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AAIC 23

ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®

JULY 16-20 > AMSTERDAM, NETHERLANDS, AND ONLINE

ISTAART Neuroimaging PIA
THE BASICS OF NEUROIMAGING SEMINAR SERIES

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The Basics of Neuroimaging Series

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BASICS OF NEUROIMAGING

Positron Emission Tomography (PET)

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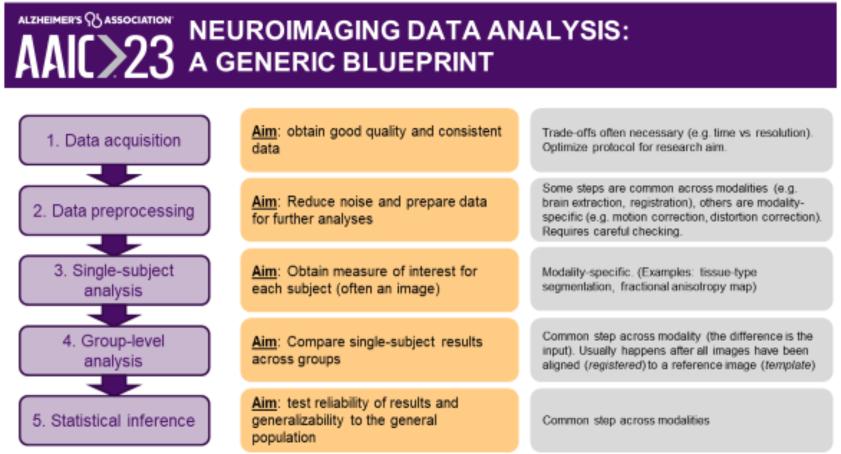
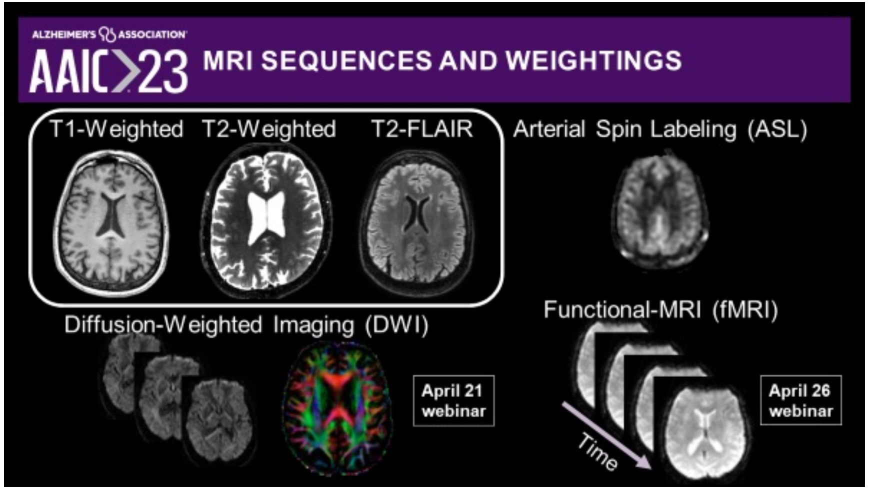
AAIC 23 PAST PRESENTATIONS REFERENCED

Basics of Neuroimaging: Data Structure and Formats
Dr. Ludovca Griffanti



Basics of Neuroimaging: Structural MRI
Dr. David Cash



Available On-Demand soon at: https://training.alz.org/research-webinars

Learning Objectives

By the end of this session, you should be able to:

- Understand the differences between PET imaging and other modalities
- Understand how PET imaging data is collected and image are created
- Perform basic PET imaging processing and quantification for tracers commonly used in ADRD

OUTLINE

Basics of PET Imaging

- How is PET different from other techniques?
- What is a PET tracer?
- How do we get an image?
- How do we quantify PET?

PET Image Processing

- MR-guided
- PET-Only
- Other Considerations

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Introduction – Basics of PET

- **How is PET different from other imaging modalities?**
- **What is a PET tracer?**
- How do we get a PET image?
- How do we quantify PET?

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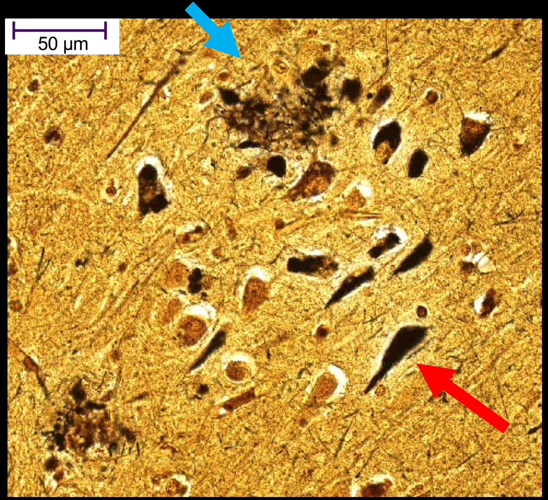
How is PET different from other techniques?

Microscopy

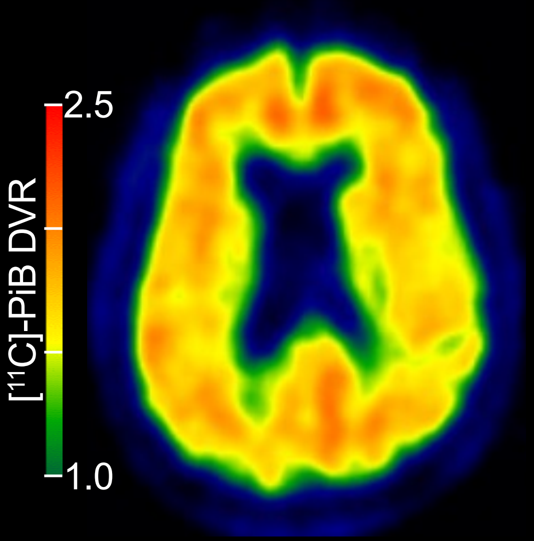


~µm resolution
Beta-amyloid plaque
Neurofibrillary tau tangle

Structural MRI

~1 mm resolution
Brain Volume and Anatomy

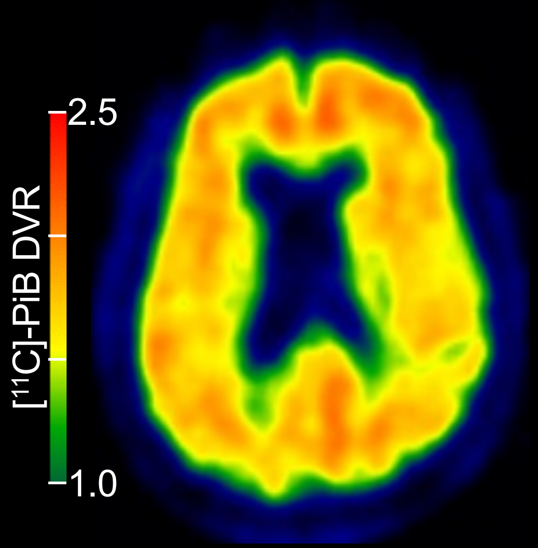
PET



~4-6 mm resolution
Biology/Physiology

How is PET different from other techniques?

PET



~4-6 mm resolution
Binding Potential

Some things PET can measure:

- Binding potential (proportional to receptor density)
- Rate Constants (e.g., influx/efflux from/to plasma and tissue, binding to and dissociation from target)
- Tissue Perfusion and Relative Perfusion
- Receptor Occupancy
- Metabolic Rate (FDG)

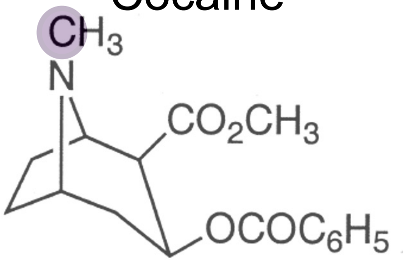
Low Spatial Resolution, High Molecular Specificity

What is a PET tracer?

- A molecule we want to image with a <u>positron emitting isotope</u> attached (i.e., <u>radiolabeled</u>)

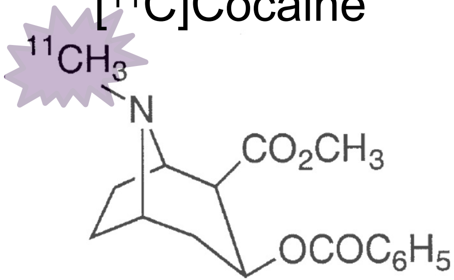
Cocaine as a PET tracer of DAT

Cocaine



Unlabeled

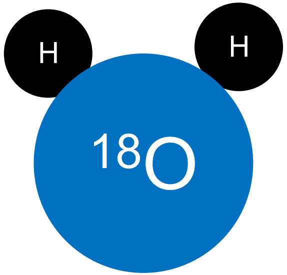
[11C]Cocaine



Radiolabeled with ^{11}C

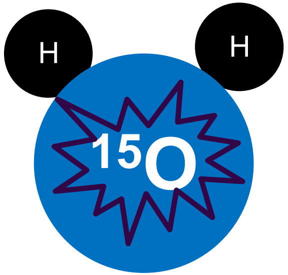
Water as a PET tracer of Perfusion

H_2O



Unlabeled

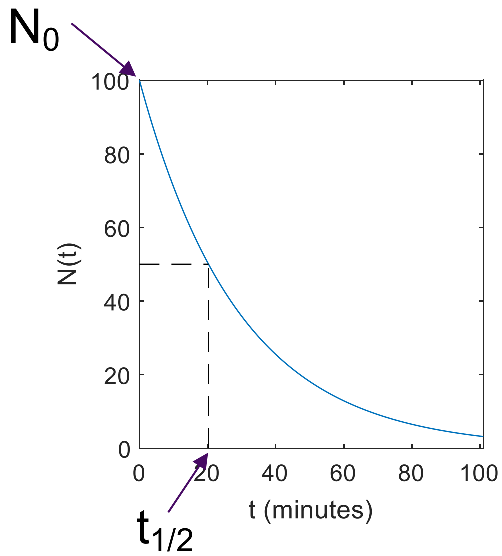
$[^{15}O]H_2O$



Radiolabeled with ^{15}O

What is a PET tracer?

- A molecule we want to image with a positron emitting isotope attached (i.e., radiolabeled)
- A radioactive isotope is a form of an element (e.g., carbon) with an unstable nucleus that undergoes radioactive decay



$$N(t) = N_0 e^{-\frac{\ln(2)t}{t_{1/2}}}$$

$t_{1/2}$ = half life

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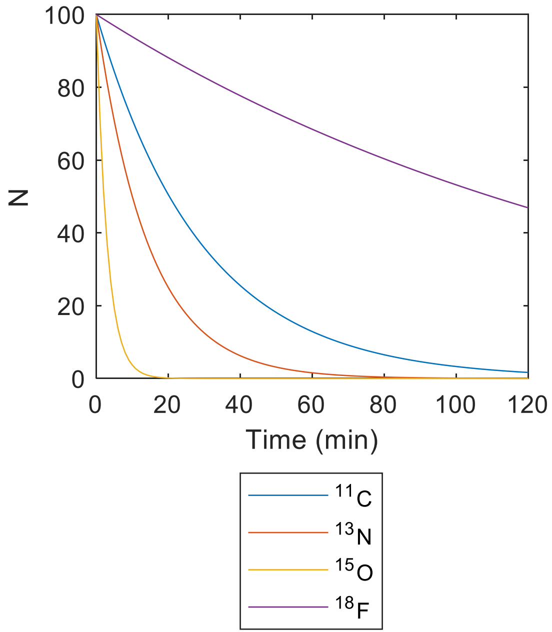
What is a PET tracer?

- A molecule we want to image with a positron emitting isotope attached (i.e., radiolabeled)
- A radioactive isotope is a form of an element (e.g., carbon) with an unstable nucleus that undergoes radioactive decay
- Match radioactive half-life to biological process we're trying to detect

PET Isotope	Half-life (minutes)
^{11}C	20.4
^{13}N	10.0
^{15}O	2.1
^{18}F	109.8



Different PET tracers for different targets

Table 5 Representative examples of radiotracers for CNS applications that have shown utility in humans

Targets Misfolded proteins	Carbon-11 labelled	Fluroine-18 labeled	Comments
β-Amyloid	[11C]PIB	[18F]Flutemetamol [18F]Florbetapir([18F]AV-45) [18F]AZD 4694 [18F]FBM [18F]FDDNP [18F]-SMIBR-W372 ([F-18]-W372) [18F]Florbetaban [18F]MK3328	
Tau		[18F] T807 (AV1451; Flortaucipir) [18F]GTP1 [18F]RO6958948 [18F]MK6240 [18F]PI-2620	Relative sensitivity to 3-repeat to 4-repeat tau isoforms remains to be confirmed.
Enzymes			
Aromatic amino acid decarboxylase (AADC).		6-[18F]-L-DOPA (FDOPA)	Used to assess dopamine synthesis capacity and storage; providing an indirect measure of functional integrity of the nigrostriatal dopaminergic pathway.
AChE	[11C]MP4A		
Aromatase	[11C]VOR		
FAAH	[11C]CURB		
MAO-A	[11C]Harmine [11C]Clorgyline [11C]Befloxatone		
MAO-B	[11C]Deprenyl-d2		May be used as a marker of astrocytes
PDE4	[11C](R)-Rolipram		
PDE10A	[11C]IMA107 [11C]MP-10 [11C]Lu AE92686	[18F]MNI659	
Receptors			
Adenosine A1		[18F]CPFPX	
Adenosine A2A	[11C]SCH442416	[18F]MNI444	
GABAA	[11C]Flumazenil	[18F]Flumazenil	
GABAA (alpha 5 preferring)	[11C]Ro15 4513		
CB1	[11C]MePPEP [11C]OMAR [11C]SD5024	[18F]FEMMEP-d2 [18F]MK-9470	
D1	[11C]NNC 112 [11C]SCH 23390		
D2/D3	[11C]Raclopride [11C]FLB 457 [11C]MNPA (agonist) [11C](+)PHNO (agonist) [11C]NPA (agonist)	[18F]Fallypride	
H1	[11C]Doxepin		
H3	[11C]GSK189254 [11C]GR 103545	[18F]FMH3	
5-HT1A	[carbonyl-11C]WAY [carbonyl-11C]DWAY [11C]CUMI (agonist)	[18F]FCWAY [18F]MefWAY [18F]MPPF	
5-HT1B	[11C]AZ10419369 [11C]P943		
5-HT2A	[11C]MDL 1000907	[18F]Altanserin [18F]Altanserin-d2	
5-HT4	[11C]SB-207145		
5-HT6	[11C]GSK-215083		

Table 5 (continued)

Targets	Carbon-11 labelled	Fluroine-18 labeled	Comments
mGluR1		[18F]FITM	
mGluR5	[11C]SP 203 [11C]ABP688	[18F]SP 203 [18F]F-FPEB	
Nicotinic (α4β2)		2-[18F]F-A-85380 (2-[18F]FA) 6-[18F]FA [18F]Nifene (agonist) [18F]AZAN	
Nicotinic (α7)		[11C]CHIBA-1001 [18F]ASEM	
NK1		[18F]SPA-RQ [18F]MK-0999 ([18F]FE-SPA-RQ)	
NMDA		[18F]GE-179	
NOP	[11C]NOP-1A		
Opiate (DOR)	[11C]Methylnaltrindole		
Opiate (MOR)	[11C]Diprenorphine [11C]Carfentanil (agonist) [11C]CLY2795050 (antagonist)	[18F]Fluoroethyl-diprenorphine	
Sigma 1	[11C]SA4503		
Transporters			
DAT	[11C]PE2I [11C]Methylphenidate	[18F]FP-CIT [18F]FE-PE2I [18F]FECNT	
Glycine T1	[11C]CFpyPB [11C]GSK 931145 [11C]RO5013853	[18F]CFPyPB	
NET	[11C]MeNER-d2	[18F]FMeNER-d2	
SERT	[11C]DASB [11C]MADAM [11C]AFM [11C]HOHMADAM		
TSPO	[11C](R)-PK 11195 [11C]PBR28 [11C]DAA1106 [11C]DPA-713 [11C]ER176	[18F]FBR [18F]FEPPA [18F]PBR111 [18F]DPA-714	Commonly referred to as a marker of microglia activation, but target sensitivity to changes in cell number versus activation state remain unclear.
VMAT2	[11C]DTBZ [11C]MTBZ	[18F]florbenazine [18F]AV-133 [18F]FP-DTBZ	
Other			
		[18F]FDG	Glucose utilization
	[15O]Oxygen		Oxygen utilization
	[15O]water		Blood flow
	[11C]leucine		Protein synthesis
SV2a	[11C]UCB-J		Marker of synaptic density
MC1		[18F]BCPP-FE	Mitochondrial complex 1 density

Suridjan, et al. Brain Imaging and Behavior. 2019

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Common Targets and Tracers for ADRD

Brain Imaging and Behavior (2019) 13:354–365

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Targets Misfolded proteins	Carbon-11 labelled	Fluroine-18 labeled	Comments
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TSPO	[11C](R)-PK 11195 [11C]PBR28 [11C]DAA1106 [11C]DPA-713 [11C]ER176	[18F]FBR [18F]FEPPA [18F]PBR111 [18F]DPA-714	Commonly referred to as a marker of microglia activation, but target sensitivity to changes in cell number versus activation state remain unclear.
SV2a	[11C]UCB-J		Marker of synaptic density
		[18F]FDG	Glucose utilization
	[15O]water		Blood flow

Suridjan, et al. Brain Imaging and Behavior. 2019

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Brain Imaging and Behavior (2019) 13:354–365 359

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β-Amyloid			
Tau			4-repeat irmed.
TSPO			r of sensitivity
	[11C]DAA1106	[18F]PBR111	to changes in cell number versus activation
	[11C]DPA-713	[18F]DPA-714	state remain unclear.
	[11C]ER176		
SV2a	[11C]UCB-J		Marker of synaptic density
		[18F]FDG	Glucose utilization
	[15O]water		Blood flow

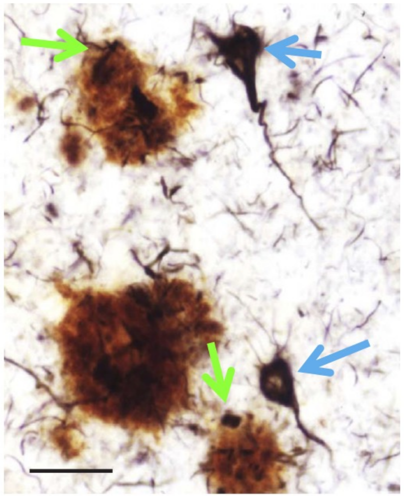
See past Neuroimaging PIA On-Demand Webinars on Amyloid, Tau, FDG, and TSPO PET Imaging

