension tissue) approach $M_0$ at different rates allowing us to differentiate things like white and grey matter – we creep close towards the image!!!
T1 and T2

T1 measures the *longitudinal relaxation* (along $B_0$) – or the rate at which the subject (and the various different constituents of that subject) reaches magnetic equilibrium

T2 measures the *transverse relaxation* (along $B_1$) – or the rate of decay of the signal after an RF pulse is delivered

T1 – *recovery* to state of magnetic equilibrium
T2 – rate of *decay* after excitation

<table>
<thead>
<tr>
<th>Tissue</th>
<th>T2 decay times (in 1.5 T magnet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>white matter</td>
<td>70 msec</td>
</tr>
<tr>
<td>grey matter</td>
<td>90 msec</td>
</tr>
<tr>
<td>CSF</td>
<td>400 msec</td>
</tr>
</tbody>
</table>
RF coils receive the net magnetization from the object placed within the coil (e.g., a subject’s head)

can also have send / receive RF coils that also deliver the RF pulse (to get the swing going) – usually the pulse is delivered by gradient coils
Proton density, recovery (T1) and decay (T2 and T2*) times.

By ‘weighting’ the pulse sequence (and point at which data is collected) different images of the brain are obtained.

Weighting is achieved by manipulating TE (time to echo) and TR (time to repetition of the pulse sequence)
Precession In and Out of Phase

all nuclei aligned and precessing in the same direction.

nuclei not aligned but still precessing in the same direction.

So MR signal will start off strong but as protons begin to precess out of phase the signal will decay.

Source: Mark Cohen’s web slides
T1 and TR

T1 = recovery of longitudinal (B₀) magnetization after the RF pulse
- used in anatomical images
- ~500-1000 msec (longer with bigger B₀)

TR (repetition time) = time to wait after excitation before sampling T1

Source: Mark Cohen’s web slides
$T_2$ and $T_E$

$T_2 =$ decay of transverse magnetization after RF pulse

$T_E$ (time to echo) = time to wait to measure $T_2$ or $T_2^*$ (after re-focusing with spin echo)

Source: Mark Cohen’s web slides
Effectively, T1 and T2 images are the inverse of one another, with T1 typically used to form anatomical images and T2* used in fMRI.
$T_2^*$

$T_2$: intrinsic decay of transverse magnetization over microscopic region (~5-10 microns)
  ~50-100 msec (shorter with bigger $B_0$)

$T_2^*$: overall decay of transverse magnetization over macroscopic region (~mm)
  decays more quickly than $T_2$ (by factor of ~2)

Source: Robert Cox’s web slides
When the RF pulse is turned off, the hydrogen protons return to their natural alignment within the magnetic field.

Energy is released.

The coil detects this signal and sends it to a computer for processing.

The signal consists of complex values which have real and imaginary components.
MRI Image Formation

Magnitude information from signal

Phase information from signal

Fourier Transform
MRI Visualization

A series of 2D MRI images can be combined together to form a **3D** volume

This volume can then be used to generate realistic visualizations and models
MRI - Benefits

- Excellent for clearly visualizing structures in soft tissues, such as the brain
- Very commonly used in:
  - Diagnosis
  - Image-guided surgery and therapy
- By adjusting scanning settings, specific features can be detected
- MRI images are 2D slices through the body at a specific location
MRI Scanner
CT scan of a patient who has had a left middle cerebral artery stroke. The arrow indicates the location of the stroke.

MRI of a patient who has had a stroke of the left hemisphere of the brain. The arrow indicates the area that was affected.
BOLD Functional MRI

**Encoding task**
Activation of left prefrontal cortex

**Retrieval task**
Activation of right prefrontal cortex

Left side of brain

Right side of brain
BOLD Functional MRI

Magnetic properties of oxyhemoglobin and deoxyhemoglobin:

L. Pauling and C. Coryell, PNAS USA 22:210-216 (1936)

BOLD effects in vivo:

S. Ogawa, et al., MRM, 14:68-78 (1990)

BOLD activation experiments:

K. K. Kwong, et al., PNAS USA, 89:5675-5679 (1992)
Mechanism of BOLD Functional MRI

Brain activity $\uparrow$

Oxygen consumption $\uparrow$
Cerebral blood flow $\uparrow\uparrow$

Oxyhemoglobin $\uparrow$
Deoxyhemoglobin $\downarrow$

Magnetic susceptibility $\downarrow$

$T2^*$ $\uparrow$

MRI signal intensity $\uparrow$
Magnetic Properties of Oxyhemoglobin and Deoxyhemoglobin

**Deoxyhemoglobin**: paramagnetic ($\chi > 0$)
paramagnetic with respect to the surrounding tissue

**Oxyhemoglobin**: diamagnetic ($\chi < 0$)
isomagnetic with respect to the surrounding tissue
Magnetic Susceptibility

\[ M = \chi H \]

if \( \chi > 0 \), paramagnetic

\( \chi < 0 \), diamagnetic
Oxyhemoglobin and Deoxyhemoglobin in Veins during Brain Activation

Rest

Normal blood flow

Activation

High blood flow

Oxyhemoglobin
Deoxyhemoglobin
$T_2^*$ Effect in fMRI

- **Effect in fMRI**
- **MR signal ($S$)**
- **Excitation**
- **Rest**
- **TE**
- **Reception**

The diagram illustrates the decay of the MR signal ($S$) over time ($t$) following excitation and during rest and action periods.
Time Series and Activation Maps
Challenges in Functional FMRI

**Sensitivity (Contrast-to-noise ratio)**

BOLD signal change is ~1-2% at 1.5 T; signal-to-noise ratio in single-shot echo-planar images (EPI) is ~100.

Physiological pulsations (cardiac and respiratory); Head motion; instrumental instability

**Specificity**

Location of activation – neurons or veins

**Susceptibility artifacts**
Challenges in Functional FMRI

Temporal resolution
Limited by BOLD impulse-response function, image sampling rate, and spin relaxation times

Spatial resolution
Limited by BOLD point-spread function, signal-to-noise ratio, and image sampling rate

Non-linearity
Neurological and hemodynamic

Acoustic noise