LIÈGE université
GIGA
CRC In vivo Imaging

PRECLINICAL IMAGING PLATFORM

GIGA Doctoral School

03/12/2020

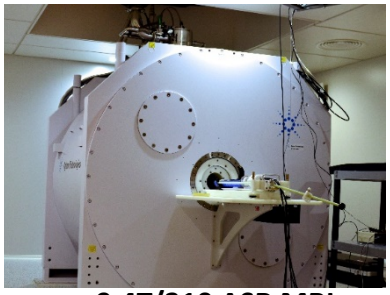
Mohamed Ali Bahri, PhD.

Logisticien de recherche principal,

GIGA-Cyclotron Research Centre: In Vivo Imaging

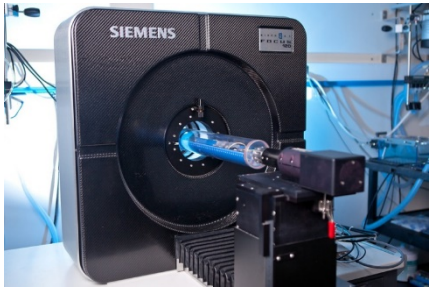
Preclinical Imaging Platform

IVC Housing

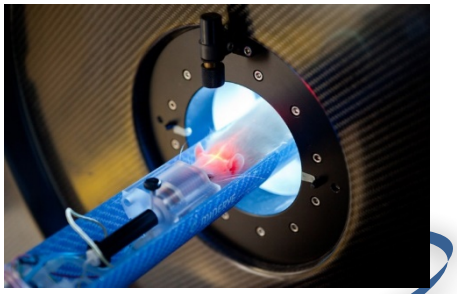


9.4T/310 ASR MRI
(Agilent/Varian)

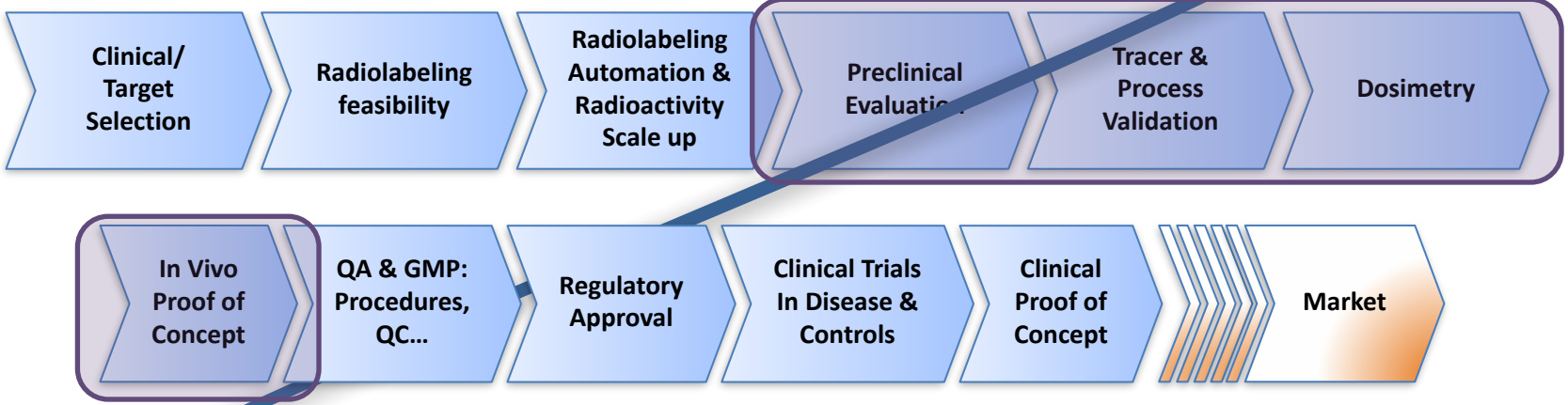
eXplore CT120
(TriFoil Imaging)



Focus120 micoPET
(Siemens)



Cell holders (Minerve)



Preclinical In Vivo Imaging

Molecular Imaging in small animals (rats & mice)

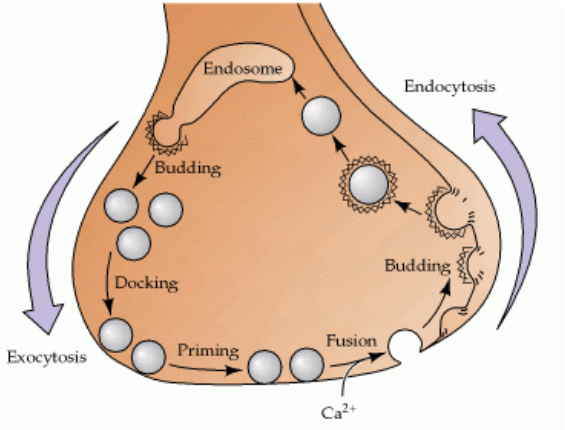
- To realize studies difficult or impossible in human
- To test new disease models (ko, transgenic, oncology…)
- To identify and test new therapies, drugs, methodologies
- To perform basic research devoted to the study of specific diseases, impairments…
- To fulfill the prerequisite for clinical trials:
  - *Proof of concept*
  - *Tissue distributions*
  - *Dosimetry*
  - …

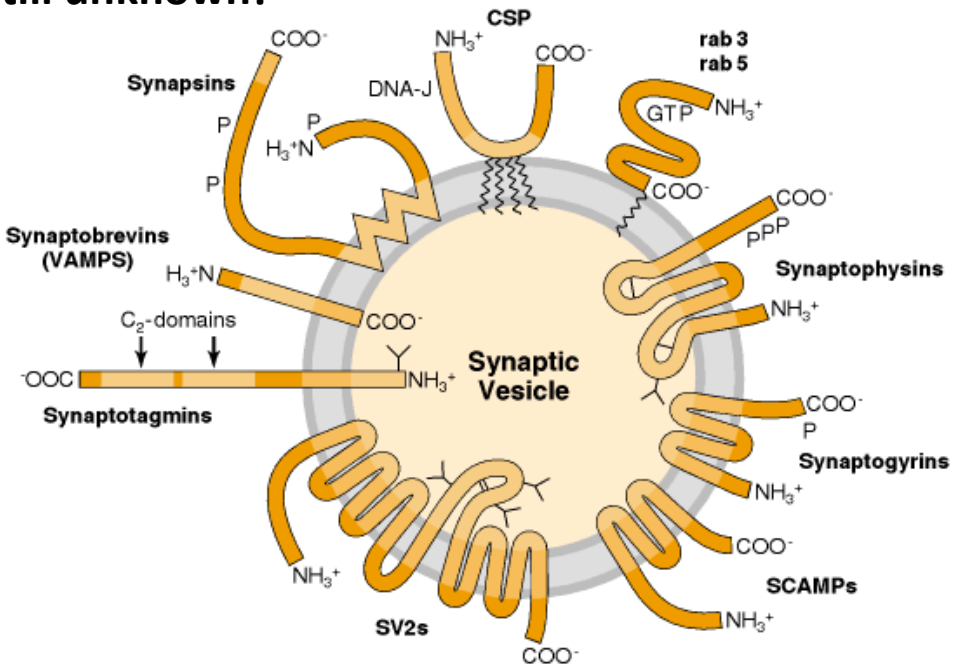
The real power of preclinical imaging:

- **“**In vivo”
- “Non invasive”
- “Longitudinal” = follow up in the same animal over a long period of time
- “Translational” = from the laboratory bench to the patient

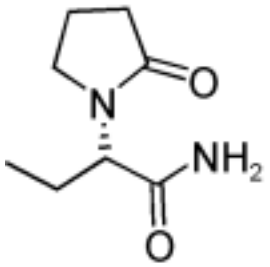
microPET example: « SV2A »

- **Why study SV2A?**
- **Exact physiological role of SV2A is still unknown!**



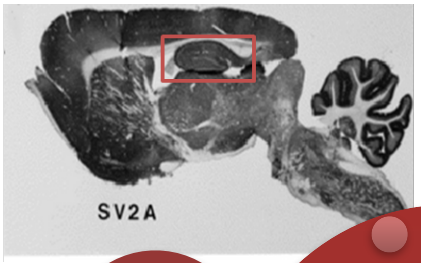


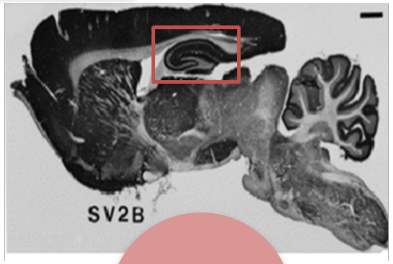
- **We know:**
  - ✓ **SV2A -/- ko mice present seizure and later will die !**
  - ✓ **Levetiracetam (Keppra®) acts on the SV2A protein**

