In vivo characterization of an agonist dopamine D1 receptors tracer [^{18}F]MNI-968 (PF-06730110) in human

Acknowledgment

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D. Alagille	Jianqing Chen
O. Barret	D. L. Gray
C. C. Constantinescu	C. Lee
K. Fabrizio	T. J. McCarthy
J. Madonia	A. Villalobos
K.Marek	Lei Zhang
T. Morley	
C. Papin	
D Russel	
C. SanDiego	
J.Seibyl	

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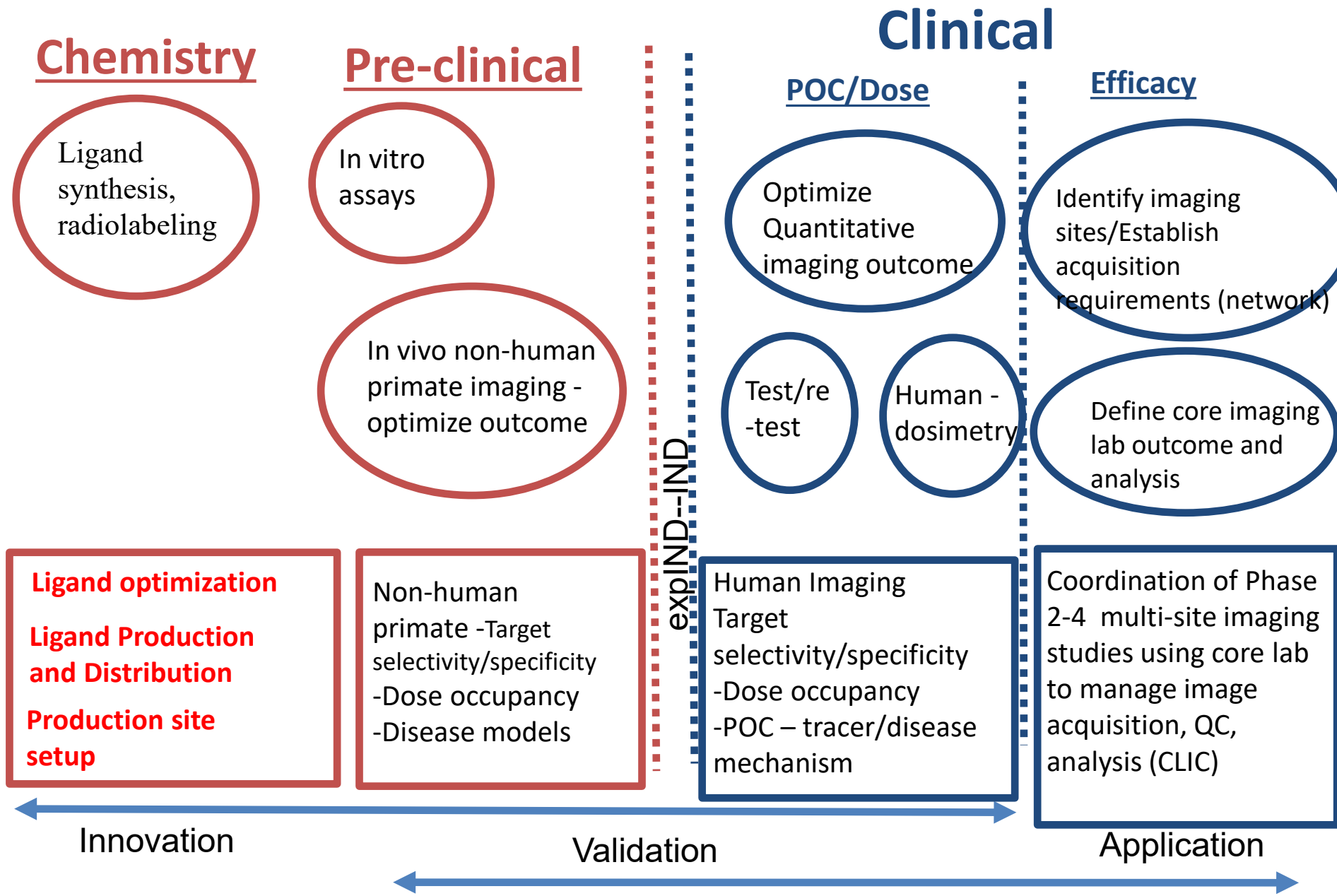
Imaging Biomarker Development and Application



Imaging with Radiolabeled Ligands

- Short-lived gamma-emitting radiotracers
- Desirable ligand characteristics:
  - **Affinity < 5 nM to target protein**
  - **Selectivity >50 versus competing sites**
  - **Log 1<D<3**
  - **Protein Binding: >0.1% free (0.5 preferable)**
  - **at least Bmax/Kd>10**
  - High specific activity/low pharmacological dose

	$T^1/_2$		$T^1/_2$
^{11}C	**20 min**	^{123}I	**13.2 h**
^{18}F	**110 min**	^{89}Zr	**4days**

Introduction

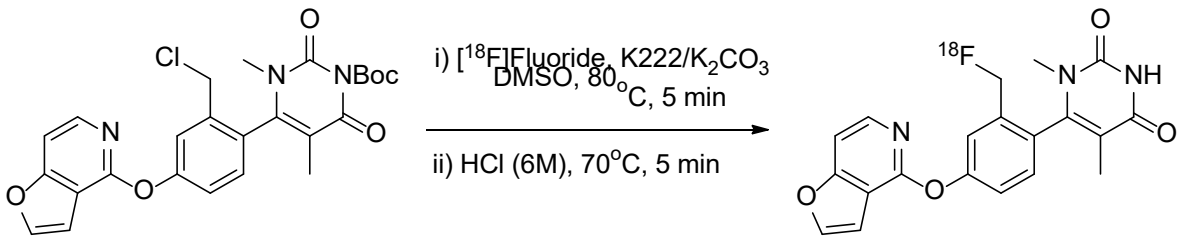
- Significance: D1 receptors, which couple to inhibitory G-proteins, have been shown to regulate neuronal growth and development, mediate some behavioral responses, and modulate dopamine receptor D2-mediated events (M.L. Paul et al., J. Neurosc. 1992), and their function has been shown to be altered in schizophrenia (A. Abi-Dhargam et. al, J. Neurosc. 2002).

- There is an increased interest in agonist radioligand that can access high affinity states of D1 receptors. To date, there is a lack of agonist PET tracers for the D1 receptors labeled with ^{18}F with relevance in clinical studies.

- Synthesis and evaluation in non-human primates [^{18}F]MNI-800 (PF-8477) and in human of [^{18}F]MNI-968 (PF-06730110), novel PET radiotracers of the D1 receptors.
- *nb: MNI-968 is the pure isomer of MNI-800*

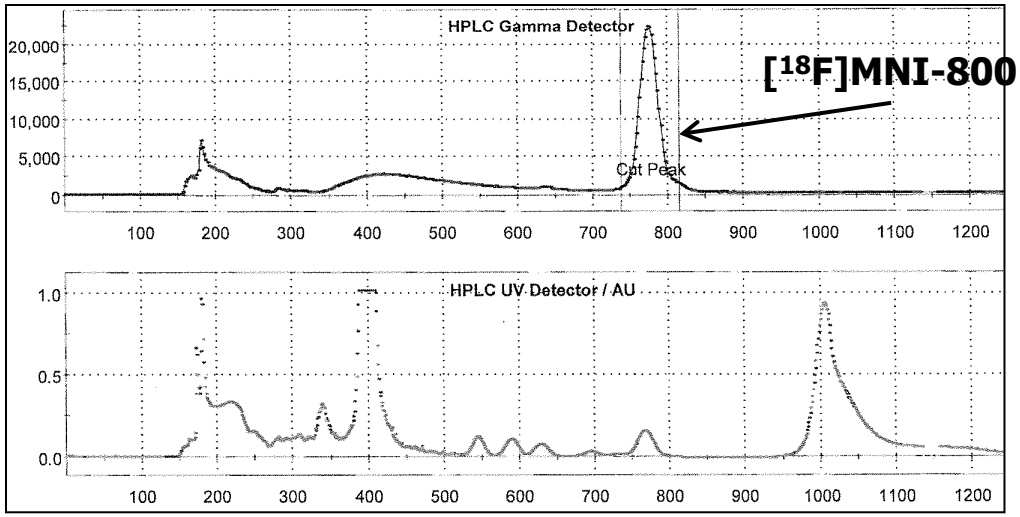
Non-Human Primate Validation Studies

[^{18}F]MNI-800 Radiosynthesis



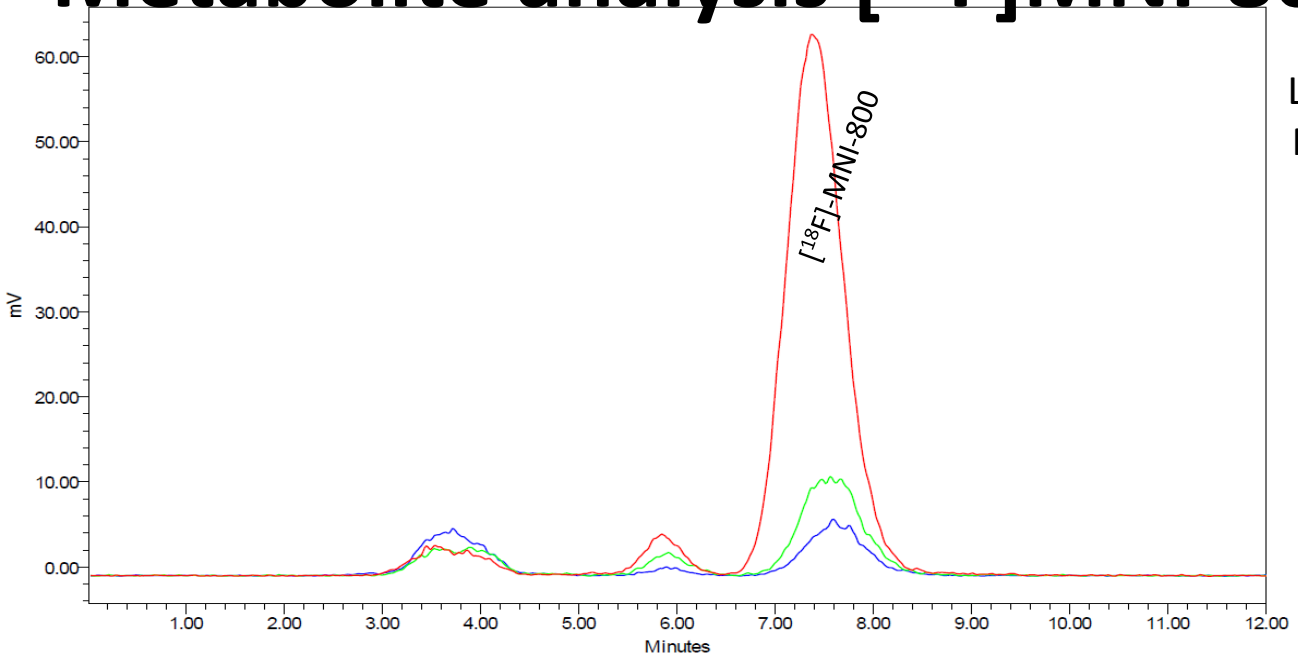
Two step production method. 1) Reaction with F-18; 2) N-Boc deprotection with HCl
Higher reaction temperatures lead to total degradation of precursor and low yields

HPLC using Phenomenex Luna C18(2), 250x10 mm
Acetonitrile/ammonium formate (50mM) (40/60 v/v) @ 4 mL/min



Start = 728 mCi
End = 93.7 mCi
DCY = **<u>18.3%</u>** in 56 min

Metabolite analysis [^{18}F]MNI-800



HPLC conditions

Luna C18 (10 µm, 10x250 mm)

MeOH/H_2O-Et_3N (0.2%) 60/40

4 mL/min

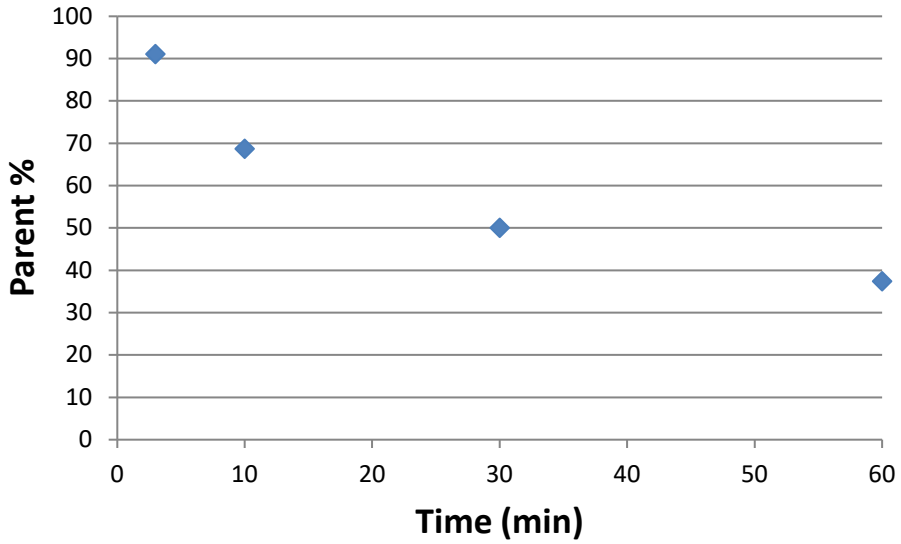
Time points

3 min ---

10 min ---

30 min ---

[^{18}F]MNI-800 parent fraction



Protein Binding:

