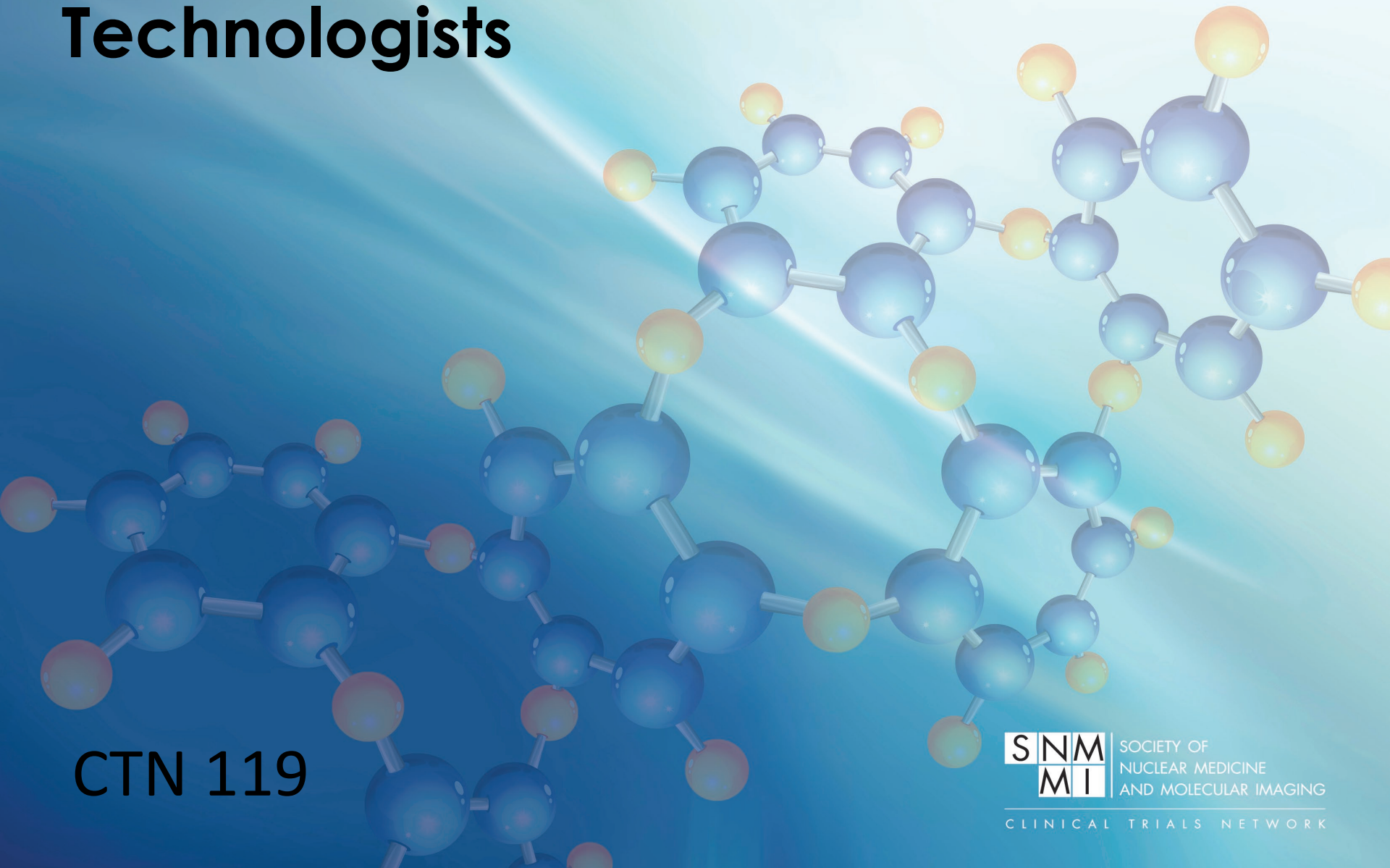
# PET Imaging of the Brain for Technologists



CTN 119

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

CLINICAL TRIALS NETWORK

# Objectives

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

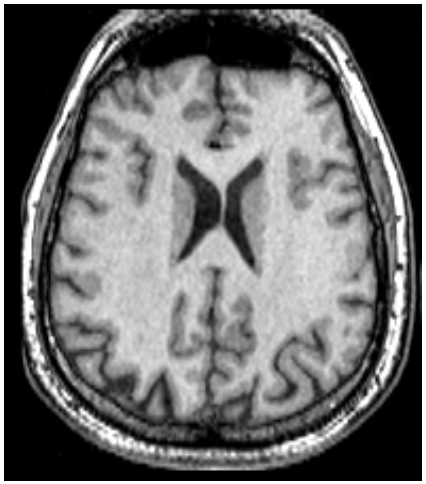
- Recognize key anatomical structures on PET, CT, and MRI images
- Identify the lobes of the brain and their major functions
- Describe key parameters used to obtain high quality PET/CT images
- Discuss the role of PET imaging in patients with brain abnormalities

# PET Brain Anatomy Review

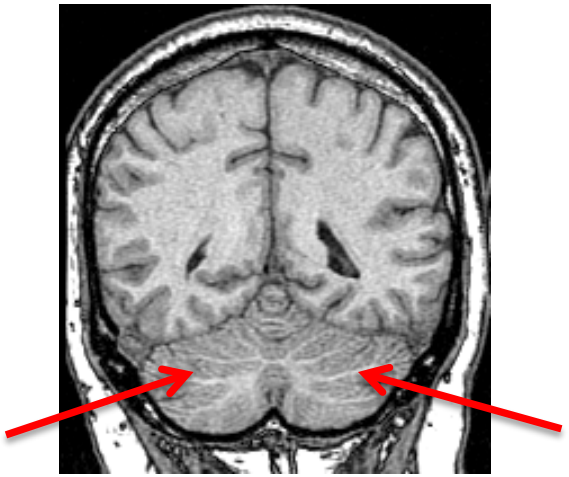
# Cortex

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.



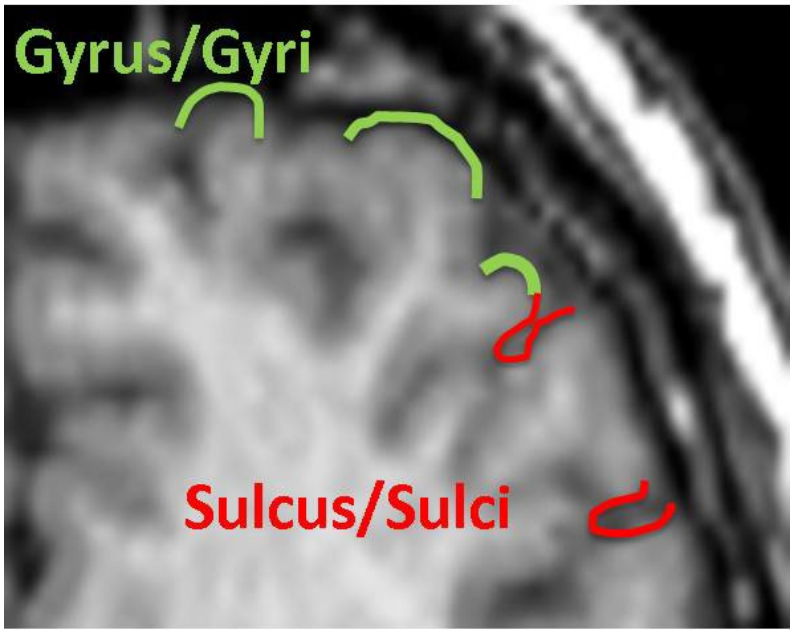
Cerebral cortex

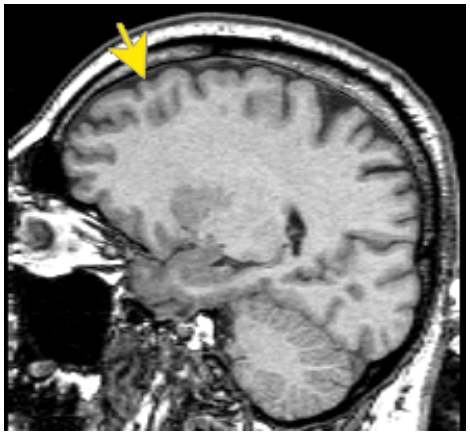


Cerebellar hemispheres

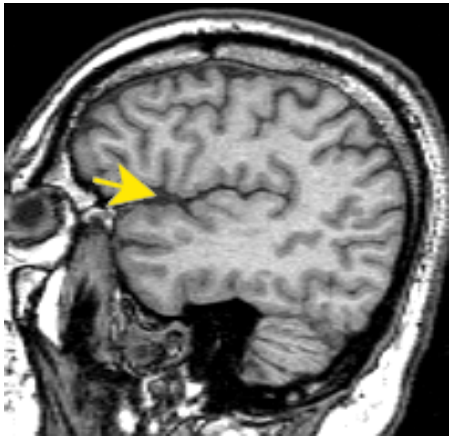
Images courtesy of "The Whole Brain Atlas", Johnson & Becker
http://www.med.harvard.edu/aanlib/home.htm

# Gyrus, Sulcus, Fissure



Superior-frontal gyrus: associated with self-awareness

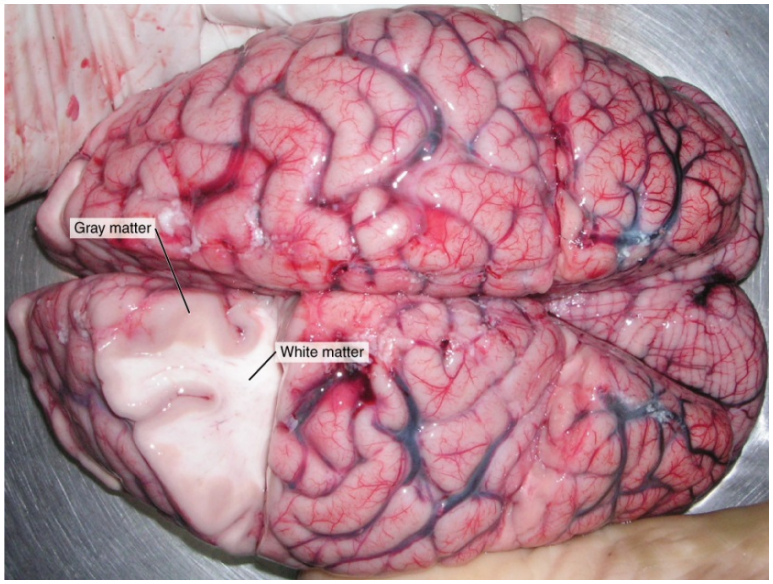


Sylvian fissure: boundary between frontal and temporal lobes

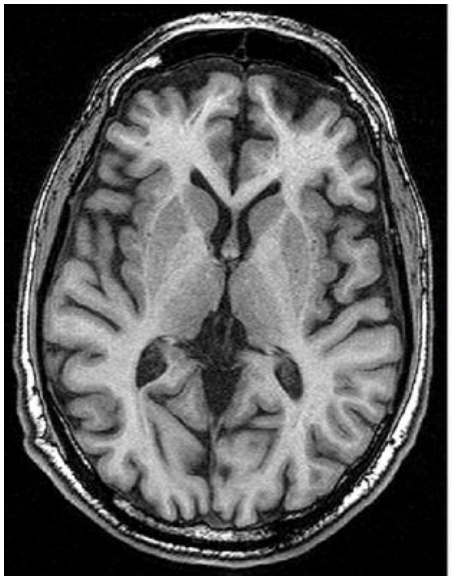
- **Gyrus:** convoluted ridge between anatomical grooves
- **Sulcus:** depression or furrow
- **Fissure:** large sulcus that divides sections of the brain

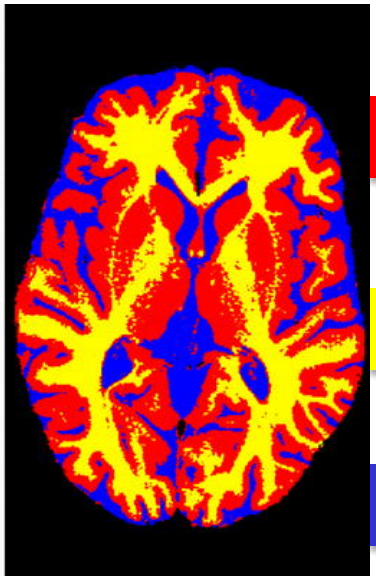
Images courtesy of "The Whole Brain Atlas", Johnson & Becker
http://www.med.harvard.edu/aanlib/home.htm

# Gray and White Matter




www.wickipedia.com





Ikram, et al. Eur J Epidemiol 2011

Gray

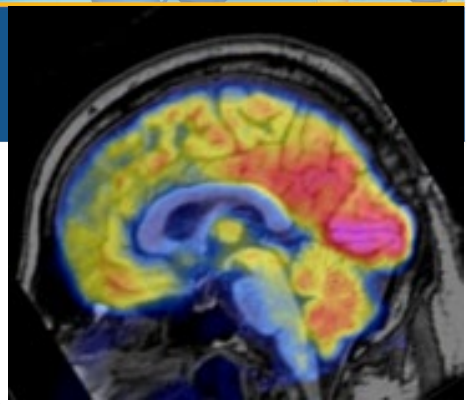
White

CSF

**Gray matter:** 40% of brain volume; uses 94% of total oxygen that goes to the brain; contains most of the brains 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