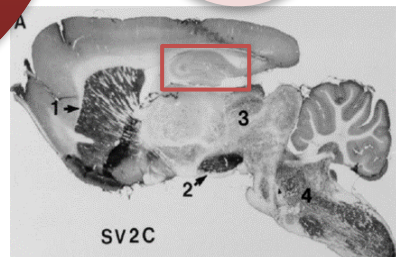


The SV2 proteins

Ubiquitous brain expression

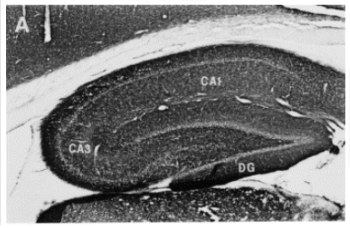






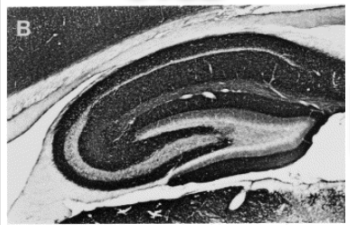
TYPE OF NEURONS

SV2A



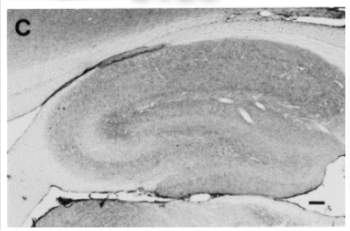
Glutamatergic
GABAergic

SV2B



Glutamatergic

SV2C



GABAergic
Dopaminergic
Cholinergic

Functional imaging of SV2A protein

PNAS | June 29, 2004 | vol. 101 | no. 26 | 9861–9866

The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam

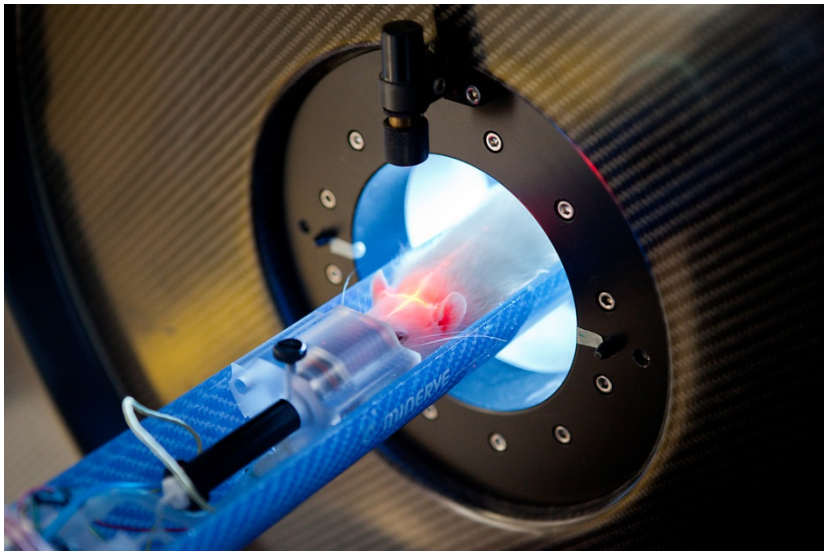
Berkley A. Lynch*†, Nathalie Lambeng‡, Karl Nocka§, Patricia Kensel-Hammes¶, Sandra M. Bajjalieh¶, Alain Matagne‖, and Bruno Fuks‡

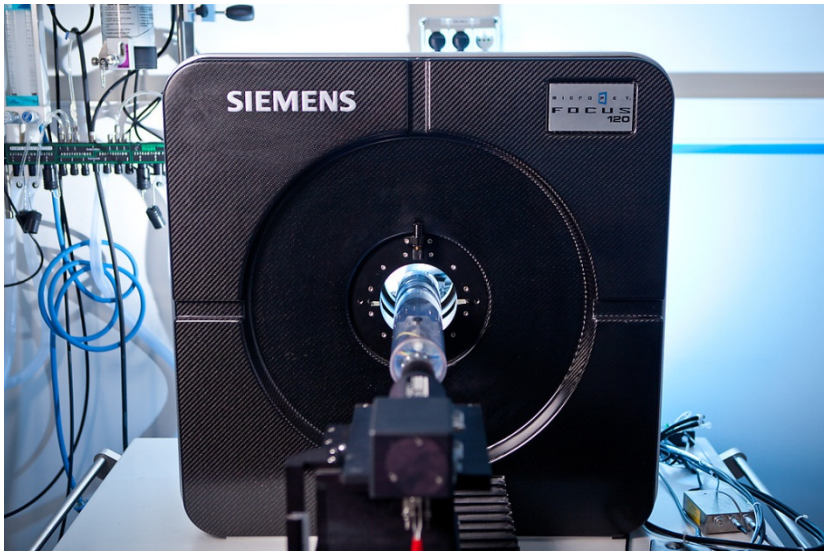
Abnormal neurotransmission in mice lacking synaptic vesicle protein 2A (SV2A)

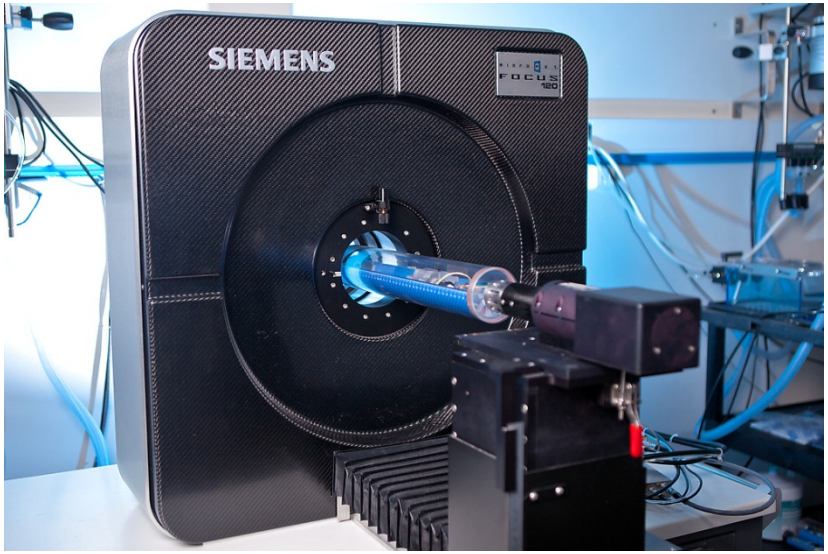
Kelly M. Crowder*†, Jane M. Gunther*†, Theresa A. Jones†‡, Brian D. Hale*, Hai Zhuan Zhang*, Michael R. Peterson§, Richard H. Scheller§, Charles Chavkin*, and Sandra M. Bajjalieh*¶

SV2A KO mice: seizures at P7 & died at P15

MicroPET FOCUS 120 CRC ULg





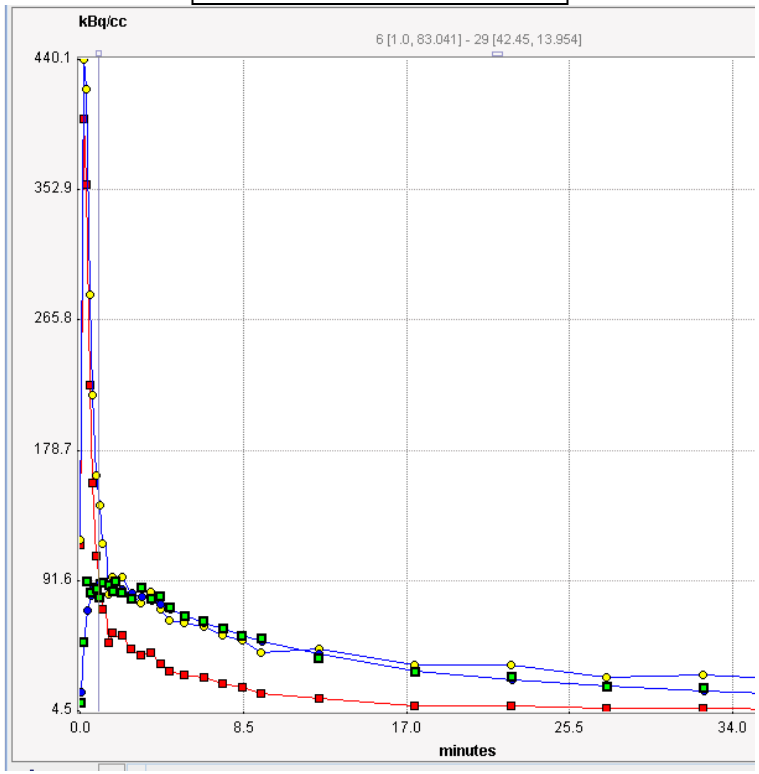


- 4 rings of 96 detectors
- Each detector = 144 crystals
- Field of view =
  - ✓7.6 cm axial
  - ✓10 cm trans axial
- Resolution ~1.5 mm