Free fraction ~ 16%

Stability in blood ex vivo

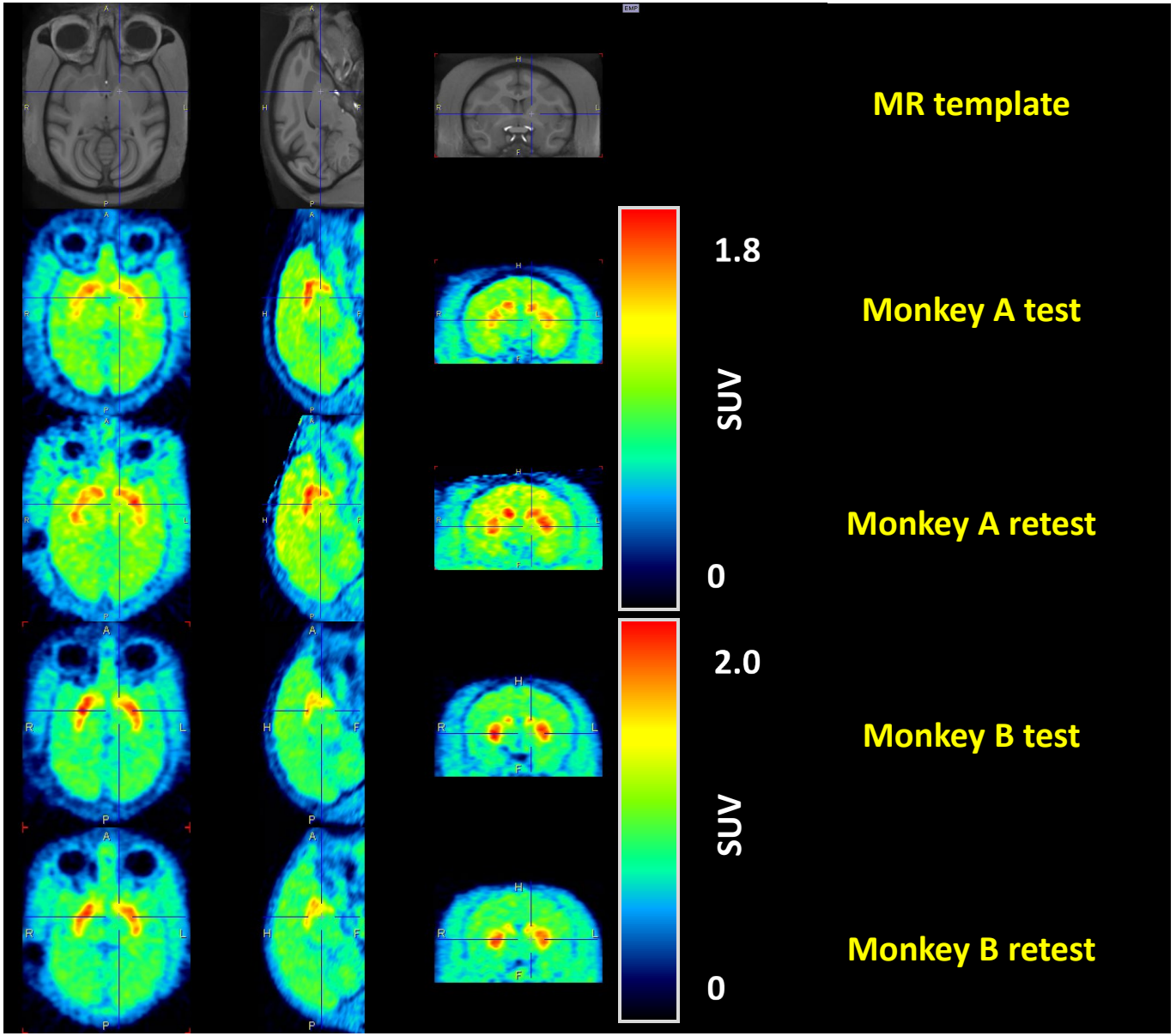
	Time before processing	Parent %
Standard B	< 5 min	94.2%
Standard A	1.5 h	94.0%

Methods

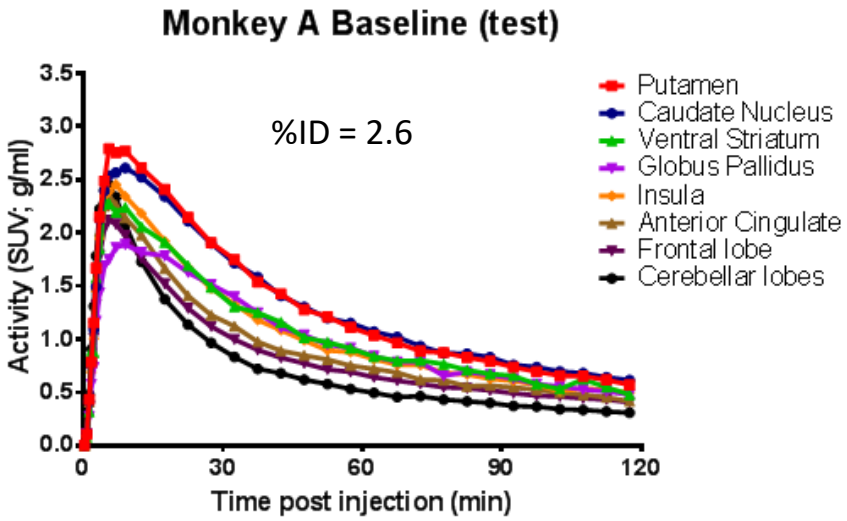
- Eight brain PET studies were conducted on a Siemens Focus 220 in two rhesus monkeys with [^{18}F]MNI-800 (injected dose 177 ± 7 MBq)
  - 4 Baselines (2 Test/Retest) and 4 pre-block with SCH-23390 (D1 antagonist)
  - Imaging from 0-120 min
  - Arterial blood data were drawn for radioactivity and metabolite analysis
  - PET data were modeled to estimate total distribution volume V_T, and binding potential BP_{ND}:
    - 1-tissue (1T) and 2-tissue (2T) compartmental models
    - Logan graphical analysis (LGA)
    - Non-invasive Logan graphical analysis (NI-LGA)
    - Cerebellar cortex as reference region.
  - Occupancy was estimated from BP_{ND} at baseline and post blockade.
- Two whole-body PET studies were performed (1 male and 1 female rhesus monkey):
  - Imaging over ~4 hours
  - Radiation absorbed dose estimates and effective dose (ED) were estimated with OLINDA/EXM 1.0.

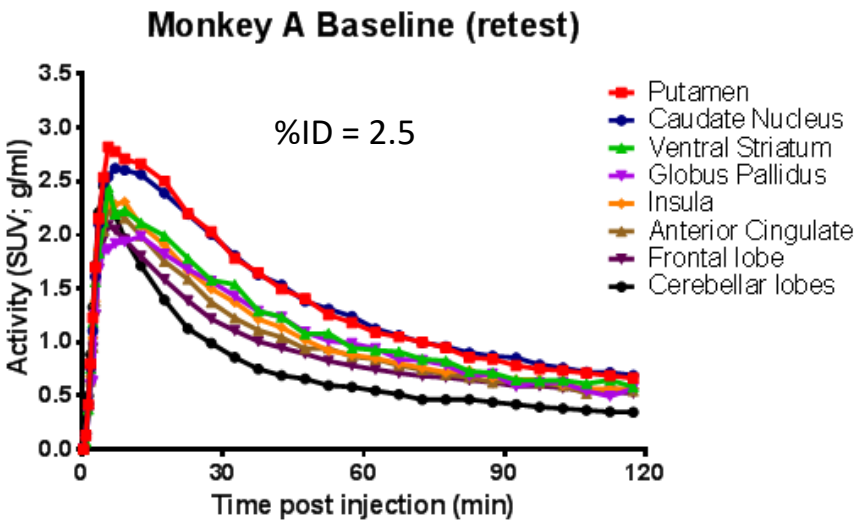
[^{18}F]MNI-800 images at baseline

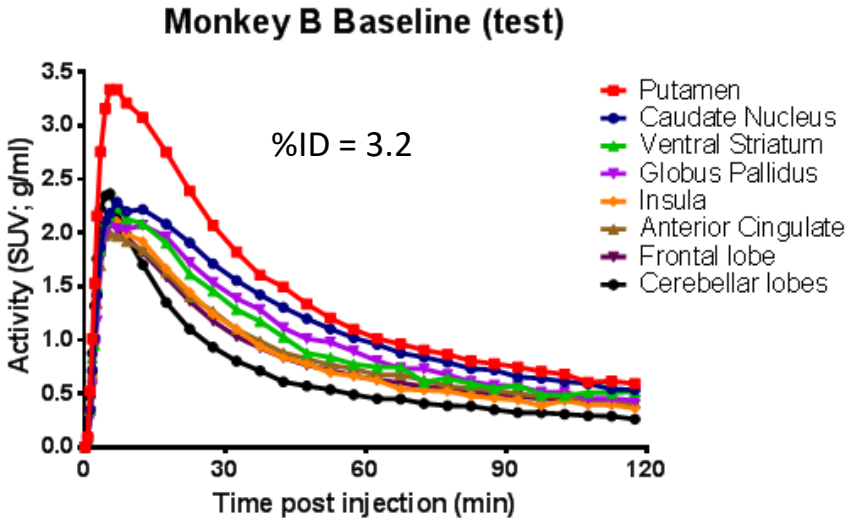
0-120 min post injection

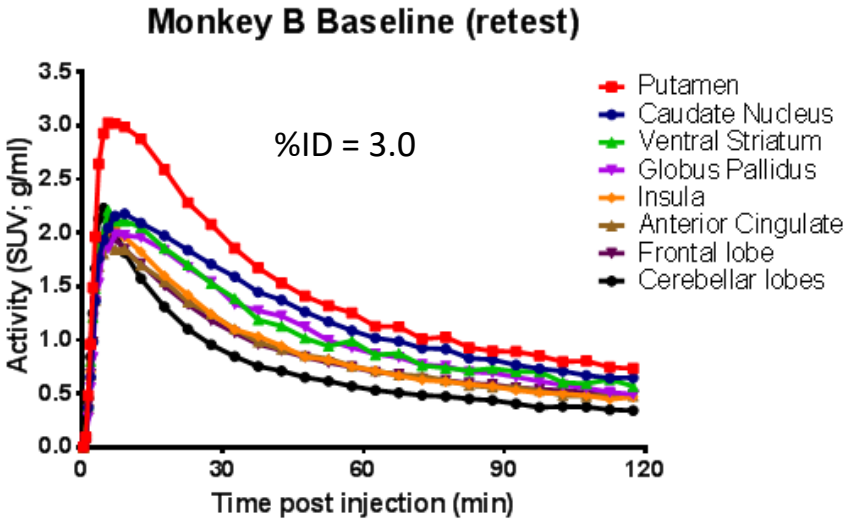


[^{18}F]MNI-800 Time-Activity Curves



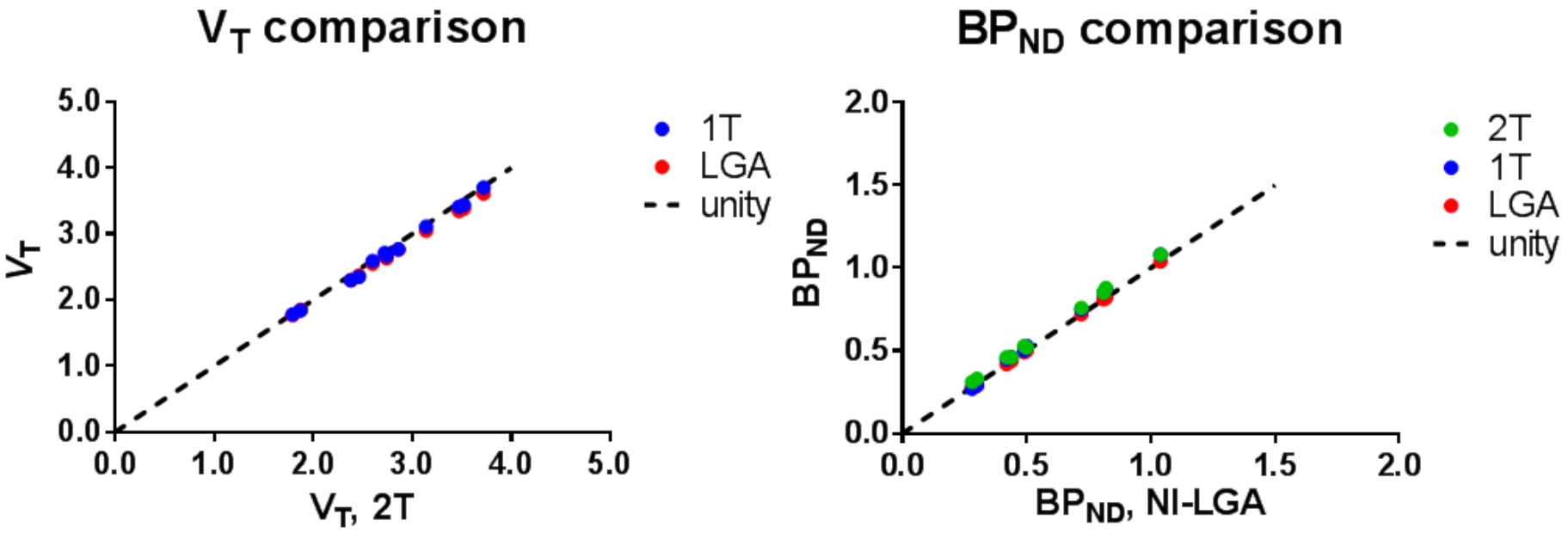






[^{18}F]MNI-800 presented highest uptake in the striatum (putamen, caudate) , medium uptake in cingulate and other cortical regions, and low uptake in cerebellar lobes (gray)

