In vivo comparison of three novel radiotracers for the NMDA receptor GluN2B subunit in non-human primates

Kelly Smart, Ming-Qiang Zheng, Hazem Ahmed, Hanyi Fang, Yuping Xu, Lisheng Cai, Daniel Holden, Michael Kapinos, Zachary Felchner, Jim R. Ropchan, Gilles Tamagnan, Robert Innis, Victor Pike, Simon M. Ametamey, Yiyun Huang, Richard E. Carson

SNMMI Annual Meeting 2021

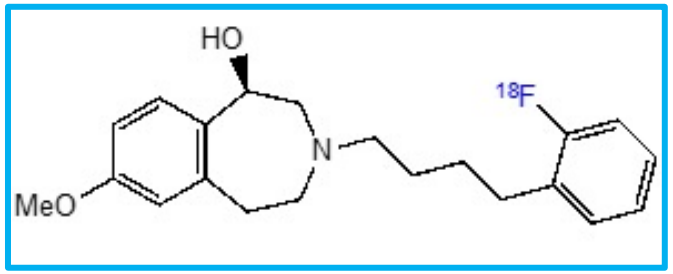
SS07 Neurosciences YIA Session

June 13, 2021

- **NMDA receptor GluN2B subunit** is important in plasticity and neurodegeneration, making it a potential drug target in neurological and psychiatric disorders.

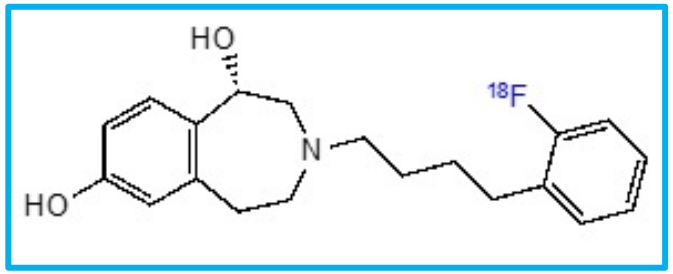
- **3 candidate GluN2B ligands compared in 2 rhesus macaques.**

(*R*)-^{18}F-OF-Me-NB1



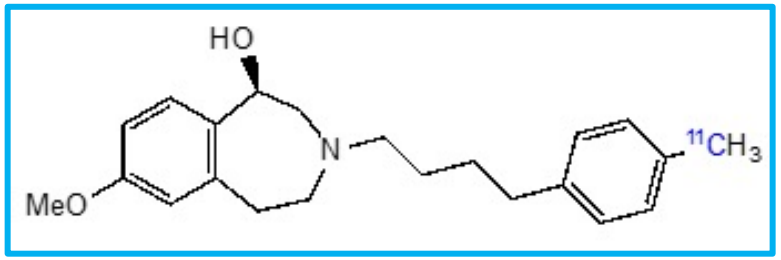
Haider et al 2019 JNM

(*S*)-^{18}F-OF-NB1



Ahmed et al 2021 JNM

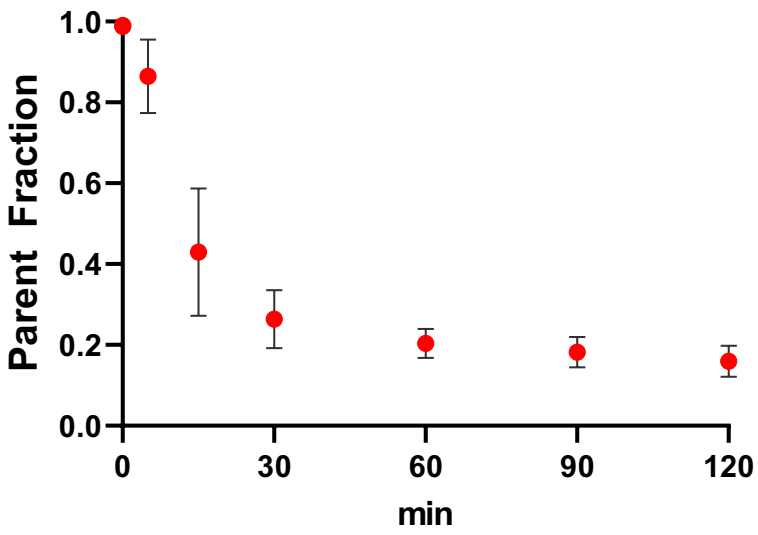
(*R*)-^{11}C-NR2B-Me



Cai et al 2020 JNM

Metabolism and plasma binding

(R)-^{18}F-OF-Me-NB1



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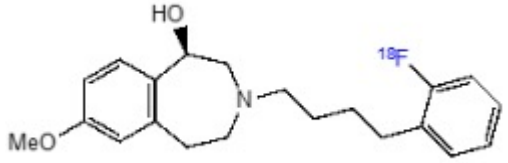

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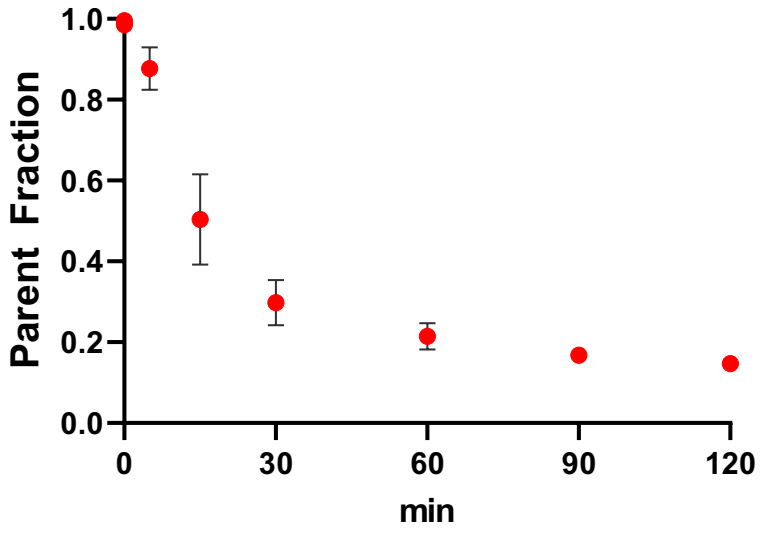

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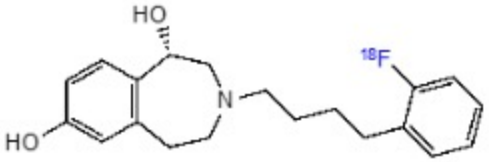
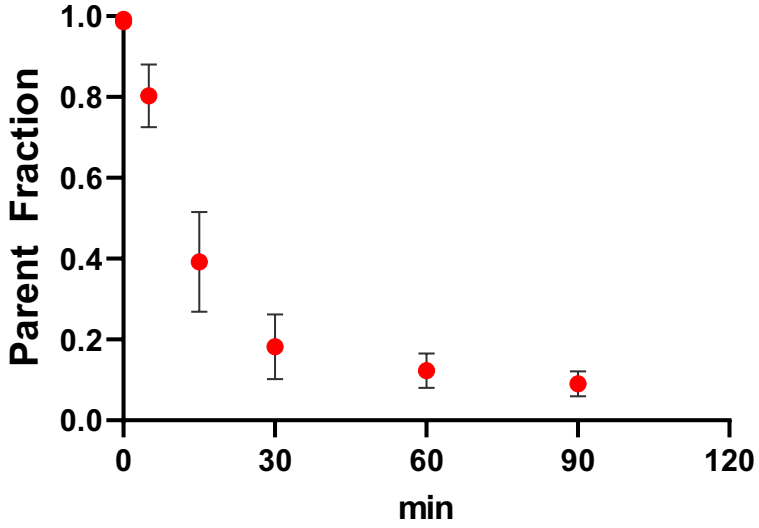


