PET Imaging of the Brain for Technologists

CTN 119
Objectives

Upon completion of this presentation, participants will be able to:

• Recognize key anatomical structures on PET, CT, and MRI images
• Identify the lobes of the brain and their major functions
• Describe key parameters used to obtain high quality PET/CT images
• Discuss the role of PET imaging in patients with brain abnormalities
PET Brain Anatomy Review
Cortex

Convoluted walls of nervous tissue (gray matter) folded within the cranial vault; convolutions increase surface area for more neurons

- **Cerebral cortex** divided into four lobes.
- **Cerebellar cortex** divided into right and left hemispheres.

Images courtesy of “The Whole Brain Atlas”, Johnson & Becker
http://www.med.harvard.edu/aanlib/home.htm
• **Gyrus**: convoluted ridge between anatomical grooves
• **Sulcus**: depression or furrow
• **Fissure**: large sulcus that divides sections of the brain

Images courtesy of “The Whole Brain Atlas”, Johnson & Becker
http://www.med.harvard.edu/aanlib/home.htm
Gray and White Matter

**Gray matter:** 40% of brain volume; uses 94% of total oxygen that goes to the brain; contains most of the brain's cell bodies; responsible for generating and processing signals; associated with processing information and cognition.

**White matter:** 60% of brain volume; composed of nerve fibers (axons) surrounded by fatty myelin sheath; responsible for transmitting signals; relays and coordinates information between parts of cerebrum; from cerebrum to cerebellum & brain stem.
Cerebrum, Cerebellum

*FDG PET fused with T1 MR image

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Frontal Lobe

- Associated with planning, reasoning, movement, parts of speech, problem solving and emotions
- Sylvian fissure
- Central sulcus

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Temporal Lobe

Temporal Lobe is associated with perception and recognition of auditory stimuli, memory, and speech. The Sylvian fissure marks the boundary between the frontal, parietal, occipital, and temporal lobes in the brain.
Parietal Lobe

Sylvian fissure

Central sulcus

Parietal

associated with movement, orientation, recognition, perception of stimuli

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Occipital Lobe

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Transaxial Anatomy

- Cerebellum
- Occipital
- Frontal
- Parietal
- Temporal

Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Coronal Anatomy

Image courtesy of “The Whole Brain Atlas” - Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Sagittal Anatomy

Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Limbic System: Hippocampus

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Key Structures on FDG Images

- Precuneus
- Pons
- Superior Sagittal Sinus
- Thalamus
- Caudate Nucleus

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
PET Brain Imaging Technique
The Brain and Glucose

• Glucose is used as a major energy source for the brain
• Since the brain does not have substantial glucose storage capacity, it requires a continuous supply of glucose from plasma to maintain its functions
• If neurons in a certain part of the brain are not functioning normally, the change can be reflected by the amount of glucose utilization

Images courtesy of: www.med-ed.virginia.edu

FDG-avid uptake in grey matter 1-2 hours post-injection
FDG – Mechanism of Action

- FDG competes with glucose for transport into the cell and for enzymatic phosphorylation by hexokinase.
- Once FDG is phosphorylated into FDG-6-phosphate, it is trapped inside the cell and does not undergo further metabolism.
- It cannot be further degraded via the glycolysis pathway nor can it undergo dephosphorylation.
FDG – Blood Sugar Levels

- High blood sugar levels can decrease FDG uptake by competitive inhibition because both glucose and FDG use the same transporters.
- It is recommended that patients fast for a minimum of 4 hours before the FDG injection.
- If the blood sugar level is > 150 – 200 mg/dL prior to injection, the scan should be rescheduled.
FDG – Blood Sugar Levels

- Diabetic patients should be scanned early in the morning before the first meal
- Doses of insulin and hypoglycemic medication should be titrated the night before and morning of the study
- Before scheduling an FDG-PET study, diabetic patients should test their ability to maintain reasonable glucose levels after fasting
There is a significant decrease in brain FDG uptake associated with progressively increasing plasma glucose levels
Uptake Time

• The environment should be stable for at least 30 minutes prior to FDG injection and subsequent uptake phase (at least 30 min)