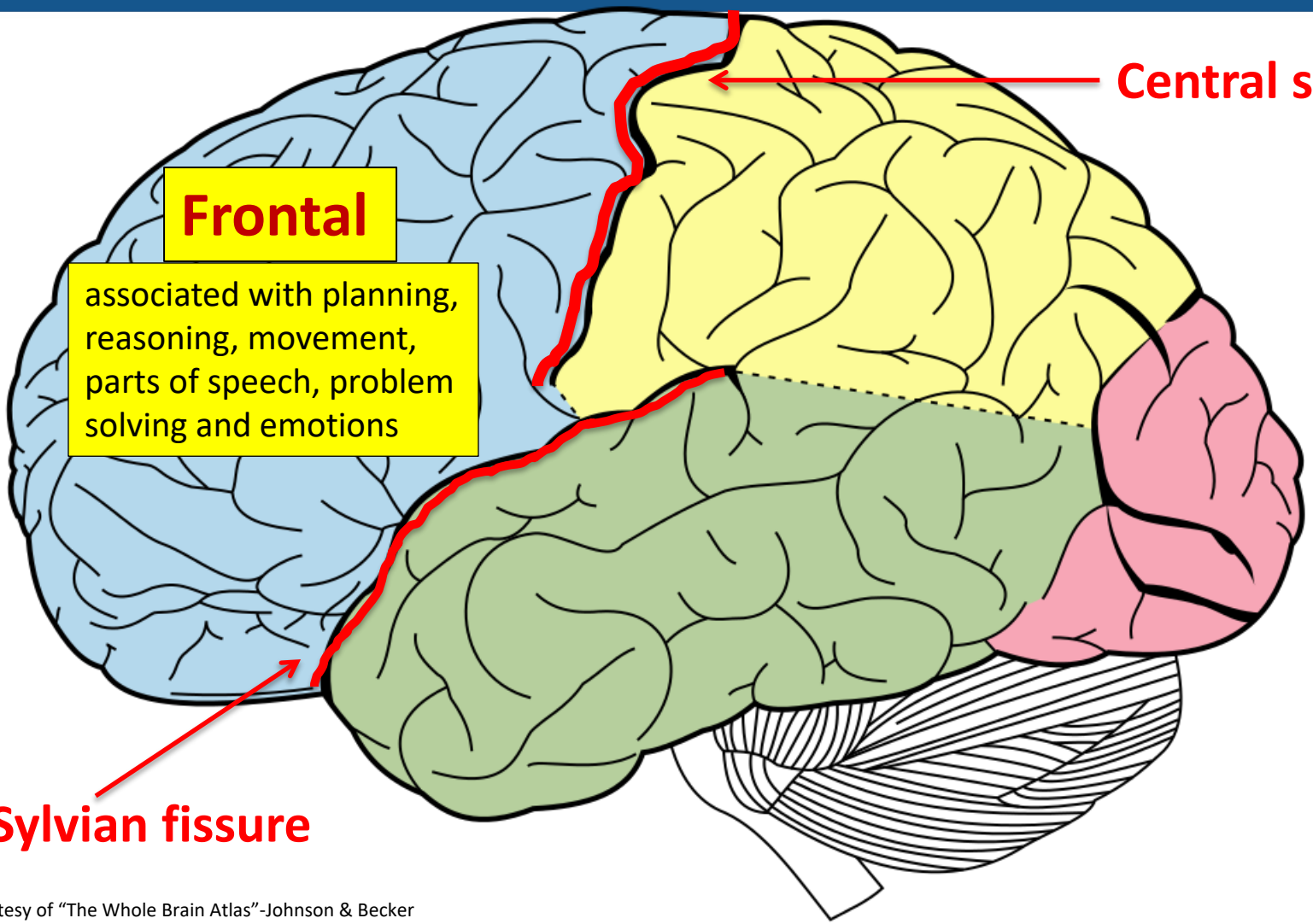



Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Temporal Lobe

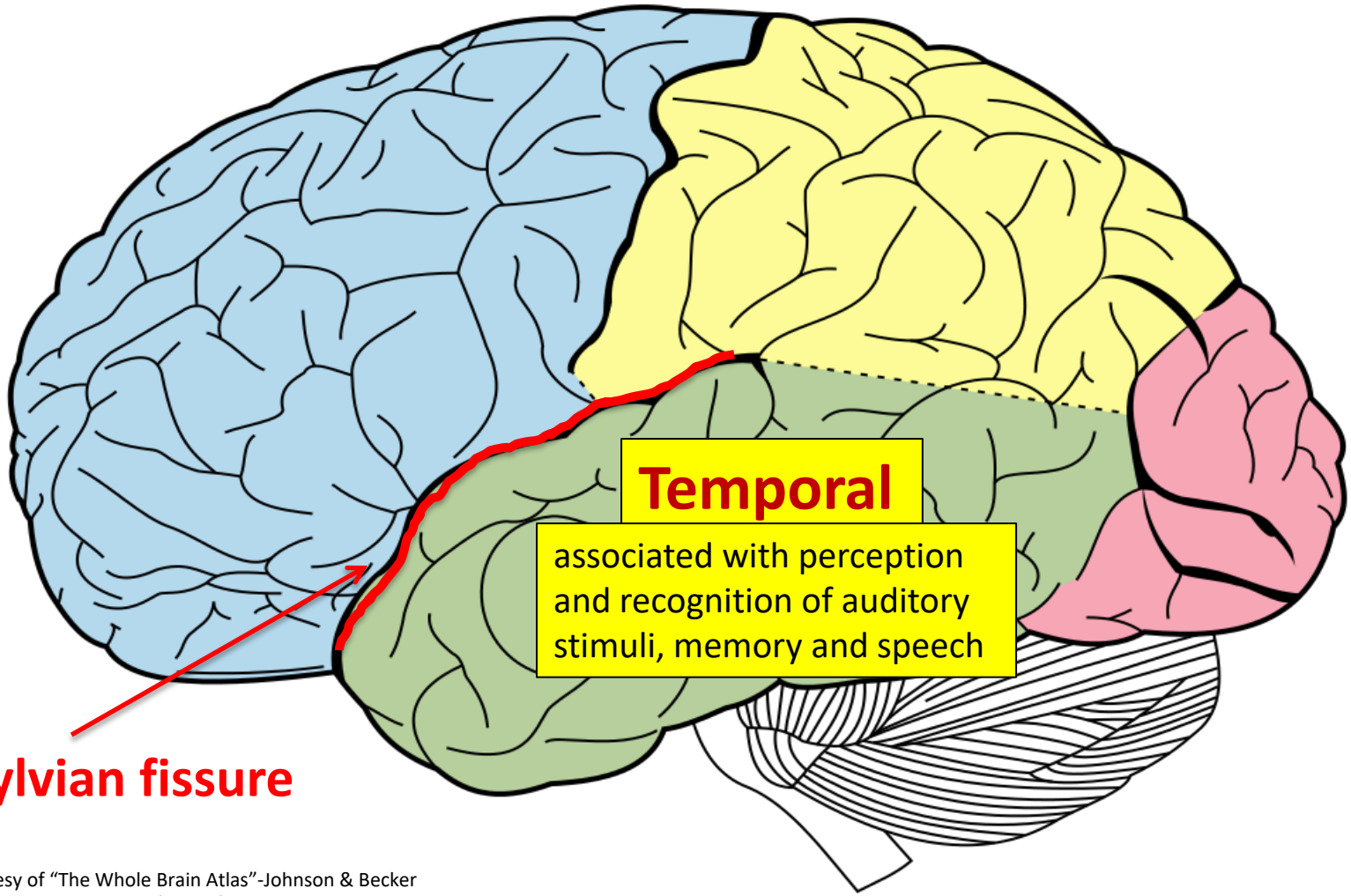



Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Parietal Lobe

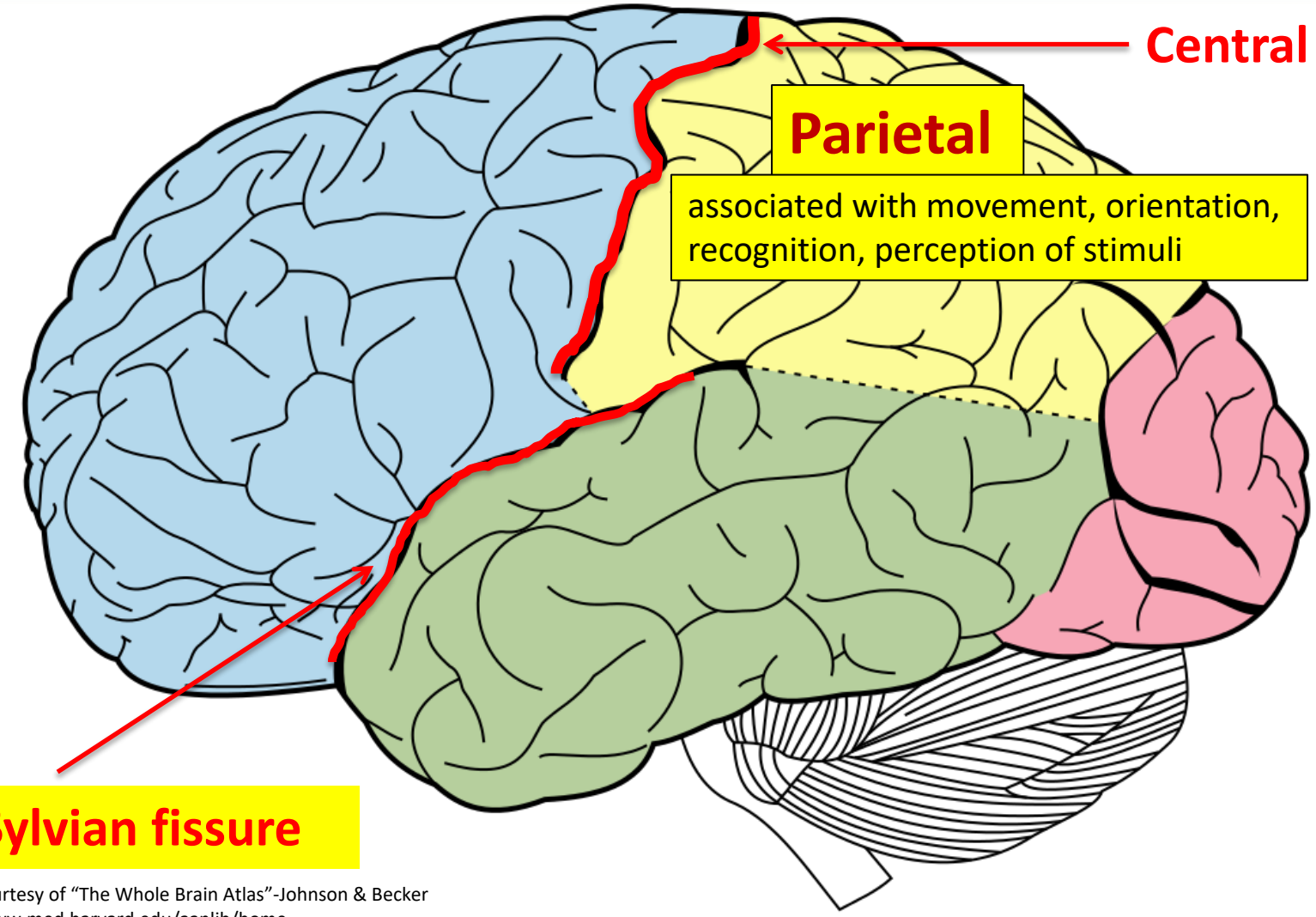



Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Occipital Lobe

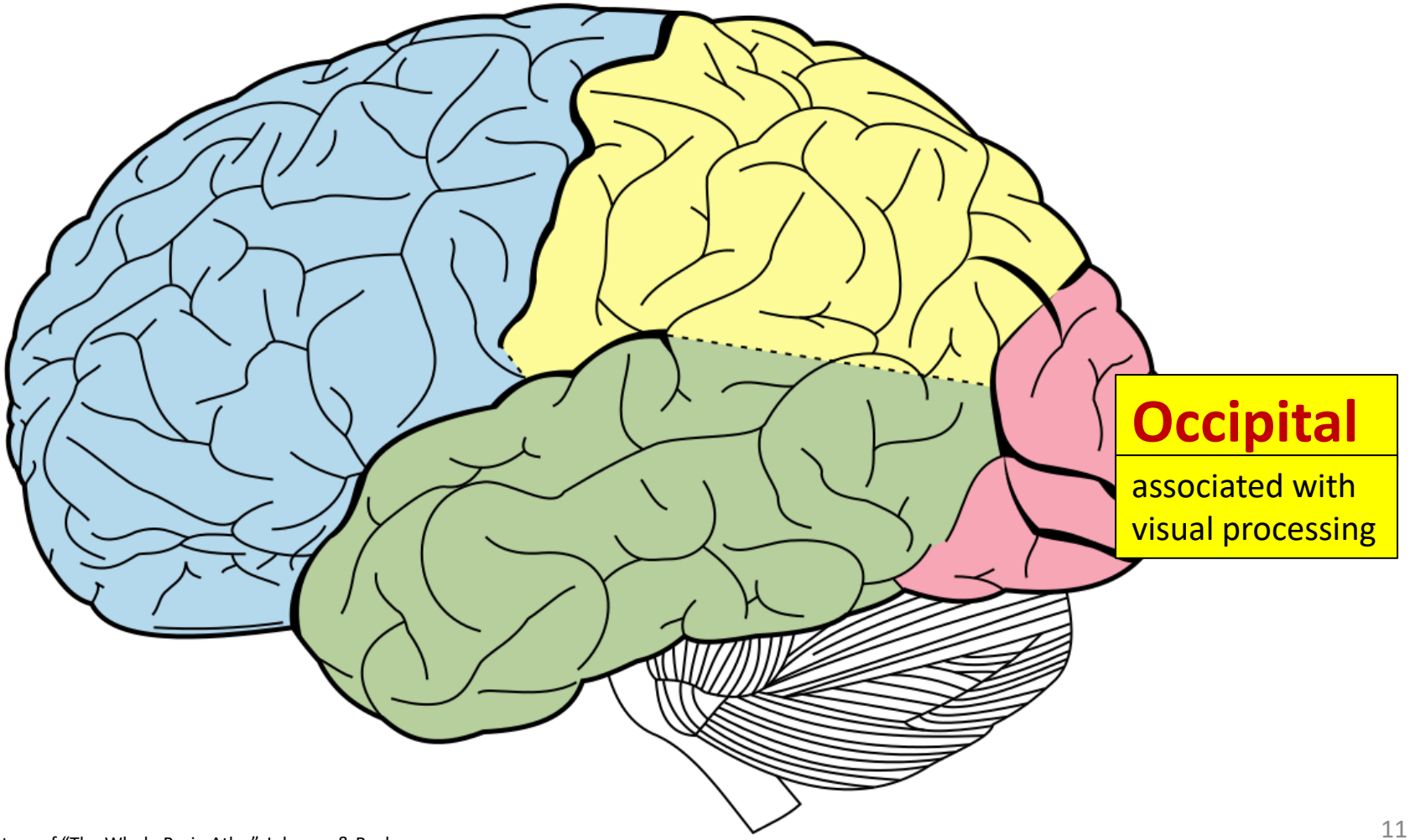



Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Transaxial Anatomy

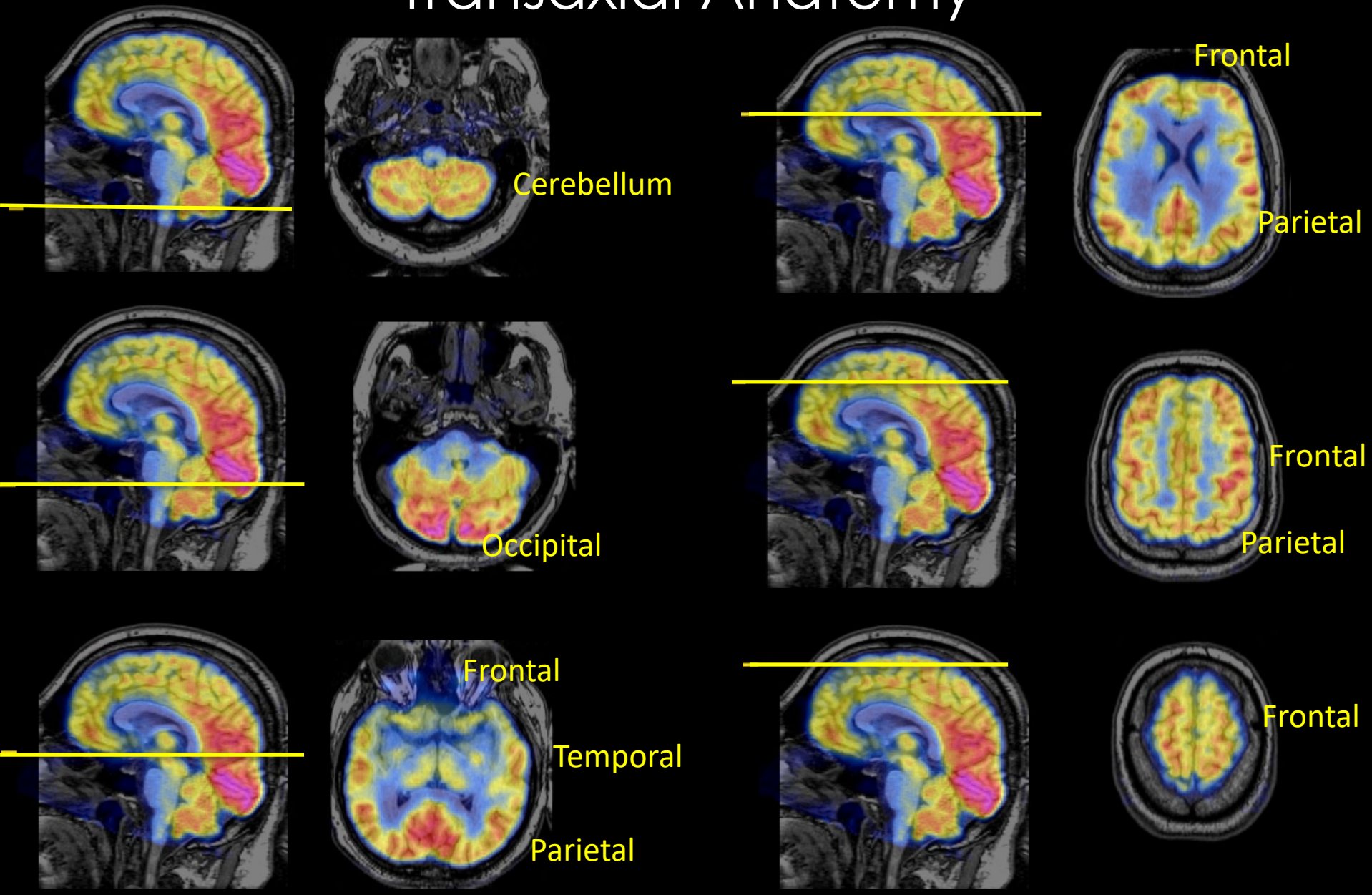



Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Coronal Anatomy

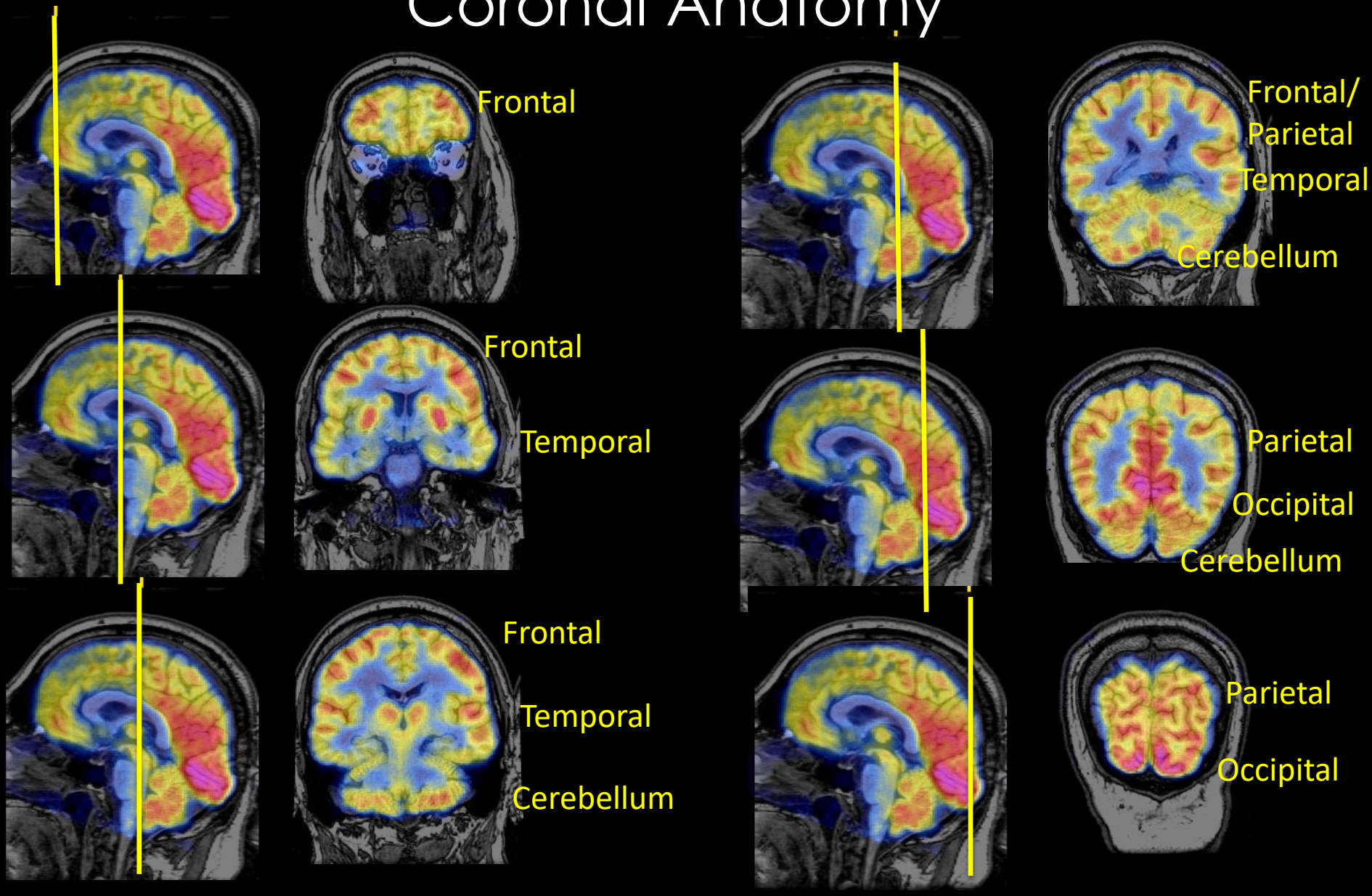
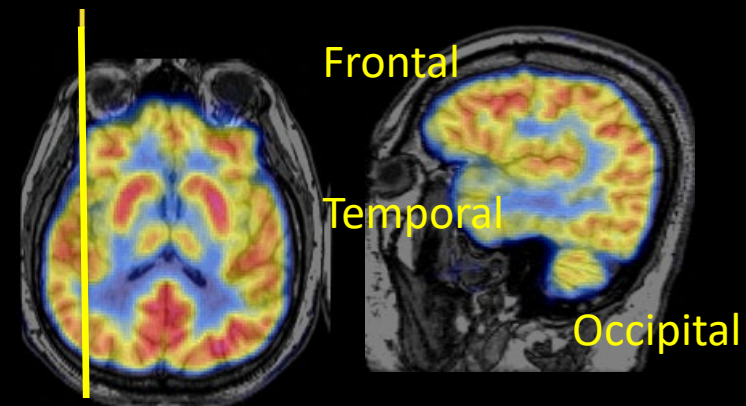