Suridjan, et al. Brain Imaging and Behavior. 2019

Amyloid and Tau Tracers

Alzheimer's Disease Pathology

- **A = Amyloid-beta plaques**
- **T = Tau neurofibrillary tangles**



Immunohistochemistry:
Aβ (brown)andTau(black)

Nelson, et al. *J Neuropathol Exp Neurol.* 2012

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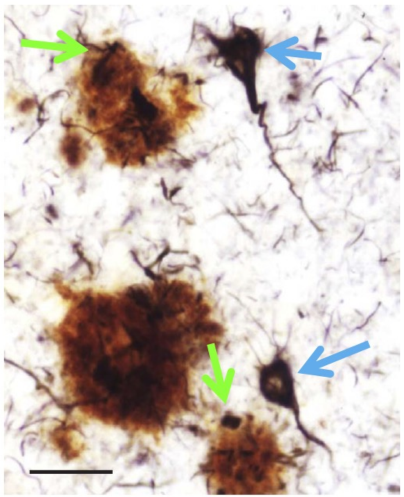


Immunohistochemistry: Aβ (brown)andTau(black)

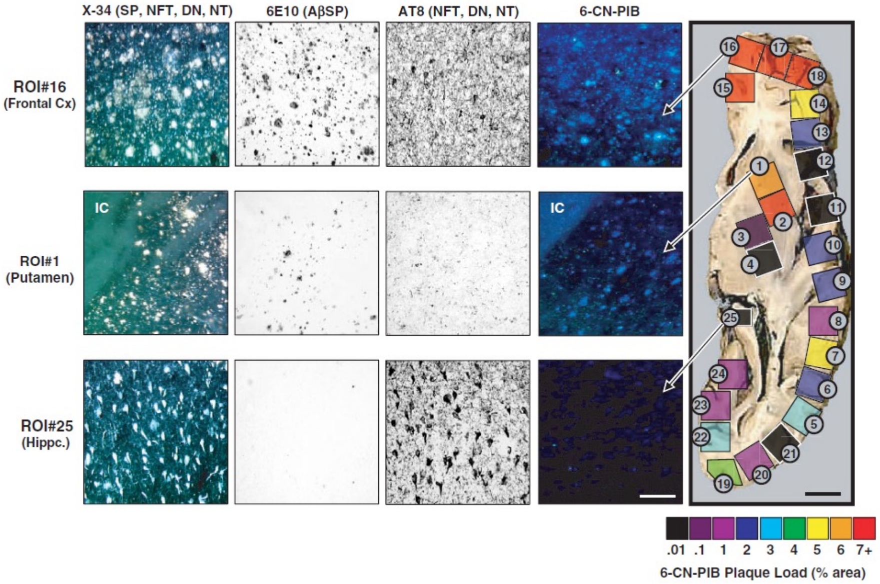
Nelson, et al. *J Neuropathol Exp* Neurol. 2012

PiB binds to insoluble, fibrillar beta-amyloid aggregates

Table 2 6-CN-PiB (10 μM) labeling intensity in different plaque types and amyloid-containing structures in 4% paraformaldehyde fixed, 40 μM thick tissue sections

Plaque type	6-CN-PiB intensity	X-34 intensity
Compact/cored (NC, PhG, Crbl)		
Neuritic	++++	++++
Non-neuritic	++++	++++
Diffuse		
Amorphous (NC, PhG)	++	++
Cloud-like (Str)	++	++
Fleecy (Crbl)	0	++
Non-plaque amyloid	**6-CN-PiB intensity**	**X-34 intensity**
Vascular	++++	++++
Neurofibrillary tangles iNFT	+[a]	++++
Neurofibrillary tangles eNFT	+++	++++
Neuropil threads	0	++++
Dystrophic neurites	0	++++

0 = no 6-CN-PiB fluorescence signal; + = very light fluorescence barely above backgrounds; ++ = light fluorescence; +++ = moderate fluorescence; ++++ = intense fluorescence. NC = neocortex; PhG = parahippocampal gyrus; Str = striatum; Crbl = cerebellum; iNFT = intracellular NFT; eNFT = extracellular NFT.
[a]Only a small proportion of tangles per section detected in entorhinal cortex and subiculum.



Ikonomovic, et al. Brain. 2008

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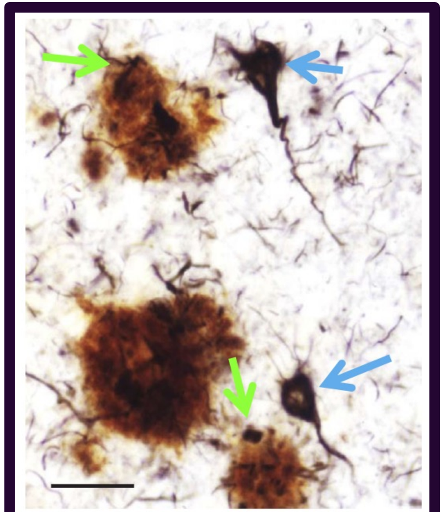
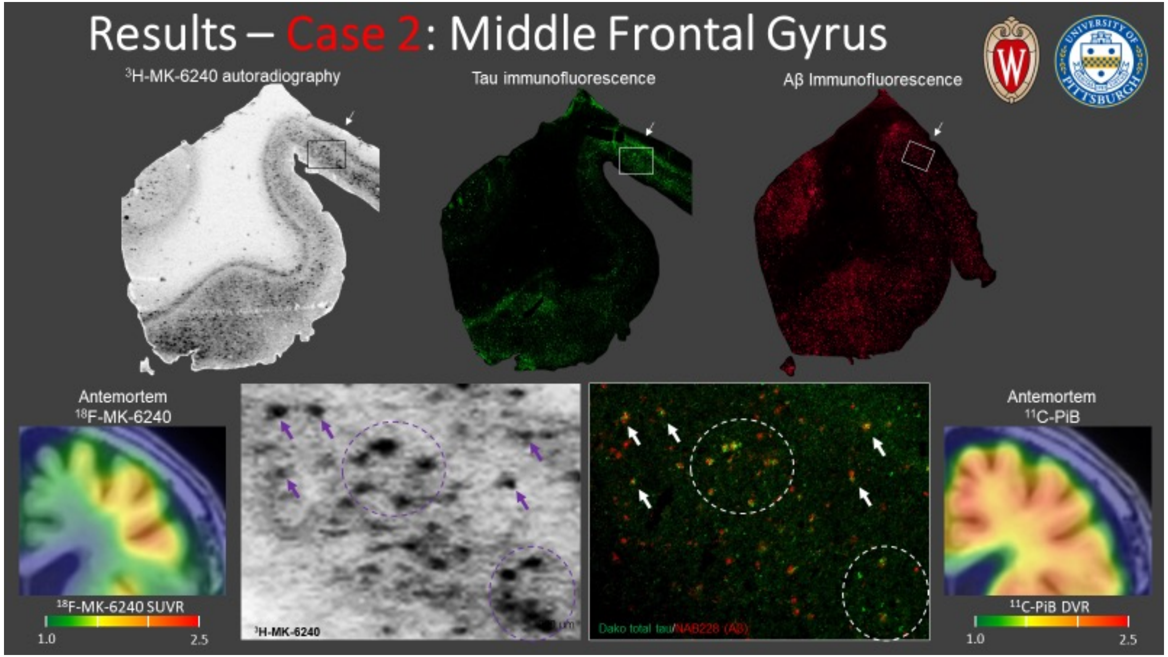


Immunohistochemistry: Aβ (brown)andTau(black)

Nelson, et al. *J Neuropathol Exp Neurol.* 2012

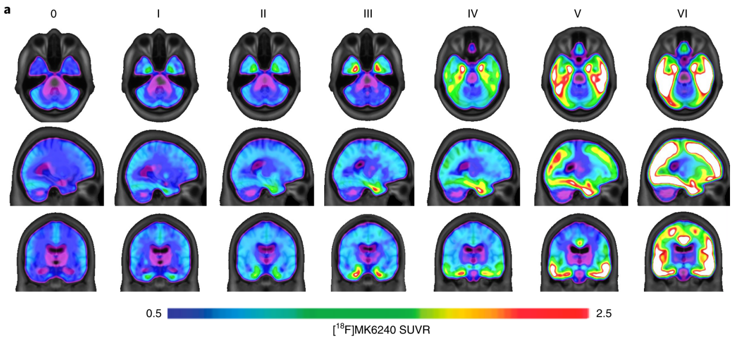
MK-6240 binds to insoluble tau aggregates: neurofibrillary tangles, neuritic pathology, neuritic plaques



Betthauser, Ikonomovic, et al. HAI 2023 (unpublished)

Amyloid and Tau Tracers

Tau PET imaging recapitulates Braak neuropathological staging



Therriault, et al. Nature Aging, 2022

Amyloid and Tau Tracers

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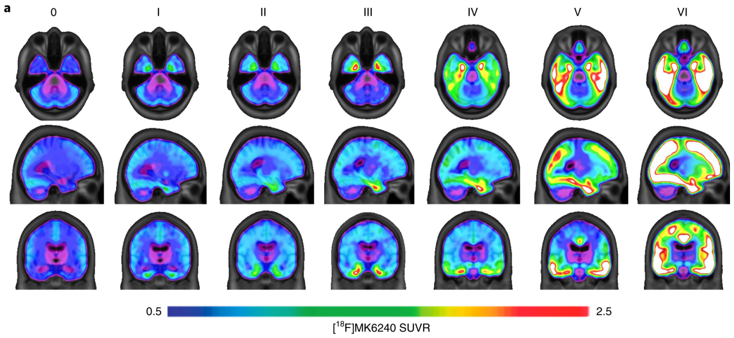
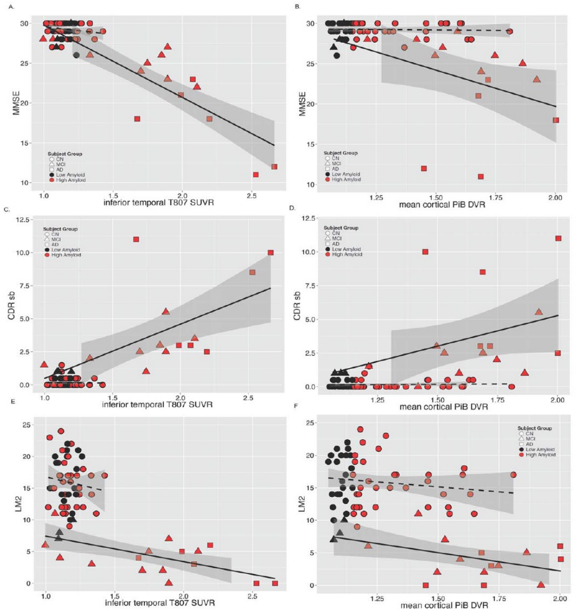


Therriault, et al. Nature Aging, 2022

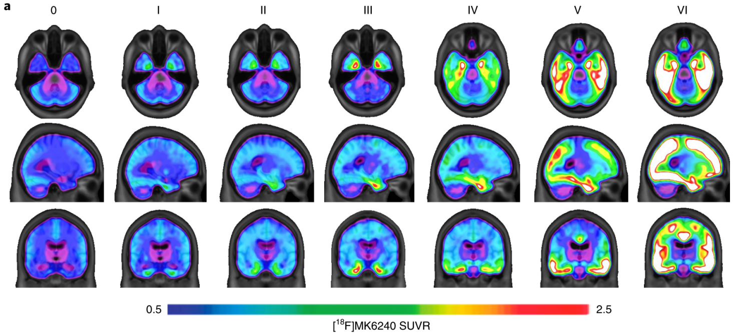
PET-measured AD pathology, especially tau, associates with cognitive deficits



Johnson KA, et al. Annals of Neurology, 2015

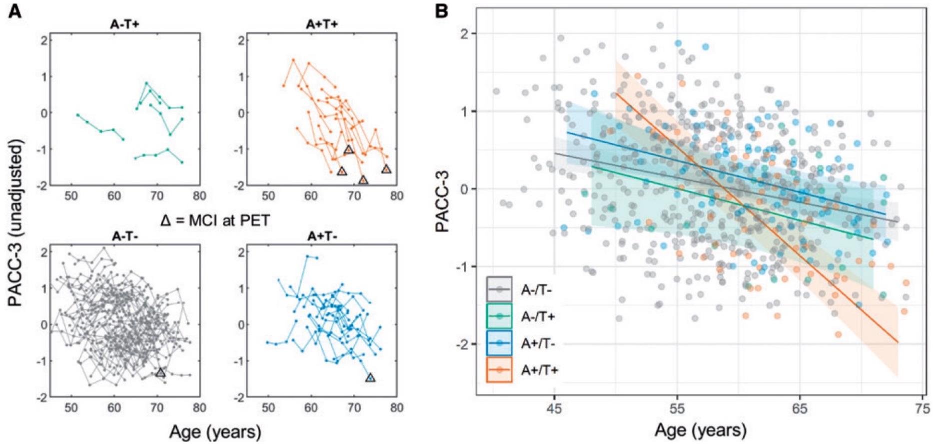
Amyloid and Tau Tracers

Tau PET imaging recapitulates Braak neuropathological staging



Therriault, et al. Nature Aging, 2022

A+T+ associates with accelerated preclinical cognitive decline



Betthauser, et al. Brain, 2020

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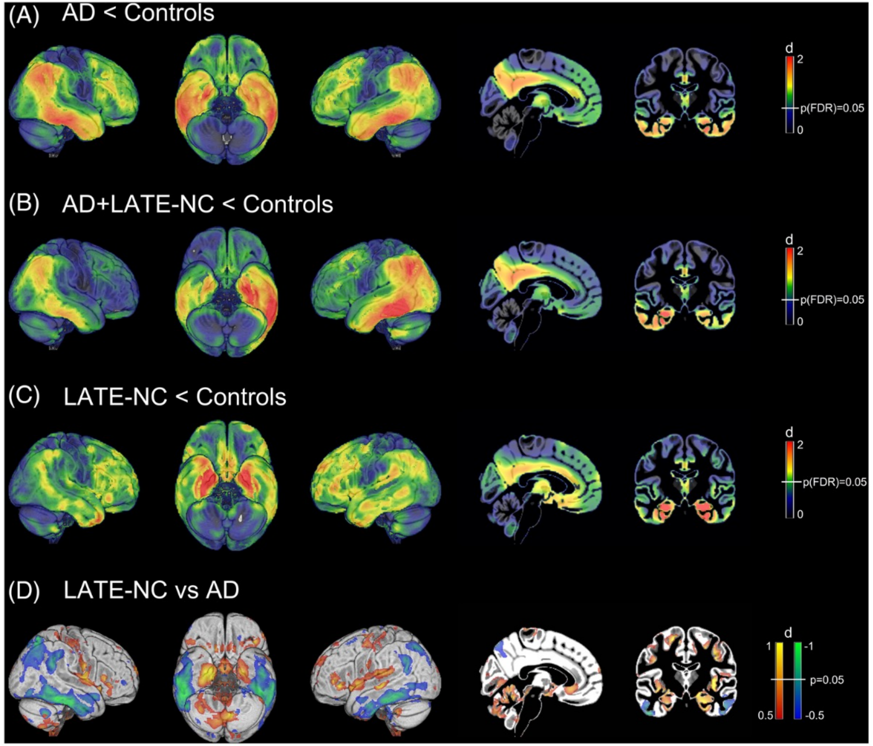
FDG PET



Grothe, et al. Alz & Demen. 2022

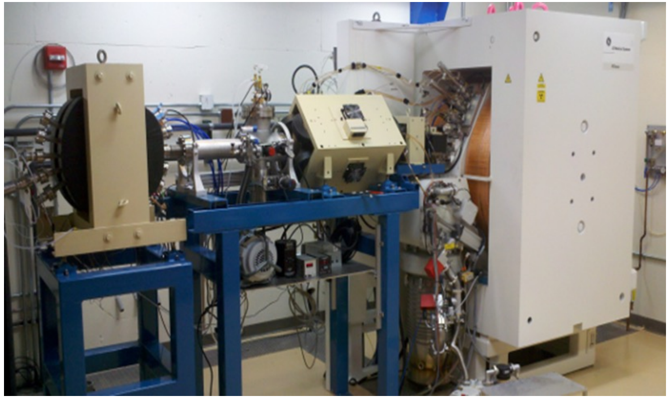
FDG hypometabolic spatial patterns may indicate underlying neuropathology

Introduction – Basics of PET

- How is PET different from other imaging modalities?
- What is a PET tracer?
- **How do we get a PET image?**
- How do we quantify PET?

