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Imaging neuroinflammation using PET

PET data analysis - example of human studies with [^{11}C]-(*R*)-PK11195

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Part I: Introduction

The Peripheral Benzodiazepine Receptor (PBR)

- The PBR is a nuclear encoded mitochondrial protein.
- The PBR is abundant in peripheral organs (particularly adrenal glands and kidney) and haematogenous cells.
- The function of the PBR still needs full elucidation but the receptor plays an important role in steroid synthesis and in the regulation of immunological responses in mononuclear phagocytes.

The PBR in diseases of the CNS

- High PBR has been observed in infiltrating blood-borne cells and activated microglia.
- Significant microglial activation occurs after mild to severe neuronal damage resulting from traumatic, inflammatory, degenerative and neoplastic disease.
- Microglia are activated in the surroundings of focal lesions but also in the distant, anterograde and retrograde projection areas of the lesioned neural pathway.

[^{11}C]-(*R*)- PK11195 as an imaging marker

- PK11195 is a selective ligand for the peripheral benzodiazepine receptor.
- PET imaging using the molecular marker [^{11}C]-(*R*)-PK11195 now provides an indicator of active disease in the brain.
- Wide applicability – in brain research used for multiple sclerosis, amyotrophic lateral sclerosis, dementia, Parkinson's disease, corticobasal degeneration, Huntington's disease, epilepsy, schizophrenia, gliomas etc.

Circulation 73, No. 3, 476–483, 1986.

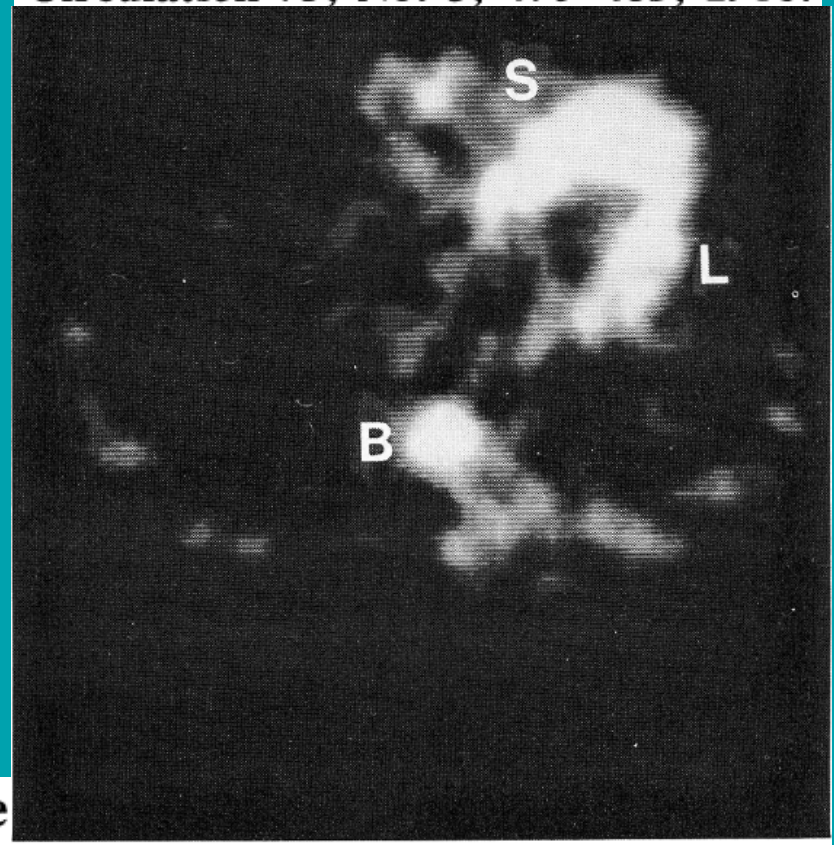

FIGURE 5. PET image of a human heart after intravenous injection of ^{11}C–PK 11195. The PET scan was obtained 15 min after injection of ^{11}C–PK 11195 (12.3 mCi, specific activity 484 mCi/μmol). At this time the septum (S) and of the lateral wall of the left ventricle (L) were clearly visualized. Radioactivity in the lung was low. B = bone marrow.