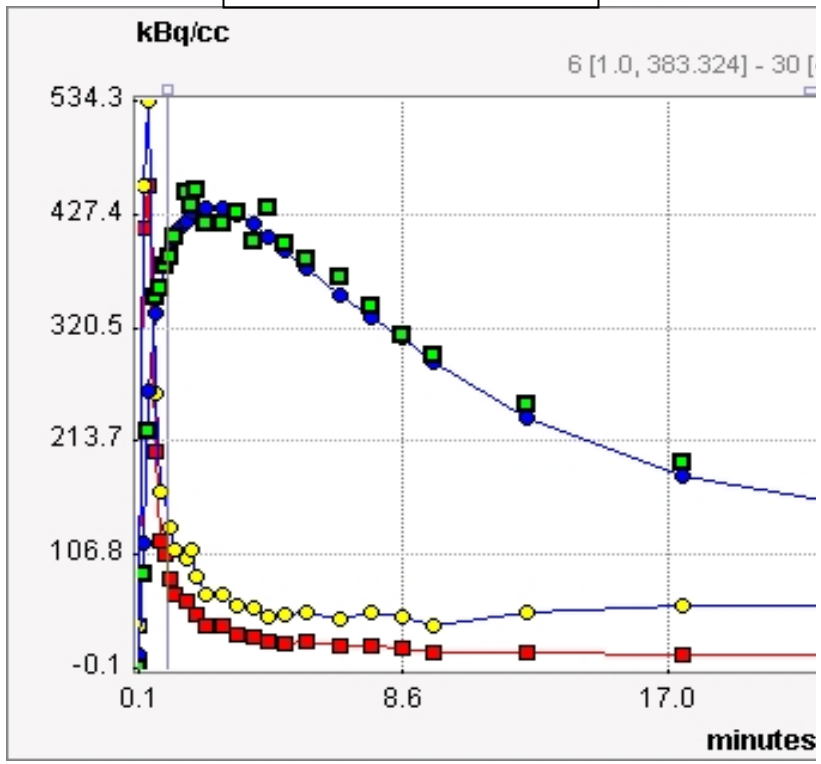
MicroPET « SV2A »:[^{18}F]UCB-H

- **Why: [^{18}F]UCB-H ?**
- **Selected from the UCB's Library**
  - Nanomolare affinity for SV2A
  - Very high specificity for SV2A
  - Very good results in vivo

UCB-D



UCB-H



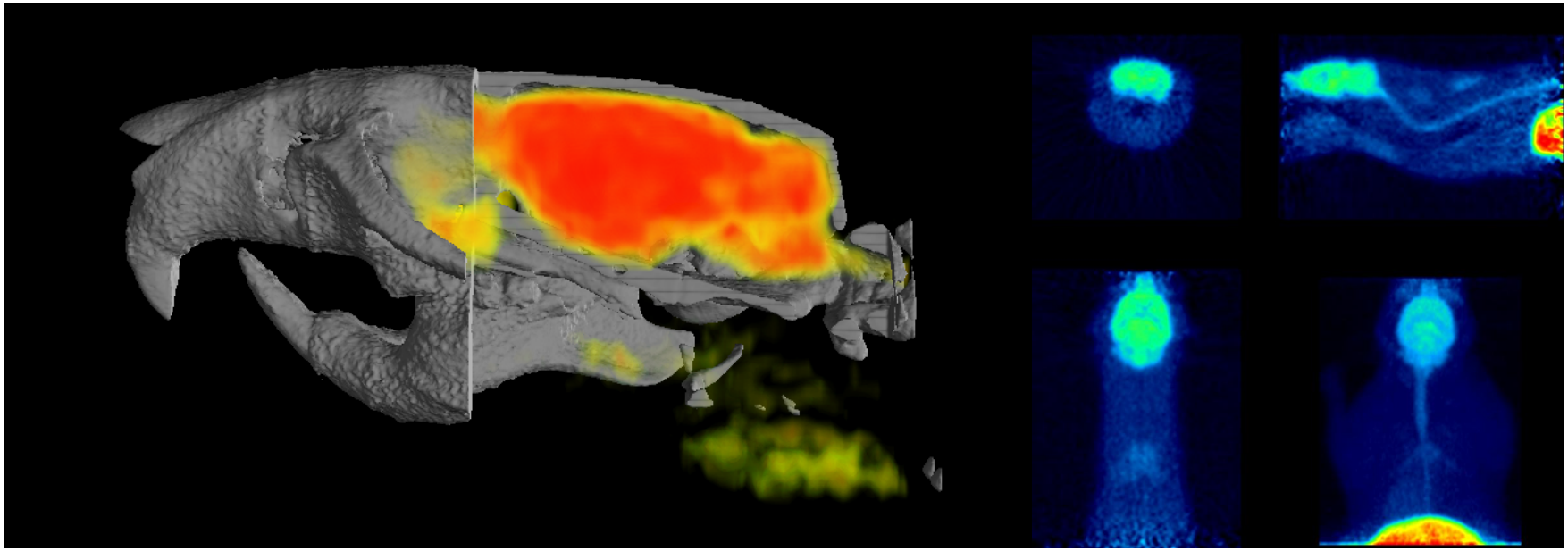
Functional imaging of SV2A protein

JNM The Journal of NUCLEAR MEDICINE

Evaluation of ^{18}F-UCB-H as a Novel PET Tracer for Synaptic Vesicle Protein 2A in the Brain

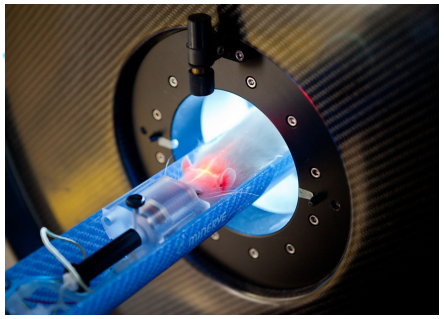
Geoffrey I. Warnock, Joël Aerts, Mohamed Ali Bahri, Florian Bretin, Christian Lemaire, Fabrice Giacomelli, Frederic Mievis, Nathalie Mestdagh, Tim Buchanan, Anne Valade, Joël Mercier, Martyn Wood, Michel Gillard, Alain Seret, André Luxen, Eric Salmon and Alain Plenevaux

J Nucl Med. 2014;55:1336-1341.
Published online: June 16, 2014.
Doi: 10.2967/jnumed.113.136143

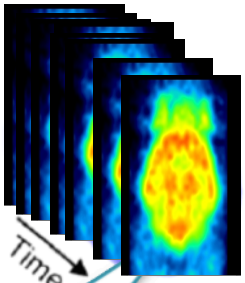


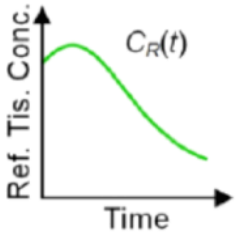
PET kinetic Modeling

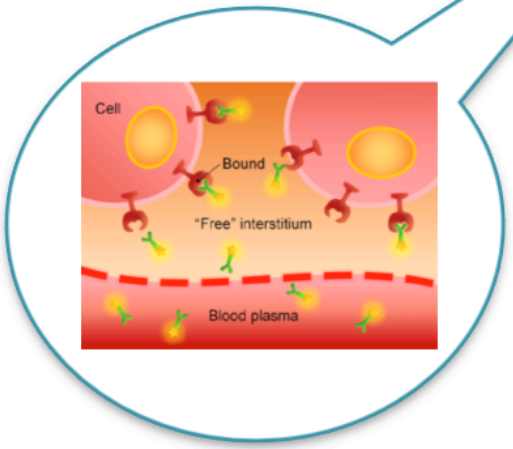
Inject during imaging



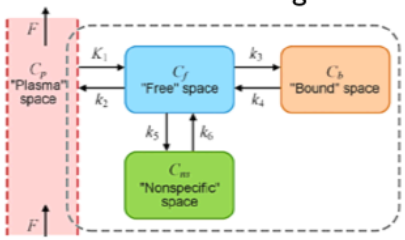
Time series of images







Kinetic modeling



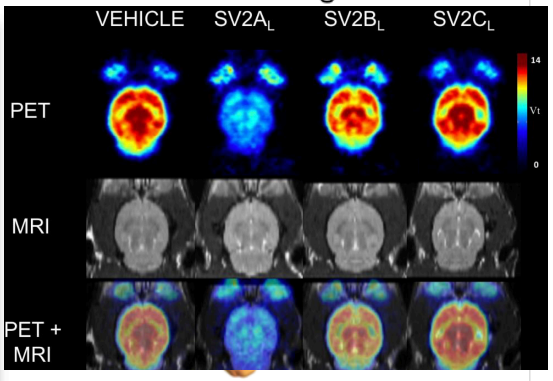
$$ROI_T(t) = \eta_T\left(v_p C_p(t) + C_f(t) + C_{ns}(t) + C_b(t)\right)$$