(R)-^{11}C-NR2B-Me



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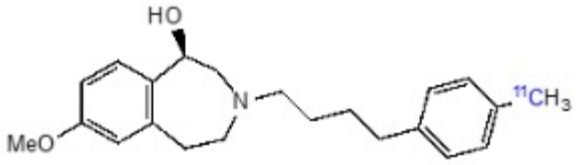
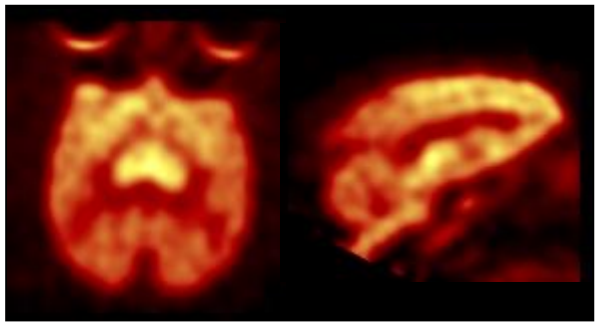
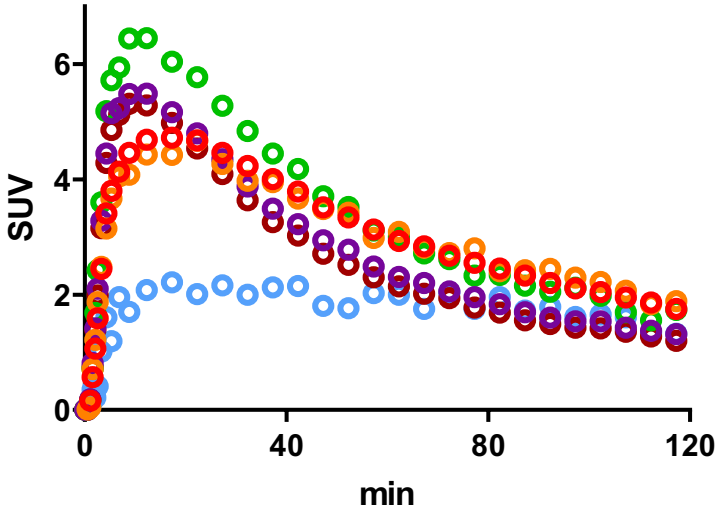


Tissue distribution and kinetics

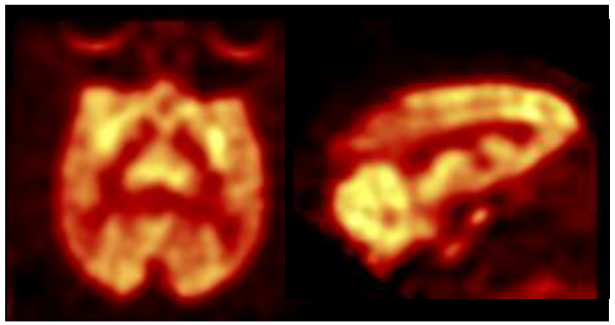
(R)-^{18}F-OF-Me-NB1



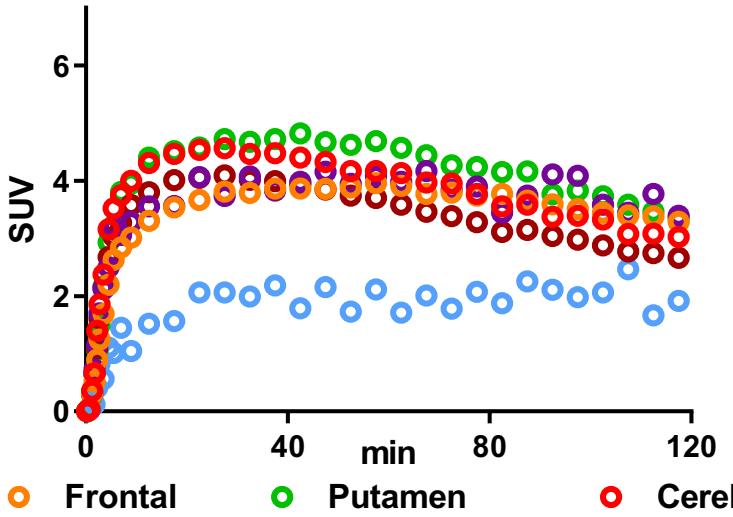
SUV 30-45 min



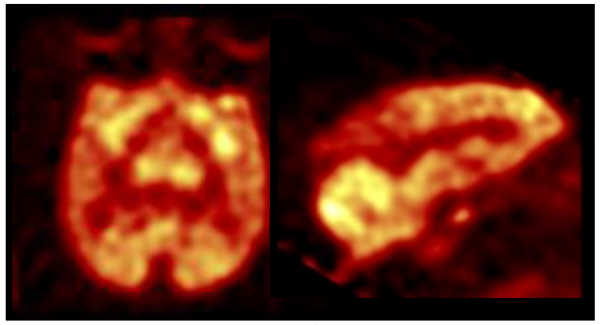
(S)-^{18}F-OF-NB1



SUV 45-60 min



(R)-^{11}C-NR2B-Me



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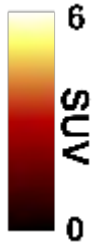
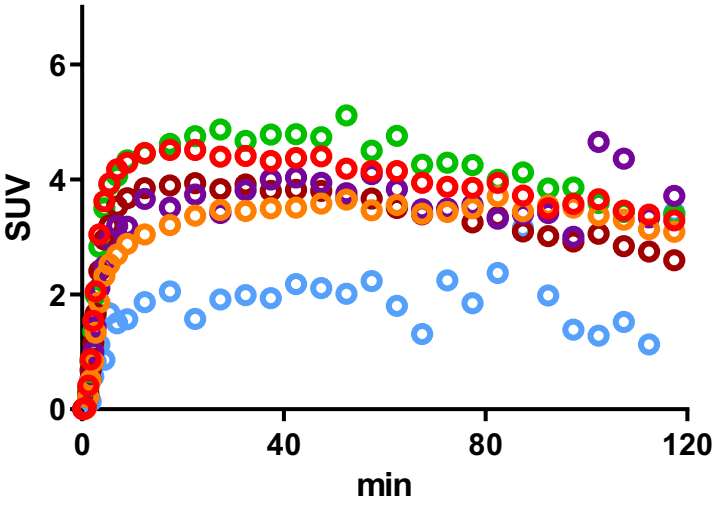
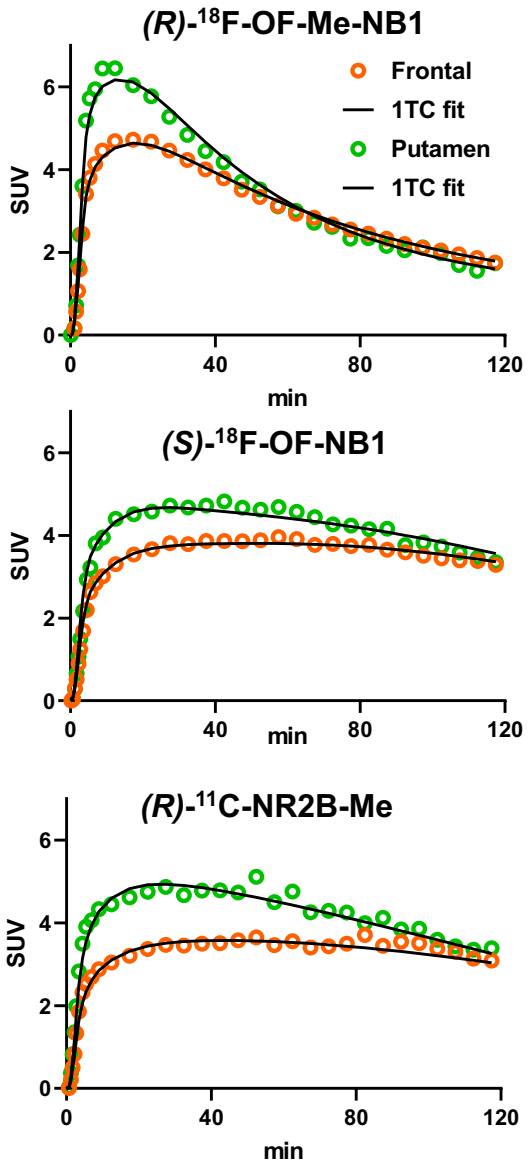