Peripheral-type benzodiazepine receptors in the living heart characterized by positron emission tomography

PIERRE CHARBONNEAU, M.D., ANDRÉ SYROTA, M.D., PH.D., CHRISTIAN CROUZEL, PH.D., JEAN-MARIE VALOIS, B.S., CHRISTIAN PRENANT, B.S., AND MONIQUE CROUZEL

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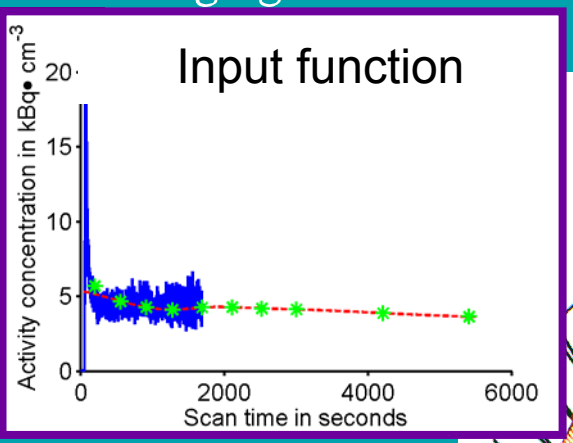
Part II: PET scannnig



Peripheral detector systems
(bioanalysis)

tubing

Radial artery

Heart

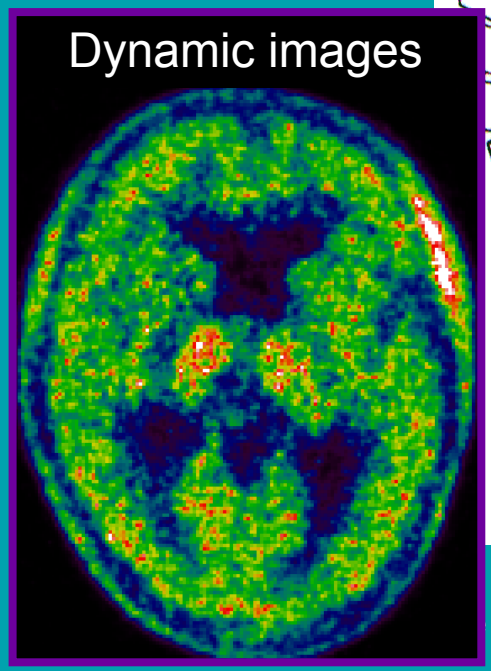
Lungs

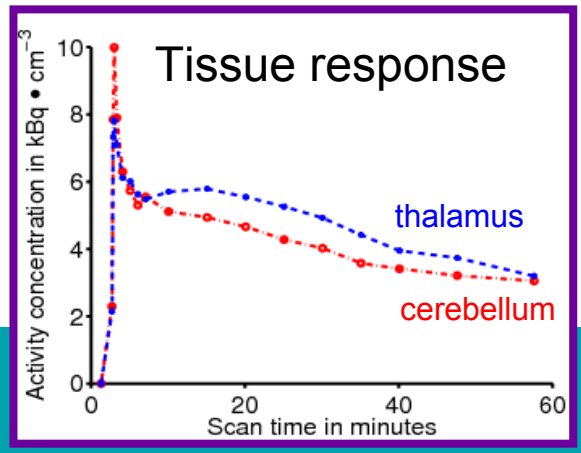
Jugular vein

Carotid artery

Brain

PET scanner





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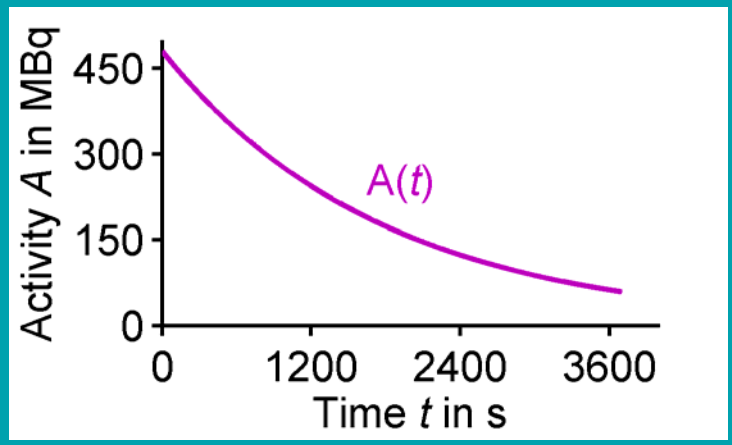
Sensitivity of PET

The radioactive decay is described with an exponential function:

$$A(t) = A_0 \cdot e^{-\lambda \cdot t}$$

- A_0 … initial activity at the time of injection,
- t … time,
- λ … time constant of the physical decay of the positron emitter.



