The future of (brain) PET – opportunities for disorders of consciousness

Tommaso Volpi
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[^{18}F]FDG PET Workshop

02/25/2026

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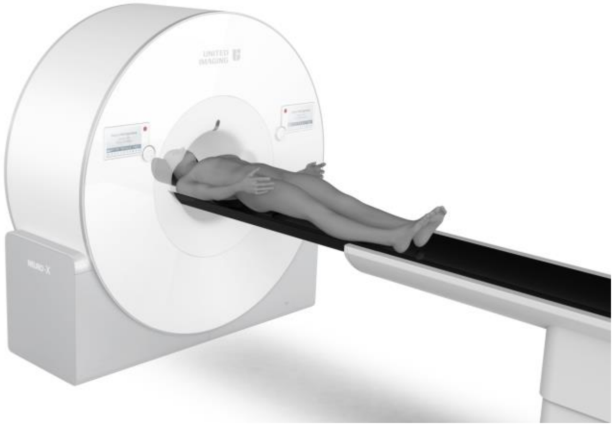
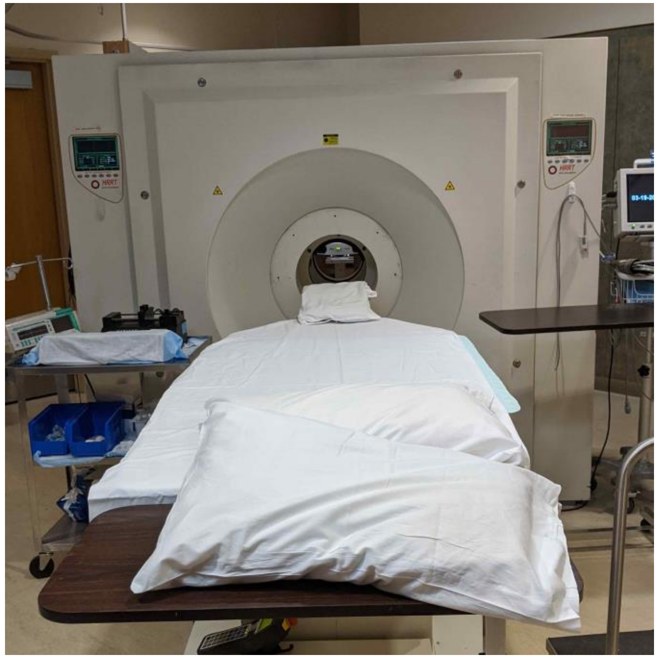
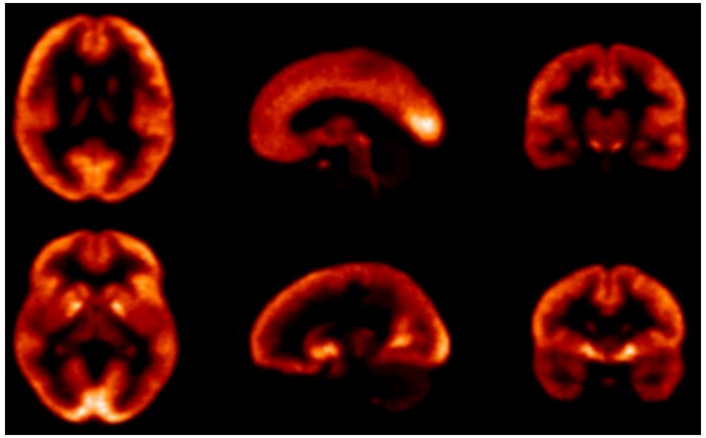
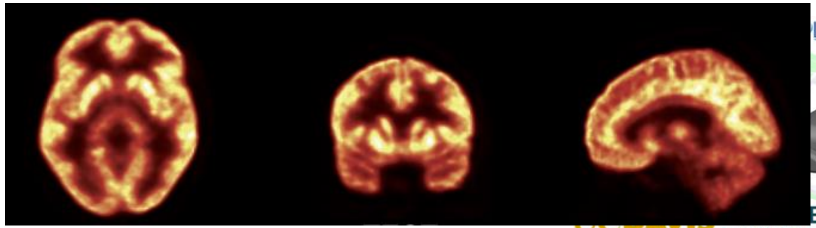


HRRT @ Yale PET Center

- State-of-the-art for brain PET
- Design > 20 years old
- >5000 human studies
- ~50 different tracers
- 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







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What have we learned 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

- We rarely can produce images at the system's best possible **spatial resolution**

- People **move**!
  - High resolution is not meaningful without great motion correction

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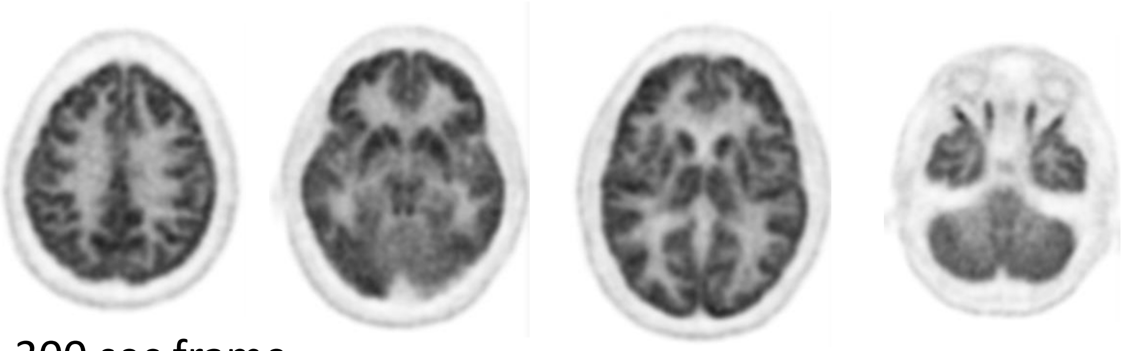
Total-body scanner uEXPLORER at UC Davis

2019

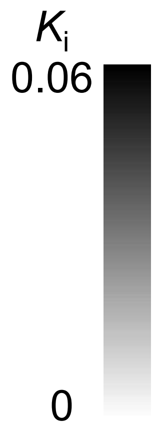
High **sensitivity** enables high signal-to-noise ratio for short scan durations

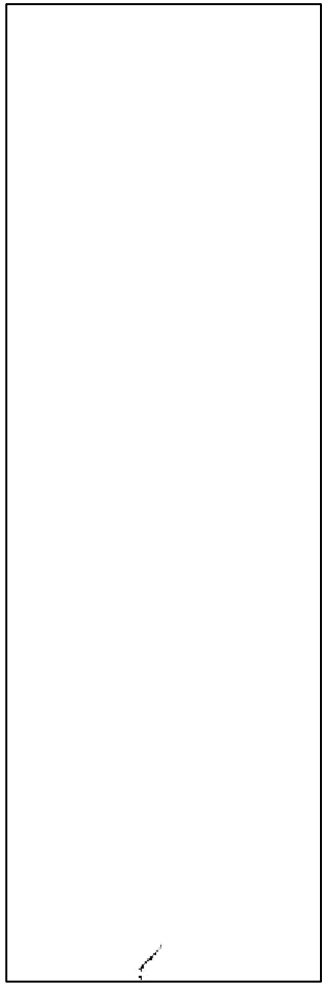


300 sec frame

Enables sub-second **temporal resolution** of the arterial input function and bolus arrival times and transit times

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





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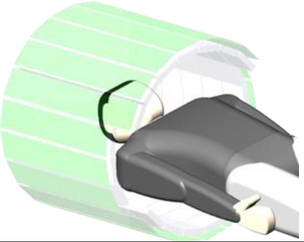