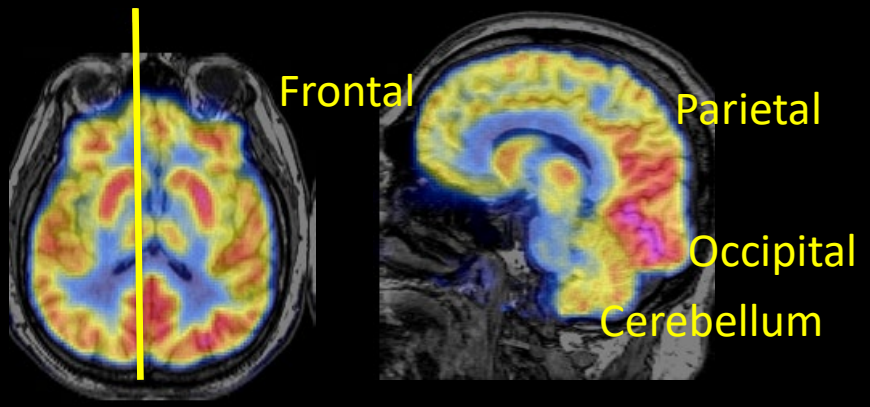
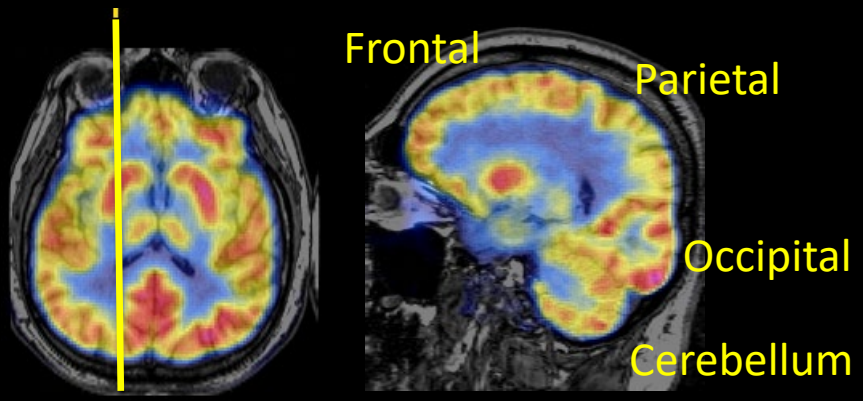



Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Sagittal Anatomy



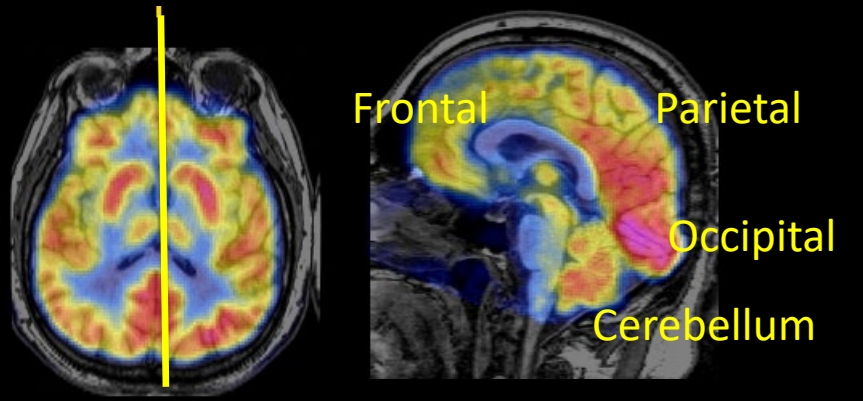
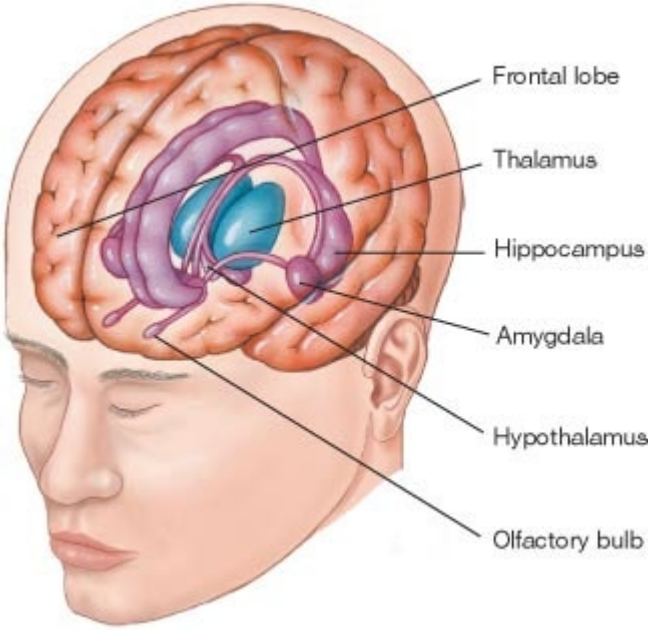
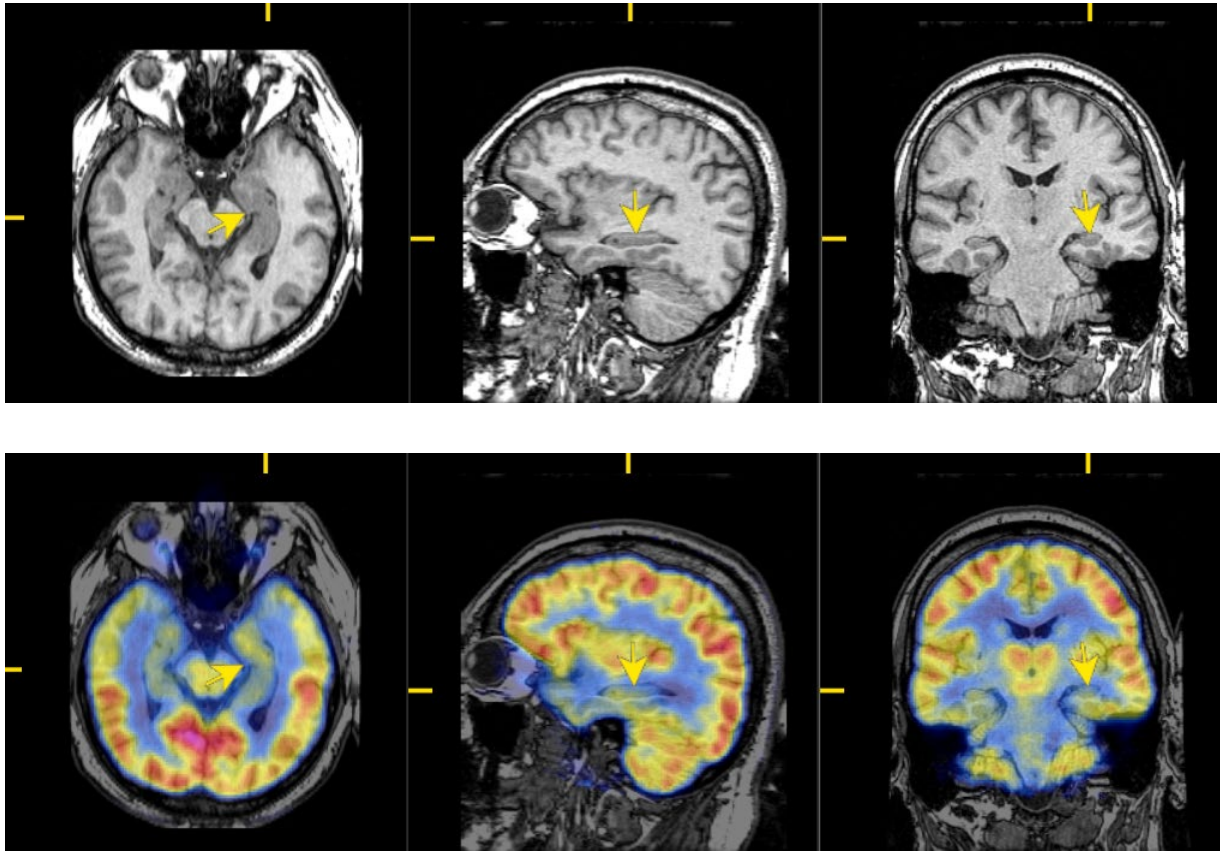




Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

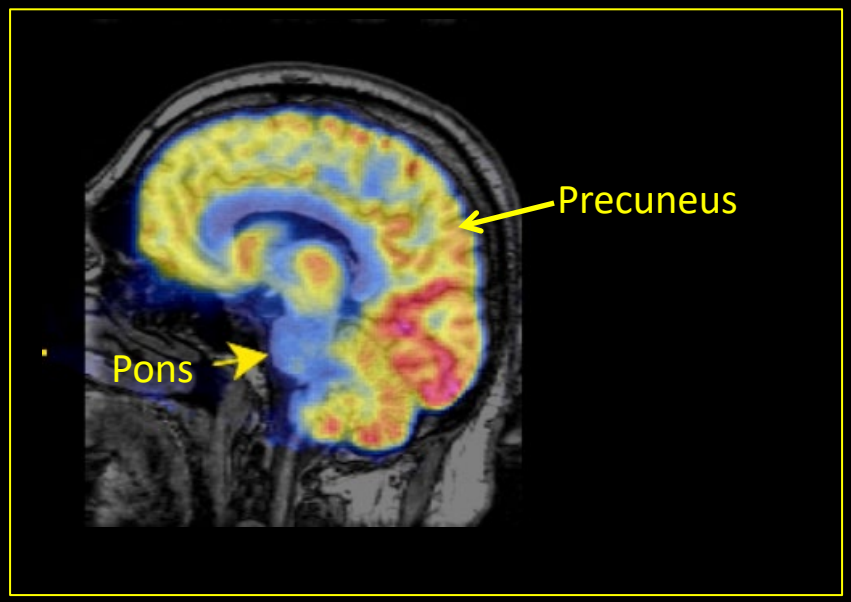
# Limbic System: Hippocampus

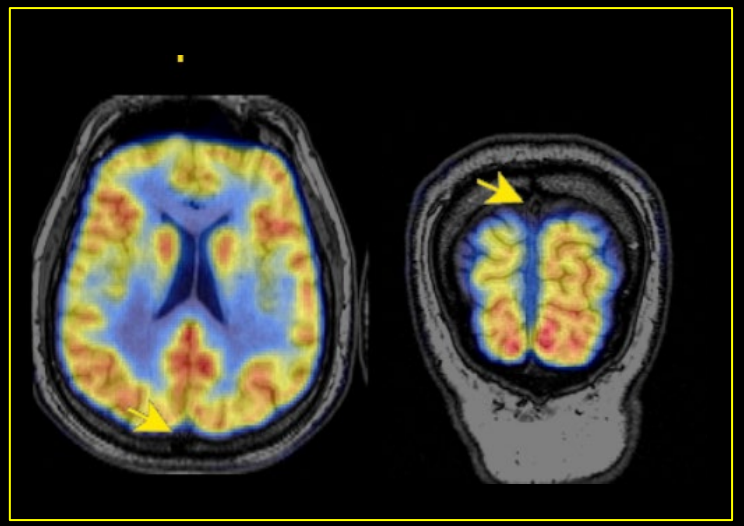


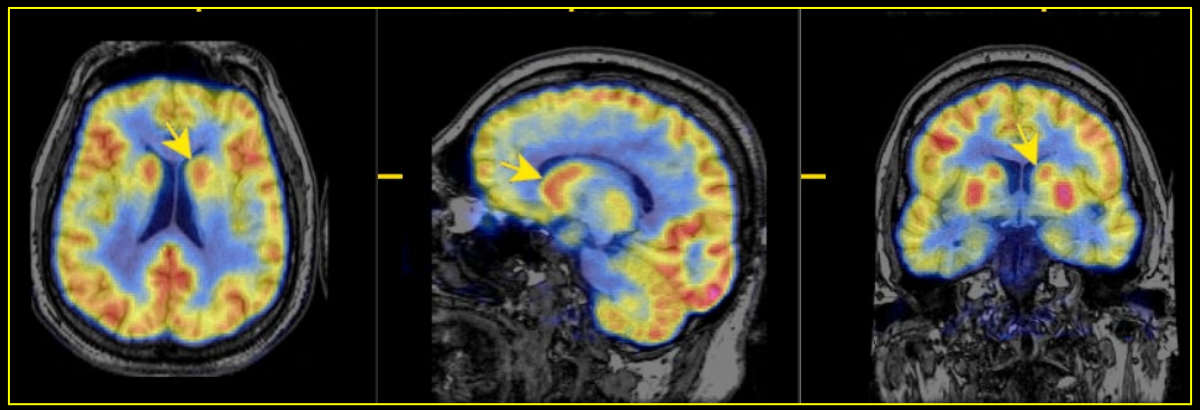
http://fab-efl.com/page1/page5/index.html
Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Key Structures on FDG Images