Frontal
Occipital
Putamen
Hippocampus
Cerebellum
Semiovale

Volume of distribution



	(R)-^{18}F-OF-Me-NB1		(S)-^{18}F-OF-NB1		(R)-^{11}C-NR2B-Me	
animal:	**1**	**2**	**1**	**2**	**1**	**2**
CORTEX	**10.6**	**10.8**	**31.9**	**29.0**	**41.4**	**46.0**
Frontal cortex	10.2	10.6	31.1	28.9	41.0	48.1
Occipital ctx	8.9	8.2	24.1	23.3	29.0	32.4
Temporal ctx	9.6	9.4	28.8	25.5	36.6	40.8
Cingulate ctx	12.2	12.8	38.8	32.3	52.1	54.6
Caudate	9.8	9.8	28.8	25.0	35.2	34.1
Putamen	10.3	10.9	31.8	24.6	39.8	33.5
Thalamus	9.6	9.2	24.6	23.3	46.0	30.8
Hippocampus	10.1	10.9	32.1	26.3	39.0	37.8
Cerebellum	9.1	8.7	27.3	25.5	32.5	34.6
Semiovale	9.0	8.7	20.3	16.9	23.5	35.5

1-tissue compartment model

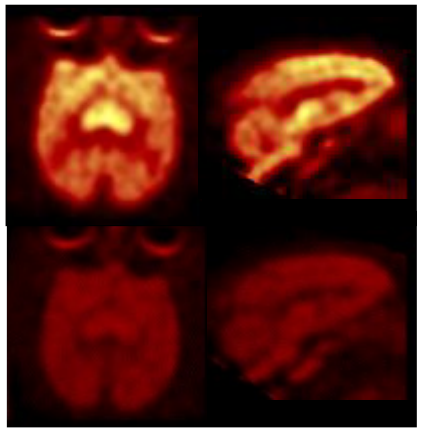
GluN2B Blocking

0.25 mg/kg Co-101,244

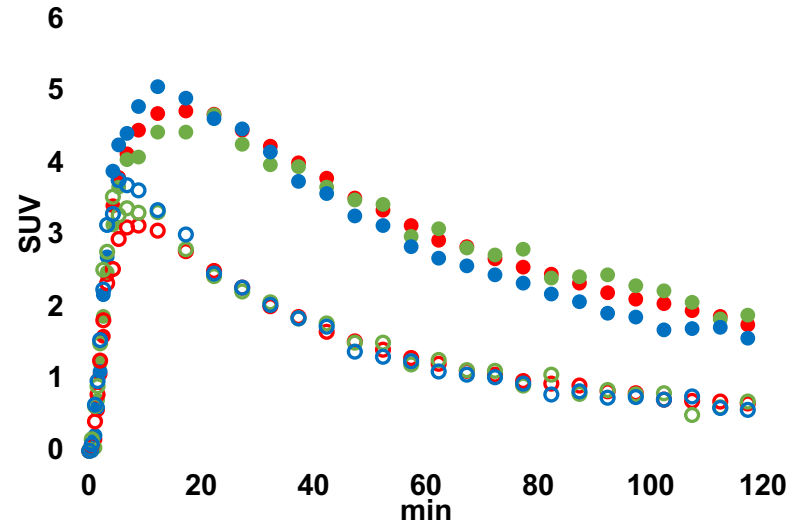
(R)-^{18}F-OF-Me-NB1

Baseline

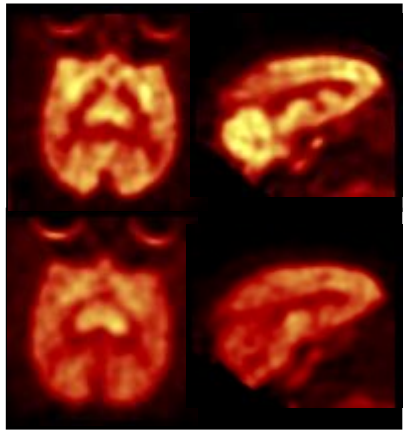
GluN2B Block



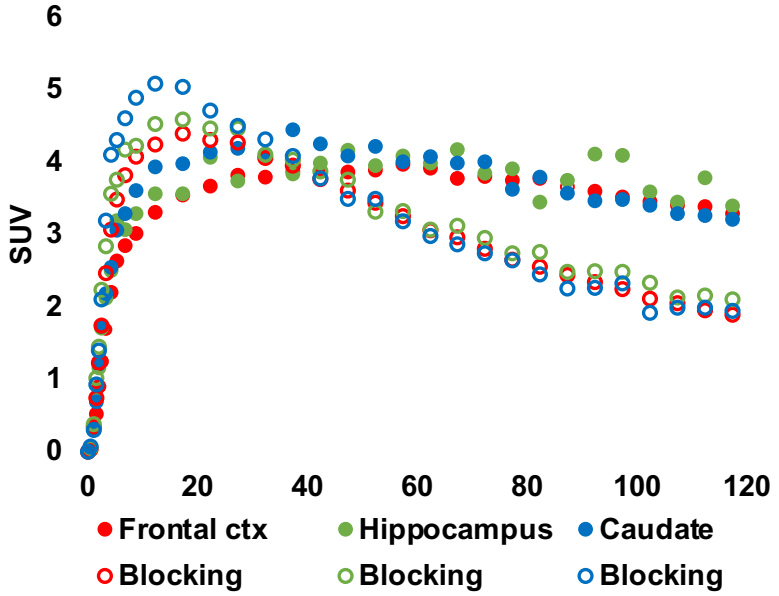
SUV 30-45 min



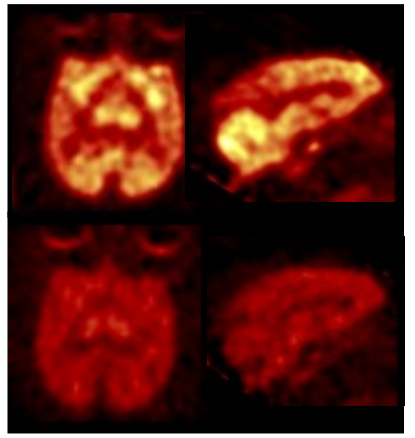
(S)-^{18}F-OF-NB1



SUV 45-60 min



(R)-^{11}C-NR2B-Me



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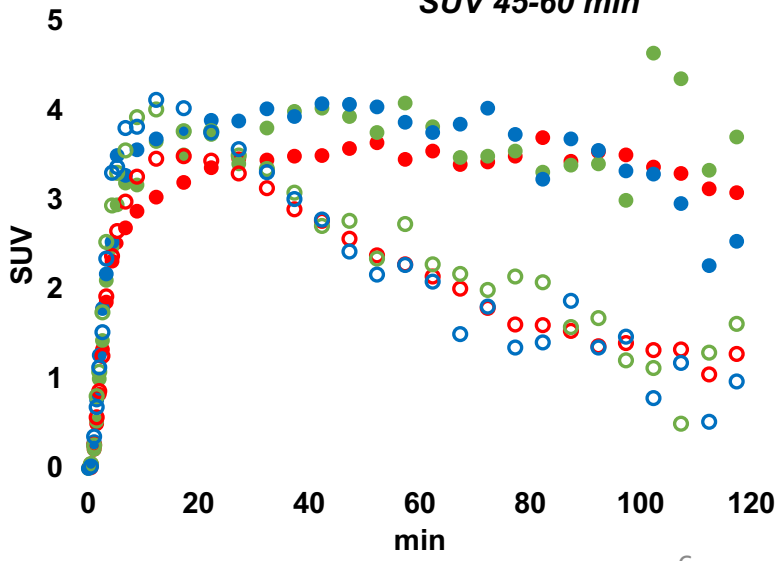