PET Scanning Overview

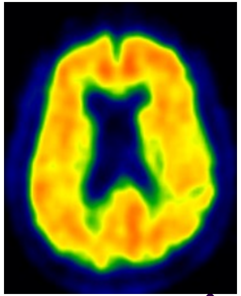
Cyclotron



PET Steps:

1) Isotope Production
2) Synthesize
3) Administer
4) Scan
5) Process

Image Processing

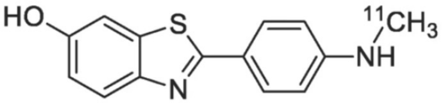


Scan

PET/CT Scanner

Radiochemical Synthesis and Purification

PET Tracer



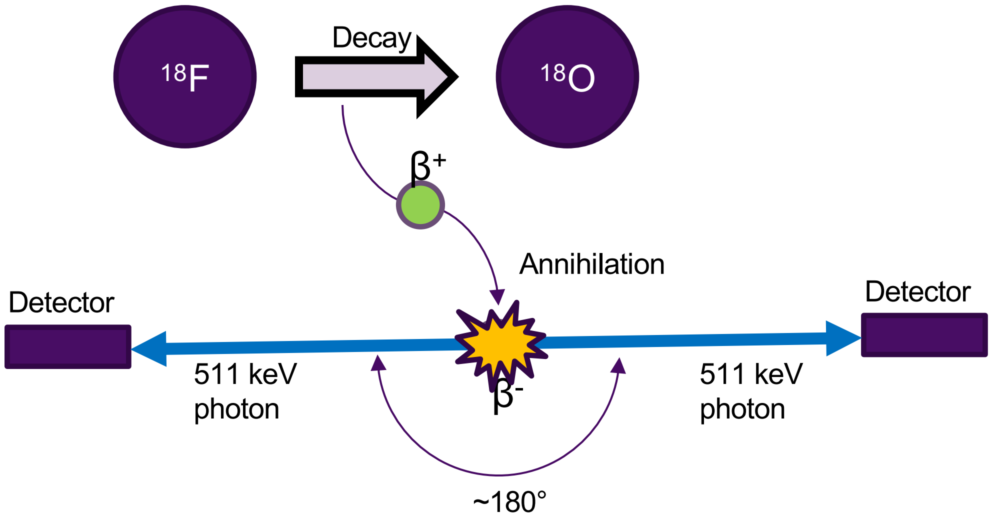
$[^{11}C]PiB$

Administer

- IV Injection
- Inhalation

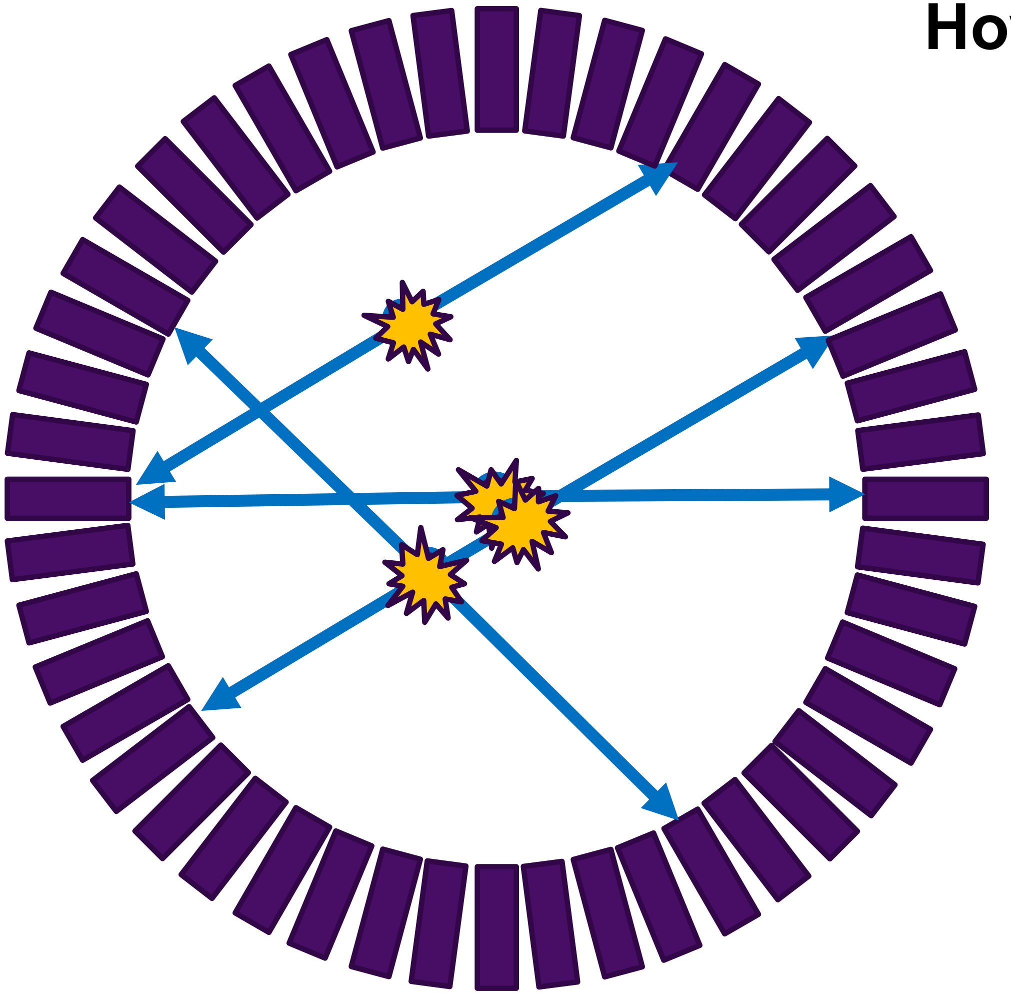
How to make a PET image

Radioactive Decay and Positron Annihilation

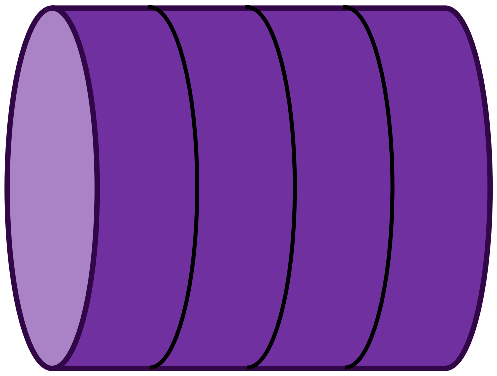


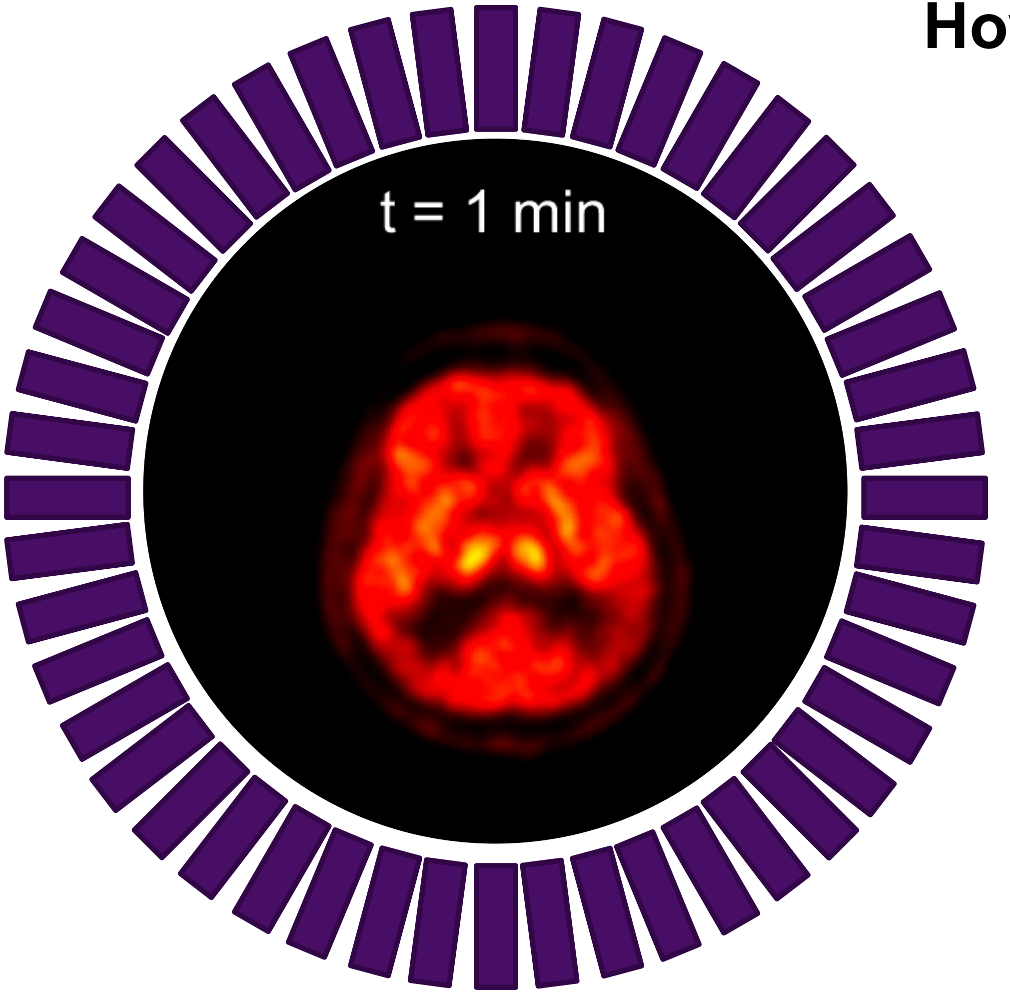
1) Radioisotope decays
2) Positron annihilation
3) “Coincident” Photons detected

How to make a PET image



1) Radioisotope decays
2) Positron annihilation
3) “Coincident” Photons detected
4) Detect many events over time

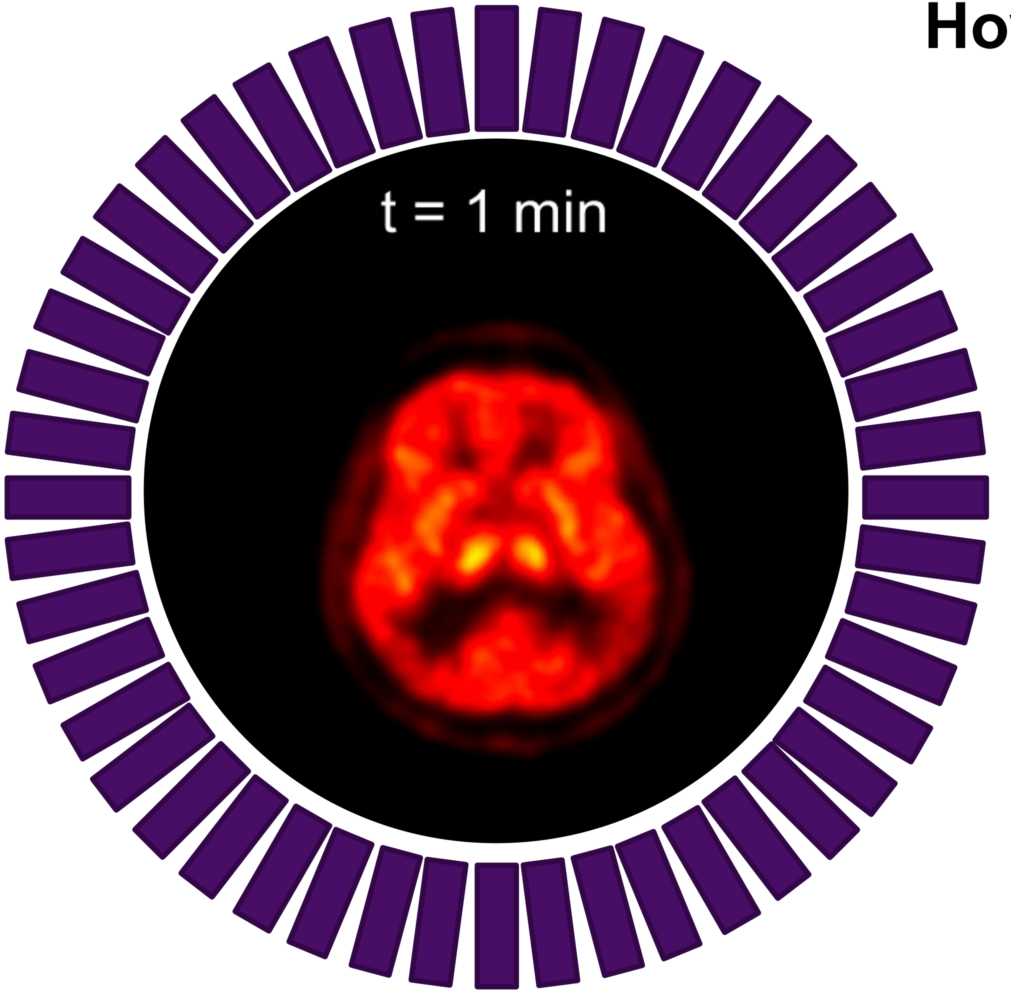




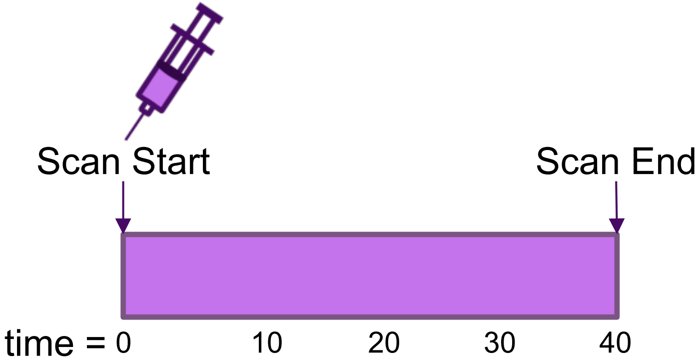
How to make a PET image

1) Radioisotope decays
2) Positron annihilation
3) “Coincident” Photons detected
4) Detect many events over time
5) Image Reconstruction

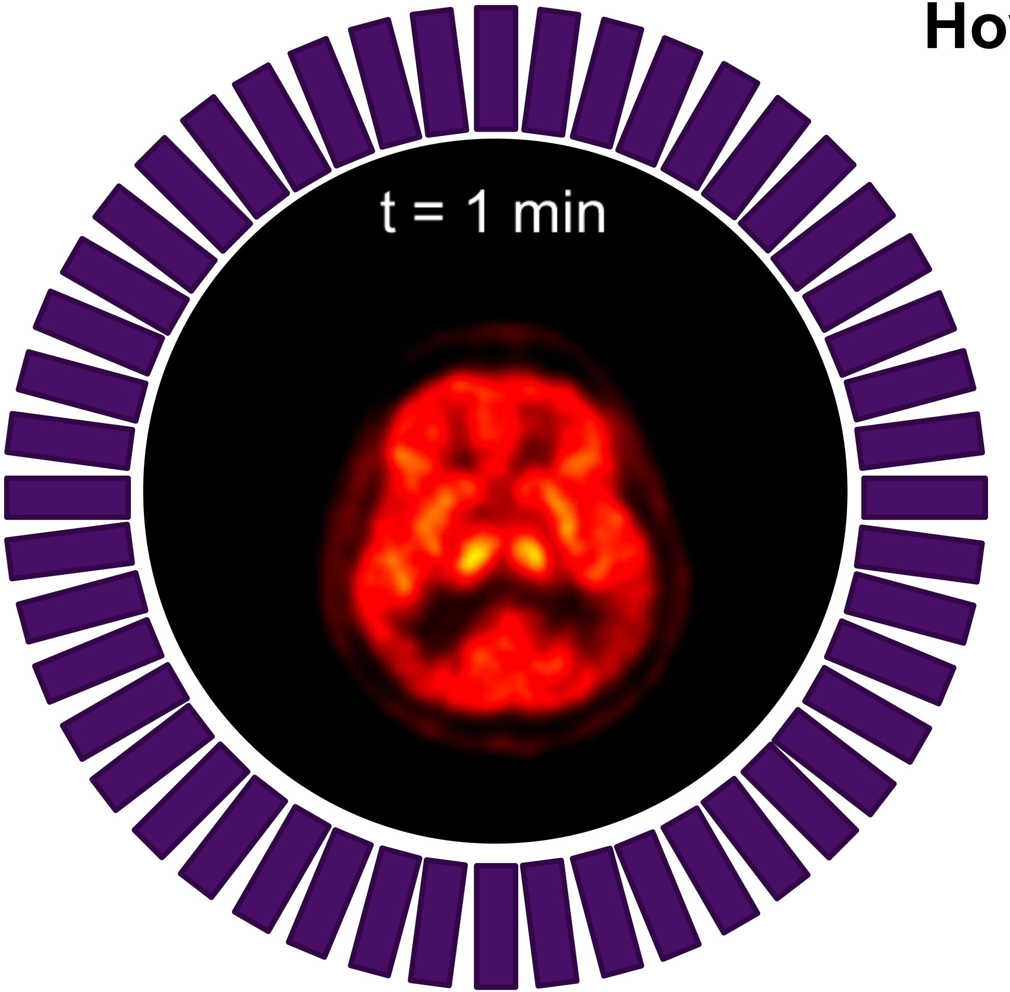
How to make a PET image



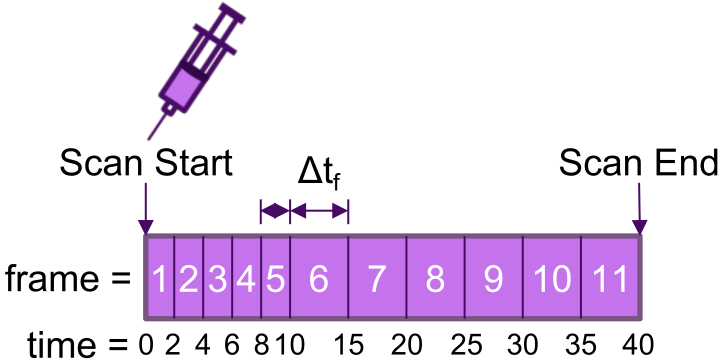
1) Radioisotope decays
2) Positron annihilation
3) “Coincident” Photons detected
4) Detect many events over time
5) Image Reconstruction



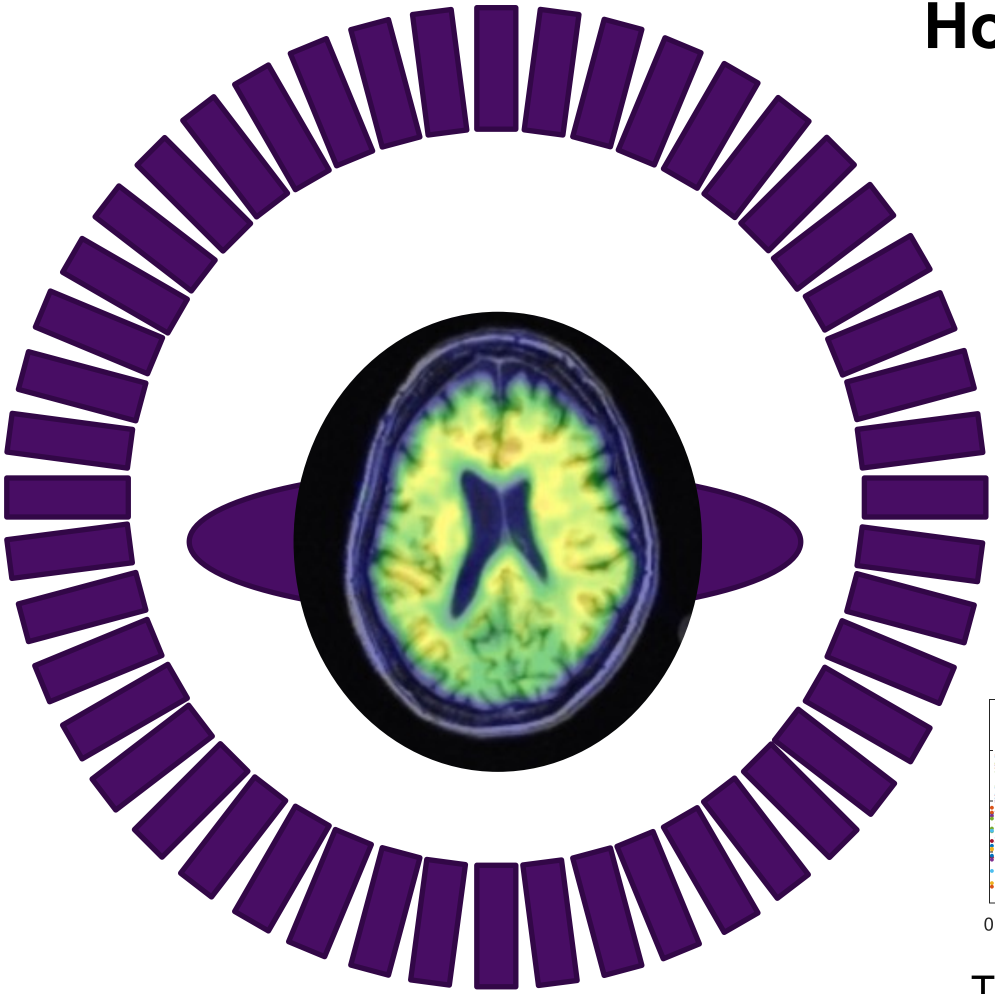
How to make a PET image



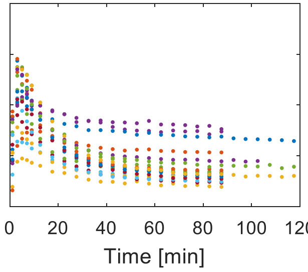
1) Radioisotope decays
2) Positron annihilation
3) “Coincident” Photons detected
4) Detect many events over time
5) Image Reconstruction



