State-of-the-Art Challenges and Emerging Technologies

Quantitative Imaging with Positron Emission Tomography in the Brain

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Positron Emission Tomography

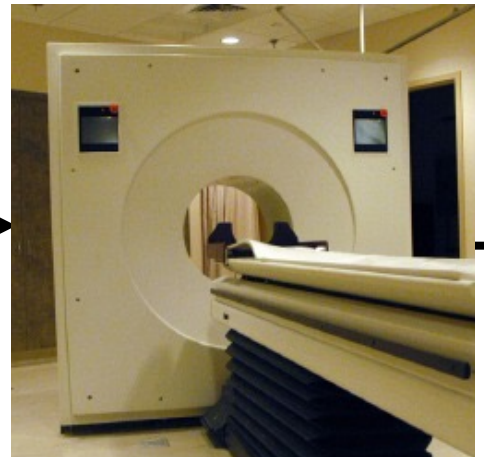
Cyclotron

C-11
F-18

Radiochemistry

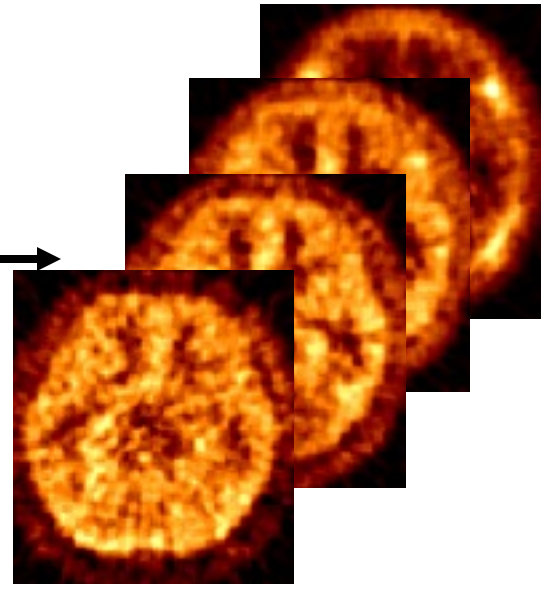
Radio-
pharmaceuticals

Inject into
subject



PET Scanner

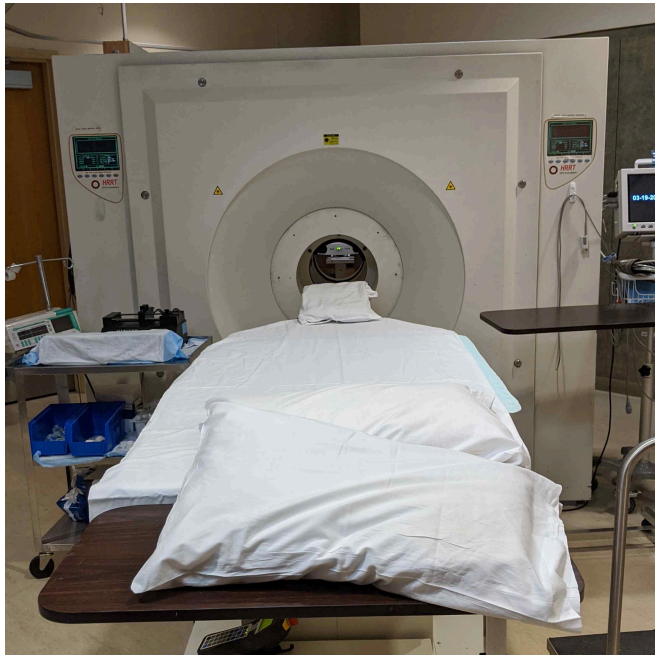
Acquire &
Reconstruct

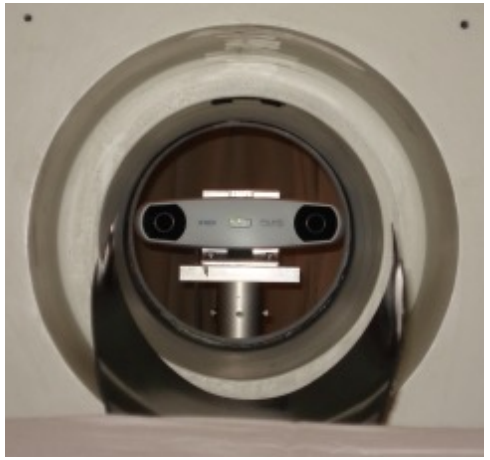


4D Quantitative
Dataset (Bq/mL)

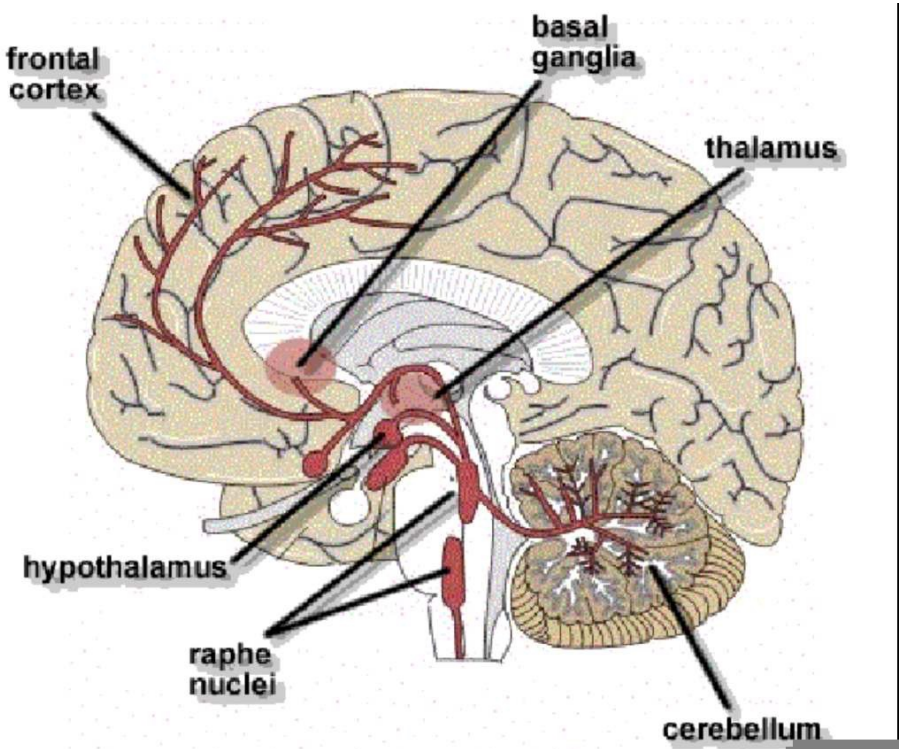
HRRT @ Yale PET Center

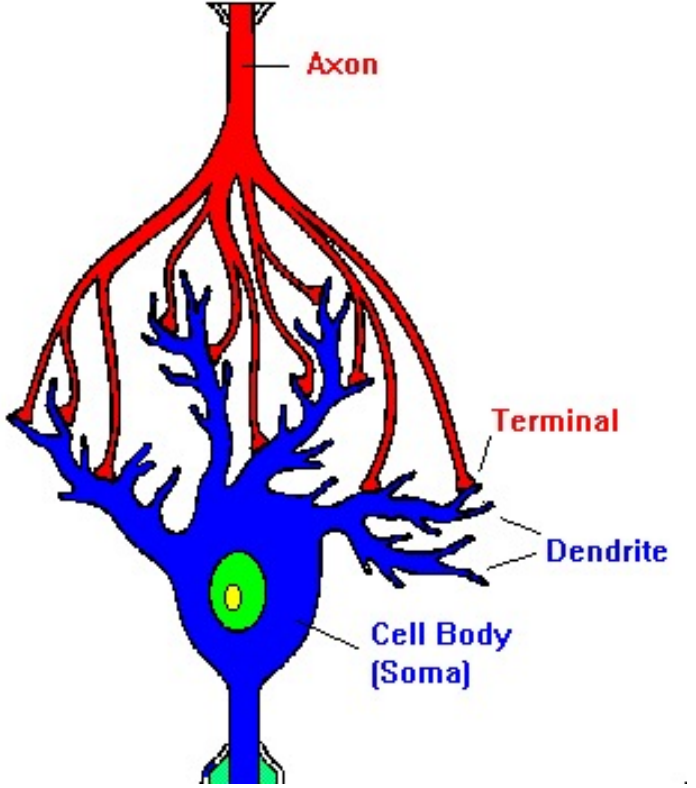
- State-of-the art for brain PET
- Design > 20 years old
- ~ 4500 human studies
- ~ 50 different tracers
- ~ 50 current NIH grants for brain PET at Yale
- Dynamic (list-mode) acquisition for 60-150 min
- Arterial blood sampling in ~ 60% of the scans
- Operating at ~ 3 mm resolution (probably)
- Online hardware motion correction

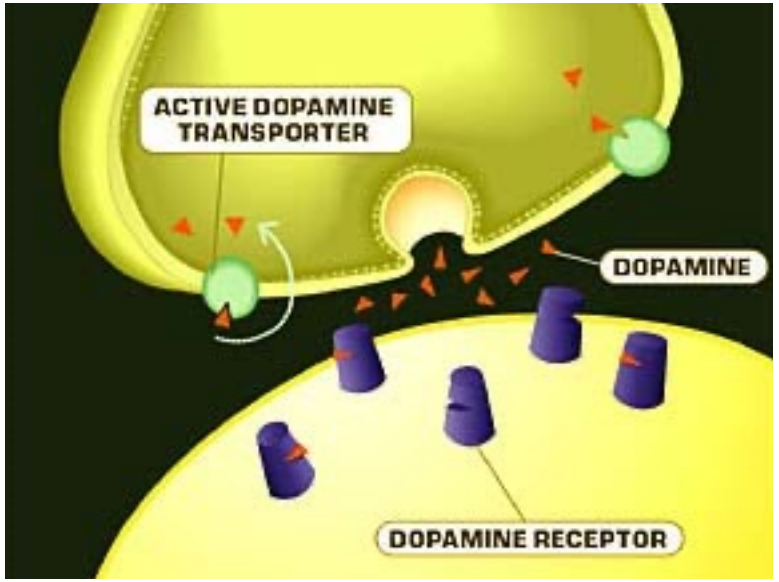




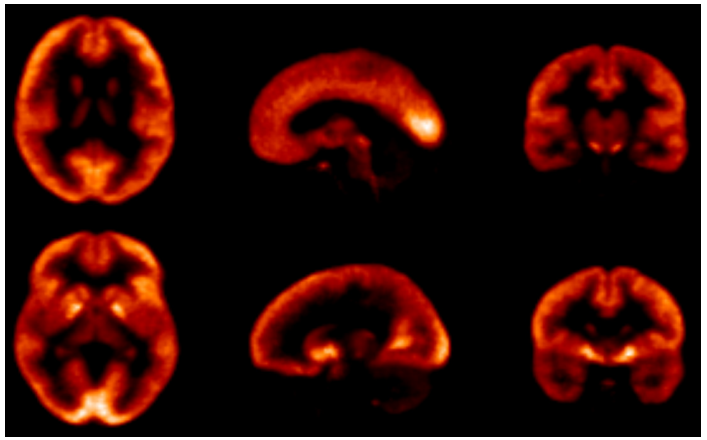
Neuroreceptors



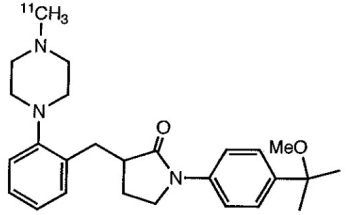


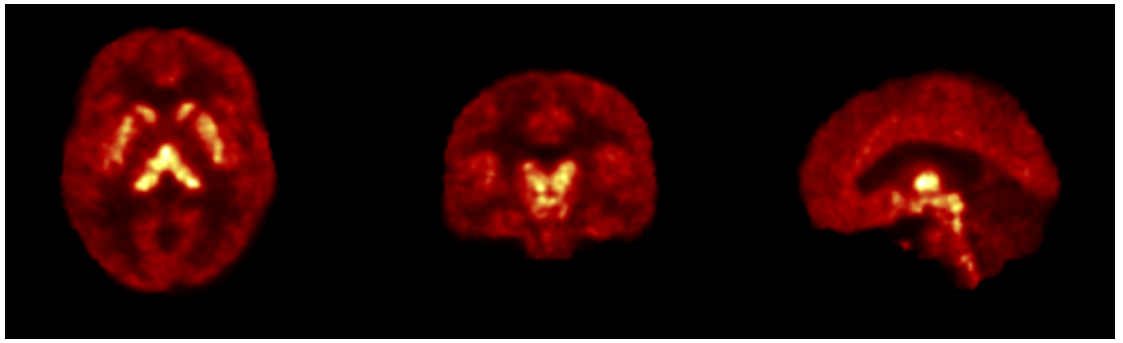


High Resolution Human Brain PET Imaging

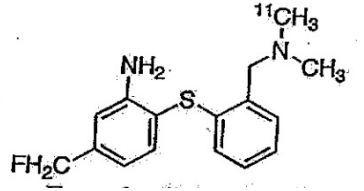


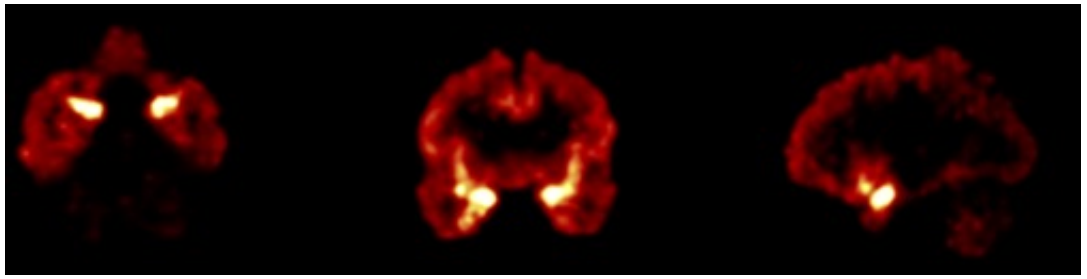
Serotonin-1B Receptors



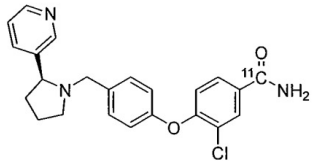


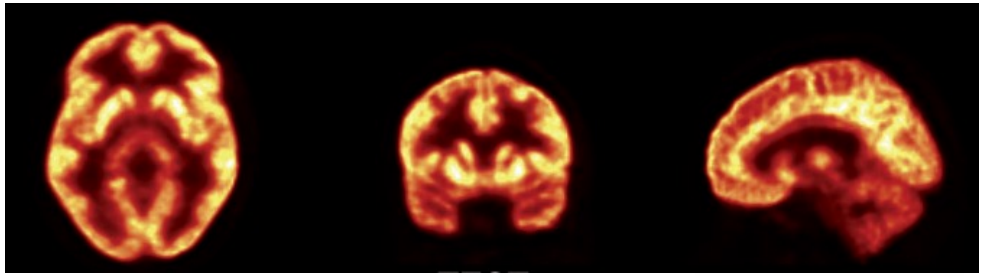
Serotonin Transporter



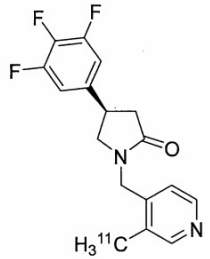


Kappa Receptors





Synaptic Density (SV2A)

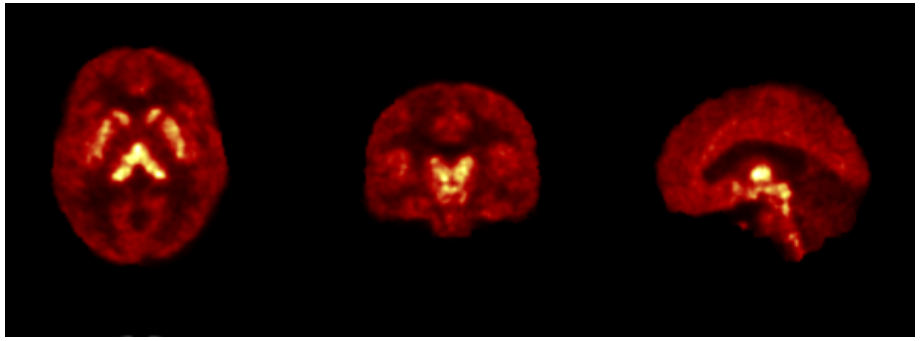


What can brain PET do?
(in principle)

- With the right radiopharmaceutical (tracer)
- … and the right imaging technology
- … and a feasible human imaging paradigm
- We can quantitatively assay virtually any physiological process throughout the brain
  - Blood Flow
  - Metabolism
  - Protein concentrations
  - Enzyme synthesis rates
  - Drug occupancy
  - Neurotransmitter dynamics
- What are the limits?
- How can advances in instrumentation and algorithms expand the scope?