• Patient should be placed in a quiet, dimly-lit room and minimize interaction prior to, during and at least 30 min post-injection

• Instruct patient to relax, not to speak or read and to avoid major movements during uptake phase
Correct Head Positioning

Vertex of head should reach head holder’s superior edge

Cantho-meatal line should be oriented vertically

Chin should rest in neutral position
Incorrect Head Positioning

Incorrect positioning of head within holder

Chin is deflected toward neck

Canthomeatal line should be oriented vertically
Motion

Artifacts in attenuation correction

Potential inaccuracy in recording location of tracer deposition

Study should be repeated with pre-exam coaching
Occipital Activation on FDG PET
## Image Acquisition

Depending on the clinical question and type of equipment available, imaging may include:

<table>
<thead>
<tr>
<th>Static</th>
<th>Dynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Static protocols offer clinical applicability, and the relative tracer uptake is of interest</td>
<td>May be used when absolute quantification of regional metabolic rates of glucose are needed</td>
</tr>
<tr>
<td>Relative tracer uptake is characterized as the Standardized Uptake Value (SUV) and details of the errors with static SUV have been well documented</td>
<td>Studies consist of a sequence of serial images in a limited FOV (1 bed position), starting at the time of tracer administration and continuing for 60-90 minutes</td>
</tr>
<tr>
<td>May impose a bias by arbitrarily choosing a single time frame to represent overall tracer metabolism</td>
<td>Requires blood samples to be obtained during imaging (venous or arterial)</td>
</tr>
</tbody>
</table>
2D vs. 3D Emission Scans

- Most systems today use 3D acquisition
  - If 2D acquisition is used, longer acquisition times are required to achieve adequate count density

<table>
<thead>
<tr>
<th>2D Emission Scan</th>
<th>Fully-3D Emission Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower sensitivity (longer acquisition time)</td>
<td>Higher sensitivity (shorter acquisition time)</td>
</tr>
<tr>
<td>Less data storage</td>
<td>More data storage</td>
</tr>
<tr>
<td>Simpler to reconstruct</td>
<td>Harder to reconstruct</td>
</tr>
<tr>
<td>FOV for random coincidences is smaller</td>
<td>FOV for random coincidences is larger</td>
</tr>
</tbody>
</table>
Image Processing

- Iterative reconstruction
- Corrections of attenuation, scatter, normalization, and random events
- TOF scanners have TOF kernel information incorporated into reconstruction
- Advanced algorithms incorporate Point-Spread-Function (PSF) in reconstruction for resolution recovery
- Refer to camera manufacturer’s recommendations for best choices of iterations, subsets, and smoothness
- Reconstructions may be tracer-specific
Image Processing

- Images are reconstructed in the form of transaxial 200 x 200, 256 x 256, 400 x 400 matrix size
- Typical pixel size is 2-4 mm
- Depending on the resolution of the PET system, a final image resolution may vary between 2.5-10 mm FWHM
  - This typically yields adequate image resolution and signal-to-noise ratios
Data Display

- A standardized image display is advocated to ensure an appropriate, symmetrical and most readily interpretable representation of the reconstructed dataset
- Internal landmarks can be used for reorientation
- Reorientation procedures based on intercommissural line are commonly used
The intercommissural line (ICL) passes through the center of the anterior and posterior commissure.

The AC-PC line goes from the superior surface of the anterior commissure to the center of the posterior commissure.
Data Display

The display of additional coronal and sagittal images are required

- 3D display optional
  - Volume surface renderings may be subject to artifacts
  - should be used in combination with standard slice displays

- Reorientation parallel to the temporal lobe in the evaluation of epilepsy
Semi-Quantitative Analysis of FDG Uptake

- Semi-Quantitative analysis of FDG uptake in the brain has been used for evaluation of epilepsy.
- Semi-Quantitative decrease in FDG uptake within the left mesial temporal lobe indicates possible region of epileptogenic focus.