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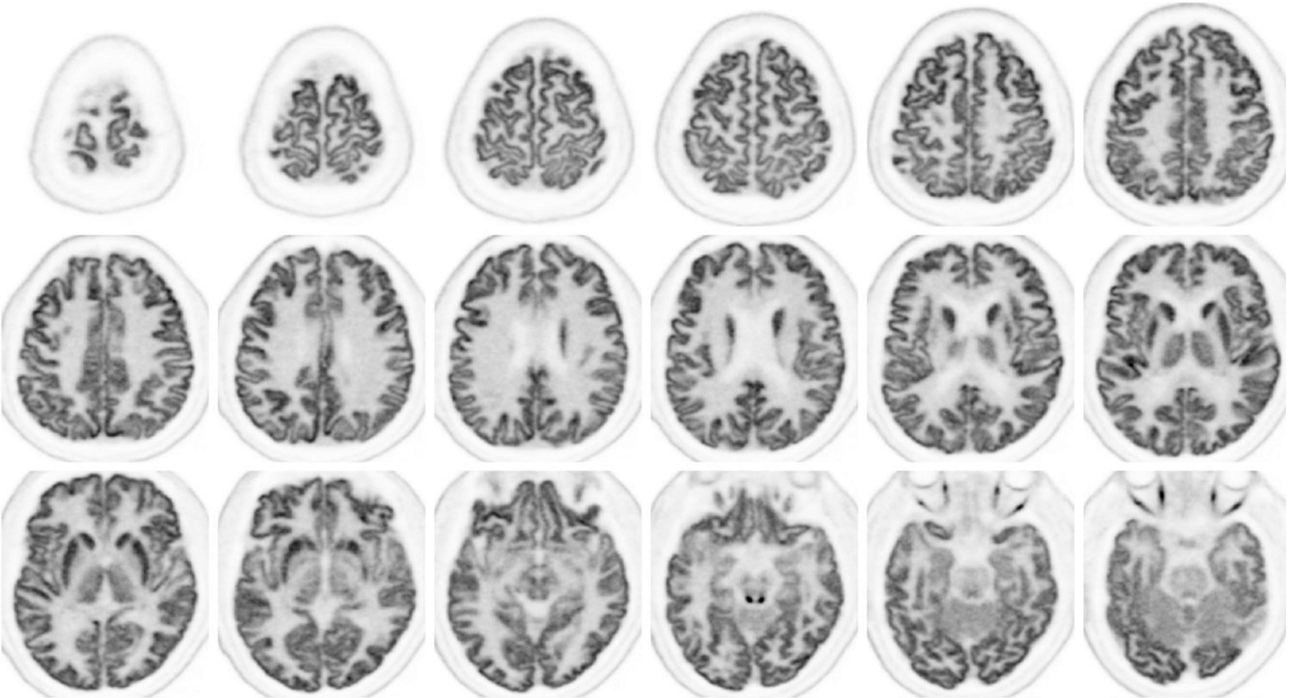
A fully-functional well-characterized commercially-available brain PET system



Key Features:

- At least **10-fold higher effective sensitivity** (TOF < 270 ps, axial FOV 50 cm + shoulder cut-out) than the HRRT
- Useable **spatial resolution** of **<2 mm** (DOI) in the human brain
- Continuous **motion correction**

Li et al. *J Nucl Med* 2024

What Can Next-generation Brain PET Accomplish?

- **International group of brain PET experts**
  - Anissa Abi-Dargham, David J. Brooks, Kelly P. Cosgrove, Lars Farde, Alexander Hammers, William J. Jagust, Gitte M. Knudsen, Diana Martinez, Rajesh Narendran, Eugenii A. Rabiner
  - Many years of experience in human brain PET research covering schizophrenia, substance use disorders, depression, dementia, epilepsy and Parkinson’s disease, as well as pharmaceutical industry applications.
- Our aim was to **identify the un-fulfilled wish lists of studies that rest upon improved scanner performance**.
- Three overall directions:
  - **New Imaging Paradigms**
  - **Radiation Dose Reduction**
  - **Methodological Improvements**

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New Imaging Paradigms

1. Imaging small brain structures
2. Spinal cord imaging
3. Dynamics
4. Measuring low-density binding sites
5. Measuring small within-subject changes
6. Atlas of therapeutic targets

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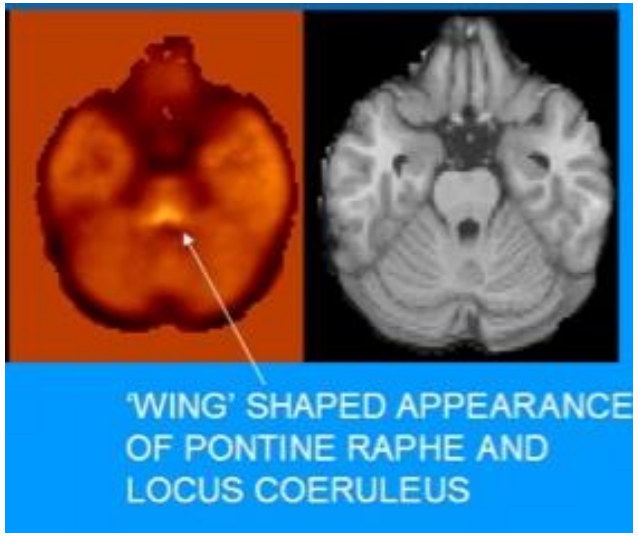
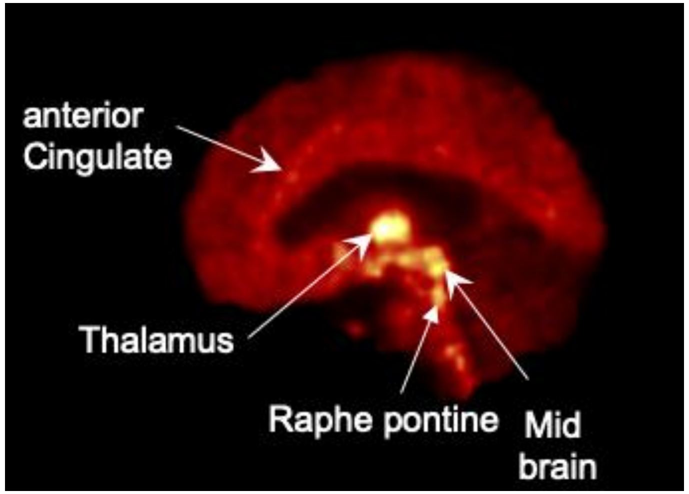
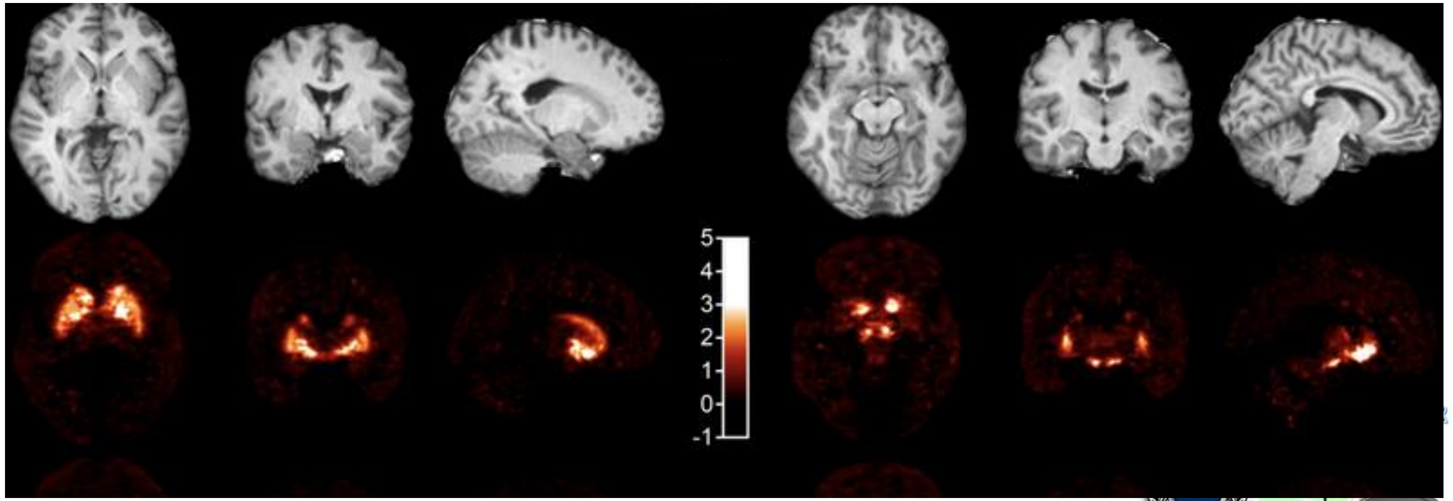
1. Imaging small brain structures

High Resolution

- Locus coeruleus
- Raphe nuclei
- Substantia nigra
- Ventral tegmental area
- Nucleus basalis of Meynert
- Sub-nuclei of thalamus
- Sub-nuclei of amygdala
- Hippocampal subfields
- …