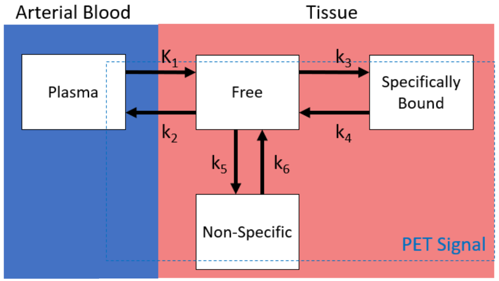
How to make a PET image



1) Radioisotope decays
2) Positron annihilation
3) "Coincident" Photons detected
4) Detect many events over time
5) Image Reconstruction
6) Image Processing

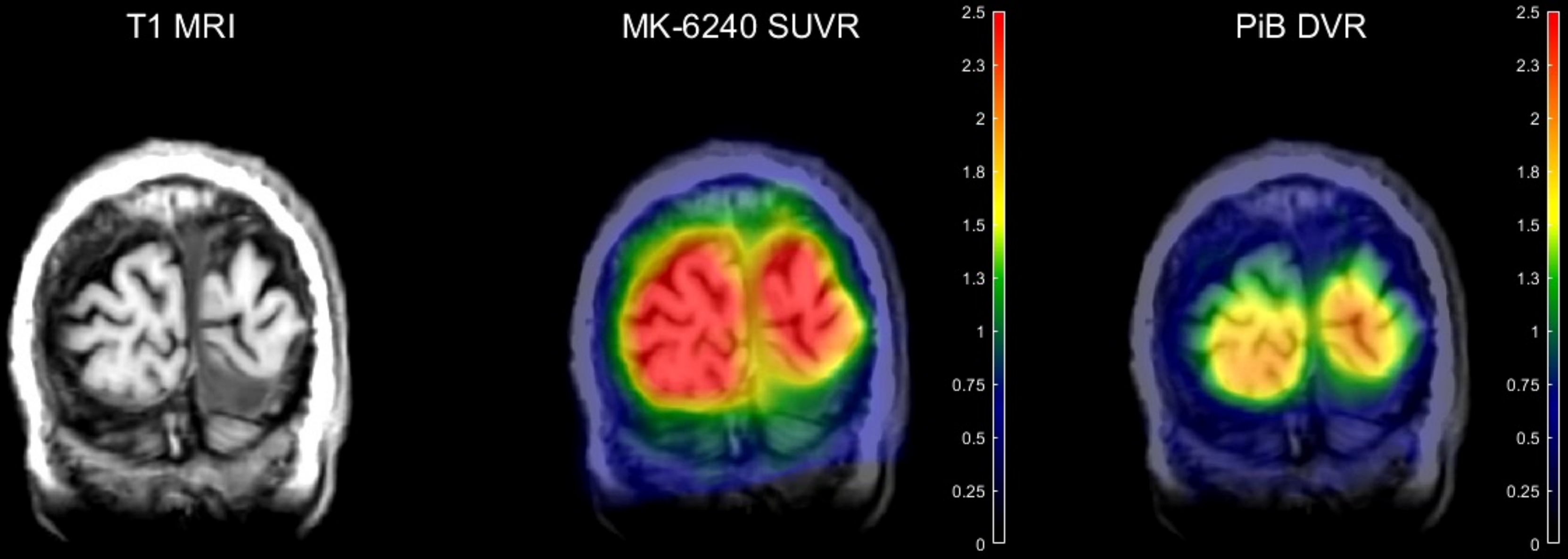


Time-Activity Curve



Kinetic Analysis

Example Parametric Images

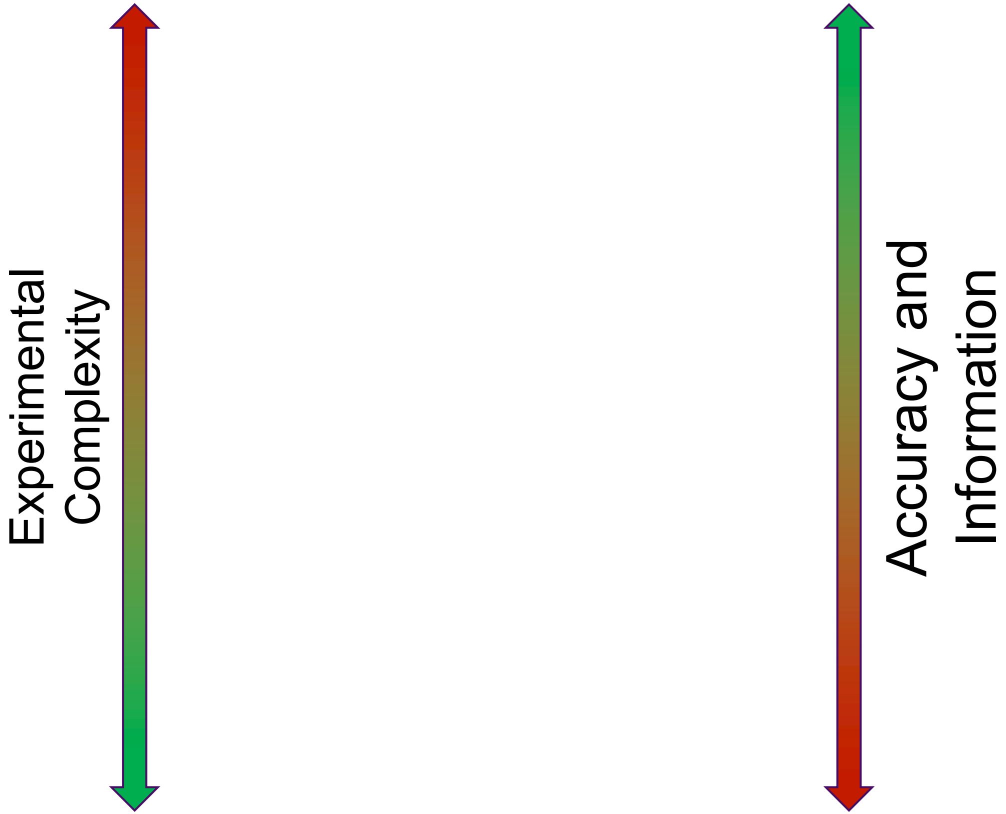


PET provides macroscopic quantitative measures of underlying molecular biology and/or physiology *in vivo*

Introduction – Basics of PET

- How is PET different from other imaging modalities?
- What is a PET tracer?
- How do we get a PET image?
- **How do we quantify PET?**

Optimal Quantification Method is a Trade-off



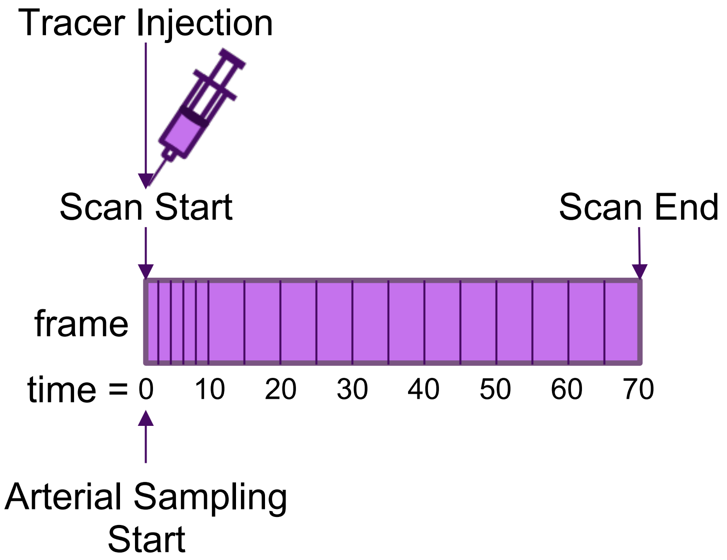
Optimal Quantification Method is a Trade-off

Experimental Complexity

PET with arterial sampling

- arterial cannulation
- long scan duration
+ full kinetic modeling

Accuracy and Information



Optimal Quantification Method is a Trade-off

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PET with arterial sampling

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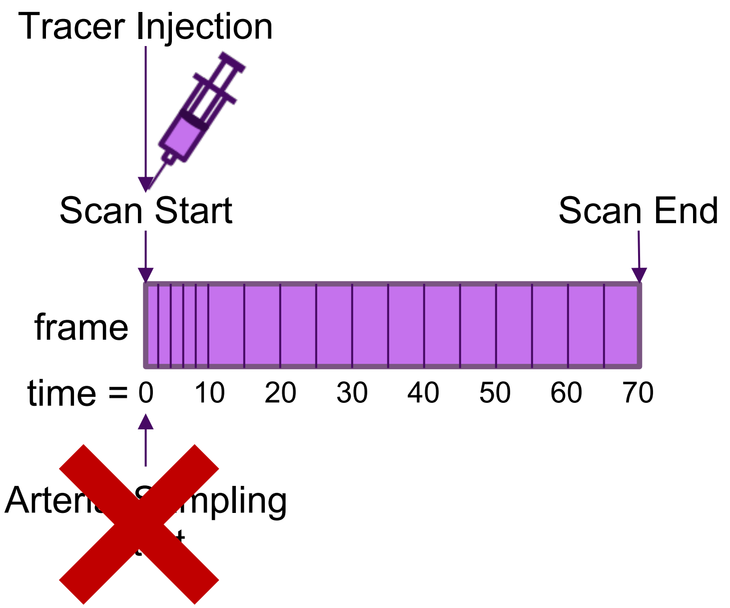
Full-Dynamic Imaging

- \+ no arterial sampling
- \- long scan duration
- \+ quantitative accuracy

Accuracy and Information



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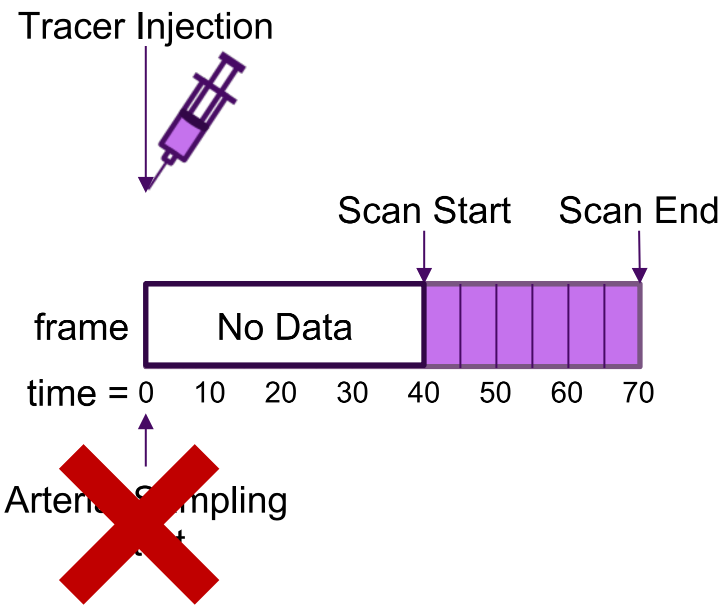
Late-frame Dynamic Imaging

- less accurate
- binding estimates impacted by blood flow
+ short scan duration
+ some kinetic information

Accuracy and Information



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Optimal Quantification Method is a Trade-off

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PET with arterial sampling
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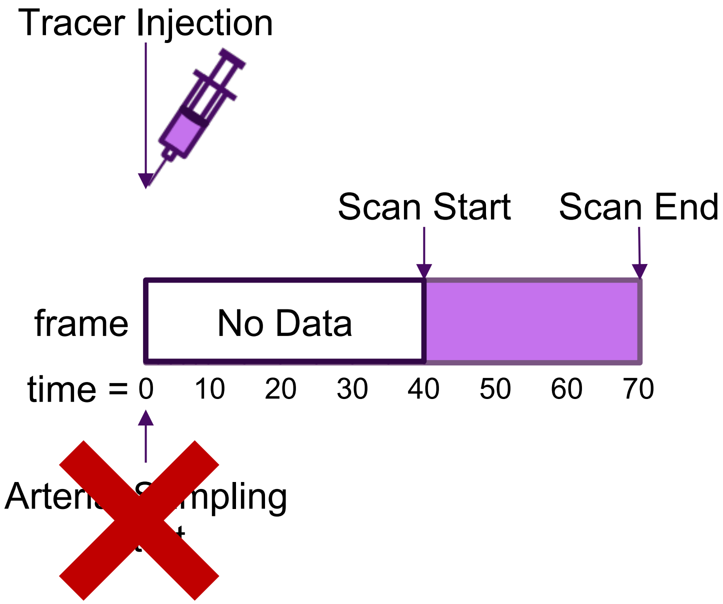
Full-Dynamic Imaging
+ no arterial sampling
- long scan duration
+ quantitative accuracy

Late-frame Dynamic Imaging
- less accurate
- binding estimates impacted by blood flow
+ short scan duration
+ some kinetic information

Late-frame Static Imaging
- less accurate
- no kinetic information
+ short scan duration
+ less data (smaller files)

