Kinetic Modeling in PET: Madness in the Methods or Method to the Madness

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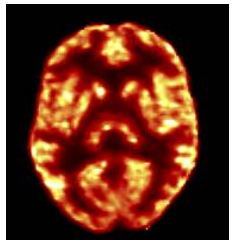
December 14, 2020

Quantitative Brain PET

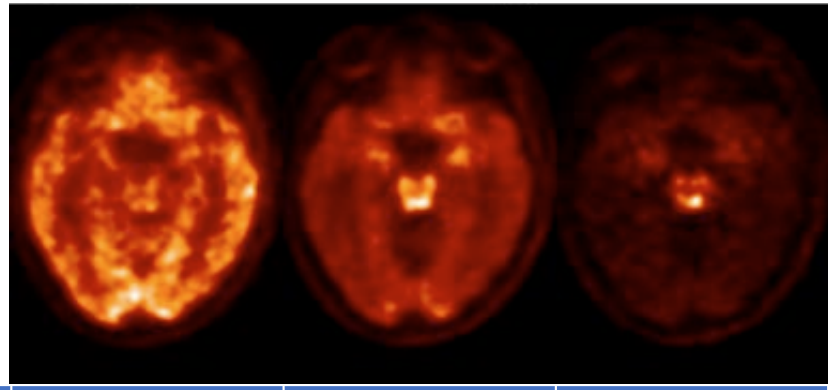


- Kinetic Modeling 101
  - Basic modeling methods
- Tracer Development and Validation
  - SV2A Tracer ^{11}C-UCB-J
  - Nonhuman primates
  - Human studies
- Using modeling to separate blood flow and binding changes
- When is modeling important?
  - When might simplified methods be misleading …
- Simplifications for Brain Imaging
  - Standard Uptake Value Ratio (SUVR) vs. Distribution Volume Ratio (DVR)
  - Time dependent relationships
- Transient Equilibrium
  - Two wrongs can make a right
- Closing thoughts

Radioactivity Patterns Change with Time

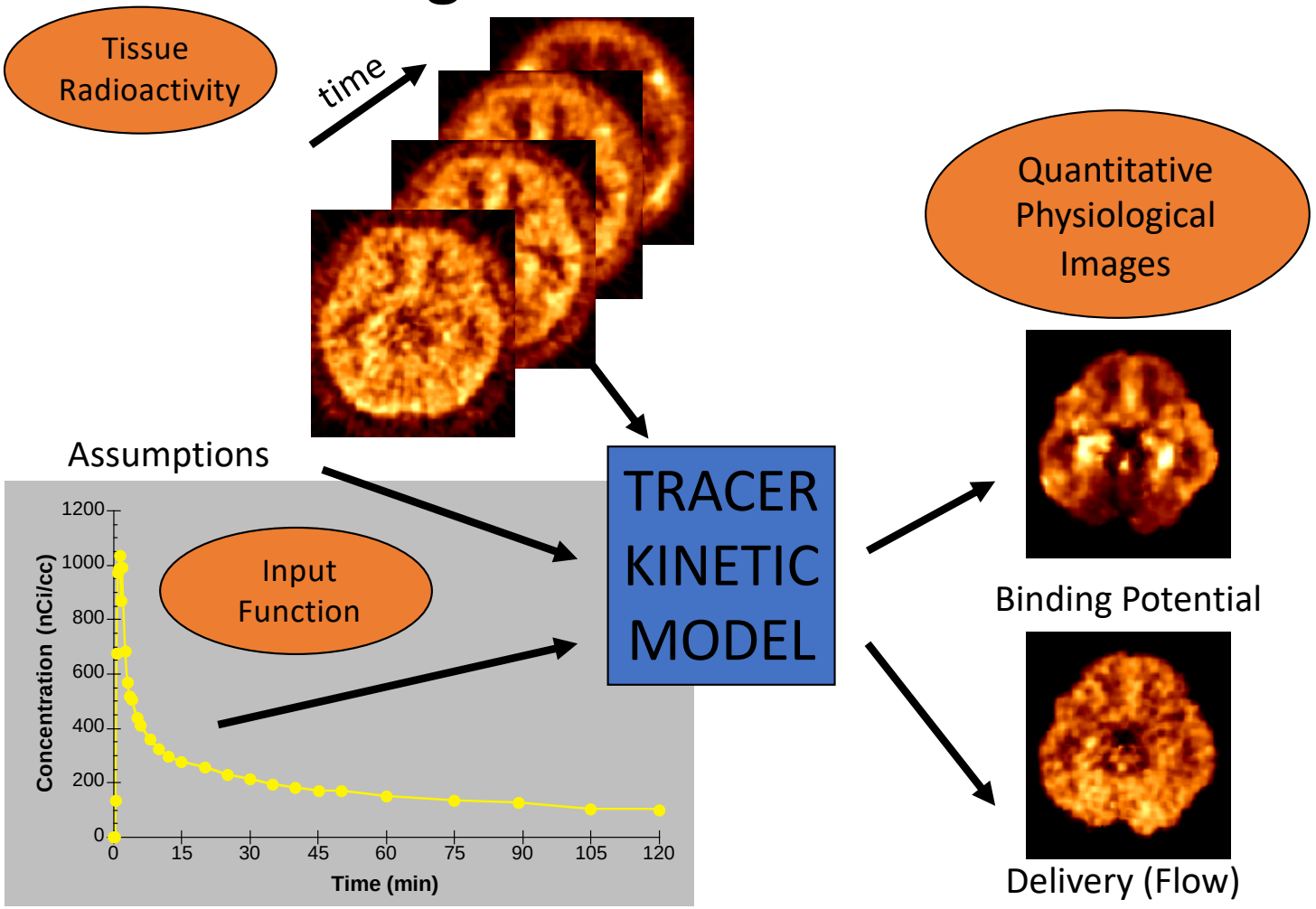
- Tracer: ^{11}C-AFM
- Target: Serotonin Transporter
- Analog of Selective Serotonin Reuptake Inhibitors (SSRI)
  - Prozac, Zoloft,…

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



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

PET Modeling



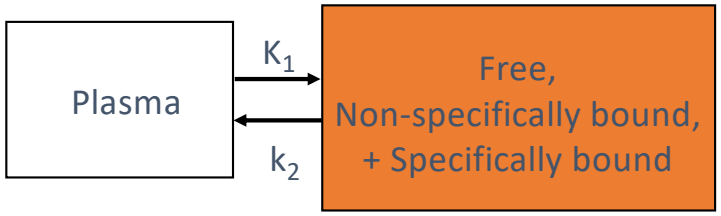
Goals of PET Modeling

- 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.

Important Kinetic Parameters for Reversible Tracers

- K_1 - tracer delivery
  - Blood flow information
- V_T – volume of distribution (DV)
  - Ratio at **equilibrium** of total tissue concentration to reference fluid
    - metabolite-corrected plasma concentration
    - Units: mL plasma / cm^3 tissue
  - Includes free, non-specifically bound, and specifically bound components.
  - Useful for tracers with reversible binding

- DVR – distribution volume ratio
  - V_T in ROI / V_T in reference region
- BP_{ND} – binding potential
  - Specific binding as ratio to nondisplaceable uptake
  - DVR + 1



- All these values relate directly to physiological parameters:
  - Receptor concentrations and affinities and blood flow

Methods to estimate V_T and BP

- Fit of dynamic data
  - Need tissue time-activity curve and plasma time-activity curve
  - Fit data to appropriate model
  - Determine V_T from model parameters
    - Model-based method to extrapolate equilibrium conditions from bolus data
  - 2 tissue compartment model:

    $V_T = K_1 / k_2 (1 + k_3 / k_4)$
  - 1 tissue compartment model (pixel-by-pixel)

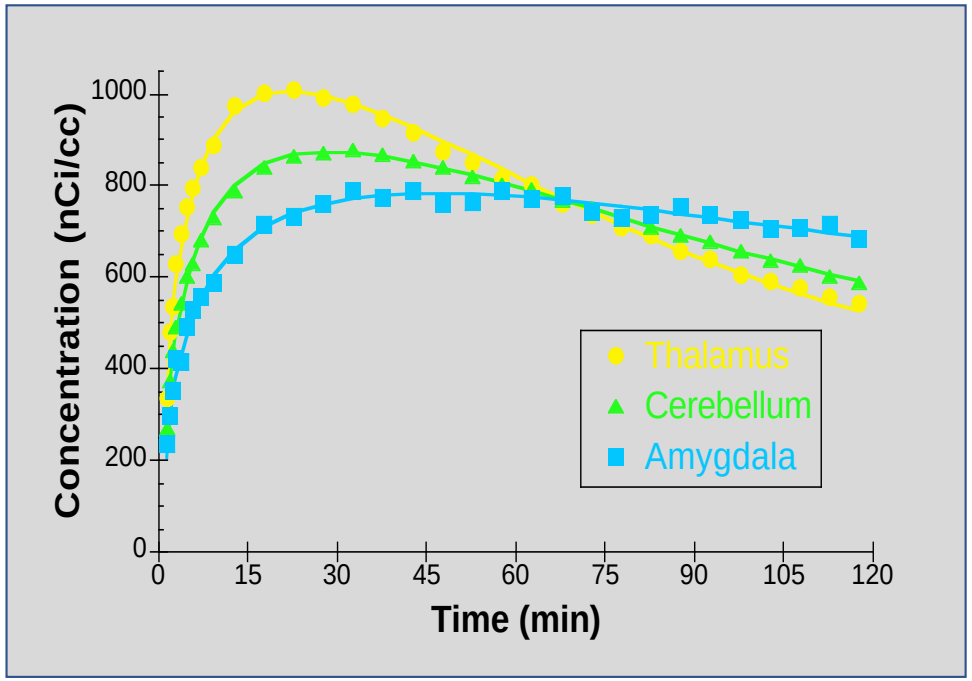
    $V_T = K_1 / k_2$
- Simplified Reference Tissue Model
  - Fit for BP_{ND} directly using TAC from region with no specific binding
  - Plasma input function inferred mathematically from reference TAC

Methods to estimate V_T and BP

- Graphical analysis - Logan plot
  - Transform data to produce a straight line
  - Use part of the data (varies between regions)
  - V_T = Slope of {integral(C_T) / C_T} versus {integral(C_p) / C_T}
- Constant infusion
  - At equilibrium, V_T = the ratio of tissue to metabolite-corrected plasma
  - V_T and BP taken directly from the data

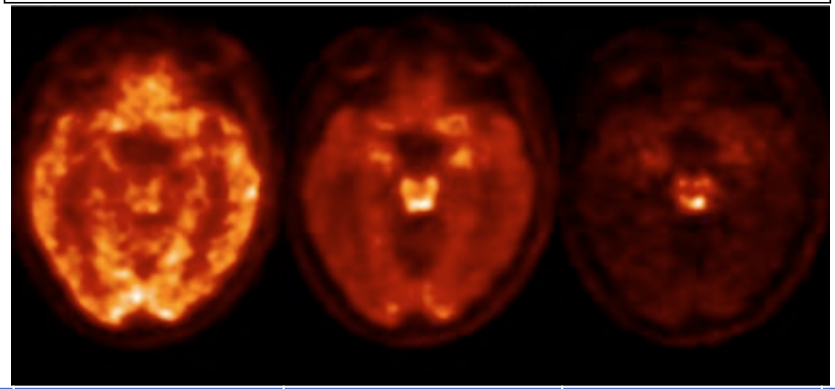
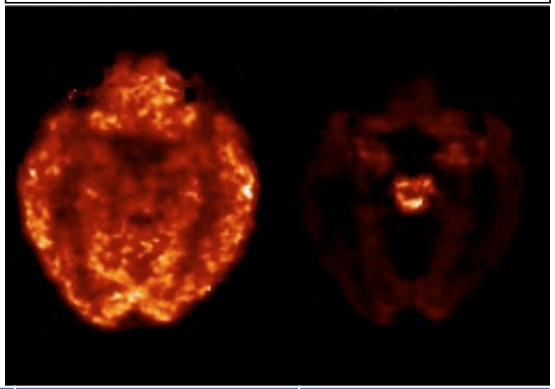
Neuroreceptor Imaging
The hard way

- Collect arterial input curve
- Collect scan data (counts)
- Reconstruct multiple images over time
- Define regions-of-interest
- Create time-activity curves
- Do least squares fit to the model
- Extract volumes of distribution and binding potentials



Radioactivity Images vs. Parametric Images

- K_1 - Blood flow
- V_T – Volume of distribution
  - Total binding to serotonin transporters plus nonspecific uptake

Radioactivity Images	Parametric Images
	

Time (min)	0-10 min	40-60 min	90-120 min		K_1	V_T
Flow information	+++	++	+		+++++	
SSRI information	+	++	+++			++++

Tracer:
^{11}C-AFM

Reference Tissue Models

- Infer the input function based on the time course of a reference region
- Neuroreceptor studies: reference region has no receptors
- Estimates relative delivery and Binding Potential ($BP=B_{max}/K_d$)
- C(t) ROI TAC
- C'(t) Reference region TAC
- For one tissue-compartment:

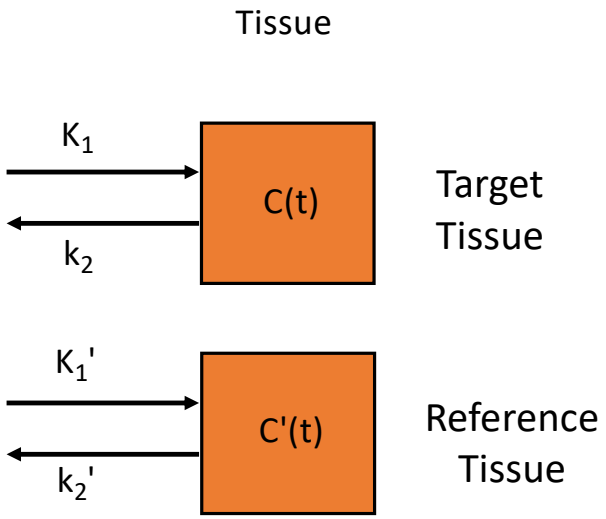
$dC/dt = K_1 C_p - k_2 C$

$dC'/dt = K_1' C_p - k_2' C'$

- Eliminate C_p (derive)

$C(t) = R_1 C'(t) + R_1 (k_2' - k_2) C' * \exp(-k_2 t)$

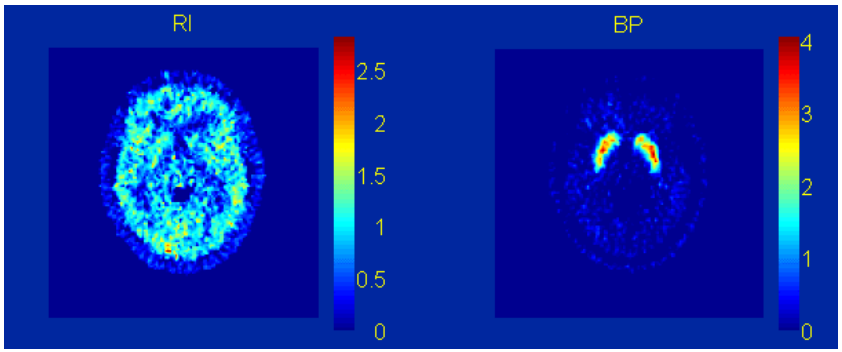
- R_1 Relative delivery (K_1 / K_1')
- $BP_{ND} = R_1 k_2'/k_2 - 1$



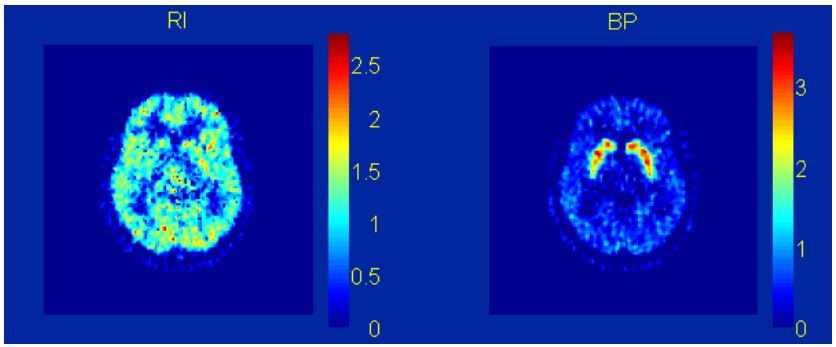
SRTM Images

Relative Delivery and Binding Potential

[^{11}C]Raclopride: D_2 Receptor



[^{11}C]SCH2339: D_1 Receptor



R. Gunn

MRC Cyclotron Unit

Logan Graphical Analysis

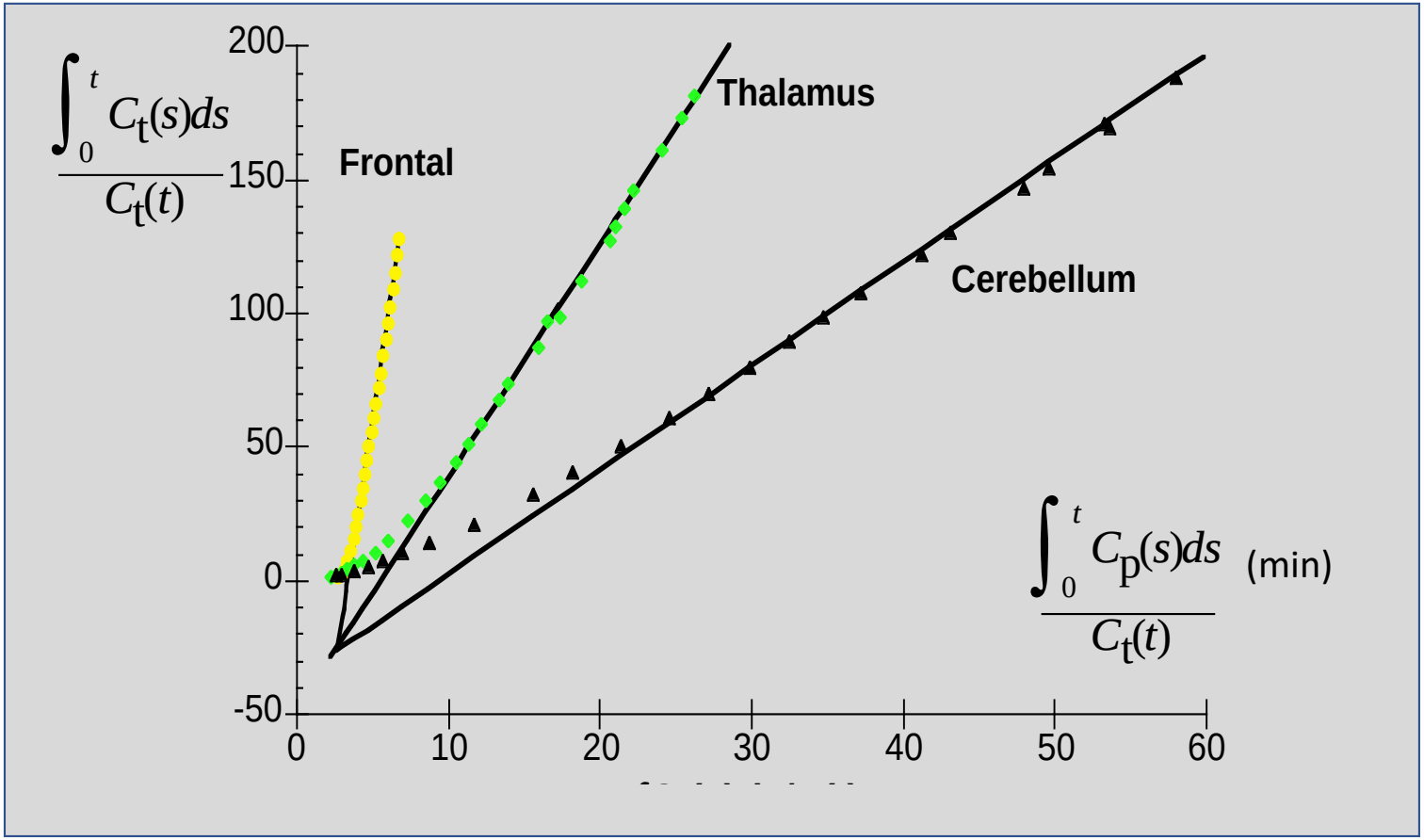
- Appropriate for tracer with reversible binding
- Derived from model with one tissue compartment
- Transforms the data so the final slope is V_T