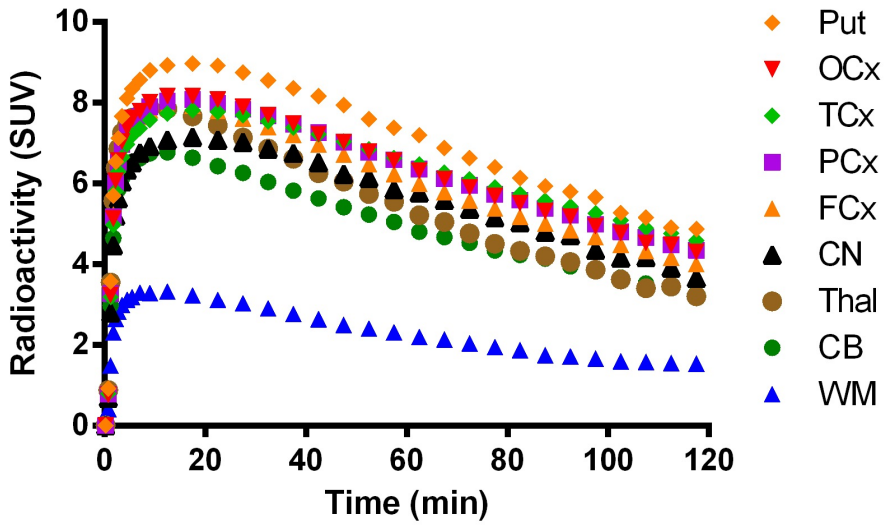
Factors that affect what brain PET can realistically do

- How much of the target protein is present in the brain (B_{max}, pM/nM)
  - Synaptic marker or α-synuclein?
- How much "background" uptake?
  - Non-specific uptake
- What size brain region is relevant to the biological question
  - Entire frontal lobe or the substantia nigra
- How efficiently do the tracers enter the brain (BBB)
  - Is blood flow a compounding factor?



Factors that affect what brain PET can realistically do

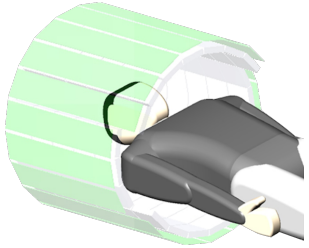
- The overall kinetics of the tracer
  - How long should the scan be?
  - Is a short scan useful? Or misleading?
- What kind of patients are we studying?
  - Can they tolerate such a protocol?



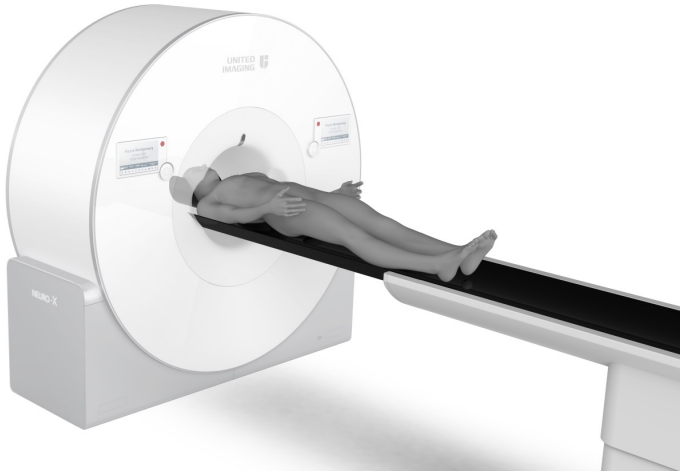
- How large is the change in disease? Or by competition with a drug?
  - 50% or 5%
- How large is the change over time?
  - 1% per year?
- Are protocols too complex even for most research centers?
  - Hospitals?

Challenges

- Sensitivity and noise
- Image resolution
- Tracer kinetics
- Human Issues
  - Input Function
  - Head Motion



NeuroEXPLORER



- BRAIN Initiative grant (U01EB029811)
- Collaboration between Yale, UC Davis, and United Imaging Healthcare America
- A fully-functional well-characterized commercially-available brain PET system
- At least 10-fold higher effective sensitivity than the HRRT
- Useable resolution of <2 mm in the human brain
- Continuous motion correction
- Dramatically expand the scope of brain PET protocols and applications
- Study of the healthy brain
- Study of pathophysiology including the earliest stages of neurodegeneration

Challenges

- **Sensitivity and noise**
- Image resolution
- Tracer kinetics
- Human Subjects
  - Head Motion
  - Input Function

Sensitivity and noise

- For a given human patient
- And a target injected radiopharmaceutical dose
- And a given scan instrumentation
- And a given scan duration
- And a given reconstruction algorithm
- And a given post-processing noise-reduction method
- And a target brain area (voxel)
- With a given quantitative outcome measure
  - Standardized uptake value
  - Binding potential
- How variable?
- Any bias?

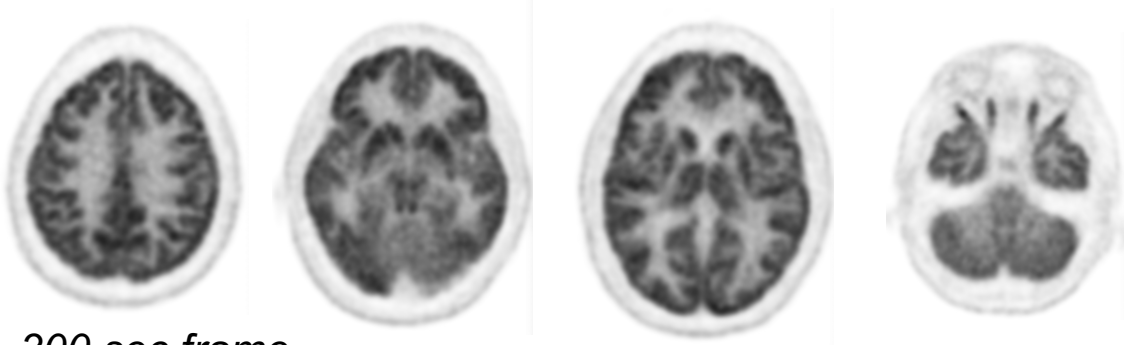
What have we learned abut sensitivity from the HRRT at Yale

- Insufficient system sensitivity
  - Counts are usually the limiting case
  - Radioactivity images are often noisy
  - Parametric images from voxel-by-voxel kinetic modeling are noisier
  - Some form of filtering / noise reduction is needed
  - Usually costs us resolution

- We <u>rarely</u> can produce images at the system's best possible resolution

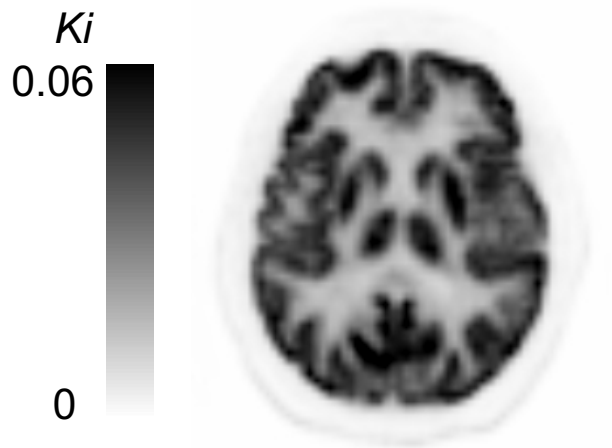
What have we learned from the EXPLORER at UC Davis

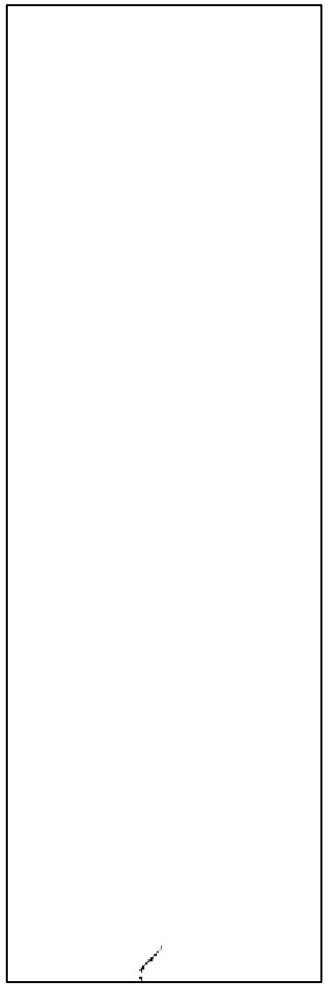
High sensitivity enables high SNR for short scan durations



300 sec frame

This enables parametric imaging at high spatial resolution with no smoothing.





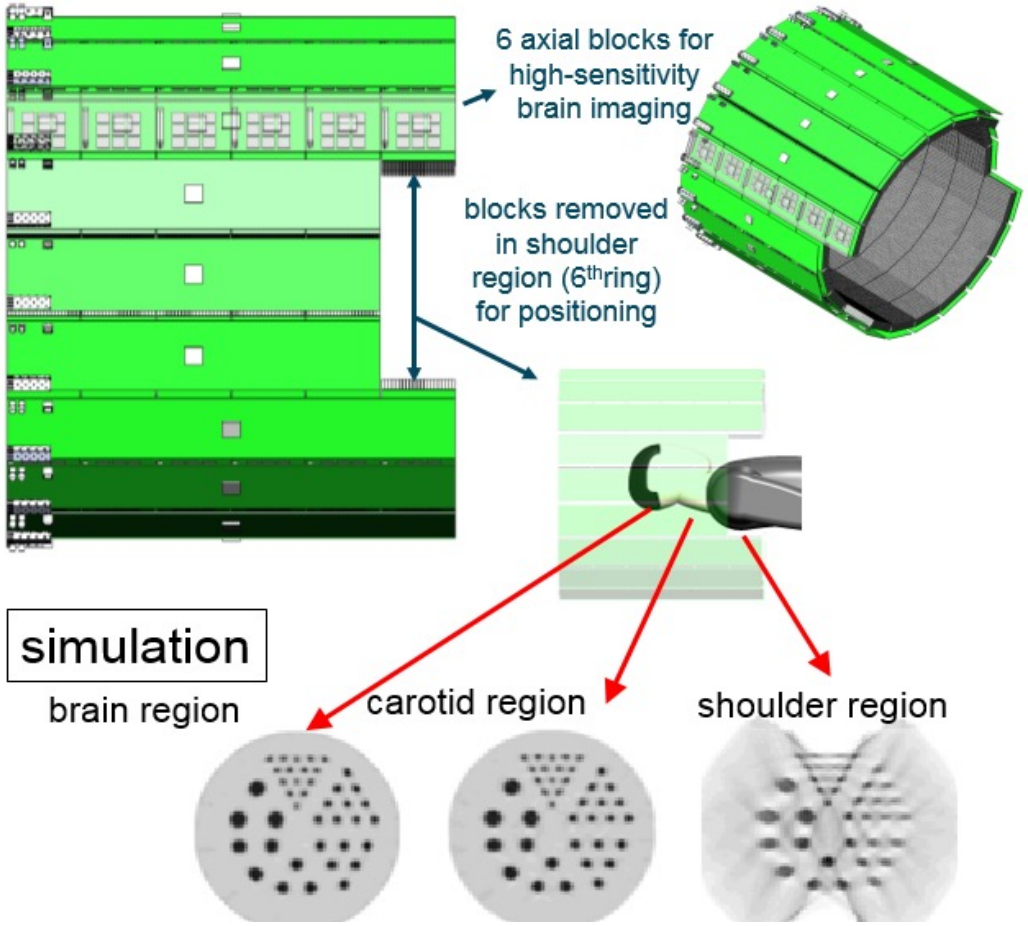
0.1 sec frames

Also enables sub-second temporal sampling of the arterial input function and bolus arrival times and transit times

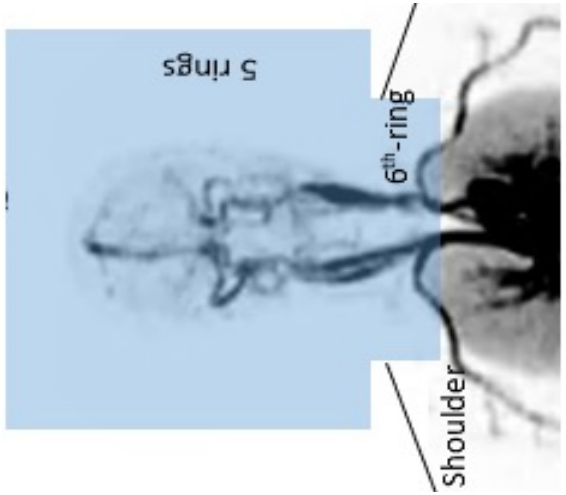
High sensitivity in Next-Generation Dedicated Brain PET

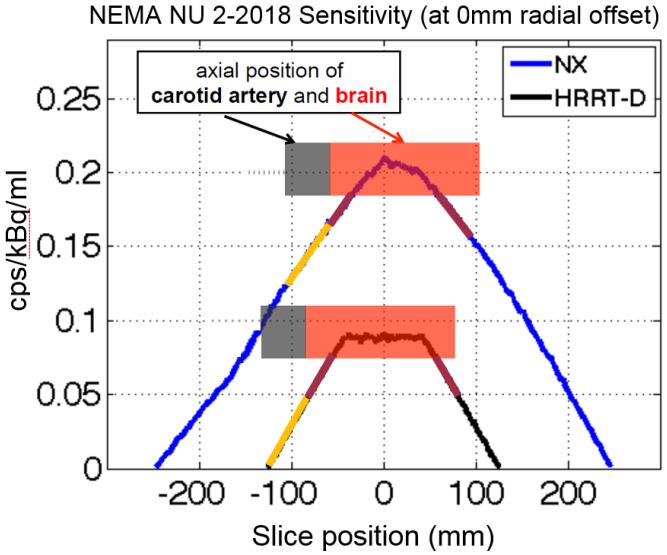
- Needed to achieve high resolution
  - Need enough counts per resolution element
- Improved quantification
  - Many useful tracers labeled with C-11 (20-min half-life)
  - For longer scans with slower kinetics, especially for regions with highest binding
  - For targets with low concentration (B_{max})
- Assess dynamics
  - Neurotransmitter release due to stimuli
  - Large changes in small regions or small changes in large regions
- Low noise
  - To precisely measure small longitudinal changes in disease
- Lower injected dose
  - Pediatric imaging
  - More repeat scans

NX – Focus on Sensitivity



- To maximize the sensitivity for the brain: 50-cm axial FOV
- Center the brain in the axial FOX
  - Uniform sensitivity throughout the brain
- Partial 6th ring to accommodate all shoulder sizes
  - 3 blocks removed on both sides
- With TOF, 10-fold higher sensitivity than the HRRT
- Even greater gain for the carotids





Regularized PET reconstruction using deep neural network

- The basic idea is to represent the unknown PET image as an output of a pre-trained deep neural network and preform a constrained maximum likelihood estimate:

$$\hat{\boldsymbol{x}} = \arg\max_{x} L(\boldsymbol{y}|\boldsymbol{x}), \quad s.t., \boldsymbol{x} = \boldsymbol{DNN}(\boldsymbol{\alpha}_{CT}, \boldsymbol{\alpha}_{PET}) \; or \; \boldsymbol{x} = \boldsymbol{DNN}(\boldsymbol{\alpha}_{MRI}, \boldsymbol{\alpha}_{PET})$$