GluN2B Blocking

0.25 mg/kg Co-101,244

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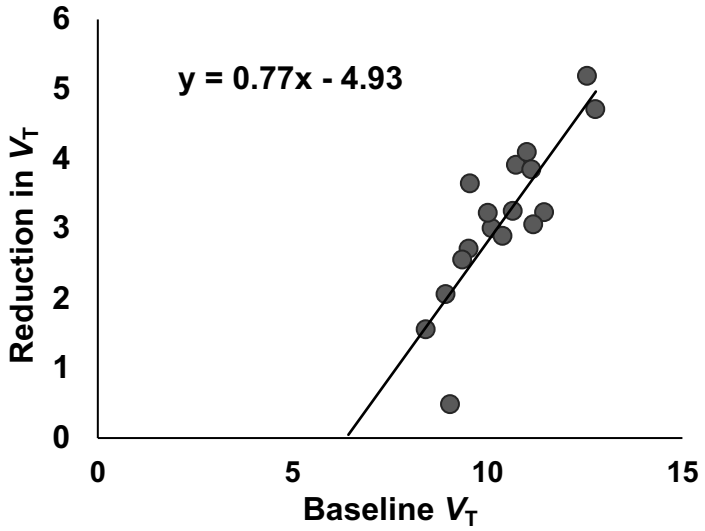
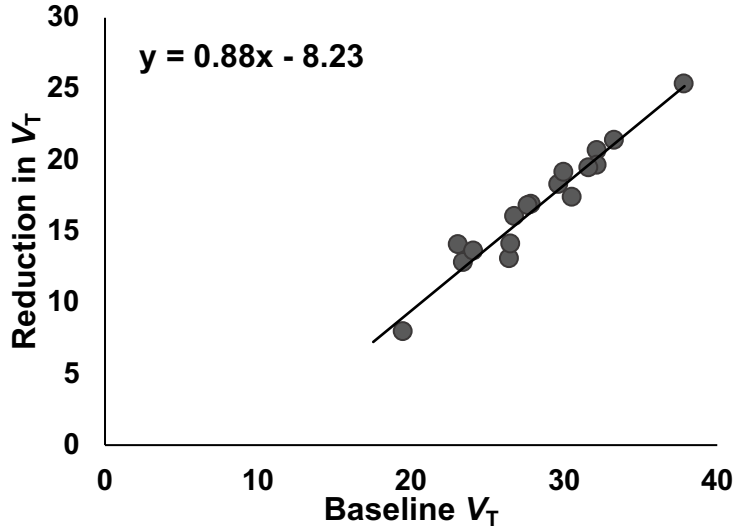
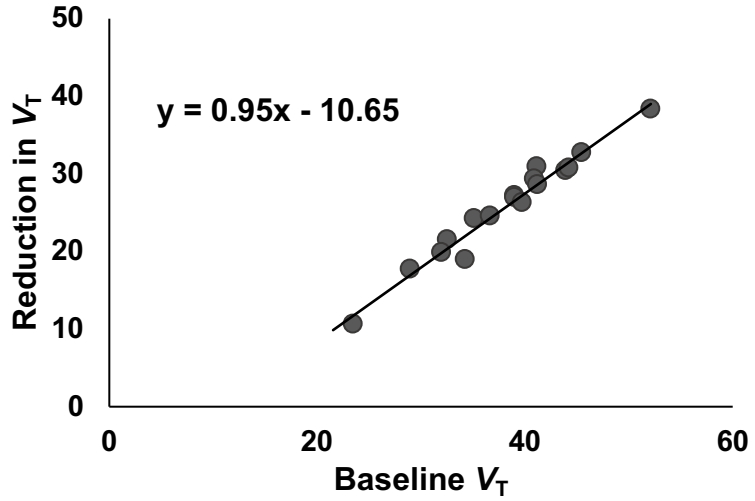


(S)-^{18}F-OF-NB1



(R)-^{11}C-NR2B-Me



	(R)-^{18}F-OF-Me-NB1	*(S)*-^{18}F-OF-NB1	*(R)*-^{11}C-NR2B-Me
Occupancy	68%, 77%	81%, 88%	95%
V_{ND} (mL/cm^3)	6.4, 6.4	7.3, 9.3	11.2

GluN2B Blocking

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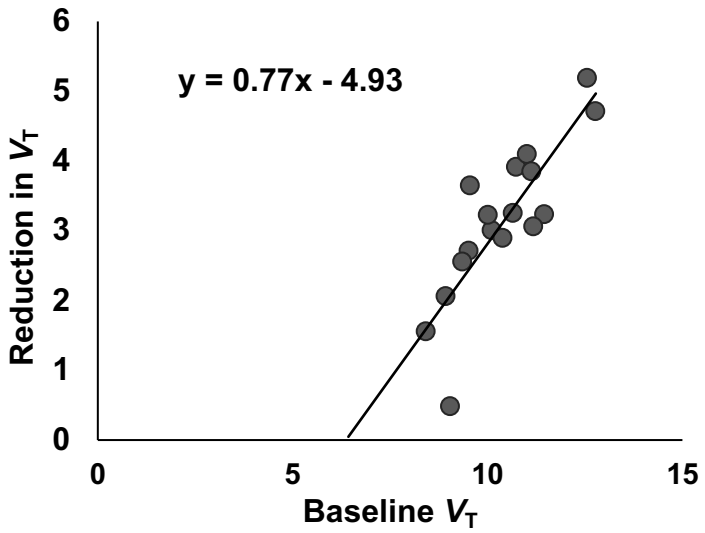

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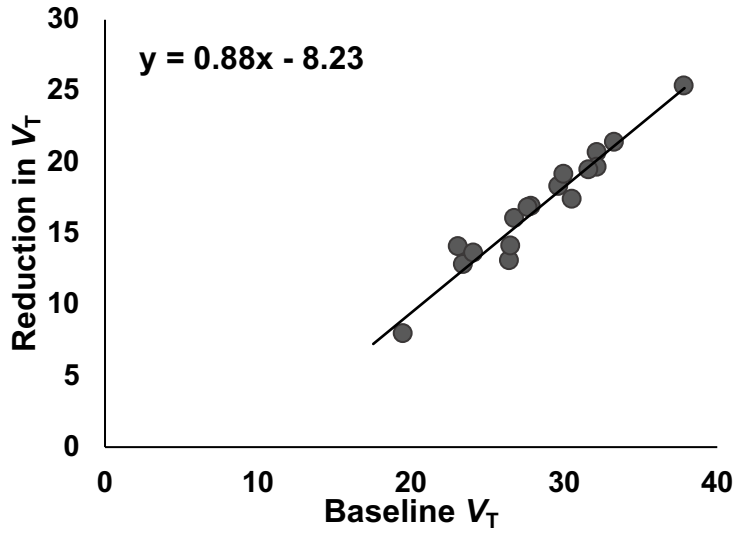

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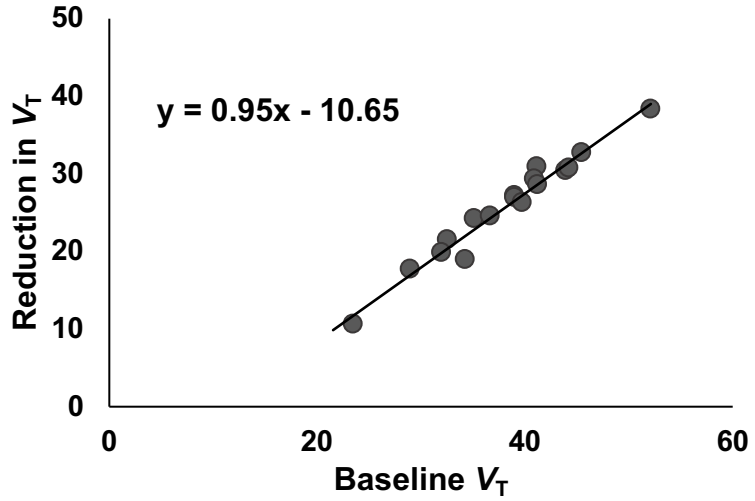