$$\int C_T\,dt / C_T = V_T \int C_P\,dt / C_T + b \qquad t > t^*$$

- Model independent

Logan Graphical Analysis

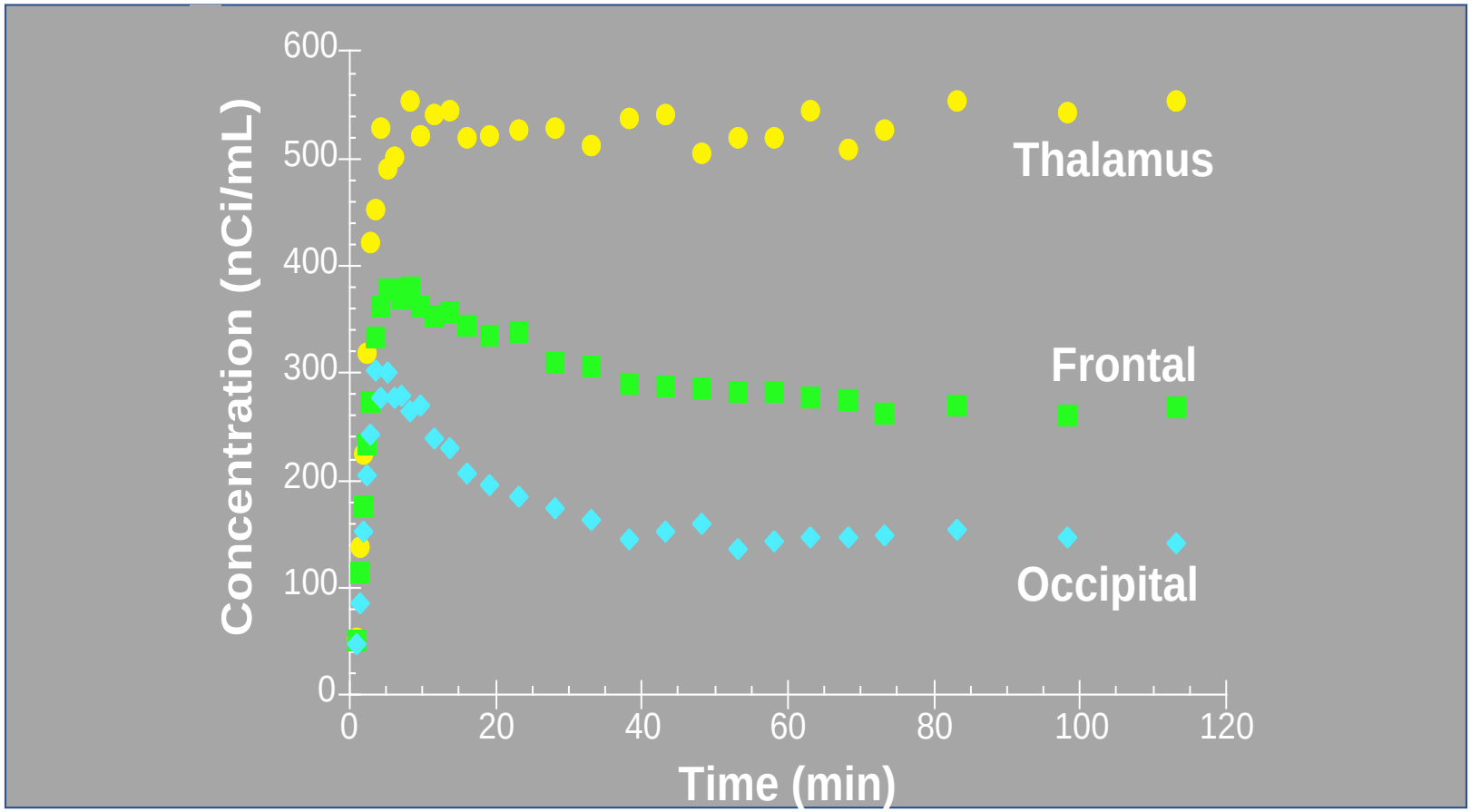
[^{18}F]FCWAY



Tracer Infusion for Equilibrium Measurements

- Administer tracer as bolus plus continuous infusion
- Achieve true equilibrium in blood and all brain regions
- Model-independent
- Determine V_T directly from concentration ratio of tissue region-of-interest (ROI) to plasma
  - $BP_P = V_T(ROI) - V_T(BKG)$ proportional to B_{avail} / K_d
- Determine BP_{ND} from tissue concentration ratios
  - $BP_{ND} = (ROI / BKG - 1)$ proportional to B_{avail} / K_d
  - No blood
- For certain tracers, rapid equilibrium achieved if proper bolus fraction is chosen

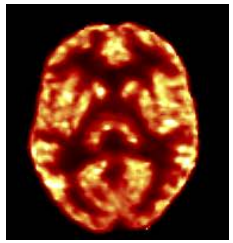
[^{18}F]Cyclofoxy Tissue Activity
Bolus + Infusion



The Challenge

- If we thoroughly understand how a tracer works…
- Can we produce a simple, clinically practical protocol that is patient-friendly, suitable for multi-center trials…
- Without losing too much accuracy…
- So that the practical advantages, which allow us to study many more patients, clearly outweigh any quantitative disadvantages.

Quantitative Brain PET



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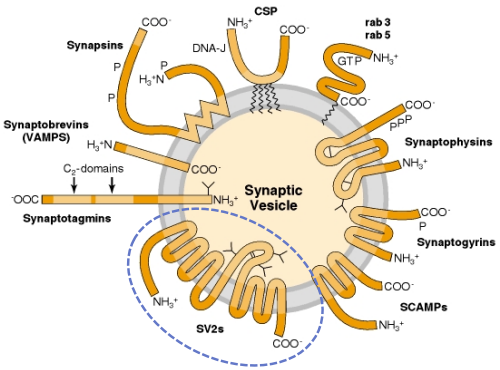
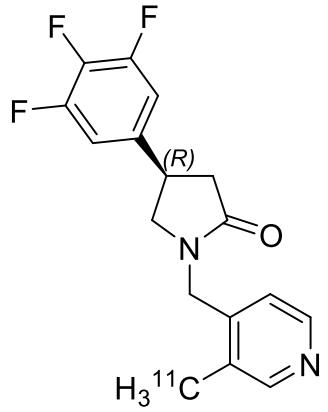
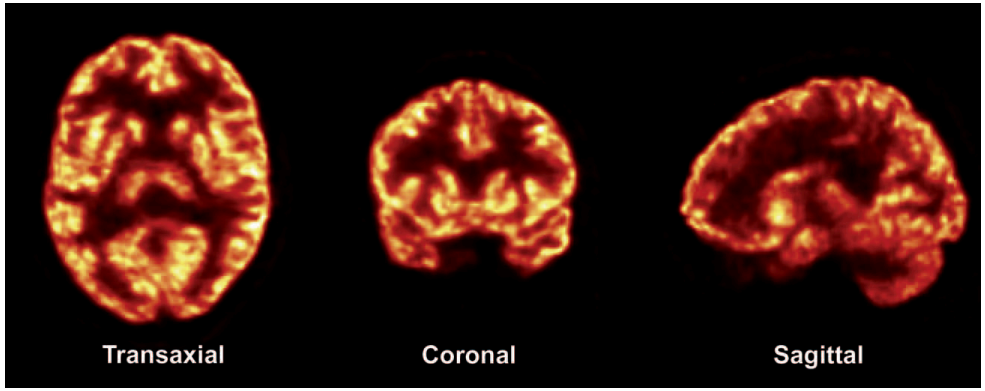
Developing and Validating a Novel Brain Tracer

- Identify target
- In vitro evaluations
- Radiochemistry
- Dynamic scans
- Arterial blood samples
- Regional or voxel analysis
- Compartment modeling
- Test/retest
- Blocking studies
- *In vivo / ex vivo* validations





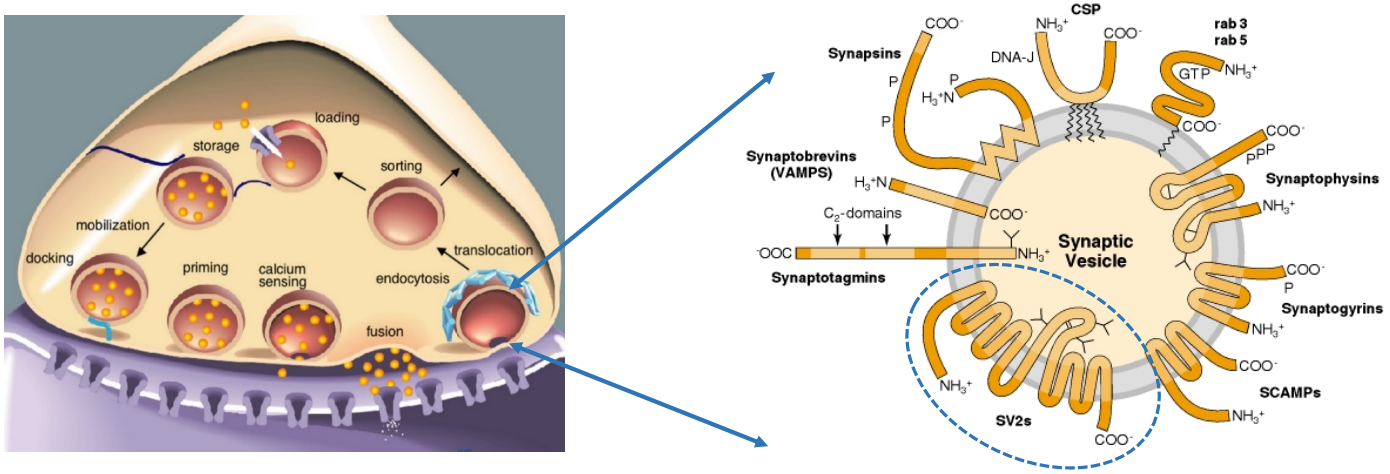
^{11}C-UCB-J



SV2A – Synaptic Density

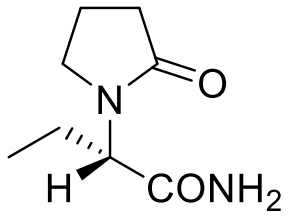
Synaptic Vesicle Glycoprotein 2

- Component of synaptic vesicles, located in presynaptic terminals
- Modulates synaptic exocytosis and endocytosis`
- Radioligand binding to SV2 may be useful for measurement of synaptic density



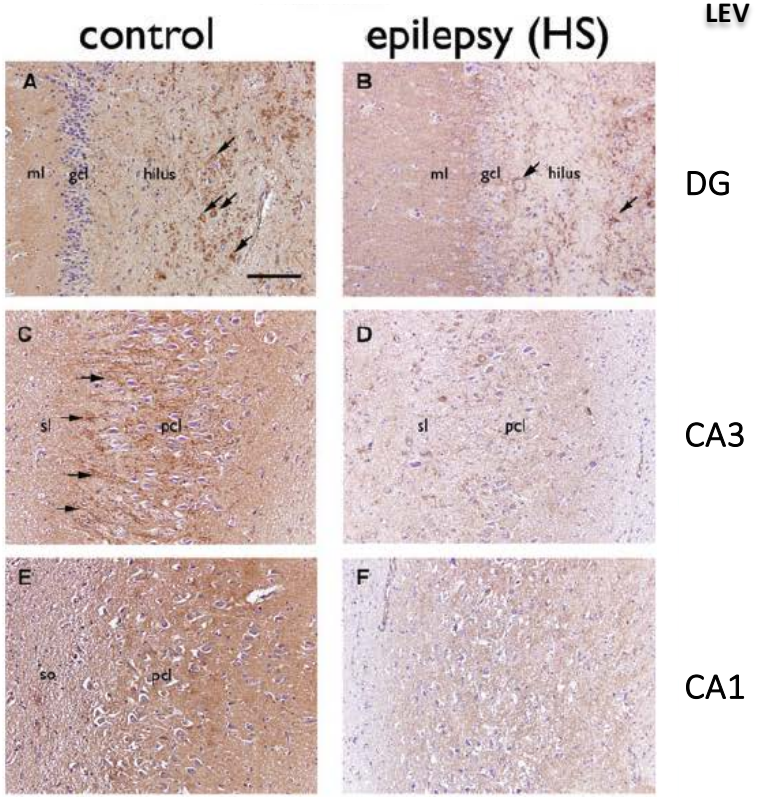
‡Mutch et al., 2011; †Takamori et al., 2006

SV2A in Epilepsy



LEV

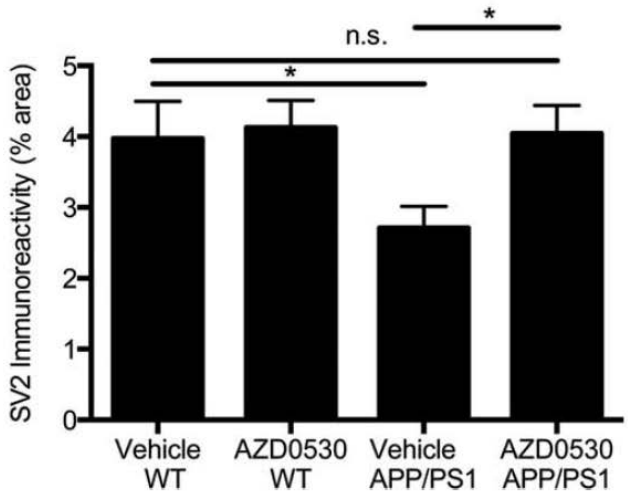
- Validated target of antiepileptic drug *levetiracetam* (LEV; Keppra®)
- Immunocytochemistry and Western blot analysis: *reduced SV2A* in hippocampus and temporal lobe in TLE with HS (similar results in FCD)
- SV2A in tumor and peritumoral tissue correlated to clinical response to LEV in patients with glioma (response prediction with 91% accuracy)
- Homozygous mutation in SV2A gene results in intractable epilepsy



Van Vliet et al. 2009, *Epilepsia*; Toering et al. 2009, *Epilepsia*; Feng et al. 2009, *J Mol Neurosci*; De Groot et al. 2011, *Neurology*; Serajee & Hug. 2015, *Pediatr. Neurol.*

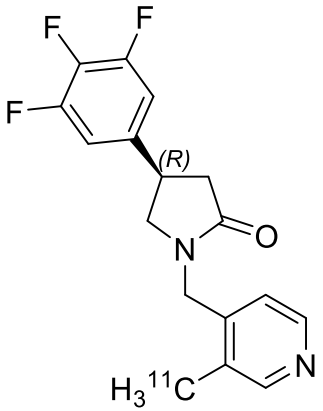
SV2 as Biomarker for Synaptic Density

- Fyn inhibitor AZD0530 reversed memory deficients in AD mouse model
- Rescue of learning and memory impairment was coupled to restoration of synaptic density (no change in Aβ)
- Recovery of synaptic density was demonstrated using SV2 immunohistochemistry



Kaufman et al., 2015

UCB-J *In Vitro* Binding



Assay/target (37°C)	K_i (nM)
recombinant human SV2A	7
recombinant human SV2B	1995
recombinant human SV2C	100

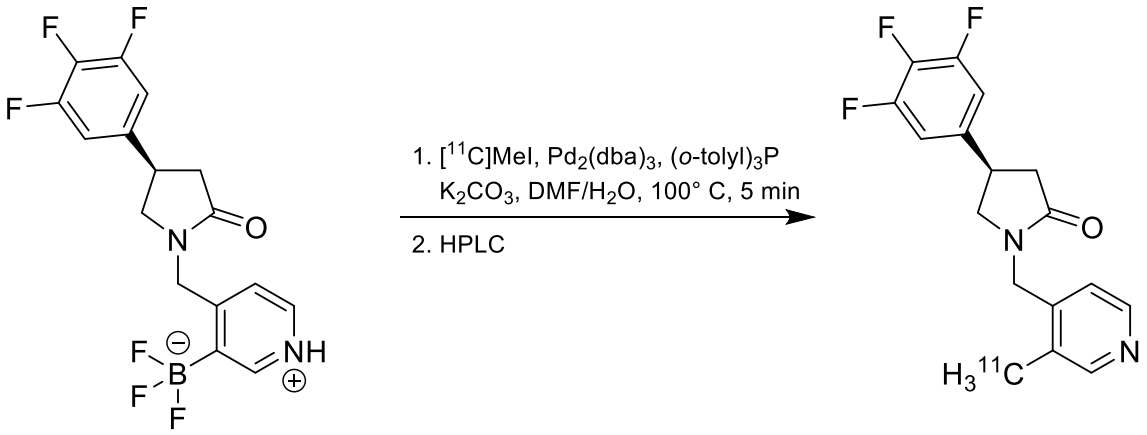
H_1	α_{2A}	α_{1A}	M_2	σ_1	κOR	D_2	5-HT_{1A}	5-HT_{2A}
3	7	-4	2	4	3	2	-2	3

% inhibition of radioligand binding to the targets when tested at 10 µM in duplicate

†Performed at UCB Pharma (Braine-l'Alleud, Belgium) and at CEREP (Celle-l'Evescault, France)

Radiolabeling

- *C*–[^{11}C]methylation via Suzuki cross-coupling

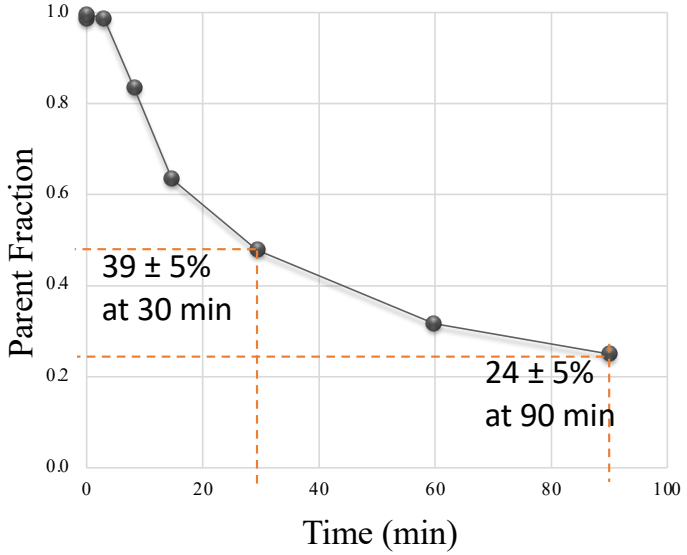


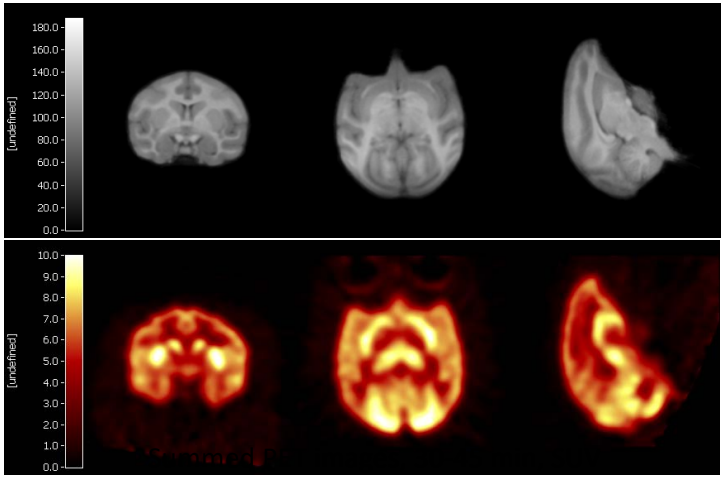
UCB1542550 **^{11}C-UCB-J**

9% yield @ EOS based on $^{11}CH_3I$; >98% CP & RCP;
S.A. 15.3 ± 7 mCi/nmol (566 ± 258 MBq/nmol) @ EOS (n = 16).