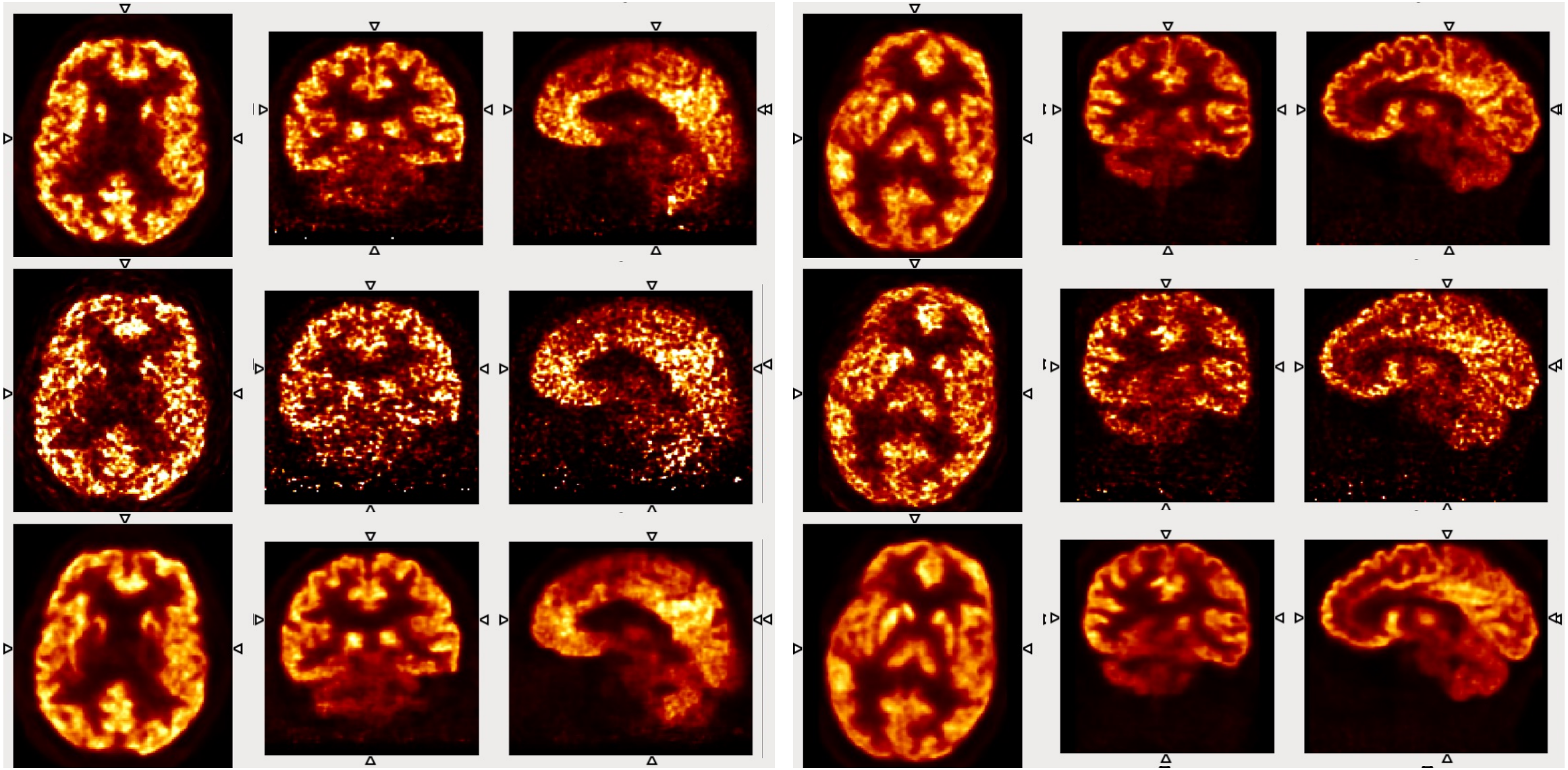
where $\boldsymbol{DNN}$: $\boldsymbol{R}^N \rightarrow \boldsymbol{R}^N$ denotes a pretrained denoising DNN and $\boldsymbol{\alpha}_{\boldsymbol{PET}}$ denotes the input (**Low-count , high-noise PET images**) to the neural network.

- Both inter-patient information and intra-patient information can be included into the iterative reconstruction framework by pre-training a DNN using high-resolution low-noise PET images obtained from existing data as labels.

[1] K Gong, J Guan, K Kim, X Zhang, J Yang, Y Seo, G El Fakhri, J Qi, Q Li. *IEEETMI*, 2018
[2] Z Xie, X Zhang, T Li, W Qi, E Asma, J Qi. SNMMI 2020

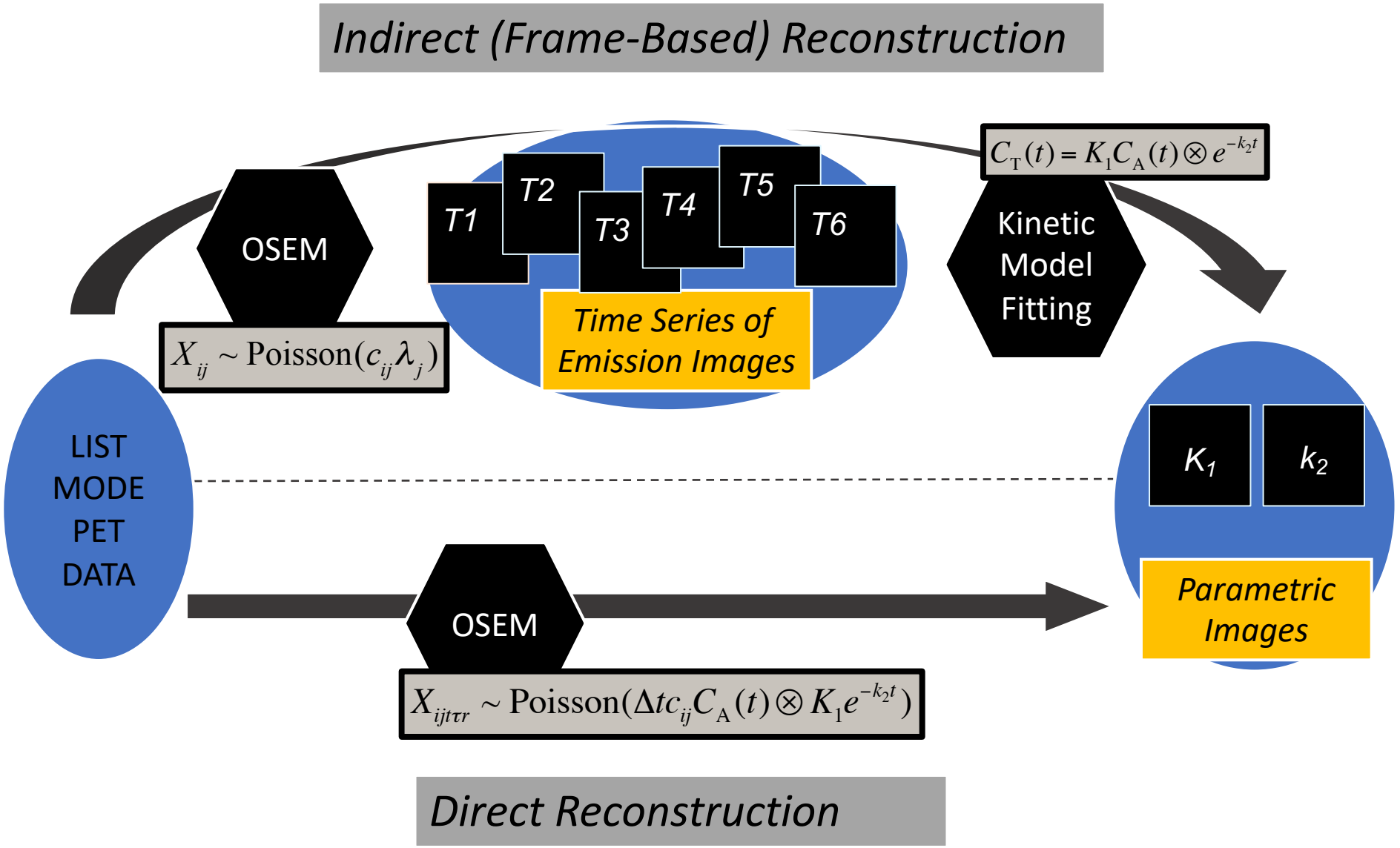
Courtesy Jinyi Qi

Deep Learning Denoising for HRRT Data (^{11}C-UCB-J)

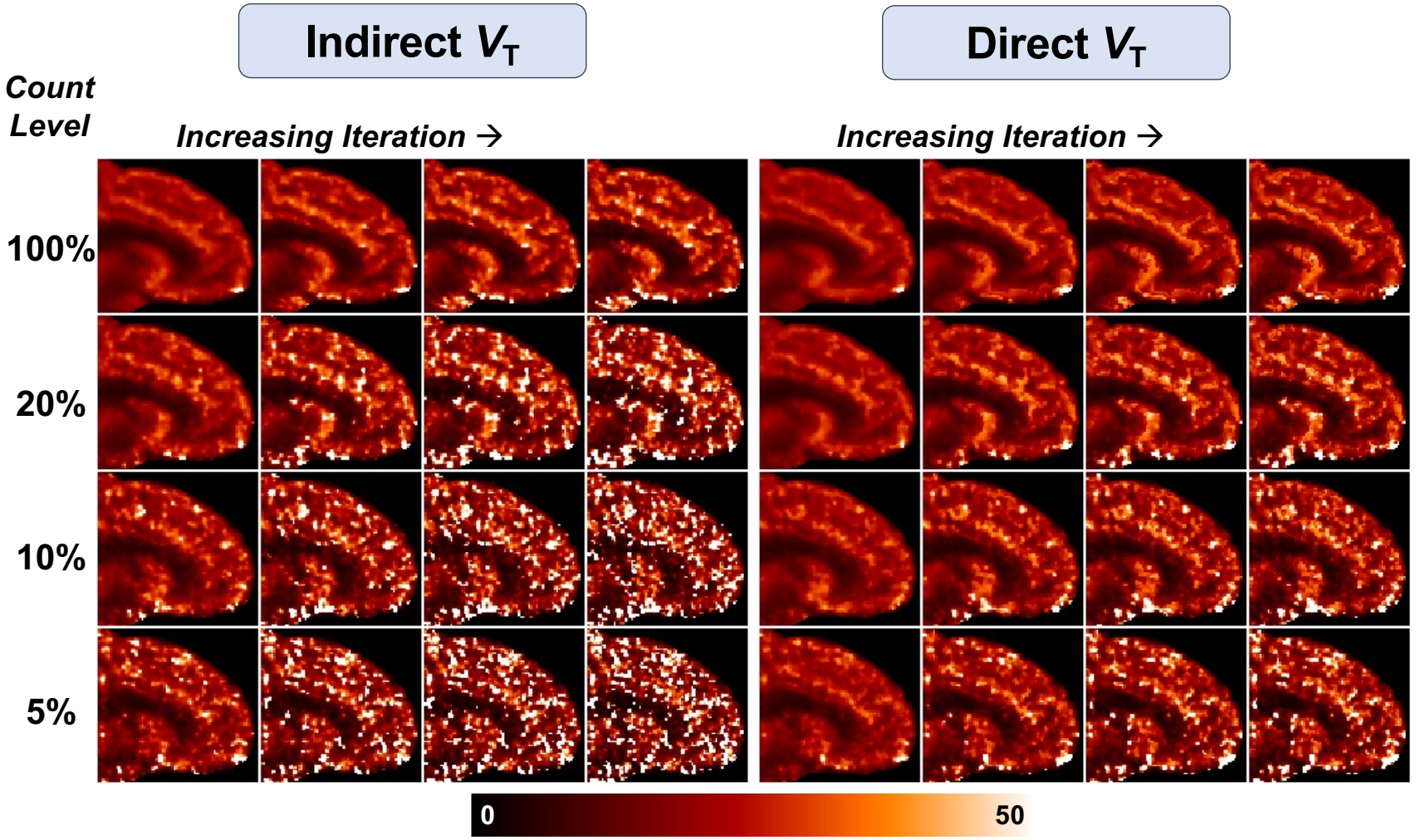


Courtesy Chi Liu

Direct Reconstruction of Parametric Images



[^{11}C]UCB-J: VT images (single replicate)



Germino et al, Phys Med Biol, 2017

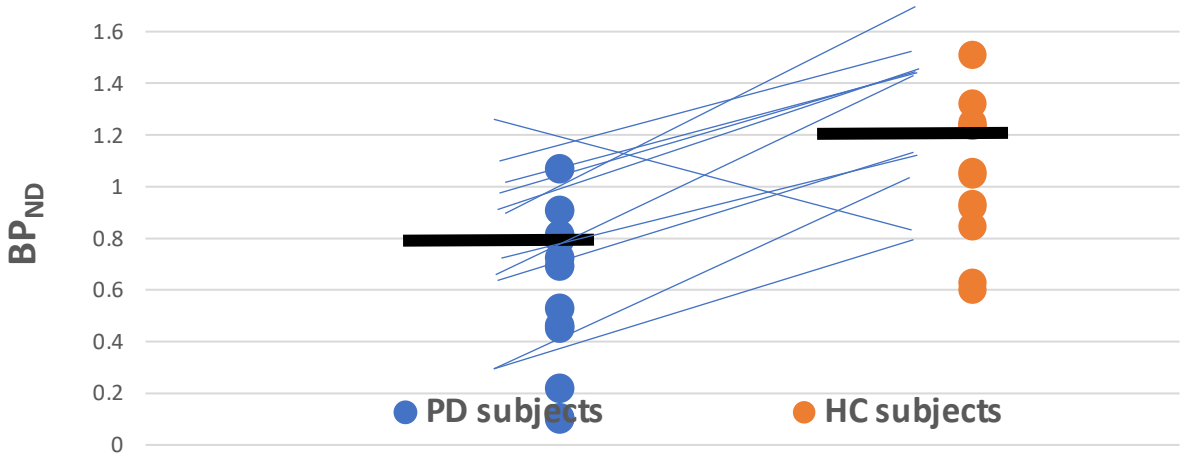
Challenges

- Sensitivity and noise
- **Image resolution**
- Tracer kinetics
- Human Issues
  - Input Function
  - Head Motion

High resolution in Next-Generation Dedicated Brain PET

- Image focal structures
  - Raphe nucleus, Locus coeruleus, substantia nigra, entorhinal cortex
  - Distinguish distribution across cortical layers (1-2 mm) in human beings
- Reduce partial volume effect
  - Distinguish atrophy effects from loss of target proteins in remaining tissue
- Ensure uniformity of image resolution
  - Over space and time
- Measure the tracer input function
  - HRRT's resolution not good enough for carotid artery quantification

Synaptic Density in the Substantia Nigra in Parkinson's Disease



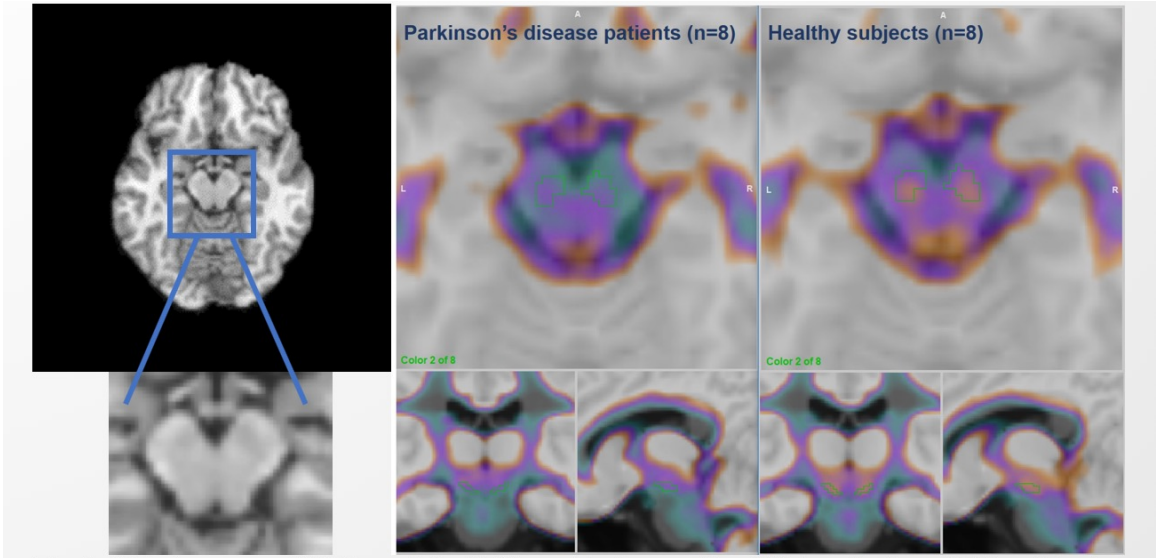
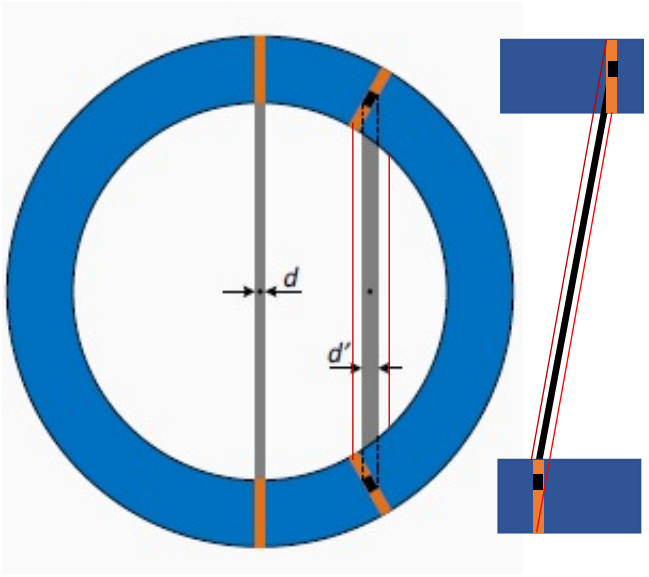


Fig 6. SN shown on MRI template (left) and between the PD (center) and HC subjects (right) on averaged group BP_{ND} ^{11}C-UCB-J images.