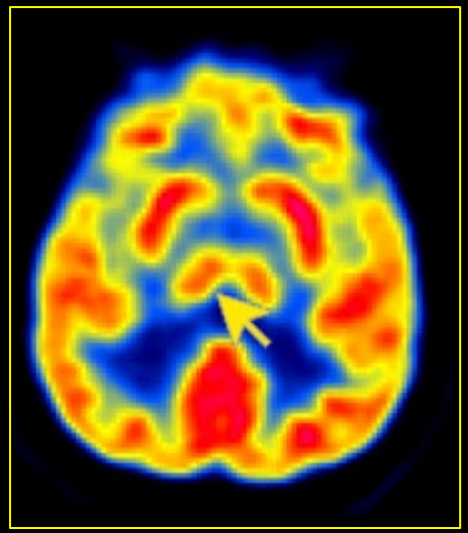


Superior Sagittal Sinus



Caudate Nucleus



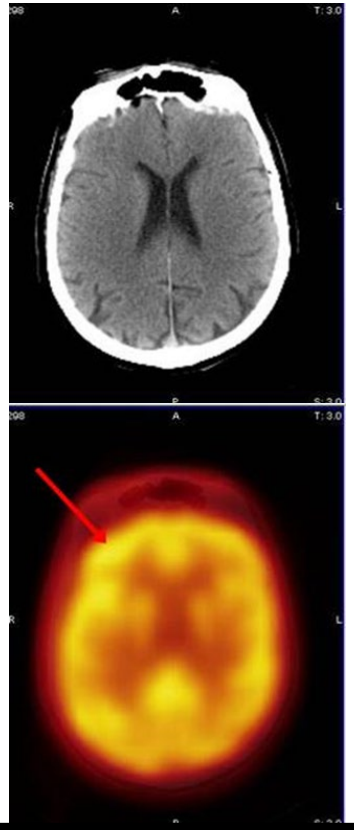
Thalamus

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



FDG-avid uptake in grey matter 1-2 hours post-injection

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

# 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

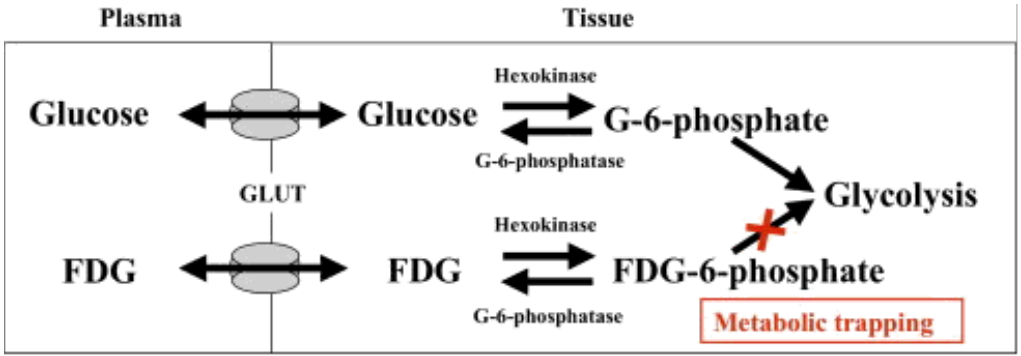


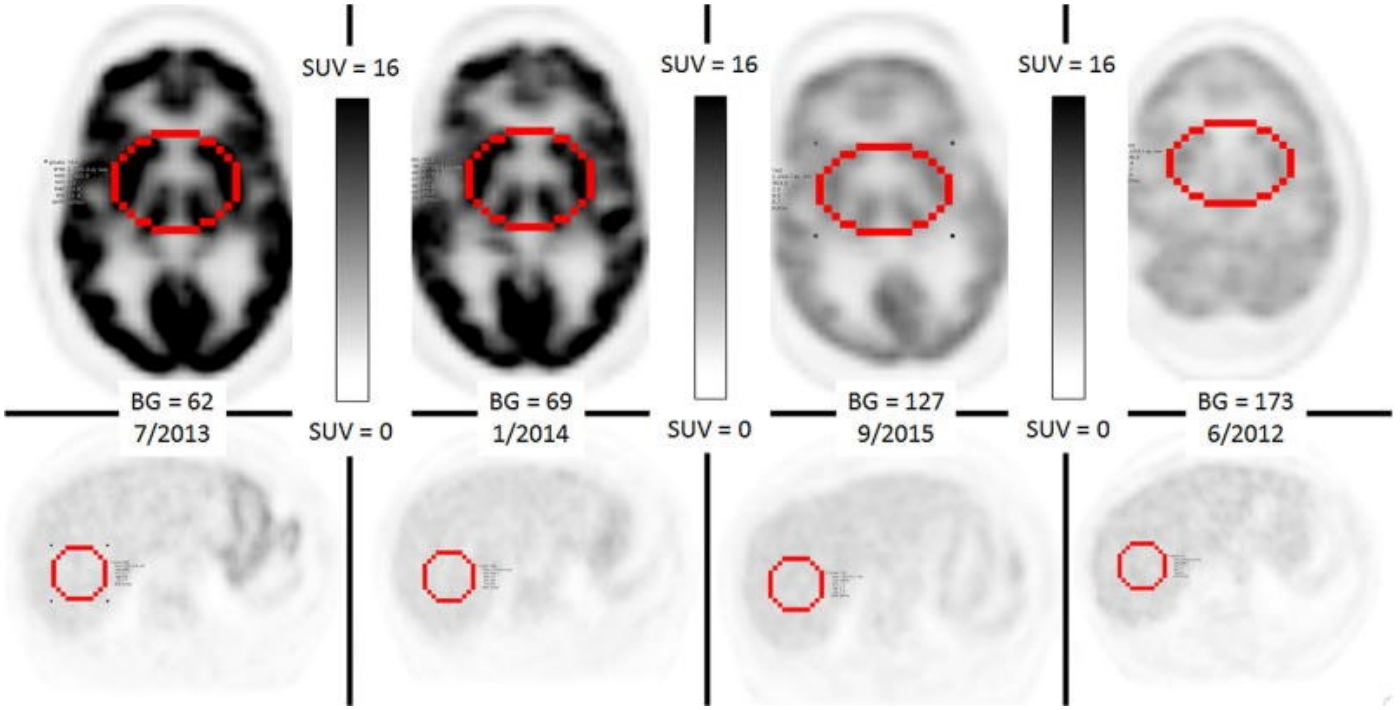

Image courtesy of content.onlinejacc.org
J Am Coll Cardiol. 2010;55(23):2527-2535.
doi:10.1016/j.jacc.2009.12.061

# 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

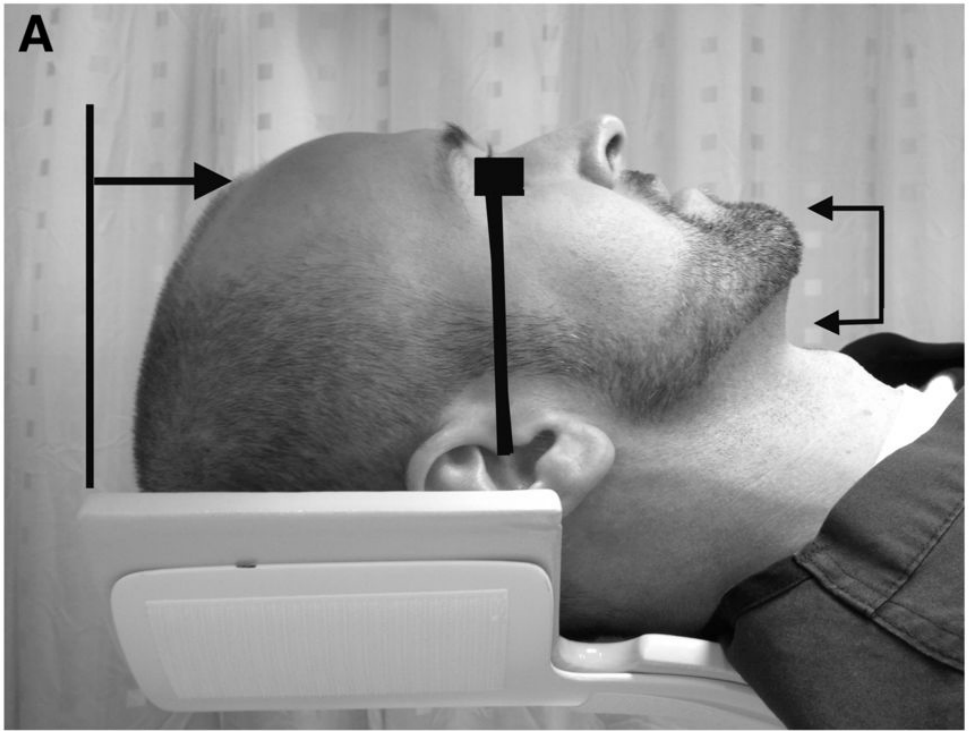
Viglianti et al (2017) "Effect of hyperglycemia on brain and liver 18F-FDG standardized uptake value (FDG SUV) measured by quantitative positron emission tomography (PET) imaging" Biomed Pharmacother 88:1038-1045

# 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**




**Chin should rest in neutral position**

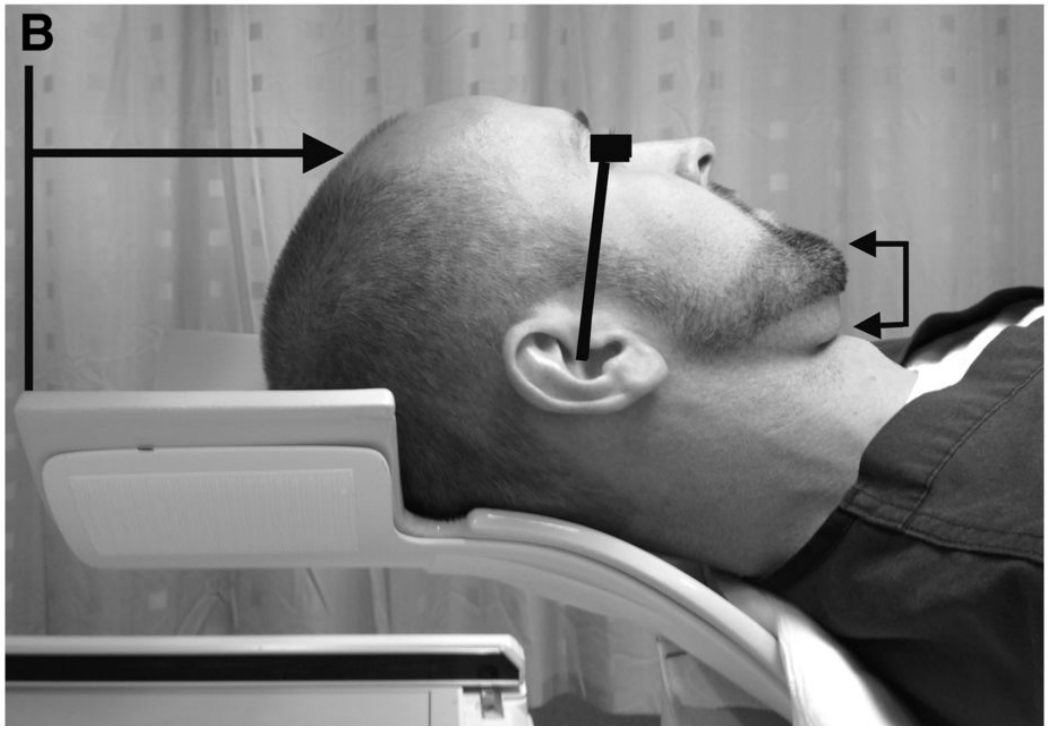
**Cantho-meatal line should be oriented vertically**



J. Nucl. Med. Technol. 2013;41:105-107

# Incorrect Head Positioning

**Incorrect positioning of head within holder**




**Chin is deflected toward neck**

**Canthomeatal line should be oriented vertically**



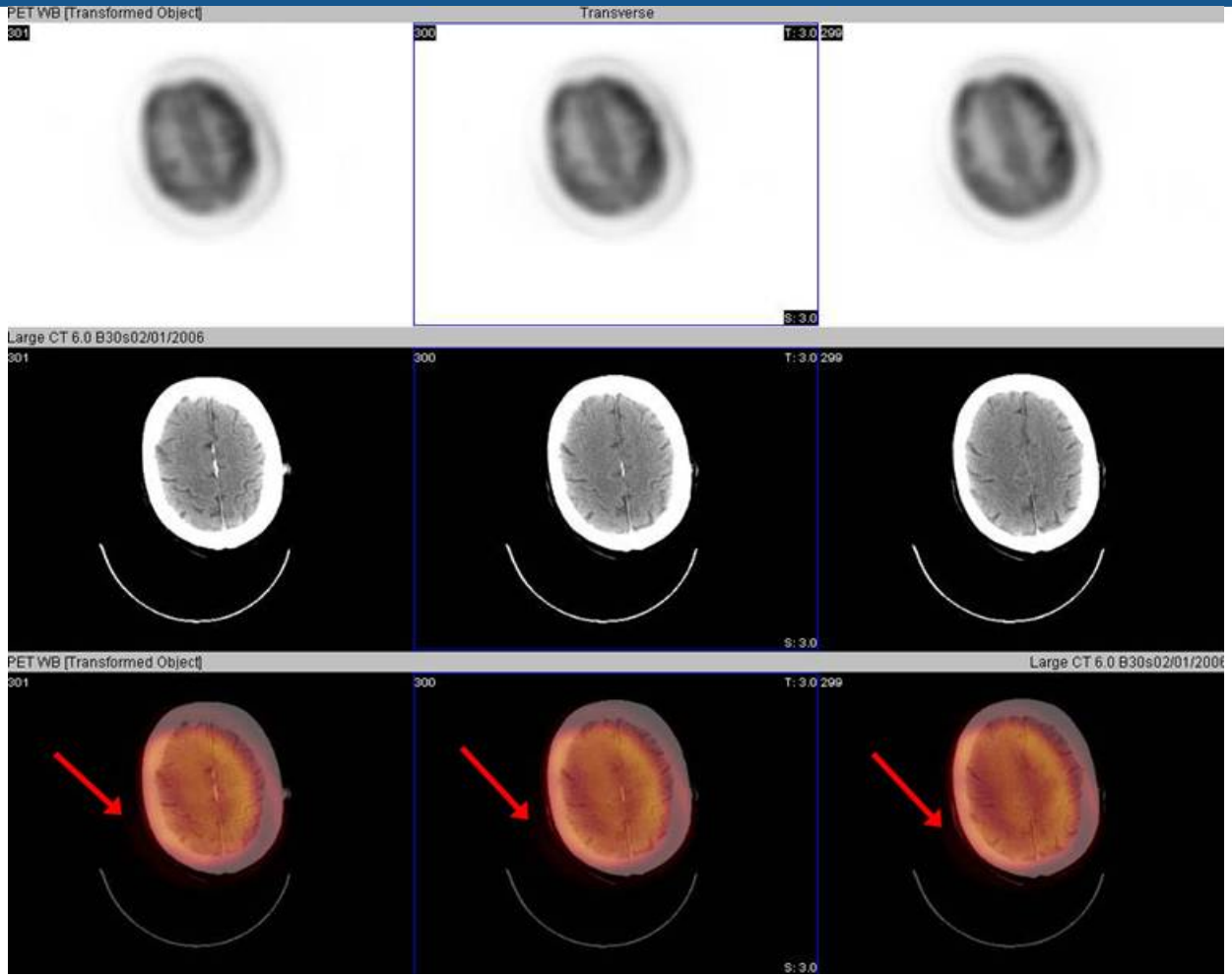
J. Nucl. Med. Technol. 2013;41:105-107

# 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



Slide courtesy of Mariam Aboian, MD

# Image Acquisition

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

| Static | Dynamic |
|---|---|
| Static protocols offer clinical applicability, and the relative tracer uptake is of interest | May be used when absolute quantification of regional metabolic rates of glucose are needed |
| Relative tracer uptake is characterized as the Standardized Uptake Value (SUV) and details of the errors with static SUV have been well documented | 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 |
| May impose a bias by arbitrarily choosing a single time frame to represent overall tracer metabolism | Requires blood samples to be obtained during imaging (venous or arterial) |