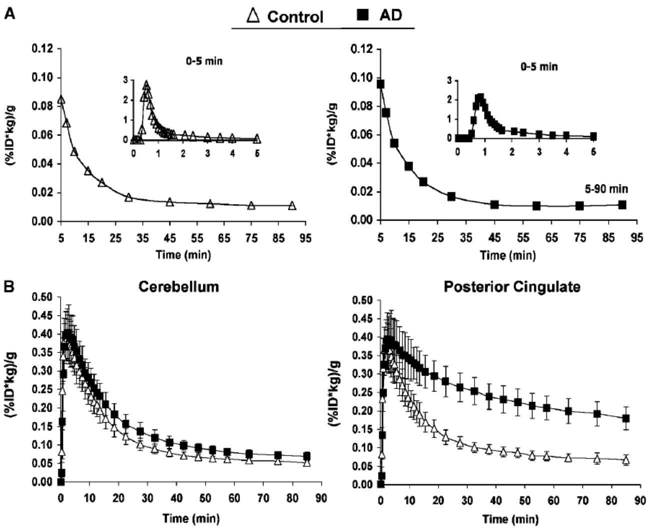
Accuracy and Information



Kinetic Modeling Primer

Arterial Input Function

Brain Time-Activity Curves

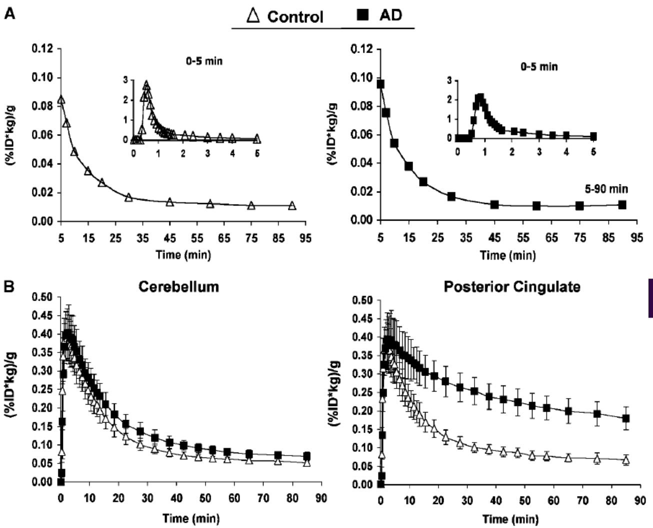


Adapted from Price, et al. JCBFM. 2005

Kinetic Modeling Primer

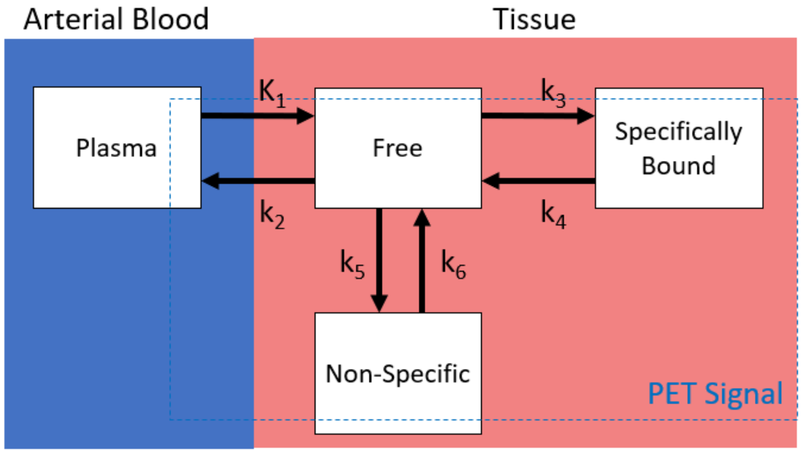
Arterial Input Function

Brain Time-Activity Curves



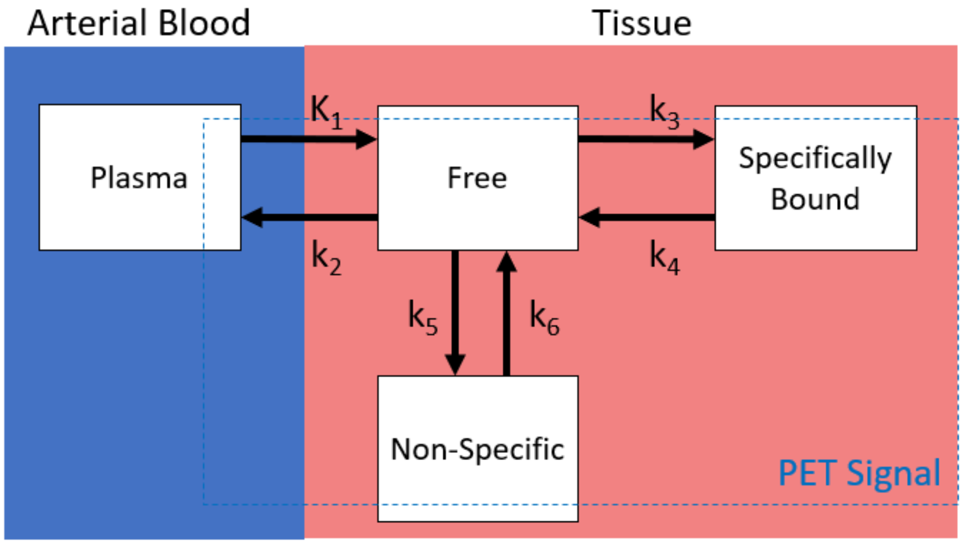
Adapted from Price, et al. JCBFM. 2005

Kinetic Model



Kinetic Modeling Primer

Kinetic Model



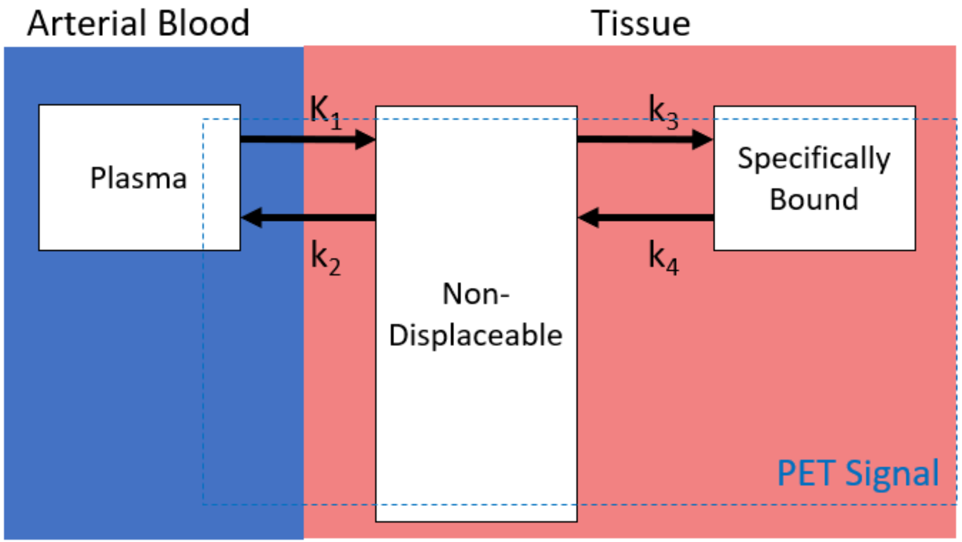
Distribution Volume

$$V_T = \frac{C_T}{C_P}$$

$$V_T = V_F + V_{NS} + V_S$$

Kinetic Modeling Primer

2-tissue Compartment Model



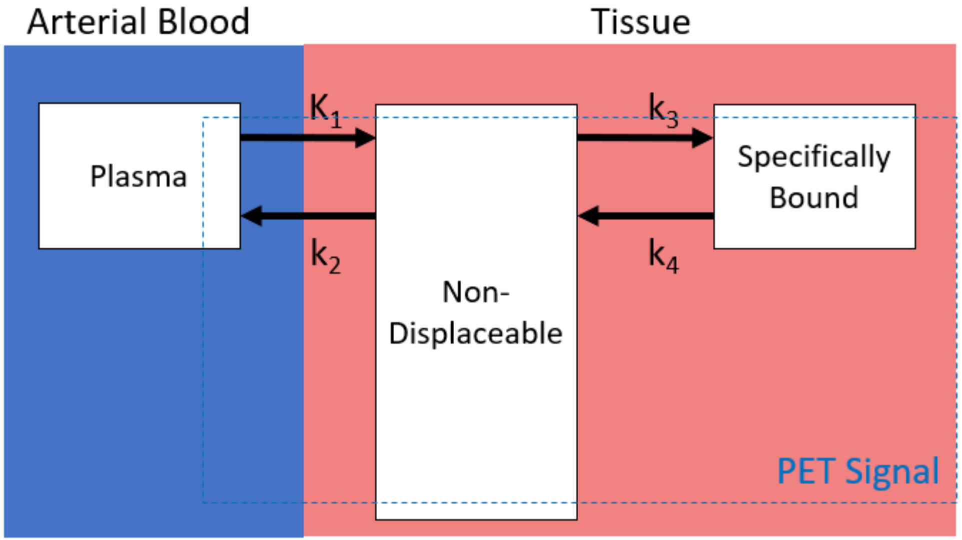
Distribution Volume

$$V_T = \frac{C_T}{C_P}$$

$$V_T = V_{ND} + V_S$$

Kinetic Modeling Primer

2-tissue Compartment Model



B_{max} is the <u>density</u> of the target receptor

$1/K_D$ is referred to as the <u>affinity</u>

Distribution Volume

$$V_T = \frac{C_T}{C_P}$$

$$V_T = V_{ND} + V_S$$

Distribution Volume Ratio (DVR)

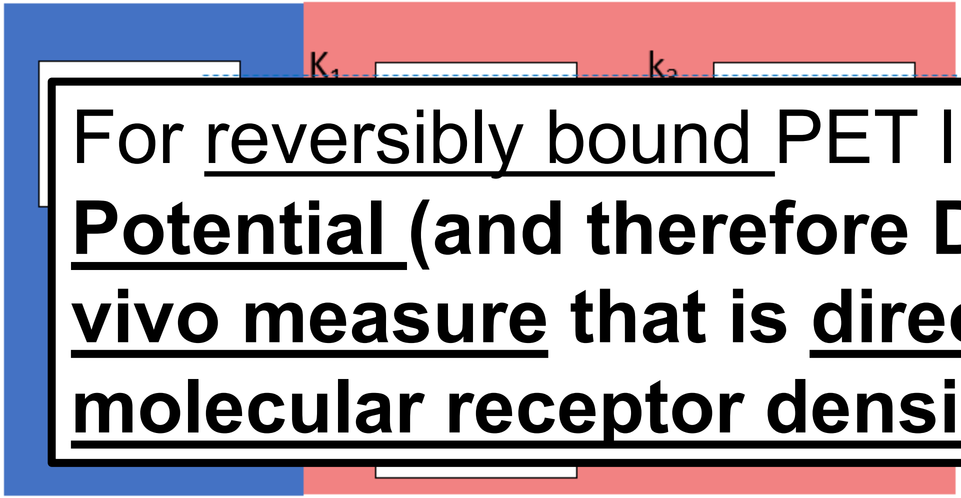
$$\frac{V_T^{target}}{V_T^{ref}} = \frac{V_{ND} + V_S}{V_{ND}}$$

$$DVR = 1 + BP_{ND}$$

$$\mathrm{BP} = \frac{B_{max}}{K_D}$$

Kinetic Modeling Primer

2-tissue Compartment Model



Distribution Volume

$$V_T = \frac{C_T}{\quad}$$

For reversibly bound PET ligands, Binding Potential (and therefore DVR) is a quantitative in vivo measure that is directly proportional to molecular receptor density

$$DVR = 1 + BP_{ND}$$

$$\mathrm{BP} = \frac{B_{max}}{K_D}$$

B_{max} is the density of the target receptor

$1/K_D$ is referred to as the affinity

Optimal Quantification Method is a Trade-off

Experimental Complexity

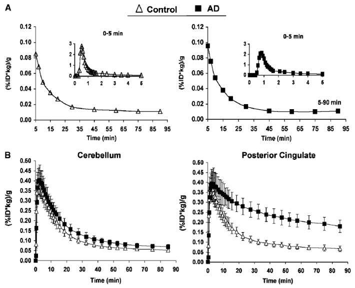
PET with arterial sampling

- V_T
- Rate Constants
- Tracer Metabolism

Accuracy and Information

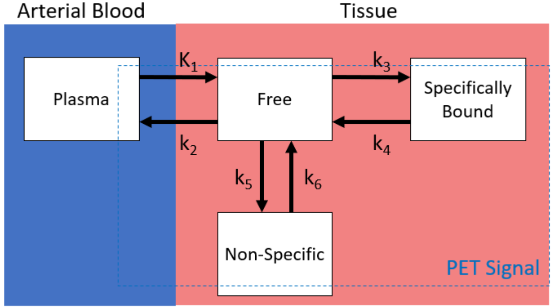
Arterial Input Function

Brain Time-Activity Curves



Adapted from Price, et al. JCBFM. 2005

Full Kinetic Modeling



Optimal Quantification Method is a Trade-off

Experimental Complexity

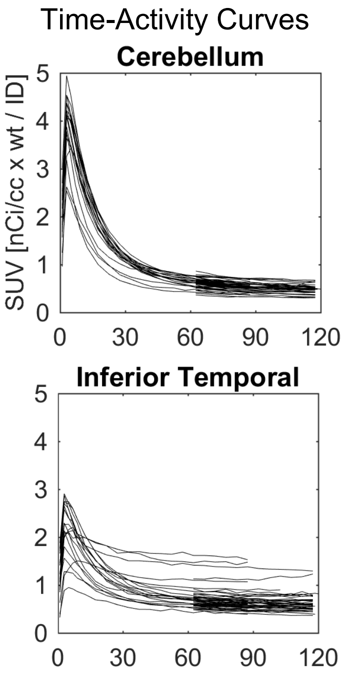
PET with arterial sampling

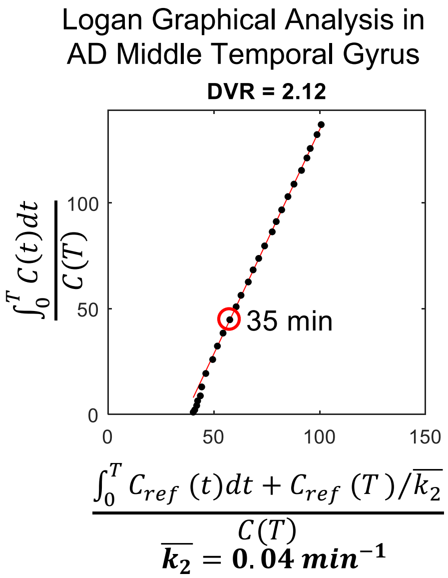
- V_T
- Rate Constants
- Tracer Metabolism

Full-Dynamic Imaging

- DVR (reference tissue methods)
- R_1 (relative perfusion)

Accuracy and Information





Optimal Quantification Method is a Trade-off

Experimental Complexity

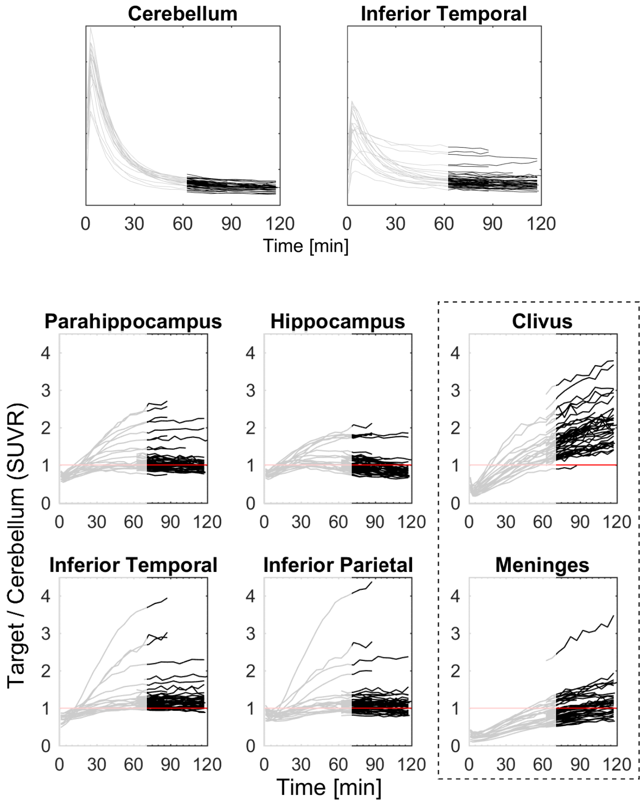
PET with arterial sampling
- V_T
- Rate Constants
- Tracer Metabolism

Full-Dynamic Imaging
- DVR (reference tissue methods)
- R_1 (relative perfusion)

Late-frame Dynamic Imaging
- SUVR

Late-frame Static Imaging
- SUVR

Accuracy and Information



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PET Image Processing

- MR-Guided Image Processing
- PET only Image Processing
- Other Considerations

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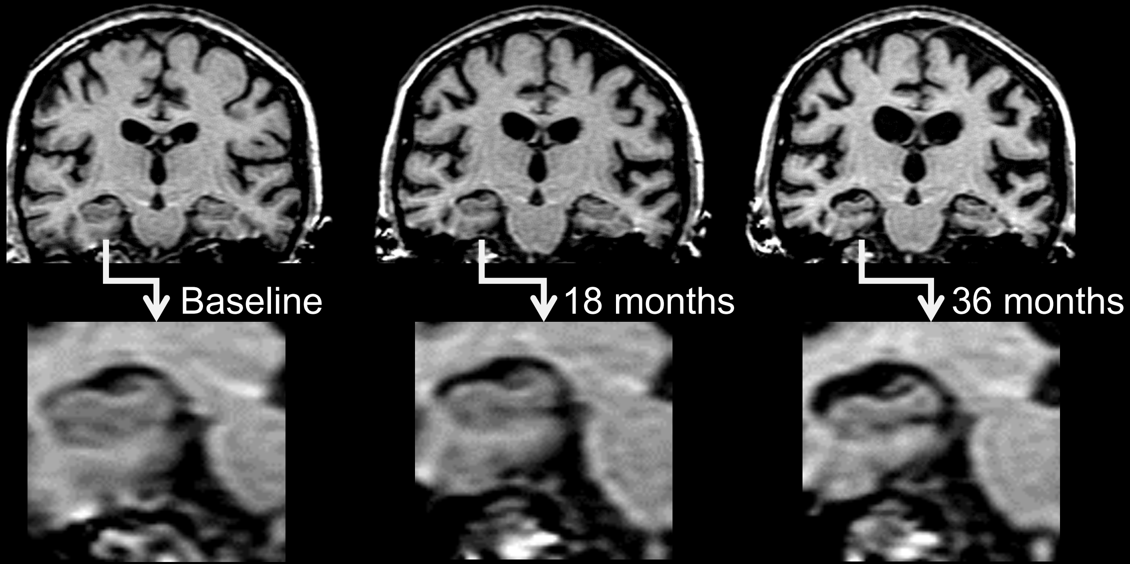
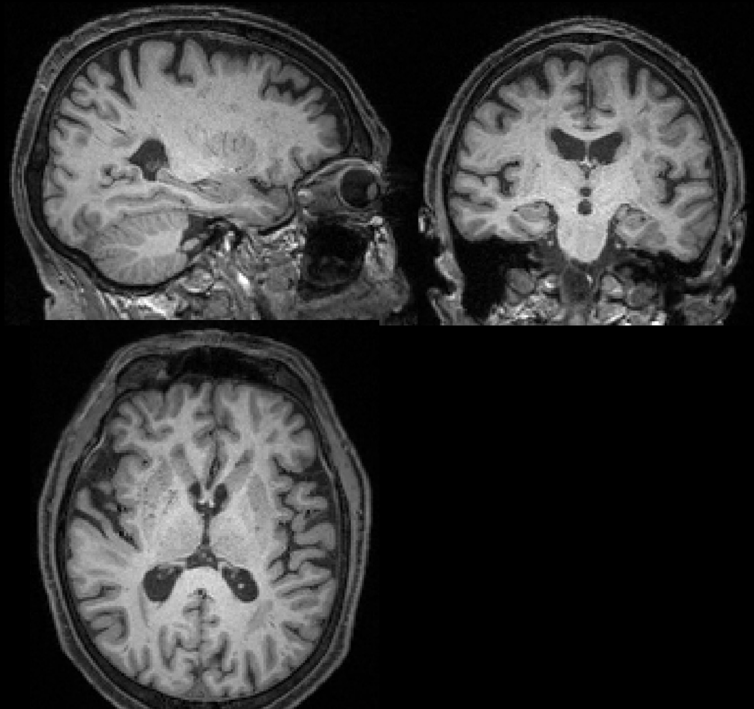
PET Image Processing

- **MR-Guided Image Processing**
- PET only Image Processing
- Other Considerations

T1-weighted MRI

- High-resolution (~1 mm) information about **neuroanatomy** and **neurodegeneration**
- Can be acquired in any orientation in ~4-6 minutes
- Good contrast between different tissues (GM, WM, CSF)

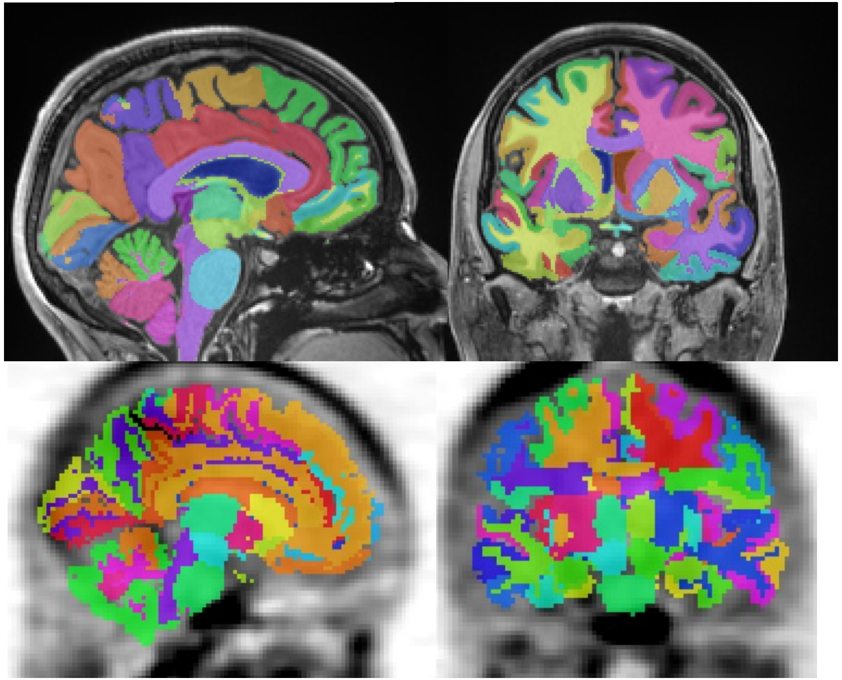




Slide courtesy of Dr. Dave Cash

Co-registration: Within subject, within session

- Structural T1 provides high-resolution anatomical context for other lower resolution modalities (fMRI, DWI, PET)
- Regions of interest (ROIs) defined on the structural T1 scan can be transferred to co-registered images
- Tissue properties from segmentation can also provide some information on partial volume effect (mixture of different tissues)