If the half life $T_{1/2}$ of the positron emitter is known, then the decay constant can by calculated

$$\lambda = \frac{\ln 2}{T_{1/2}}$$

Symbol	Half life $T_{1/2}$	Decay constant λ
^{18}F	109.7 min	0.0001053 s^{-1}
^{11}C	20.4 min	0.0005663 s^{-1}
^{15}O	122.55 s	0.005656 s^{-1}

The total number of radioactive nuclei N is equal to the integral of the activity from time zero to infinity:

$$N = \int_0^\infty A(t)\,dt = A_0 \cdot \int_0^\infty e^{-\lambda \cdot t}\,dt = \frac{A_0}{\lambda}$$

With the Avogadro constant $N_A = 6.022 \cdot 10^{23}$ mol^{-1}, the number n of radiolabelled molecules is:

$$n = \frac{N}{N_A} = \frac{A_0}{\lambda \cdot N_A}$$

480 MBq mean injected activity of [^{11}C]-(*R*)-PK11195:

$$n = \frac{480 \cdot 10^6\ s^{-1}}{0.0005663\ s^{-1} \cdot 6.022 \cdot 10^{23}\ mol^{-1}} = 1.4075 \cdot 10^{-12}\ mol \approx 1.4\ pmol$$

$m = n \cdot RMM = 1.4075 \cdot 10^{-12}$ mol $\cdot$ 352 g·mol^{-1} $= 4.95 \cdot 10^{-10}$ g ≈ 0.5 ng

What is specific activity?

The specific activity *SpAct* is defined as the ratio of radioactivity over the total amount of ligand injected:

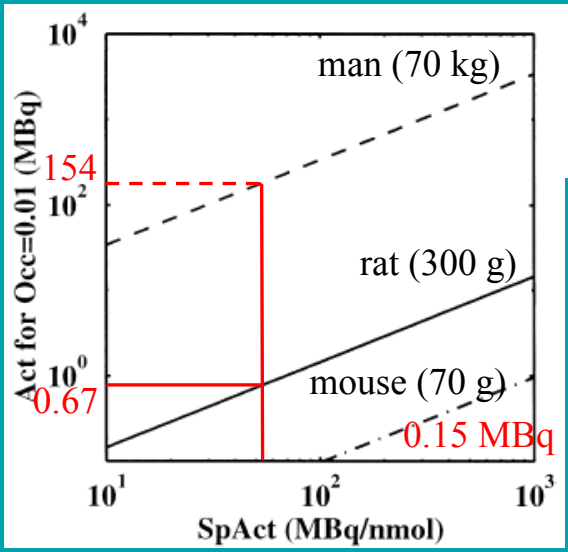
$$SpAct = \frac{A_0}{n_{total}} = \frac{A_0}{m_{total}} \cdot RMM$$

with n_{total} as the total number of molecules of the receptor ligand (unlabelled and labelled) injected and with m_{total} as the total mass of the receptor ligand (unlabelled and labelled) injected.

Mean injected mass of PK11195: 3.7 µg

$$SpAct = \frac{480\ \text{MBq}}{3.7\ \mu\text{g}} \cdot 352\ \text{g} \cdot \text{mol}^{-1} = 45665\ \text{MBq} \cdot \mu\text{mol}^{-1} \approx 45.7\ \text{GBq} \cdot \mu\text{mol}^{-1}$$

How much specific activity is needed?