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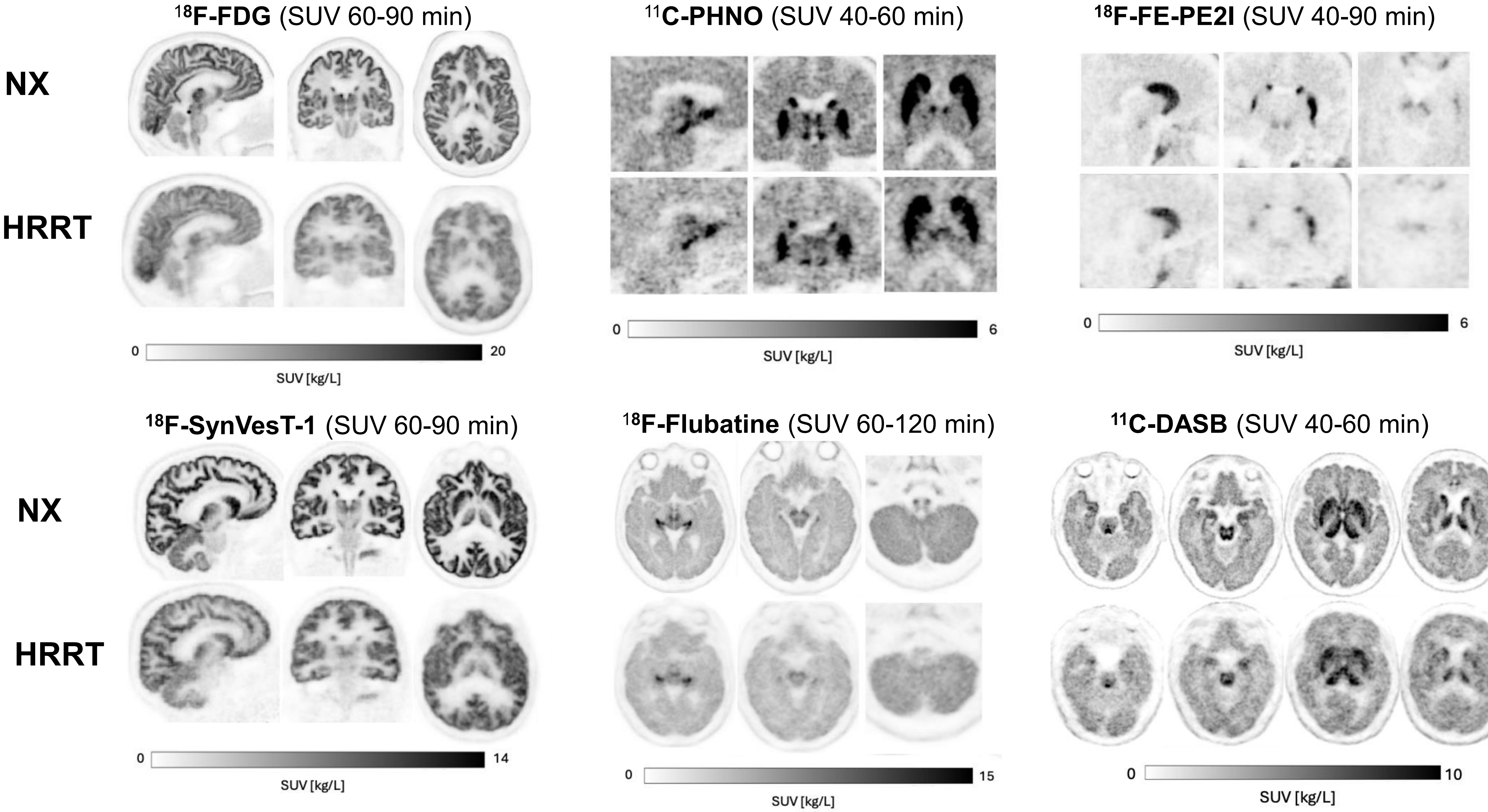

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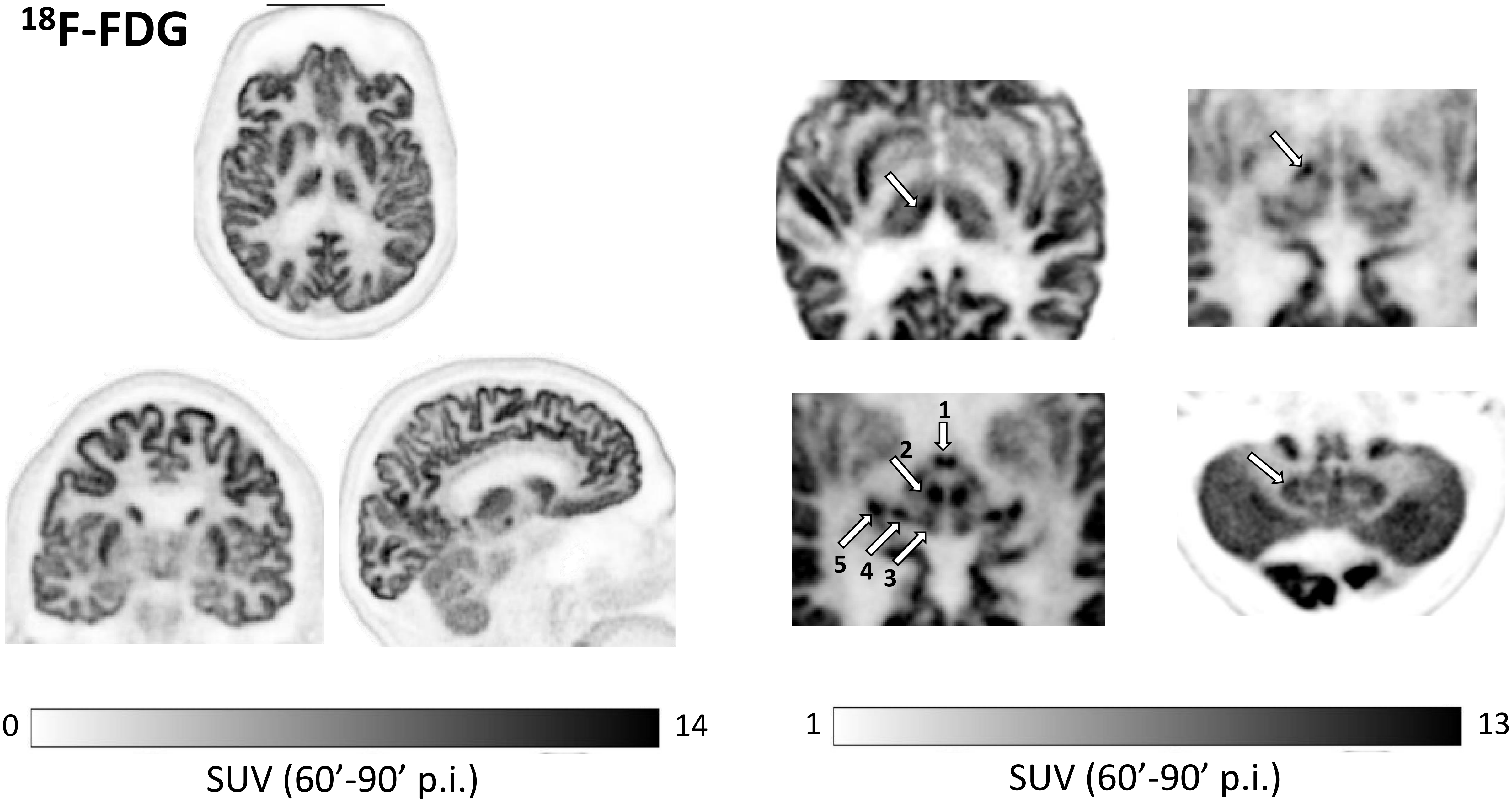
^{18}F-FDG