Nabulsi et al, *J Nucl Med*, 2016

^{11}C-UCB-J Plasma Analysis & PET Images

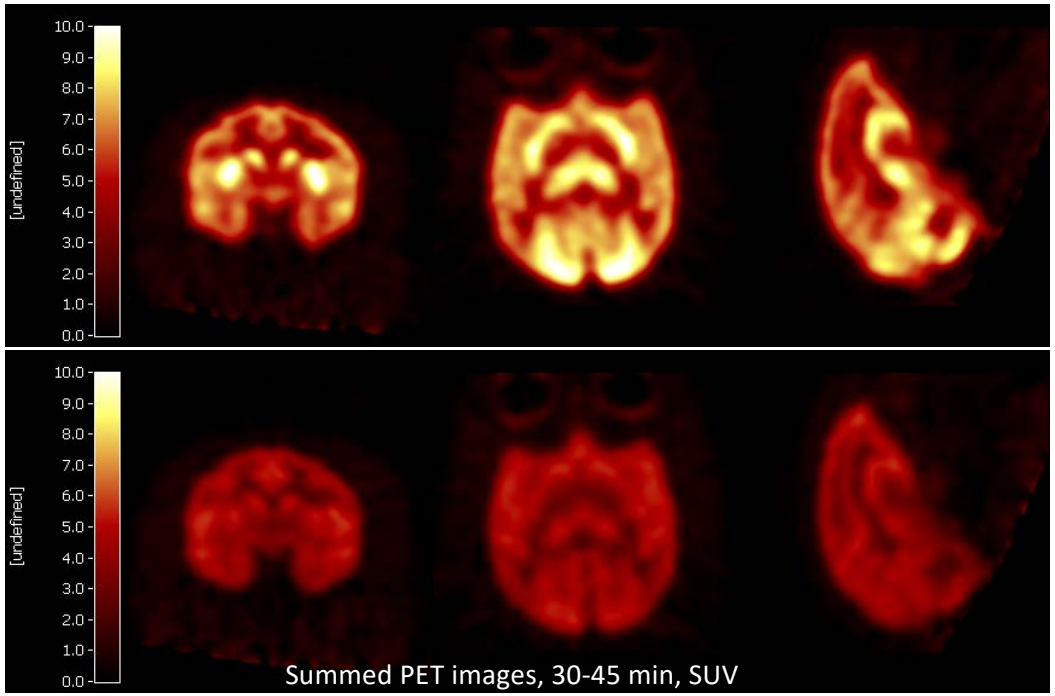




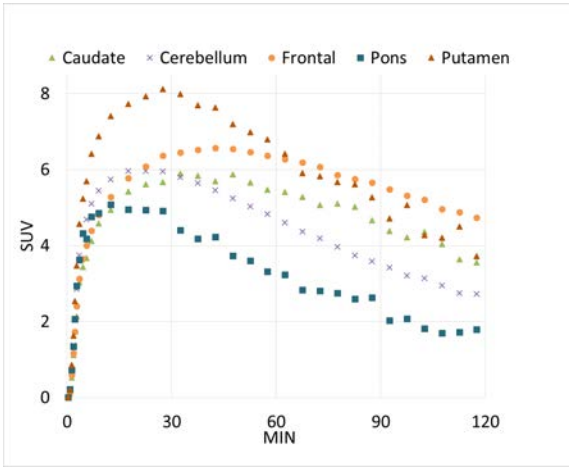
$f_p = 46 \pm 2\%$ ($n = 10$)

Log P = 2.52 ± 0.03 (n=9)

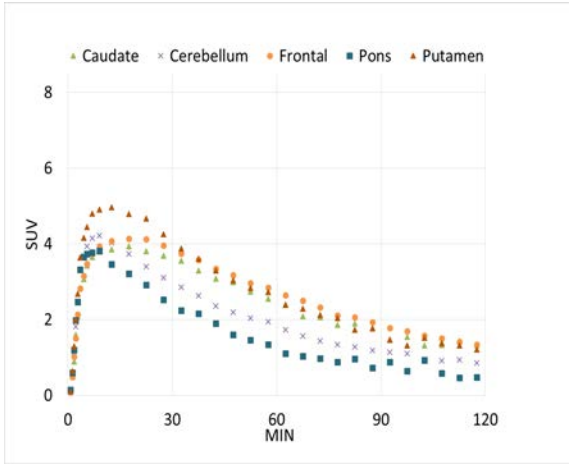
^{11}C-UCB-J Blocking with LEV (10 mg/kg)



Baseline

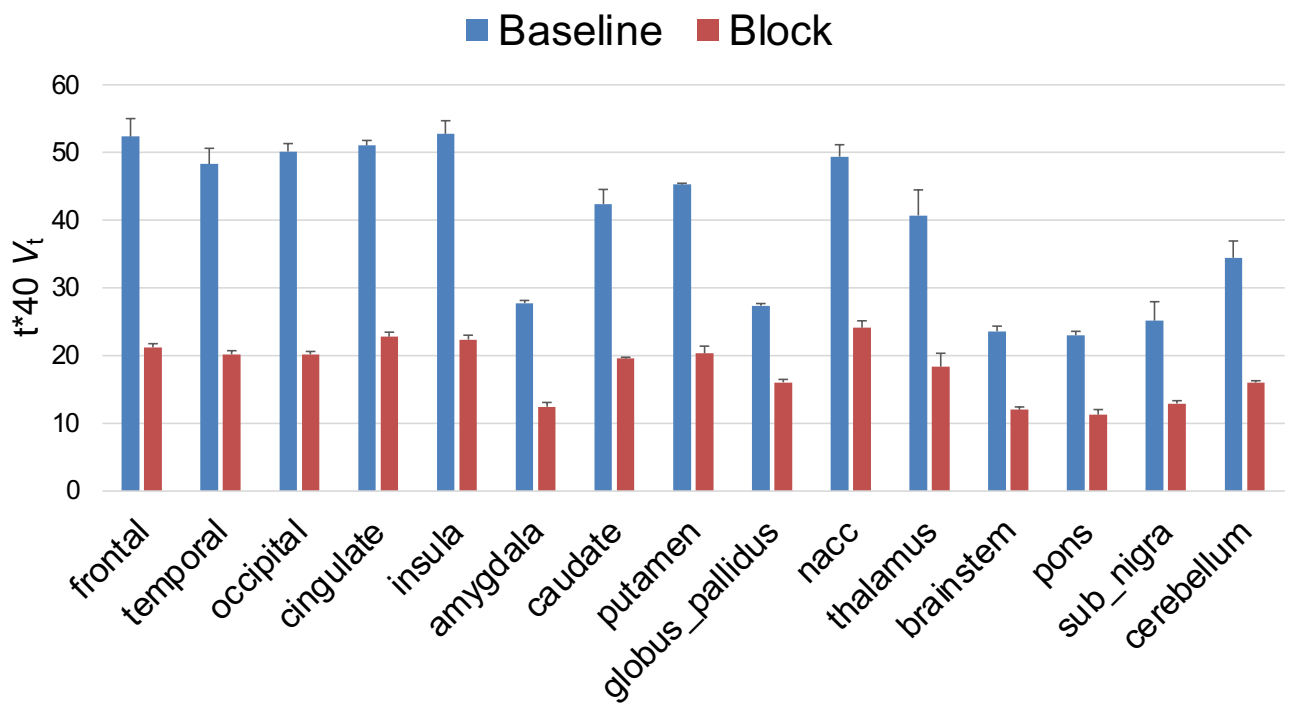


Blocked ~65% RO

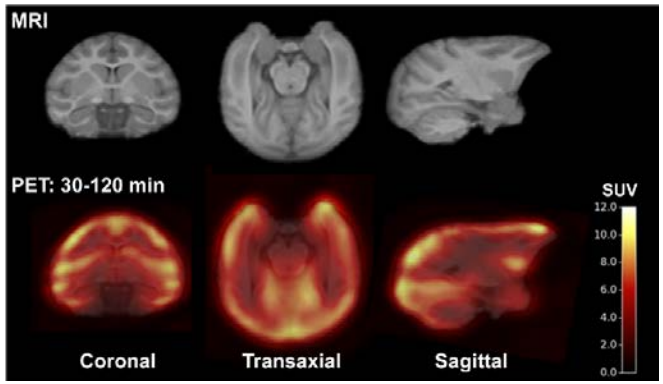


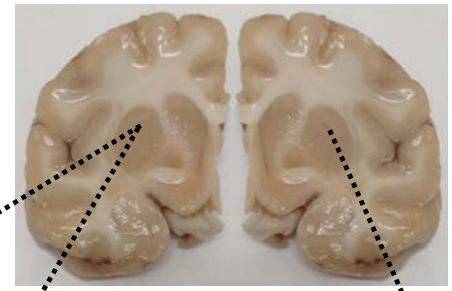
^{11}C-UCB-J Blocking with Levetiracetam

Pre-blocking with 10 mg/kg LEV; ~ 65±3% occupancy (*n*=2)



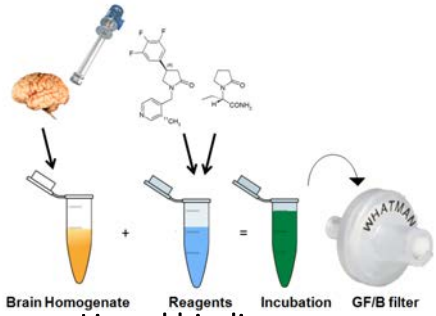
Validation study: SV2A vs. Synaptophysin (SYN)



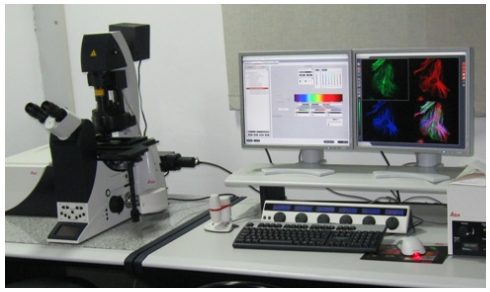


Frozen Fixed

Western blot
Regional SV2A - SYN

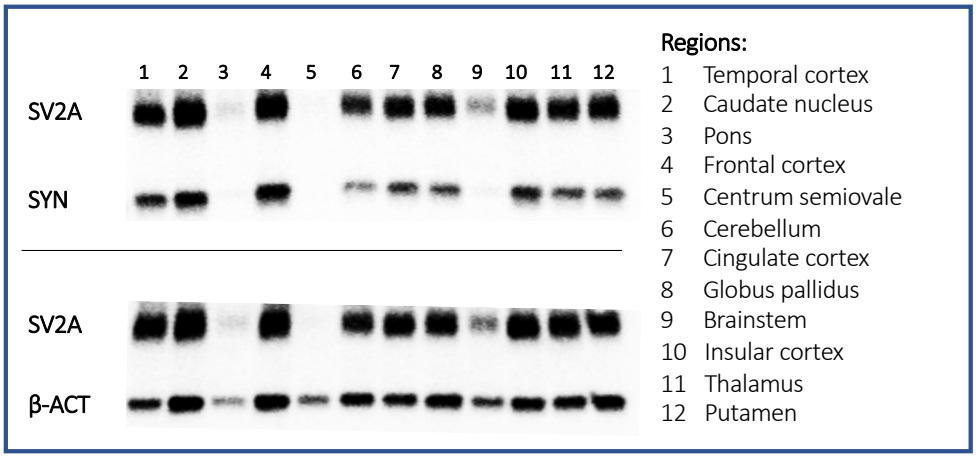


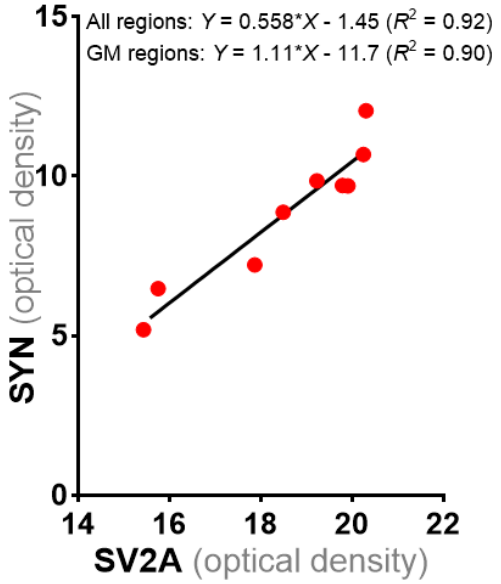
Ligand binding assay
SV2A *in vivo – in vitro*



Confocal microscopy
Cellular SV2A - SYN

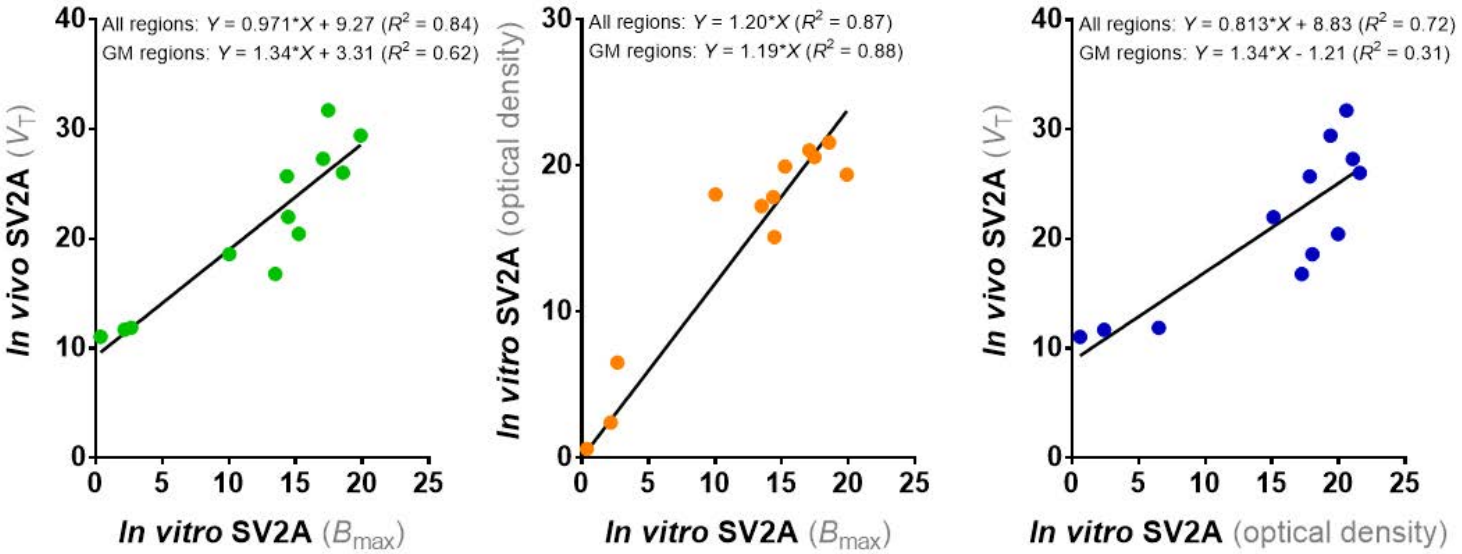
Western blot analysis





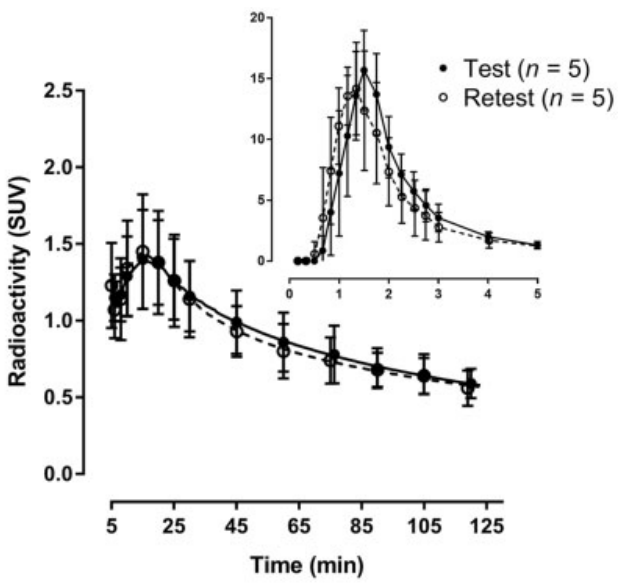
SV2A is valid alternative to SYN

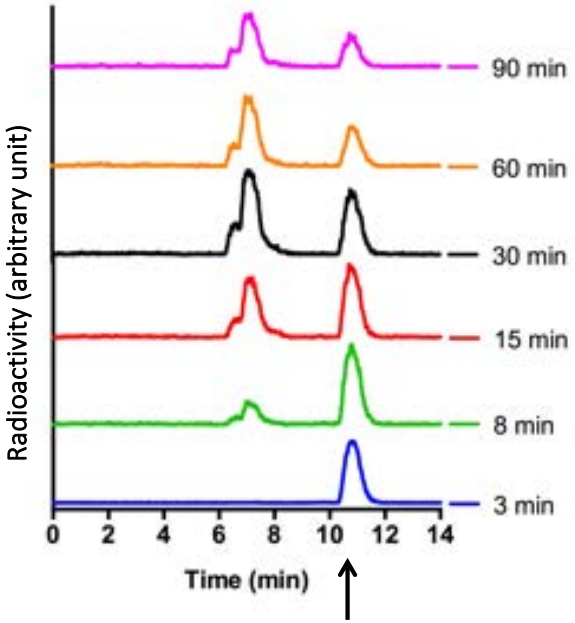
Correlation *in vitro* / *in vivo* SV2A

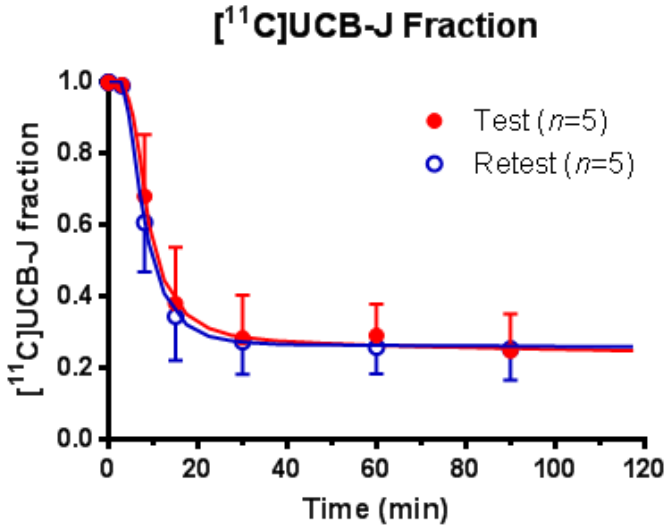


Good regional correlation *in vitro* and *in vivo* SV2A binding
Regional differences *in vivo* ^{11}C-UCB-J binding relate to SV2A density