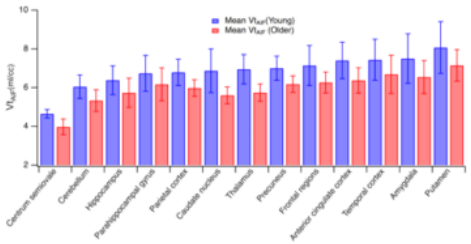
$$\frac{dC_f}{dt} = K_1 C_p - (k_2 + k_3 + k_5) C_f + k_4 C_b + k_6 C_{ns}$$

$$\frac{dC_{ns}}{dt} = k_5 C_f - k_6 C_{ns}$$

$$\frac{dC_b}{dt} = k_3 C_f - k_4 C_b$$

Parametric image

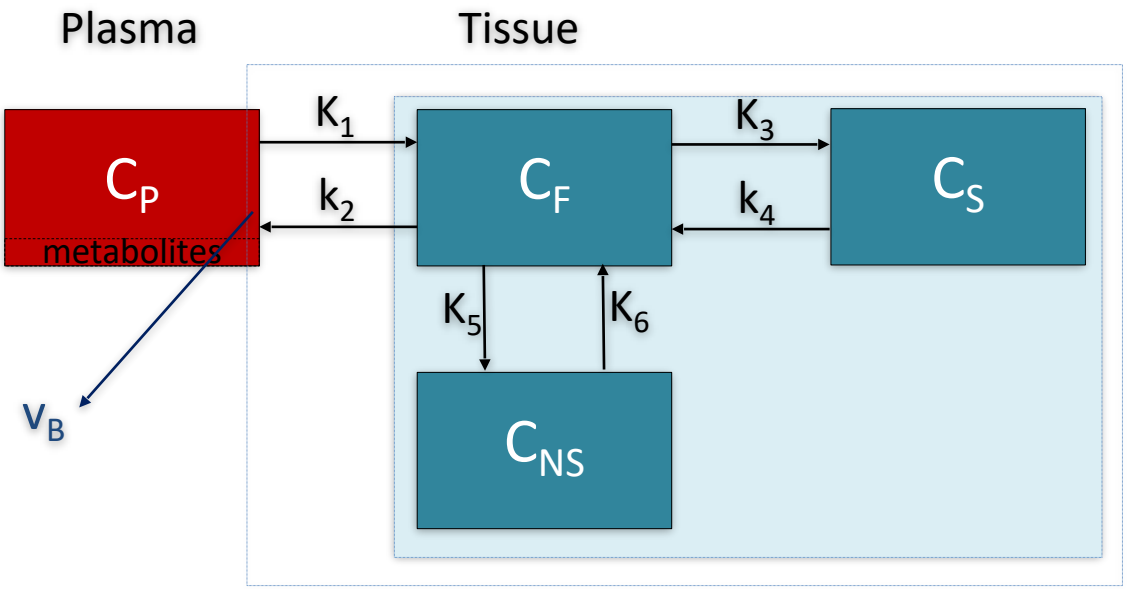


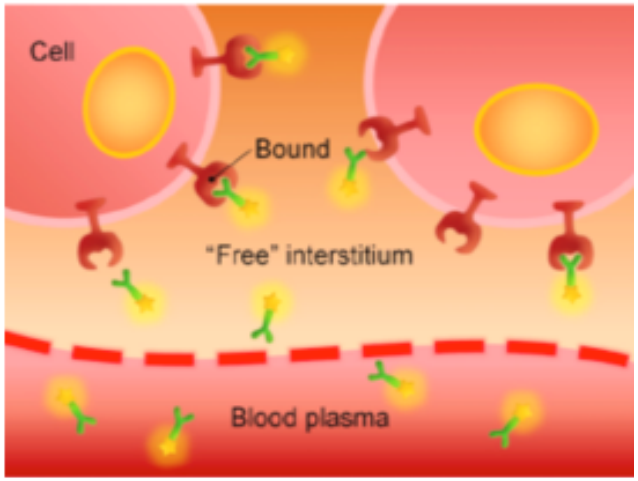


Quantitative data

Bahri et al. Alzheimer's & Dementia: TRCI 2017

Three-Tissue Compartment Model





PET measurement

$$C_{PET}(t) = (1 - V_B) * C_T(t) + V_B * C_{WB}(t)$$

$$C_T(t) = C_{ND}(t) + C_S(t)$$

Differential equations

$$dC_{ND}(t)/dt = K_1C_p(t) - k_2C_{ND}(t) - k_3C_{ND}(t) + k_4C_S(t)$$

$$dC_S(t)/dt = k_3C_{ND}(t) - k_4C_S(t)$$

Volume of distribution

Equilibrium – partition coefficient

$dC_T(t)/dt = 0$; $dC_A(t)/dt = 0$

$V_T = C_T/C_A$

Non-equilibrium

$V_T = \int C_T / \int C_A$

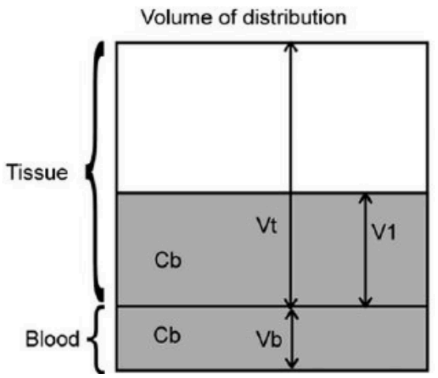
Single tissue compartment model

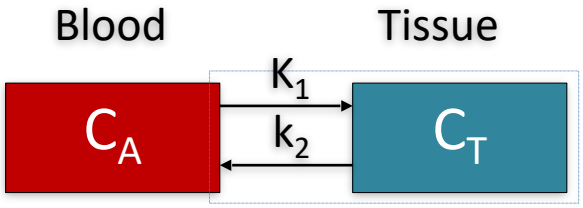
$dC_T(t)/dt = K_1C_A(t) - k_2C_T(t)$

At equilibrium:

$K_1C_A(t) - k_2C_T(t) = 0 \rightarrow V_T = C_T/C_A = K_1/k_2$

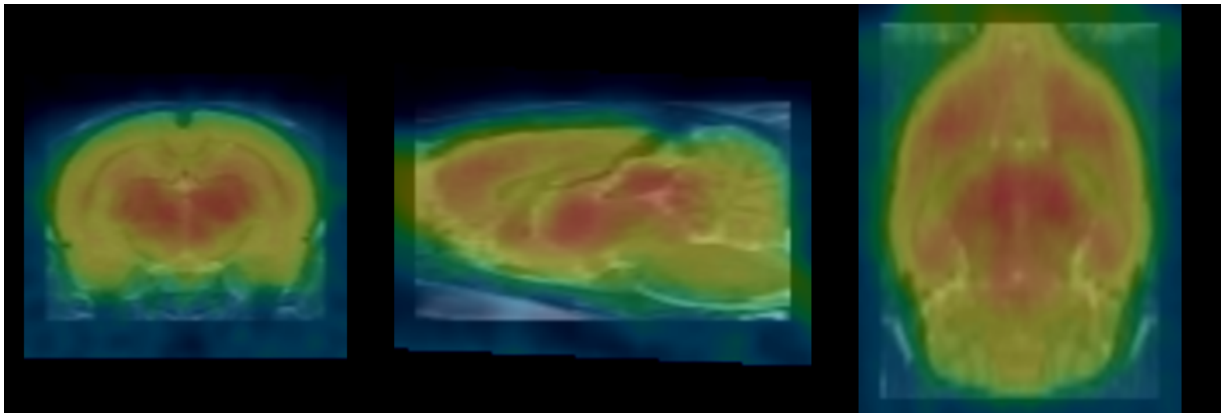
The volume of distribution (Vd) is the volume of tissue (V1) that should contain the same concentration as in blood (Cb) relative to total tissue volume (Vt):