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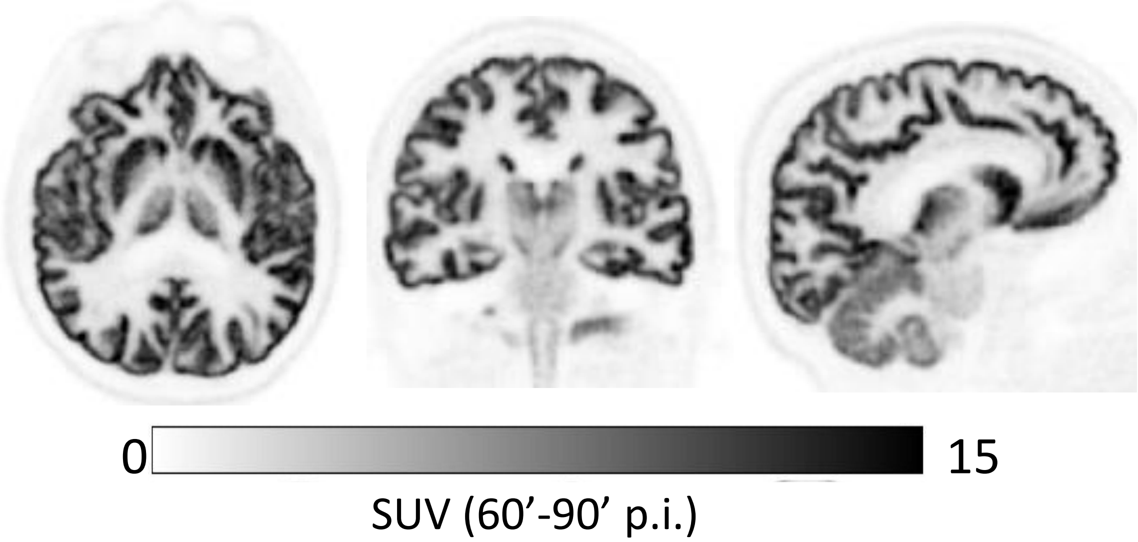
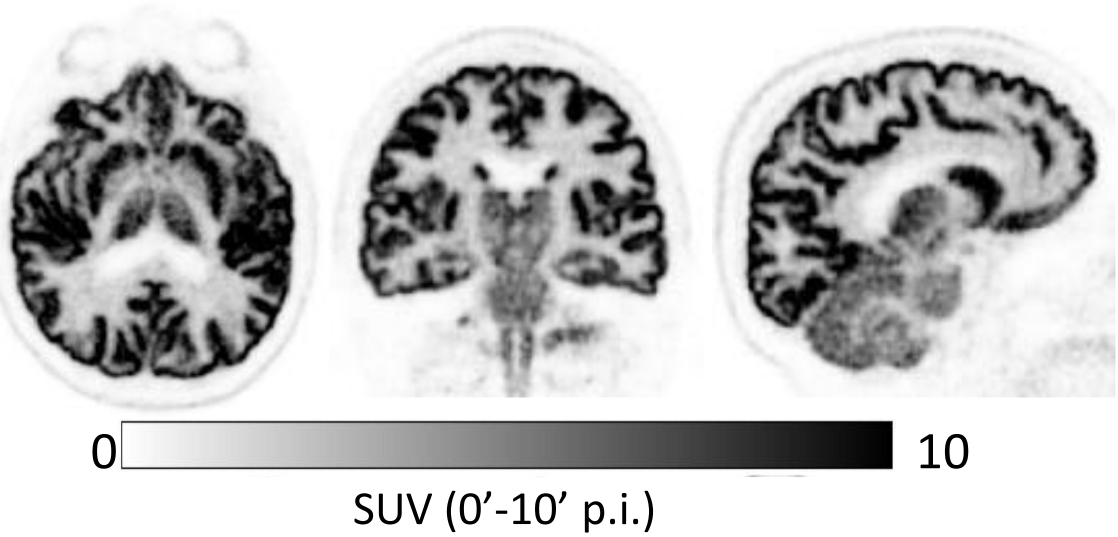
^{18}F-SynVesT-1





^{18}F-SynVest-1 kinetic parameters derived with a 1TC model within small nuclei (FreeSurfer, MASSP 2.0 ROIs; NX, *n*=5). ROI volumes are reported. Data are presented as mean (percent SD), and divided by region (thalamus, subthalamic nucleus, brainstem, hippocampus, cerebellum).

Region	ROI vol. [cm^3]	V_T [mL/cm^3]	BP_{ND} [unitless]	K_1 [mL/cm^3/min]	k_2 [min^{-1}]
Thalamus, Pulvinar	3.6 (7%)	21.2 (9%)	5.7 (10%)	0.48 (4%)	0.023 (9%)
Thalamus, Medial nuclei	2.2 (4%)	20.0 (19%)	5.2 (13%)	0.60 (12%)	0.030 (17%)
Thalamus, Lateral nuclei	0.23 (18%)	16.6 (13%)	4.2 (15%)	0.53 (8%)	0.032 (19%)
Thalamus – Anterior nuclei	0.27 (12%)	15.1 (25%)	3.7 (20%)	0.49 (14%)	0.033 (21%)
Thalamus – Ventral nuclei	5.4 (4%)	14.5 (19%)	3.5 (14%)	0.51 (6%)	0.036 (17%)
Thalamus, Lateral geniculate	0.24 (8%)	11.2 (17%)	2.5 (30%)	0.48 (29%)	0.043 (21%)
Thalamus, Medial geniculate	0.09 (8%)	17.3 (26%)	4.4 (23%)	0.49 (12%)	0.029 (21%)
Subthalamic nuclei	0.35 (8%)	8.2 (14%)	1.6 (14%)	0.46 (13%)	0.058 (22%)
Brainstem, Red nuclei	0.66 (7%)	9.0 (15%)	1.8 (17%)	0.47 (13%)	0.053 (21%)
Brainstem, Substantia nigra	1.6 (9%)	9.5 (13%)	2.0 (17%)	0.32 (16%)	0.034 (15%)
Brainstem, Inferior colliculi	0.16 (11%)	13.6 (10%)	3.3 (24%)	**0.74** (11%)	0.055 (15%)
Brainstem, Superior colliculi	0.27 (10%)	15.0 (5%)	3.7 (14%)	0.54 (13%)	0.036 (17%)
Hippocampus, CA 1	1.98 (5%)	17.7 (20%)	4.5 (19%)	0.35 (17%)	0.020 (20%)
Hippocampus, CA 2/3	0.70 (4%)	14.2 (35%)	3.4 (37%)	0.38 (13%)	0.029 (34%)
Hippocampus, Dentate gyrus	1.1 (6%)	19.5 (17%)	5.1 (14%)	0.42 (10%)	0.022 (18%)
Hippocampus, Subiculum	2.1 (8%)	16.9 (9%)	4.3 (12%)	0.37 (16%)	0.022 (18%)
Cerebellum, dentate nuclei	1.2 (20%)	5.4 (9%)	0.7 (22%)	0.54 (7%)	**0.100** (12%)

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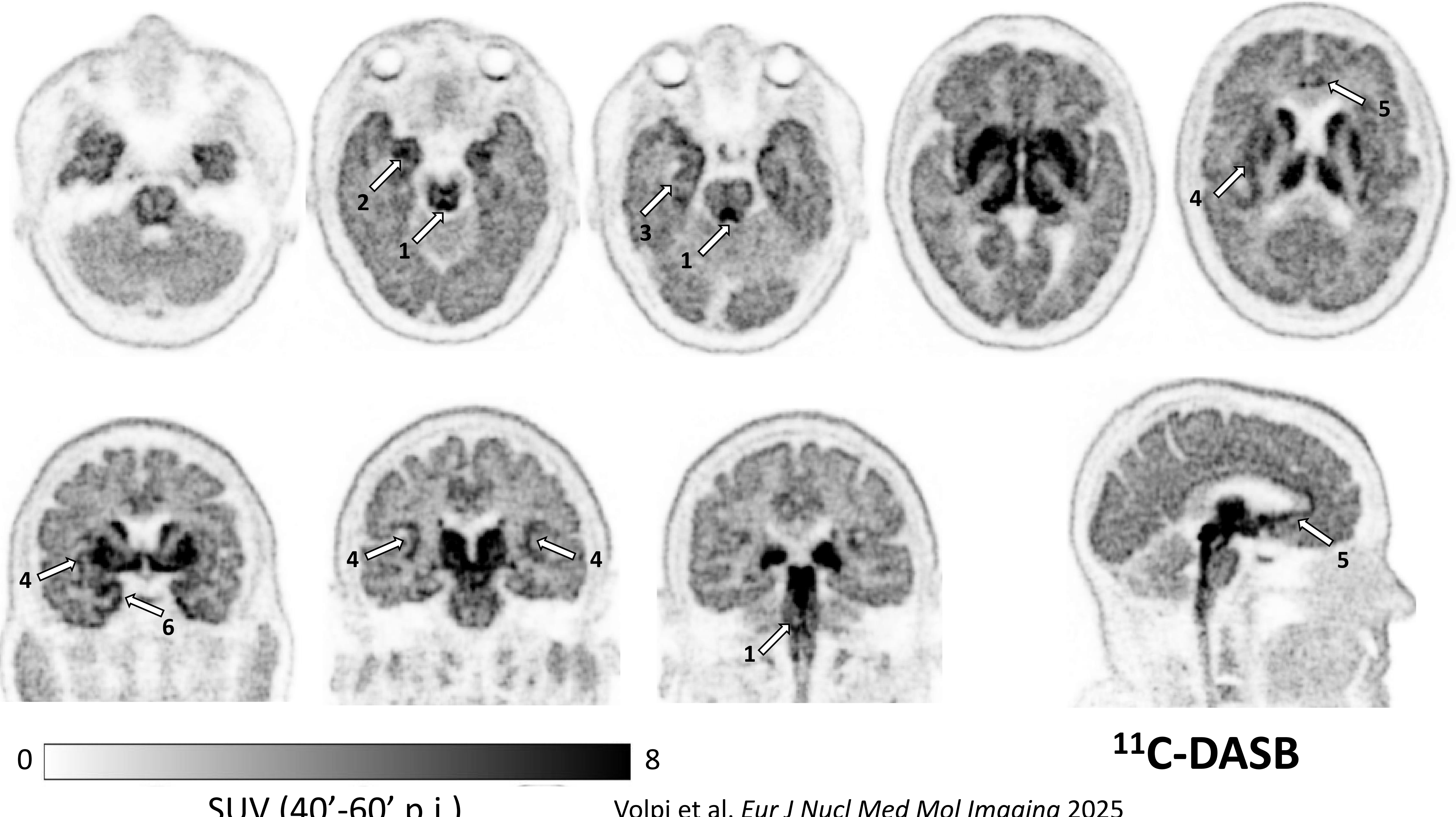