# 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

| 2D Emission Scan | Fully-3D Emission Scan |
|---|---|
| Lower sensitivity (longer acquisition time) | Higher sensitivity (shorter acquisition time) |
| Less data storage | More data storage |
| Simpler to reconstruct | Harder to reconstruct |
| FOV for random coincidences is smaller | FOV for random coincidences is larger |

# 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

Matti et al (2019) "How do the more recent reconstruction algorithms affect the interpretation criteria of PET/CT images?" Nuclear Medicine and Molecular Imaging 53:216-222
Society of Nuclear Medicine Procedure Guideline for FDG PET Brain Imaging v1.0

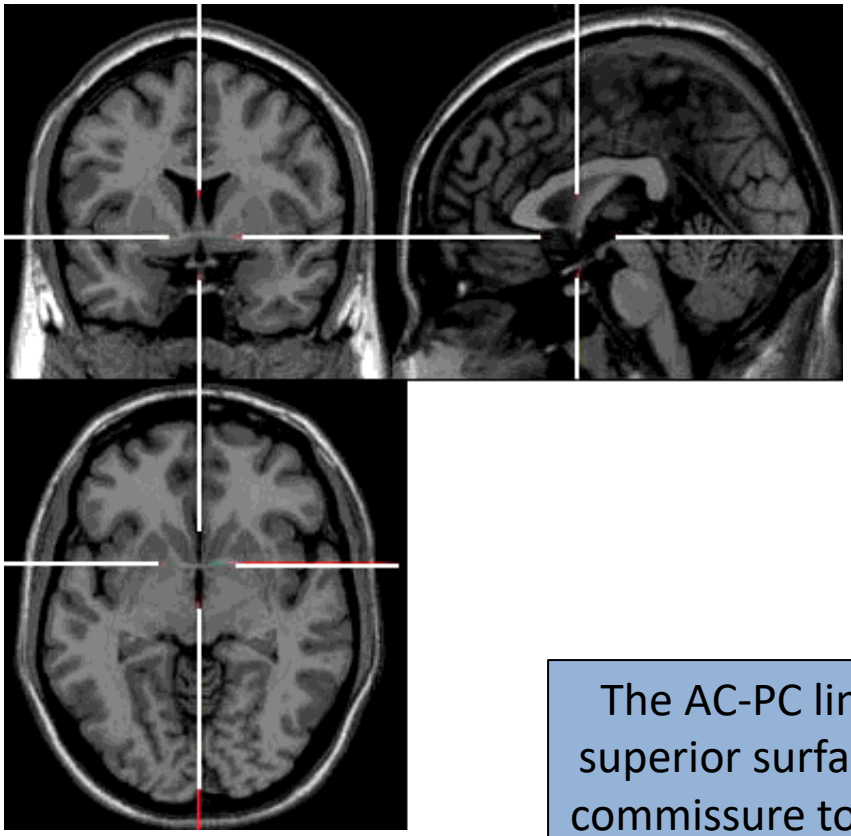
# Image Processing

- 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

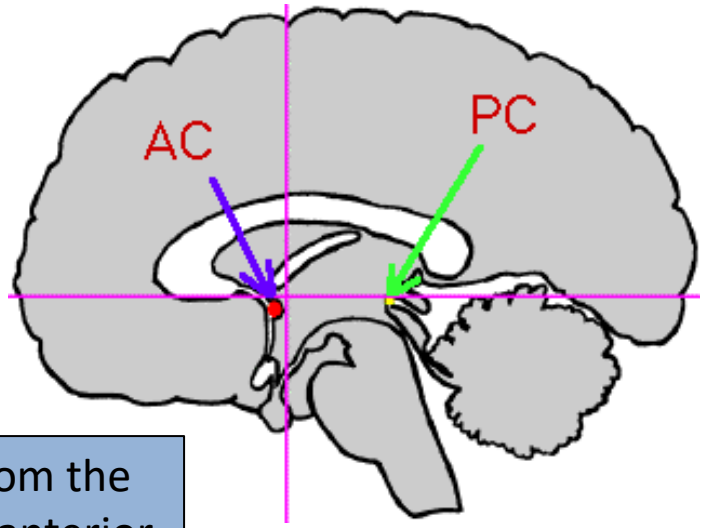
# Data Display

- 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

# Intercommissural line (ICL)



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

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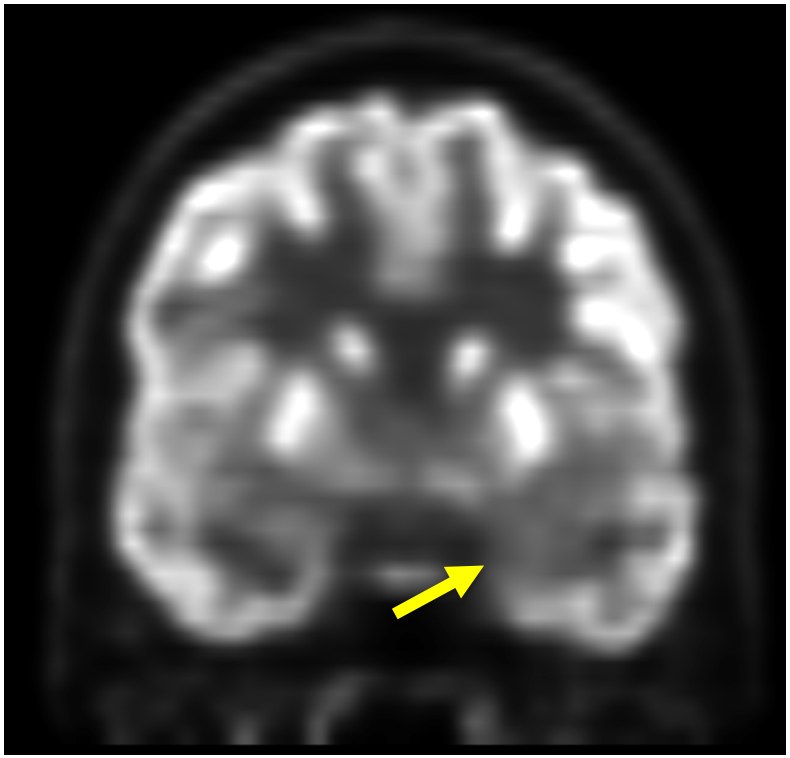
# Semi-Quantitative Analysis of FDG Uptake

- 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

| Atlas | Structure | Z-S... | L Z-Score | R Z-Score | L-R % Diff | L-R % Diff Z-Score |
|---|---|---|---|---|---|---|
| Single Brain Atlas | Medial Temporal Lobe | -1.77 | -2.04 | -1.36 | -1.42 | -0.67 |
| Single Brain Atlas | Amygdala | -1.78 | -1.89 | -1.51 | -4.04 | -0.41 |
| MIM Probabilistic Atlas | Amygdala 8/10 | -1.87 | -1.81 | -1.61 | 1.47 | 0.08 |
| MIM Probabilistic Atlas | Medial Temporal Lobe 8/10 | -2.04 | -2.39 | -1.54 | -2.24 | -0.86 |
| Single Brain Atlas | Hippocampus | -2.06 | -2.5 | -1.43 | -6.89 | -1.37 |
| Single Brain Atlas | Pontine Tegmentum | -2.21 | N/A | N/A | N/A | N/A |
| Single Brain Atlas | Globus Pallidus | -2.25 | -1.92 | -2.47 | 3.75 | 0.39 |
| Single Brain Atlas | Middle Cerebellar Peduncle | -2.32 | -2.3 | -2.11 | 0.61 | -0.11 |
| MIM Probabilistic Atlas | Hippocampus 8/10 | -2.34 | -2.75 | -1.6 | -9.11 | -1.6 |

Courtesy of Mariam Aboian, MD

# FDG Pitfalls, Artifacts, Sources of Error

Medications altering cerebral metabolism include:

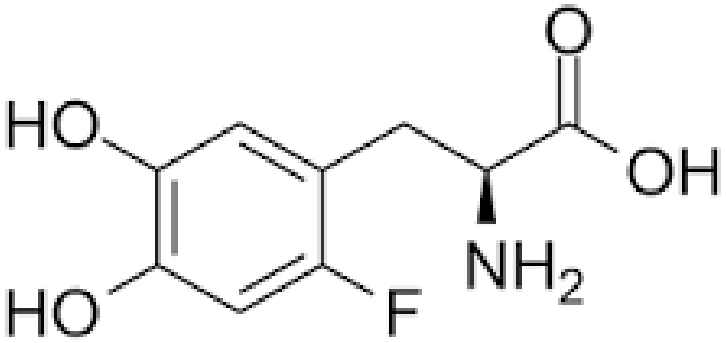
- Sedatives
- Drugs such as amphetamines, cocaine
- Narcotics
- Anti-psychotic medications
- Corticosteriods

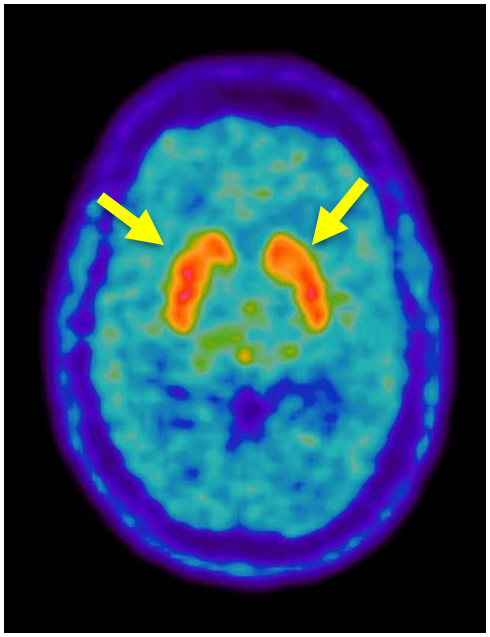
# Additional Neuroimaging PET Tracers:

- Amino Acid
- Amyloid
- Tau

# $^{18}$F-FDOPA

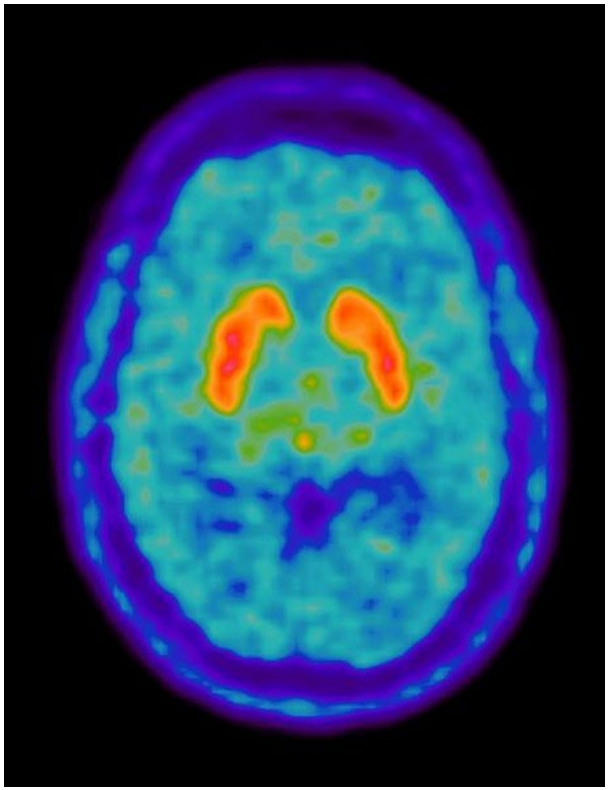
- FDOPA is an $^{18}$F form of L-DOPA
- Imported into cell via LAT1 transporter
- Measures amino acid metabolism
- Can be used to visualize dopaminergic nerve terminals
- Symmetric homogeneous uptake within the striatum
- Has been approved for evaluation of Parkinson's
- Evaluation is visual and is based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



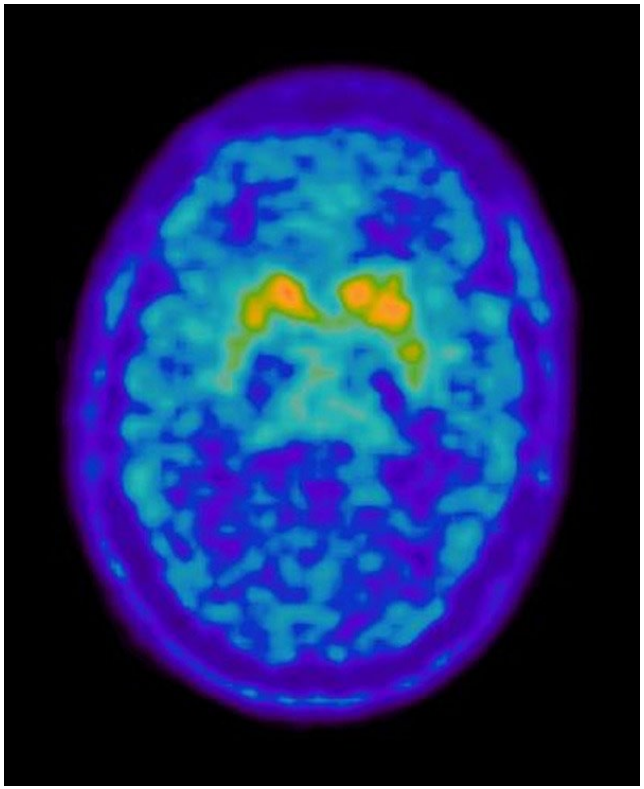



https://pubchem.ncbi.nlm.nih.gov/compound/Fluorodopa-_18F
https://en.wikipedia.org/wiki/Fluorodopa#/media/File:Fluorodopa.png
Ibrahim et al, 2016, "The sensitivity and specificity of F-DOPA PET in a movement disorder clinic" Am J Nucl Med Mol Imaging 6(1):102-109

## Normal



## Parkinson's Disease



Ibrahim et al, 2016, "The sensitivity and specificity of F-DOPA PET in a movement disorder clinic" Am J Nucl Med Mol Imaging 6(1):102-109

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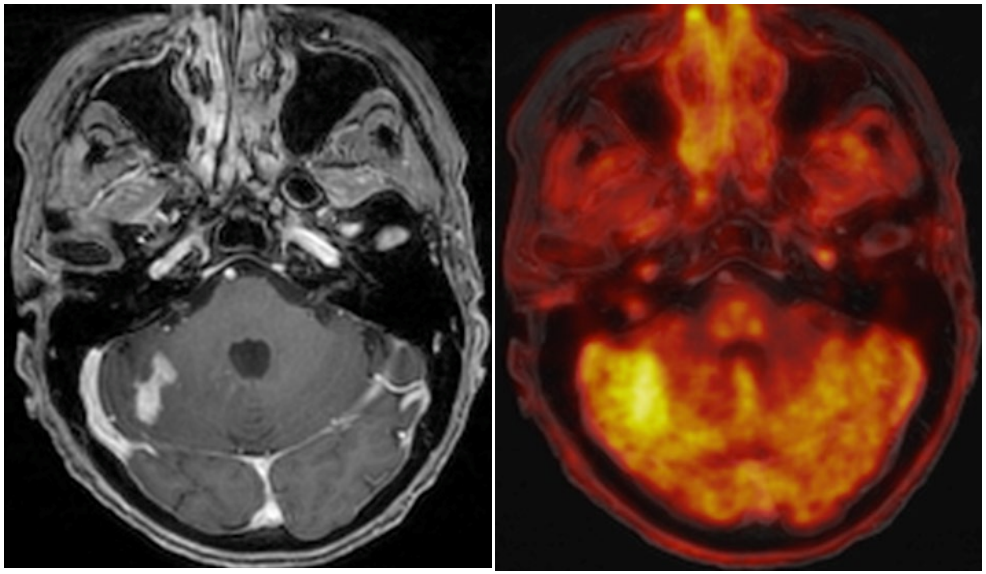
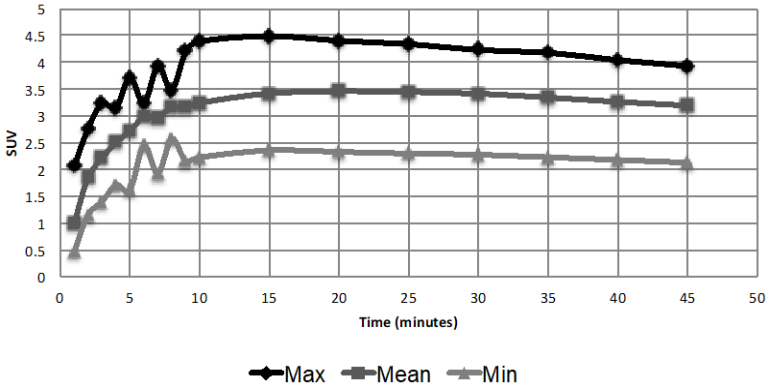
CLINICAL TRIALS NETWORK