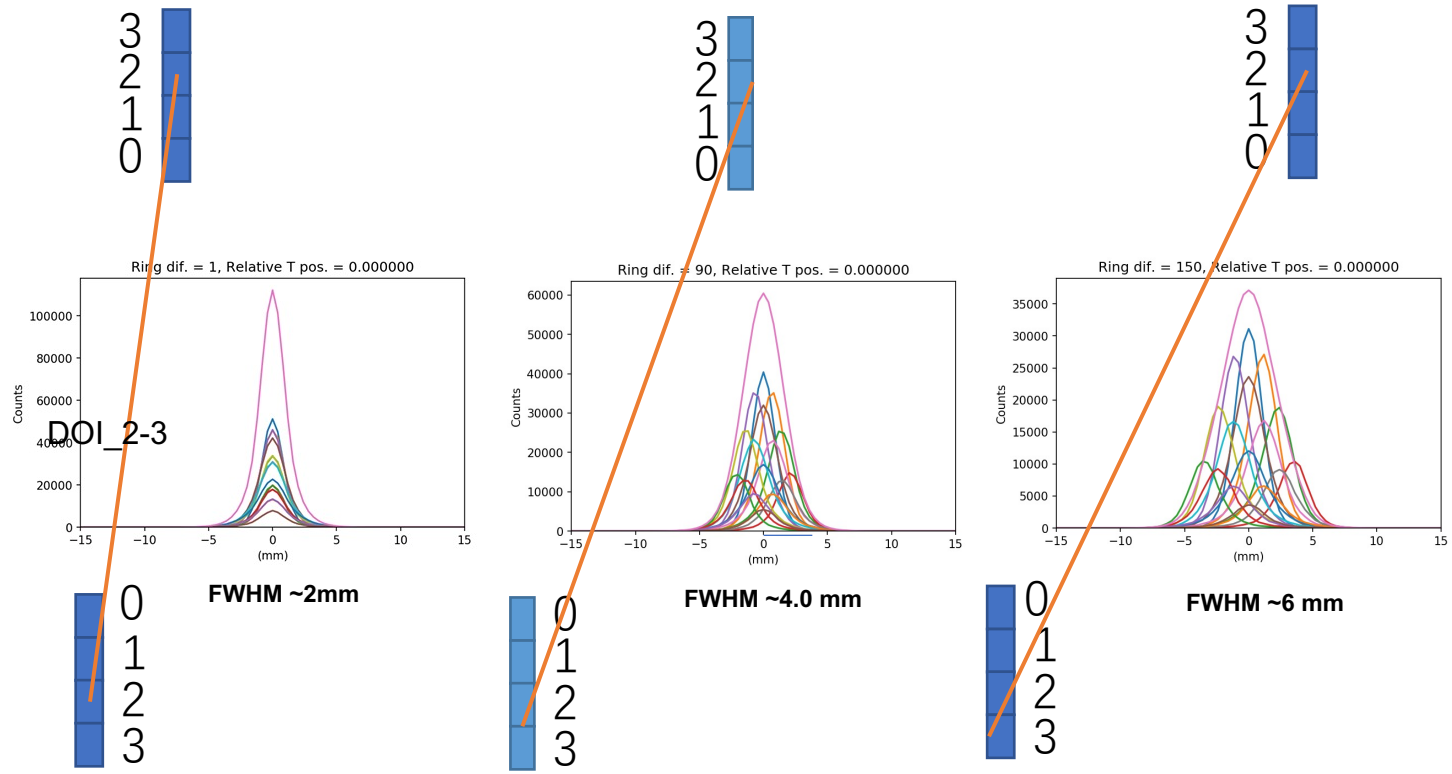
Matuskey et al, *Ann Neurol, 2020*

What have we have learned from the EXPLORER?

- Depth-of-interaction (DOI) is essential for high-resolution imaging

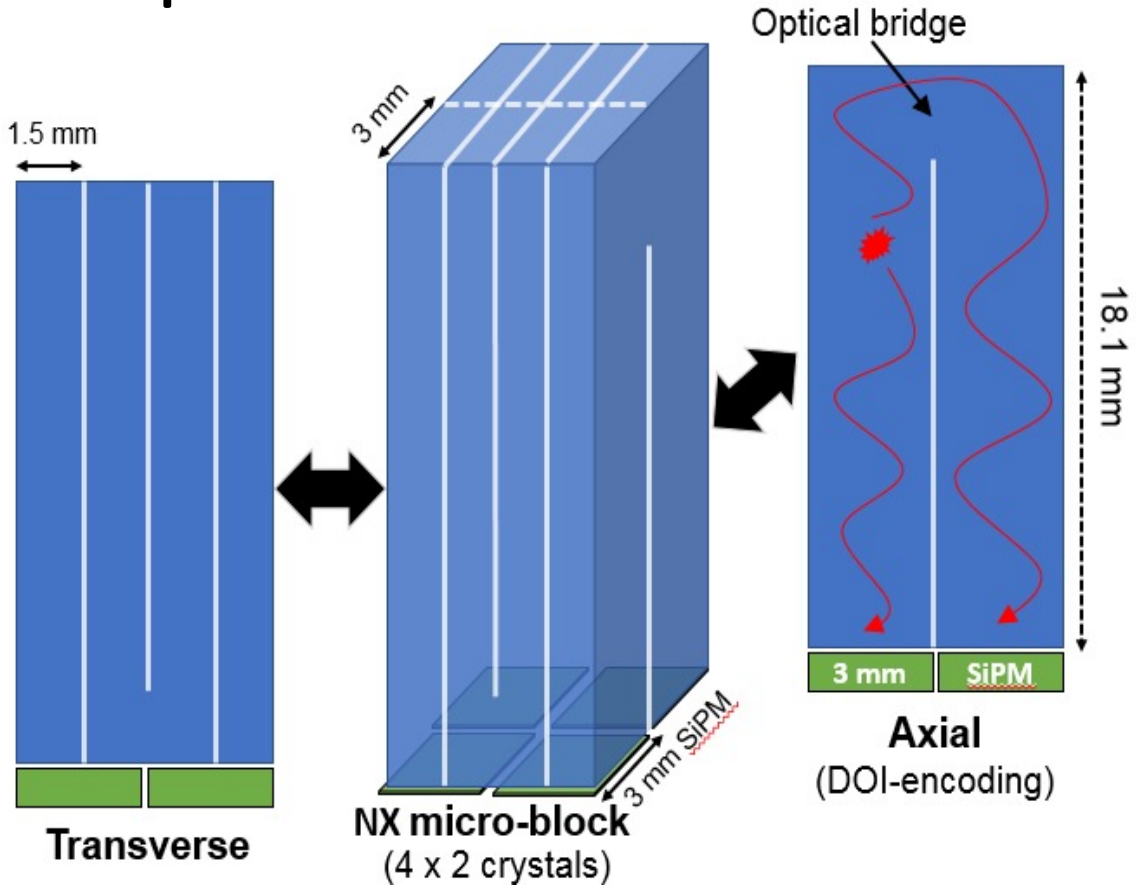


DOI is essential for transverse and axial resolution



Monte Carlo PSF modeling with / without DOI

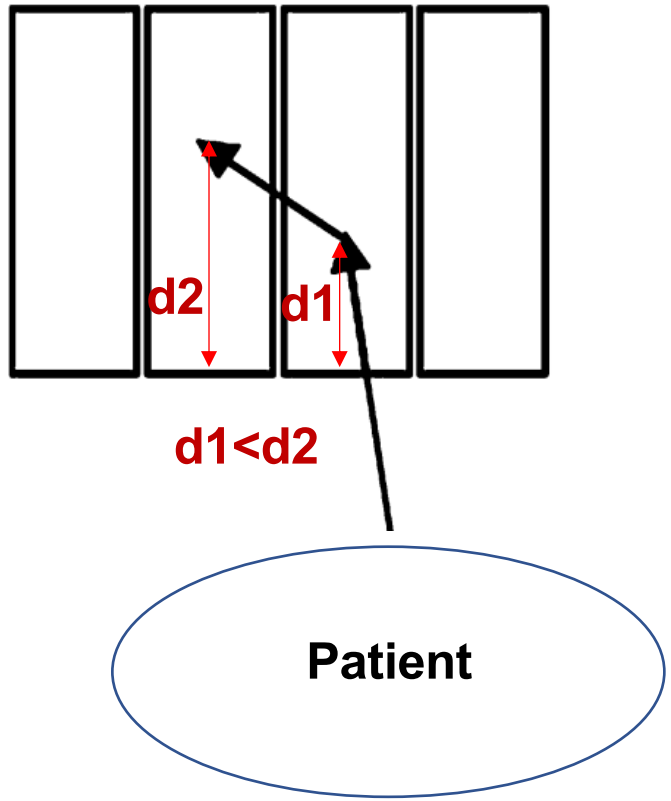
Depth-of-Interaction and Inter-Crystal Scatter detection



NX micro-block detector

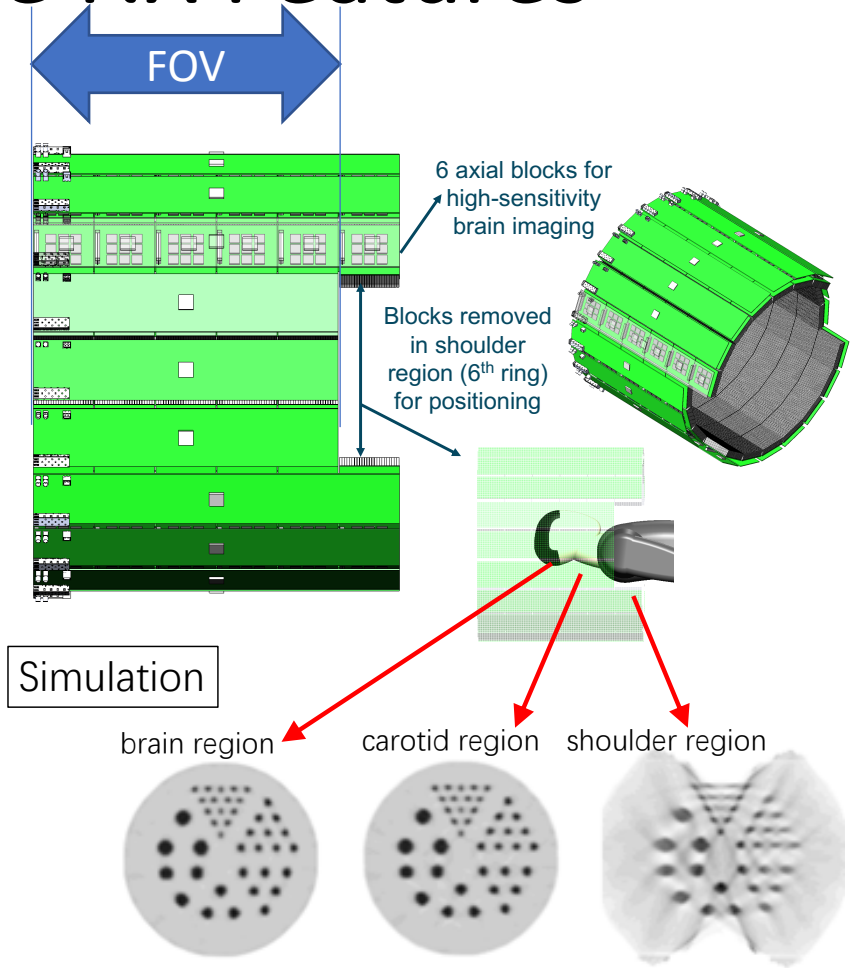
- Single-end readout
- Easy to manufacture / low-cost
- Good DOI resolution < 4mm

Inter-crystal scatter (ICS) up to 30%



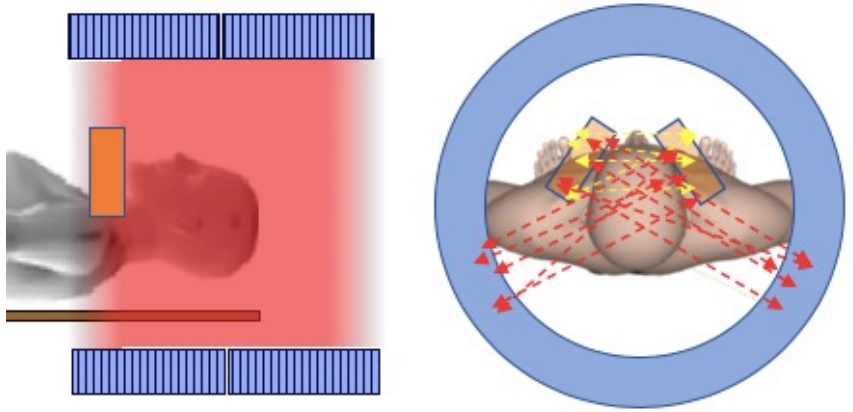
Novel Reconstruction to use Unique NX Features