1
2
3
4
5
6
0
8
SUV (40'-60' p.i.)
^{11}C-DASB
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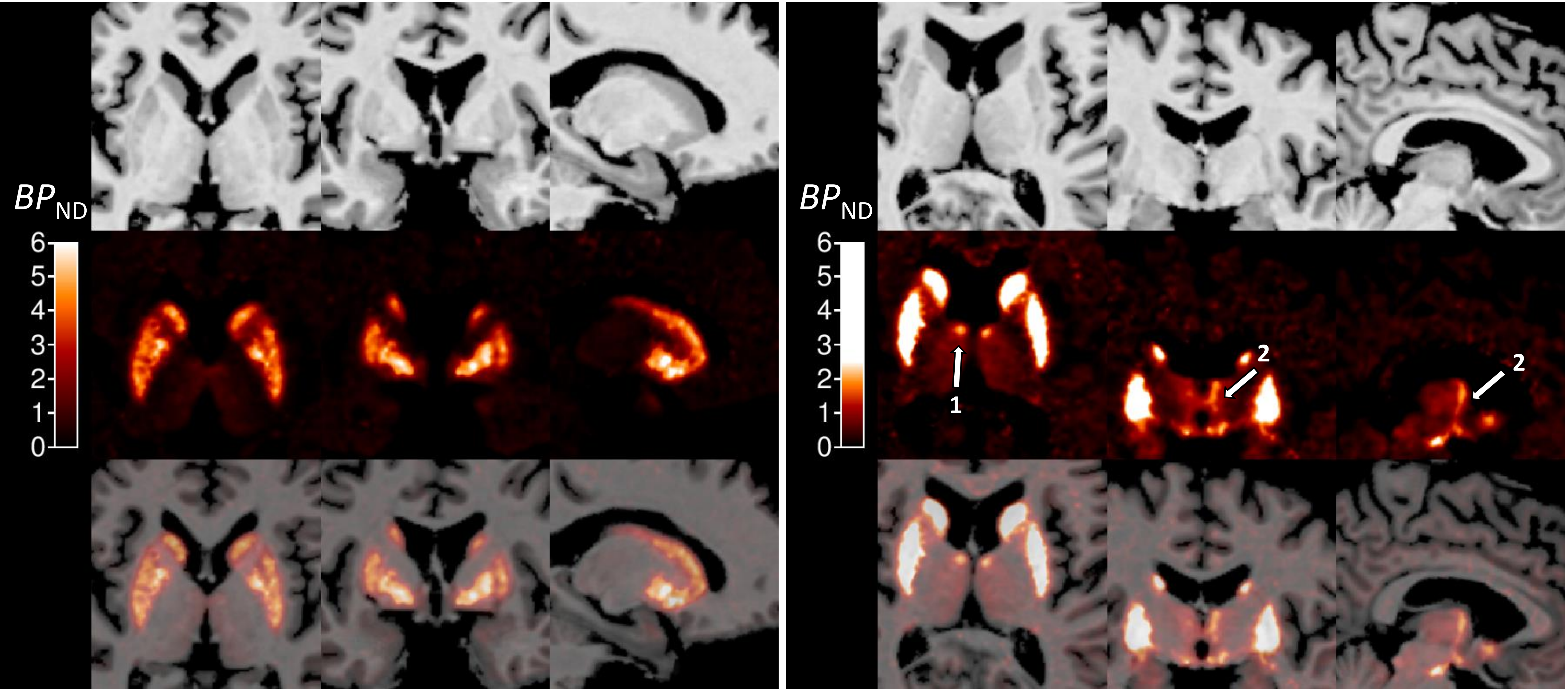
^{11}C-PHNO



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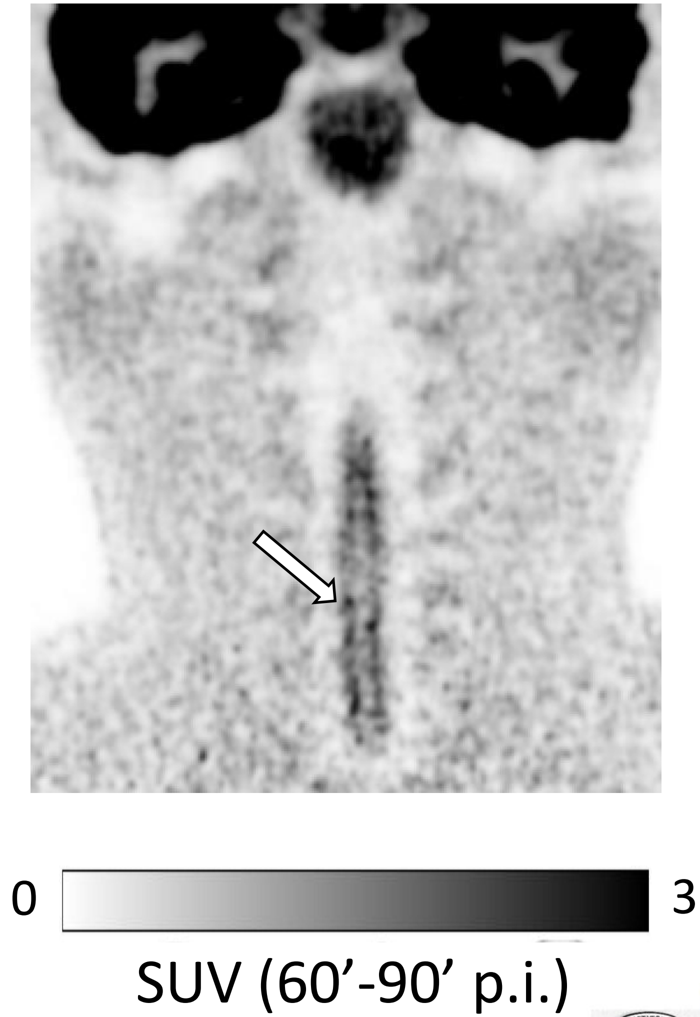
2. Spinal cord imaging

- High relevance to spinal cord injury and ALS
- Small diameter (8-12 mm)
- Low target densities

- Dedicated brain systems need high sensitivity, high resolution and long axial FOV to image cervical cord

^{18}F-SynVesT-1



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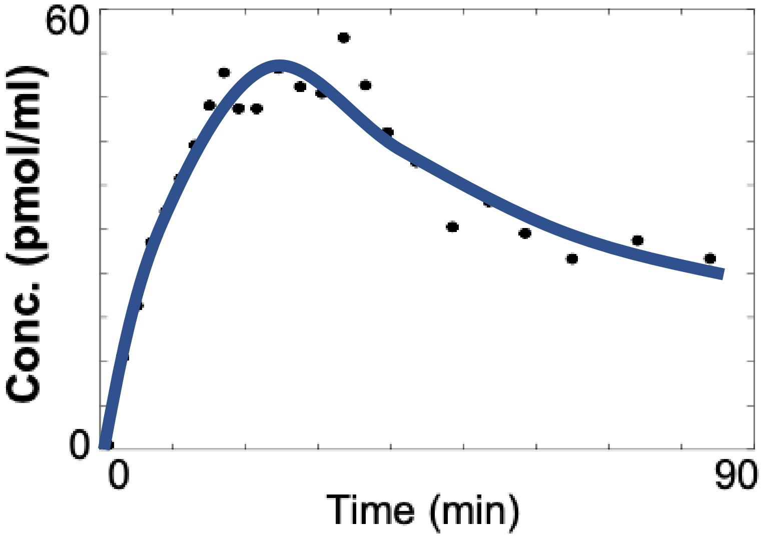
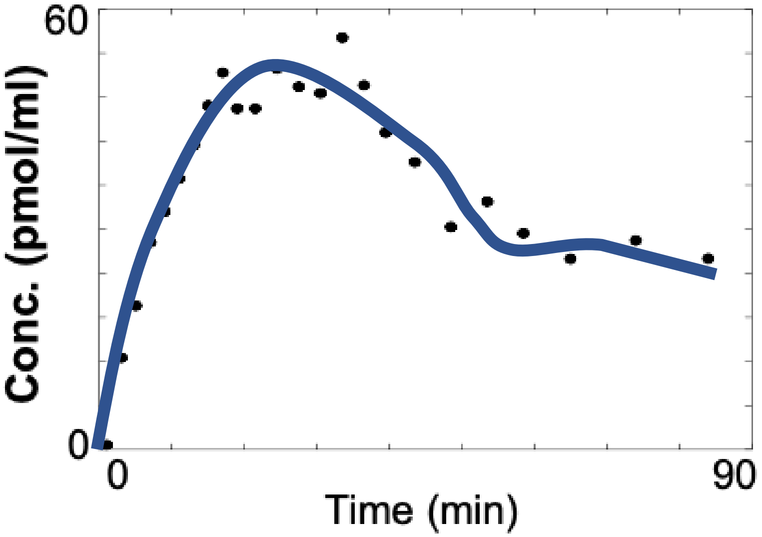
3. Dynamics: neurotransmitter release