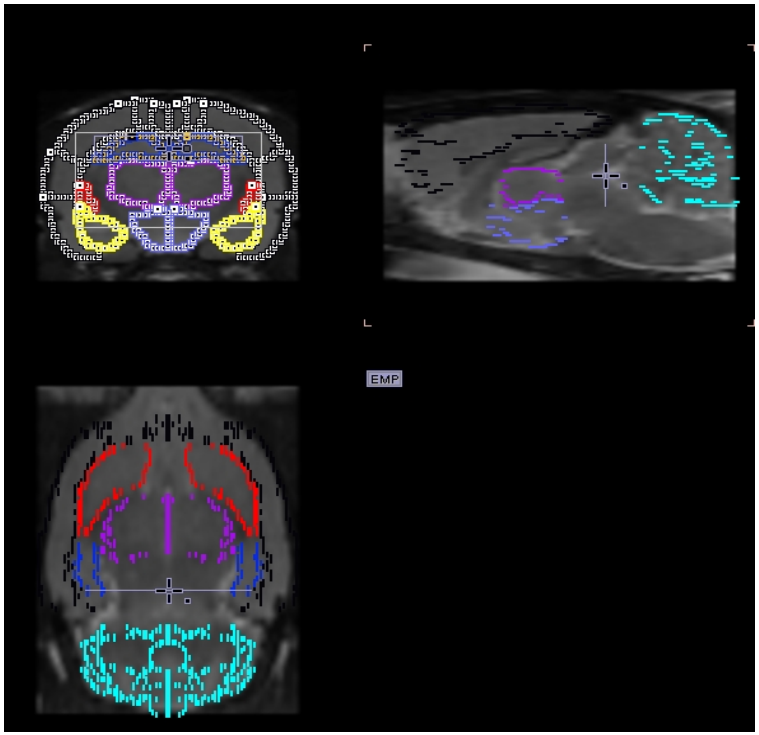




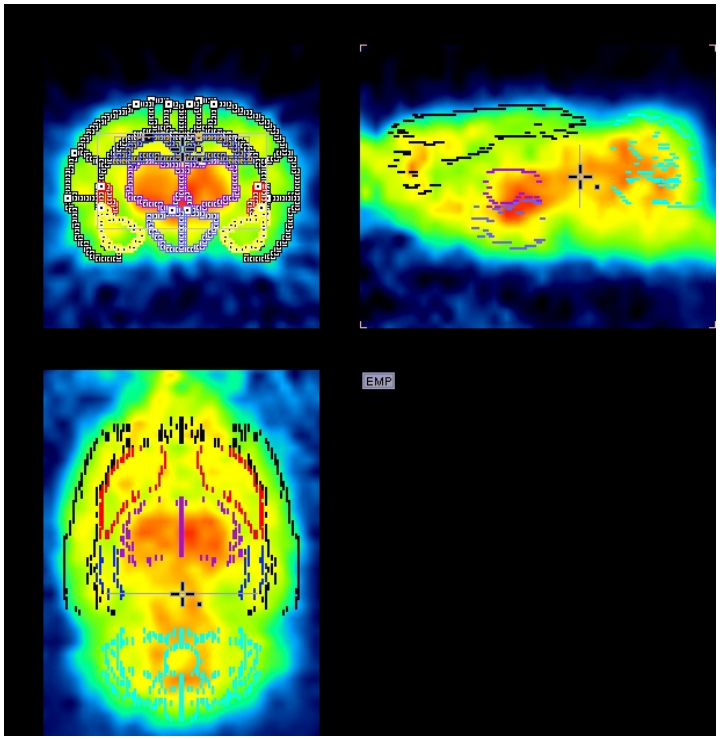
$dC_T/dt = K_1 * C_A - k_2 * C_T$

[^{18}F]UCB-H: Fusion and ROIs

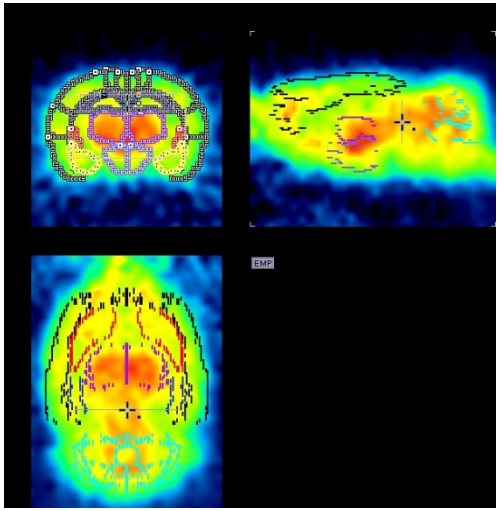


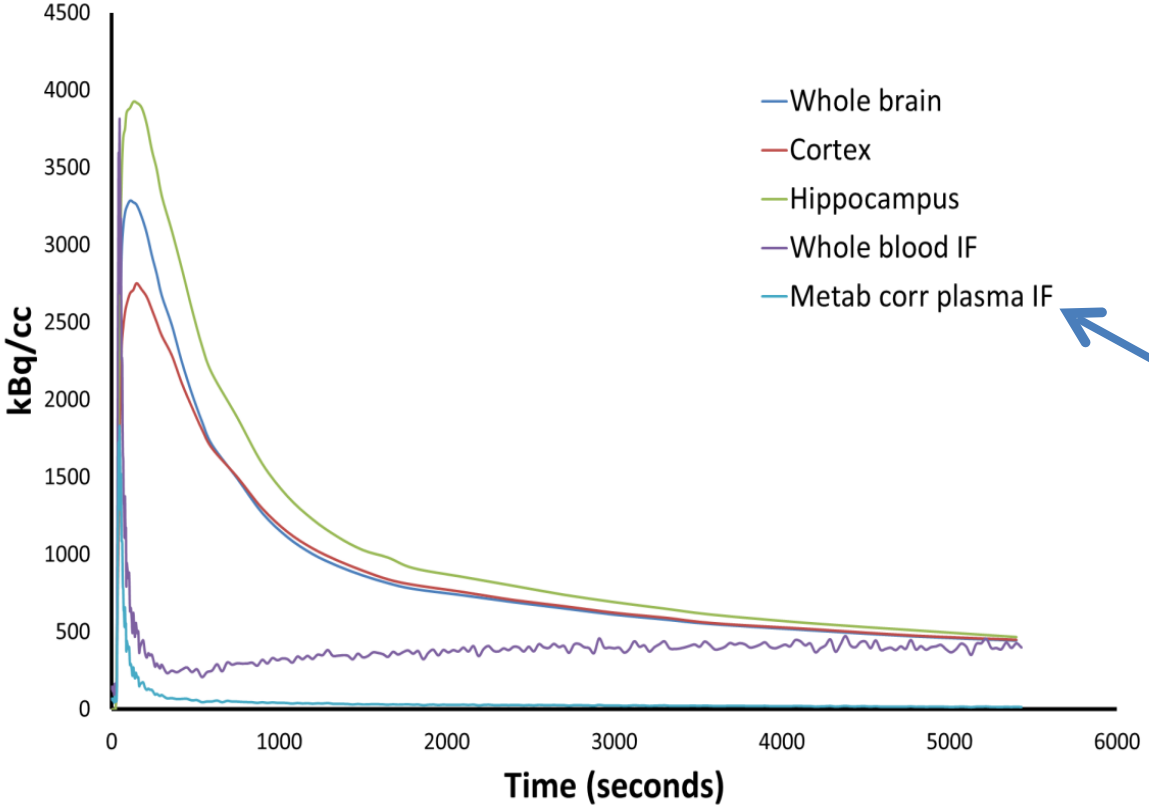


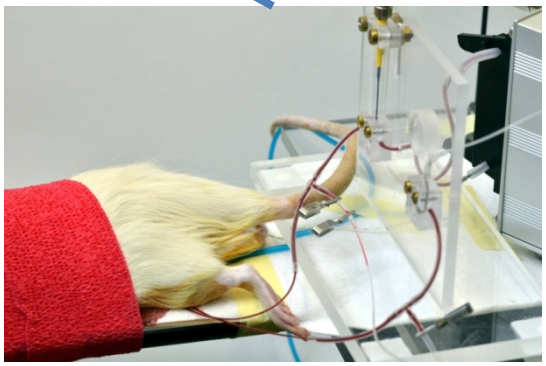
	Cortex
	Thalamus
	Striatum
	Amygdala
	Hypothalamus
	Cerebellum
	Hippocamp