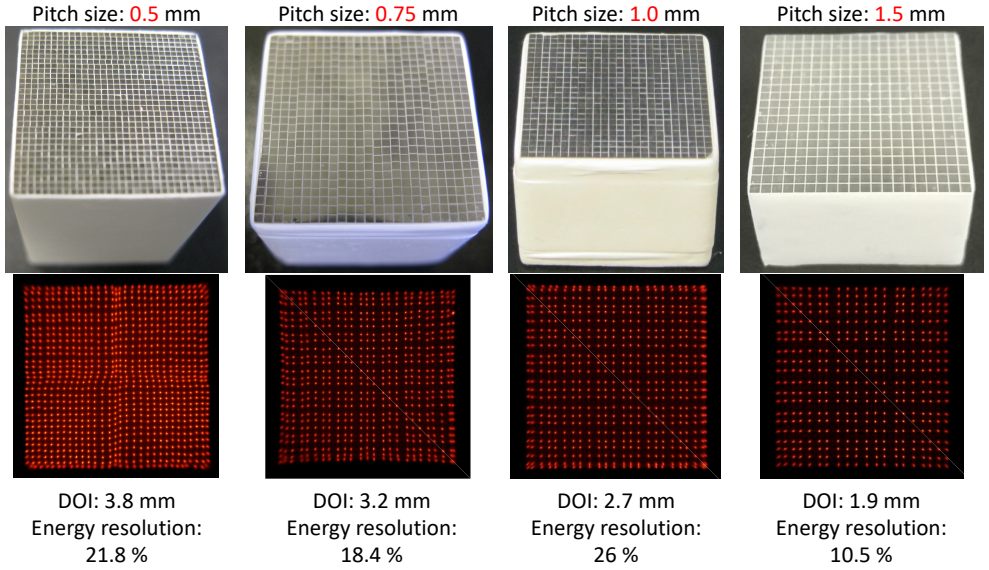
- Depth of interaction (<4mm DOI resolution)
  - Uniform resolution in space
  - Improve axial resolution by using DOI-induced oversampling
- Shoulder cutouts
  - Take advantage of the added oblique LORs without introducing artifacts into FOV
  - Deep learning can be used to reduce limited angle artifact when necessary
- With a huge number of counts, push spatial resolution by accurately modeling the physics:
  - Positron range
  - Photon-pair acollinearity
  - Inter-crystal scatter



Ultra-high resolution insert

- Open platform for zoom-in or multi-organ imaging
- Improve resolution and sensitivity for imaging carotid artery
- Image reconstruction using all events:
  - NX coincidences
  - NX-insert coincidences (higher res.)
  - Insert-insert coincidences (highest res.)
- Goal: high-resolution images without limited angle artifacts



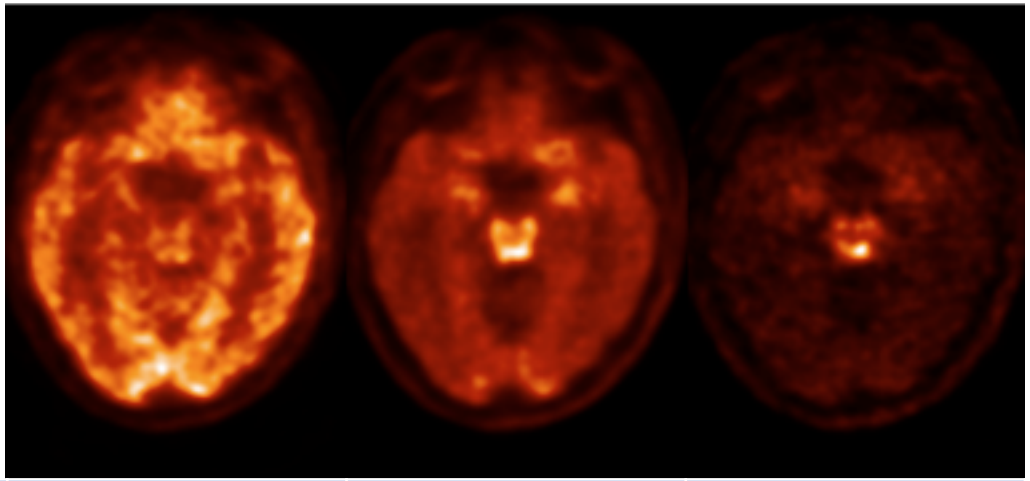


Challenges

- Sensitivity and noise
- Image resolution
- **Tracer kinetics**
- Human Issues
  - Input Function
  - Head Motion

Radioactivity Patterns Change with Time

- Tracer: ^{11}C-AFM
- Target: Serotonin Transporter
- Analog of Selective Serotonin Reuptake Inhibitors (SSRI)
  - Prozac, Zoloft,…



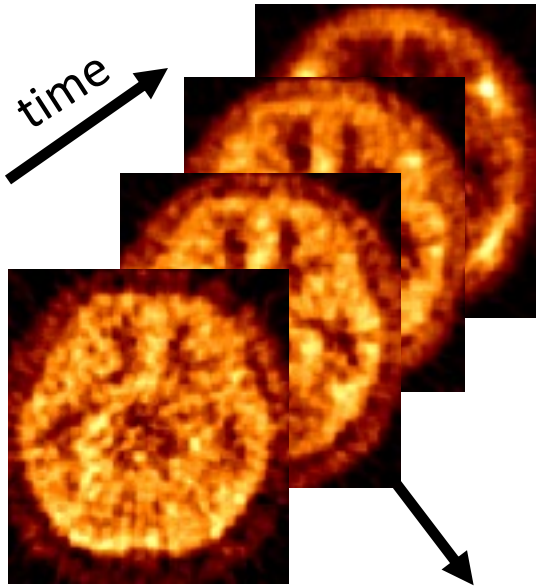
Time (min)	0-10	40-60	90-120
Flow information	+++	++	+
SSRI information	+	++	+++

- Time-varying distributions
- Is there a best single time to scan?
- What can we do with dynamic data?
- How to analyze this?

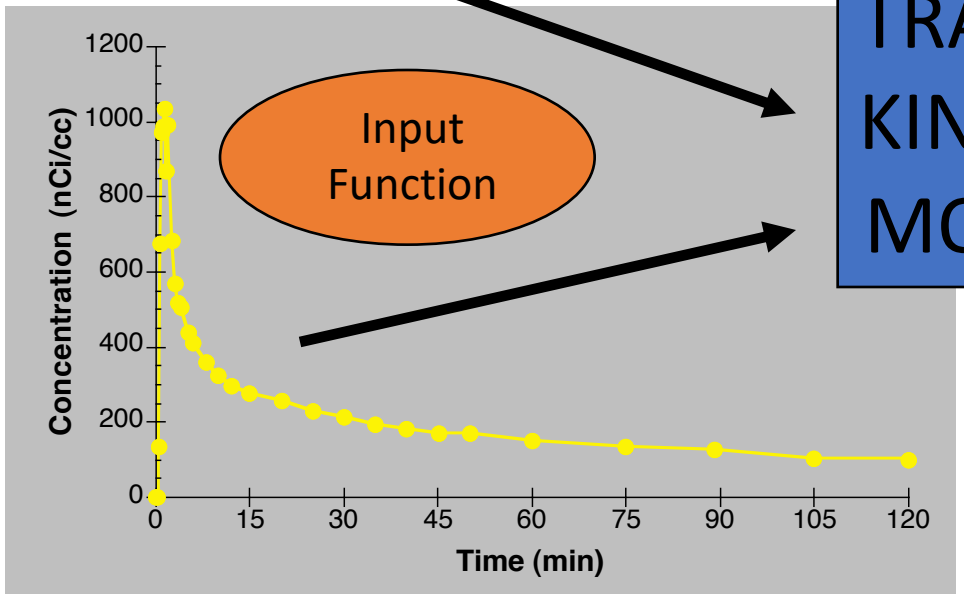
PET Modeling

Tissue Radioactivity

time

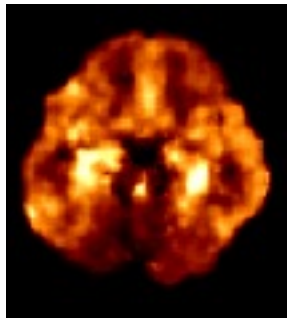


Assumptions

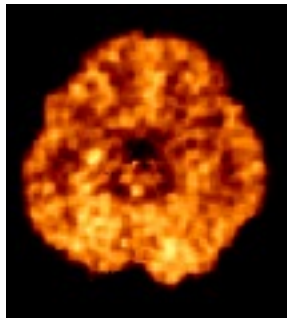


TRACER KINETIC MODEL

Quantitative Physiological Images



Binding Potential



Delivery (Flow)

Goals of PET Modeling

- Understand the relationship between the tissue measurements and the underlying physiology (blood flow, metabolism, etc.)
- Account for the effects of tracer availability (input function).
- Determine what parameters can be measured
- Devise study methodology
- Prove that the method measures the parameter(s) of interest.
- Verify that the method is not influenced by other parameters.
- Produce images of physiological parameters (parametric images)
- Produce a simple and accurate patient protocol.

Amyloid Example Where Modeling Helps

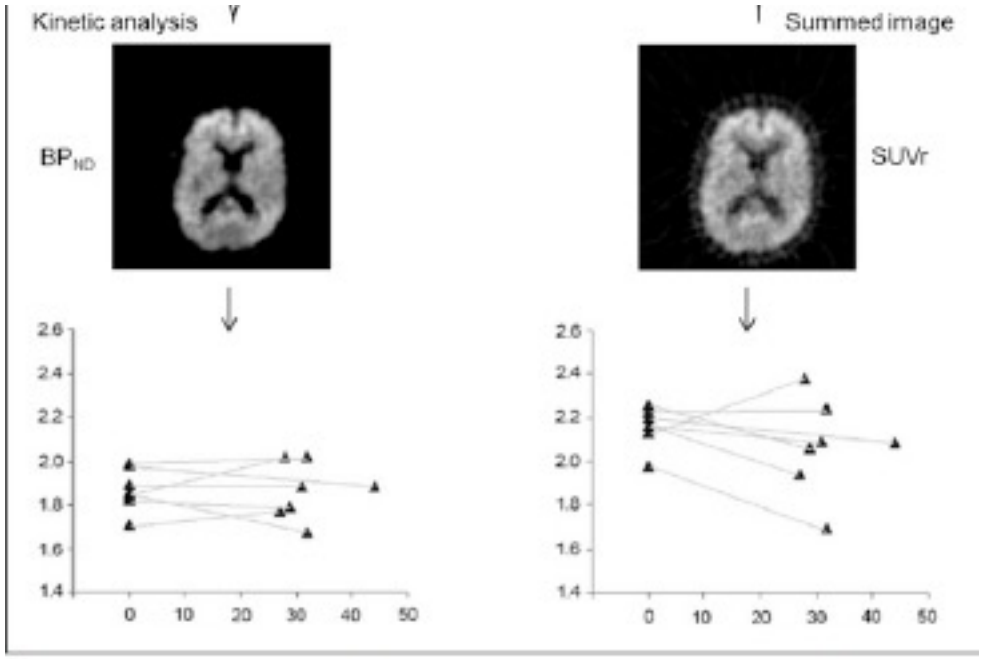


FIGURE 6. BP_{ND} and SUVr (60–90 min after injection) for ^{11}C-Pittsburgh compound B scans of Alzheimer disease patients at 2 time points 2–4 y apart (horizontal axes represent months after baseline scan). Patients did not receive antiamyloid therapy during interval between scans. SUVr shows a small but significant counterintuitive decrease in amyloid load, whereas BP_{ND} remains unchanged.

- Test-retest study
- Less variability in modeling results

Forward to the Past: The Case for Quantitative PET Imaging

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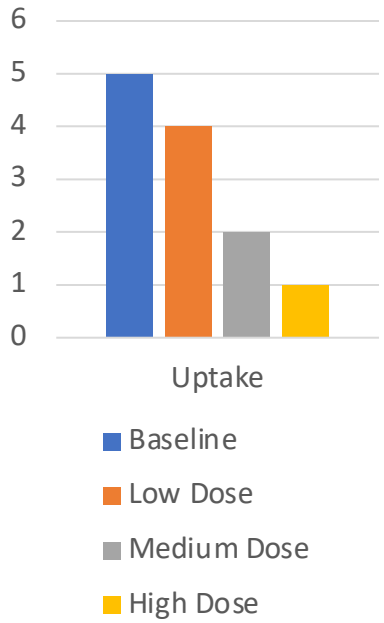
J Nucl Med 2017; 58:1019–1024
DOI: 10.2967/jnumed.116.188029

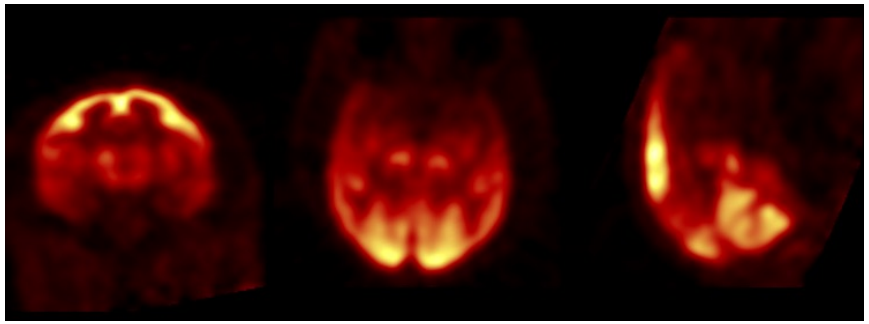
Studying Drug Effects: Input Functions



- Drug and tracer target the same site
- We expect dose-dependent reductions in specific tracer binding following administration of a competing drug
- Typically, blocking drugs reduce tracer in tissue, and increase tracer in the blood
  - Increased bioavailability (the input function)
  - Increased nonspecific uptake
- Net effect depends on relative magnitude of specific and non-specific uptake, and tracer's kinetics