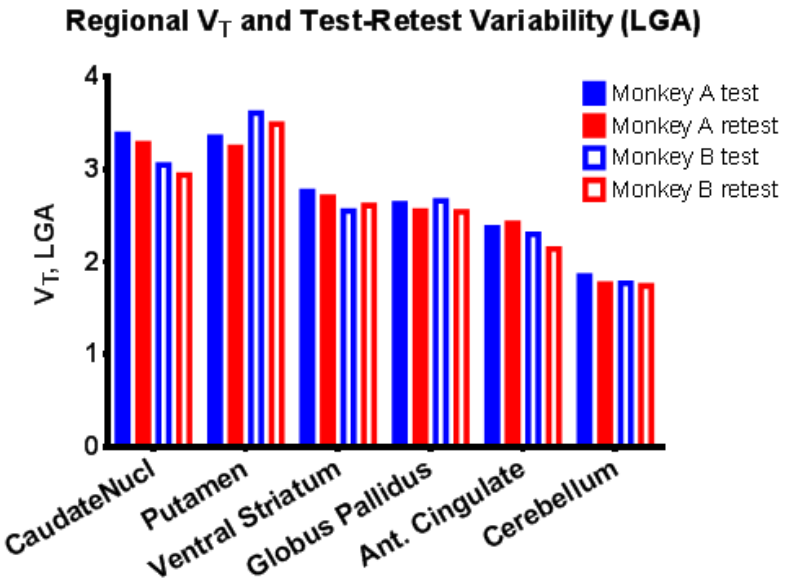
Comparison of V_T and BP_{ND} from different models

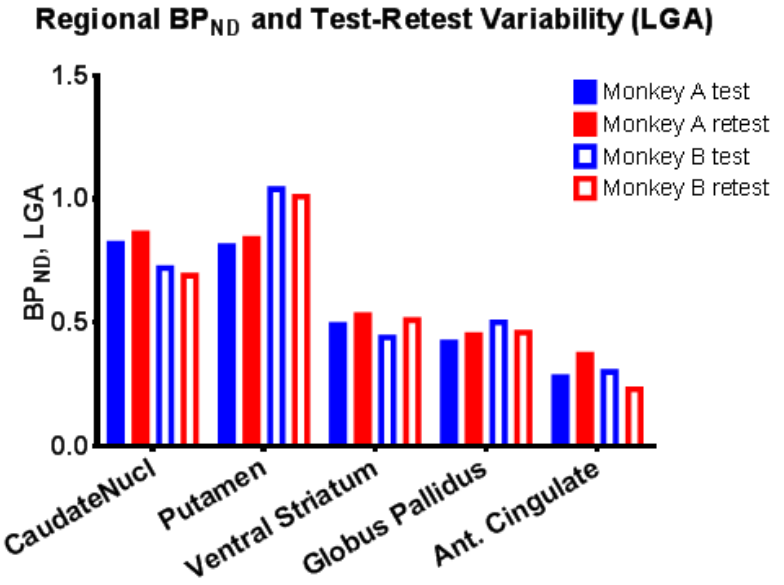


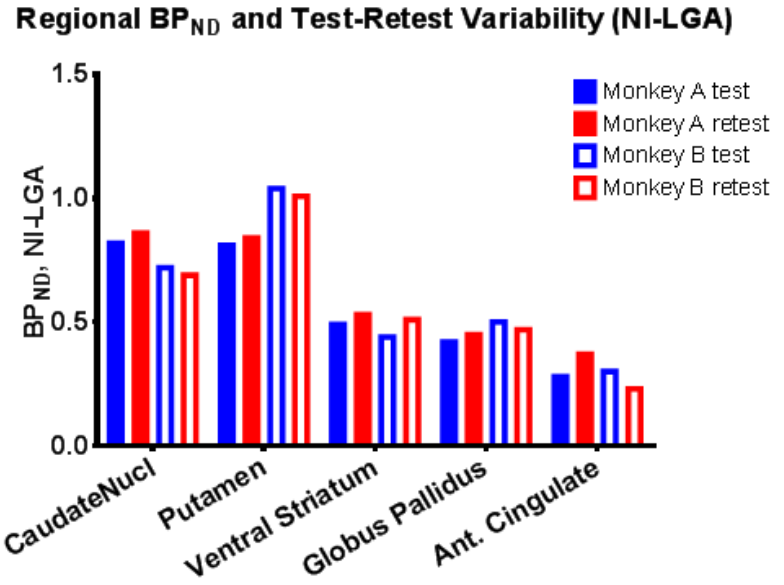
2T model fitted data better than 1T model (Akaike information criterion)

Low bias and high correlation were found between V_T , and BP_{ND} values estimated with different models.

Regional V_T , BP_{ND} and Test-Retest Variability





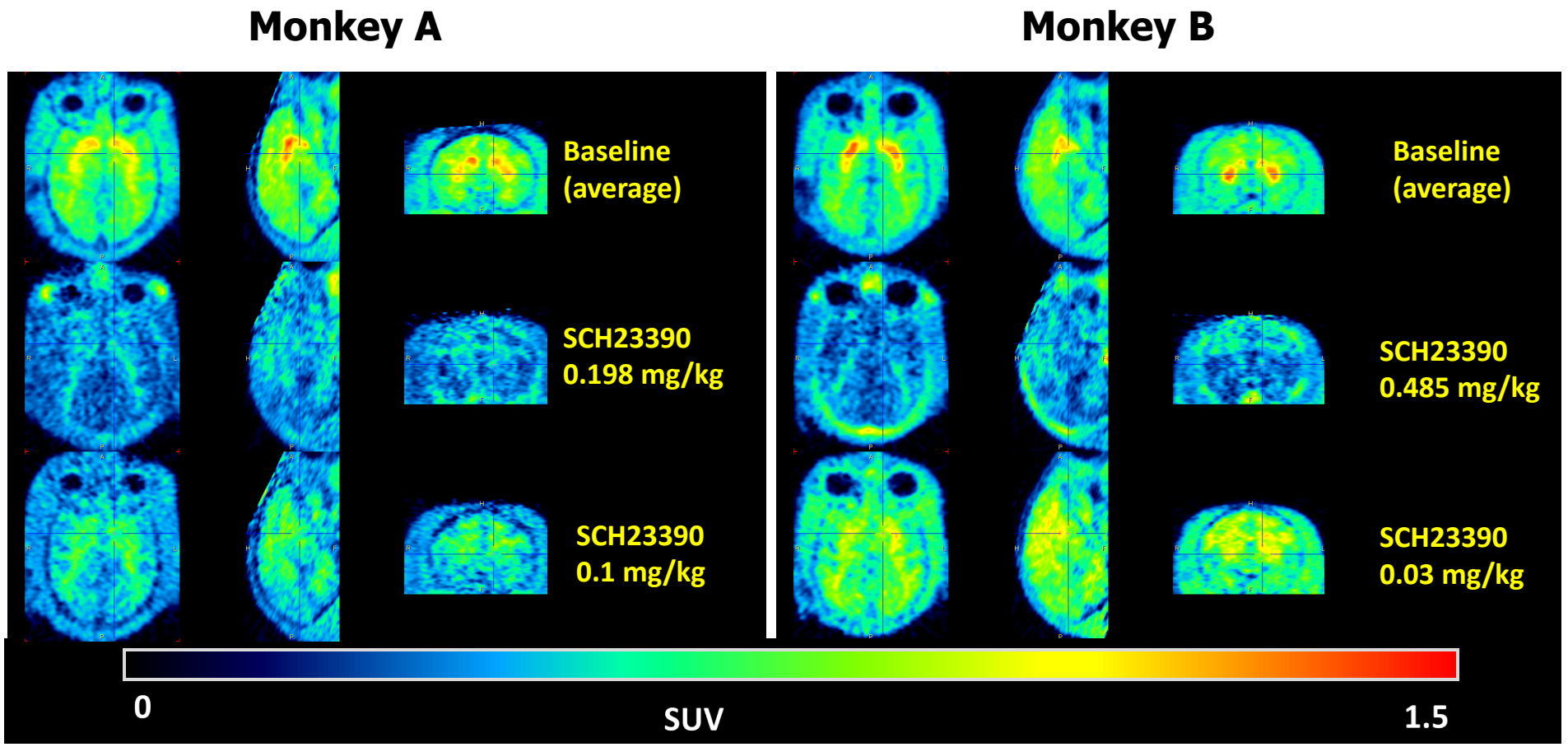


% TRT Caudate\Putamen:

V_T, LGA = 3-4 %
BP_{ND}, LGA = 3-4 %
BP_{ND}, NI-LGA = 3-4 %

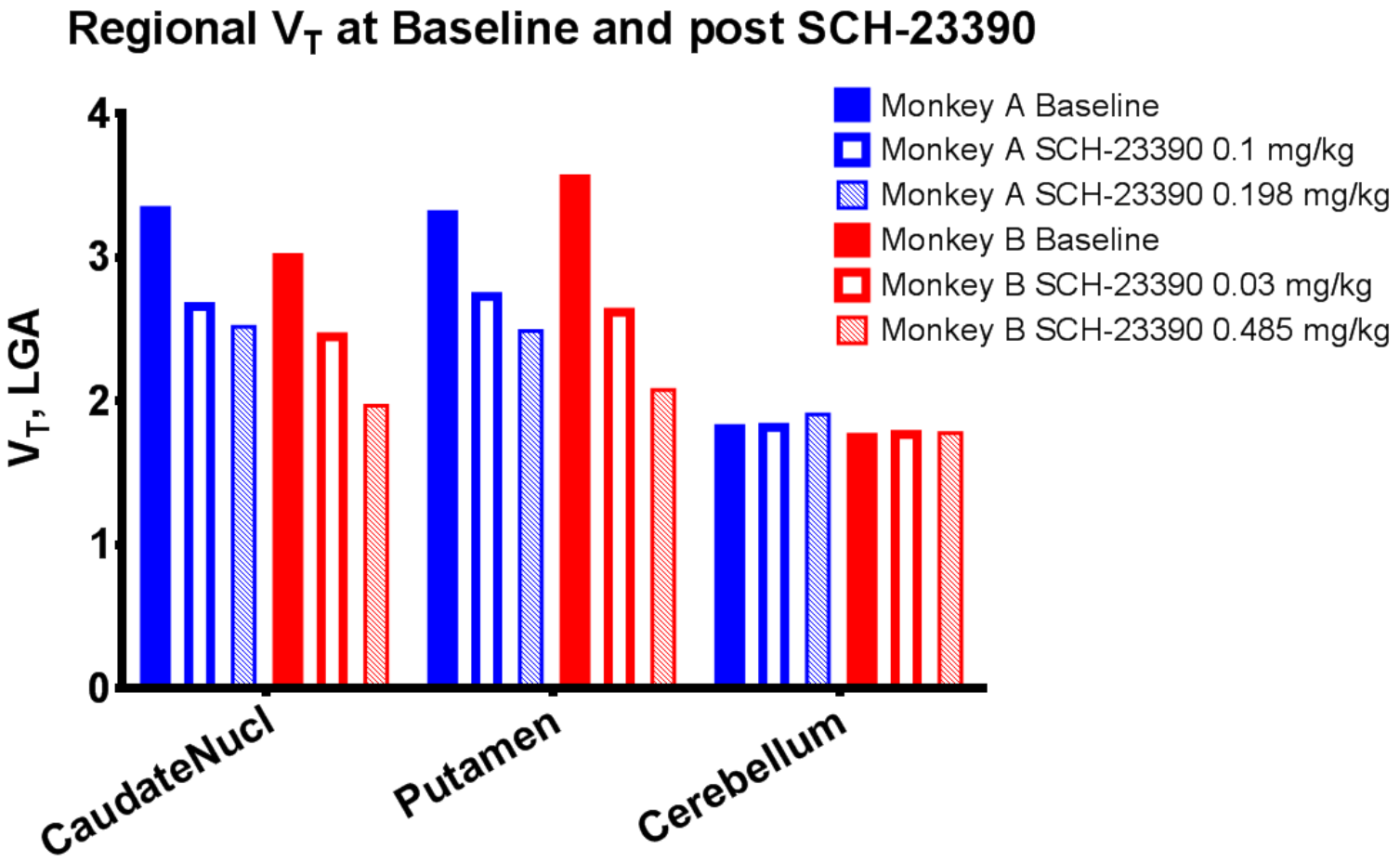
% TRT = (Test-Retest)/Test x 100

Blocking with SCH-23390 (D1 antagonist)