# $^{18}$F-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






Courtesy of Mariam Aboian, MD

# 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

# beta-amyloid

- 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)

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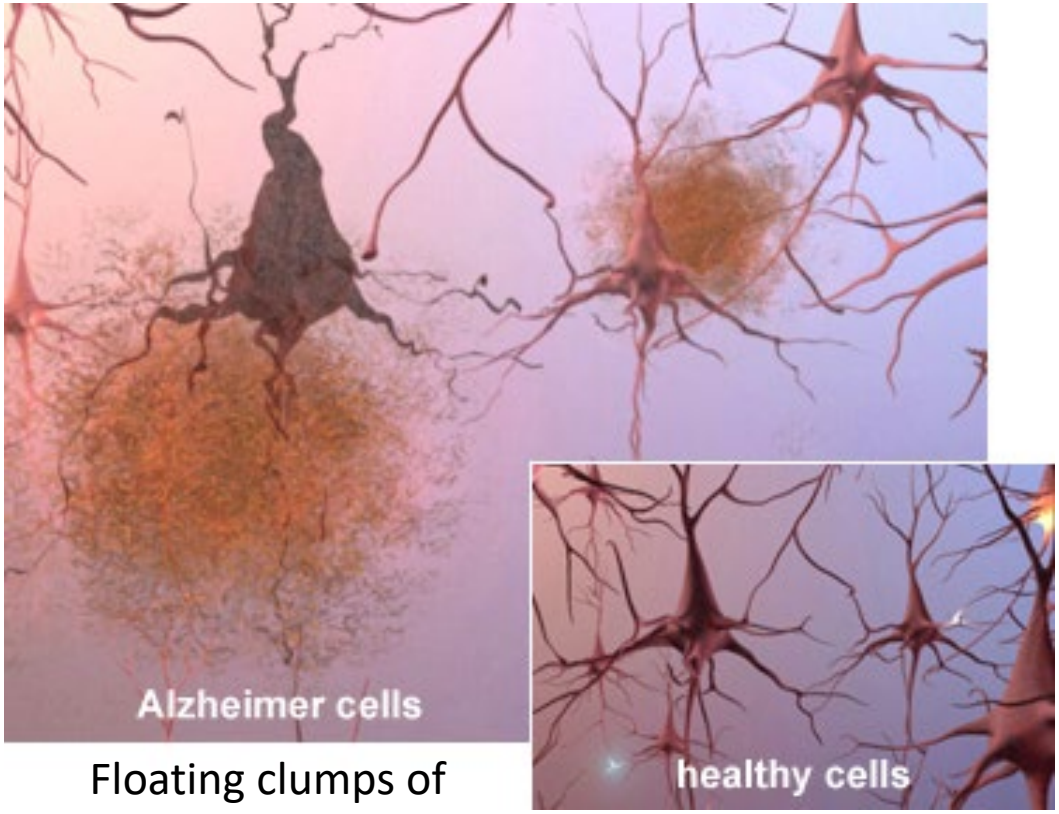
# Alzheimer's Disease



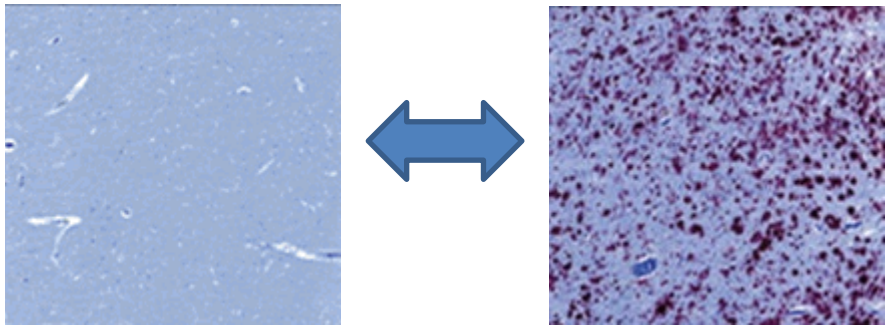

Floating clumps of protein fragments that block synapses

- 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

# 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

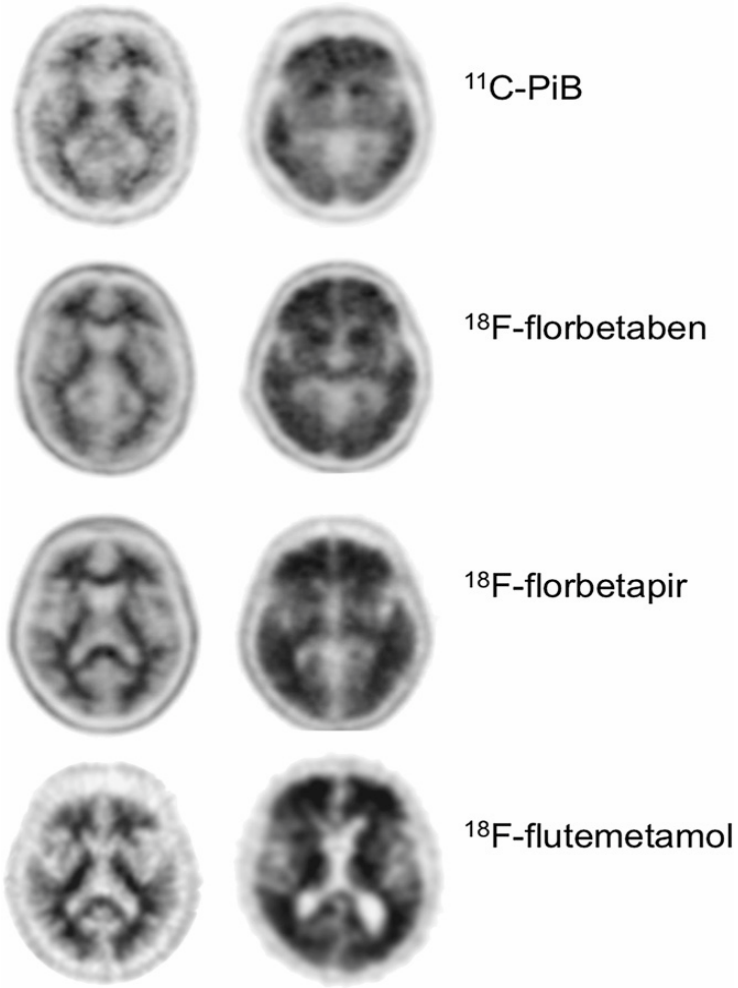
No evidence of amyloid plaques



High levels of amyloid plaques

Images from www.amyvid.com

# Amyloid Imaging




- 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)

J Nucl Med 2011; 52:1733-1740

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# Indication Statement

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.


[4] Eli Lilly and Company (2012). Amyvid ™ Florbetapir F 18 Injection: Highlights of Prescribing Information. Indianapolis, IN.

[5] GE Healthcare (2013). Vizamyl ™ Flutemetamol F 18 Injection: Highlights of Prescribing Information. Arlington Heights, IL

[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

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CLINICAL TRIALS NETWORK

# Product Specific Administration and Dosing

| | Dose | Injection Supplies | Injection | Flush | Patient instructions |
|---|---|---|---|---|---|
| **Florbetapir** | 10mCi (370MBq) 10mL or less | Catheter less than 1.5 inches; use HDPE syringe[4] | Single Bolus | | |
| **Flutemetamol** | 5 mCi (185 MBq) 10mL or less | | Bolus IV within 40 seconds | 10-15mL saline | Hydrate and encourage voiding before and after injection[5] |
| **Florbetaben** | 8.1 mCi (300 MBq) 0.5-10mL | | Slow bolus IV (6 sec/mL) | 10mL saline | Avoid close contact with young children and pregnant women for 24 hours post injection[7] |

Eli Lilly and Company (2012). Amyvid™ Florbetapir F 18 Injection: Highlights of Prescribing Information. Indianapolis, IN
GE Healthcare (2020). Vizamyl™ Flutemetamol F 18 Injection: Highlights of Prescribing Information. Arlington Heights, IL
Piramal Imaging (2014). NeuraCeq™ Florbetaben F 18 Injection: Highlights of Prescribing Information. Matran, Switzerland

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# Imaging Workflow

| Amyloid Imaging Agent | Standard Uptake Time | Acquisition Scan Time | Patient Positioning |
|---|---|---|---|
| **Florbetapir** | 30-50 minutes post injection | 10 minutes | 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] |
| **Flutemetamol** | 60-120 minutes post injection | 10-20 minutes | Position the patient supine with the brain (including the cerebellum) within a single field of view. The patients 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] |
| **Florbetaben** | 45-130 minutes post injection | 15-20 minutes | 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] |

Eli Lilly and Company (2012). Amyvid™ Florbetapir F 18 Injection: Highlights of Prescribing Information. Indianapolis, IN
GE Healthcare (2020). Vizamyl™ Flutemetamol F 18 Injection: Highlights of Prescribing Information. Arlington Heights, IL
Piramal Imaging (2014). NeuraCeq™ Florbetaben F 18 Injection: Highlights of Prescribing Information. Matran, Switzerland

# Amyloid Imaging Display

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.

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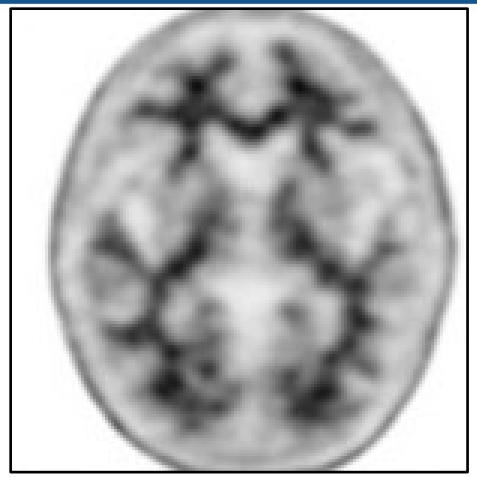
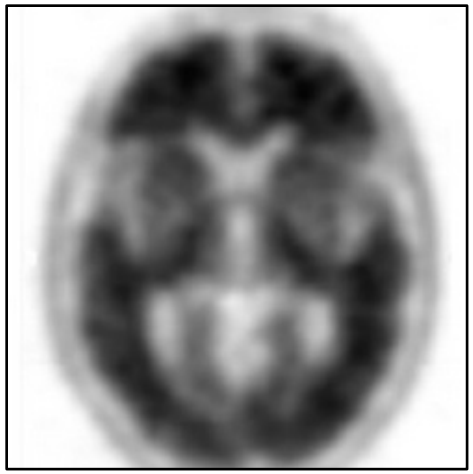
# Amyvid (florbetapir)

Negative



Positive



- 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)

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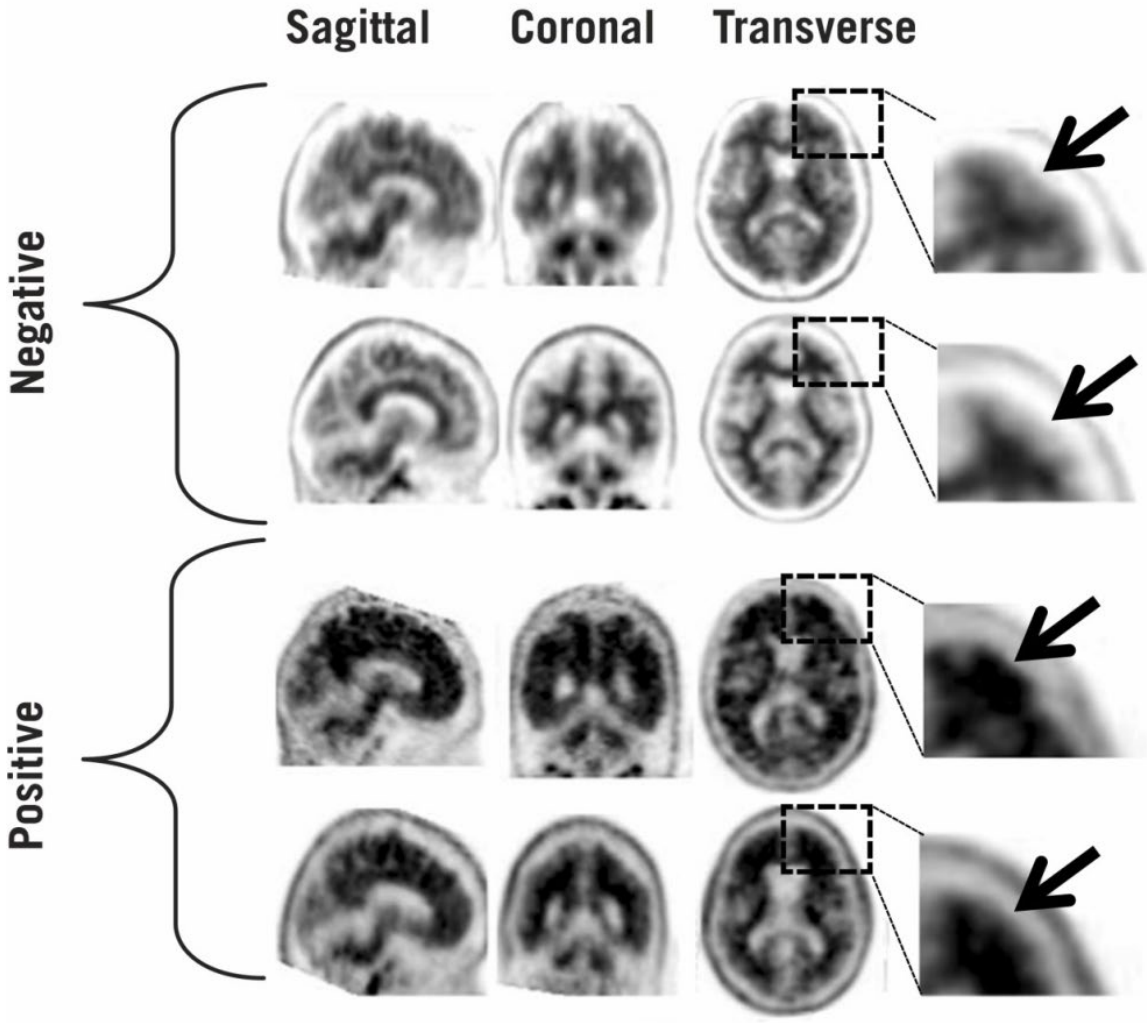
CLINICAL TRIALS NETWORK

# Amyvid (florbetapir)




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

Decreased gray-white contrast with increased cortical radioactivity that is comparable to the radioactivity in the adjacent white matter

Florbetapir Package Insert

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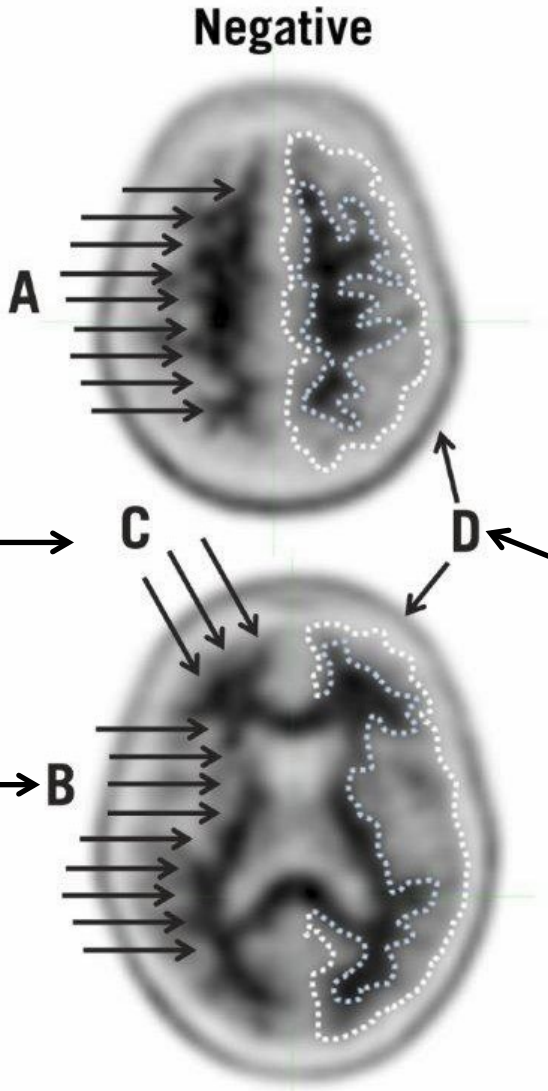
CLINICAL TRIALS NETWORK