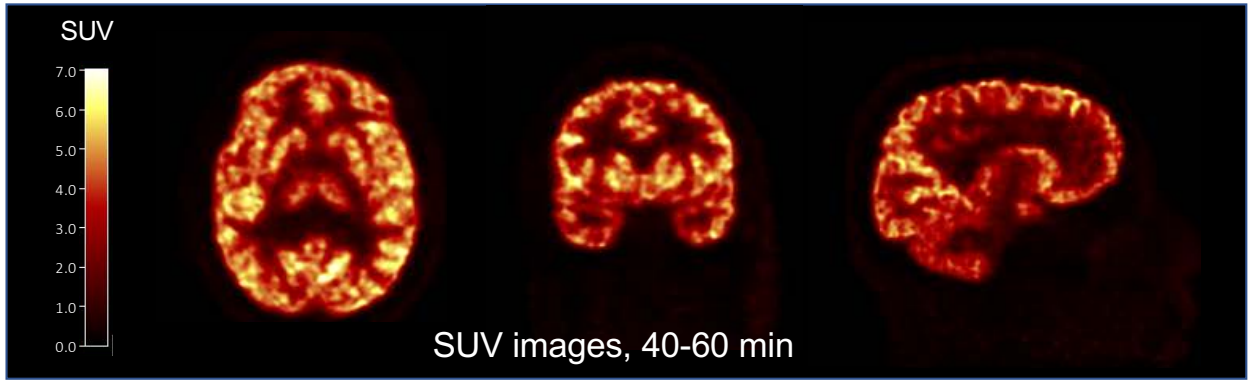
Human Arterial Input Function and Radiolabeled Metabolites

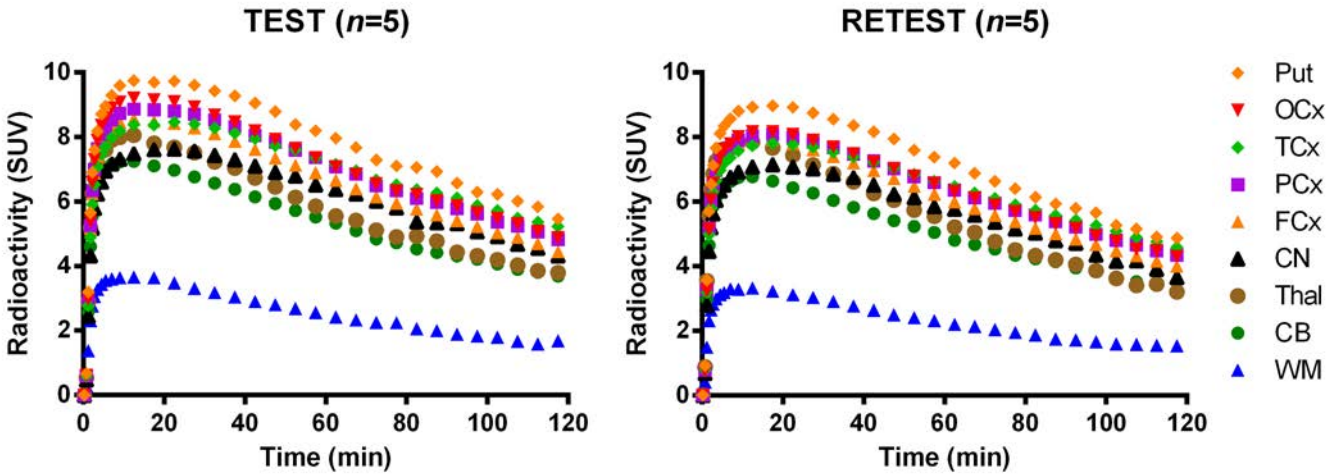




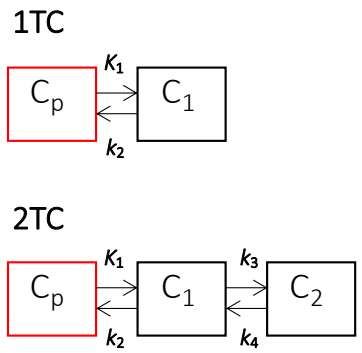


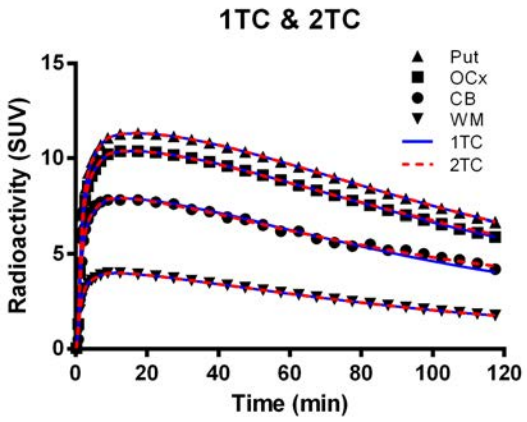
Regional Distribution of ^{11}C-UCB-J

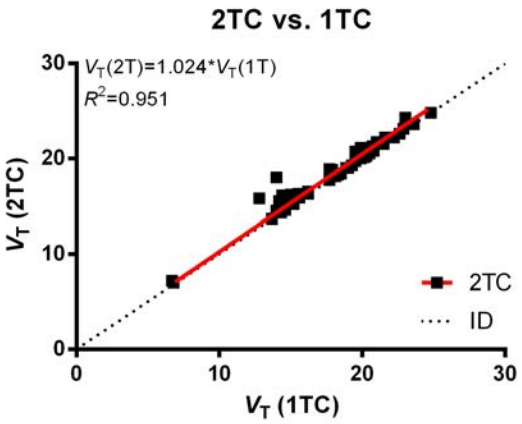




Quantification of Distribution Volume (V_T)



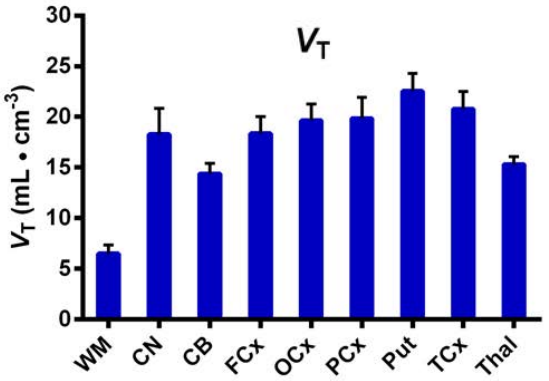


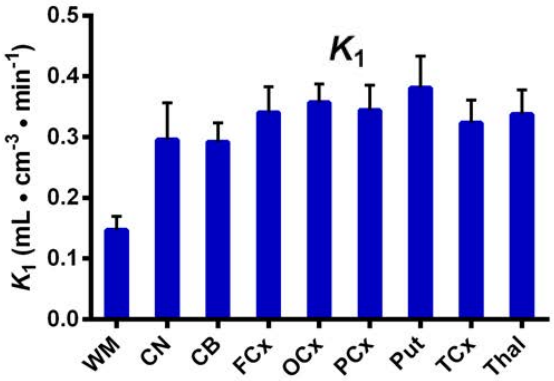


K_1 - Blood flow

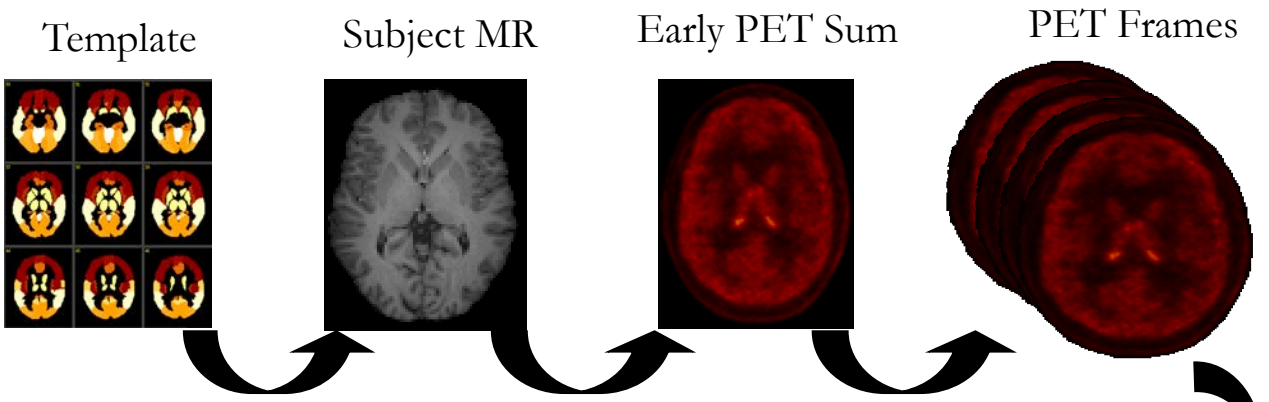
V_T – Volume of distribution

- Total binding to SV2A plus nonspecific uptake

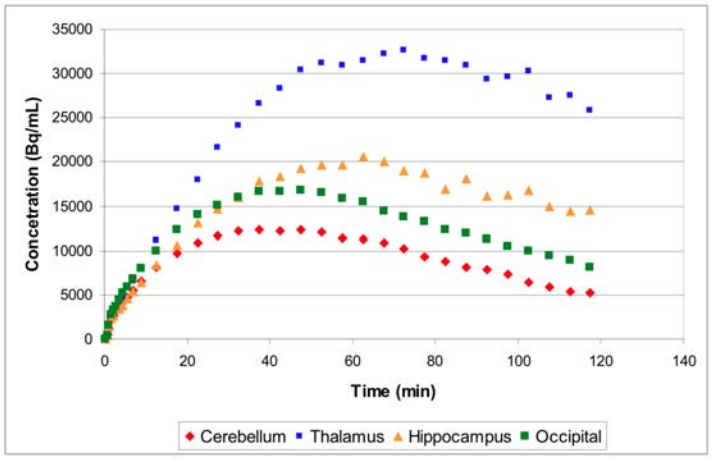




Region Definition and TAC Computation

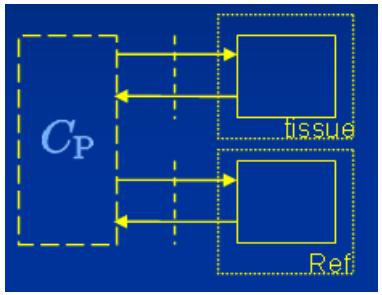


Time Activity Curves (TACs)

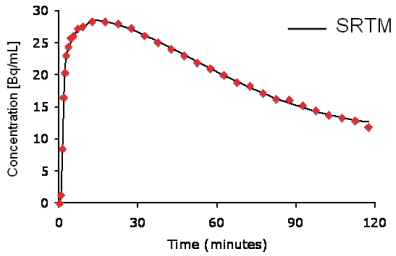


Outcome Measure Computation

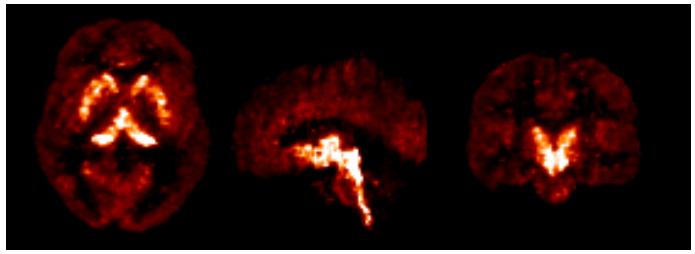
Compartment modeling

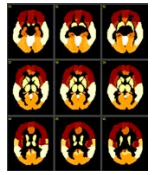


Reference region TAC fit



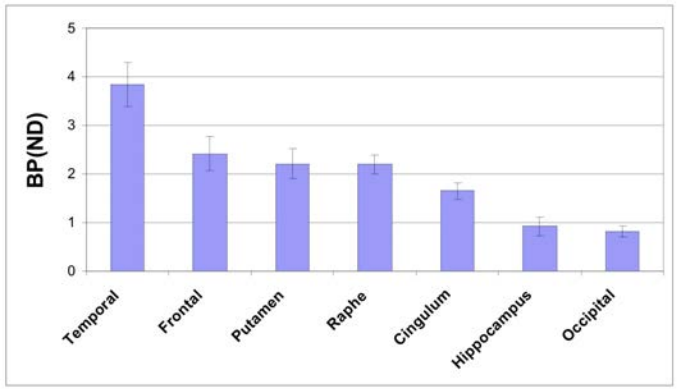
BP_{ND} parametric image





	BP_{ND}	
ROI	Mean	SD
Temporal	**3.850**	**0.454**
Frontal	**2.420**	**0.363**
Putamen	**2.213**	**0.304**
Raphe	**2.194**	**0.187**
Cingulum	**1.650**	**0.164**
Hippocampus	**0.926**	**0.188**
Occipital	**0.817**	**0.113**

Mean regional BP_{ND} values



Test-Retest Reliability of V_T [%]

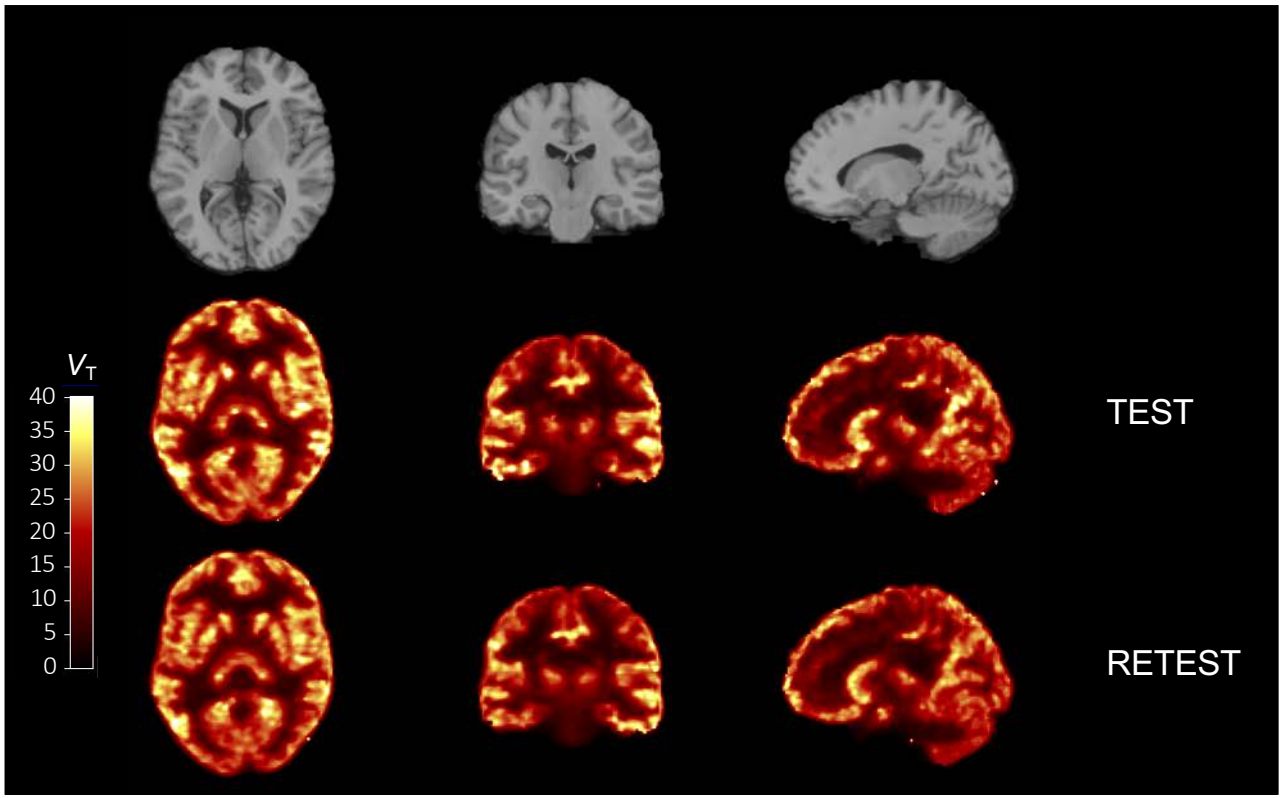
Measure	Subject	WM	CN	CB	FCx	OCx	PCx	Put	TCx	Thal
Difference (%)	Subj. 1	-4	0	-1	-2	-6	-4	-2	-4	0
	Subj. 2	3	5	2	3	3	5	4	4	6
	Subj. 3	-7	-9	5	-1	1	1	-7	-4	-1
	Subj. 4	-3	-2	1	-2	-5	-5	2	-3	-1
	Subj. 5	2	0	-1	5	1	1	5	2	4
	Mean	-2	-1	1	1	-1	0	0	-1	2
Absolute Variability (%)	**Mean**	**4**	**3**	**2**	**3**	**3**	**3**	**4**	**3**	**3**

Difference: (RETEST-TEST)/((RETEST+TEST)*0.5)*100%
Variability: |RETEST-TEST|/((RETEST+TEST)*0.5)*100%

Parametric Maps of V_T Calculated on Voxel Level

V_T – Volume of distribution

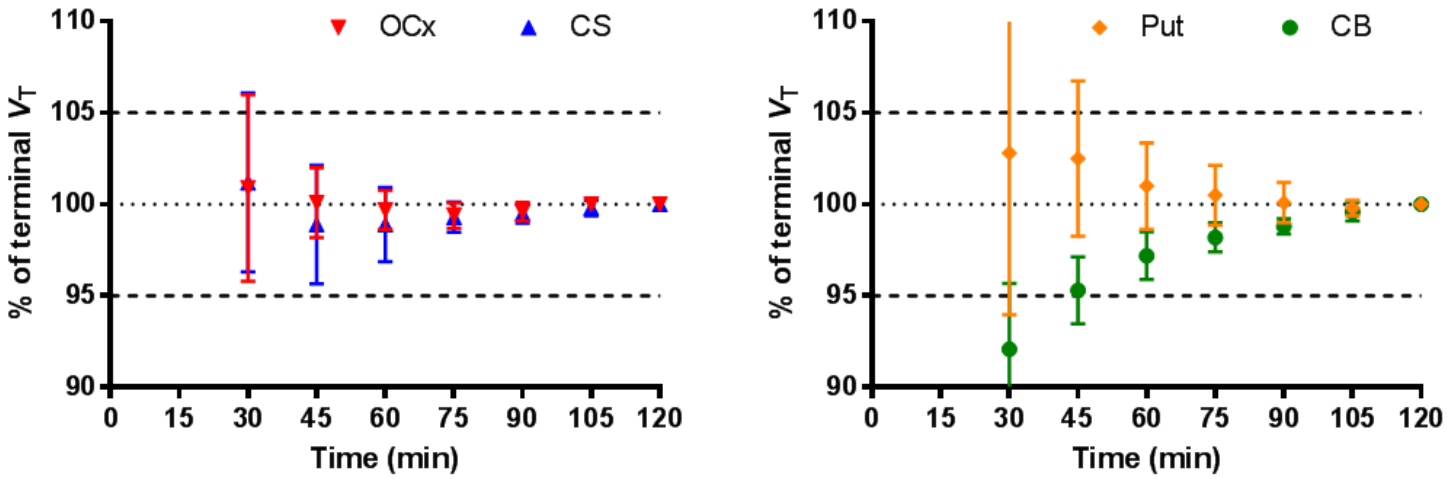
- Total binding to SV2A plus nonspecific uptake