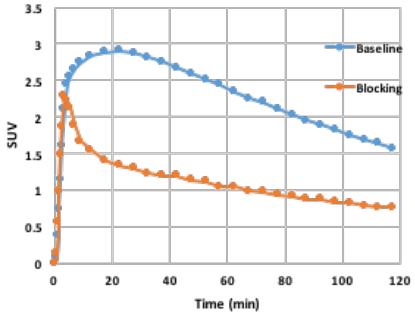
Brain Enzyme Inhibitor Study

Differences Among Brain Regions Without Modeling

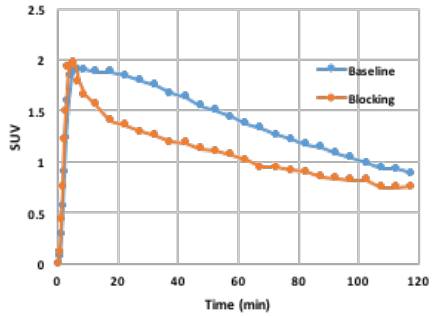


SUV

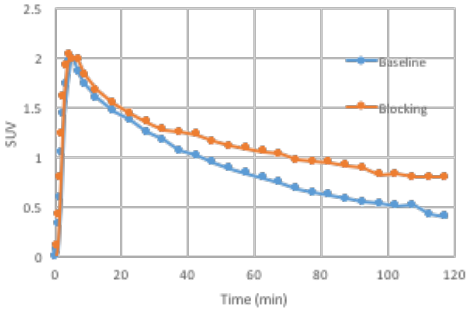
Occipital cortex



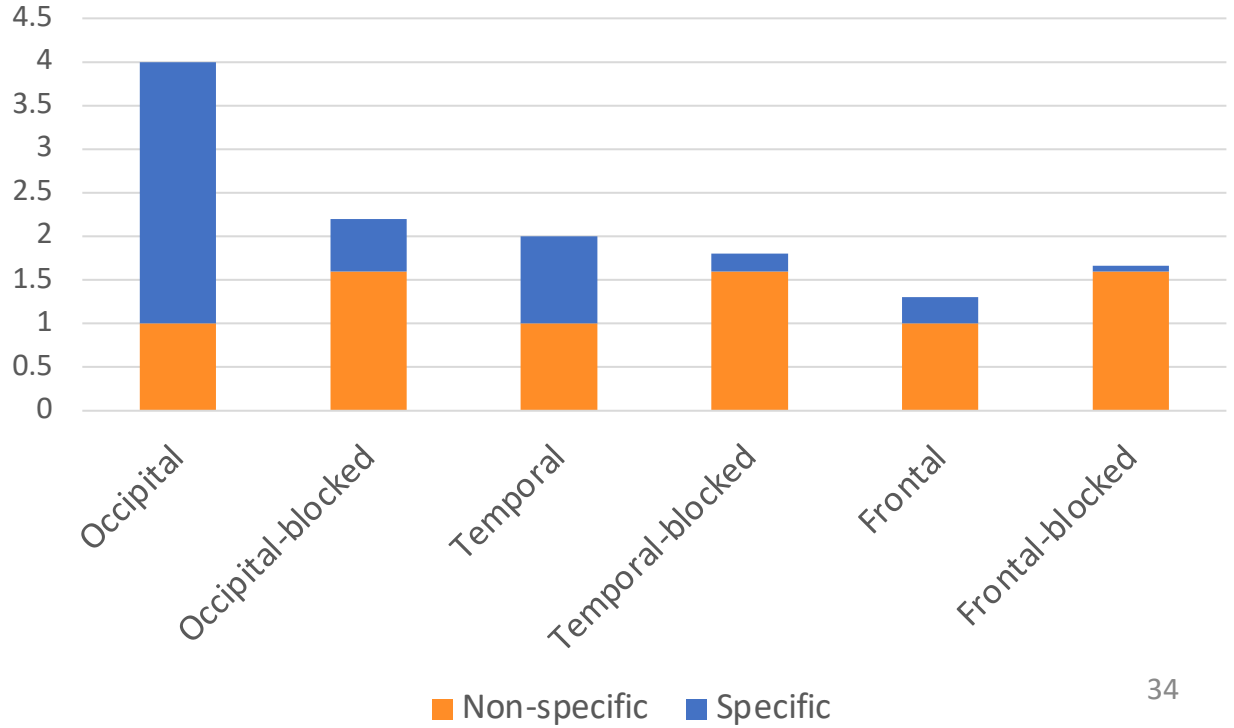
Temporal cortex



Frontal cortex



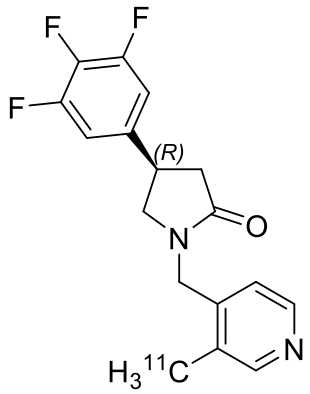
Baseline
Blocking

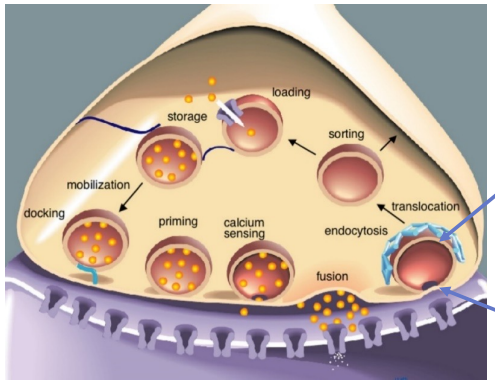


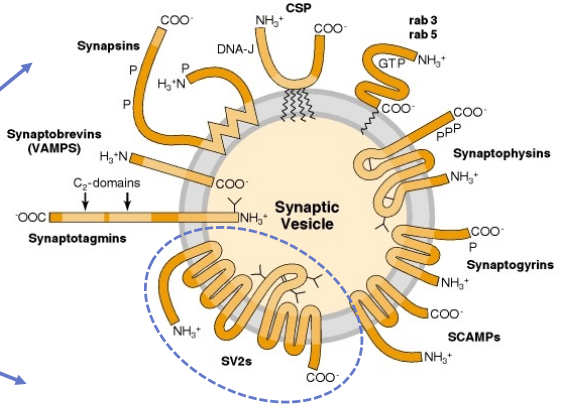
- Occipital: large decrease
- Temporal: small decrease
- Frontal: small increase!

- ??

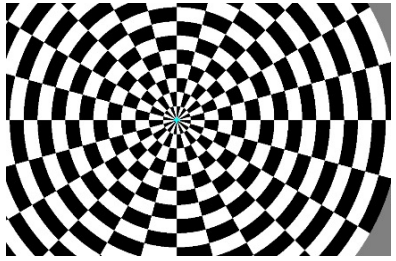
Brain Activation – Separating Blood Flow from Synaptic Density





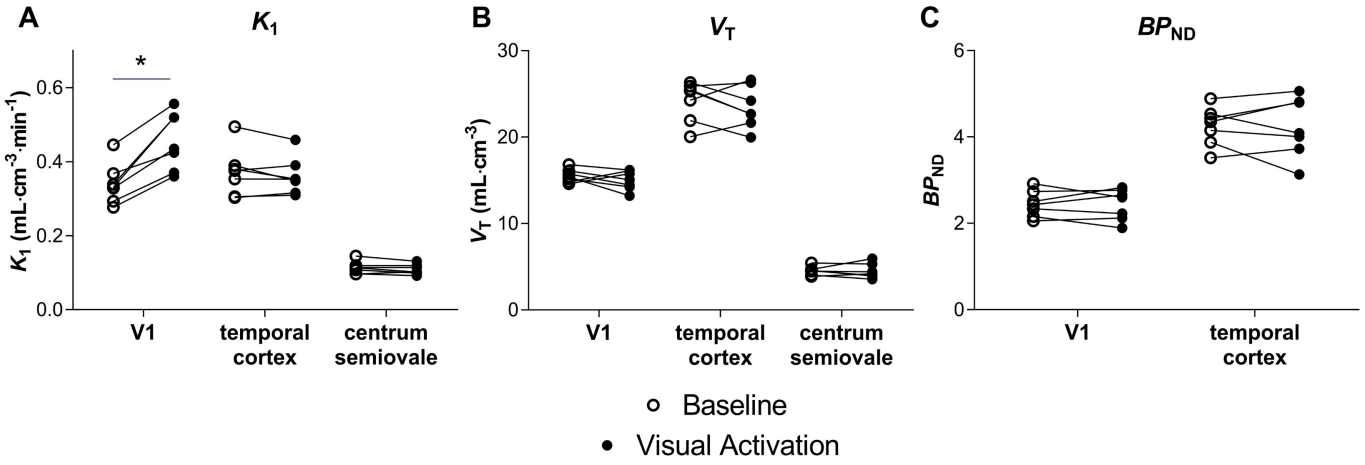


- 7 healthy subjects
- 2 [^{11}C]UCB-J scans
- 60 min. baseline
- 60 min. with continuous intermittent visual activation
- 8Hz flickering radial checkerboard



- Is synaptic quantification affected by changes in blood flow (tracer delivery)?

Results



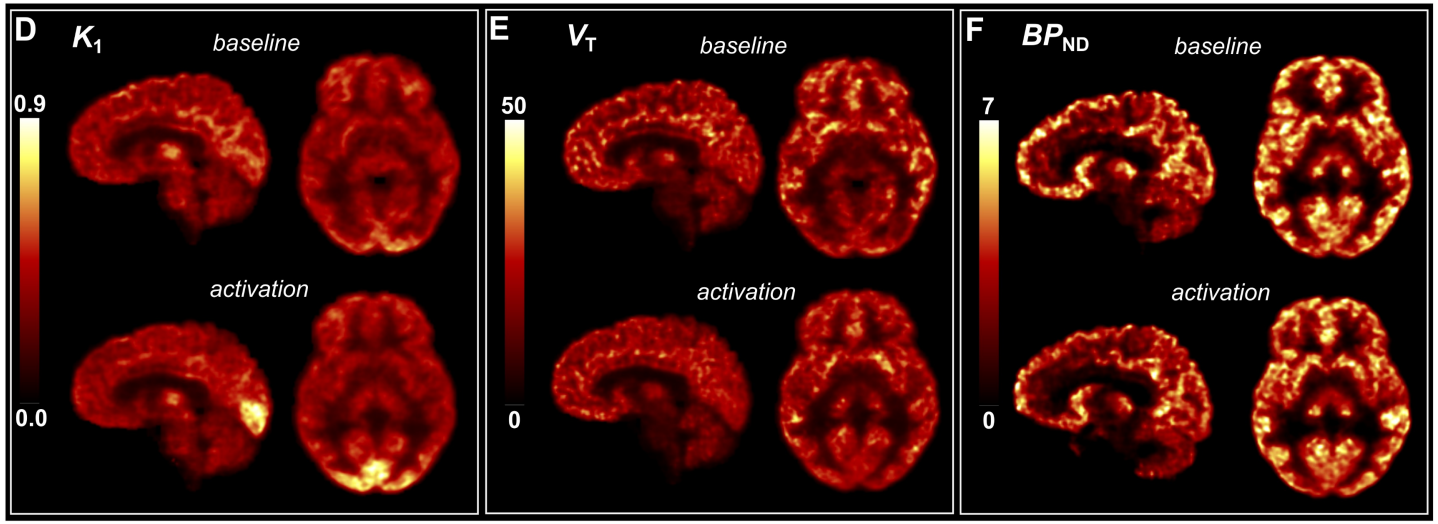


Fig. 4

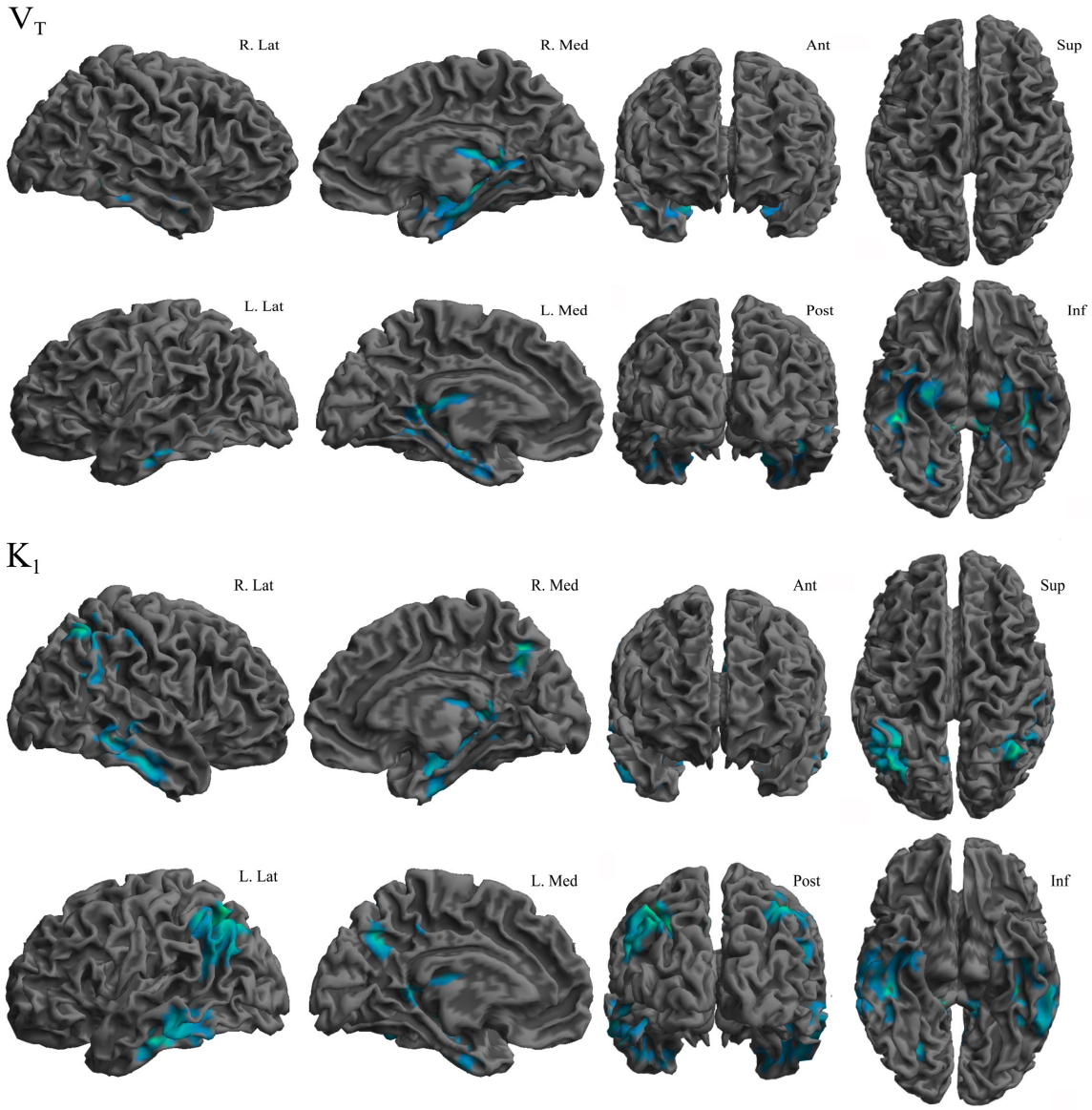
- 35% increase in K1 in primary visual cortex.
- **No change in V_T or BP_{ND}.**
- **Could not separate the 2 effects without kinetic modeling**
- **^{11}C-UCB-J binding is a stable *in vivo* measure of SV2A density despite increased vesicle release.**

Smart et al, JCBFM, 2020

Synaptic Density in Alzheimer's Disease
Separating blood flow from binding

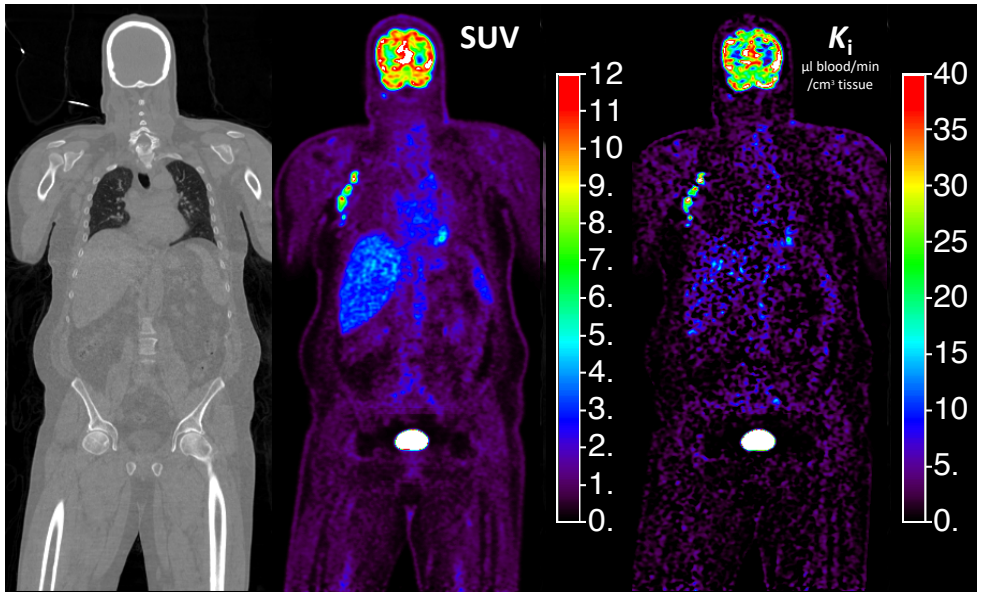
V_T

K_1



Tradeoffs of PET Modeling Studies

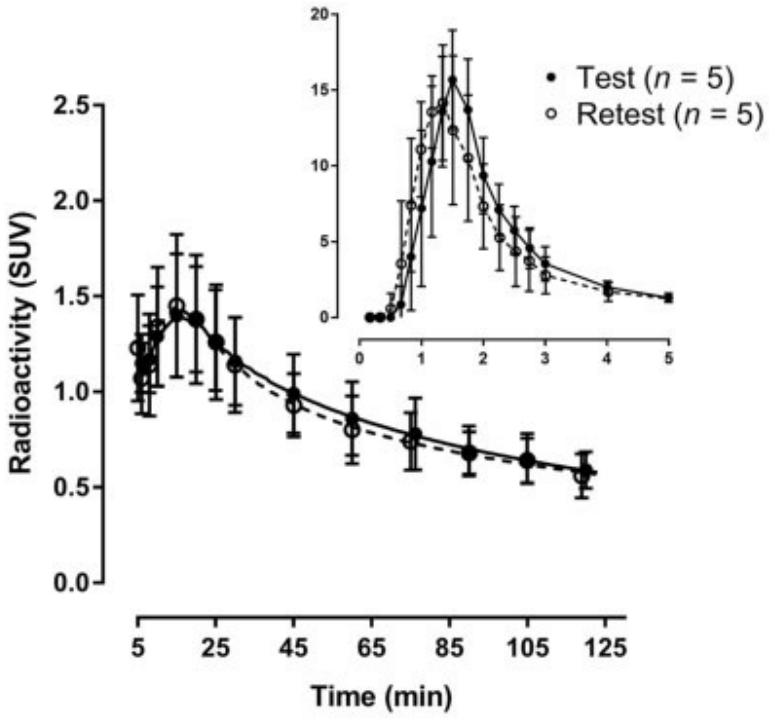
- Absolute quantitative outcome measures vs. relative, sometimes ad hoc indices
  - What is the biological or clinical question?
- Typical modeling results have higher noise than radioactivity images
- Scan durations are longer
  - Can be partially compensated with higher sensitivity, larger regions, or lower spatial resolution
- More complex and expensive
- Can (sometimes) provide more specific information or avoid misinterpretation of results