Slide courtesy of Dr. Dave Cash

Co-registration: Within subject, within session

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- Regions of interest (ROIs) defined on the structural T1
co-registered
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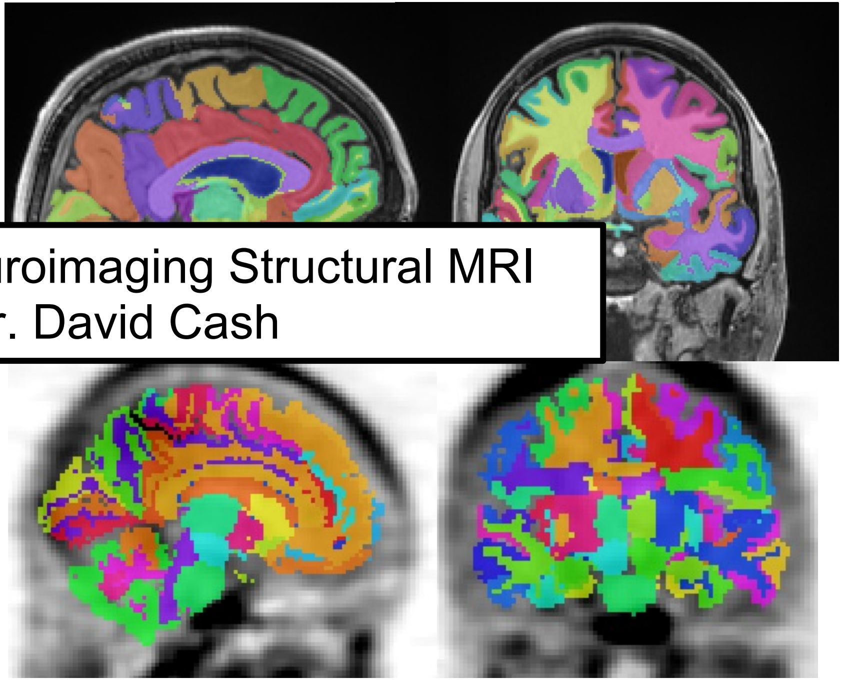
also provide some information on partial volume effect (mixture of different tissues)

See Previous Basics of Neuroimaging Structural MRI presented by Dr. David Cash



Slide courtesy of Dr. Dave Cash

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MR-Guided PET Image Processing

Process MRI
(ROI Parcellation)

Smooth/De-noise

Interframe Alignment
(i.e., motion correction)

Co-Registration to MRI

Extract Reference
Region TAC

Generate Parametric
Image(s)

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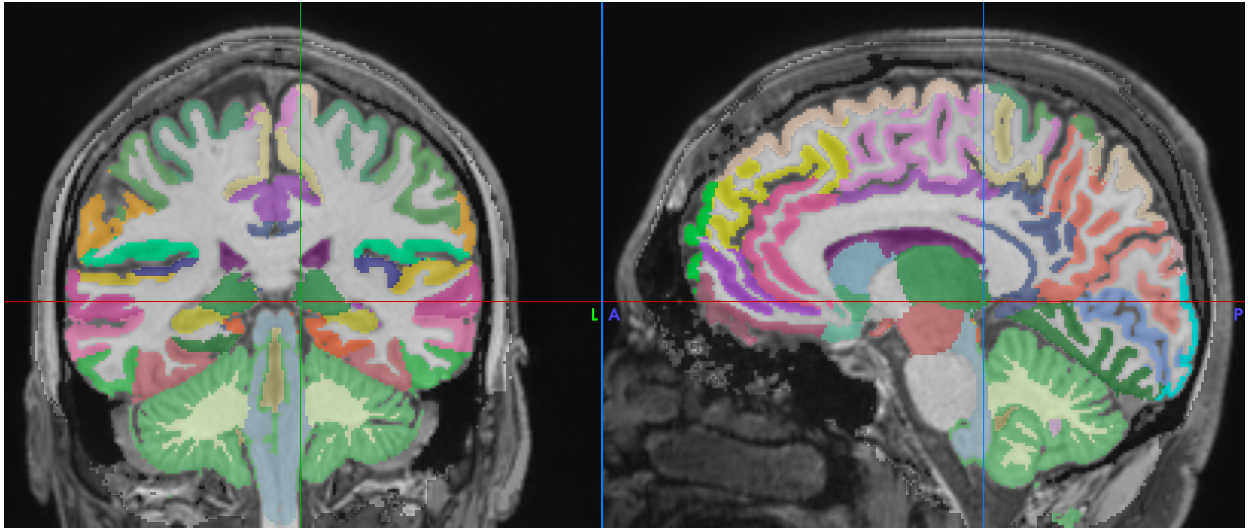


See Previous Basics of Structural MRI Webinar presented by Dr. Dave Cash

MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

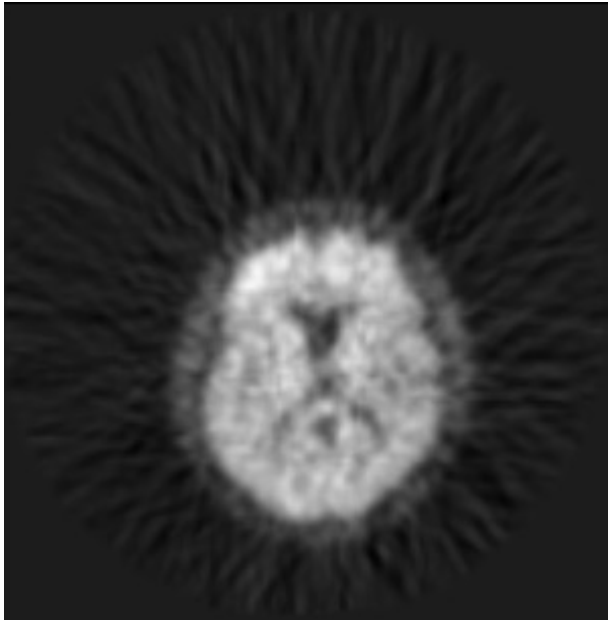
Interframe Alignment (i.e., motion correction)

Co-Registration to MRI

Extract Reference Region TAC

Generate Parametric Image(s)

Individual PET frames are noisy!



Single [^{11}C]PiB PET Frame (30-35 min)

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MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

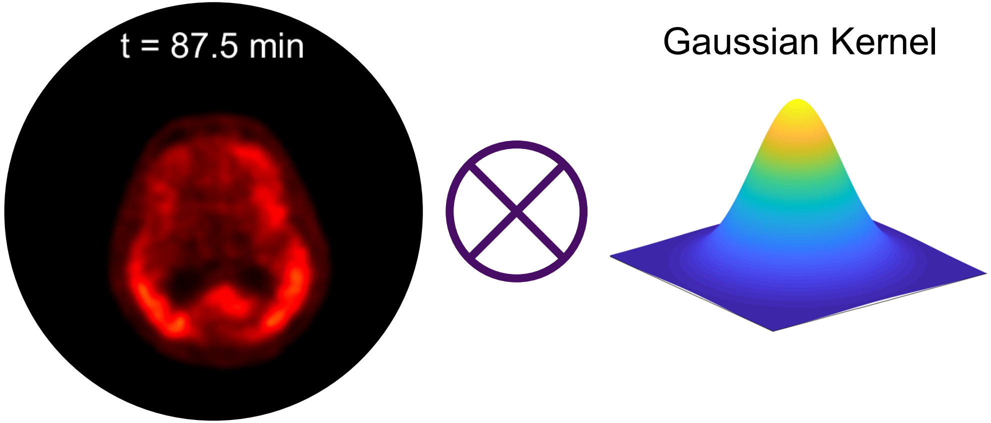
Interframe Alignment (i.e., motion correction)

Co-Registration to MRI

Extract Reference Region TAC

Generate Parametric Image(s)

Spatial Smoothing



- Spatial smoothing reduces voxel variance but increase covariance of adjacent voxels
- Can be applied during or after image reconstruction
- Over smoothing reduces spatial resolution

MR-Guided PET Image Processing

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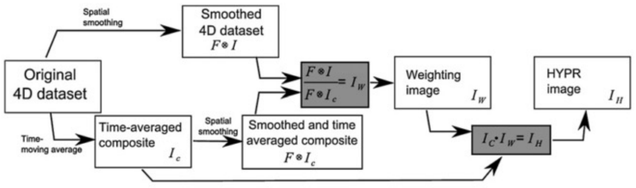
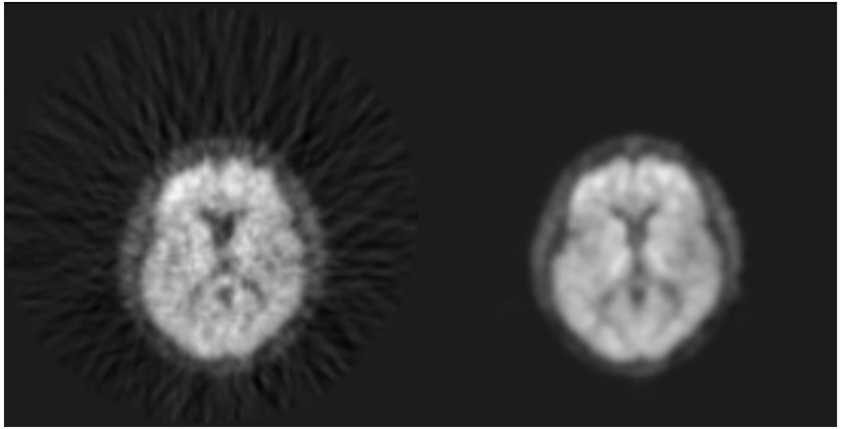


Christian, et al. *J Nucl Med.* 2010

3mm Smoothing   3mm Smoothing + HYPR-LR



Single [^{11}C]PiB PET Frame (30-35 min)

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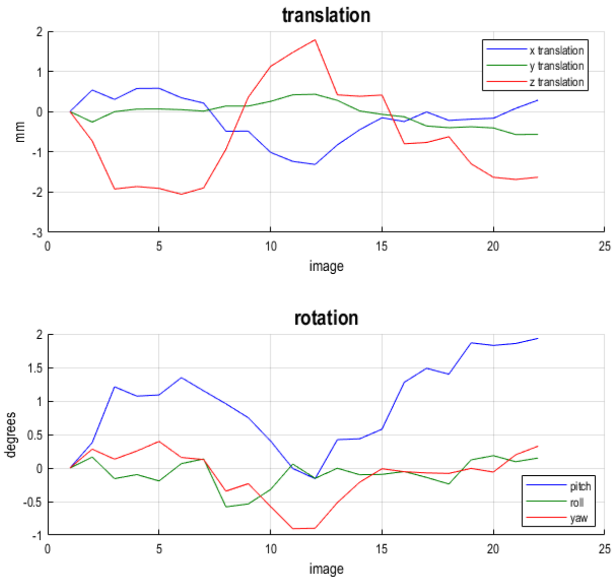

Degrees of Freedom

- Translation (x3)
- Rotation (x3)
- Shear (x3)
- Scaling/Zoom (x3)

Rigid Body (Translation, Rotation)

- Correction for motion between PET frames
- Will not correct for misaligned attenuation maps
- Will not correct for motion within a frame

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MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

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Extract Reference Region TAC

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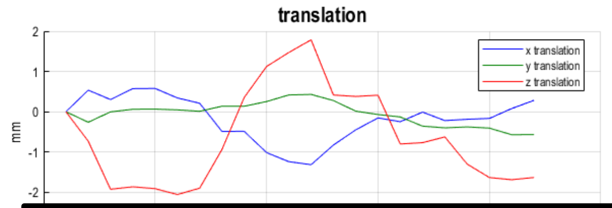
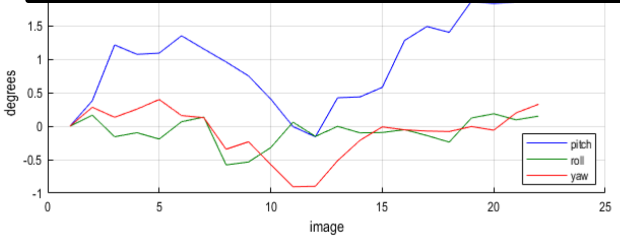


Degrees of Freedom

- Translation (x3)
- Rotation (x3)
- Shear (x3)

} Rigid Body

See Previous Basics of Neuroimaging Data Structure and Formats presented by Dr. Ludovca Griffanti



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MR-Guided PET Image Processing

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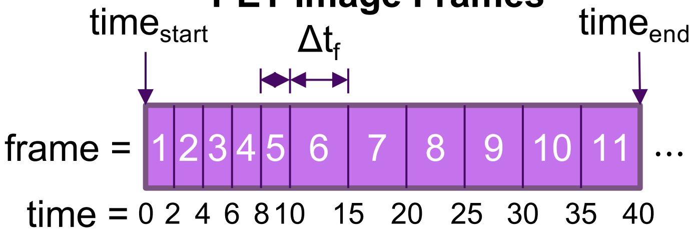
- Extract Reference Region TAC
- Generate Parametric Image(s)

PET frames can be different durations

PET Image Frames



SUM PET Image

$$\frac{\sum_{f=time_{start}}^{time_{end}} C(t)_f \times \Delta t_f}{\sum_{f=time_{start}}^{time_{end}} \Delta t_f}$$

List Mode

$$\sum_{i=t_{start}}^{t_{end}} \frac{counts_i}{t_i}$$

- Start with SUM PET image (time duration-weighted average)
- Register each frame to SUM image (can do this iteratively)

*Note that an average of PET frames is equivalent to a SUM image <u>only if all the frames are the same duration</u>

MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

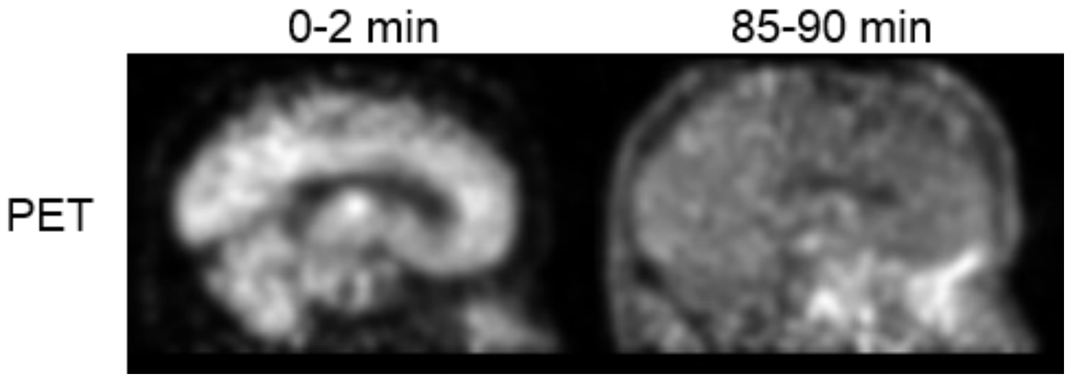
Interframe Alignment (i.e., motion correction)

Co-Registration to MRI

Extract Reference Region TAC

Generate Parametric Image(s)

Spatial information can change dramatically during the scan



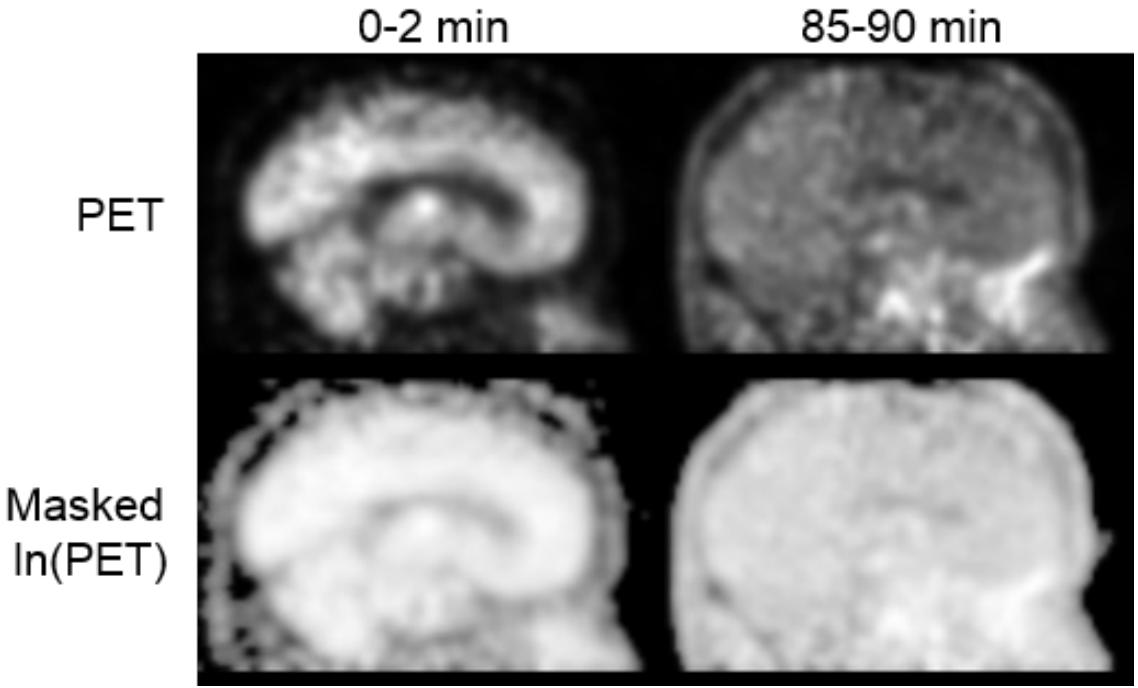
[^{18}F]MK-6240

- Can create challenges for inter-frame alignment

MR-Guided PET Image Processing

- Process MRI (ROI Parcellation)
- Smooth/De-noise
- **Interframe Alignment (i.e., motion correction)**
- Co-Registration to MRI
- Extract Reference Region TAC
- Generate Parametric Image(s)

Image transforms can help reduce dissimilarities between frames



$[^{18}F]$MK-6240

MR-Guided PET Image Processing

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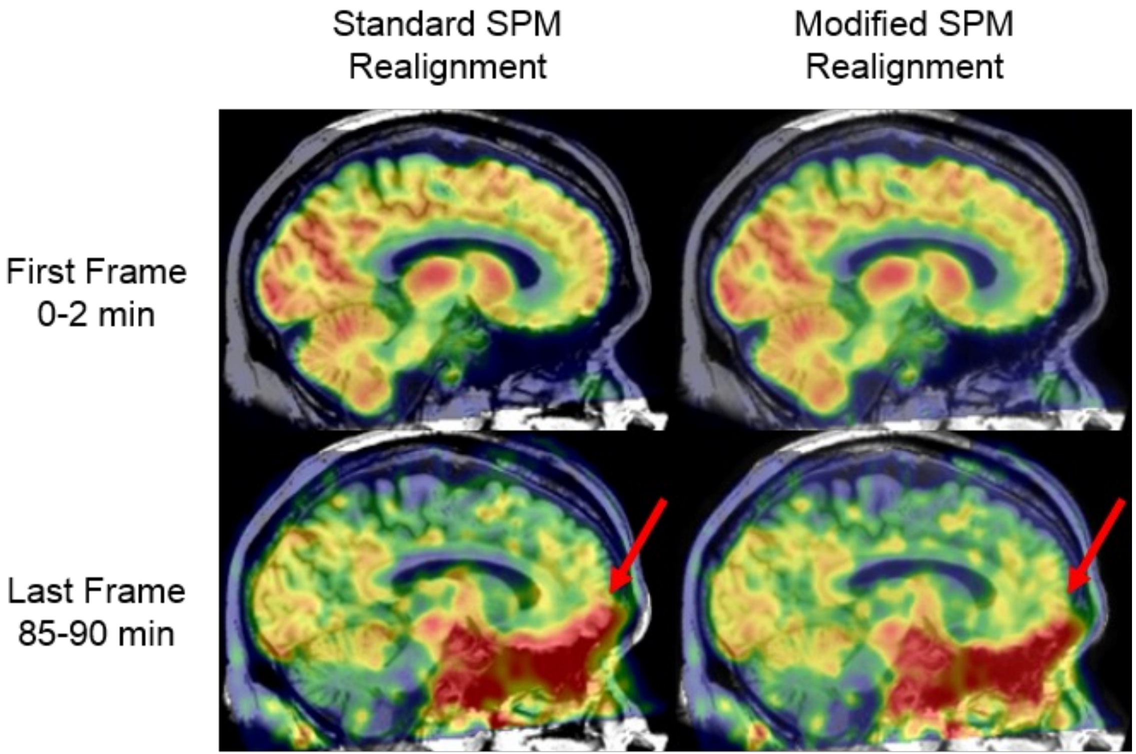