# Amyvid (florbetapir)




White matter tracks can be delineated from the frontal lobe to parietal lobe

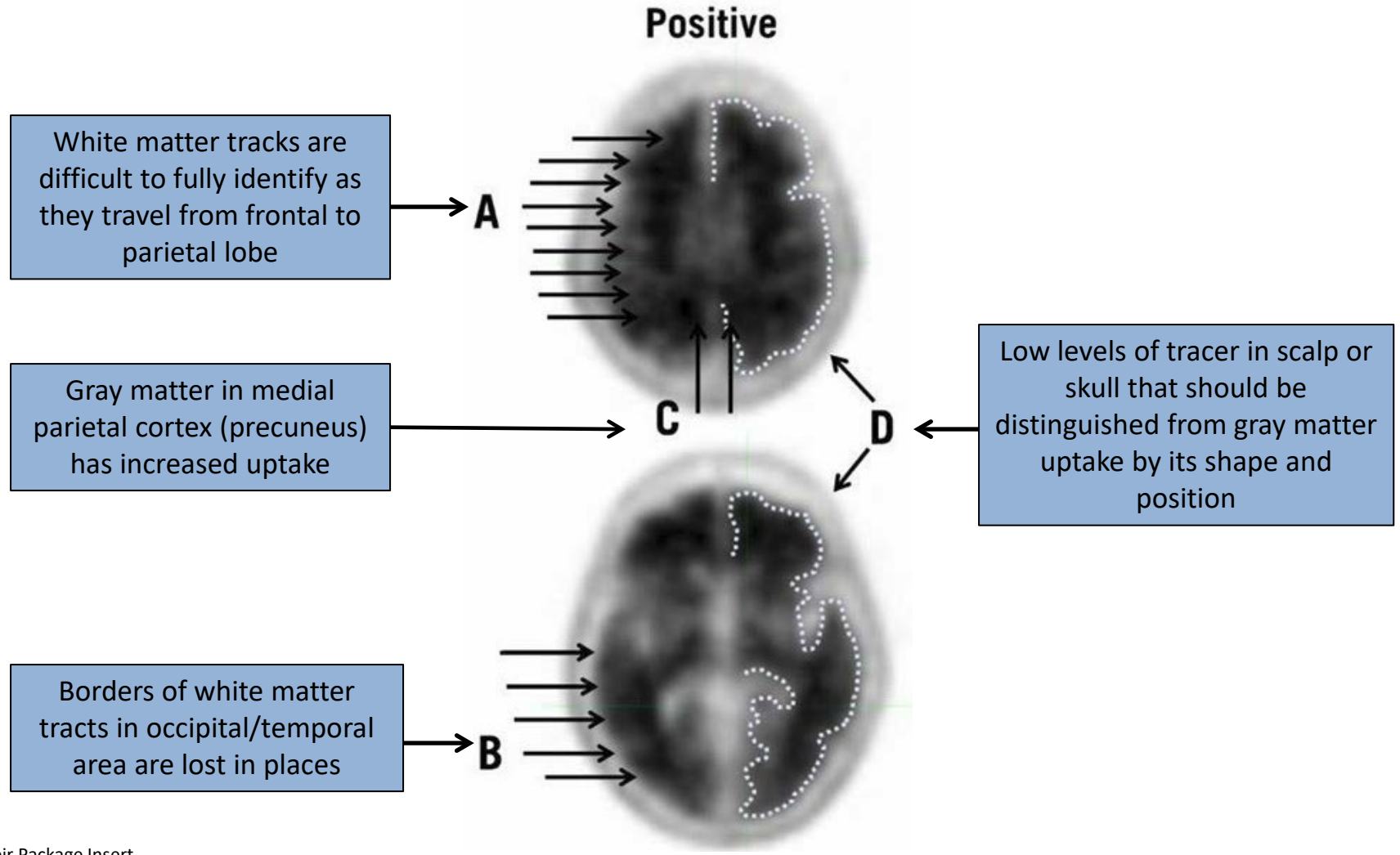
Scalloped appearance is seen with “fingers” of white matter in the frontal cortex

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

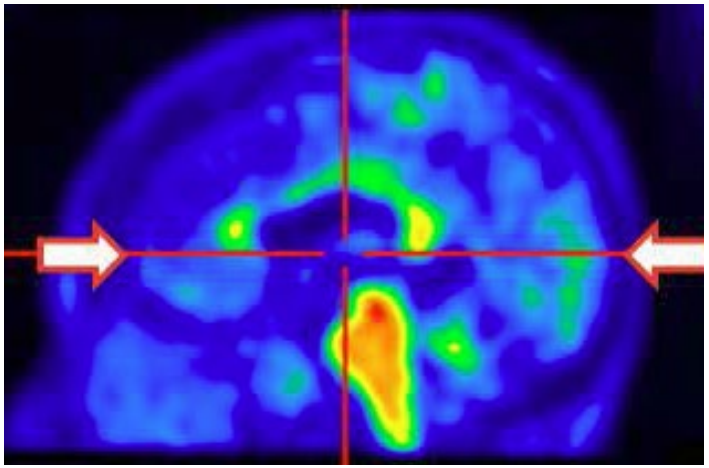
Florbetapir Package Insert

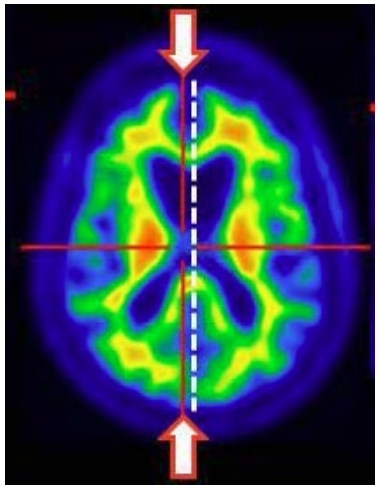
# Amyvid (florbetapir)

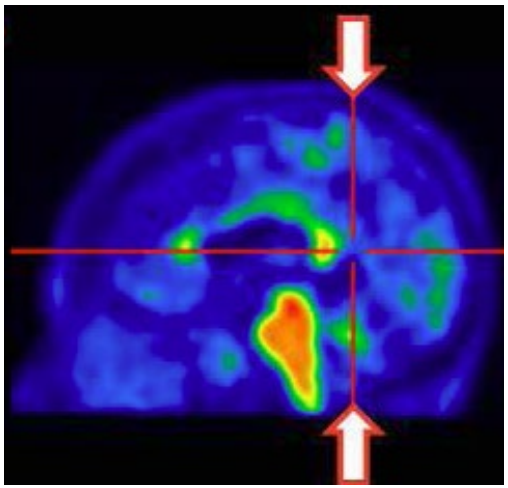



Florbetapir Package Insert

# 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

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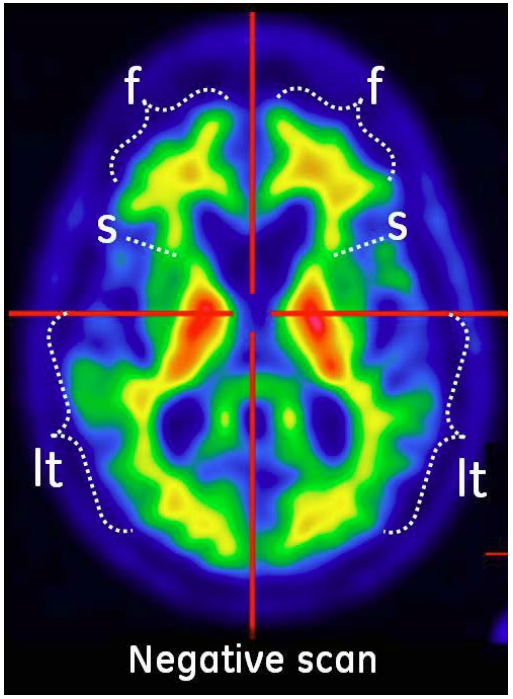
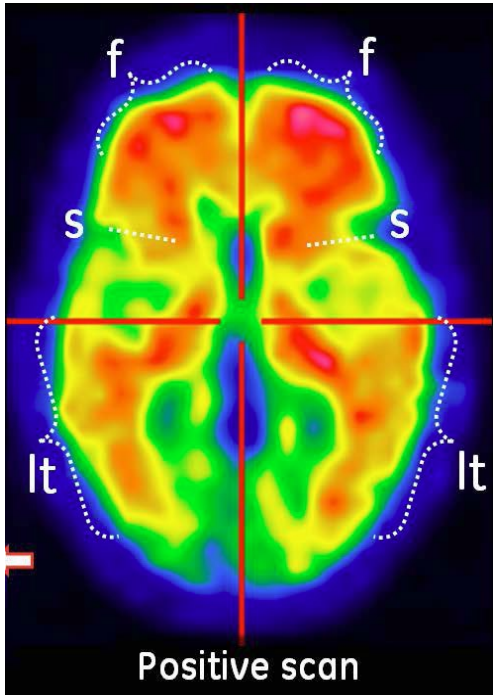
CLINICAL TRIALS NETWORK

# Vizamyl (flutemetamol)

Less uptake in striatal regions

White matter sulcal pattern with a color intensity that tapers to the periphery



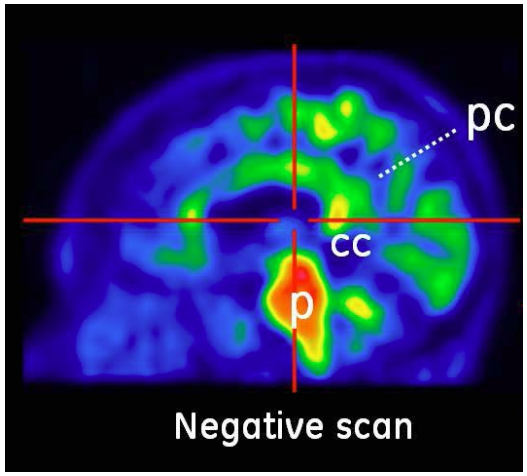




More radioactivity in the striatal regions

Absence of white matter sulcal pattern with intensity radiating to a sharply defined convex edge

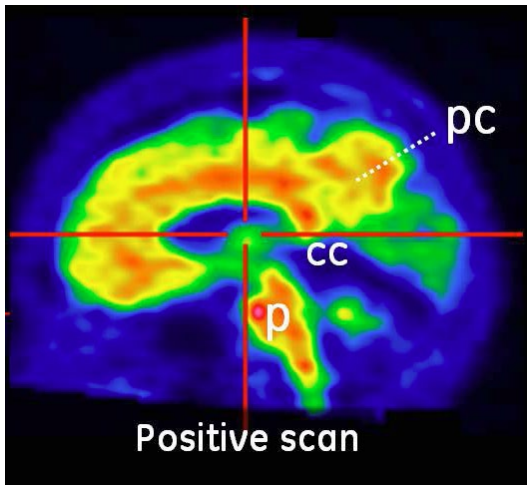
In both the frontal and lateral temporal regions, the intensity is higher in the gray matter regions when comparing the Positive and Negative scans

# Vizamyl (flutemetamol)



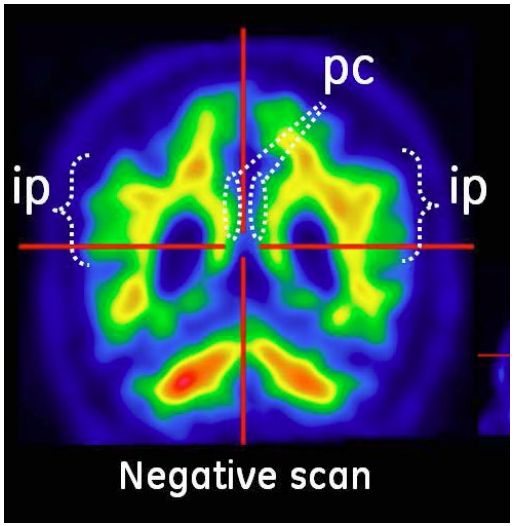

The posterior cingulate (pc) region which is superior and posterior to the corpus callosum - the intensity is below 50% of peak

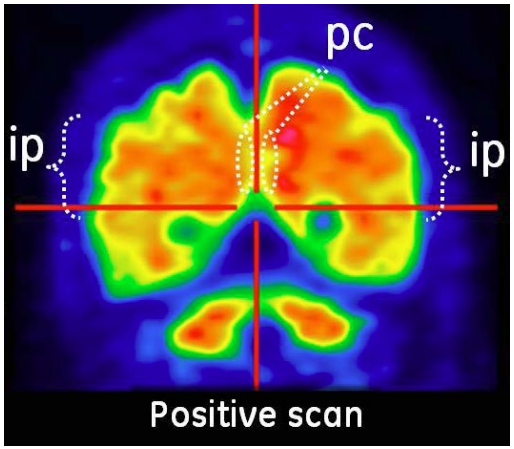
White matter sulcal pattern in inferior parietal (ip) regions that is not evident on the positive image

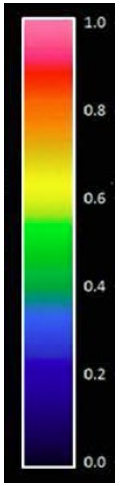



The posterior cingulate (pc) region which is superior and posterior to the corpus callosum - the intensity is below 50% of peak

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



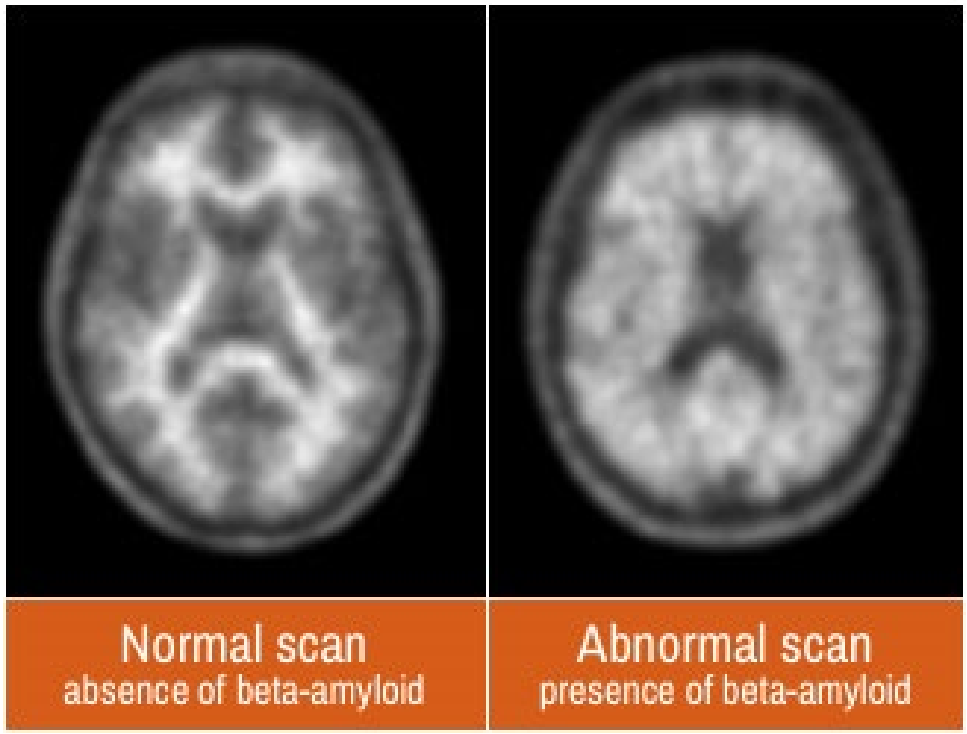






Flutemetamol Package Insert

# Neuraceq (florbetaben)

- Electronic Media- or In-person training is provided by manufacturer
- Images should be interpreted only by readers who successfully complete training