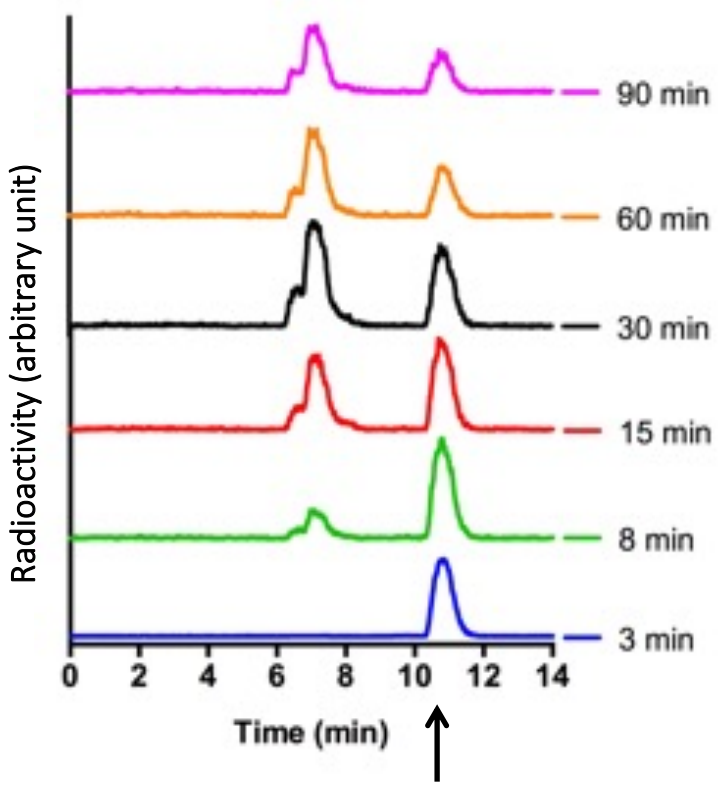


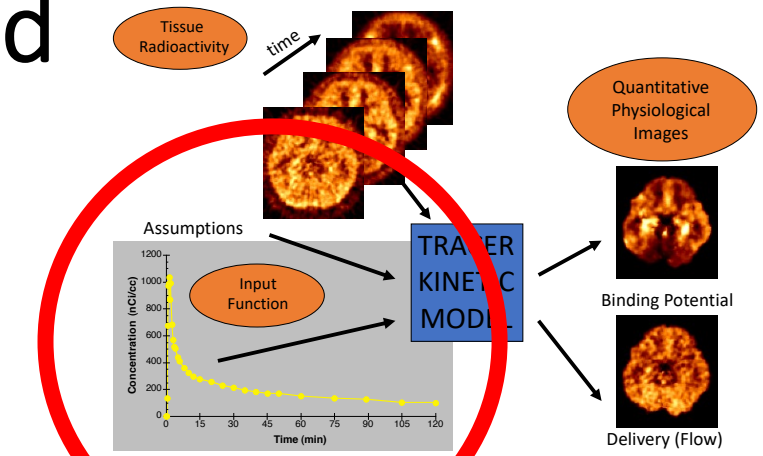
Challenges

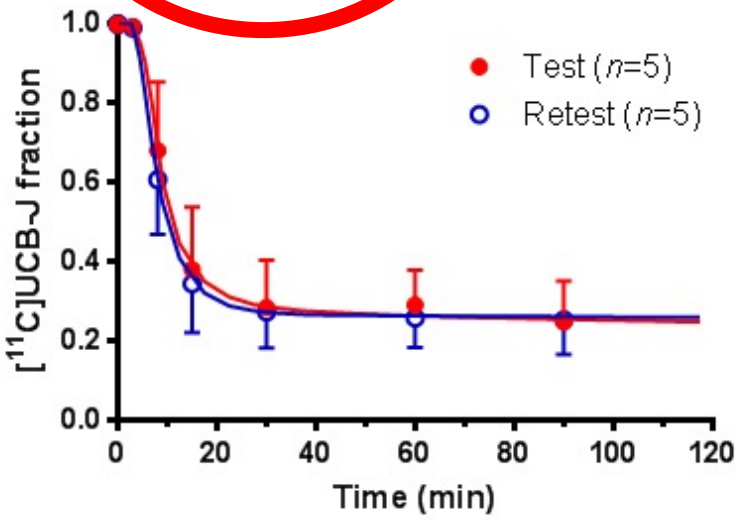
- Sensitivity and noise
- Image resolution
- Tracer kinetics
- **Human Issues**
  - Input Function
  - Head Motion

Human Arterial Input Function and Radiolabeled Metabolites

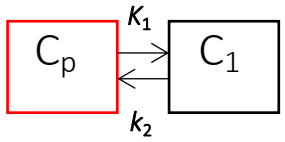


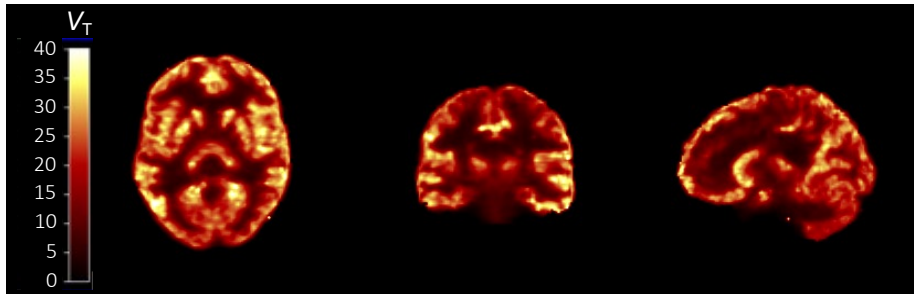






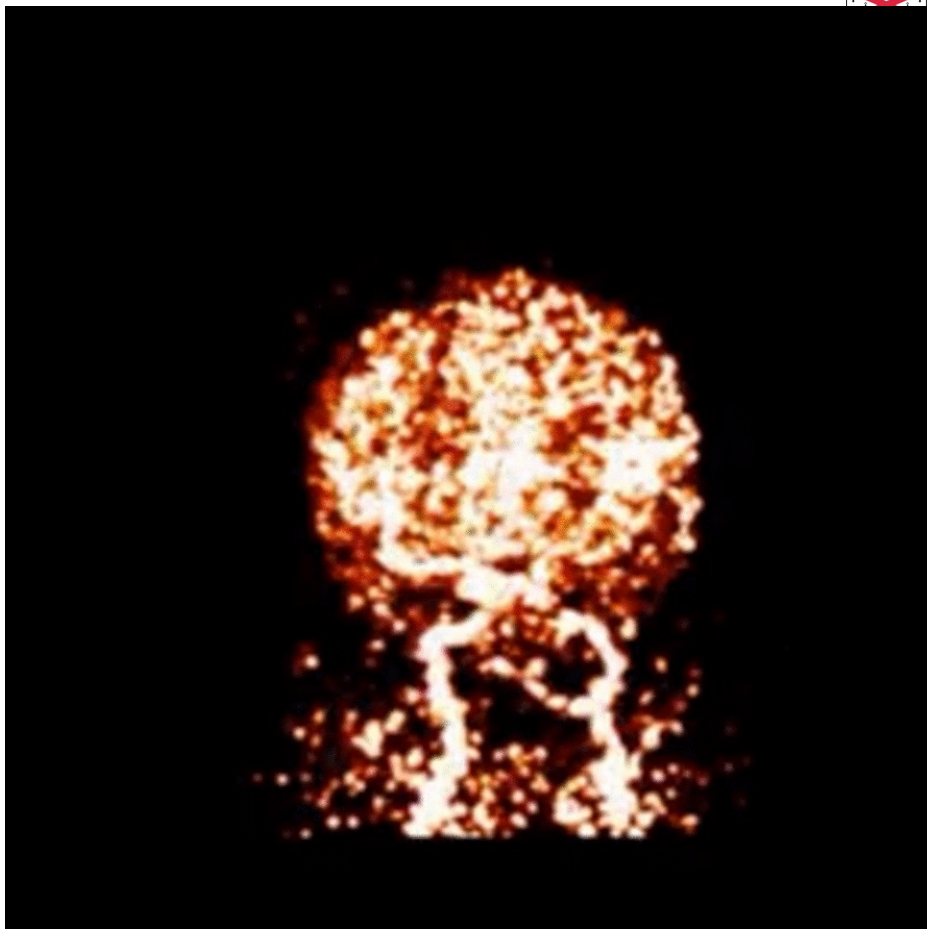
1TC





Carotid Artery Imaging

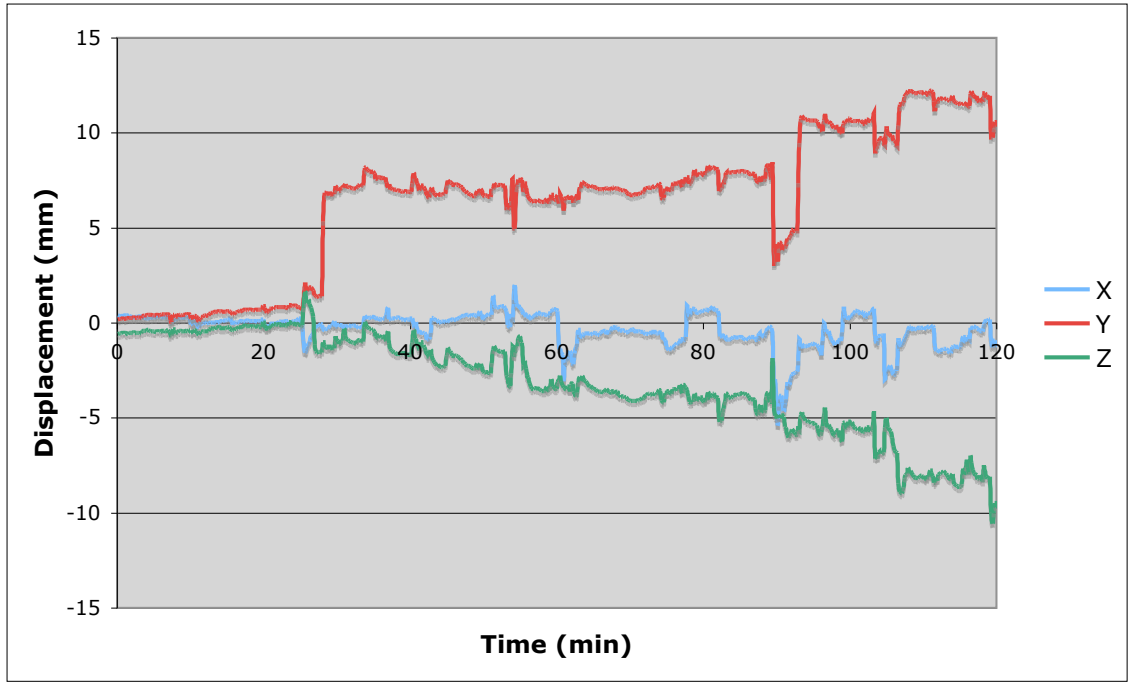
- Accurate input function for kinetic analysis
- Arterial sampling is invasive and less desirable
- Image-derived input function is more desirable, but we only have carotid artery in the FOV
- Challenges:
  - Small size of the carotid arteries
  - Different tracers
  - Dynamic range of contrast
- Validation of the carotid artery input function
  - Validation using phantoms (digital or physical phantoms)
  - Validation using human data (arterial samples)
  - Validation of different tracer uptakes

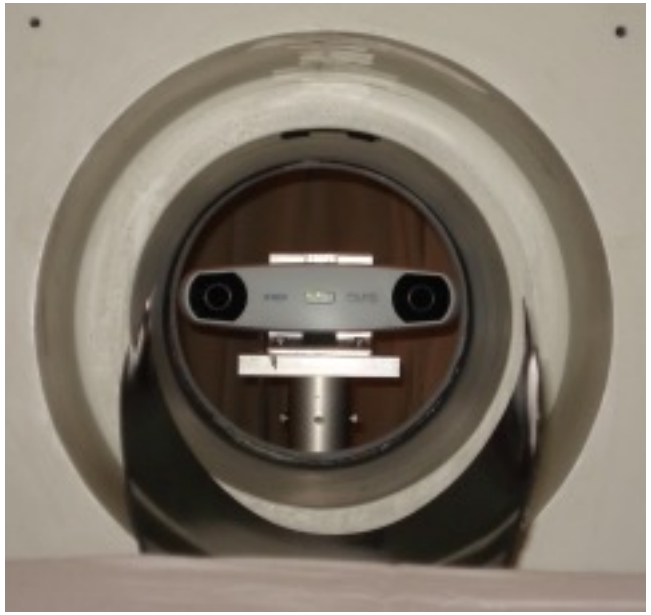


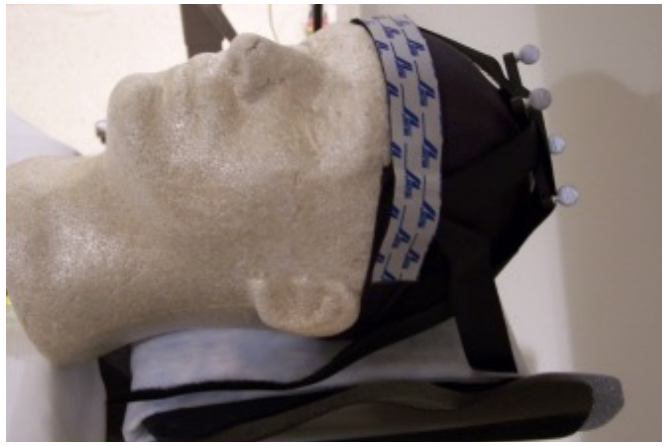
Tracer: ^{11}C-LSN3172176
Target : Muscarinic (M_1) Receptor
Image : MIP of summed activity (0 – 1 min)
Scanner: HRRT

HRRT Online Motion Correction

- Vicra
- Target on subject's head
- Provides motion information at up to 20 measurements per sec
- Put each event back where it belongs