High Sensitivity

Problem: Looking for a Neurotransmitter Needle in ^{11}C-Raclopride Haystack

PET signal





Which is better?

Dopamine signal?

or

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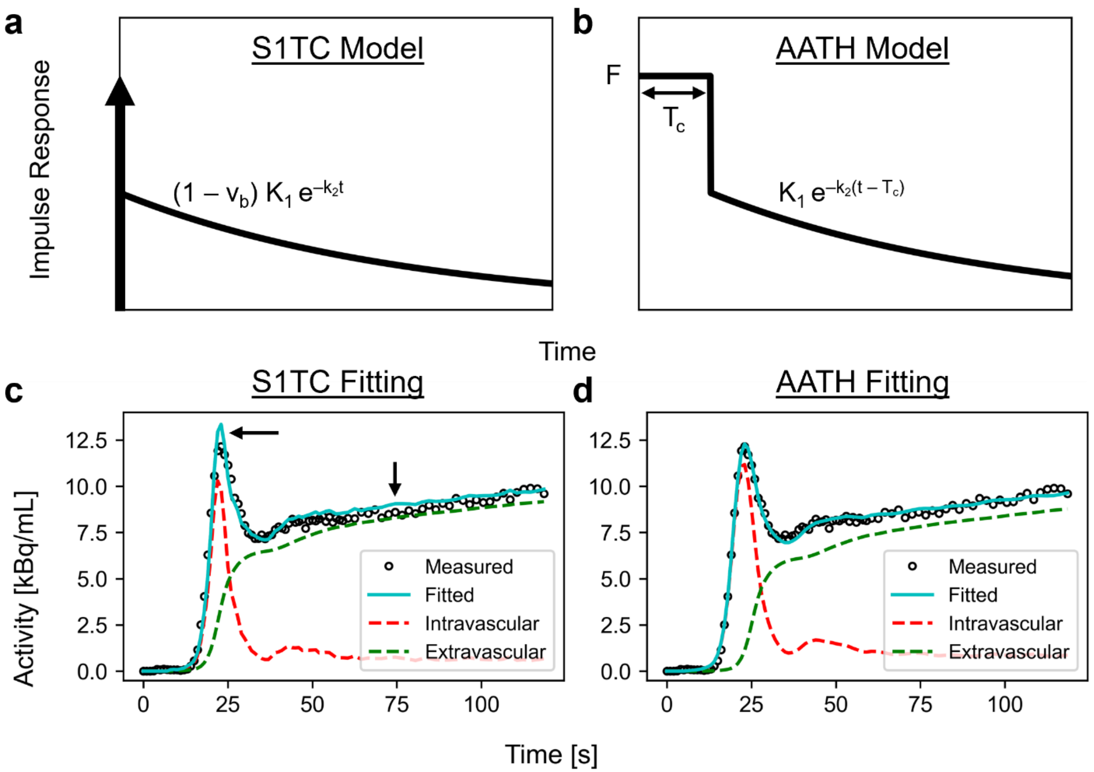
3. Dynamics: Fast Early Kinetics

<u>High Sensitivity</u>

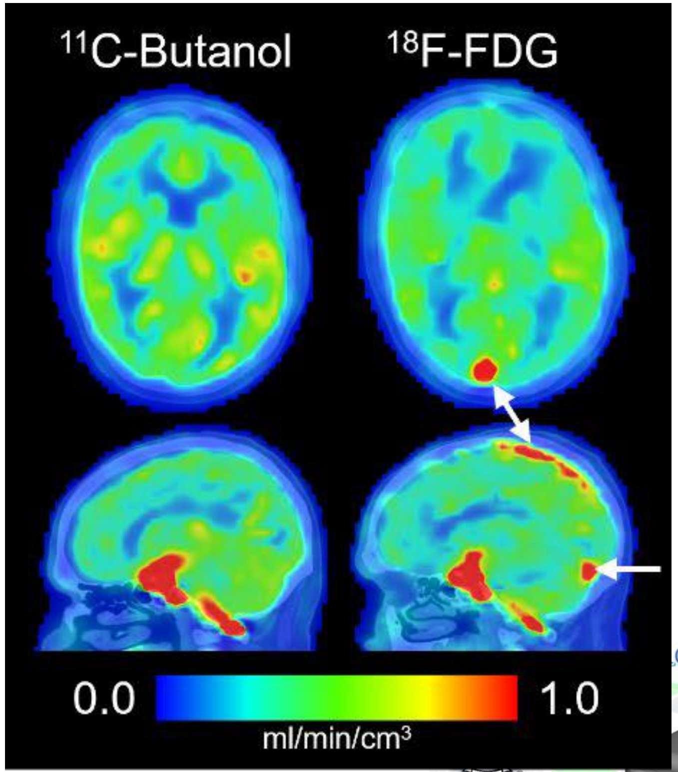


Time-varying 1TC Model

tracer uptake divided into 2 phases:

1) ***vascular*** transport

2) ***tissue*** uptake



0.1 sec frames

Chung et al. J Nucl Med, Nat Commun 2025

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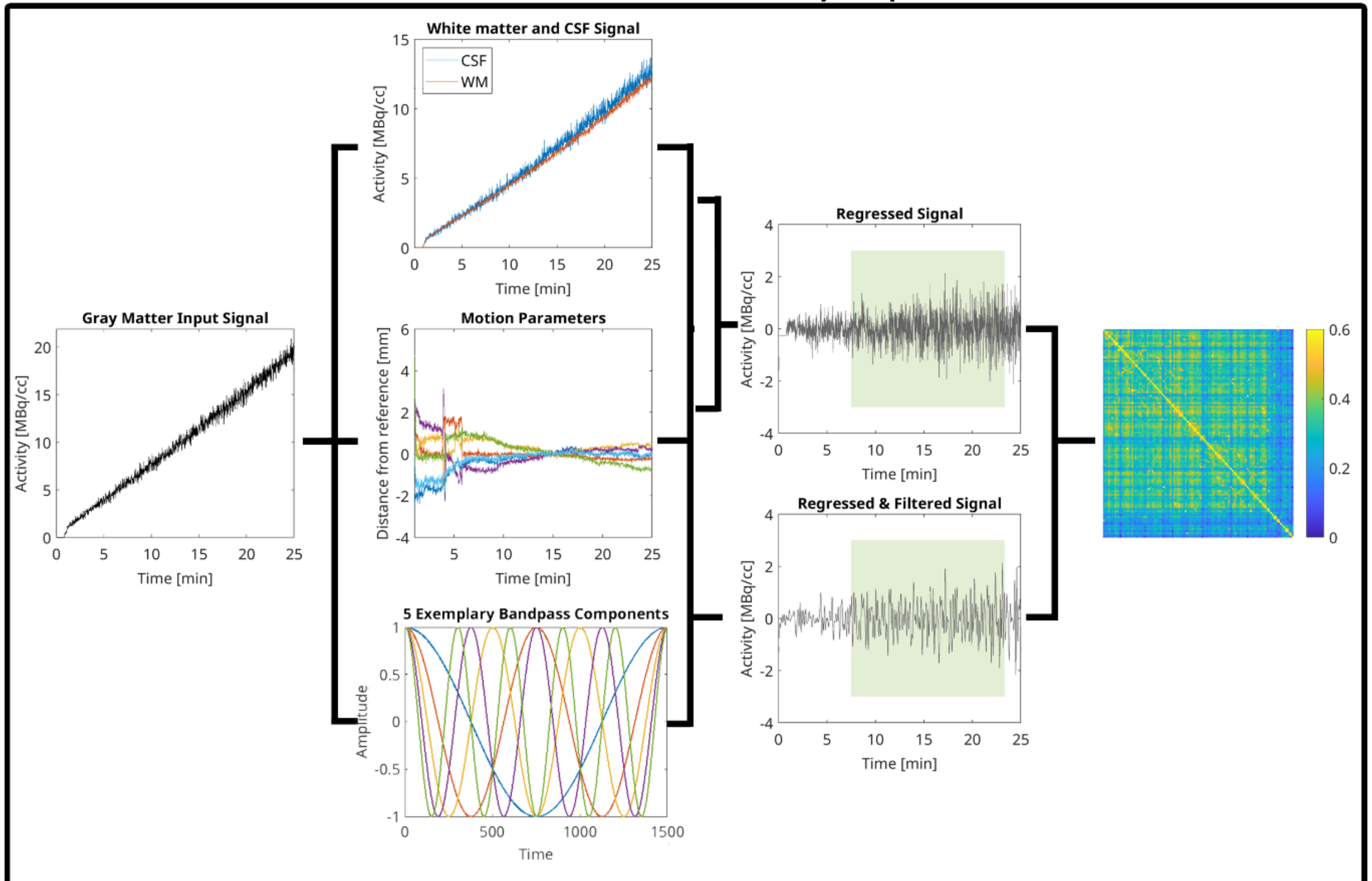
3. Dynamics: Fluctuations in fPET