[^{18}F]MK-6240

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MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

Interframe Alignment (i.e., motion correction)

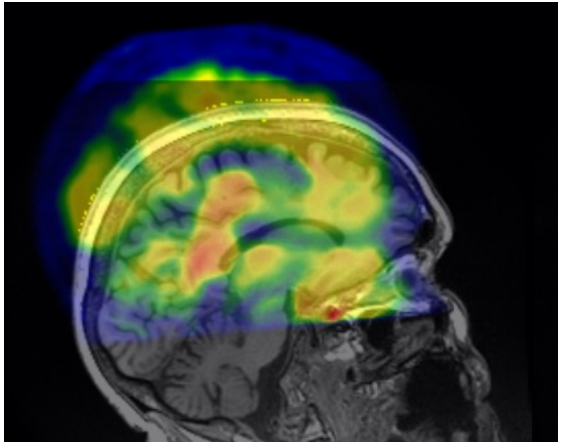
Co-Registration to MRI

Extract Reference Region TAC

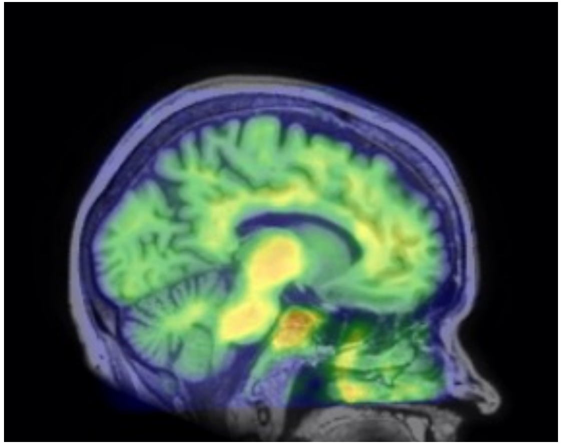
Generate Parametric Image(s)

Intermodal Registration (PET to T1-w MRI)

Unregistered



Registered



Reference Image: MRI

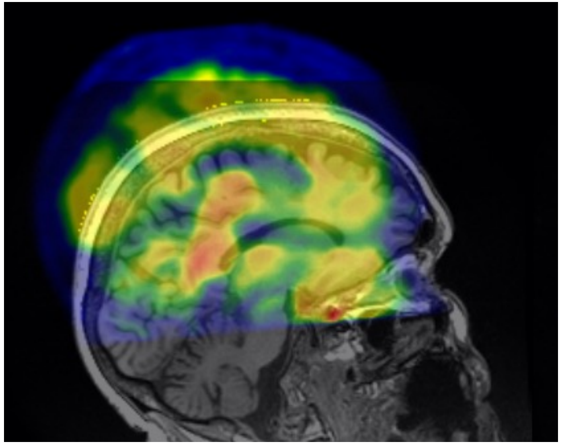
Source Image: SUM PET

MR-Guided PET Image Processing

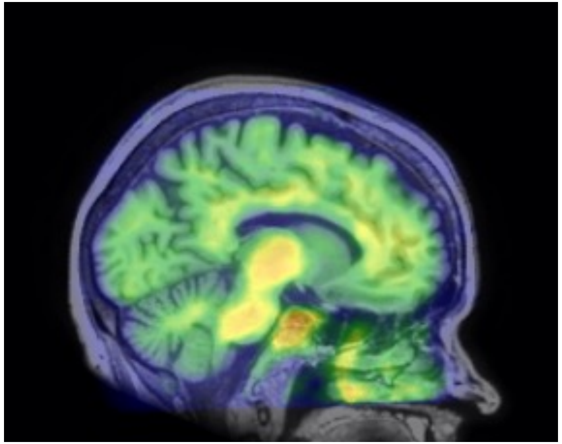
- Process MRI (ROI Parcellation)
- Smooth/De-noise
- Interframe Alignment (i.e., motion correction)
- **Co-Registration to MRI**
- Extract Reference Region TAC
- Generate Parametric Image(s)

Intermodal Registration (PET to T1-w MRI)

Unregistered



Registered



- Can apply transformation to the PET image using header OR
- Can **reslice** the registered PET image to match voxel-voxel with MRI (requires interpolation but enables extracting ROI-level data)

MR-Guided PET Image Processing

- Process MRI (ROI Parcellation)
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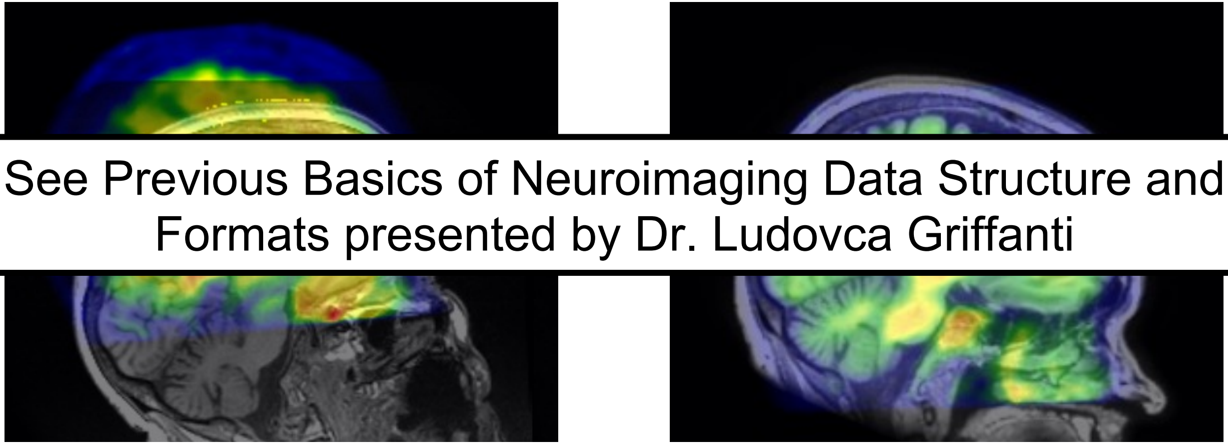
Intermodal Registration (PET to T1-w MRI)

Unregistered | Registered



See Previous Basics of Neuroimaging Data Structure and Formats presented by Dr. Ludovca Griffanti

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MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

Interframe Alignment (i.e., motion correction)

Co-Registration to MRI

Extract Reference Region TAC

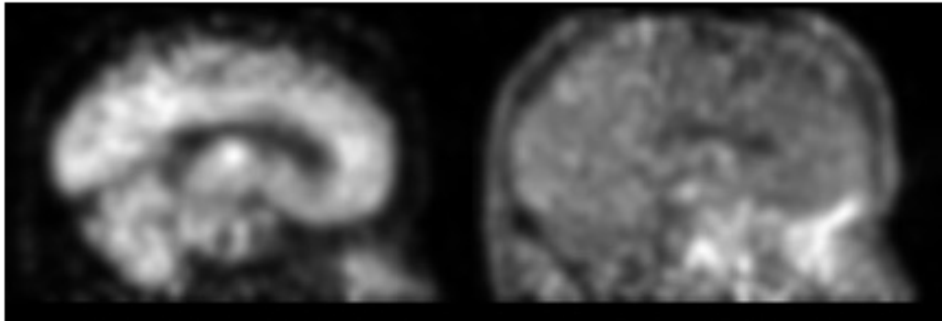
Generate Parametric Image(s)

Summing Different Frames Can Improve Registration

Early Frame 0-2 min

Late Frame 85-90 min

MK-6240



GM TPM

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MR-Guided PET Image Processing

Process MRI (ROI Parcellation)

Smooth/De-noise

Interframe Alignment (i.e., motion correction)

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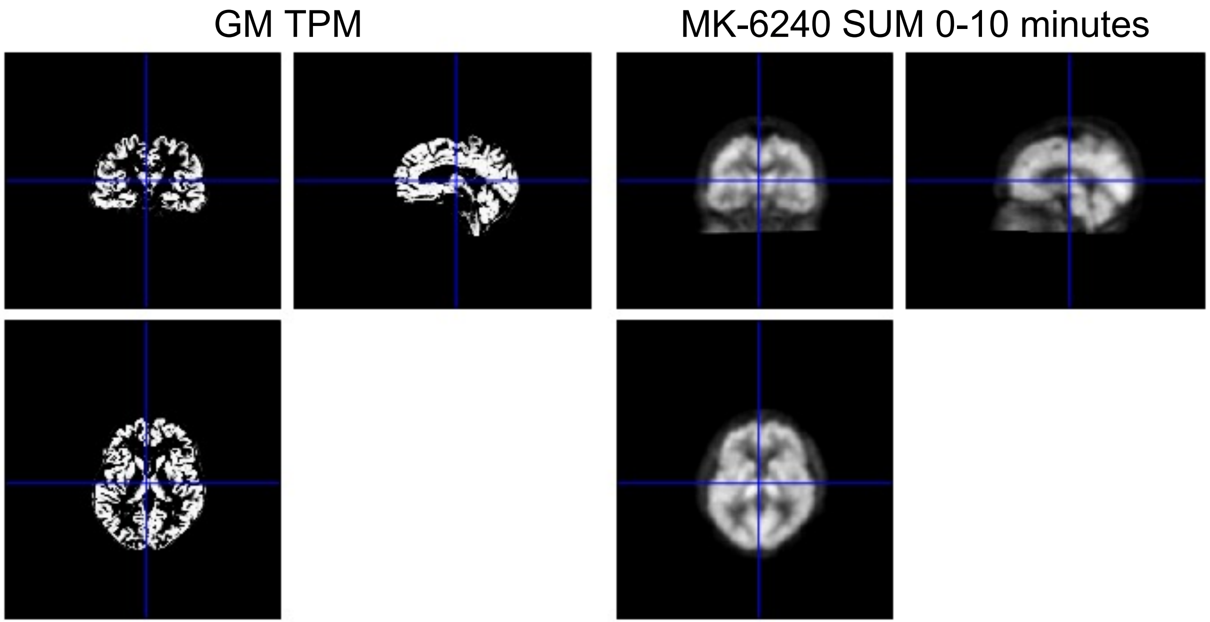
Extract Reference Region TAC

Generate Parametric Image(s)

Summumming Different Frames Can Improve Registration



- More mutual information between early frame-data and GM TPM compared to late-frame data

MR-Guided PET Image Processing

- Process MRI (ROI Parcellation)
- Smooth/De-noise
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- Extract Reference Region TAC
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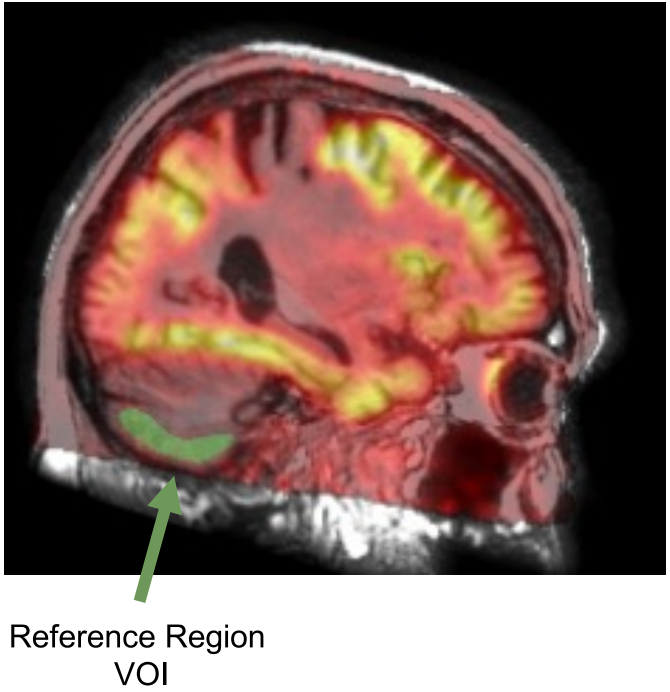
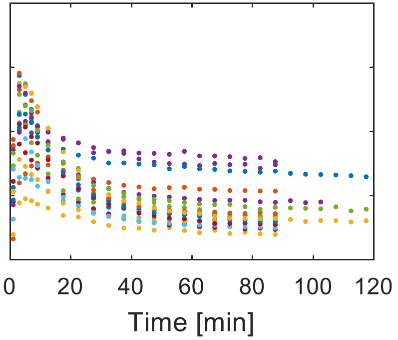
Coregistered PET to MRI



Time-Activity Curves



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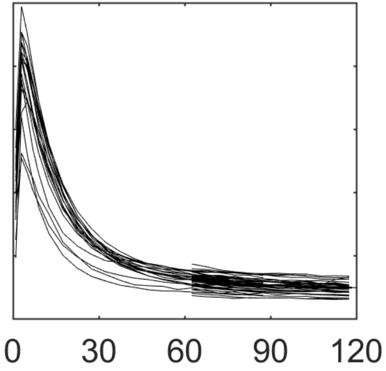
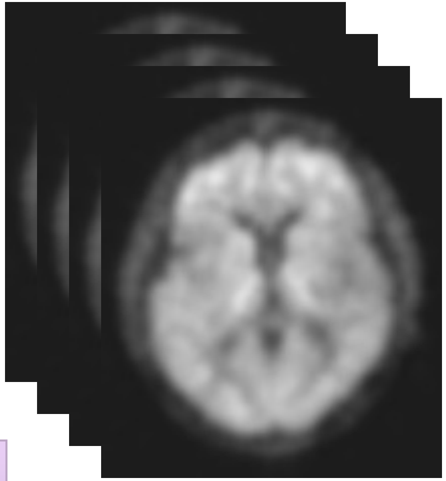
Cerebellum



4D PET



$$\frac{\int_0^T C(t)dt}{C(T)} = DVR\left[\frac{\int_0^T C_{ref}(t)dt + C_{ref}(T)/\bar{k}_2}{C(T)}\right] + int$$

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MR-Guided PET Image Processing

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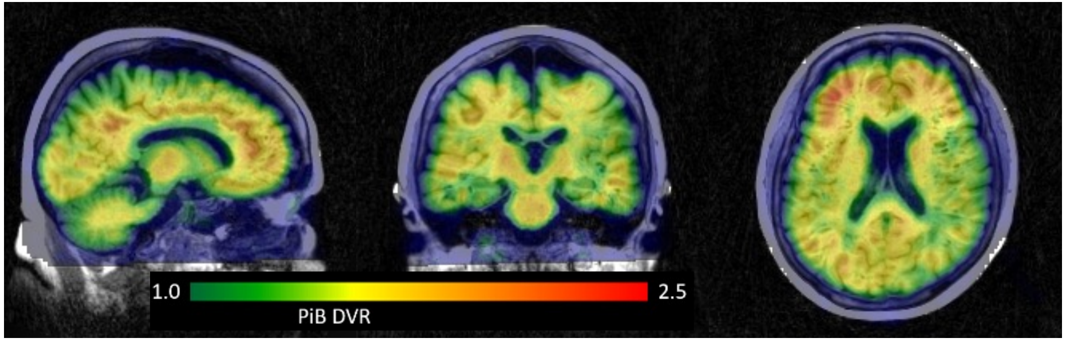
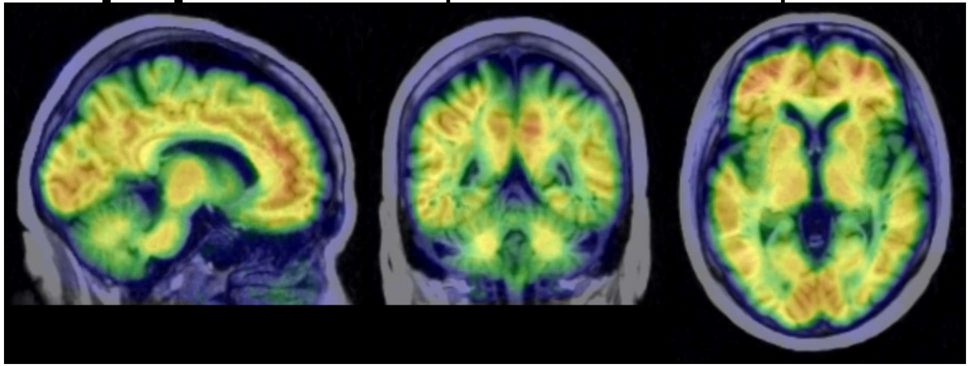
[11C]PiB DVR Coregistered to MRI



[11C]PiB DVR Warped to MNI-152 Space

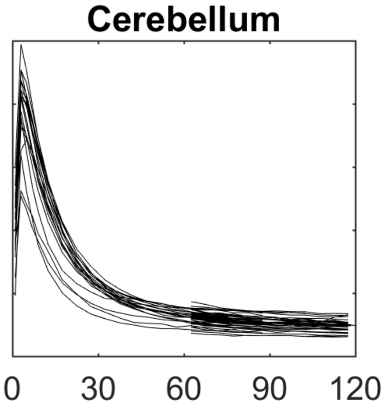


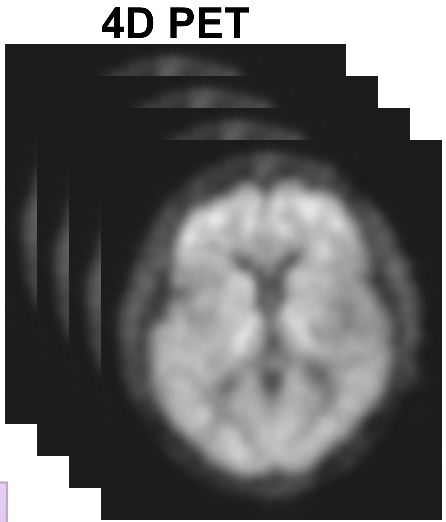
Apply MRI deformation field from T1-w spatial normalization