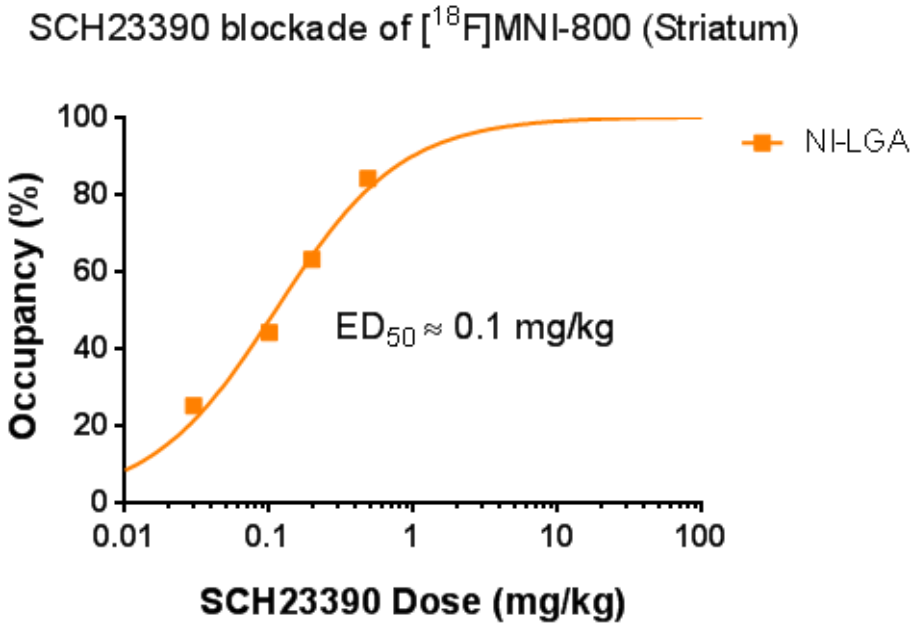
Images were averaged over 30-120 min post tracer injection

D1 receptor occupancy by SCH-23390



V_T values were computed with Logan graphical analysis (LGA)

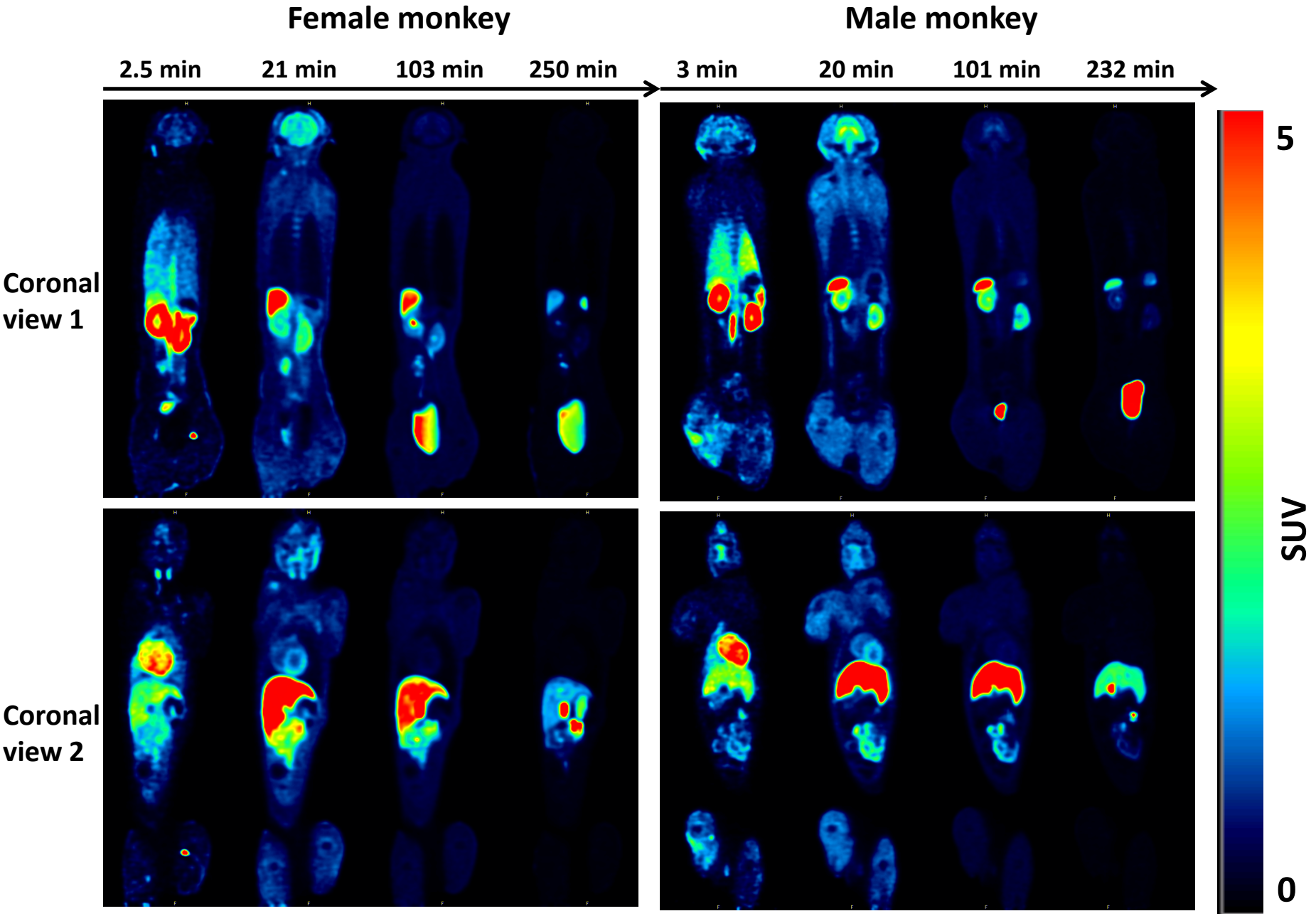
D1 receptor occupancy by SCH-23390



Region	0.485 mg/kg SCH-23390	0.198 mg/kg SCH-23390	0.1 mg/kg SCH-23390	0.03 mg/kg SCH-23390
Caudate Nucl.	85%	63%	47%	17%
Putamen	84%	63%	40%	33%
Ventral Striatum	103%	56%	59%	52%
Globus Pallidus	63%	38%	34%	24%
Ant. Cingulate	64%	52%	29%	12%
Mean (Caudate + Putamen)	**84%**	**63%**	**44%**	**25%**

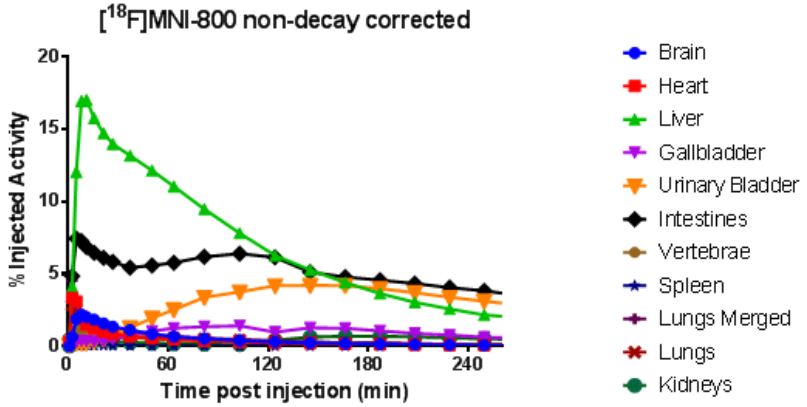
BP_{ND} values were computed with Non-Invasive Logan Gaphical Analysis (NI-LGA), cerebellar lobes = reference region, t* = 10 min

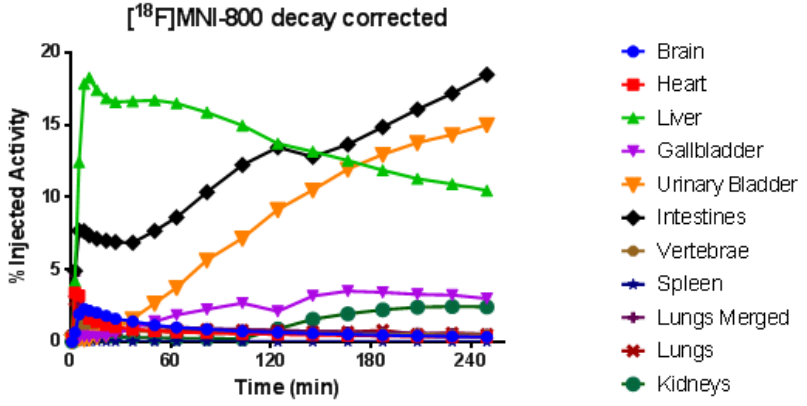
[^{18}F]MNI-800 Dosimetry and Biodistribution



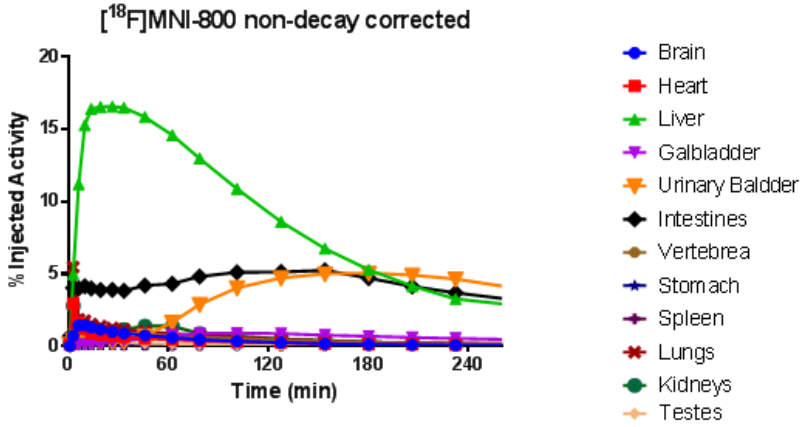
Organ time-activity curves (% ID)

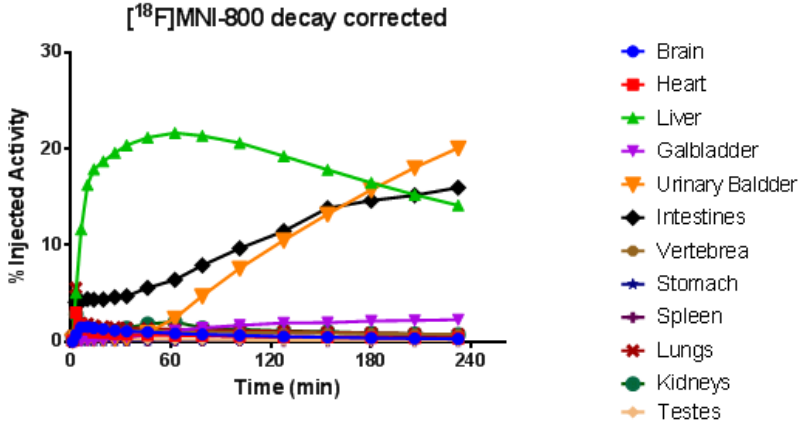
Female monkey





Male monkey





[18F]MNI-800 was eliminated primarily via hepatobiliary pathway.

Total absorbed doses

Target Organ	Dose (mSv/MBq) Monkey A (female)	Dose (mSv/MBq) Monkey C (male)
Adrenals	1.58E-02	1.37E-02
Brain	8.05E-03	5.64E-03
Breasts	8.36E-03	6.62E-03
Gallbladder Wall	1.17E-01	7.88E-02
LLI Wall	2.21E-02	1.82E-02
Small Intestine	3.95E-02	3.16E-02
Stomach Wall	1.81E-02	1.12E-02
ULI Wall	4.31E-02	3.50E-02
Heart Wall	2.44E-02	1.92E-02
Kidneys	2.43E-02	2.89E-02
Liver	6.69E-02	6.38E-02
Lungs	1.83E-02	1.64E-02
Muscle	1.05E-02	8.54E-03
Ovaries	1.80E-02	1.45E-02
Pancreas	1.64E-02	1.36E-02
Red Marrow	1.22E-02	1.19E-02
Osteogenic Cells	1.61E-02	1.28E-02
Skin	7.31E-03	5.85E-03
Spleen	1.00E-02	1.09E-02
Testes		1.05E-02
Thymus	1.05E-02	8.17E-03
Thyroid	8.00E-03	6.59E-03
Urinary Bladder Wall	**1.46E-01**	**1.26E-01**
Uterus	2.03E-02	1.78E-02
Total Body	1.27E-02	1.06E-02
Effective Dose (ED, ICRP-60)	**2.47E-02**	**2.11E-02**