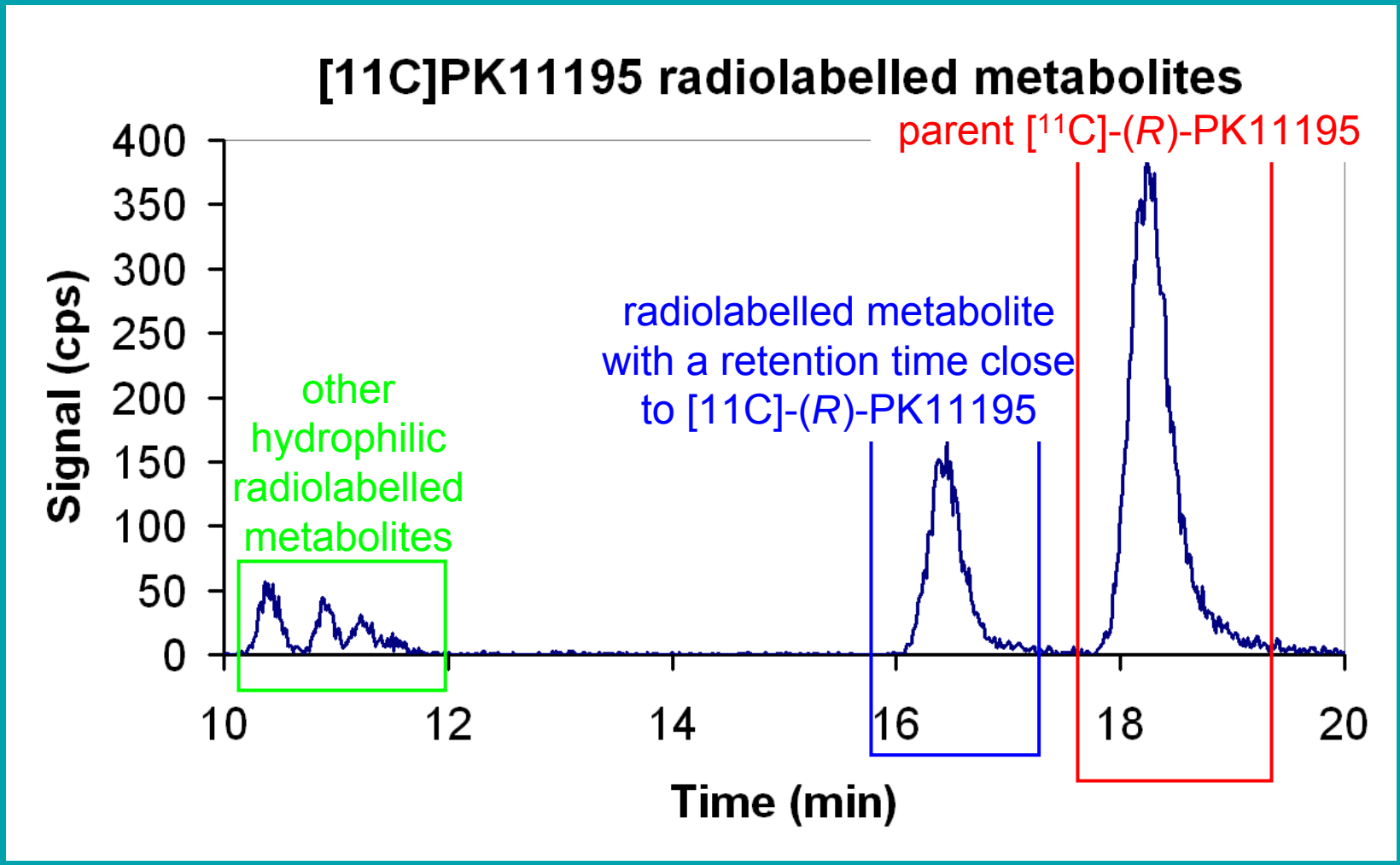


Act as a function of *SpAct* for the constraint *Occ* = 0.01, for **WAY-100635**. (Figure from Hume SP, Gunn RN, Jones T, *Eur J Nucl Med* **25** (1998), 173-6)

High specific activity essential for:

- high affinity ligands (e.g. [^{11}C]WAY-100635),
- small animal studies.

Analysis of radiolabelled metabolites



Example radiochromatogram obtained from an essay with hepathic microsomes.