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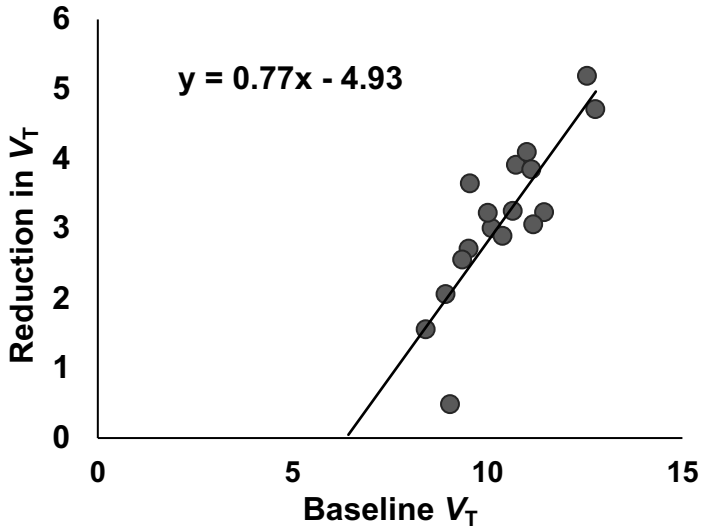
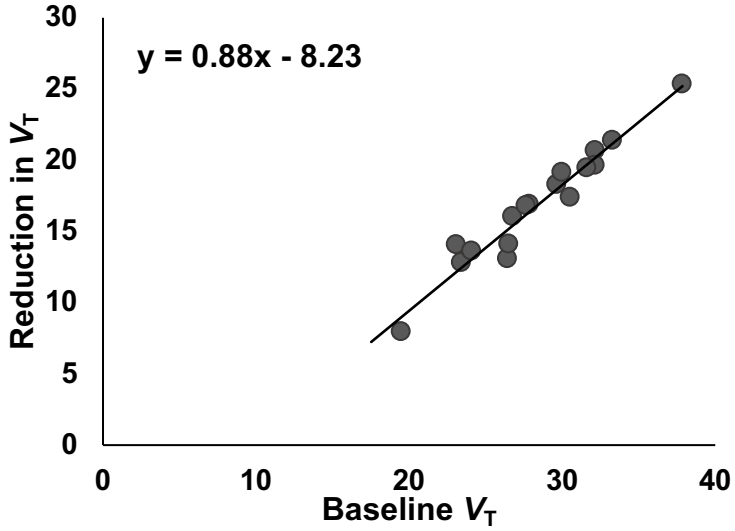
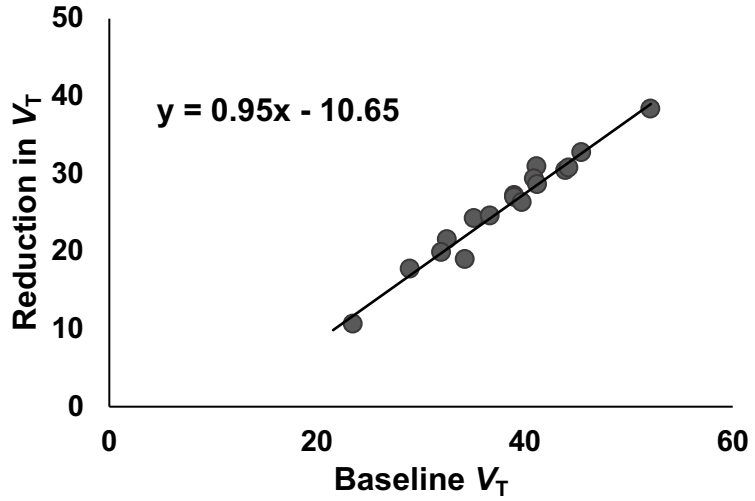


(S)-^{18}F-OF-NB1



(R)-^{11}C-NR2B-Me



	(R)-^{18}F-OF-Me-NB1	*(S)*-^{18}F-OF-NB1	*(R)*-^{11}C-NR2B-Me
Occupancy	68%, 77%	81%, 88%	95%
V_{ND} (mL/cm^3)	6.4, 6.4	7.3, 9.3	11.2

σ1 Drug Effects

σ1 drug effects on binding in rodent studies may reflect:

- Binding of σ1-targeting drugs at the GluN2B site.
- Binding of GluN2B radiotracers at the σ1 site.
- Modulation of GluN2B sites by σ1 receptors.

σ1 Drug Effects

0.027-0.125 mg/kg FTC-146

***(R)*-^{18}F-OF-Me-NB1**

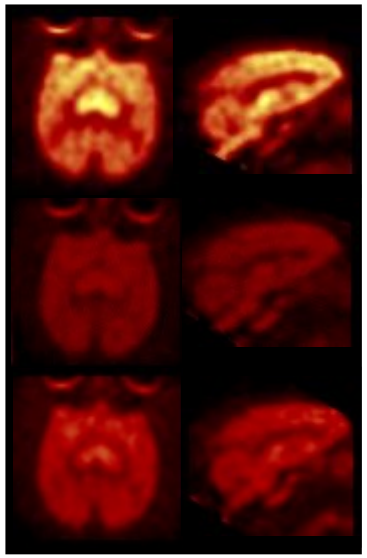
***(S)*-^{18}F-OF-NB1**

***(R)*-^{11}C-NR2B-Me**

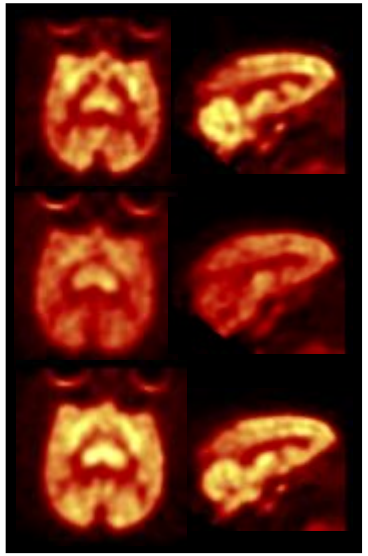
Baseline

GluN2B Block

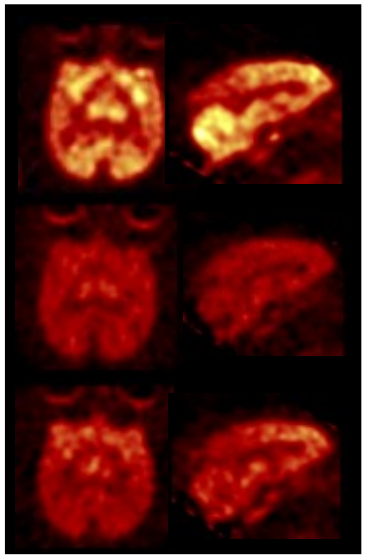
σ1 Block



SUV 30-45 min



SUV 45-60 min



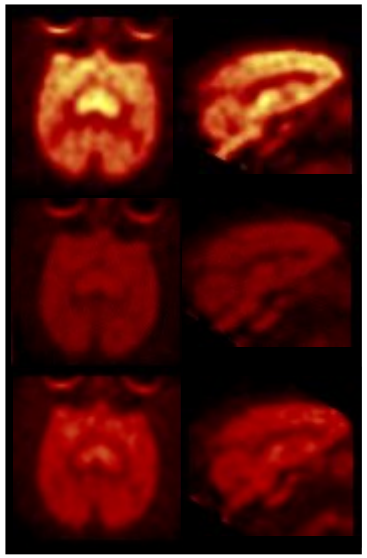
SUV 45-60 min

	***(R)*-^{18}F-OF-Me-NB1**	***(S)*-^{18}F-OF-NB1**	***(R)*-^{11}C-NR2B-Me**
GluN2B: Co-101,244 (0.25 mg/kg)	77%	81%, 88%	95%
σ1: FTC-146 (0.027 mg/kg)	30%	49%	nd
FTC-146 (0.125 mg/kg)		48%	56%