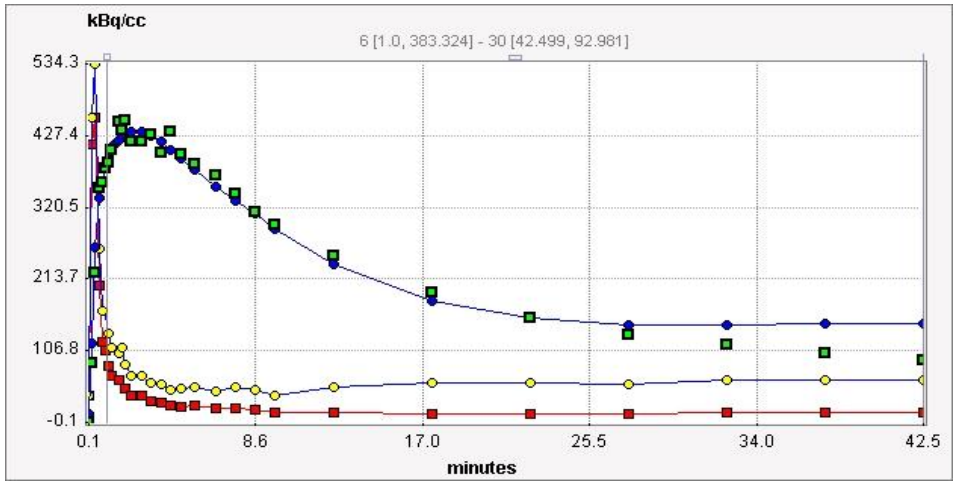
[^{18}F]UCB-H: TACs







[^{18}F]UCH-H: Math modeling 2 TC



PMOD Technologies

REGION	MODEL	vB	K1	k2	k3	k4	Vs	Vt	K1/k2	k3/k4
			ml/ccm/min	1/min	1/min	1/min	ml/ccm	ml/ccm	ml/ccm	
Cortex	2-TC	0.05	1.57	0.16	0.03	2.64	0.1	9.68	9.58	0.01
Thalamus	2-TC	0.05	3.05	1.59	8	1.45	10.56	12.47	1.91	5.52
Striatum	2-TC	0.05	2.02	0.19	0.69	6.99	1.03	11.45	10.42	0.1
Amygdala	2-TC	0.05	1.88	0.23	0.09	0.73	0.97	9.25	8.28	0.12
Hypothalamus	2-TC	0.05	3.21	3.19	8	0.82	9.81	10.82	1	9.76
Cerebellum	2-TC	0.05	2.47	0.32	0.25	1.03	1.86	9.55	7.68	0.24
Hippocamp	2-TC	0.05	3.18	5.37	8	0.45	10.46	11.05	0.59	17.67

- **1-TC: No fit**
- **2-TC: fit is not perfect & important variability**

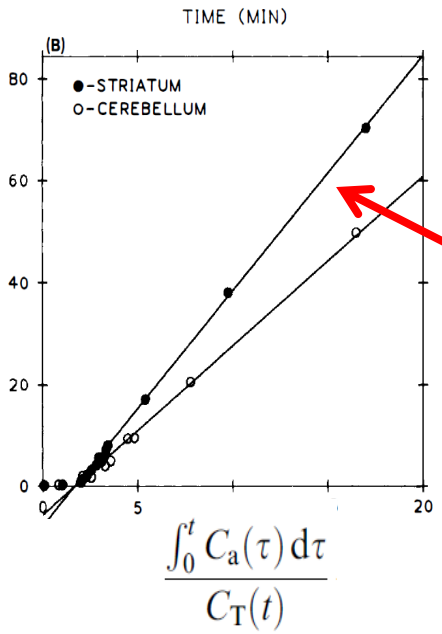
- **Logan???**

[^{18}F]UCH-H: Math modeling Logan

$$\frac{\int_0^t C_T(\tau)\,d\tau}{C_T(t)} = V_T \frac{\int_0^t C_a(\tau)\,d\tau}{C_T(t)} + b,$$

$$b = \begin{cases} \frac{-1}{k_2}, \\ \frac{-1}{k_2 k_4} \frac{-(k_3+k_4)C_T(t) - k_2 C_3(t)}{C_T(t)}. \end{cases}$$

JCBF (2007) 27:1533 & (1990) 10:740



Slope = V_T

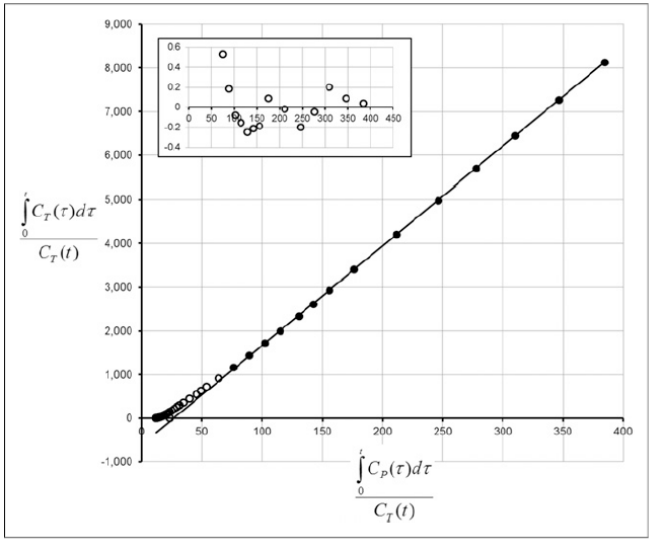


FIGURE 5. Example of Logan graphic analysis of ^{18}F-UCB-H binding in hippocampal region. Main plot: ○, data points excluded from fit; ●, data points included in fit; solid line represents fit. Subplot: fit residuals.

Warnock et al. J Nucl Med (2014) 55:1336

[^{18}F]UCB-H: Volume of distribution using “Logan” model

Brain Region	Vt Logan	Reproducibility delta %
Nucleus accumbens	10.9 ± 0.5	10.7 ± 9.5
Amygdala	9.0 ± 0.3	10.8 ± 7.0
Cerebellum	9.0 ± 0.2	9.7 ± 7.5
Cerebral cortex	9.4 ± 0.4	10.1 ± 6.8
Striatum	11.3 ± 0.5	11.1 ± 7.7
Hippocampus	10.7 ± 0.5	11.3 ± 7.1
Hypothalamus	9.9 ± 0.2	10.3 ± 6.9
Medulla	8.5 ± 0.4	9.4 ± 6.3
Olfactory bulbs	9.0 ± 0.2	10.1 ± 5.9
Pons	8.2 ± 0.3	11.4 ± 4.0
Septum	10.5 ± 0.4	14.9 ± 8.4
Thalamus	12.1 ± 0.6	10.0 ± 8.4
Whole brain average	9.8 ± 0.5	10.4 ± 6.6

Good reproducibility
For [^{18}F]UCB-H with « Logan » in rats

Functional imaging of SV2A protein

The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam

Berkley A. Lynch*†, Nathalie Lambeng‡, Karl Nocka§, Patricia Kensel-Hammes¶, Sandra M. Bajjalieh¶, Alain Matagne‖, and Bruno Fuks‡

PNAS | June 29, 2004 | vol. 101 | no. 26 | 9861–9866

[^{18}F]UCB-H: Validation “displacement”

- **Brivaracetam = = specific SV2A ligand to be used as challenger**

- **The displacement study gives important information on the <u>in vivo</u> specificity of the radiopharmaceutical for its target and on the reversibility of the binding**

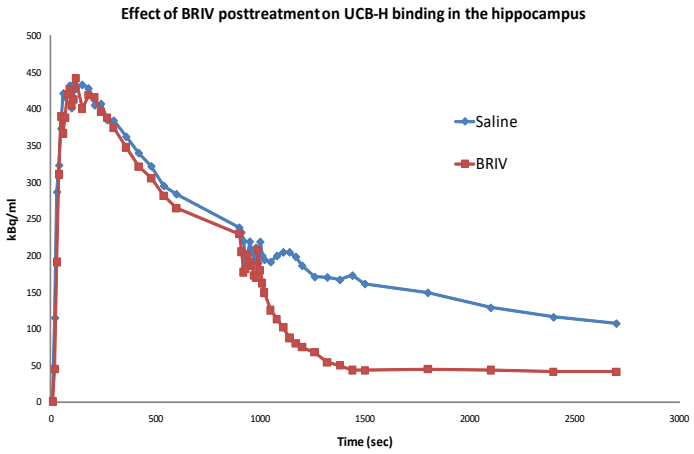
  - D1 « test »
    - ✓ T0: administration [^{18}F]UCB-H + microPET
    - ✓ T0 + 15’: administration « Saline »

  - D1 + 7 «displacement »
    - ✓ T0: administration [^{18}F]UCB-H + microPET
    - ✓ T0 + 15’: administration « BRIV » 10 mg/kg