Quantitative V_T images

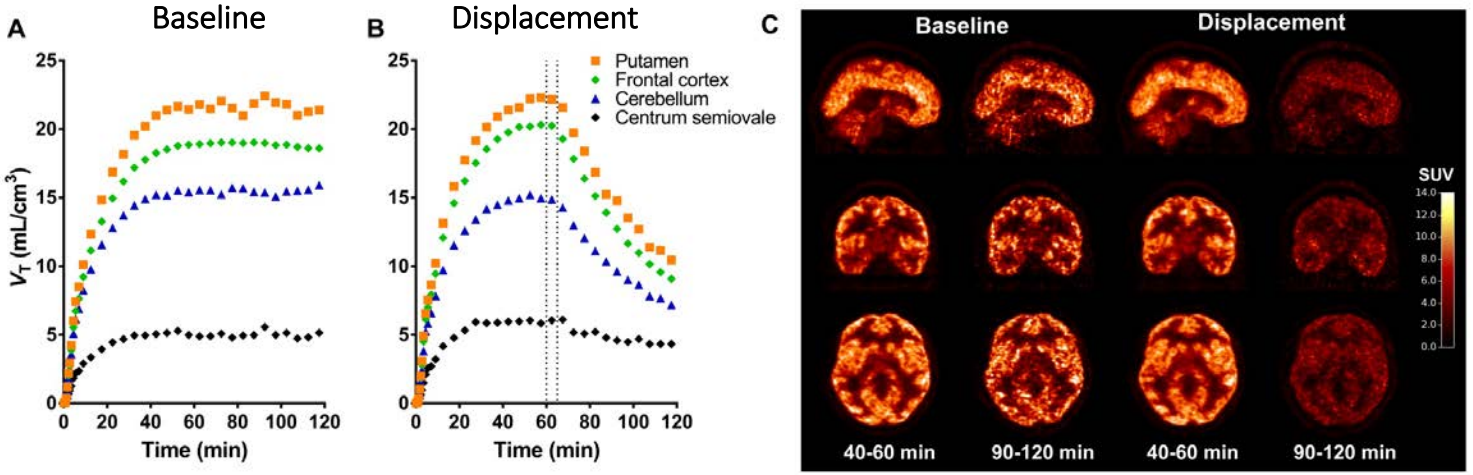
Finnema et al, *JCBFM*, 2017

Stability of V_T over Time



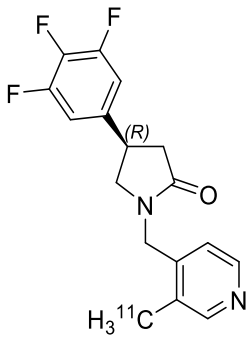
Displacement Studies with Levetiracetam

- Baseline and displacement study
- Very helpful to have approved specific blocking drug
- Levetiracetam (Keppra, 1500 mg i.v. infusion 60-65 min)



Finnema et al, *Sci Transl Med,* 2016

SV2A/Synaptic Density Validation Still a Long Way to Go

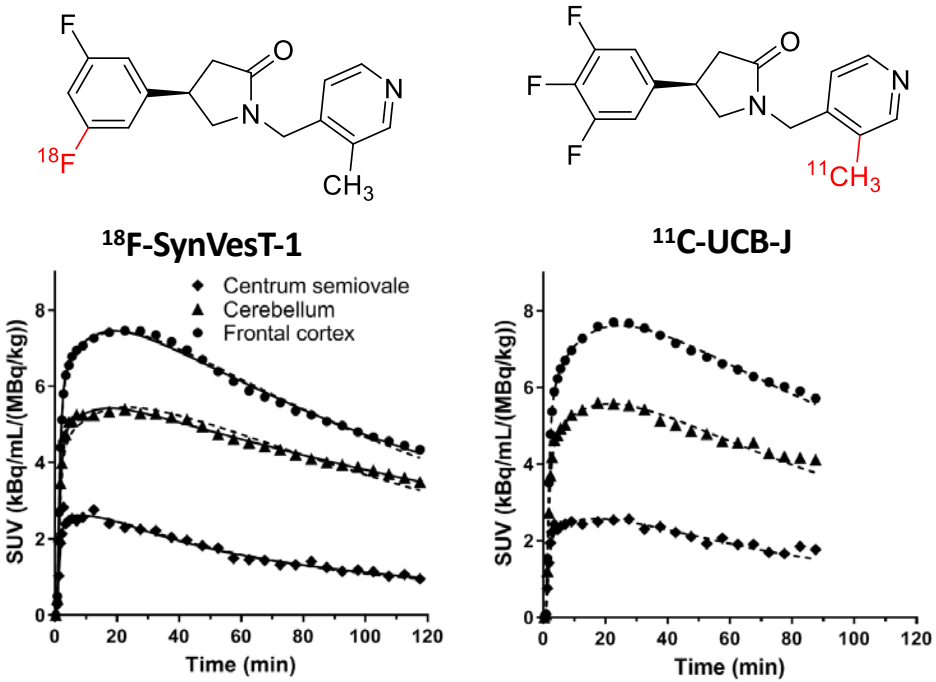


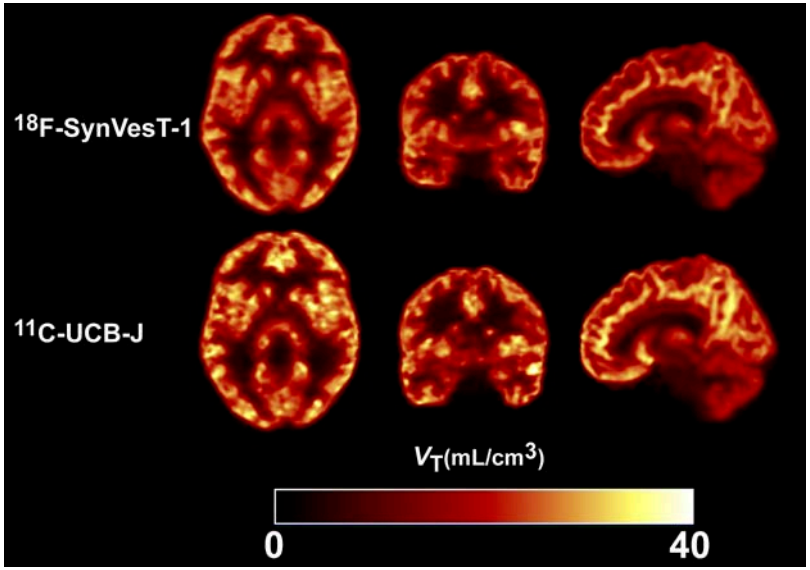
- Technical issues:
  - **Choice of outcome measures**
  - **Choice of a reference region**
  - **C-11 vs. F-18**
- SV2A as a general marker of synaptic density
  - # of SV2A per vesicle and # of vesicles per synapse
  - Validation of SV2A as a synaptic density marker in health and diseases
  - Effect of vesicle exocytosis and recycling on SV2A binding
- Clinical interpretation:
  - Utility in specific diseases to monitor progression
    - Alzheimer's disease, epilepsy, Depression, PTSD, Schizophrenia, Cannabis Use, Cocaine Use, Parkinson's, Alcohol dependence, Multiple Sclerosis, Huntington's Disease, Autism Spectrum Disorder
  - Imaging biomarker of synaptic regrowth
    - NCT03493282: Effect of CT1812 Treatment on Brain Synaptic Density
  - Utility in animal models: Epilepsy, AD, depression, stroke

SV2A/Synaptic Density Technical Issues

- **Choice of outcome measures**
  - V_T
    - Needs arterial data, includes nonspecific binding
  - V_T / f_p – correct for protein binding
    - Relevant if there are group differences or substantial intersubject variability in free fraction
  - BP (binding potential)
    - Is there an ideal reference region with no specific binding?
  - DVR (Distribution volume ratio)
    - Normalize to a suitable region
- **Choice of a reference region**
  - Centrum semiovale
    - Some specific binding
    - No difference seen in AD, epilepsy, and PD
    - Differences seen in MDD
    - CS is small, so adds noise
    - Sensitive to partial volume effect
  - Disease-specific normalizing region
    - Cerebellum in AD

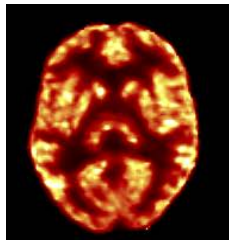
F-18 SV2A Ligand: SynVesT-1





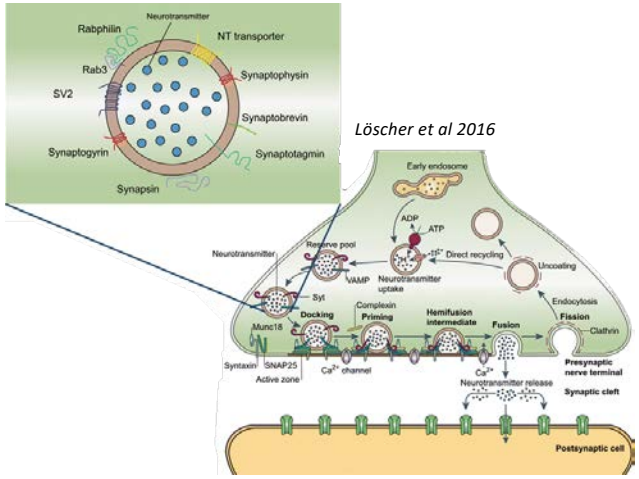
- ^{18}F-SynVesT-1 *vs.* ^{11}C-UCB-J: Similarly high brain uptake, fast tissue kinetics and regional distribution

Quantitative Brain PET



- Kinetic Modeling 101
  - Basic modeling methods
- Tracer Development and Validation
  - SV2A Tracer ^{11}C-UCB-J
  - Nonhuman primates
  - Human studies
- **Using modeling to separate blood flow and binding changes**
- When is modeling important?
  - When might simplified methods be misleading …
- Simplifications for Brain Imaging
  - Standard Uptake Value Ratio (SUVR) vs. Distribution Volume Ratio (DVR)
  - Time dependent relationships
- Transient Equilibrium
  - Two wrongs can make a right
- Closing thoughts

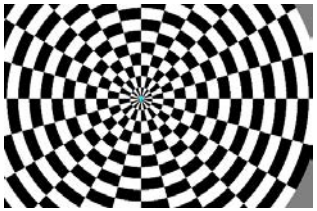
Is the SV2A signal sensitive to neuronal activation?



Löscher et al 2016

- SV2A is involved in regulating vesicle release, a complex and highly mediated process involving interactions with other proteins or with Ca^{2+}
- **Tracer binding sites may become more or less accessible** during active vesicle release. If so, **changes in ^{11}C-UCB-J binding would reflect influence of local activity** as well as synaptic vesicle number.
- **Need modeling to separate blood flow effects from changes in binding**

Study Design



- 7 healthy subjects
- 2 [^{11}C]UCB-J scans
  - 60 min. baseline
  - 60 min. with continuous intermittent visual activation
    - 8Hz flickering radial checkerboard
- 1 fMRI scan with checkerboard stimulation
  - 6 x 30s on/off (fMRI-optimized)
  - 3 x 3’ on / 2’ off (PET-optimized)

Results

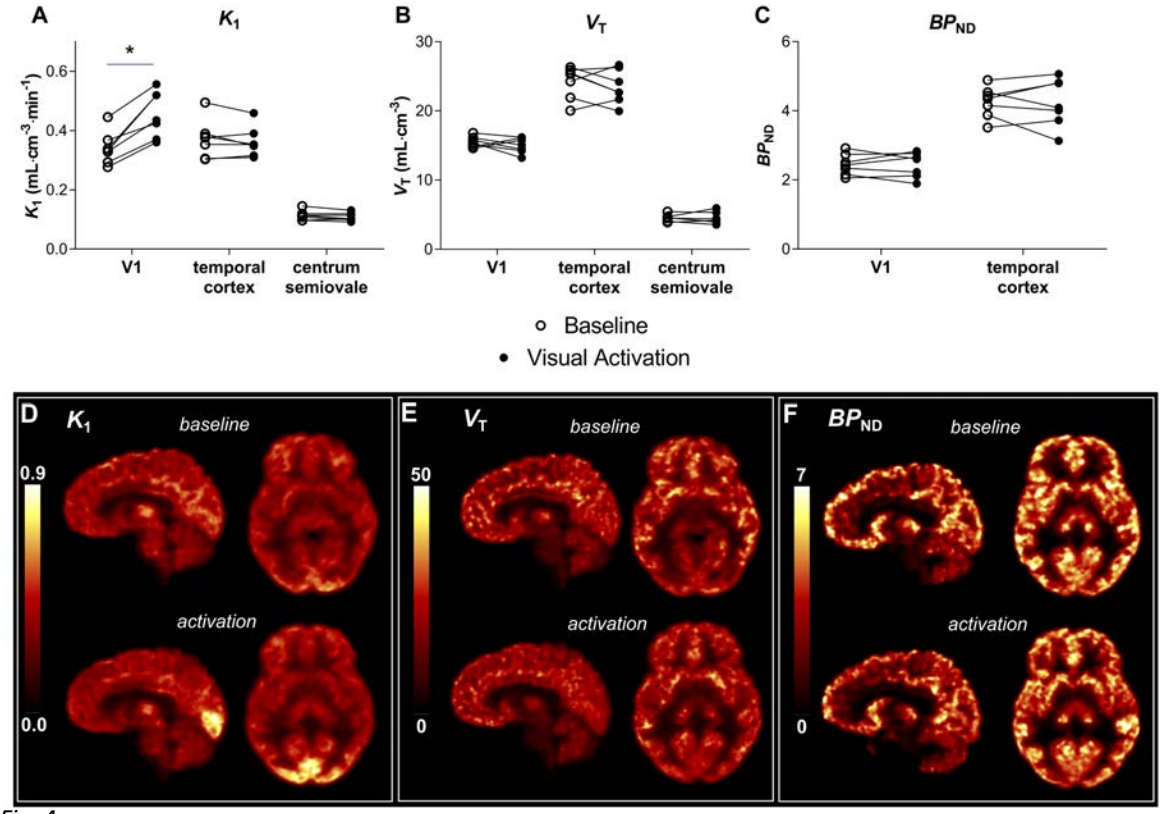


Fig. 4

- 35% increase in K1 in primary visual cortex.
- **No change in V_T or BP_{ND}.**

→ ^{11}C-UCB-J binding is a stable *in vivo* measure of SV2A density despite increased vesicle release.

Results

- fMRI BOLD increase in V1 and LGN.
- PET K1 increase in V1.

- **Change in K1 is correlated with change in fMRI BOLD signal in visual cortex.**

→ **K1 tracks brain activity.**

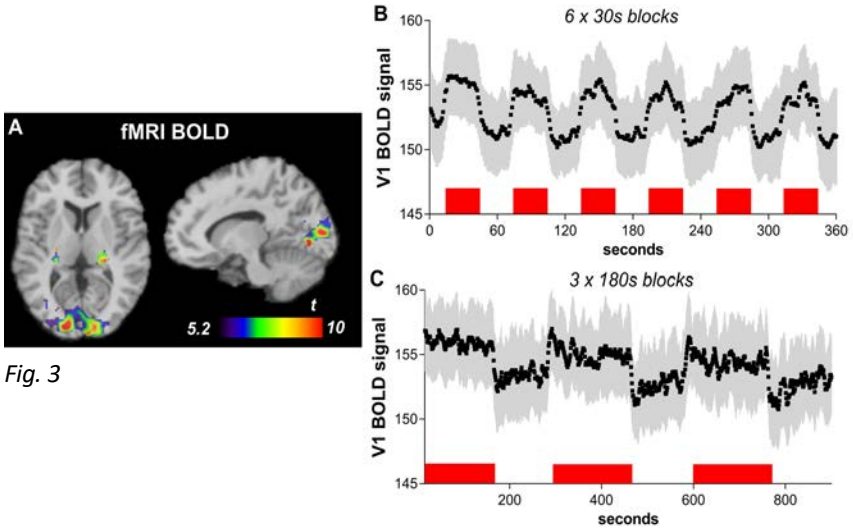


Fig. 3

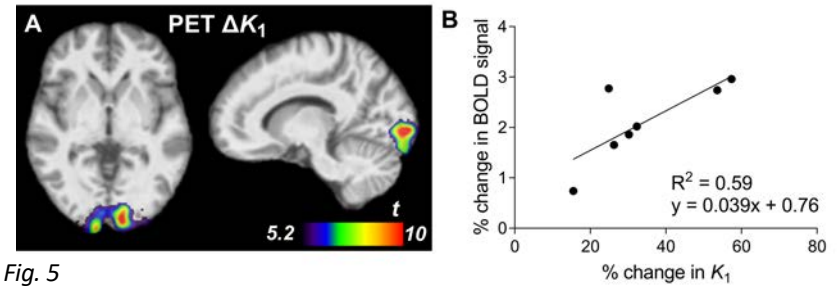


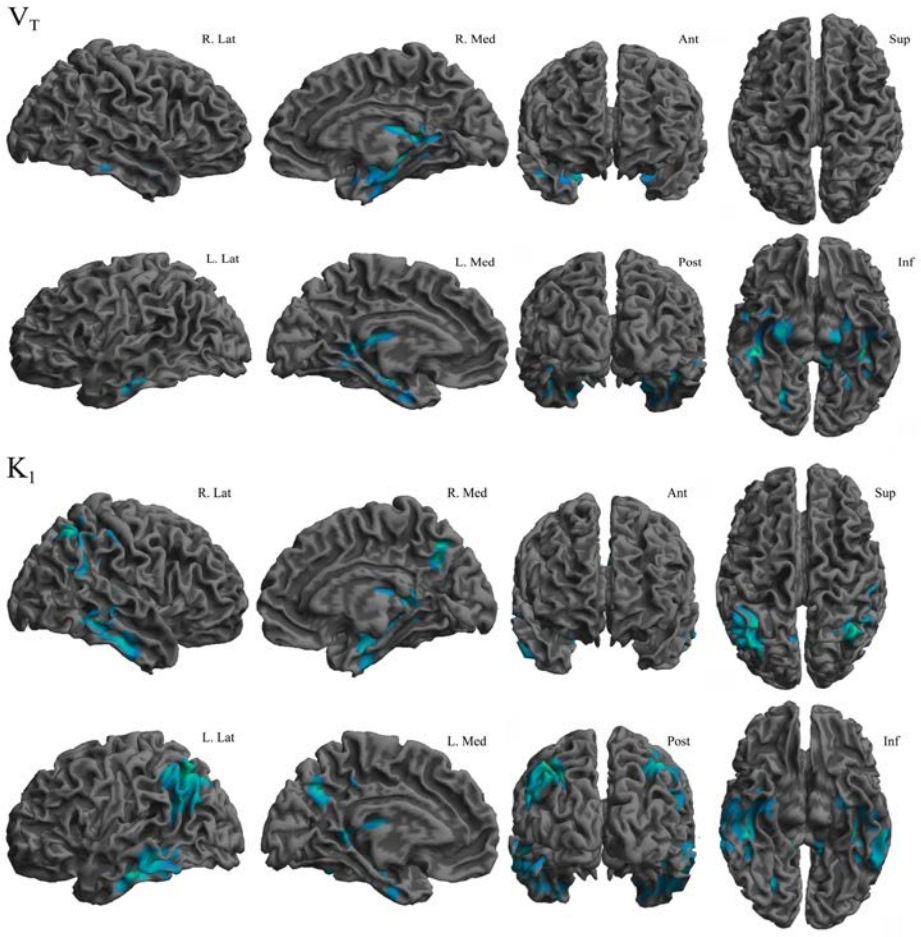
Fig. 5

Smart et al, JCBFM, 2020

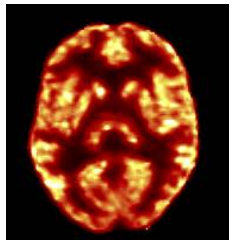
Synaptic Density in Alzheimer's Disease

V_T

K_1



Quantitative Brain PET



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Amyloid Example Where Modeling Helps