σ1 Drug Effects

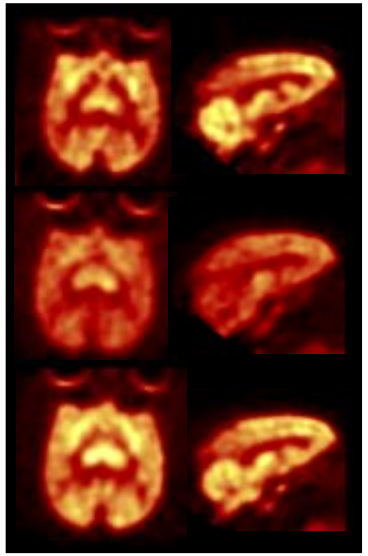
0.027-0.125 mg/kg FTC-146

(*R*)-^{18}F-OF-Me-NB1



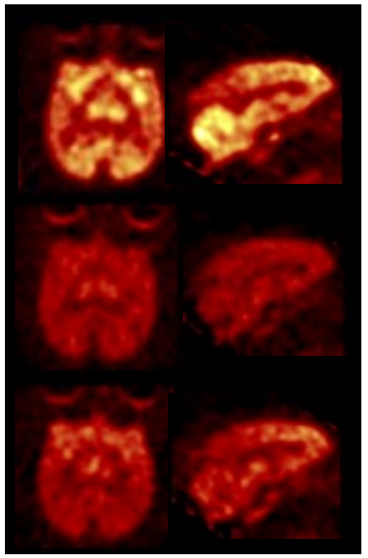
SUV 30-45 min

(*S*)-^{18}F-OF-NB1



SUV 45-60 min

(*R*)-^{11}C-NR2B-Me



SUV 45-60 min

	(*R*)-^{18}F-OF-Me-NB1	(*S*)-^{18}F-OF-NB1	(*R*)-^{11}C-NR2B-Me
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0.027-0.125 mg/kg FTC-146

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	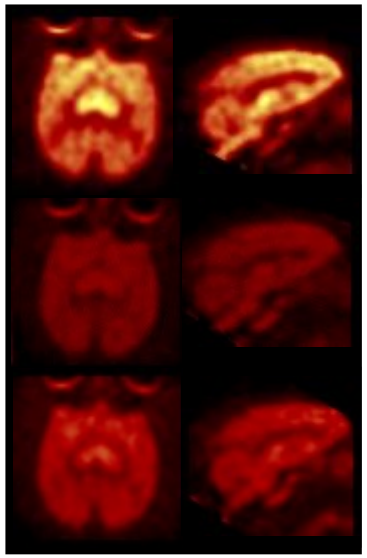	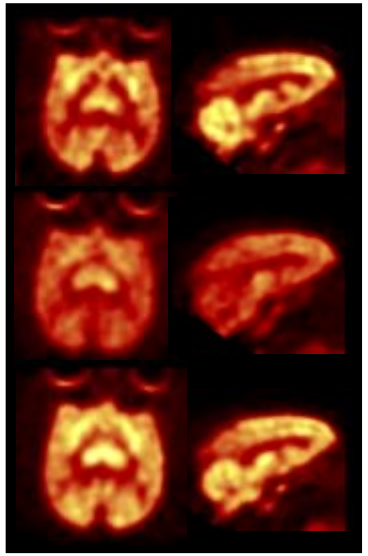	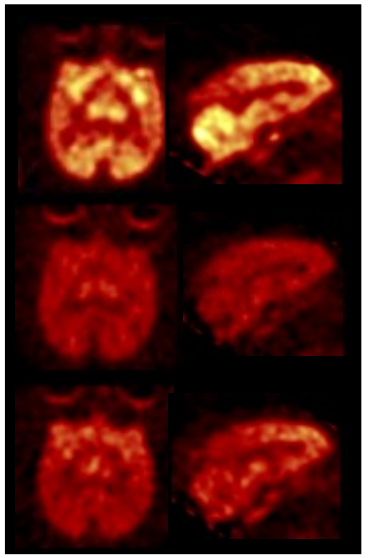
	SUV 30-45 min	***SUV 45-60 min***	***SUV 45-60 min***

Baseline

GluN2B Block

σ1 Block

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GluN2B: Co-101,244 (0.25 mg/kg)	77%	81%, 88%	95%
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0.027-0.125 mg/kg FTC-146

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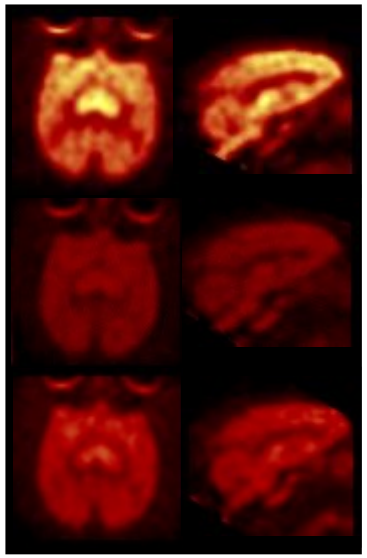
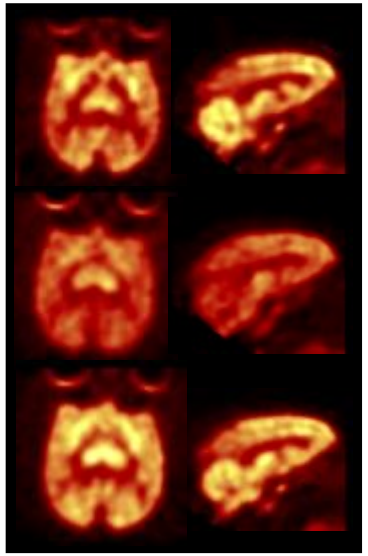
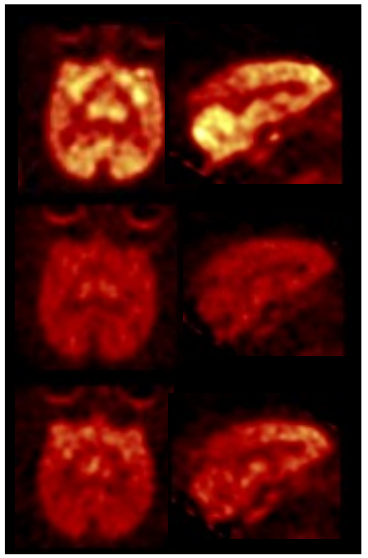
			