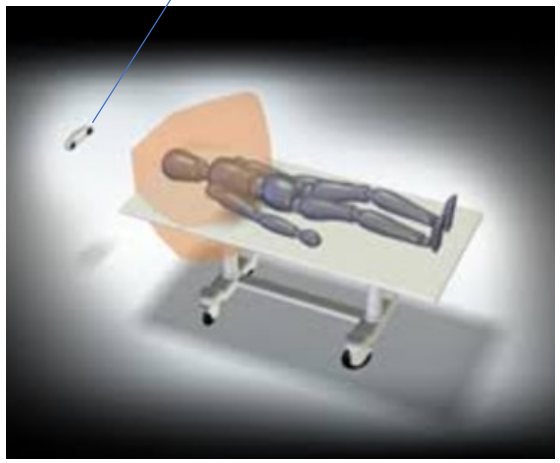




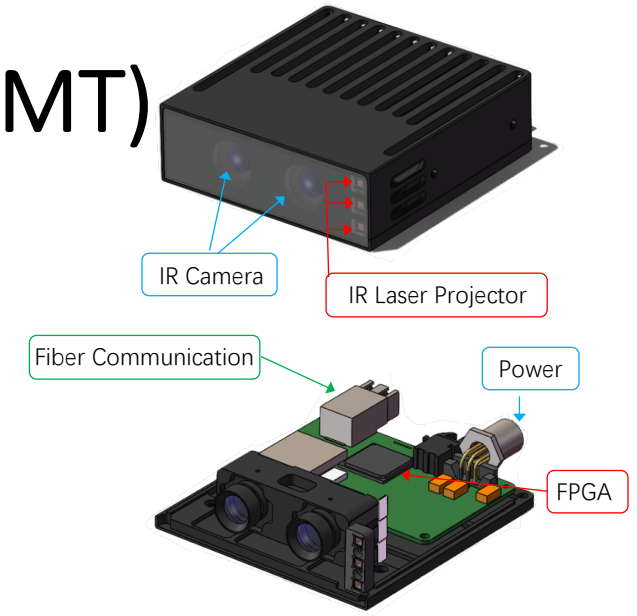
Head motion correction in PET

- **Hardware**
  - Marker-based
    - Vicra, >4000 scans at Yale, continuous, accurate
    - Subjective to light reflector mounting issue or positioning
  - Markerless
    - Stereo camera-based, Yale has a proto-type
    - May be subject to face expression and hair
- **Multi acquisition frame (MAF): "registration among predefined frames"**
  - Registering predefined frames with attenuation correction (AC)
    - Easy to apply, but suffer both AC mismatch artifacts and intra-frame motion
  - Registering predefined frames *without* AC
    - Extra recons required, but still suffers intra-frame motion
- **Data-driven**
  - List-mode based motion detection + MAF
    - Detection using Centroid-Of-Distribution (Yale) or Principal Component Analysis
  - Analytical continuous motion estimation
    - Proto-type
  - Deep-learning based continuous motion estimation
    - Yale is leveraging the >4000 Vicra as gold-standard to develop neural network to estimate head motion

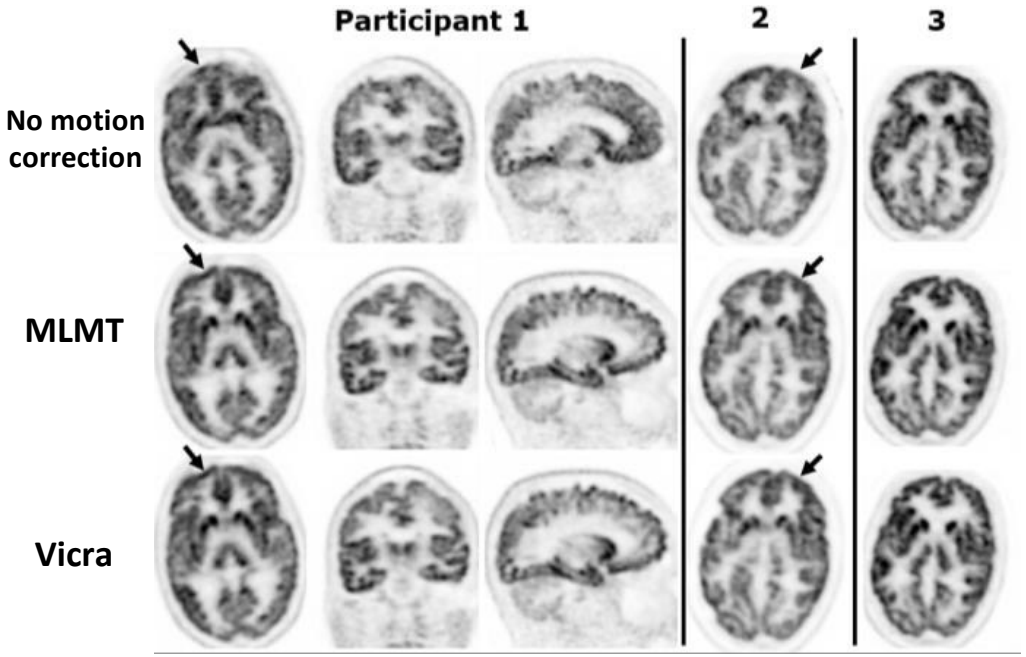
Polaris Vicra
(Yale uses it on HRRT and Siemens mCT)



Real-time Markerless Motion Tracking (MLMT) Stereovision with Structured Light

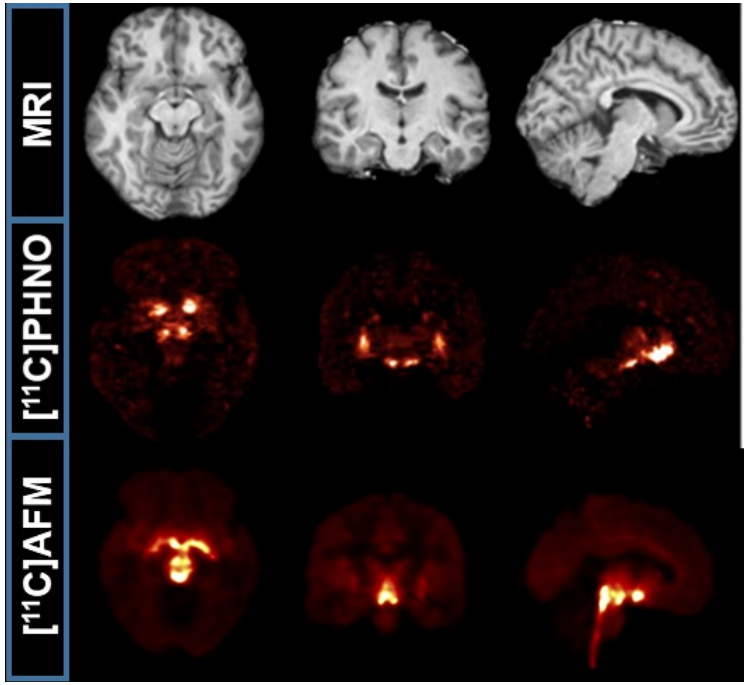


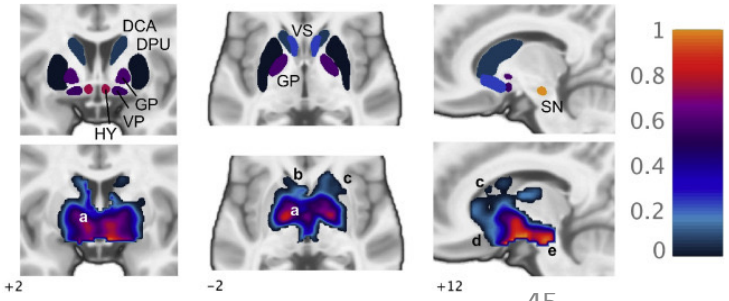
- Top-class precision enabled by unique WindMill™ structured light technology
- Independent of ambient light with advanced laser technology
- Real-time streaming of 3D point clouds provided by novel fiber communication design and state-of-the-art processor
- **Ongoing human testing on Siemens mCT**
  - "Head-to-head" vs. Vicra



Pushing the envelope: Small brain nuclei with slow kinetics

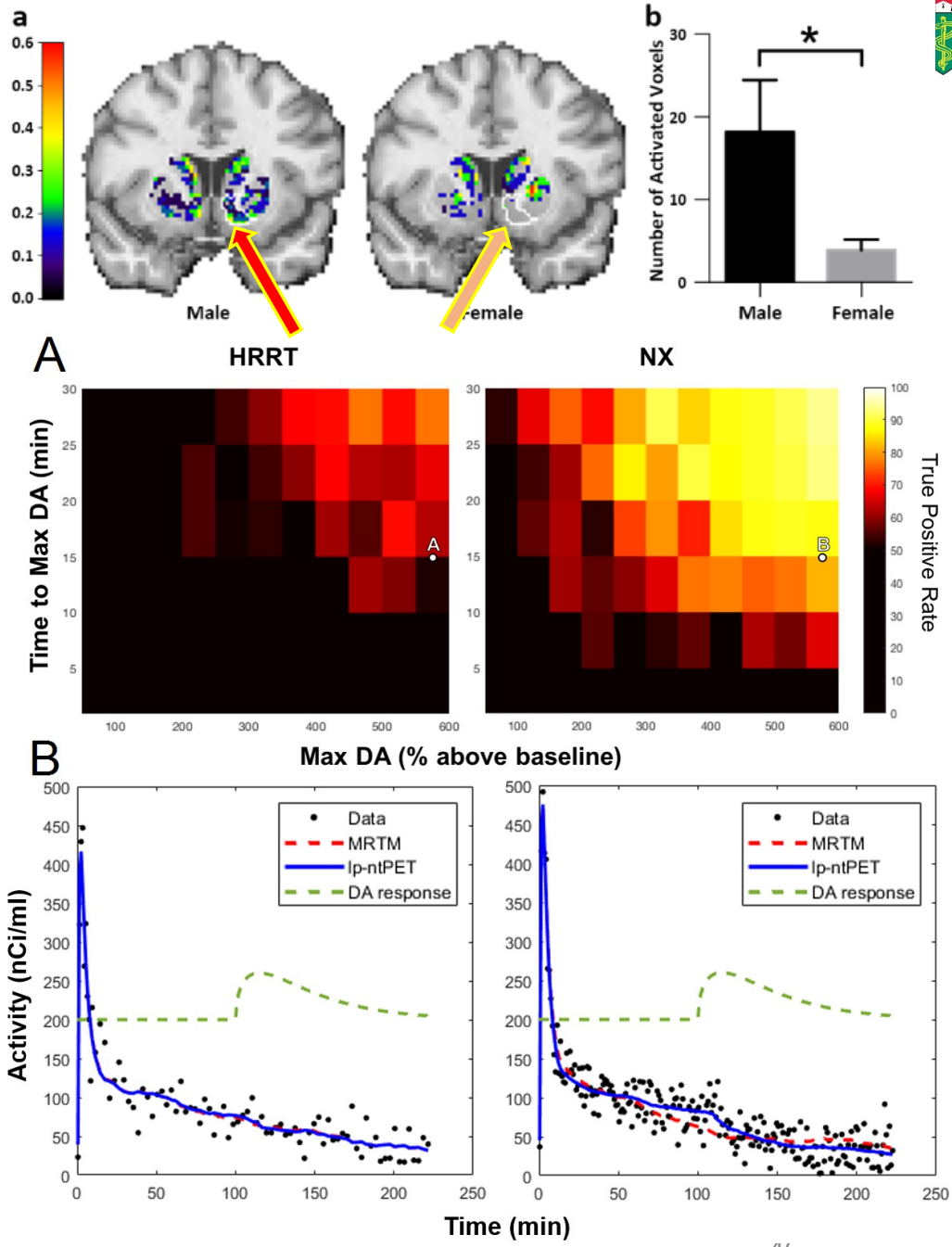
- Small midbrain nuclei (raphe nuclei, substantia nigra, ventral tegmental area)
- ^{11}C-PHNO (D_2/D_3 receptors) BP_{ND} in SN and VTA
- ^{11}C-AFM (serotonin transporters) BP_{ND} in the raphe
- Current PET systems have poor reliability in these regions
  - ^{11}C-PHNO binding potential (BP_{ND}) in SN has 20% reproducibility.



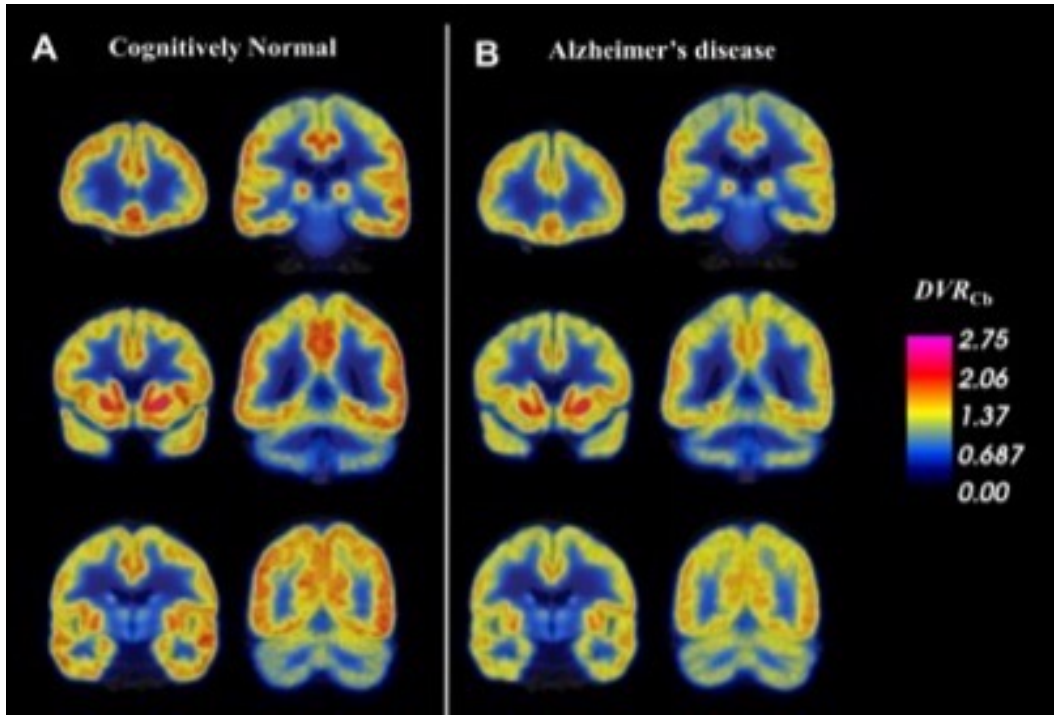


Pushing the envelope: Dopamine release in frontal cortex with a stress task

- We have previously measured smoking-induced dopamine release in the striatum with dynamic modeling: lpntPET
- We propose to do the same in the cortex with a stress task
  - Small DA response in a large (?) region
- Simulations show the increased NX count sensitivity will dramatically increase detection sensitivity to DA dynamics



Pushing the envelope in Neuropsychiatric Disorders

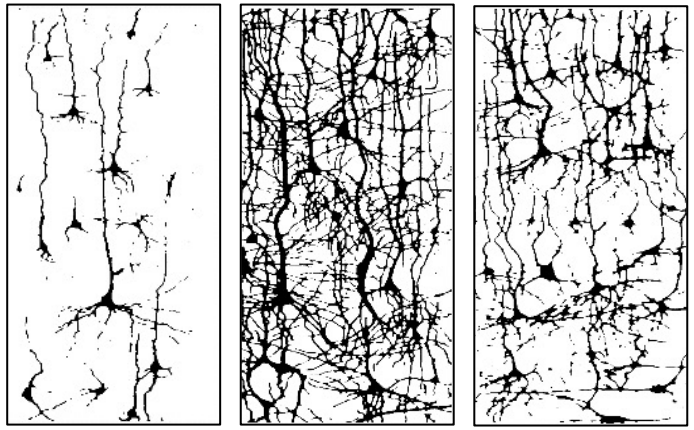


- Earliest stage of neurodegeneration in AD and other dementias
  - Entorhinal cortex
- Earliest stage in Parkinson's disease
  - Substantia nigra
- Smaller brain nuclei
  - Locus coeruleus
- Measure protein targets within layers of cerebral cortex
  - ~ 2 mm wide

Research Scanning in Adolescents?

- Can we use our synaptic marker ^{11}C-UCB-J in adolescents (without sedation):
  - Autism
  - Schizophrenia
- One tenth the radioactive dose limit
- Parental consent
- Can we do the scan for the equivalent radiation dose of a “cross-country” flight?

Pruning – Autism & Schizophrenia



At Birth 6 Years Old 14 Years Old

- How to get there?
  - Great sensitivity
  - Great head motion correction
  - Great algorithms (Direct reconstruction, Deep learning)

Summary

- PET imaging provides a superb window into normal biology and pathophysiology in humans and animals
- Brain PET has been a particularly fertile area of development of novel tools and *in vivo* assays through the combination of innovative radiopharmaceuticals and quantification algorithms
- Improved hardware (higher sensitivity and resolution) always helps
- Cool, elegant algorithms can too, but they should be validated for each imaging situation and radiopharmaceutical
- Good basic science can translate into powerful and clinically relevant imaging methods
- Next generation of instrumentation and algorithms will open many new and exciting windows on brain function and disease.

Acknowledgments