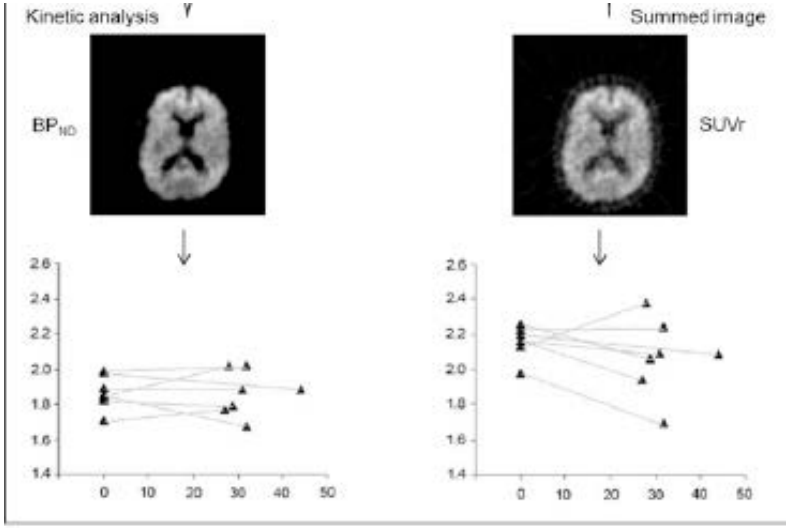

FIGURE 6. BP_{ND} and SUVr (60–90 min after injection) for ^{11}C-Pittsburgh compound B scans of Alzheimer disease patients at 2 time points 2–4 y apart (horizontal axes represent months after baseline scan). Patients did not receive antiamyloid therapy during interval between scans. SUVr shows a small 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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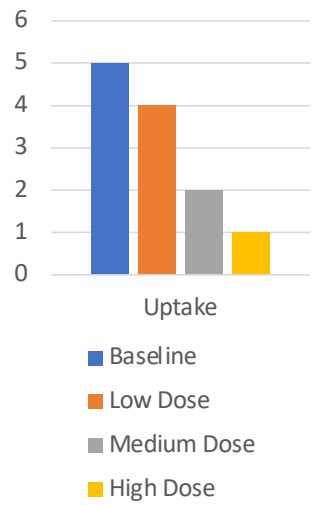
J Nucl Med 2017; 58:1019–1024
DOI: 10.2967/jnumed.116.188029

Goals of PET Modeling

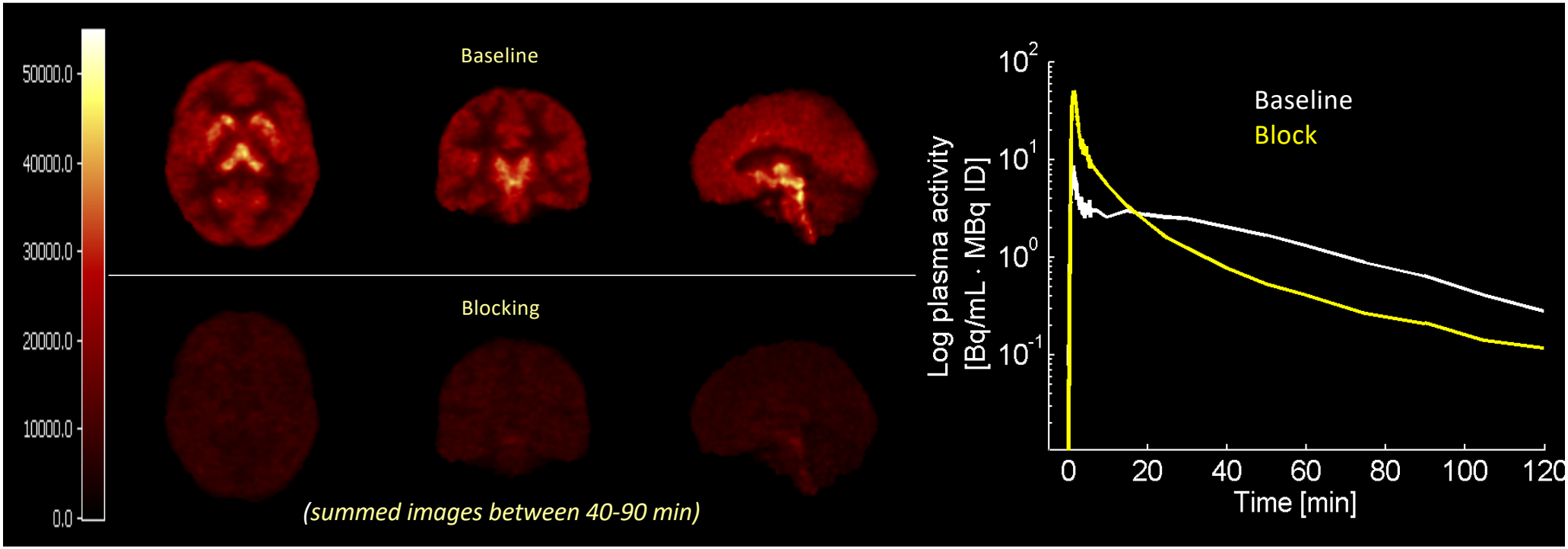
- Understand the relationship between the tissue measurements and the underlying physiology (blood flow, metabolism, etc.)
- **Account for the effects of tracer availability (input function).**
- Determine what parameters can be measured
- Devise study methodology
- Prove that the method measures the 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.

Studying Drug Effects: Input Functions

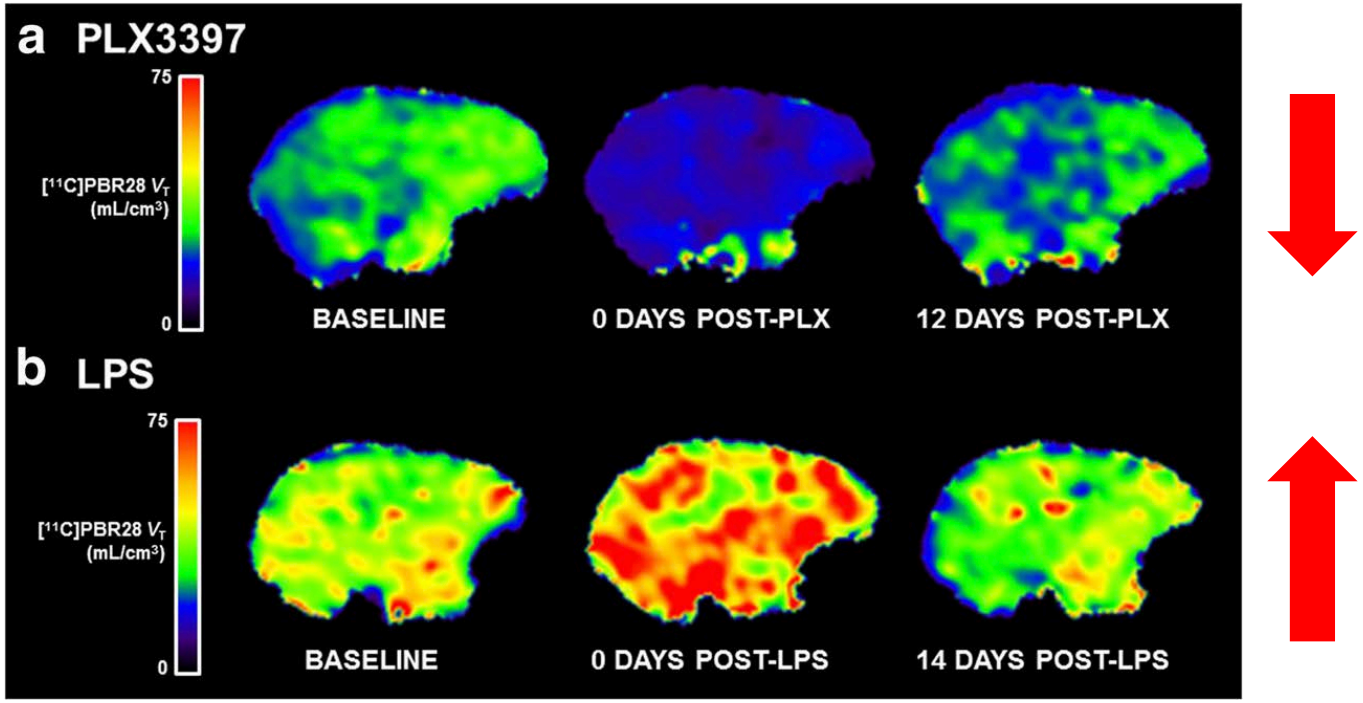


- Drug and tracer target the same site
- We expect dose-dependent reductions in specific tracer binding following administration of a competing drug
- Typically, blocking drugs reduce tracer in tissue, and increase tracer in the blood
  - Increased bioavailability (the input function)
  - Increased nonspecific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

^{11}C-AFM: SERT Tracer
Blocking Studies (Citalopram)

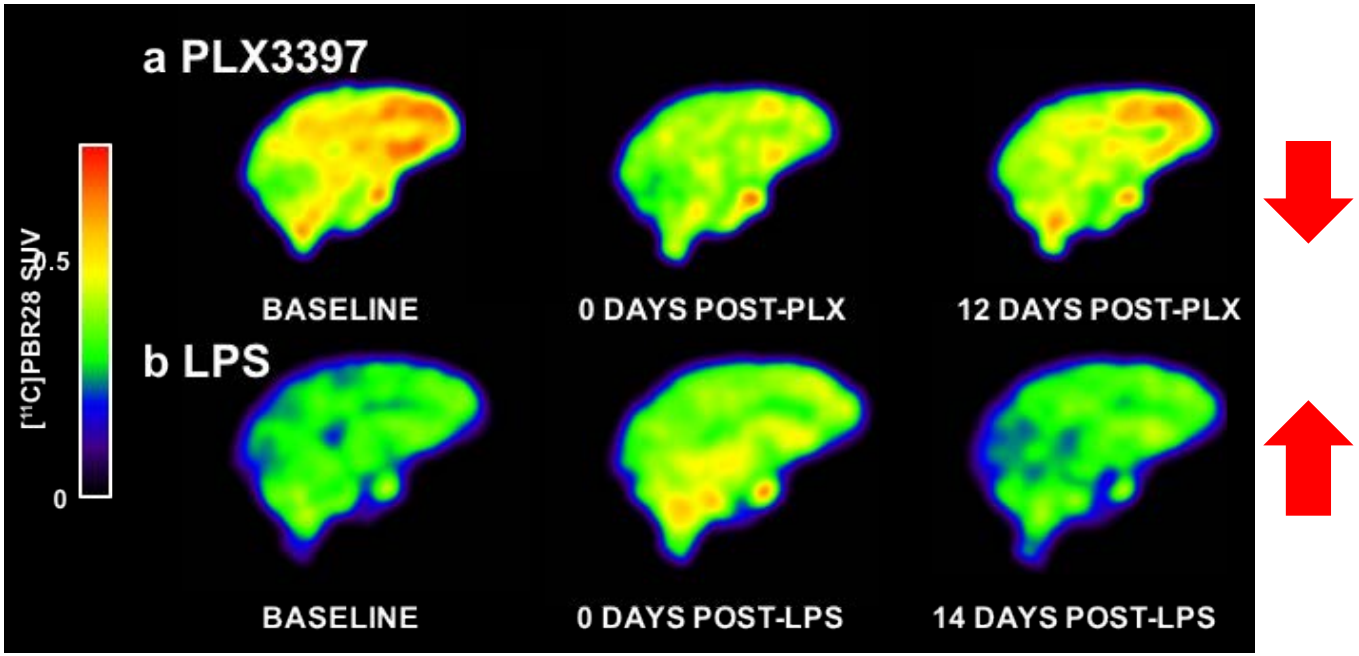


Microglial Activation and Depletion Results with Modeling



Hillmer et al, Eur J Nuc Med Res, 2017

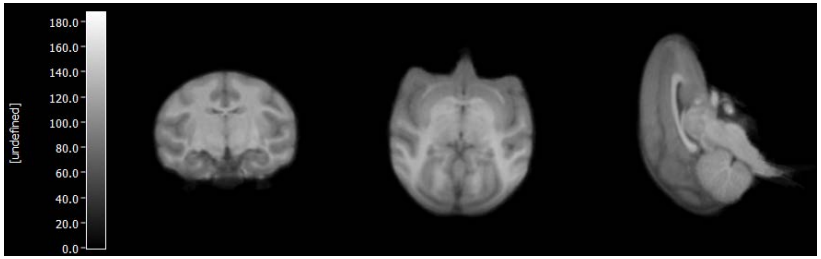
Microglial Activation and Depletion Results without Modeling



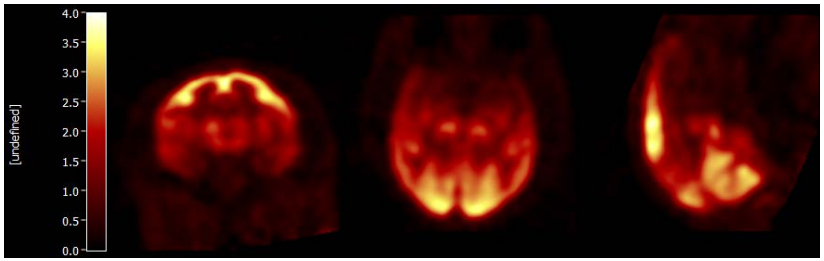
Magnitude of change reduced without modeling

Hillmer et al, Eur J Nuc Med Res, 2017

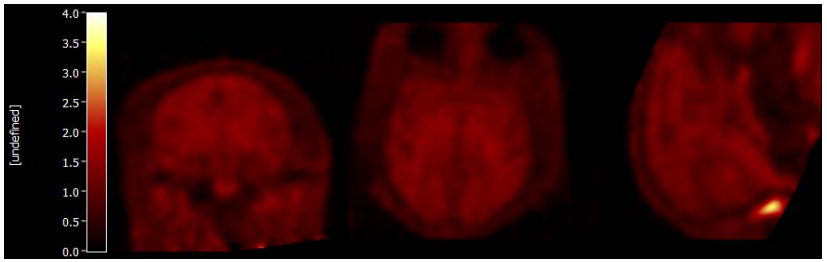
Brain Enzyme Inhibitor Study
SUV Images



MR



Baseline



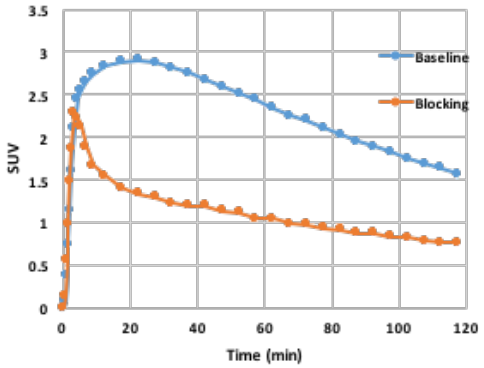
Inhibitor

Variation in specific binding among brain regions

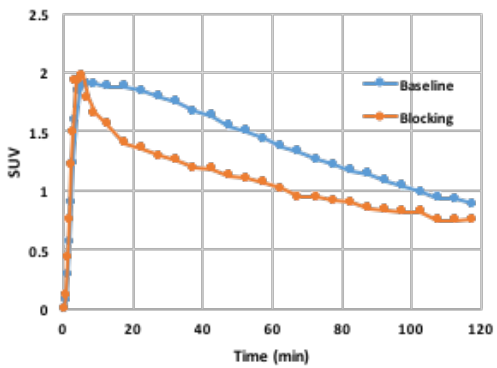
Brain Enzyme Inhibitor Study

Differences Among Brain Regions Without Modeling

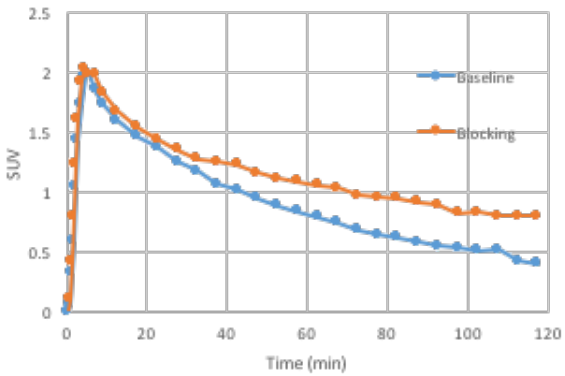
Occipital cortex



Temporal cortex



Frontal cortex

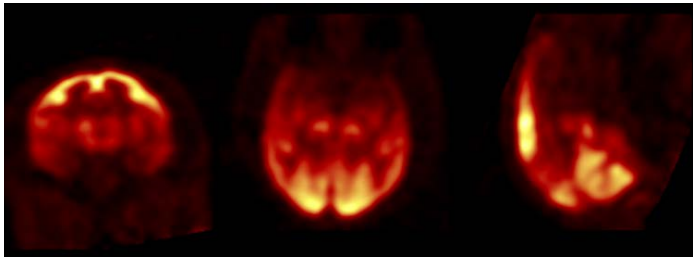


SUV

Baseline
Blocking

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

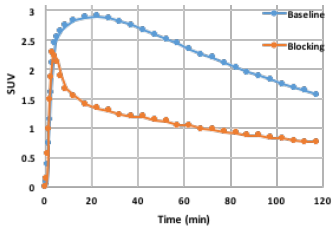
- ??



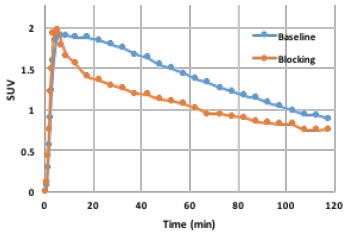
Brain Enzyme Inhibitor Study

Differences Among Brain Regions Without Modeling

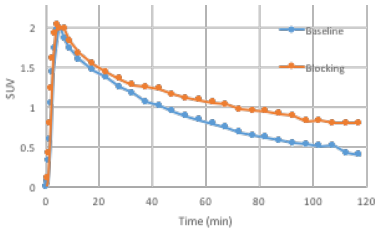
Occipital cortex

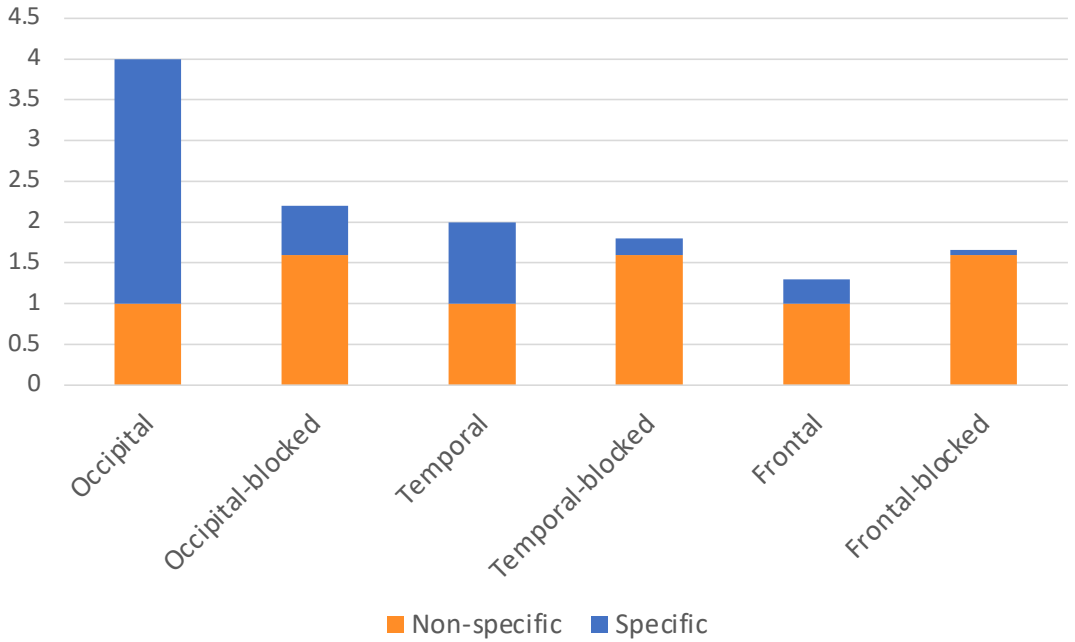


Temporal cortex

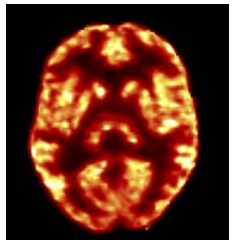


Frontal cortex





Quantitative Brain PET



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  - SV2A Tracer ^{11}C-UCB-J
  - Nonhuman primates
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- Using modeling to separate blood flow and binding changes
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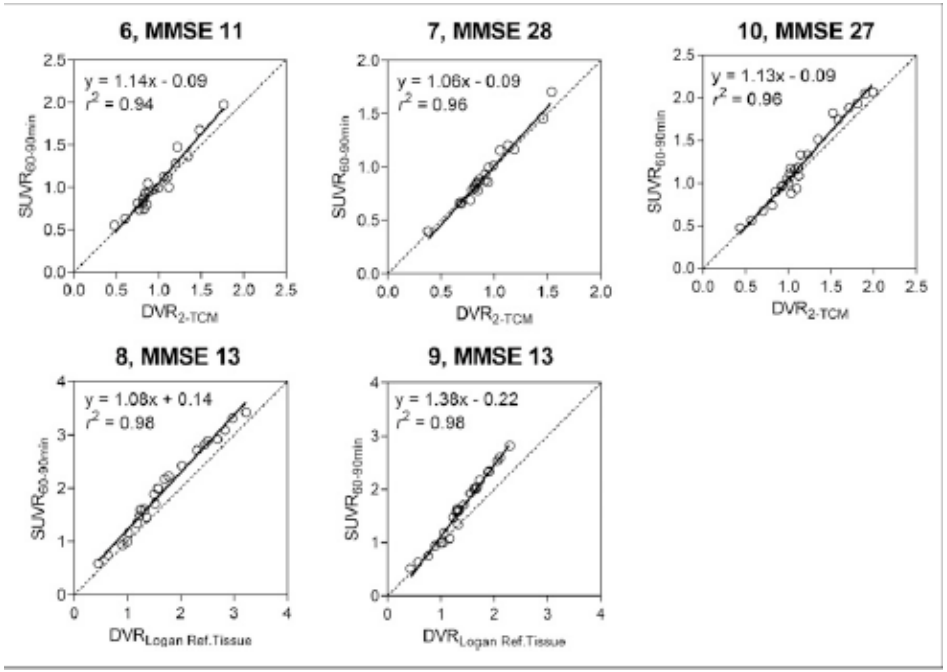
- **Simplifications for Brain Imaging**
  - Standard Uptake Value Ratio (SUVR) vs. Distribution Volume Ratio (DVR)
  - Time dependent relationships
- Transient Equilibrium
  - Two wrongs can make a right
- Closing thoughts