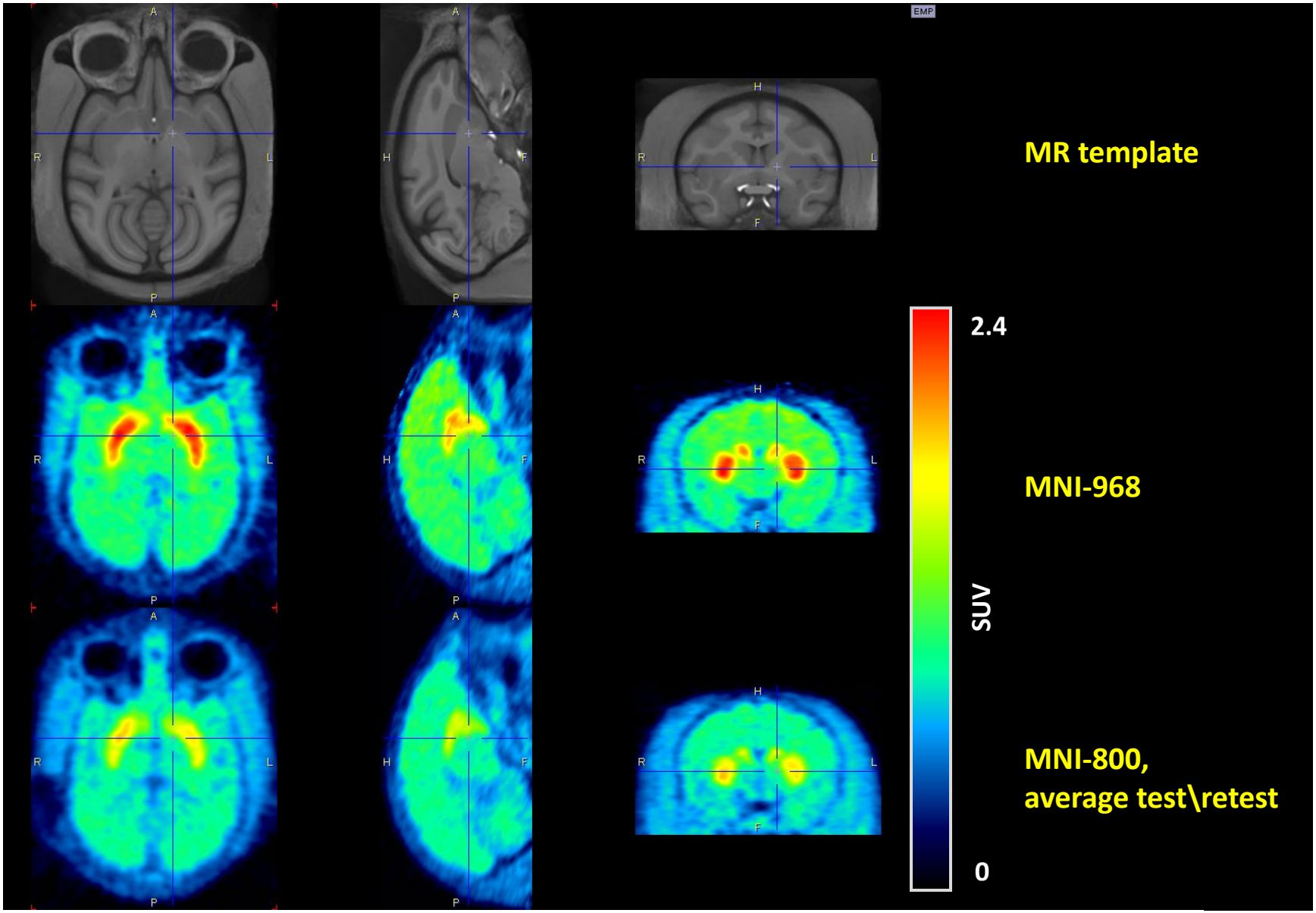
Critical organ = Urinary Bladder

Methods: Comparison of MNI-800 and MNI-968

- Six PET studies were conducted on a Siemens Focus 220 in two rhesus monkeys and two cynomolgus monkeys with [^{18}F]MNI-800 and [^{18}F]MNI-968
  - 2 Baselines in Rhesus with [^{18}F]MNI-968 in same monkeys part of the test/retest with [^{18}F]MNI-800
  - 4 baselines in two cynomolgus with [^{18}F]MNI-800 and [^{18}F]MNI-968
  - Imaging from 0-120 min
  - Arterial blood data were drawn for radioactivity and metabolite analysis
  - Within-animal comparison of [^{18}F]MNI-800 and [^{18}F]MNI-968

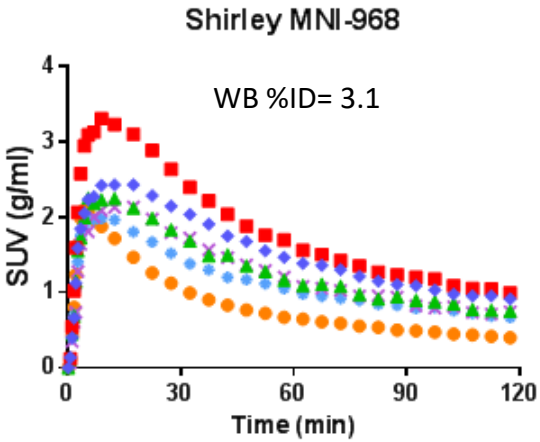
MNI-968\MNI-800 SUV images 0-120 min

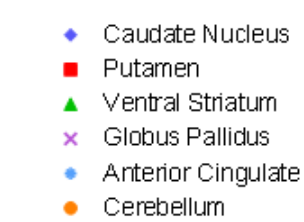
(Rhesus)

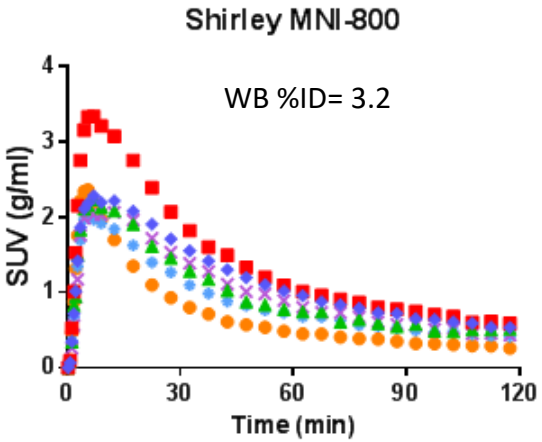


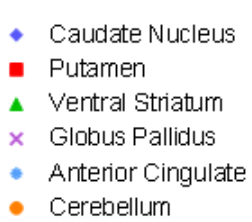
MNI-968\MNI-800 SUV images 0-120 min

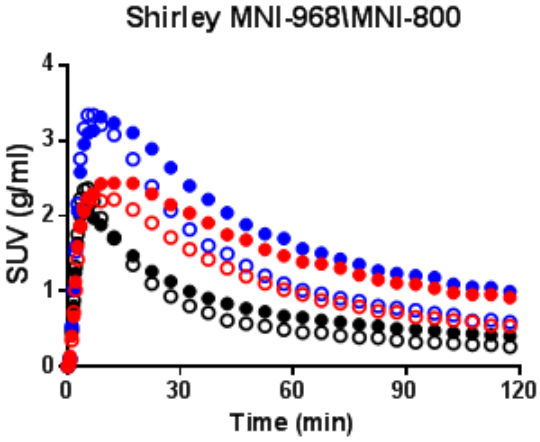
(Rhesus)

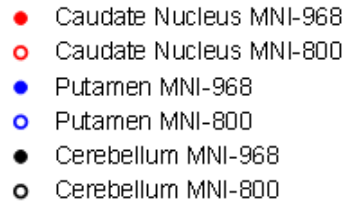












BP_{ND}

	MNI-968	MNI-800
Caudate Nucleus	0.94	0.72
Putamen	1.26	1.04
Ventral Striatum	0.63	0.44
Globus Pallidus	0.59	0.50

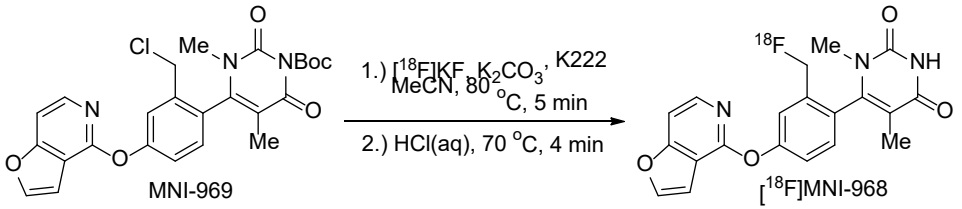
NI-LGA: $BP_{ND}^{MNI-968}$ ~28% higher than $BP_{ND}^{MNI-800}$

Human Validation Studies

[^{18}F]MNI-968 as a marker for
D1 receptors in healthy subjects:

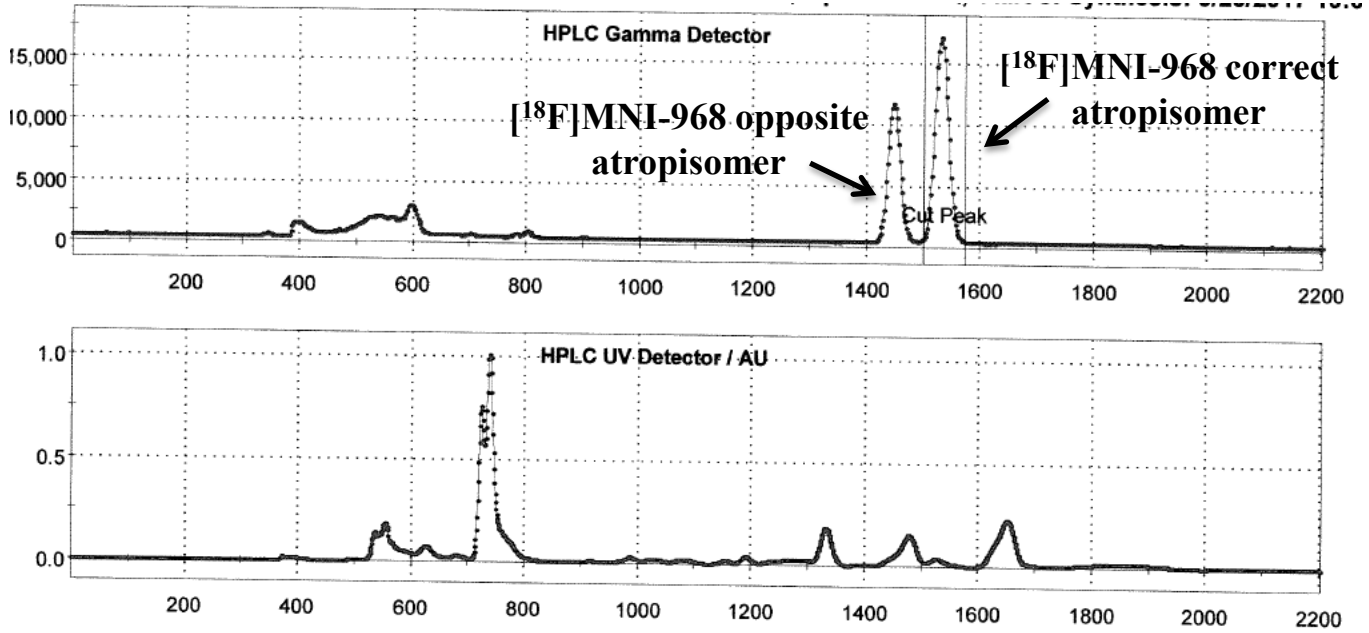
Test-retest and Dosimetry

MNI-968 Production



DCY: 7.43% ± 3.01% (n=13)

Production HPLC Trace



*F-18 production purification involves a two column setup- Chiralcel OJ-H followed by Phenomenex Luna C18

Methods

- Six brain PET studies were conducted on a Siemens HR+ with [^{18}F]MNI-968
  - Imaging from 0-90 min and optionally (in 2 subjects) from 120-180 min
  - Arterial blood data were drawn for radioactivity and metabolite analysis
  - PET data were modeled to estimate total distribution volume V_T, and binding potential BP_{ND}:
    - 1-tissue (1T) and 2-tissue (2T) compartmental models
    - Logan graphical analysis (LGA)
    - Non-invasive Logan graphical analysis (NI-LGA)
    - Cerebellar cortex as reference region.
- Six whole-body PET studies were performed (three males and three females):
  - Imaging over ~6 hours (2 breaks, urine collection during breaks and end of imaging)
  - Radiation absorbed dose estimates and effective dose (ED) were estimated with OLINDA/EXM 1.0.