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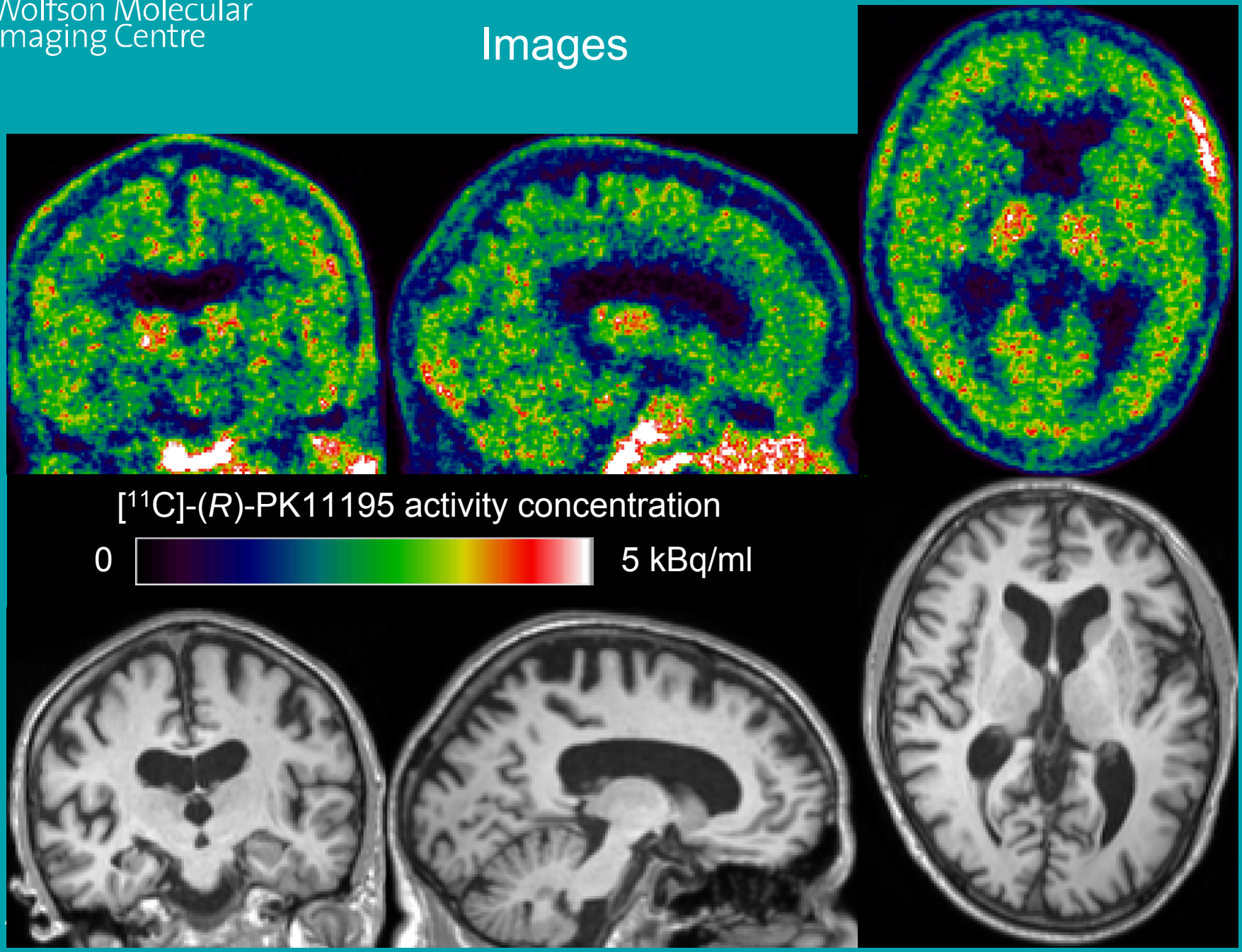
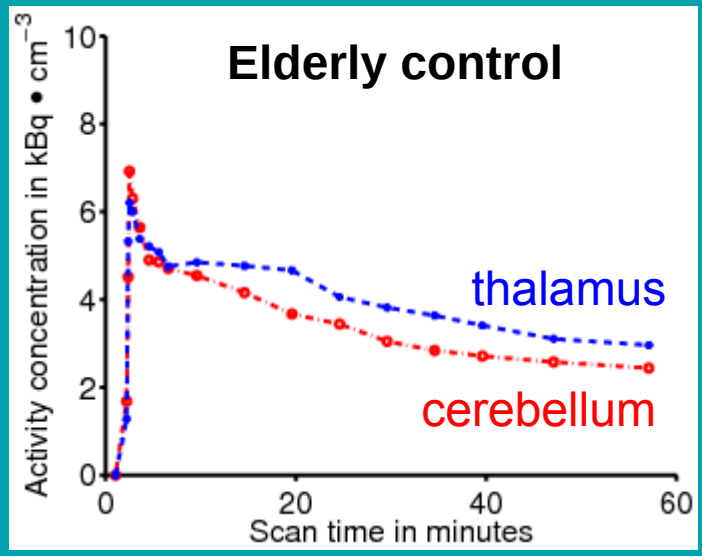
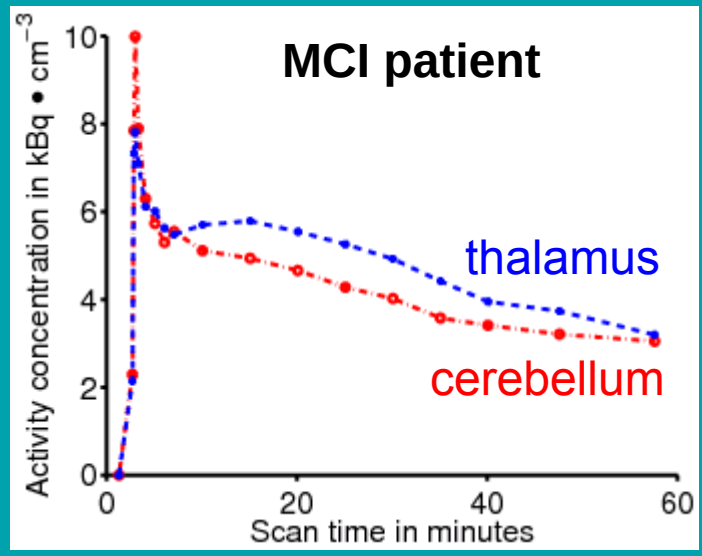
Images