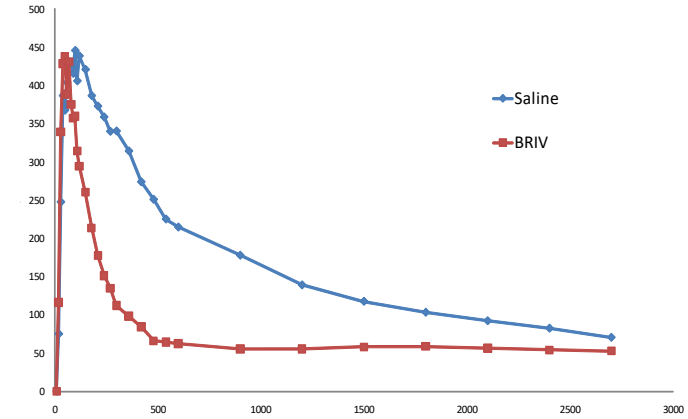
Functional imaging of SV2A protein

Pharmacological studies: tool for screening news drugs

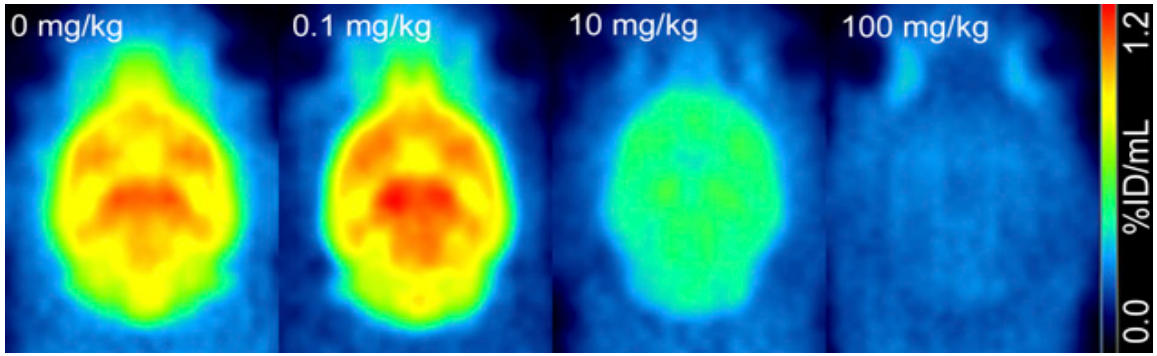
Displacement
(post-injection)



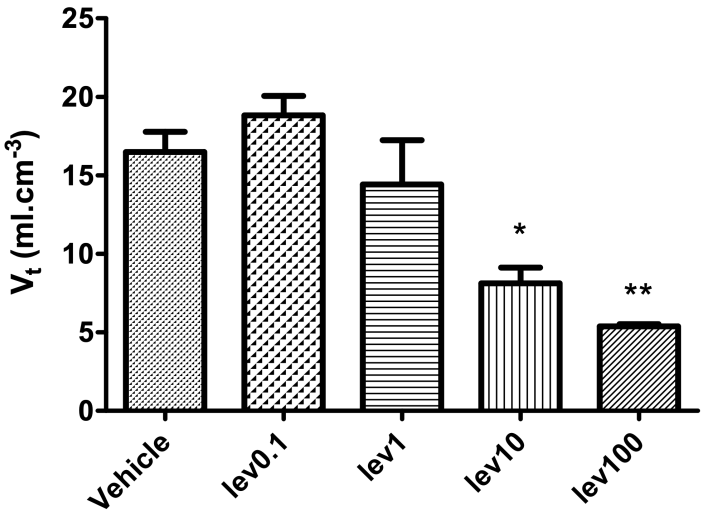
Blocking
(pre-injection)

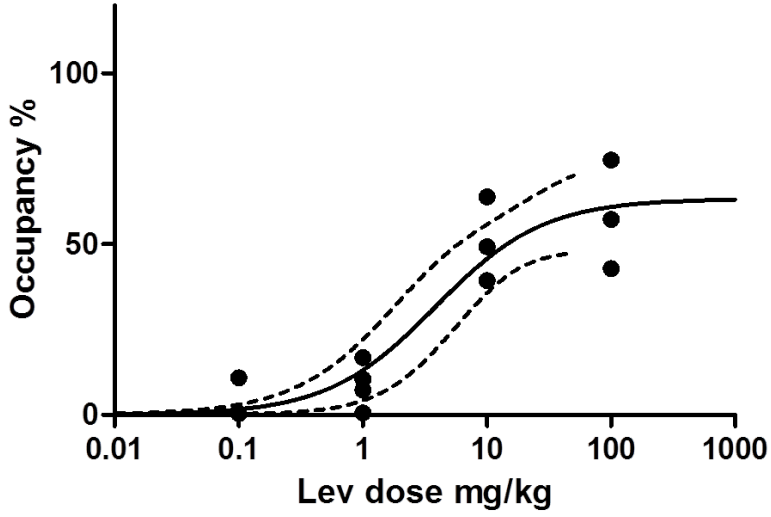


Functional imaging of SV2A protein



Occupancy of SV2a after Levetiracetam treatment



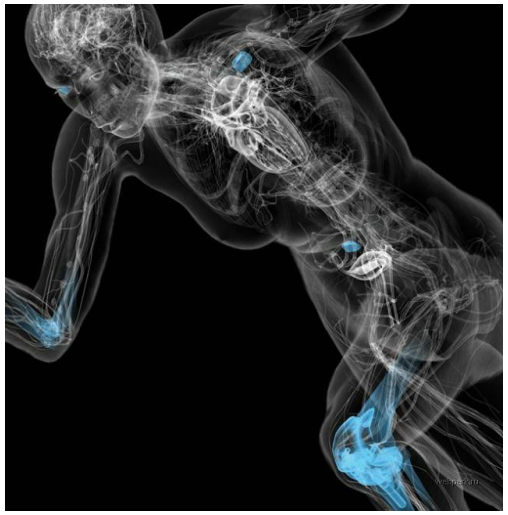


50% occupancy at 100 mg/kg…

Wranock et al. JNuclMed 2014:55-1336

Brain volumetric changes induced by voluntary physical exercise

It is known that physical exercise will increase or maintain brain volume in human