MNI-968 Test-Retest Scans

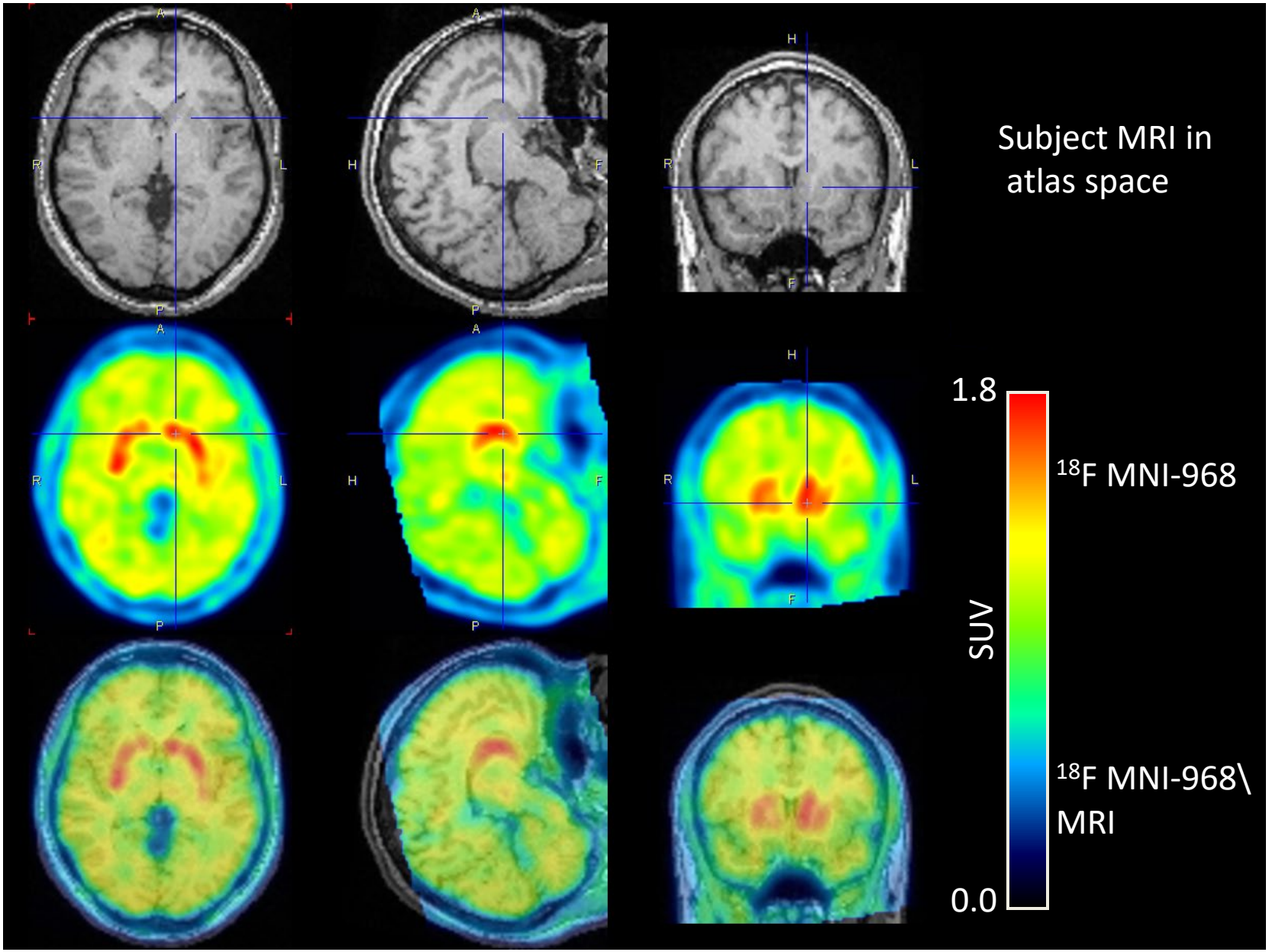
Subject	Date		Injected dose (mCi)		Injected mass (μg/kg)		f_p (%)	
	Test	RT	Test	RT	Test	RT	Test	RT
MNI968_01_01_03	3/30/17	4/11/17	9.3	7.0	0.01	0.01	11.5	10.4
MNI968_01_01_01	4/12/17	4/27/17	9.4	9.2	0.02	0.01	13.0	13.4
MNI968_01_01_02	4/19/17	5/2/17	9.0	9.2	0.00	0.01	11.8	10.0
MNI968_01_01_05	4/21/17	4/28/17	9.7	9.1	0.01	0.01	13.4	11.3
MNI968_01_01_06	5/16/17	5/23/17	9.2	9.4	0.01	0.02	14.7	11.6
MNI968_01_01_07	5/16/17	5/23/17	9.0	9.2	0.01	0.01	11.4	14.6

RT=retest
f_p=free fraction

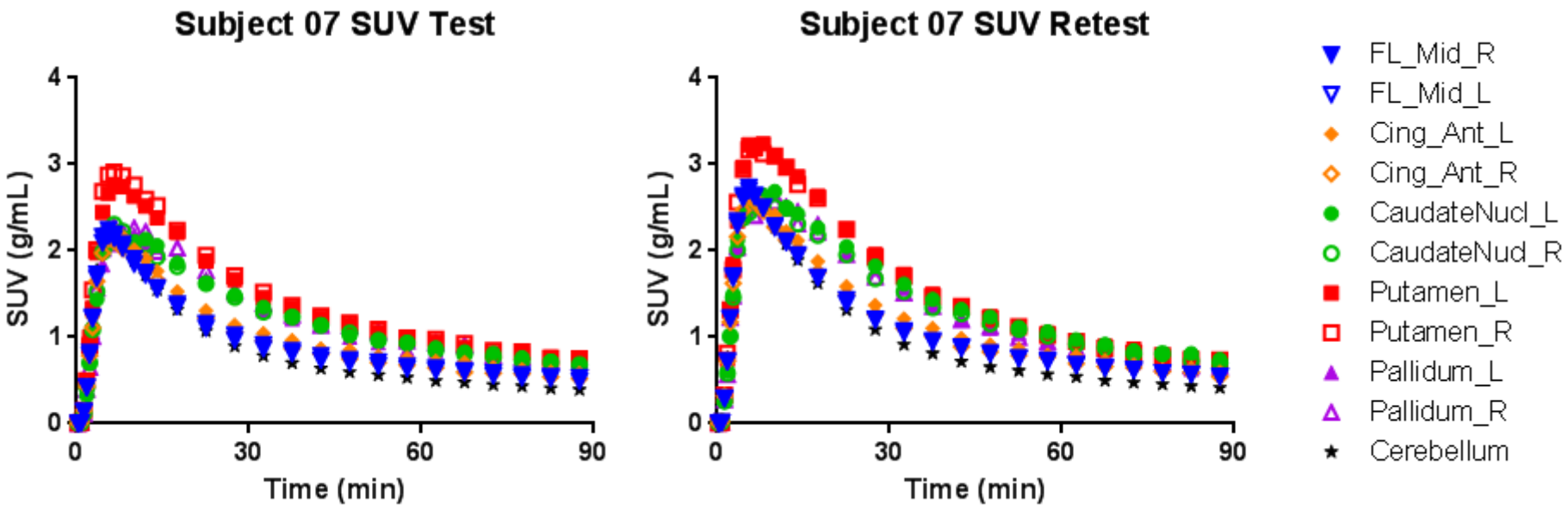
Demographics

Subject Number	Cohort	Gender	Age at Screen	Race	Ethnicity
MNI968_01_01_03	HC	Male	44	African-American	Non-hispanic/latino
MNI968_01_01_01	HC	Male	48	African-American	Non-hispanic/latino
MNI968_01_01_02	HC	Male	50	African-American	Non-hispanic/latino
MNI968_01_01_05	HC	Male	29	African-American	Non-hispanic/latino
MNI968_01_01_06	HC	Female	41	Puerto Rican	Hispanic/Latino
MNI968_01_01_07	HC	Female	32	African-American	Non-hispanic/latino

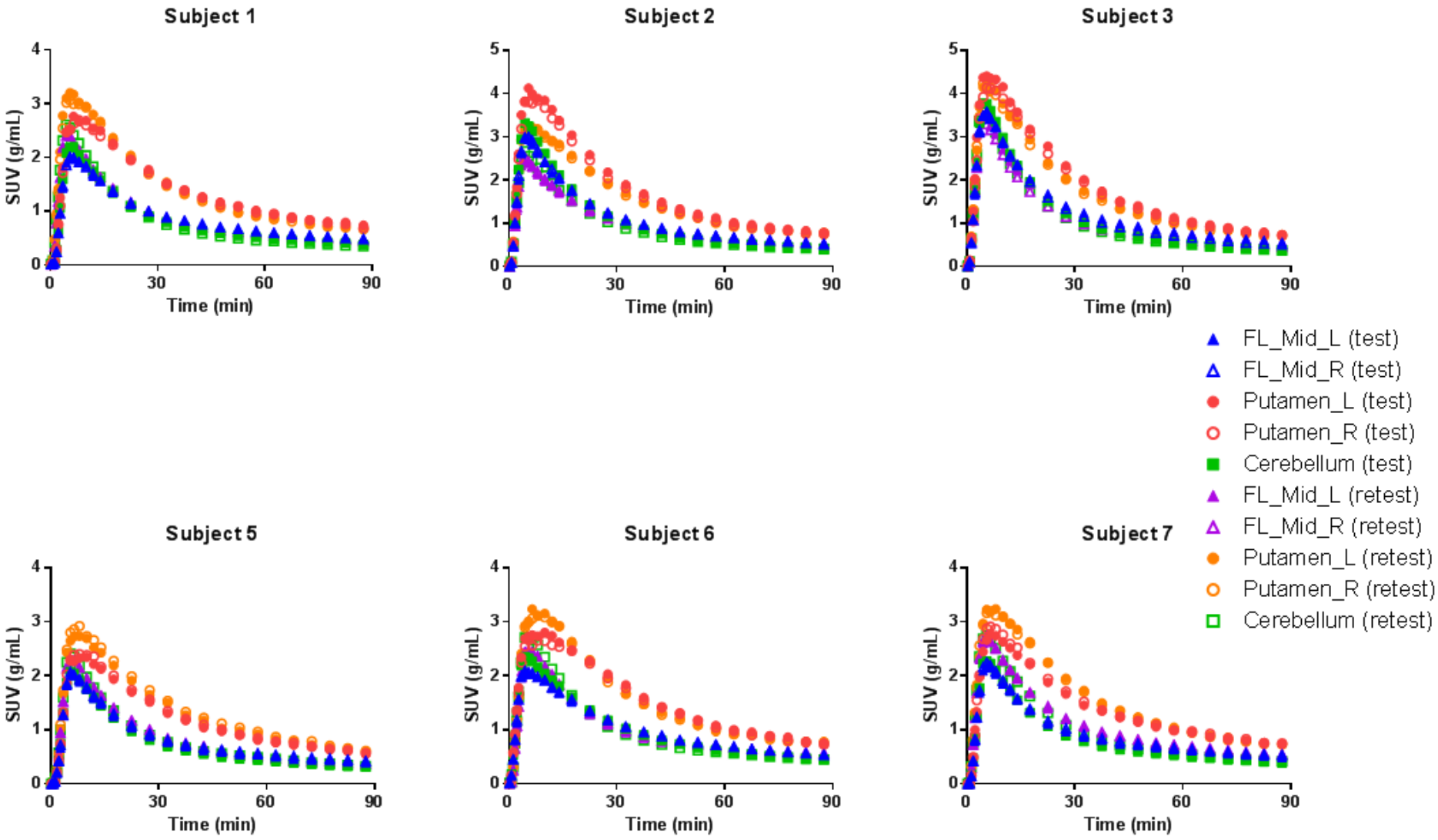
Subject MNI968_01_01_07 (0-90 min)