Semi-Quantitative Evaluation of FDG uptake using MIM

<table>
<thead>
<tr>
<th>Atlas</th>
<th>Structure</th>
<th>Z-Score</th>
<th>L-Z Score</th>
<th>R-Z Score</th>
<th>L-R % Diff</th>
<th>R-L % Diff</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Brain Atlas</td>
<td>Medial Temporal Lobe</td>
<td>-1.77</td>
<td>-2.04</td>
<td>-1.36</td>
<td>-1.42</td>
<td>-0.67</td>
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</tr>
<tr>
<td>Single Brain Atlas</td>
<td>Amygdala</td>
<td>-1.78</td>
<td>-1.89</td>
<td>-1.51</td>
<td>-4.04</td>
<td>-0.41</td>
<td></td>
</tr>
<tr>
<td>MIM Probabilistic Atlas</td>
<td>Amygdala 8/10</td>
<td>-1.87</td>
<td>-1.81</td>
<td>-1.61</td>
<td>1.47</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>MIM Probabilistic Atlas</td>
<td>Medial Temporal Lobe 8/10</td>
<td>-2.04</td>
<td>-2.39</td>
<td>-1.54</td>
<td>-2.24</td>
<td>-0.86</td>
<td></td>
</tr>
<tr>
<td>Single Brain Atlas</td>
<td>Hippocampus</td>
<td>-2.06</td>
<td>-2.5</td>
<td>-1.43</td>
<td>-6.89</td>
<td>-1.37</td>
<td></td>
</tr>
<tr>
<td>Single Brain Atlas</td>
<td>Pontine Tegmentum</td>
<td>-2.21</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Single Brain Atlas</td>
<td>Globus Pallidus</td>
<td>-2.25</td>
<td>-1.92</td>
<td>-2.47</td>
<td>3.75</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Single Brain Atlas</td>
<td>Middle Cerebellar Peduncle</td>
<td>-2.32</td>
<td>-2.3</td>
<td>-2.11</td>
<td>0.61</td>
<td>-0.11</td>
<td></td>
</tr>
<tr>
<td>MIM Probabilistic Atlas</td>
<td>Hippocampus 8/10</td>
<td>-2.34</td>
<td>-2.75</td>
<td>-1.6</td>
<td>-9.11</td>
<td>-1.6</td>
<td></td>
</tr>
</tbody>
</table>
FDG Pitfalls, Artifacts, Sources of Error

Medications altering cerebral metabolism include:

- Sedatives
- Drugs such as amphetamines, cocaine
- Narcotics
- Anti-psychotic medications
- Corticosteriods
Additional Neuroimaging PET Tracers:

- Amino Acid
- Amyloid
- Tau
FDOPA is an \(^\text{18F}\) form of L-DOPA
- Imported into cell via LAT1 transporter
- Measures amino acid metabolism
- Can be used to visualize dopaminergic nerve terminals
- Symmetric homogeneous uptake within the striatum
- Has been approved for evaluation of Parkinson’s
- Evaluation is visual and is based on interpretation of shape and signal intensity within the putamen and caudate

[Chemical structure of FDOPA]

[Image of FDOPA uptake in the brain]

Normal

Parkinson’s Disease

18F-FDOPA

- FDOPA can be used to study amino acid metabolism in neuro-oncology
- Increased tracer uptake within tumor has been correlated with higher grade tumor and tumor recurrence in the setting of radiation necrosis
Amyloid Imaging

• PET with amyloid imaging agents have the ability to determine *in vivo* plaque density
  – Beta-amyloid neuritic plaque density is the hallmark of Alzheimer’s disease (AD)

• Presently there are no disease-modifying treatments for AD
  – Confirmation or rule out of AD provides an opportunity for clinical trial eligibility and family/caregiver planning
The brains of people with AD have an abundance of abnormal structures. Amyloid plaques are found in the spaces between the brain’s nerves cells. Plaques consist largely of insoluble deposits of an apparently toxic protein peptide (beta-amyloid).
Alzheimer’s Disease

- Alzheimer’s tissue has many fewer nerve cells and synapses than a healthy brain.
- Plaques, abnormal clusters of protein fragments, build up between nerve cells.