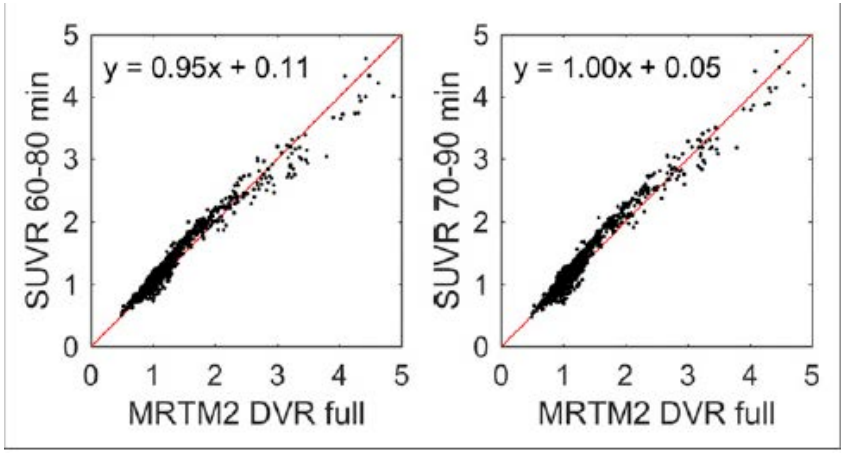
Simplifications for Brain Imaging

- Use our understanding of the model to produce a protocol and analysis that balances patient simplicity with physiological accuracy
- Find a reference region for normalization – skip the arterial samples
- Look for a static time period that best correlates with the “gold standard” distribution volume ratio **DVR**
- The holy grail: Tissue-to-reference ratio: **SUVR**
- Apply in patient populations and clinical trials

DVR vs. SUVR ^{18}F-MK6240



Lohith et al, JNM, 2019



Regression	Coefficient	β– *(SE)*	95% confidence interval	R^2
SUVR (40–60) vs. LGA (full)	Slope	0.814 (0.004)	0.806 to 0.822	0.96
	Intercept	0.245 (0.005)	0.235 to 0.255	
SUVR (50–70) vs. LGA (full)	Slope	0.934 (0.004)	0.926 to 0.941	0.971
	Intercept	0.131 (0.005)	0.122 to 0.141	
SUVR (60–80) vs. LGA (full)	Slope	1.014 (0.004)	1.006 to 1.022	0.972
	Intercept	0.048 (0.005)	0.038 to 0.058	
SUVR (70–90) vs. LGA (full)	Slope	1.073 (0.005)	1.064 to 1.082	0.970
	Intercept	−0.015 (0.006)	−0.026 to −0.004	
SUVR (40–60) vs. MRTM2 (full)	Slope	0.757 (0.004)	0.748 to 0.766	0.947
	Intercept	0.299 (0.006)	0.288 to 0.310	
SUVR (50–70) vs. MRTM2 (full)	Slope	0.869 (0.004)	0.861 to 0.878	0.960
	Intercept	0.192 (0.006)	0.181 to 0.203	
SUVR (60–80) vs. MRTM2 (full)	Slope	0.945 (0.004)	0.937 to 0.954	0.964
	Intercept	0.112 (0.006)	0.101 to 0.123	
SUVR (70–90) vs. MRTM2 (full)	Slope	1.002 (0.005)	0.993 to 1.011	0.964
	Intercept	0.052 (0.006)	0.040 to 0.063	

Betthauser et al, JNM, 2019

Simplifying ^{11}C-UCB-J SV2A Imaging

- 90 min scan on the HRRT scanner
  - Bolus injection over 1 min.
  - Arterial blood sampling and metabolite analysis for gold standard values (V_T and BP_{ND}) Reference region = Centrum semiovale

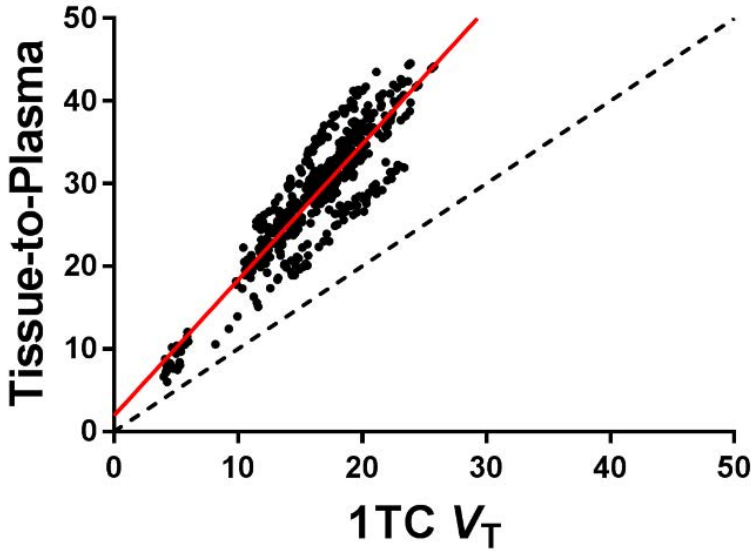
- 2 datasets
  - Healthy controls (**HC**)
  - Alzheimer's disease (**AD**)

- Tissue-to-plasma ratio (a.k.a. the apparent volume of distribution, $V_{T(A)}$) compared to V_T
  - Tissue-to-plasma ratio at equilibrium = V_T

- Tissue-to-reference ratio (a.k.a. **SUVR**) compared to **DVR**
  - **SUVR =** $V_{T(A)}$(ROI) / $V_{T(A)}$(Reference)
  - **SUVR-1 compared to** BP_{ND}

^{11}C-UCB-J: Healthy Control Data
Tissue-to-Plasma Ratio

- **$V_{T(A)}$ (60-90 min) substantially overestimates V_T**

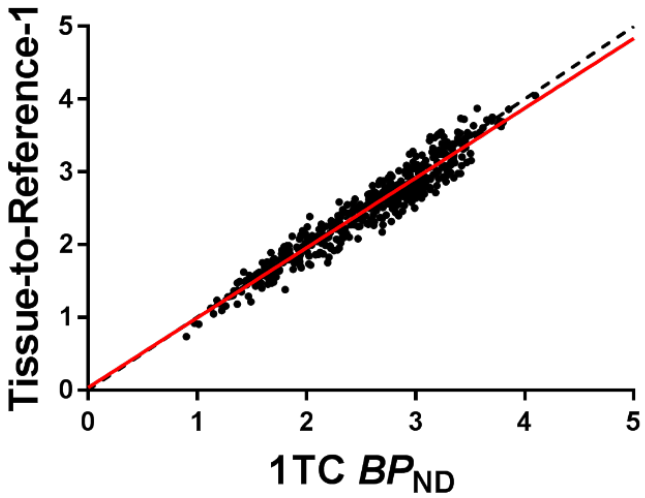


$V_{T(A)} = 1.64 \times V_T + 1.94$
$R^2 = 0.81$

- **Why?**
  - Plasma and tissue are not at equilibrium

^{11}C-UCB-J: Healthy Control Data Tissue-to-Reference (SUV) Ratio

- **SUVR-1 (60-90 min) very similar to BP_{ND}**
  - **% difference between SUVR-1 and BP_{ND}** -2 ± 7%



SUVR-1=0.96×BP_{ND}+0.03
R^2=0.93

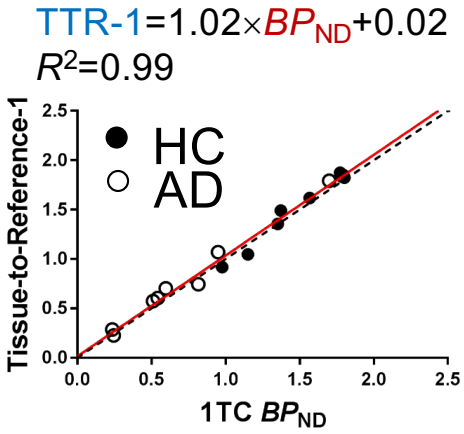
^{11}C-UCB-J: SUVR in HC/AD comparison

- **Hippocampus SUVR-1 was similar to BP_{ND}**
  - 4 ± 10%

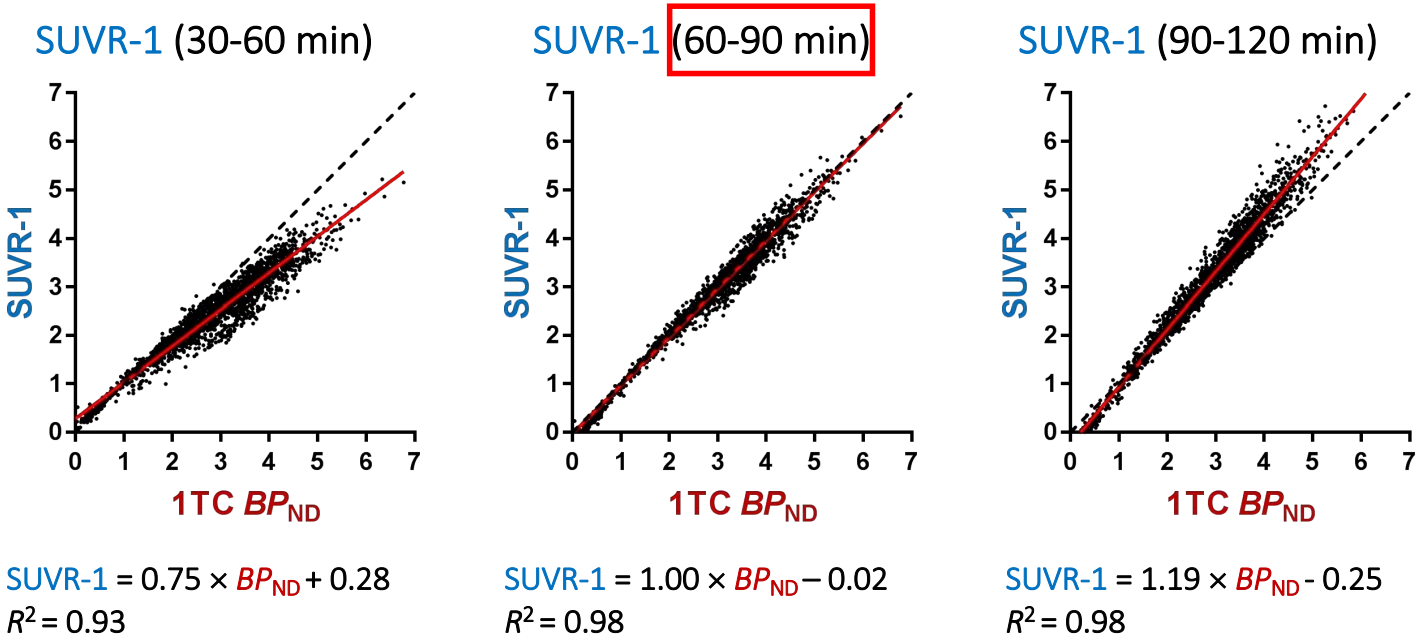
- **The HC-AD group difference was significant using both BP_{ND} and SUVR-1**

	HC (n=7)	AD/MCI (n=9)	P-value
BP_{ND}	1.43 ± 0.31	0.82 ± 0.57	0.024
TTR-1	1.45 ± 0.37	0.87 ± 0.59	0.041

- **Slightly lower significance**



^{11}C-UCB-J agreement between SUVR-1 and BP_{ND} is time-dependent



SUVR-1 = 0.75 × BP_{ND} + 0.28
R^2 = 0.93

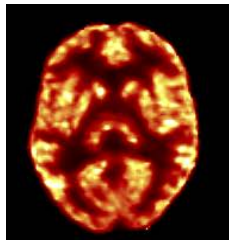
SUVR-1 = 1.00 × BP_{ND} – 0.02
R^2 = 0.98

SUVR-1 = 1.19 × BP_{ND} - 0.25
R^2 = 0.98

- Same as virtually every successful reversible PET tracer
- What's going on?

Naganawa et al, JNM, 2020

Quantitative Brain PET



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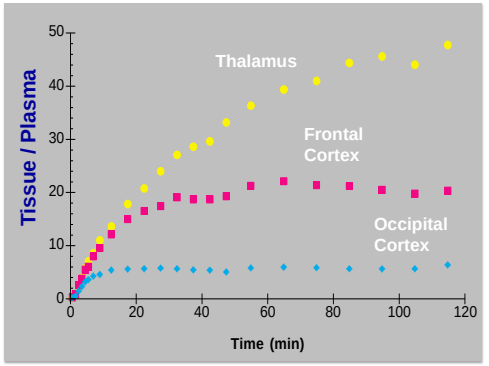
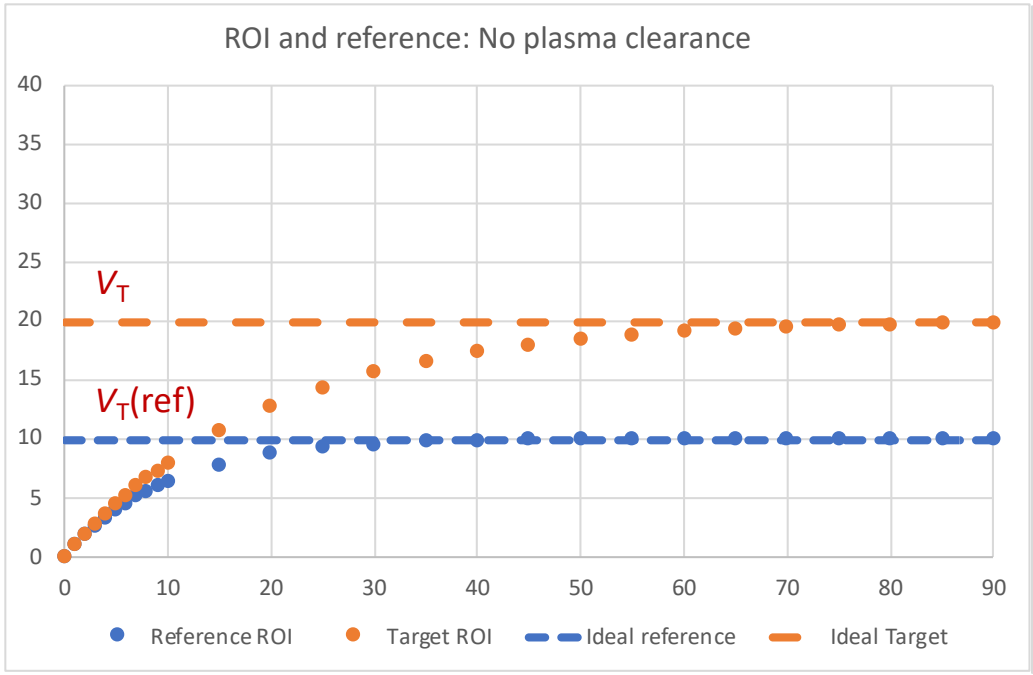
For a reversible tracer, following a bolus injection…



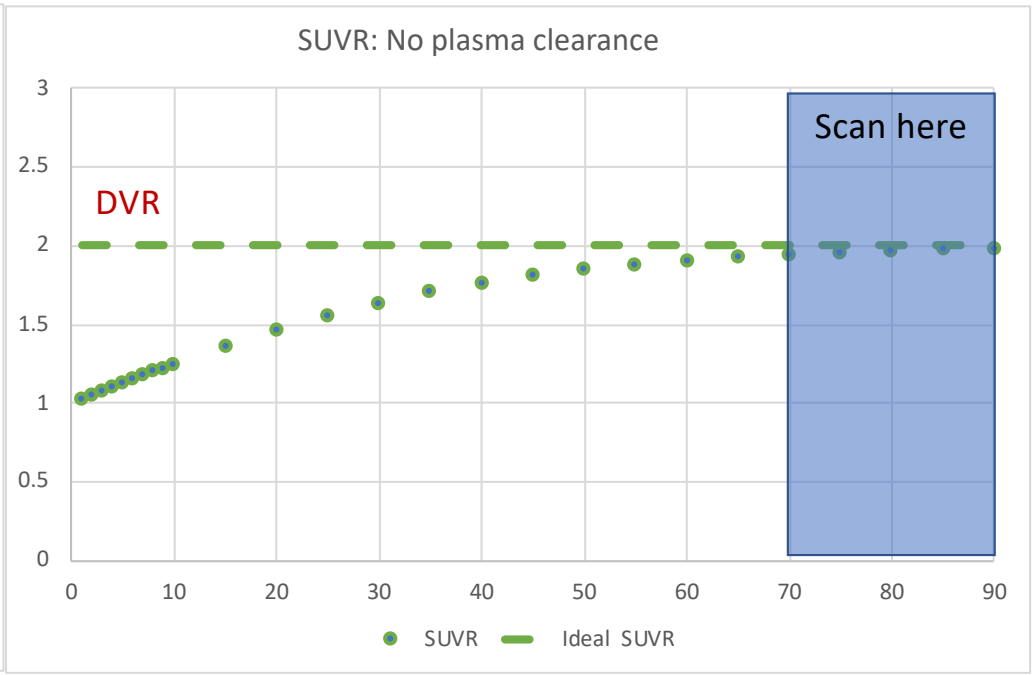
- As time proceeds, the tissue:plasma ratio typically rises until a constant ratio is reached
  - **Transient equilibrium**
- Typically, higher binding regions take longer to reach transient equilibrium
- The tissue:plasma ratio at transient equilibrium (the apparent volume of distribution, $V_{T(A)}$) is **greater** than the ratio at equilibrium (the true volume of distribution, V_T)
- The faster the plasma clearance, the greater the difference between $V_{T(A)}$ and V_T
- Typically, regions with higher V_T have a greater bias