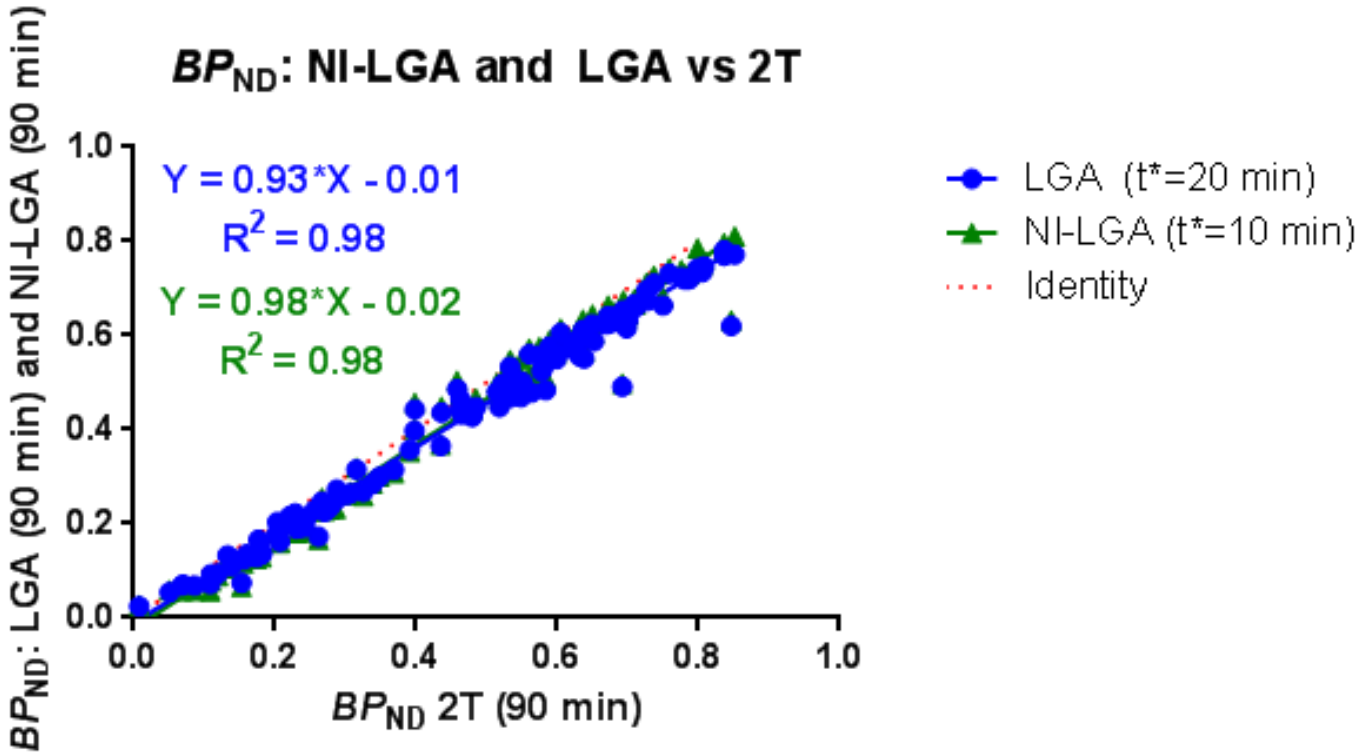
Subject MNI968_01_01_07 SUV TACs



SUV TACs for T/RT in putamen and cerebellum



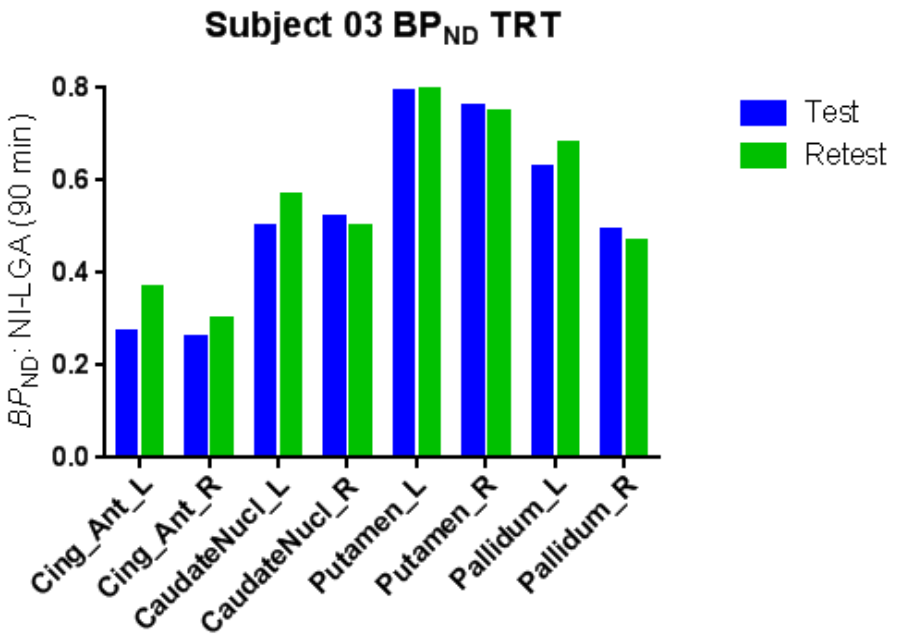
BP_{ND}: NI-LGA and LGA vs 2T



Subject 01 BP_{ND} (NI-LGA 90 min): Test and Retest

Region	BP_{ND} Test	BP_{ND} Retest	% Diff
Cing_Ant_L	0.27	0.37	-31%
Cing_Ant_R	0.26	0.30	-14%
CaudateNucl_L	**0.50**	**0.57**	**-14%**
CaudateNucl_R	**0.52**	**0.50**	**3%**
Putamen_L	**0.79**	**0.80**	**-1%**
Putamen_R	**0.76**	**0.75**	**1%**
Pallidum_L	**0.63**	**0.68**	**-7%**
Pallidum_R	**0.49**	**0.47**	**5%**

Cerebellum was used as the reference region



2T: T-RT Summary for V_T

V_T	Subject 1			Subject 2			Subject 3			Subject 5			Subject 6			Subject 7			ABS (TRTV)
VOI	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	MEAN
CaudateNucl_L	1.66	1.84	-10%	1.50	1.42	6%	1.75	2.02	-14%	1.71	1.61	6%	1.50	1.47	2%	1.90	1.76	7%	8%
CaudateNucl_R	1.64	1.75	-6%	1.59	1.38	14%	1.89	2.11	-11%	1.65	1.87	-12%	1.43	1.43	0%	1.83	1.69	8%	9%
Cerebellum	1.06	1.13	**-6%**	0.98	0.93	**5%**	1.15	1.30	**-12%**	1.03	1.10	**-6%**	1.02	0.96	**6%**	1.16	1.10	**5%**	**7%**
Cing_Ant_L	1.39	1.62	-16%	1.18	1.25	-6%	1.47	1.62	-10%	1.37	1.35	2%	1.26	1.22	3%	1.59	1.42	11%	8%
Cing_Ant_R	1.38	1.52	-10%	1.25	1.16	8%	1.46	1.81	-21%	1.30	1.39	-7%	1.18	1.07	10%	1.43	1.33	8%	10%
FL_Mid_L	1.25	1.31	-4%	1.11	1.10	2%	1.42	1.67	-16%	1.19	1.11	7%	1.13	1.08	5%	1.37	1.30	5%	7%
FL_Mid_R	1.24	1.33	-7%	1.10	1.13	-3%	1.32	1.41	-7%	1.28	1.16	10%	1.14	1.12	2%	1.43	1.30	10%	6%
Pallidum_L	1.96	1.97	-1%	1.56	1.52	2%	1.93	2.10	-9%	1.75	1.85	-6%	1.68	1.59	5%	1.77	1.63	8%	5%
Pallidum_R	1.64	1.67	-2%	1.55	1.47	5%	1.82	1.98	-8%	1.59	1.68	-5%	1.49	1.47	2%	1.97	1.61	20%	7%
Putamen_L	1.96	2.07	-5%	1.74	1.64	6%	1.99	2.23	-11%	1.79	1.89	-5%	1.69	1.58	7%	2.07	1.86	11%	8%
Putamen_R	1.91	2.04	-7%	1.67	1.62	3%	1.94	2.18	-12%	1.84	1.99	-8%	1.63	1.57	4%	2.13	1.84	15%	8%

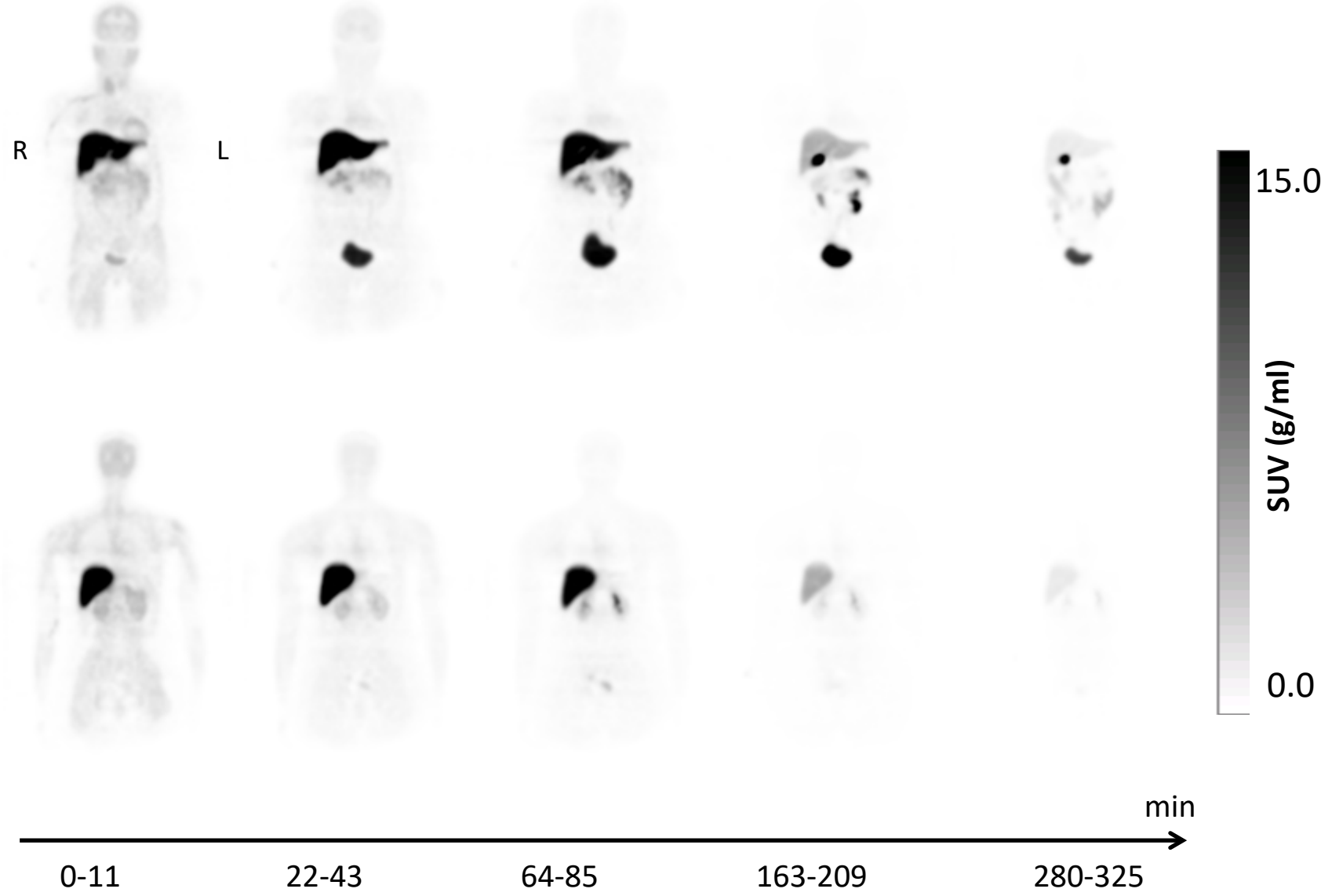
2T: T-RT Summary for V_T

V_T	Subject 1			Subject 2			Subject 3			Subject 5			Subject 6			Subject 7			ABS (TRTV)
VOI	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	T	RT	TRTV	MEAN
CaudateNucl_L	1.66	1.84	-10%	1.50	1.42	6%	1.75	2.02	-14%	1.71	1.61	6%	1.50	1.47	2%	1.90	1.76	7%	**8%**
CaudateNucl_R	1.64	1.75	-6%	1.59	1.38	14%	1.89	2.11	-11%	1.65	1.87	-12%	1.43	1.43	0%	1.83	1.69	8%	**9%**
Cerebellum	1.06	1.13	-6%	0.98	0.93	5%	1.15	1.30	-12%	1.03	1.10	-6%	1.02	0.96	6%	1.16	1.10	5%	7%
Cing_Ant_L	1.39	1.62	-16%	1.18	1.25	-6%	1.47	1.62	-10%	1.37	1.35	2%	1.26	1.22	3%	1.59	1.42	11%	8%
Cing_Ant_R	1.38	1.52	-10%	1.25	1.16	8%	1.46	1.81	-21%	1.30	1.39	-7%	1.18	1.07	10%	1.43	1.33	8%	10%
FL_Mid_L	1.25	1.31	-4%	1.11	1.10	2%	1.42	1.67	-16%	1.19	1.11	7%	1.13	1.08	5%	1.37	1.30	5%	7%
FL_Mid_R	1.24	1.33	-7%	1.10	1.13	-3%	1.32	1.41	-7%	1.28	1.16	10%	1.14	1.12	2%	1.43	1.30	10%	6%
Pallidum_L	1.96	1.97	-1%	1.56	1.52	2%	1.93	2.10	-9%	1.75	1.85	-6%	1.68	1.59	5%	1.77	1.63	8%	**5%**
Pallidum_R	1.64	1.67	-2%	1.55	1.47	5%	1.82	1.98	-8%	1.59	1.68	-5%	1.49	1.47	2%	1.97	1.61	20%	**7%**
Putamen_L	1.96	2.07	-5%	1.74	1.64	6%	1.99	2.23	-11%	1.79	1.89	-5%	1.69	1.58	7%	2.07	1.86	11%	**8%**
Putamen_R	1.91	2.04	-7%	1.67	1.62	3%	1.94	2.18	-12%	1.84	1.99	-8%	1.63	1.57	4%	2.13	1.84	15%	**8%**