Floating clumps of protein fragments that block synapses.
Amyloid – Mechanism of Action

- Amyloid imaging agents bind to β-amyloid (AB) plaques in the cortical gray matter in cases of Alzheimer’s Disease.
- The amyloid imaging tracer binds to the β-amyloid plaques and the radioisotope produces a positron signal to be detected by the PET scanner.

Images from www.amyvid.com

No evidence of amyloid plaques

High levels of amyloid plaques
The first PET tracer specific for β-amyloid plaques was labeled with $^{11}$C (Pittsburgh compound B).

The FDA has approved three $^{18}$F-labeled amyloid tracers:
- $^{18}$F-Florbetapir (Amyvid)
- $^{18}$F-Flutemetamol (Vizamyl)
- $^{18}$F-Florbetaben (Neuraceq)
Limitations of Use

• A positive AIA scan does not establish a diagnosis of AD or other cognitive disorder.

• Safety and effectiveness of AIA have not been established for:
  – Predicting development of dementia or other neurologic condition;
  – Monitoring responses to therapies.

Package Insert references for slides 49-50 (all three agents) listed below.

7 Piramal Imaging (2014). NeuraCeq™ Florbetaben F 18 Injection: Highlights of Prescribing Information. Matran, Switzerland
Amyloid Imaging Patient Preparation

Patient prep for amyloid imaging

- NPO not required
- No discontinuation of medications
- Glucose monitoring not required
- Environment post injection (e.g., no need for dark room or limitation of stimulus)
- Tracer-specific requirements for fluids post-injection
<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Injection Supplies</th>
<th>Injection</th>
<th>Flush</th>
<th>Patient instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florbetapir</td>
<td>10mCi (370MBq) 10mL or less</td>
<td>Catheter less than 1.5 inches; use HDPE syringe⁴</td>
<td>Single Bolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutemetamol</td>
<td>5 mCi (185 MBq) 10mL or less</td>
<td>Bolus IV within 40 seconds</td>
<td>10-15mL saline</td>
<td></td>
<td>Hydrate and encourage voiding before and after injection⁵</td>
</tr>
<tr>
<td>Florbetaben</td>
<td>8.1 mCi (300 MBq) 0.5-10mL</td>
<td>Slow bolus IV (6 sec/mL)</td>
<td>10mL saline</td>
<td></td>
<td>Avoid close contact with young children and pregnant women for 24 hours post injection⁷</td>
</tr>
<tr>
<td>Amyloid Imaging Agent</td>
<td>Standard Uptake Time</td>
<td>Acquisition Scan Time</td>
<td>Patient Positioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Florbetapir</td>
<td>30-50 minutes post injection</td>
<td>10 minutes</td>
<td>The patient should be supine and head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible restraints may be employed.⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutemetamol</td>
<td>60-120 minutes post injection</td>
<td>10-20 minutes</td>
<td>Position the patient supine with the brain (including the cerebellum) within a single field of view. The patient's head should be tilted so that the anterior commissure-posterior commissure plane is at a right angle to the bore-axis of the PET scanner, with head positioned in a suitable head support. Reducing head movement with tape or other flexible restraints may be employed.⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Florbetaben</td>
<td>45-130 minutes post injection</td>
<td>15-20 minutes</td>
<td>Patient should be supine with the head positioned to the center of the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed.⁷</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eli Lilly and Company (2012). Amyvid™ Florbetapir F 18 Injection: Highlights of Prescribing Information. Indianapolis, IN
Piramal Imaging (2014). NeuraCeq™ Florbetaben F 18 Injection: Highlights of Prescribing Information. Matran, Switzerland
This discussion of display techniques for PET brain amyloid agents is not a substitute for manufacturer specific reader training.

For details on image display and interpretation for each amyloid tracer, refer to the product labels.
Amyvid (florbetapir)

• Eli Lilly and Company has developed online resources for physicians and technologists
  – Recommended dosing and administration instructions
  – Image acquisition
  – Image display
  – Image interpretation (reader training)

Negative

Positive

www.amyvidhcp.com
Amyvid (florbetapir)

**Negative**
- Normal preserved gray-white contrast with cortical radioactivity less than the adjacent white matter.

**Positive**
- Decreased gray-white contrast with increased cortical radioactivity that is comparable to the radioactivity in the adjacent white matter.
White matter tracks can be delineated from the frontal lobe to parietal lobe.