	SUV 30-45 min	***SUV 45-60 min***	***SUV 45-60 min***

Baseline

GluN2B Block

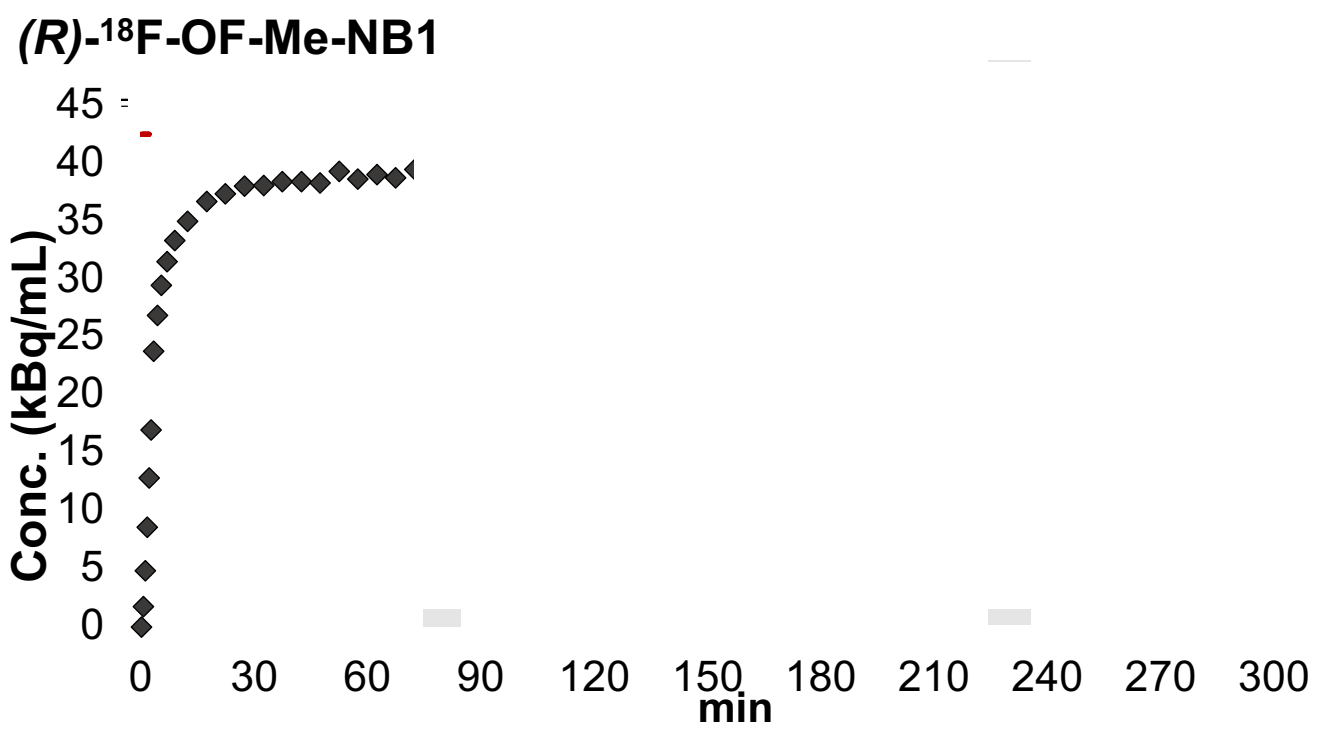
σ1 Block

	***(R)*-^{18}F-OF-Me-NB1**	***(S)*-^{18}F-OF-NB1**	***(R)*-^{11}C-NR2B-Me**
GluN2B: Co-101,244 (0.25 mg/kg)	77%	81%, 88%	95%
σ1: **FTC-146 (0.027 mg/kg)**	30%	49%	**nd**
FTC-146 (0.125 mg/kg)		48%	**56%**

σ1 Drug Effects

A σ1 receptor antagonist administered *with* or *after* a GluN2B antagonist doesn't cause additional binding reductions.

	(R)-^{18}F-OF-Me-NB1	*(S)*-^{18}F-OF-NB1	*(R)*-^{11}C-NR2B-Me
GluN2B: Co-101,244 (0.25 mg/kg)	77%	**81%, 88%**	95%
σ1: FTC-146 (0.027 mg/kg)	30%	49%	nd
FTC-146 (0.125 mg/kg)		48%	56%
GluN2B + σ1 pre-block		**82%**	



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	(R)-^{18}F-OF-Me-NB1	*(S)*-^{18}F-OF-NB1	*(R)*-^{11}C-NR2B-Me
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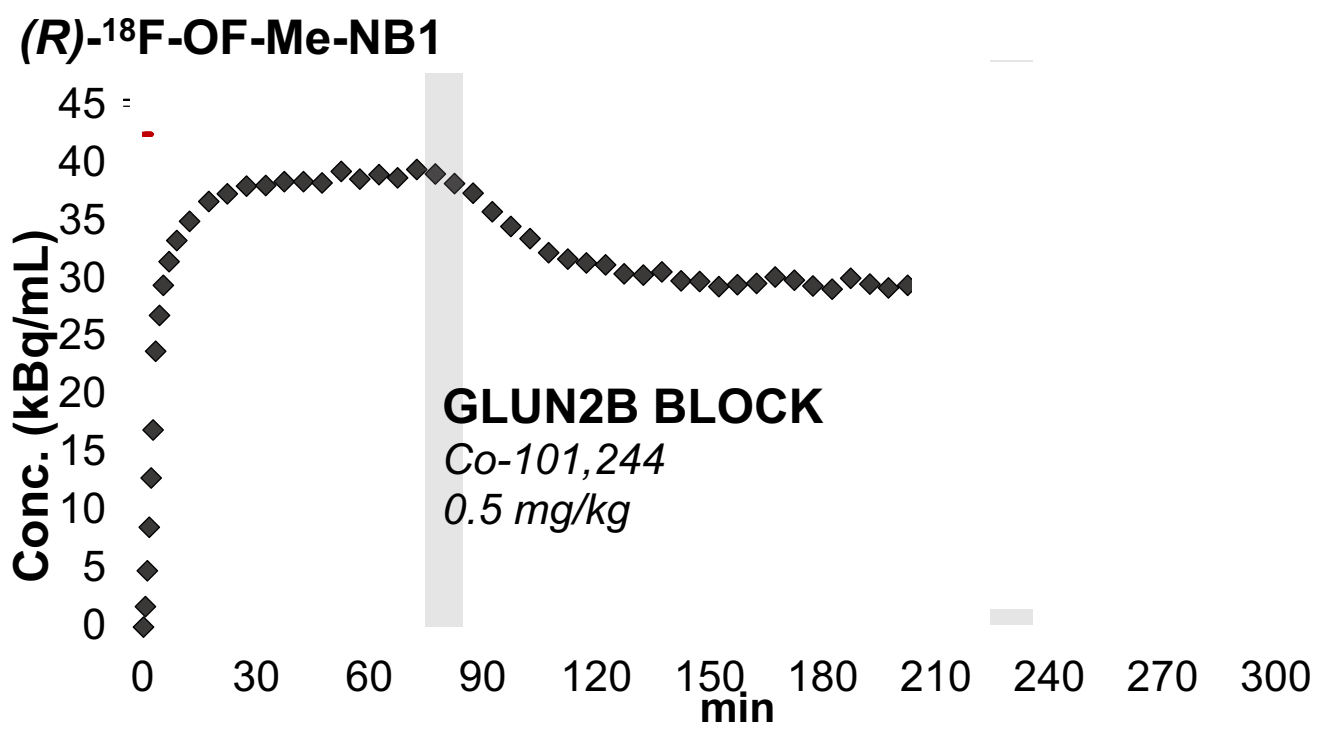

σ1 Drug Effects

A σ1 receptor antagonist administered *with* or *after* a GluN2B antagonist doesn't cause additional binding reductions.

→ σ1 drugs may be affecting binding at the GluN2B site.