Brain volumetric changes induced by voluntary physical exercise

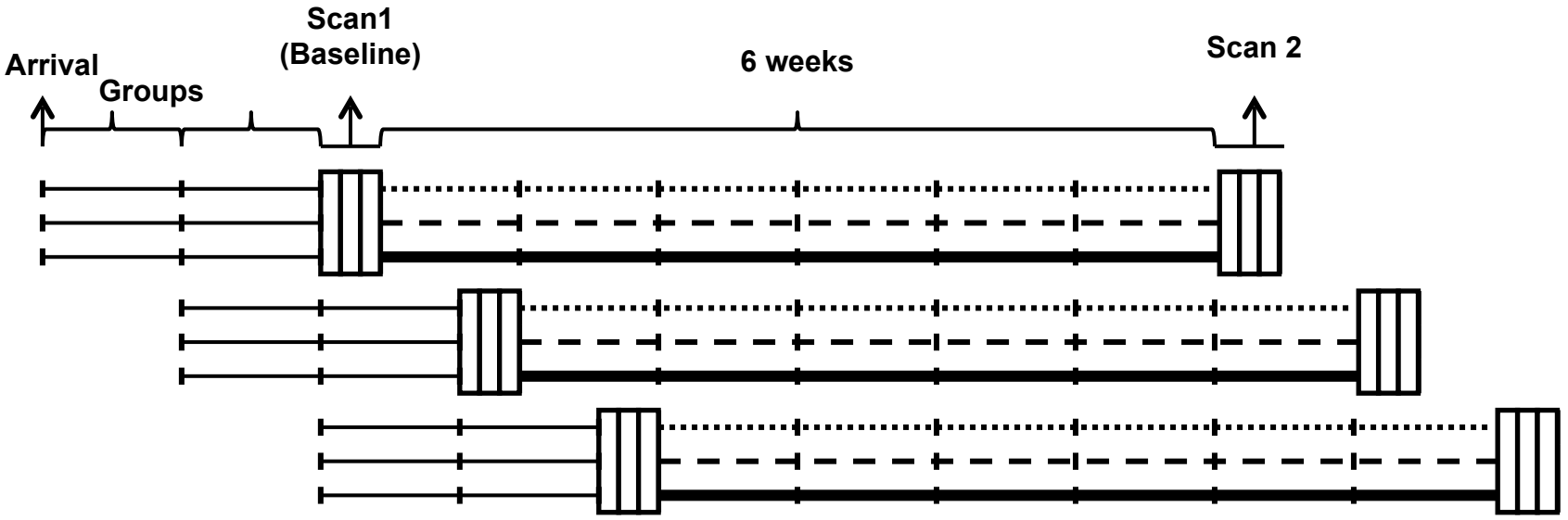
3 groups

Free wheel
n=24

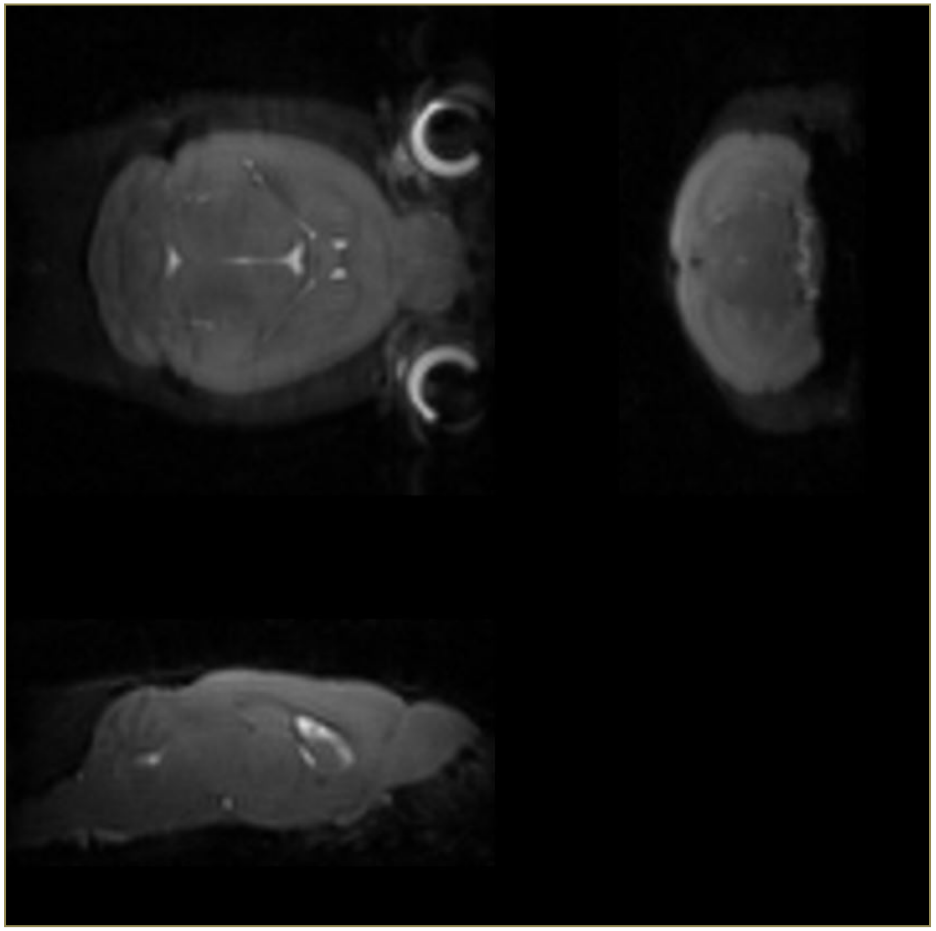
No wheel
n=18

Locked wheel
n=18

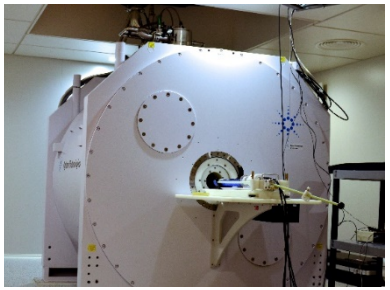
Brain volumetric changes induced by voluntary physical exercise



Brain volumetric changes induced by voluntary physical exercise



T2 Sequence



TR 3000ms

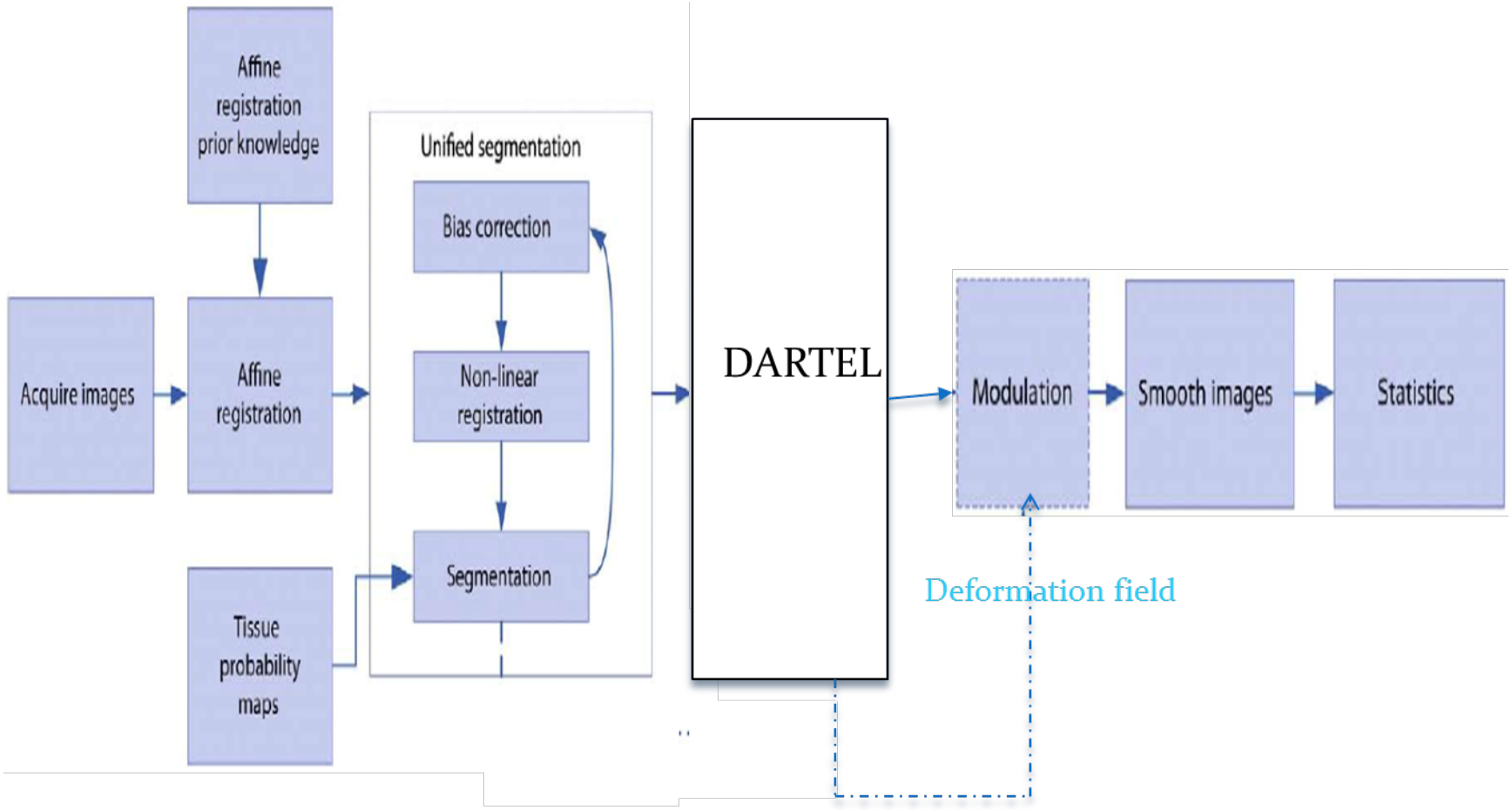
TE 42.8ms

Matric 96 x 96 x 48

FOV 20 x 20 x 10 mm

Voxel size 0.07 x 0.07 x 0.07 mm

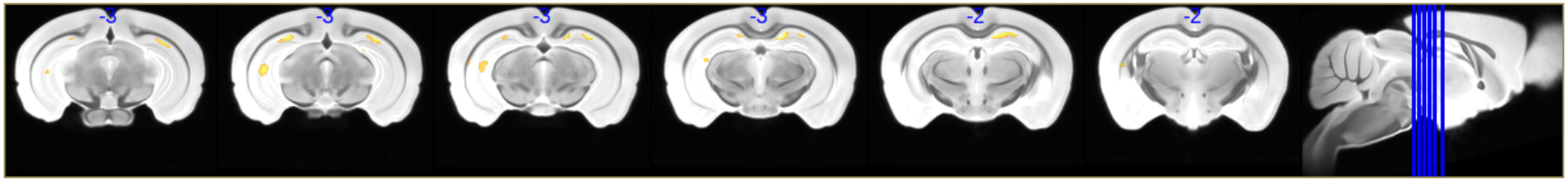
Brain volumetric changes induced by voluntary physical exercise



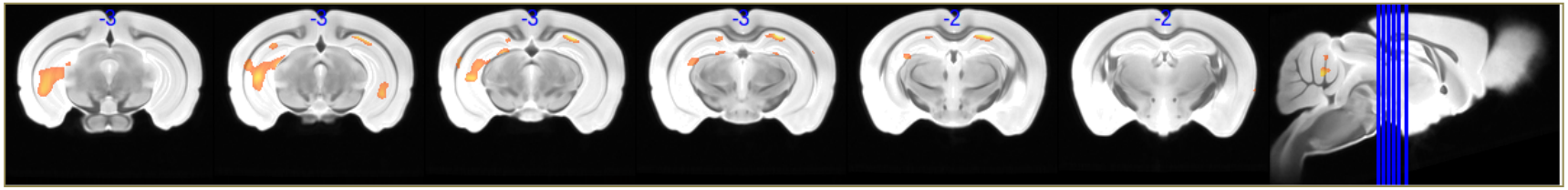
Brain volumetric changes induced by voluntary physical exercise

Parametric images

Free wheel vs No wheel



Free wheel vs Blocked wheel



- Effect of exercise on GM
- Effect of exercise on hippocampus

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GIGA

Thank you for your attention