MR-Guided PET Image Processing

- Process MRI (ROI Parcellation)
- Smooth/De-noise
- Interframe Alignment (i.e., motion correction)
- Co-Registration to MRI
- Extract Reference Region TAC
- **Generate Parametric Image(s)**

Can generate other Parametric Images also (e.g., R_1)





Simplified Reference Tissue Method (SRTM)

$$C(T) = \mathbf{R_1} C_{ref}(t) + \left\{k_2^{ref} - \frac{R_1 k_2^{ref}}{1+BP}\right\} C_{ref}(t) \otimes e^{-\left[\frac{k_2^{ref}}{(1+BP)}+\lambda\right]t}$$

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MR-Guided PET Image Processing

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- Interframe Alignment (i.e., motion correction)
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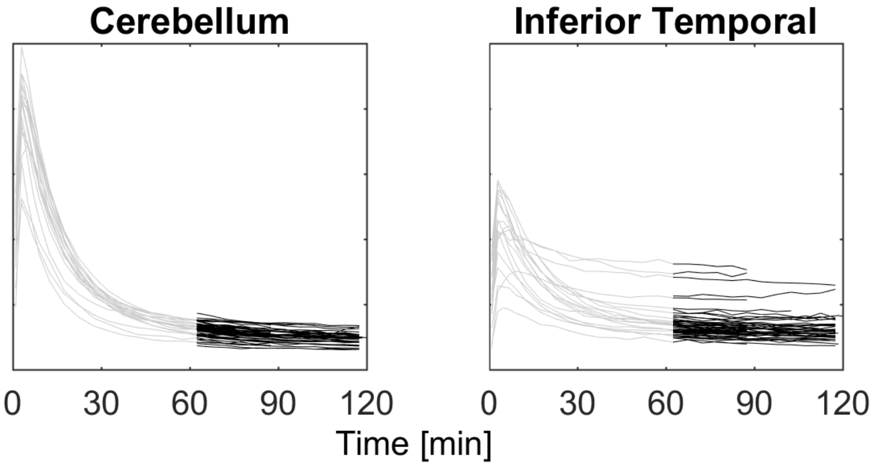
- Generate Parametric Image(s)

For **SUVR quantification**, we only have late-frame data



$$\frac{\int_0^T C(t)dt}{C(T)} = DVR\left[\frac{\int_0^T C_{ref}(t)dt + C_{ref}(T)/\bar{k}_2}{C(T)}\right] + int$$

MR-Guided PET Image Processing

- Process MRI (ROI Parcellation)
- Smooth/De-noise
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- **Generate Parametric Image(s)**

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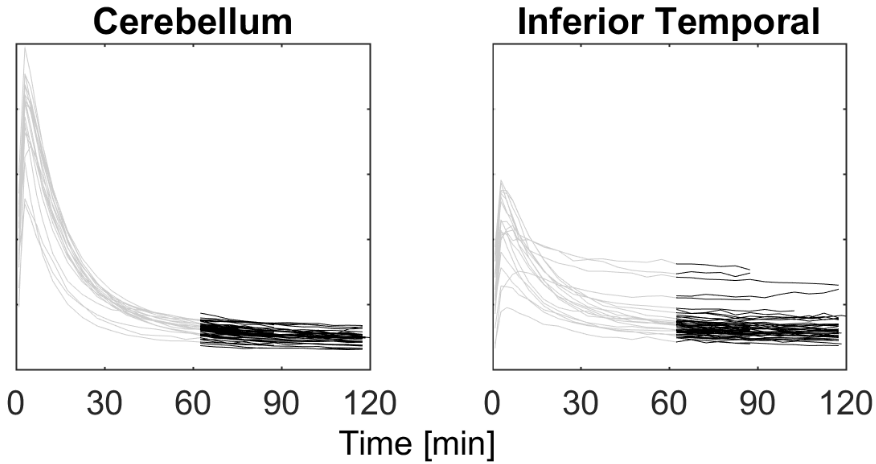

$$SUVR = \frac{C(\Delta t)}{C_{ref}(\Delta t)}$$

MR-Guided PET Image Processing

- Process MRI (ROI Parcellation)
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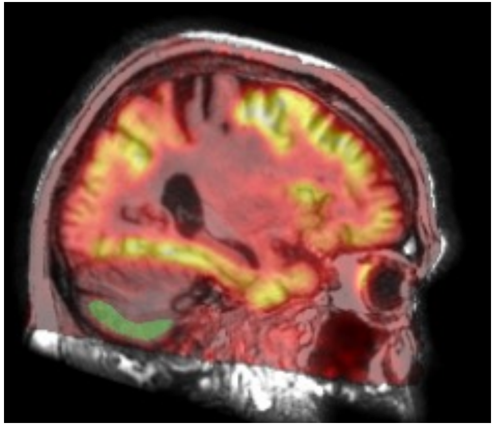
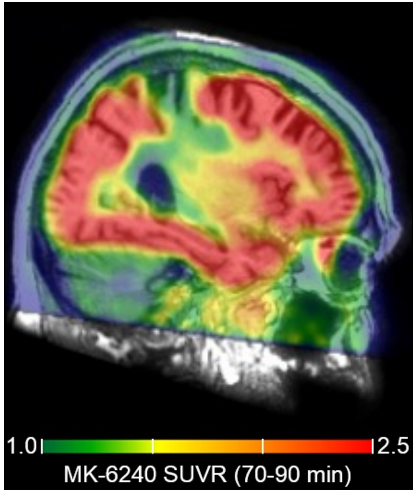
Create SUVR image by dividing entire image by mean activity concentration in the reference region

Coregistered Summed PET



$$\frac{I_{SUM}}{mean(I_{SUM,ref})}$$

SUVR Image



MR-Guided PET Image Processing

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- Process MRI (ROI Parcellation)
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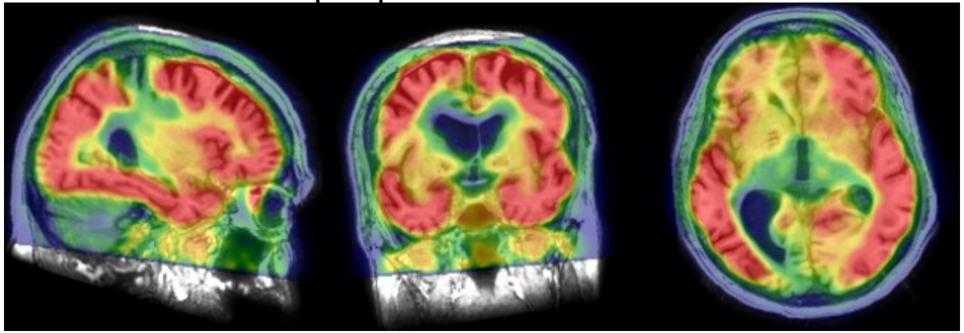
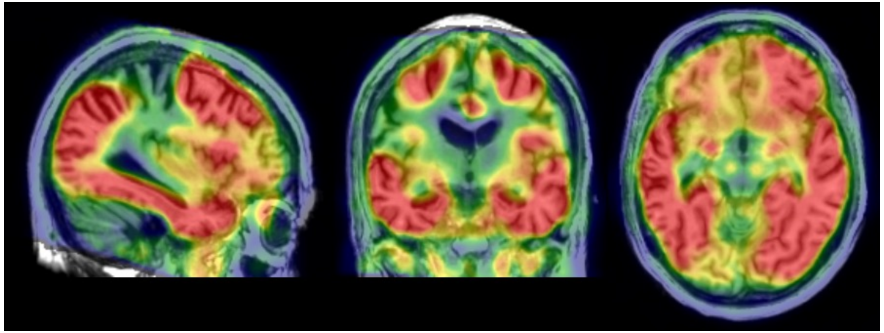
[^{18}F]MK-6240 SUVR



[^{18}F]MK-6240 SUVR Warped to MNI Space

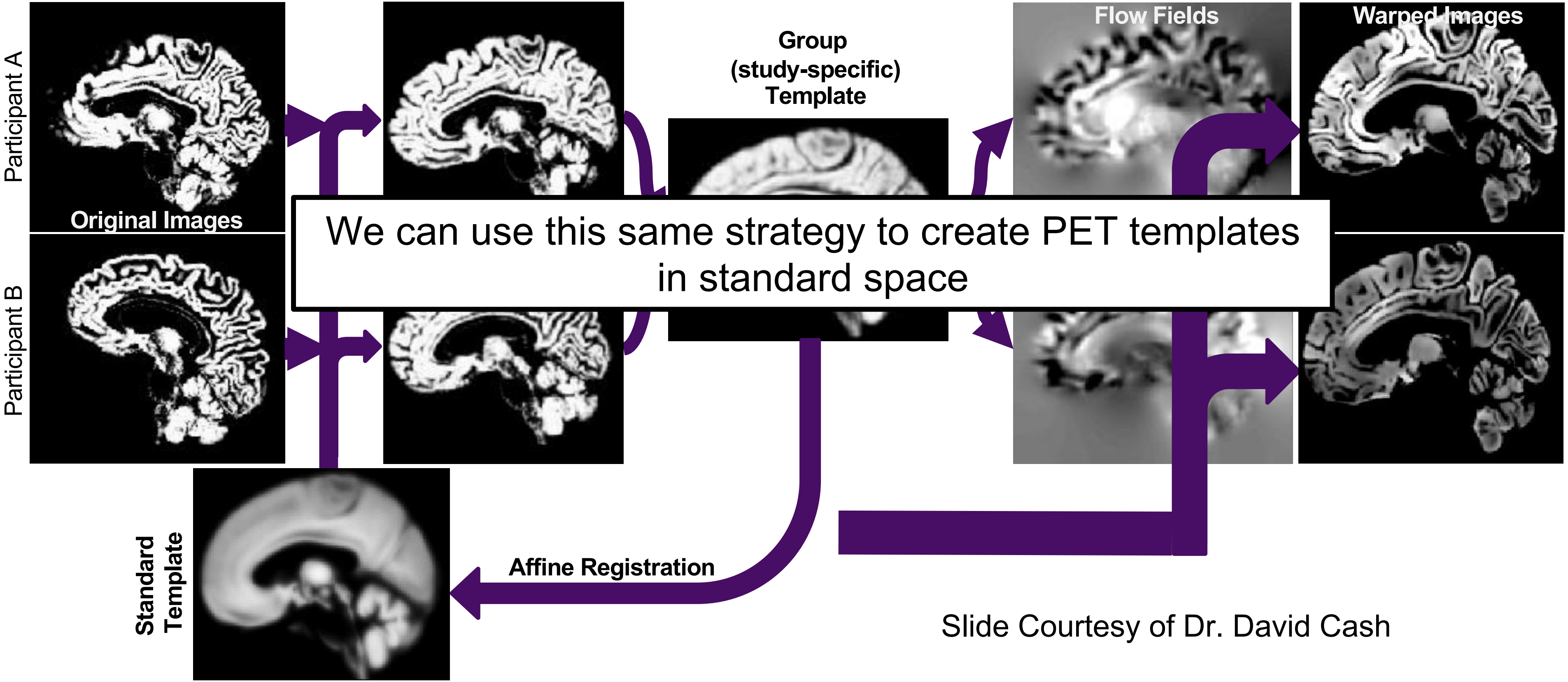


Apply MRI deformation field from T1-w spatial normalization

PET Image Processing

- MR-Guided Image Processing
- **PET only Image Processing**
- Other Considerations

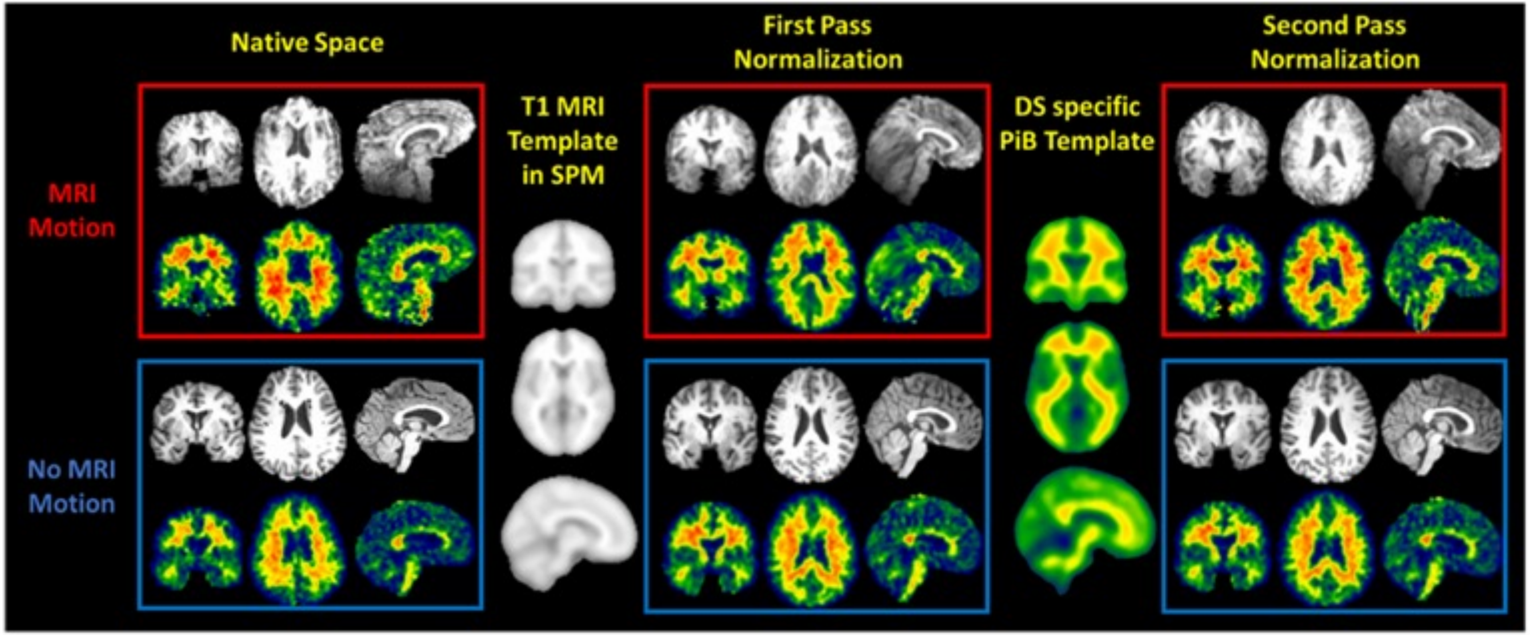
Creating a study-specific template to reduce errors in spatial normalisation



We can use this same strategy to create PET templates in standard space

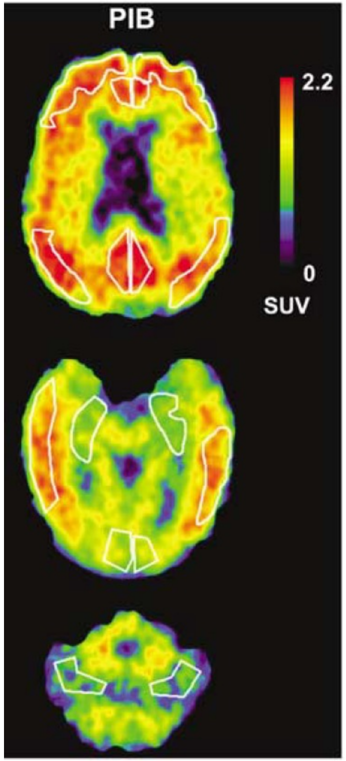
Slide Courtesy of Dr. David Cash

PET-Only Processing (PET template)



Lao, et al., Brain Imaging and Behavior, 2019

PET-Only Processing (Hand Drawn)



Adapted from Price, et al. JCBFM. 2005

ROIs can also be Hand drawn on SUM or SUV Images

- Create SUM PET image
- Manually draw ROIs on image
- Extract TACs or regional mean
- Generate parametric image

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PET Image Processing

- MR-Guided Image Processing
- PET only Image Processing
- **Other Considerations**

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Other Considerations

- Reconstruction parameters (corrections for deadtime, scatter, attenuation, decay, etc.,)
- Standardization across tracers, sites, acquisition protocols, etc.,
- Partial Volume Effects
- Reference region selection
- Off-target binding
- Brain-penetrable radiometabolites

POP QUIZ!

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QUESTION 1

Which of the following statements best describes PET imaging?:

a) High spatial resolution, high molecular specificity
b) Low spatial resolution, high molecular specificity
c) High spatial resolution, low molecular specificity
d) Low spatial resolution, low molecular specificity

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QUESTION 1

Which of the following statements best describes PET imaging?:

a) High spatial resolution, high molecular specificity
b) Low spatial resolution, high molecular specificity
c) High spatial resolution, low molecular specificity
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QUESTION 2

The signal we detect with PET imaging is:

a) Single gamma photons
b) Beta particles
c) X-rays
d) Coincident gamma photons

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QUESTION 3

PET radiotracers for amyloid and tau mostly reflect:

a) Soluble protein fragments
b) Transient pathological changes in beta-amyloid and tau
c) Insoluble protein aggregates
d) None of the above

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QUESTION 4

Registering PET to MRI provides:

a) Less noisy images
b) Anatomical reference and regions of interest
c) The underlying radiotracer distribution at higher resolution
d) Regional radiotracer perfusion information

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QUESTION 4

Registering PET to MRI provides:

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d) Regional radiotracer perfusion information

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QUESTION 5

A SUM PET image is:

a) A time-weighted average of all or some PET frames
b) A quantitative measure of binding potential
c) Always a straight average of all of some PET frames
d) A quantitative measure of perfusion

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QUESTION 5

A SUM PET image is:

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b) A quantitative measure of binding potential

c) Always a straight average of all of some PET frames

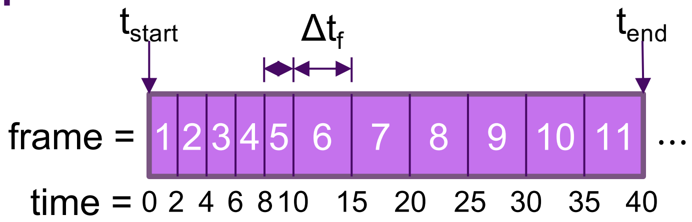
d) A quantitative measure of perfusion

List Mode

$$\sum_{i=t_{start}}^{t_{end}} \frac{counts_i}{t_i}$$

Reconstructed Image Frames

$$\frac{\sum_{f=frame_{start}}^{frame_{end}} C(t)_f \times \Delta t_f}{\sum_{f=frame_{start}}^{frame_{end}} \Delta t_f}$$



ISTAART Neuroimaging PIA

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THANK YOU!

@tobeybetthauser
tjbetthauser@medicine.wisc.edu

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21 April, 2023; 9AM – 10AM CT
- Basics of Neuroimaging: Functional Magnetic Resonance Imaging (FMRI) by Luigi Lorenzini
26 April, 2023; 10AM – 11AM CT

GETTING STARTED WITH NEUROIMAGING WORKSHOP Friday, July 14 8:00-12:00 Amsterdam