High Sensitivity



- Continuous infusion to achieve equilibrium
- Task-based paradigms
- Resting state for PET connectivity analysis
- Neuronal fluctuations?

Reed et al. biorxiv 2025

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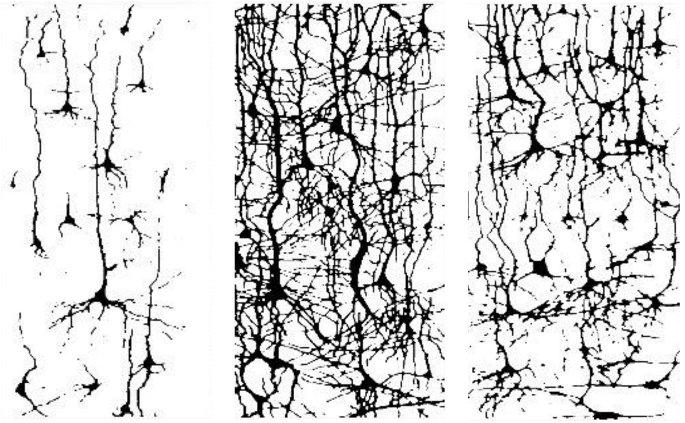
Radiation Dose Reduction

High Sensitivity

Pruning – Autism & Schizophrenia



At Birth | 6 Years Old | 14 Years Old

- **Adolescent** imaging
  - Epilepsy
  - ASD, Schizophrenia
  - Synaptic pruning
  - Need **ultra-low dose (e.g., 1:10)** and excellent motion correction
- **Longitudinal** follow-up (**multi-tracer, multi-modal**)
  - DOC, Dementia, Substance use …
- Healthy **Controls**
  - Ease recruitment challenges
- Target radiation dose:

  Dose of an intercontinental flight

Denoising (DL?)

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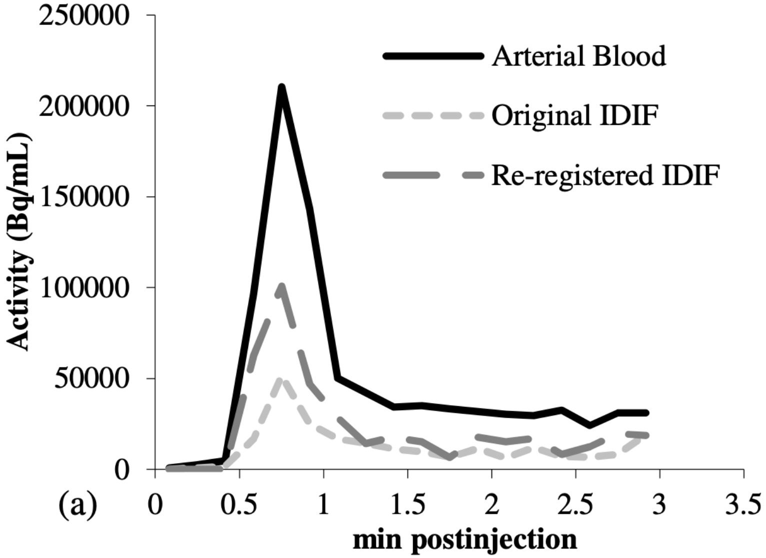
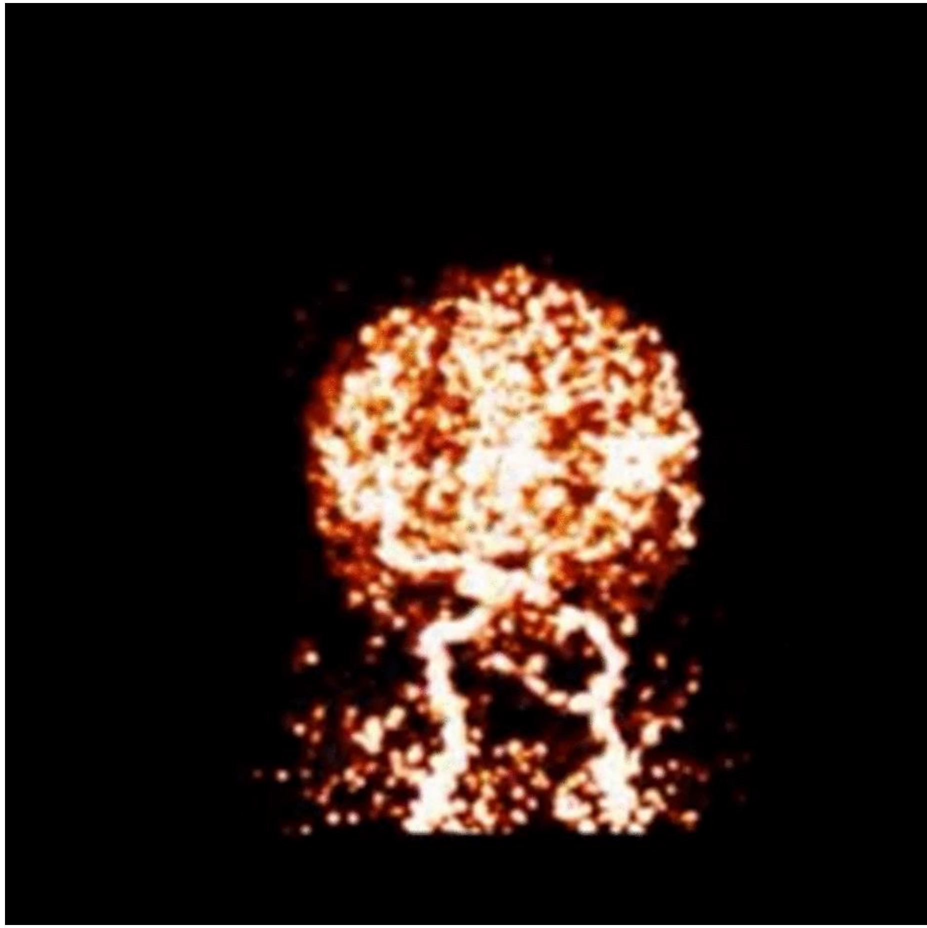
Methodological improvements

Carotid Artery Imaging

- Accurate input function for kinetic analysis
- Image-derived input function is more desirable
- Challenges:
  - Small size of the carotid arteries
  - Different tracers
  - Both high and low contrast
- Whole blood vs. plasma
- Radiolabeled metabolites



(a)