A simple simulation: No plasma clearance

$V_{T(A)}$: Apparent volume of distribution

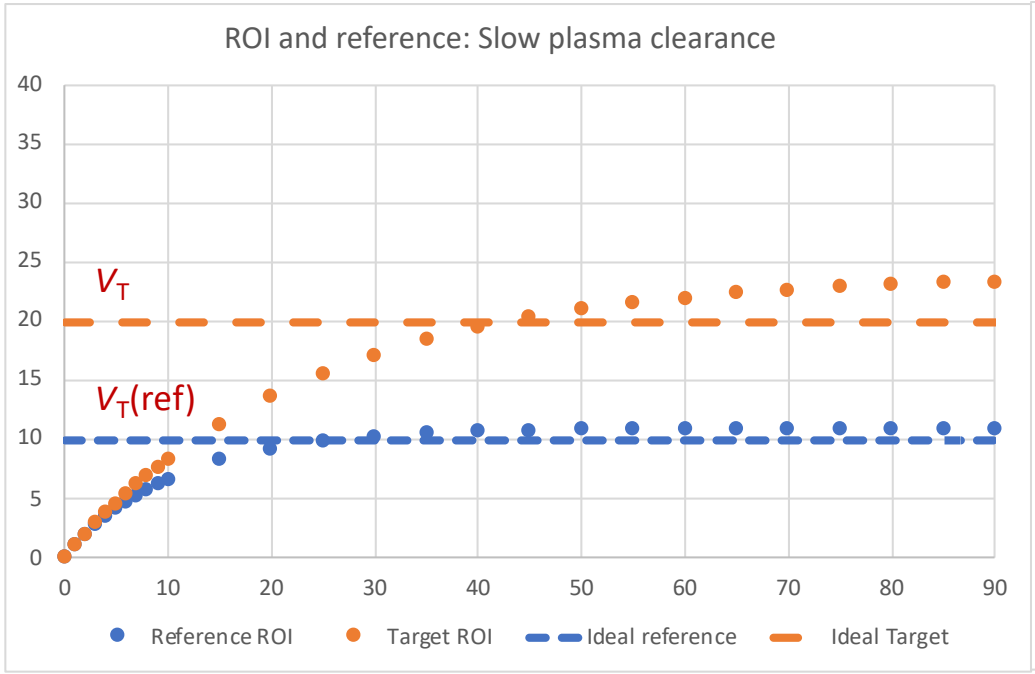


SUVR

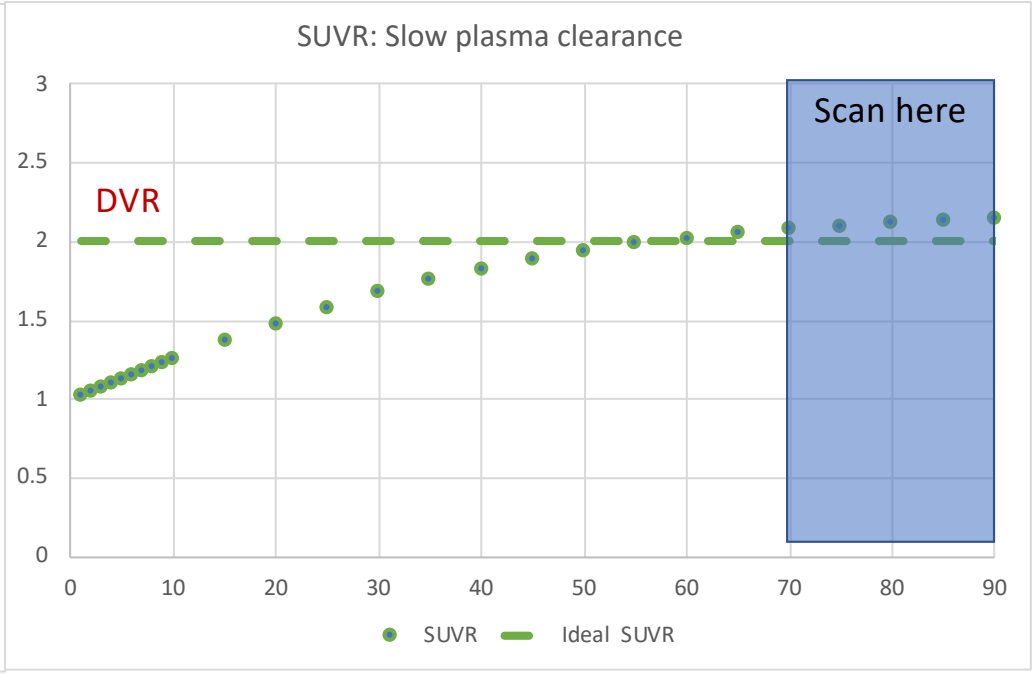


A simple simulation: Slow plasma clearance

$V_{T(A)}$: Apparent volume of distribution

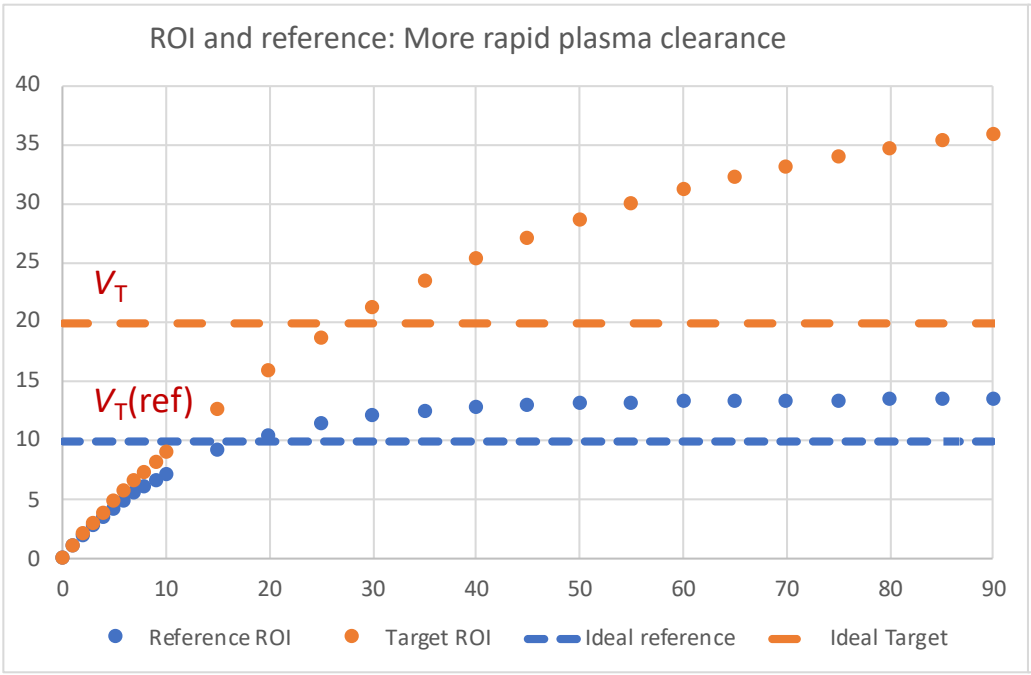


SUVR

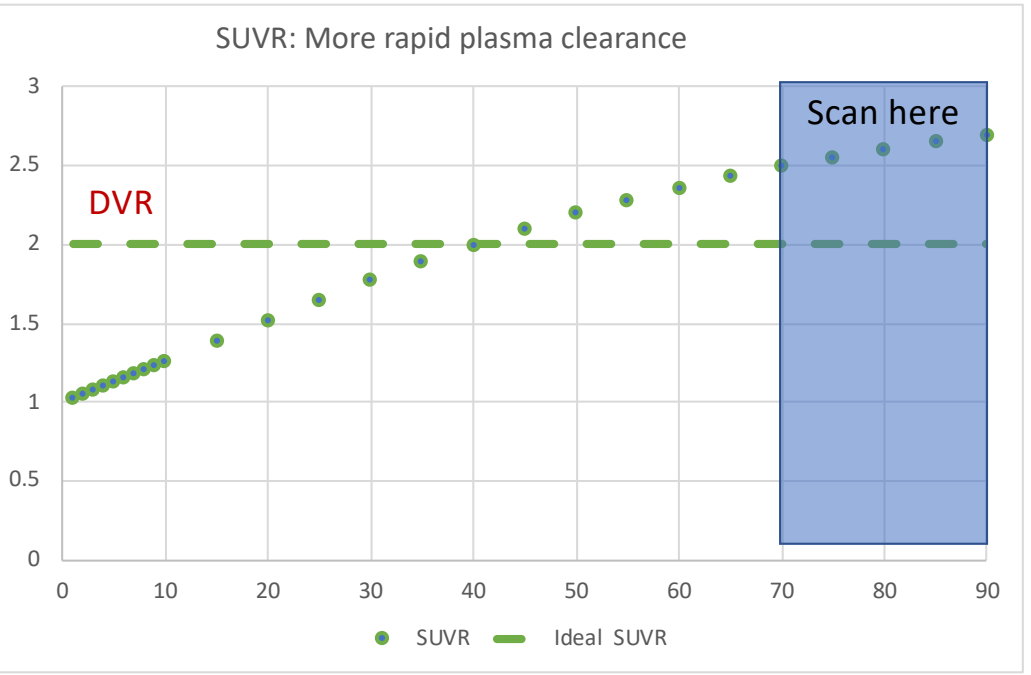


A simple simulation: Faster plasma clearance

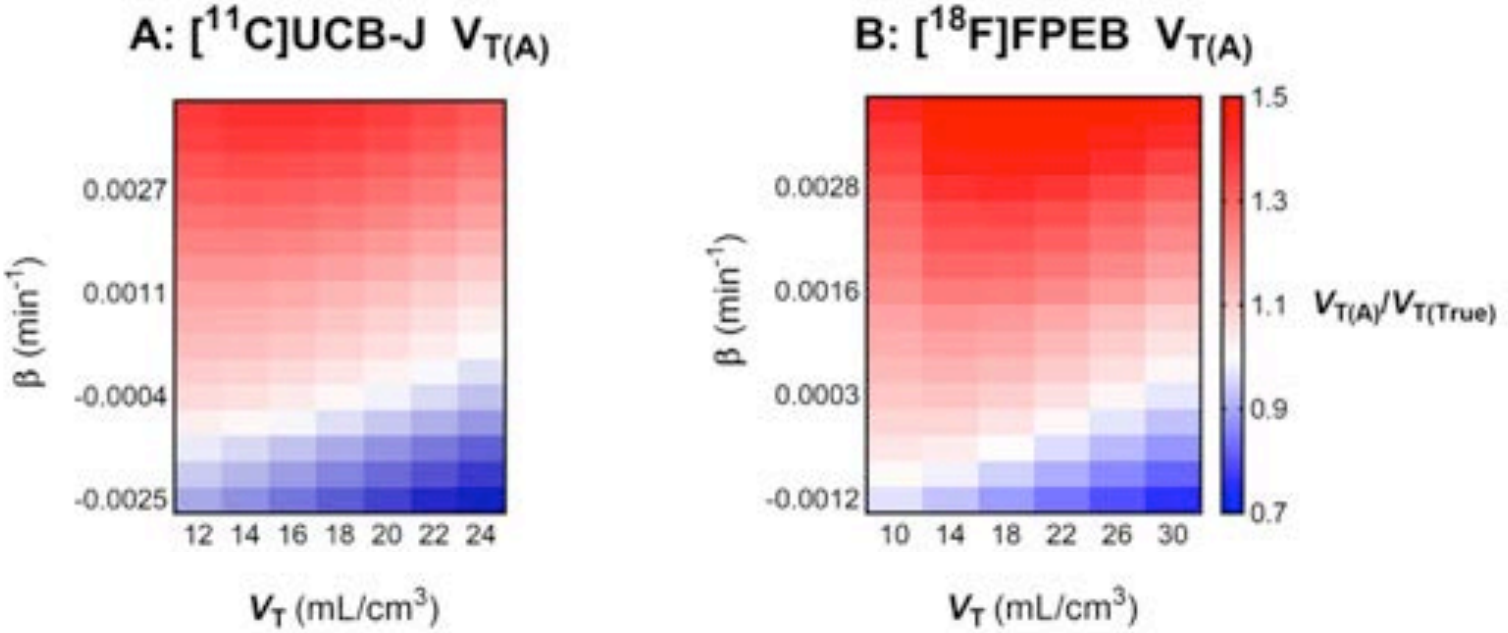
$V_{T(A)}$: Apparent volume of distribution



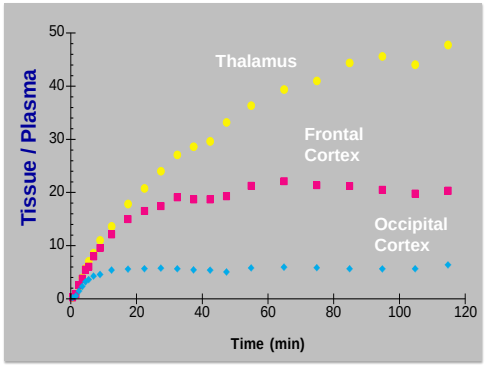
SUVR



Equilibrium Overshoot Varies with Binding Level as well as Measurement Time



Following a bolus injection…



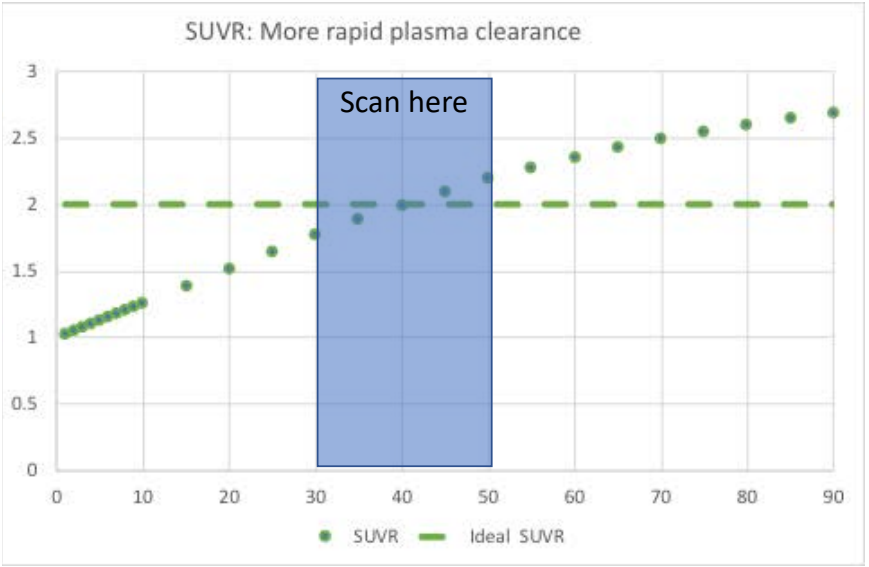
- The tissue:plasma ratio at transient equilibrium ($V_{T(A)}$) is **greater** than the ratio at equilibrium (V_T)
- The faster the plasma clearance, the greater the difference between $V_{T(A)}$ and V_T
- Regions with higher V_T (typically, the ROI) have a greater bias
- **SUVR** is the ratio of $V_{T(A)}$ of the ROI to $V_{T(A)}$ of the reference region
- So **SUVR** at transient equilibrium, is positively biased with respect to **DVR**.
  - Maybe a little, maybe a lot…
- But, higher binding regions take longer to reach transient equilibrium
- We can "help" by scanning earlier, before transient equilibrium is achieved

Can two “wrongs” make a right?

- If we wait until transient equilibrium is achieved, **SUVR** will overestimate **DVR**

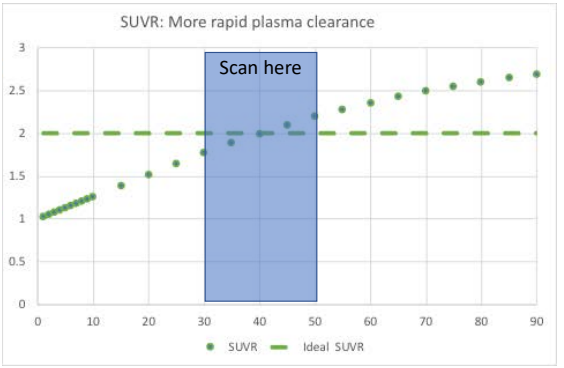
- If we scan “too early”, we can get the right answer…

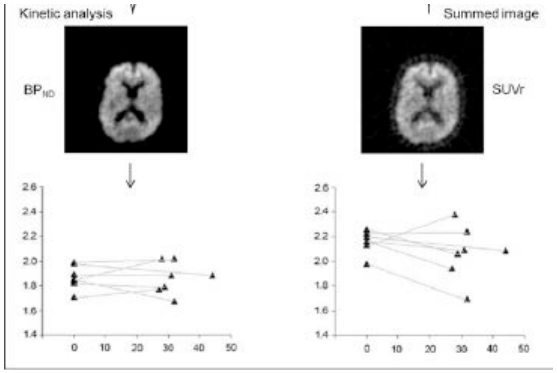
- Any imaging scenario with **SUVR** = **DVR** has 2 factors that cancel each other out
  - Transient equilibrium
  - Scanning early

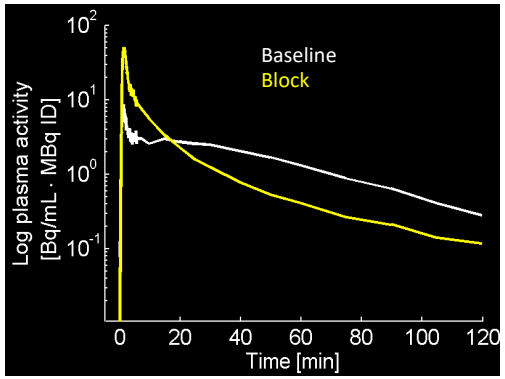


What could possibly go wrong?

- Will we always get the timing right so that the two effects cancel out?
- "Optimal" time depends on the magnitude of tracer binding
  - Best time varies with extent of disease
- Interindividual variation in tracer plasma clearance
  - Age
  - Sex
- Does drug treatment affect plasma clearance of tracer?





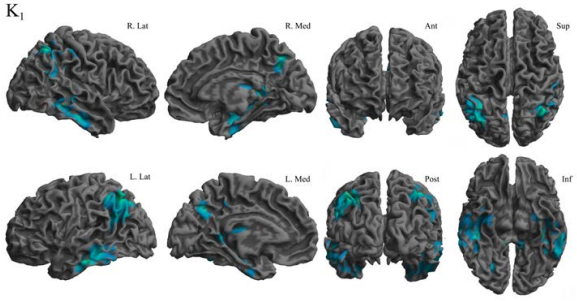


Closing Thoughts

- Modeling methods permit us to measure many aspects of physiology and pathology *in vivo* with great accuracy.
- Great accuracy may not always be clinically important
- Modeling studies tend to be more complex, so we typically trade accuracy for increased patient numbers (and cost)
- Modeling also helps us develop simpler, more patient-friendly assays.
- The simpler methods come with lots of assumptions that are routinely ignored.

Take-home Messages for Simplified Brain Imaging

- Need well-validated tracers with reliable kinetic models
  - Understand all sources of binding *in* vivo
  - Do these validation studies get the priority they need?
- Use the understanding from a well validated model to optimize each simplified scan protocol
  - So far, we just use models to choose the best time for SUVR measurement
- But, also…
  - Understand the factors that corrupt SUVR
  - Understand the impact of these effects on specific study paradigms
  - Correct them (if needed)
- Don’t give up on dynamic scans
  - Automatically correct kinetic effects
  - Provide tracer delivery (flow) information (K_1, R_1)



Acknowledgments