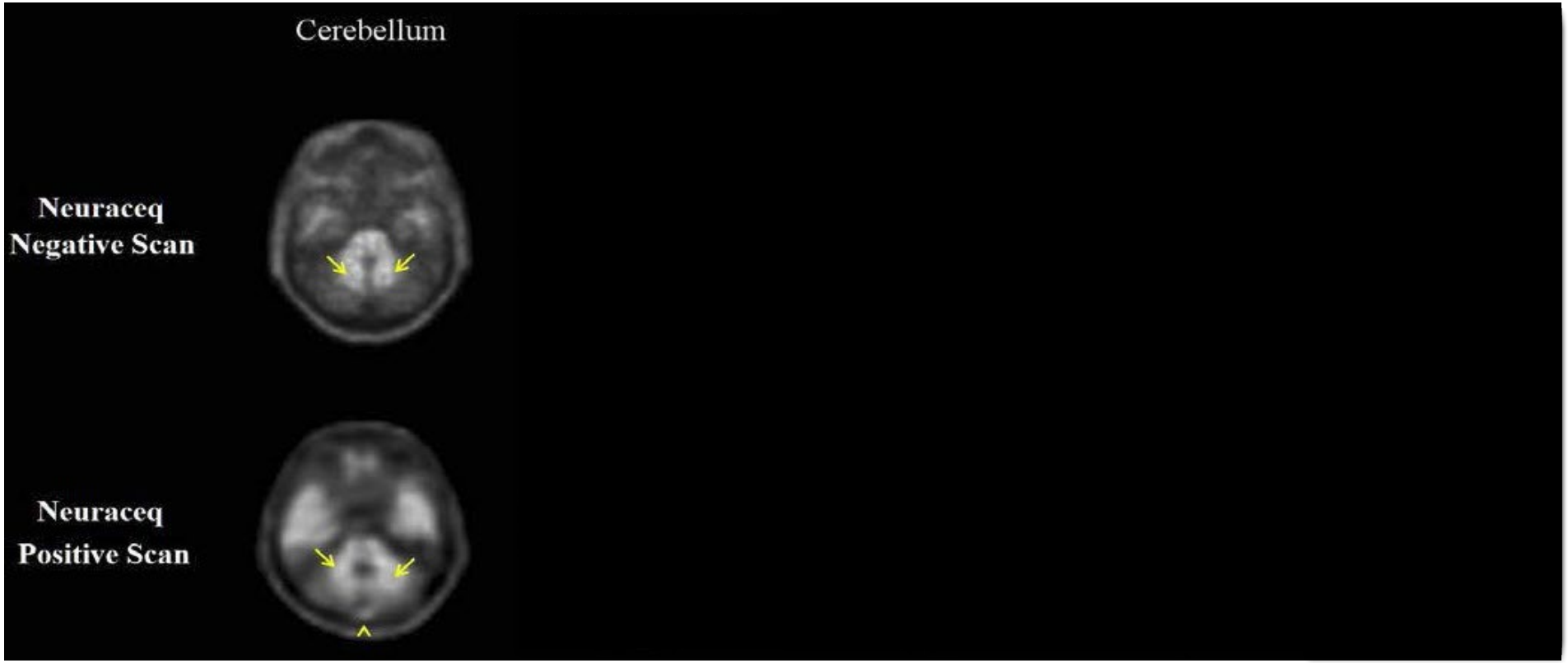



- Online resources provided for healthcare professionals



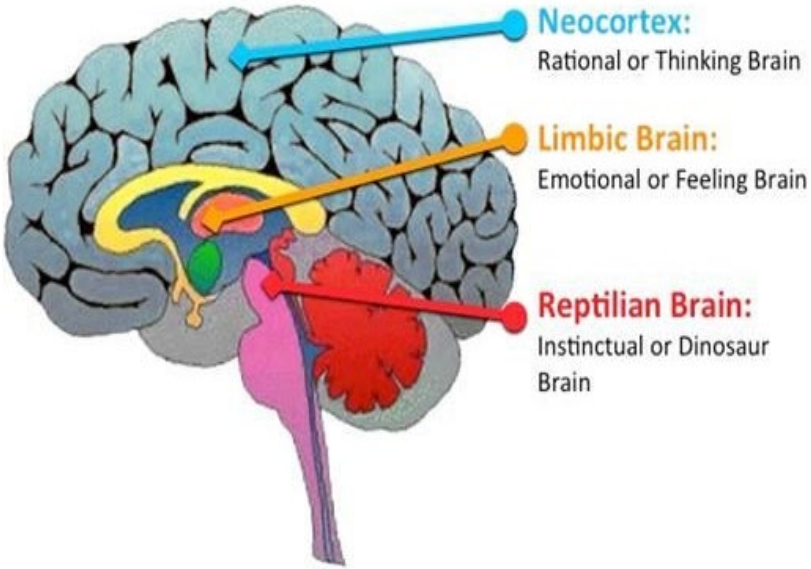
Florbetaben Package Insert.
www.piramal.com

# 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 [Package Insert]. Indianapolis, IN: Lilly USA, LLC; 2020
Eli Lilly and Company (2020). Flortaucipir F 18 (18F-AV-1451) Imaging. SNMMI 2020 Annual meeting.
Image courtesy of Researchgate.net www.researchgate.net/figure/Reptilian-limbic-brain-and-neocortex_fig3_329218319

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# TAUVID (Flortaucipir F-18)

| | Dose | Injection | Flush | Standard Uptake Time | Image Acquisition Time |
|---|---|---|---|---|---|
| **Flortaucipir** | 10 mCi (370 MBq)<br>10 mL or less<br>Max 1:5 dilution by end user; use within 3 hours of dilution | Single Bolus | 10mL saline | 80 minutes | 20 minutes |



TAUVID [Package Insert]. Indianapolis, IN: Lilly USA, LLC; 2020

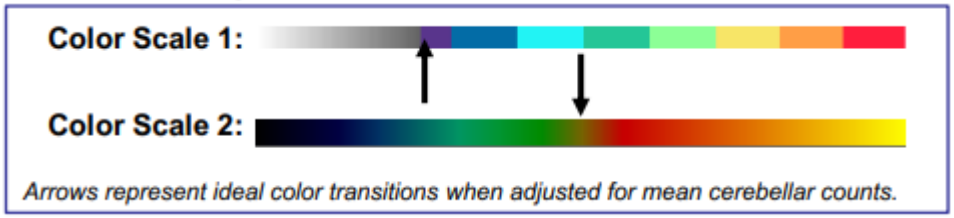
# TAUVID (Flortaucipir F-18)

- 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

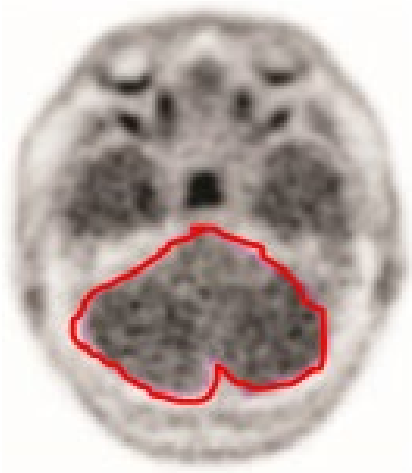


Eli Lilly and Company (2020). Flortaucipir F 18 (18F-AV-1451) Imaging. SNMMI 2020 Annual Meeting.

# TAUVID (Flortaucipir F-18)




Examples of Appropriate Color Scales to Display Flortaucipir Images



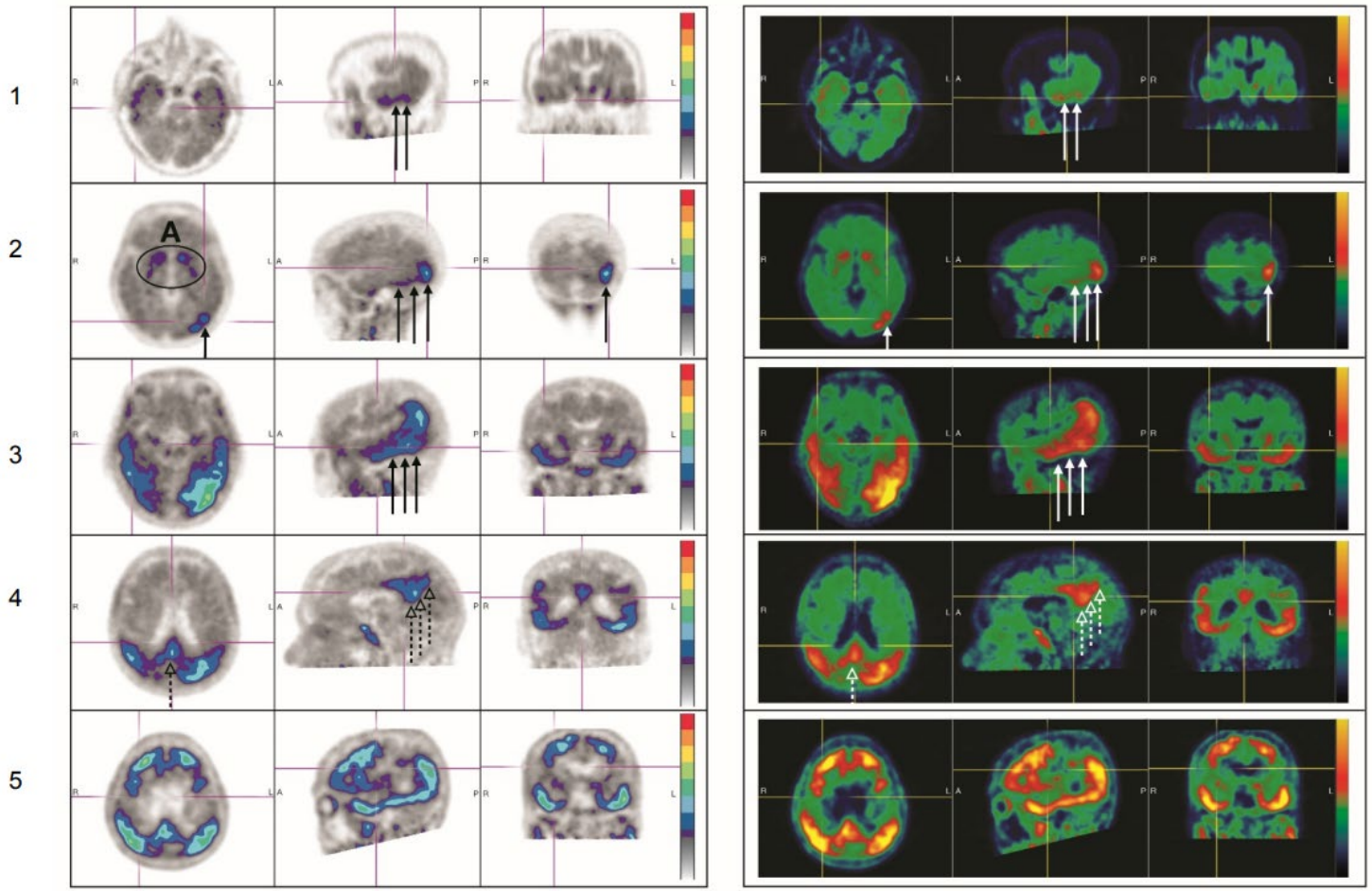
Cerebellar Region of Interest

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



Eli Lilly and Company (2020). Flortaucipir F 18 (18F-AV-1451) Imaging. SNMMI 2020 Virtual Annual Meeting.

# TAUVID (Flortaucipir F-18)






TAUVID [Package Insert]. Indianapolis, IN: Lilly USA, LLC; 2020

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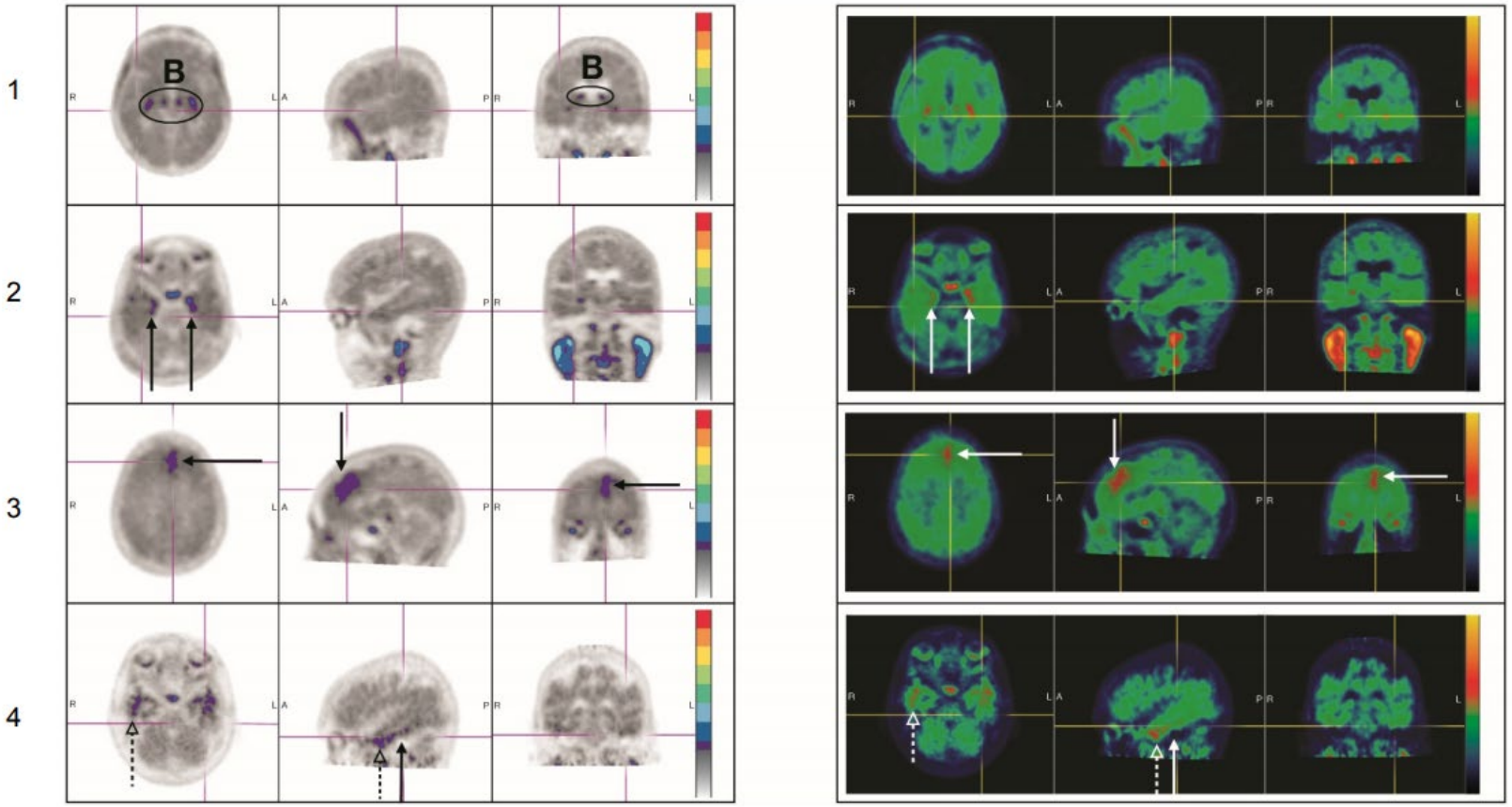
CLINICAL TRIALS NETWORK

# TAUVID (Flortaucipir F-18)






TAUVID [Package Insert]. Indianapolis, IN: Lilly USA, LLC; 2020

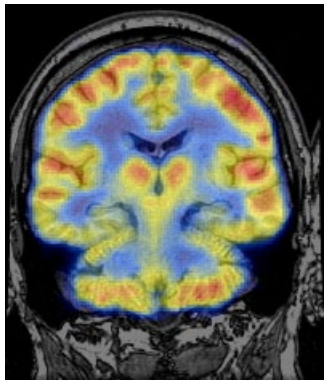
# PET: Pitfalls, Artifacts, Sources of Error

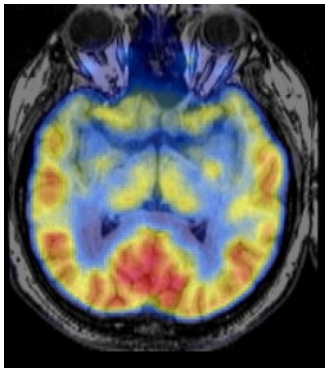
- Patient motion during the data acquisition may result in image artifacts and render the study non-interpretable
- Misregistration between the emission and transmission scans
- Incorrect tracer-specific uptake time
- Positioning

# 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 |
| --- |
| $^{18}$F-FDG |
| $^{18}$F-FDOPA |
| $^{18}$F-Florbetapir |
| $^{18}$F-Flutemetamol |
| $^{18}$F-Florbetaben |
| $^{18}$F-Flortaucipir |





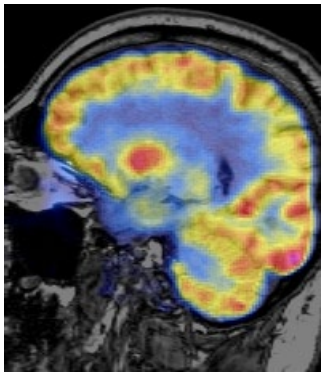


Image courtesy of "The Whole Brain Atlas"-Johnson & Becker
http://www.med.harvard.edu/aanlib/home

# Resources

**Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [$^{18}$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