	(R)-^{18}F-OF-Me-NB1	*(S)*-^{18}F-OF-NB1	*(R)*-^{11}C-NR2B-Me
GluN2B: Co-101,244 (0.25 mg/kg)	77%	**81%, 88%**	95%
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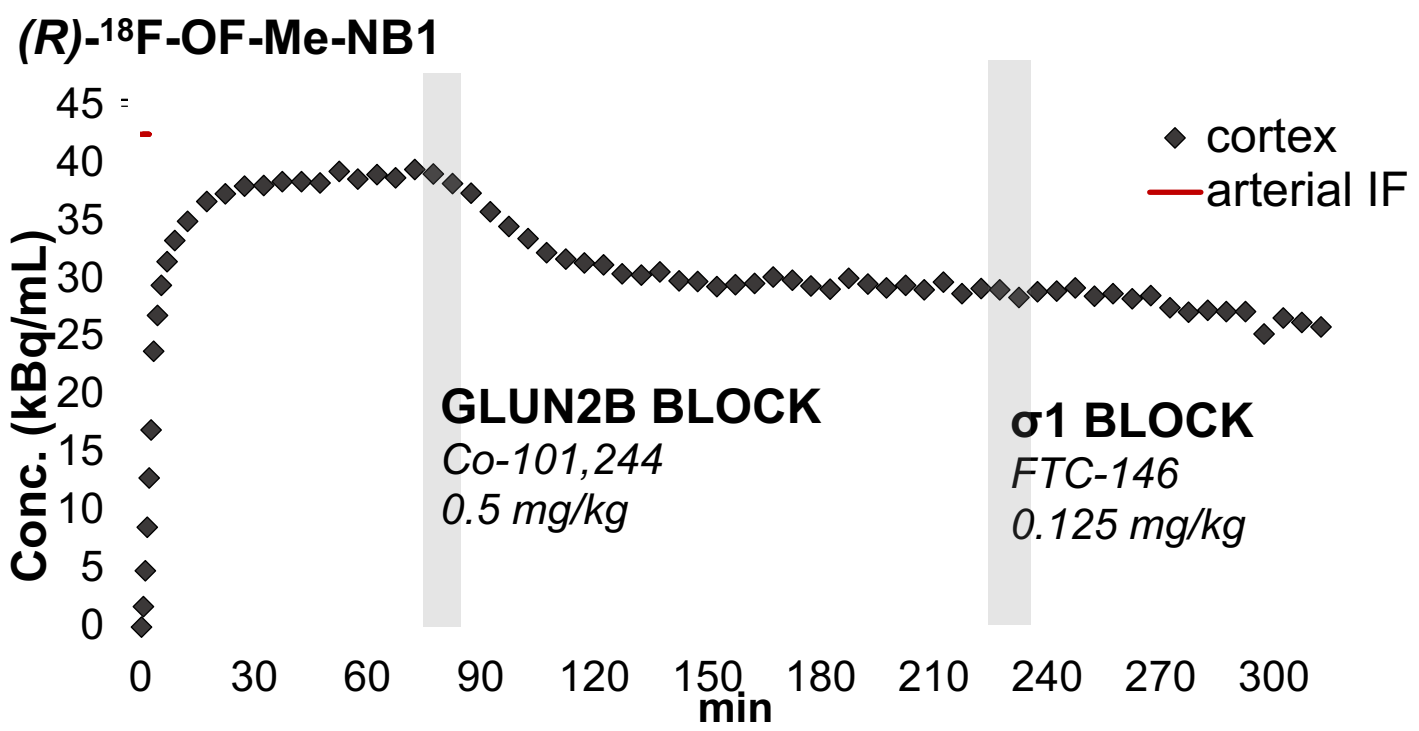
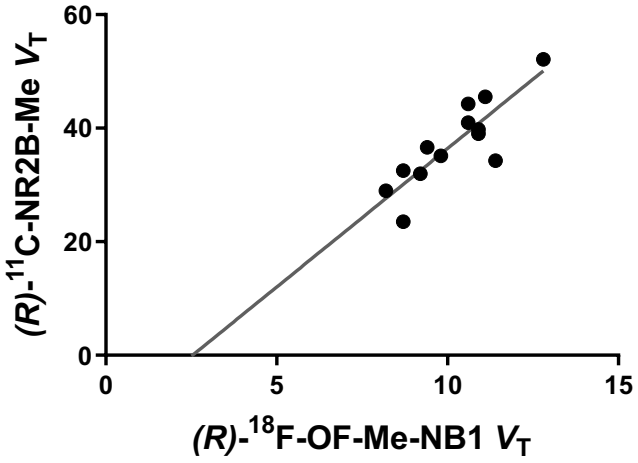
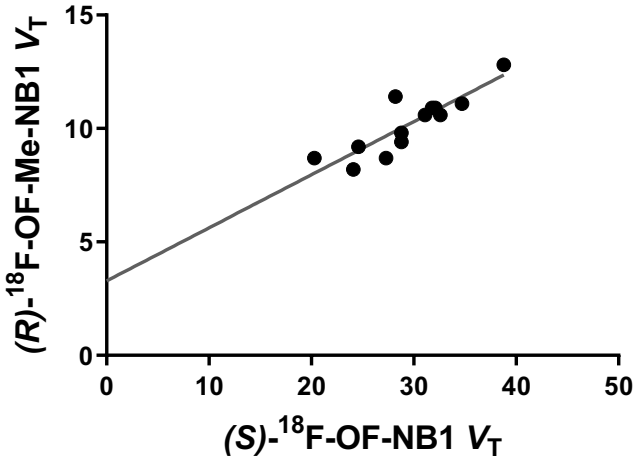
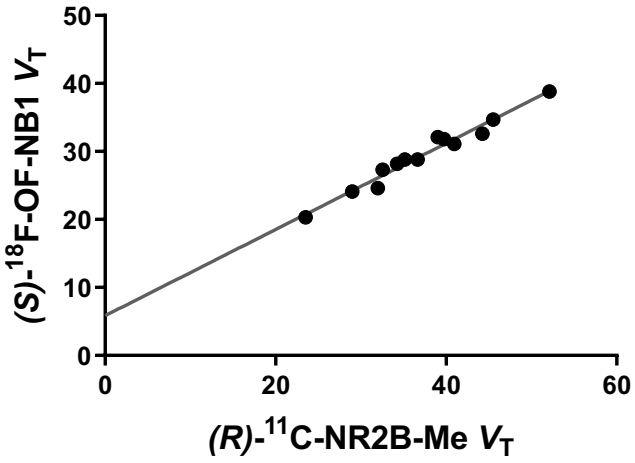


Comparing Binding Parameters

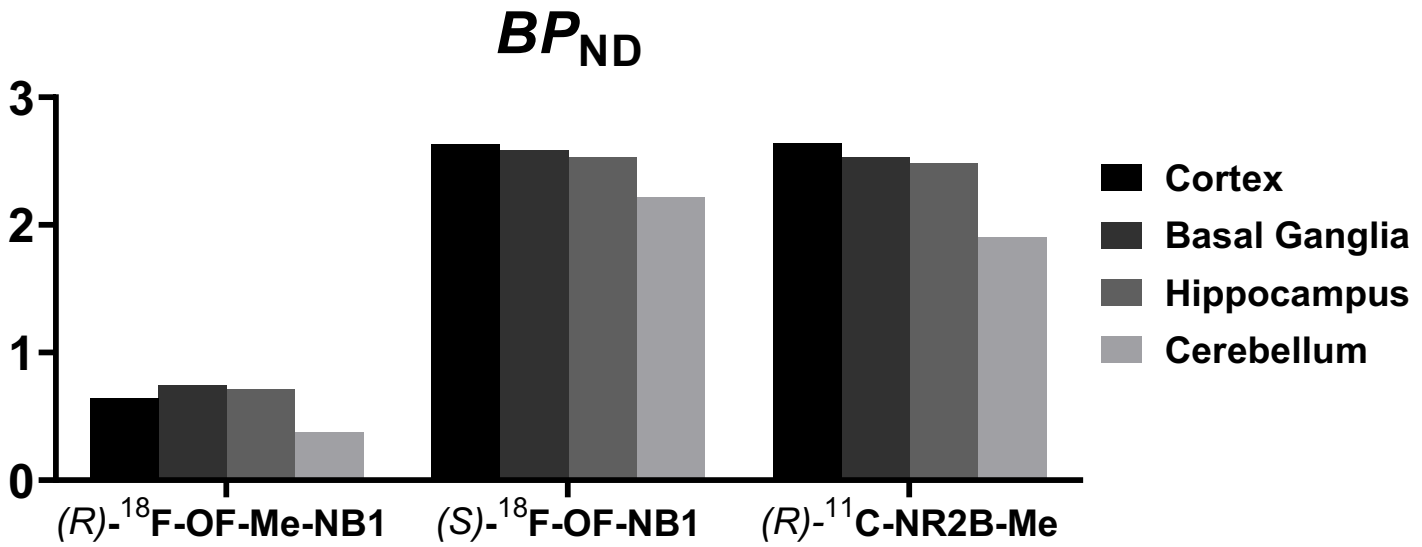






BP_{ND}(R)-18F-OF-Me-NB1 < BP_{ND}(S)-18F-OF-NB1 ≲ BP_{ND}(R)-11C-NR2B-Me

$BP_{ND} = V_T/V_{ND} - 1$



Summary

- ***(R)*-^{18}F-OF-Me-NB1**, ***(S)*-^{18}F-OF-NB1**, and ***(R)*-^{11}C-NR2B-Me** show promise for specific labeling of GluN2B.

- ***(S)*-^{18}F-OF-NB1** and ***(R)*-^{11}C-NR2B-Me** have BP_{ND} values of 2-3 and may be good candidates for evaluation in humans.

- σ1 receptor modulation may affect binding at the GluN2B site.

- Displaceable binding in the cerebellum suggests off-target binding may still be a concern.

***(R)*-^{18}F-OF-Me-NB1: poster #1622 (Zheng)**
***(S)*-^{18}F-OF-NB1: SS01 #4 (Ahmed)**

National Institute of Mental Health
U01MH107803
medicine.yale.edu/pet/mhprd/

Yale PET Center
Rich Carson
Henry Huang
Gilles Tamagnan

ETH Zurich
Simon Ametamey

NIMH
Robert Innis
Victor Pike

kelly.smart@yale.edu