MNI-968 Whole-body Scans

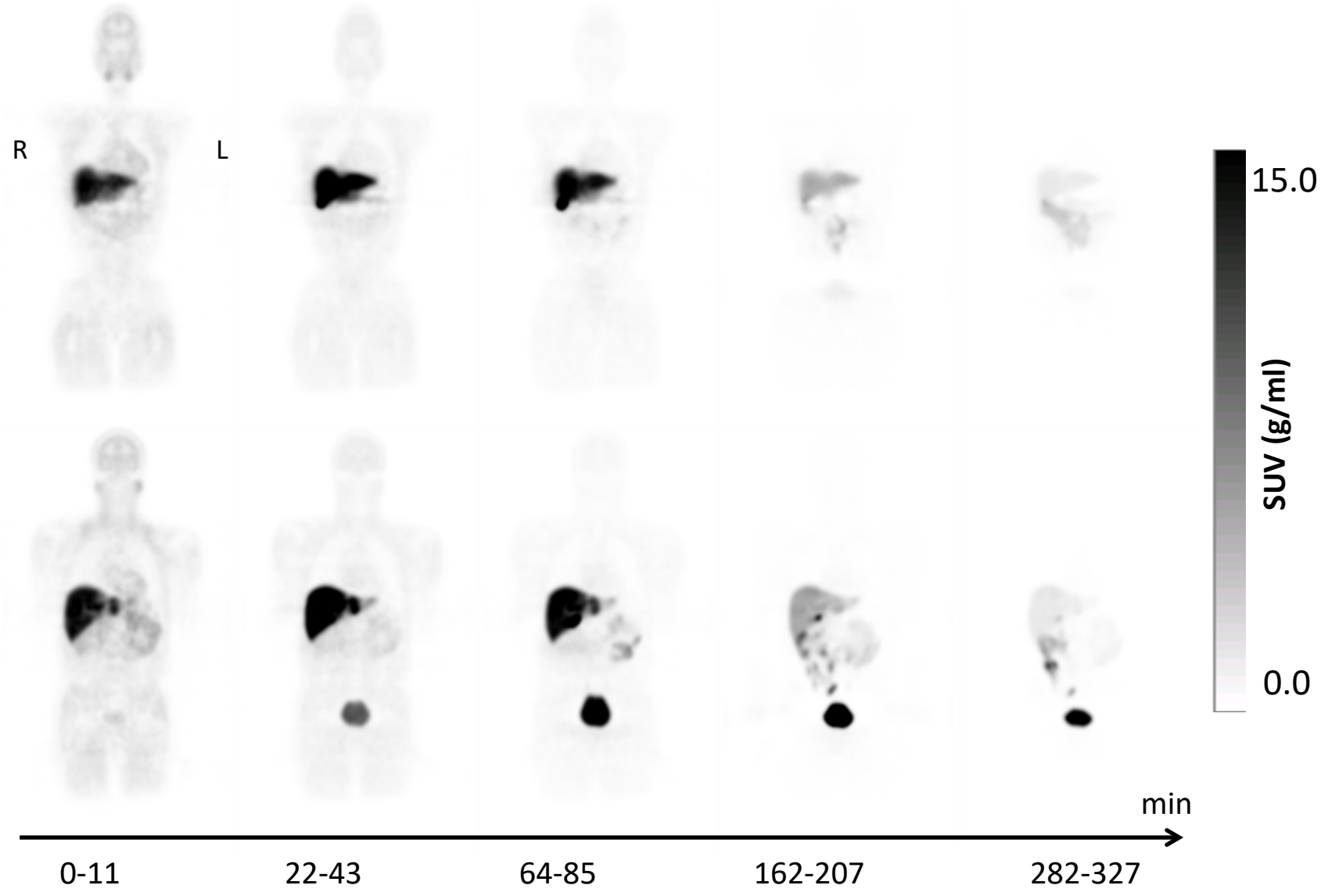
Subject	Gender	Age (y)	Weight (kg)	Dose (mCi)
MNI968-03-01-02	Female	36	89.36	9.788
MNI968-03-01-03	Female	39	73.94	9.463
MNI968-03-01-07	Female	34	79.38	9.676
MNI968-03-01-04	Male	27	88.00	9.647
MNI968-03-01-05	Male	43	70.76	9.594
MNI968-03-01-06	Male	41	139.25	9.624
Mean		37	90.1	9.6
SD		6	25.2	0.1

Subject MNI968-03-01-03 (female, age 39, 9.647 mCi)



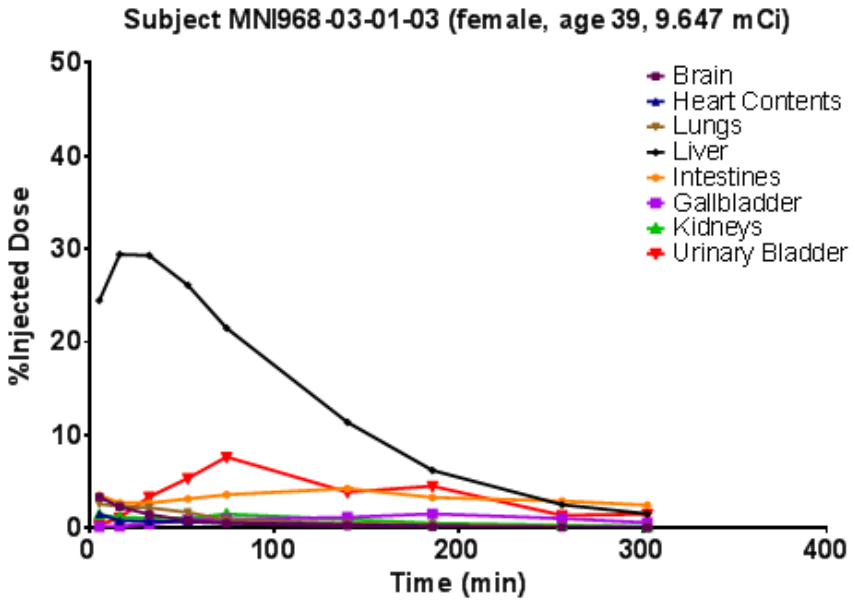
12 mm smoothing applied

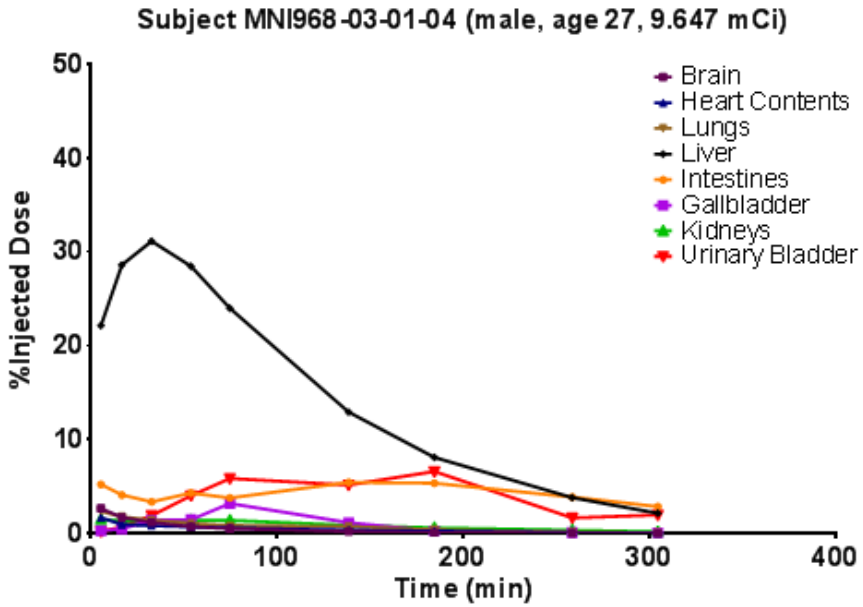
Subject MNI968-03-01-04 (male, age 27, 9.647 mCi)



12 mm smoothing applied

Non-decay corrected time activity curves in 1 male and 1 female healthy volunteer





Organ doses (mSv/MBq)

Urinary Bladder Model : voiding = 2h interval

Target Organ	MNI968-03-01-02	MNI968-03-01-03	MNI968-03-01-07	Female, Mean ± SD			MNI968-03-01-04	MNI968-03-01-05	MNI968-03-01-06	Male, Mean ± SD		
Adrenals	1.68E-02	1.40E-02	1.59E-02	1.56E-02	±	1.43E-03	1.31E-02	1.36E-02	1.16E-02	1.28E-02	±	1.04E-03
Brain	7.19E-03	5.24E-03	6.69E-03	6.37E-03	±	1.01E-03	4.18E-03	5.65E-03	4.22E-03	4.68E-03	±	8.37E-04
Breasts	5.70E-03	3.84E-03	5.37E-03	4.97E-03	±	9.92E-04	3.92E-03	4.48E-03	4.22E-03	4.21E-03	±	2.80E-04
Gallbladder Wall	7.96E-02	1.39E-01	1.60E-01	1.26E-01	±	4.17E-02	1.04E-01	1.16E-01	7.87E-02	9.96E-02	±	1.90E-02
LLI Wall	3.00E-02	2.87E-02	3.65E-02	3.17E-02	±	4.18E-03	2.80E-02	2.18E-02	2.35E-02	2.44E-02	±	3.20E-03
Small Intestine	7.02E-02	6.76E-02	9.15E-02	7.64E-02	±	1.31E-02	6.61E-02	4.80E-02	5.20E-02	5.54E-02	±	9.51E-03
Stomach Wall	1.21E-02	9.70E-03	1.26E-02	1.15E-02	±	1.55E-03	9.03E-03	9.00E-03	8.48E-03	8.84E-03	±	3.09E-04
ULI Wall	7.67E-02	7.39E-02	9.99E-02	8.35E-02	±	1.43E-02	7.56E-02	5.49E-02	5.91E-02	6.32E-02	±	1.09E-02
Heart Wall	1.39E-02	1.32E-02	1.76E-02	1.49E-02	±	2.36E-03	1.26E-02	1.17E-02	1.16E-02	1.20E-02	±	5.51E-04
Kidneys	3.37E-02	3.88E-02	3.51E-02	3.59E-02	±	2.64E-03	3.92E-02	2.66E-02	2.18E-02	2.92E-02	±	8.99E-03
Liver	1.26E-01	1.13E-01	1.11E-01	1.17E-01	±	8.14E-03	9.78E-02	1.02E-01	7.88E-02	9.29E-02	±	1.24E-02
Lungs	1.49E-02	1.48E-02	1.69E-02	1.55E-02	±	1.18E-03	1.17E-02	1.20E-02	1.11E-02	1.16E-02	±	4.58E-04
Muscle	8.42E-03	6.62E-03	8.36E-03	7.80E-03	±	1.02E-03	6.29E-03	6.57E-03	6.35E-03	6.40E-03	±	1.47E-04
Ovaries	2.05E-02	1.93E-02	2.36E-02	2.11E-02	±	2.22E-03	1.70E-02	1.46E-02	1.52E-02	1.56E-02	±	1.25E-03
Pancreas	1.63E-02	1.38E-02	1.63E-02	1.55E-02	±	1.44E-03	1.29E-02	1.33E-02	1.15E-02	1.26E-02	±	9.45E-04
Red Marrow	8.92E-03	7.10E-03	9.11E-03	8.38E-03	±	1.11E-03	7.10E-03	7.09E-03	6.83E-03	7.01E-03	±	1.53E-04
Osteogenic Cells	9.52E-03	6.03E-03	8.93E-03	8.16E-03	±	1.87E-03	6.05E-03	6.94E-03	6.86E-03	6.62E-03	±	4.92E-04
Skin	5.02E-03	3.39E-03	4.73E-03	4.38E-03	±	8.70E-04	3.47E-03	3.91E-03	3.81E-03	3.73E-03	±	2.31E-04
Spleen	8.83E-03	6.68E-03	8.82E-03	8.11E-03	±	1.24E-03	6.19E-03	6.33E-03	6.06E-03	6.19E-03	±	1.35E-04
Testes							5.33E-03	5.78E-03	5.91E-03	5.67E-03	±	3.04E-04
Thymus	6.25E-03	4.11E-03	6.12E-03	5.49E-03	±	1.20E-03	4.25E-03	4.84E-03	4.75E-03	4.61E-03	±	3.18E-04
Thyroid	4.21E-03	2.07E-03	3.75E-03	3.34E-03	±	1.13E-03	2.60E-03	3.39E-03	3.45E-03	3.15E-03	±	4.74E-04
Urinary Bladder Wall	**1.85E-01**	**2.41E-01**	**1.77E-01**	**2.01E-01**	**±**	**3.49E-02**	**1.46E-01**	**1.39E-01**	**1.37E-01**	**1.41E-01**	**±**	**4.73E-03**
Uterus	2.25E-02	2.28E-02	2.42E-02	2.32E-02	±	9.07E-04	1.92E-02	1.74E-02	1.78E-02	1.81E-02	±	9.45E-04
Total Body	1.24E-02	1.03E-02	1.23E-02	1.17E-02	±	1.18E-03	9.60E-03	9.70E-03	8.92E-03	9.41E-03	±	4.24E-04
Effective dose (ED, ICRP-60)	**2.95E-02**	**3.04E-02**	**3.03E-02**	**3.01E-02**	**±**	**4.93E-04**	**2.39E-02**	**2.24E-02**	**2.13E-02**	**2.25E-02**	**±**	**1.31E-03**

Critical organ = Urinary Bladder

Summary #1
NHP

- [^{18}F]MNI-800 and [^{18}F]MNI-968 presented good brain uptake (%ID ~2.5-3.0) and low test\retest variability for V_T and BP_{ND} in the caudate and putamen (~5 %).

- [^{18}F]MNI-800 was successfully blocked by SCH23390 and the occupancy was dose dependent.

- [^{18}F]MNI-968 is a promising agonist PET radiotracer for imaging D1 receptors that can be quantified non-invasively and has favorable dosimetry.

Summary #2
HUMAN

1. [^{18}F]MNI-968 presented good brain uptake (%ID ~2.5-3.0) and low test\retest

1. Elimination of the tracer is mainly via hepatobiliary pathway.

1. The Effective Dose (ED) per 185 MBq (5 mCi) injection is 5.56 mSv (adult female) and 4.17 mSv (adult male) with 2h UB voiding interval, which compares favorably to other ^{18}F radiopharmaceuticals.

2. Based on ED, dosimetry permits 9 injections/year.

•Limits are according to Title 21 CFR 361.1.