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

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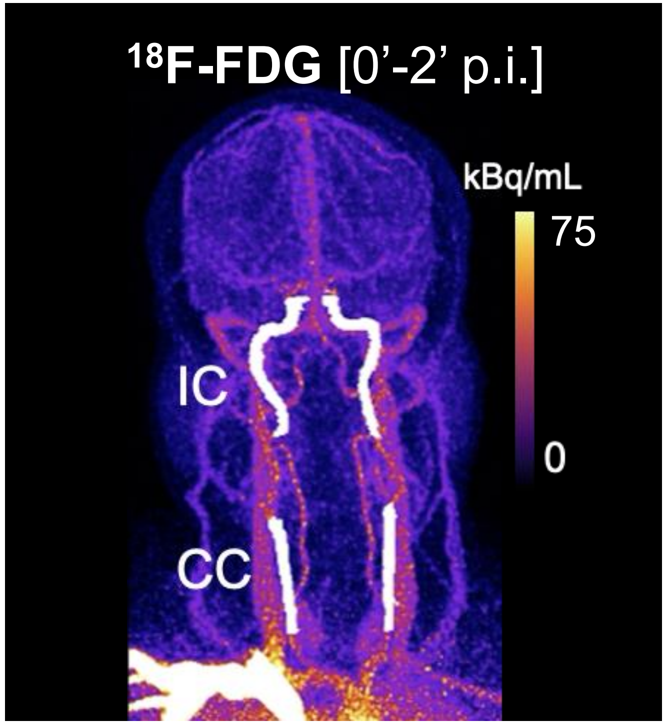
Internal Carotid (IC)
Common Carotid (CC)
Arterial blood samples

High Resolution



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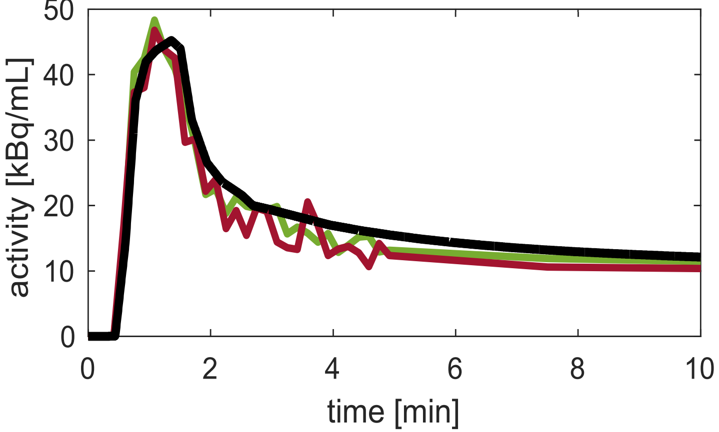
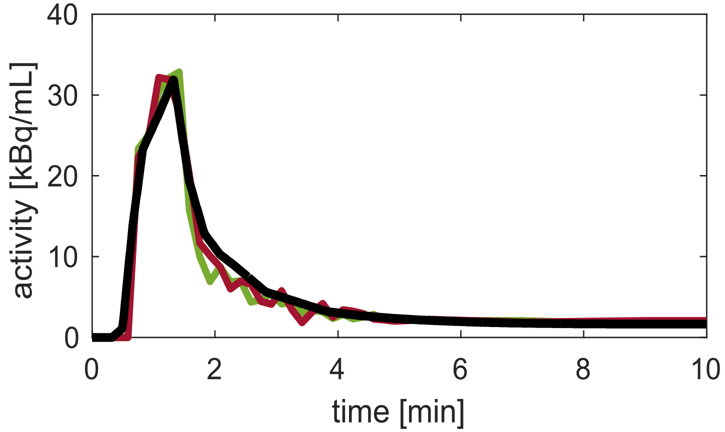
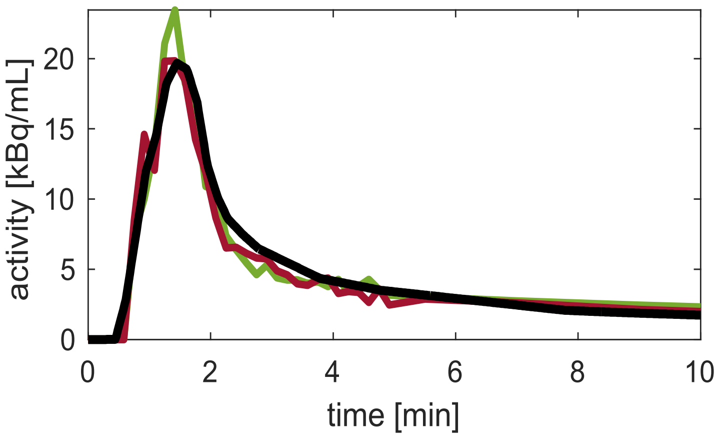


^{18}F-SynVesT-1



^{18}F-Flubatine



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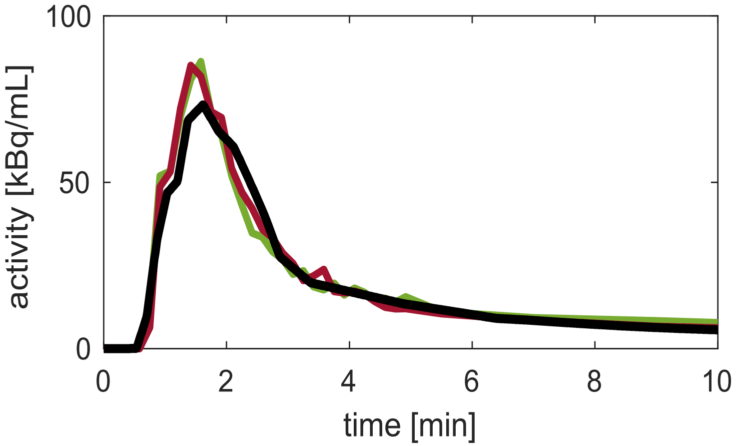
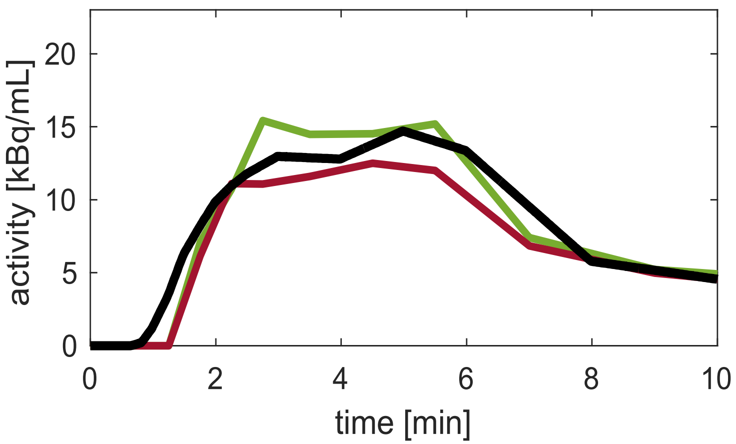


^{11}C-PHNO



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<u>High sensitivity</u> in Next-Generation Dedicated Brain PET

- Needed to achieve **high resolution**
  - Need enough counts per resolution element
- Improved **quantification**
  - Many useful **short-lived tracers** labeled with ^{11}C (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
  - **Short frames** for fast kinetics or assessing activity fluctuations (fPET)
- Low **noise**
  - To precisely measure **small longitudinal** changes in disease
- Lower injected **dose**
  - **Pediatric** imaging
  - More **repeat scans**

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<u>High resolution</u> in Next-Generation Dedicated Brain PET

- Image **focal structures**
  - Raphe nucleus, Locus coeruleus, substantia nigra etc.
  - 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
- Measure the **tracer input function**
  - HRRT's resolution not good enough for carotid artery quantification
- Ensure **uniformity** of image resolution
  - Over space and time

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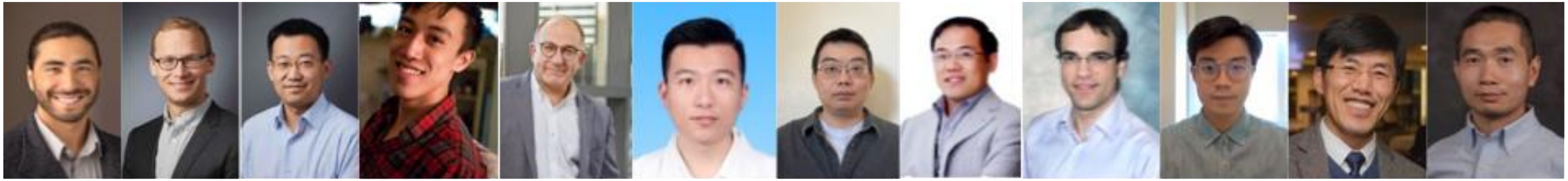
Acknowledgment: U01EB029811 and the NX Team



Alaaddin Ibrahimy | Ansel Hillmer | Chi Liu | Edwin Leung | Evan Morris | Gong Wang | Haoran Chang | Hongdi Li | JD Gallezot | Jiazhen Zhang | Jinyi Qi | Junwei Du

Kathryn Fontaine | Katya Shanina | Lance Hu | Liang Guo | Negar Omidvari | Nikki Khattar | Paul Gravel | Qian Wang | Ramsey Badawi | Richard Carson | Simon Cherry

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Thank you!

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