Scalloped appearance is seen with “fingers” of white matter in the frontal cortex.

White matter tracts are clearly identified throughout the occipital/temporal area.

Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.
Amyvid (florbetapir)

White matter tracks are difficult to fully identify as they travel from frontal to parietal lobe.

Gray matter in medial parietal cortex (precuneus) has increased uptake.

Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.

Borders of white matter tracts in occipital/temporal area are lost in places.
Vizamyl (flutemetamol)

- GE Healthcare developed and launched an electronic reader program
- The program instructs physicians in the appropriate method to interpret Vizamyl images
- Can be accessed by healthcare professionals online at www.ReadVizamyl.com
Vizamyl (flutemetamol)

- Less uptake in striatal regions
- White matter sulcal pattern with a color intensity that tapers to the periphery
- In both the frontal and lateral temporal regions, the intensity is higher in the gray matter regions when comparing the Positive and Negative scans
- More radioactivity in the striatal regions
- Absence of white matter sulcal pattern with intensity radiating to a sharply defined convex edge
Vizamyl (flutemetamol)

The posterior cingulate (pc) region which is superior and posterior to the corpus callosum - the intensity is below 50% of peak.

White matter sulcal pattern in inferior parietal (ip) regions that is not evident on the positive image.

The posterior cingulate (pc) region which is superior and posterior to the corpus callosum - the intensity is below 50% of peak.

Increased intensity in the posterior cingulate (pc) and increased radial extent of high intensity to the lateral surfaces of the parietal lobes.
Neuraceq (florbetaben)

- Electronic Media- or In-person training is provided by manufacturer
- Images should be interpreted only by readers who successfully complete training
- Online resources provided for healthcare professionals
Neuraceq (florbetaben)
TAUVID (Flortaucipir F-18)

- Flortaucipir F 18 binds to aggregated tau protein
- Estimates the density and distribution of aggregated tau neurofibrillary tangles (NFTs)
- FDA approved in May 2020
### TAUVID (Flortaucipir F-18)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Injection</th>
<th>Flush</th>
<th>Standard Uptake Time</th>
<th>Image Acquisition Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flortaucipir</td>
<td>Single Bolus</td>
<td>10mL saline</td>
<td>80 minutes</td>
<td>20 minutes</td>
</tr>
<tr>
<td>10 mCi (370 MBq)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mL or less</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Max 1:5 dilution by end user; use within 3 hours of dilution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TAUVID (Flortaucipir F-18)

• Image acquisition
  – 20 minute scan, 80 minutes post injection
  – Dynamic mode allows for use of motion correction

• Reconstruction
  – Iterative reconstruction algorithm
  – 256 X 256 matrix size
  – 3.0 FWHM
  – 4 iterations
  – 16 subsets

TAUVID (Flortaucipir F-18)

- Image analysis and display
- Images displayed in a color scale and adjusted relative to the cerebellar reference region

Examples of Appropriate Color Scales to Display Flortaucipir Images

Cerebellar Region of Interest
TAUVID (Flortaucipir F-18)
PET: Pitfalls, Artifacts, Sources of Error

- Patient motion during the data acquisition may result in image artifacts and render the study non-interpretable
- Misregistration between the emission and transmission scans
- Incorrect tracer-specific uptake time
- Positioning
Summary

- Reviewed key anatomical structures on PET, CT, and MRI images
- Identified the lobes of the brain and their major functions
- Described key parameters used to obtain high quality PET/CT images
- Discussed the role of PET imaging in patients with brain abnormalities

Tracers

| 18F-FDG   |  
| 18F-FDOPA |  
| 18F-Florbetapir |  
| 18F-Flutemetamol |  
| 18F-Florbetaben |  
| 18F-Flortaucipir |  

Image courtesy of “The Whole Brain Atlas”-Johnson & Becker
http://www.med.harvard.edu/aanlib/home
Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and $[^{18}\text{F}]$FDG: version 1.0

SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0

https://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414