Tissue time-activity curves

Examples of regional tissue time-activity curves

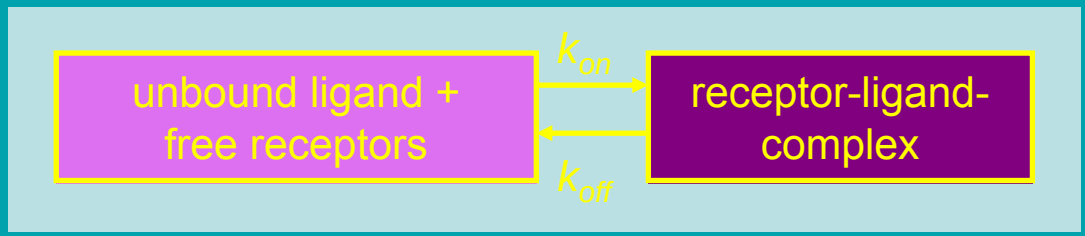




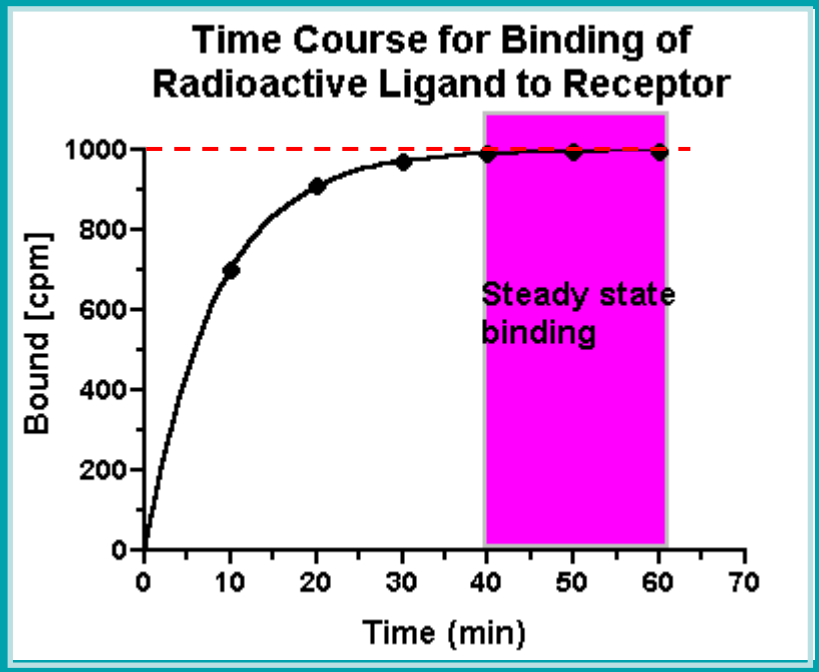
Kinetic analysis of the dynamic data

Part III: Quantification of radioligand binding

Reversible binding of a ligand to a receptor (in vitro binding assay):



$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [RL]$$



law of mass action:

$$\frac{d\,[RL]}{d\,t} = k_{on} \cdot [L] \cdot [R] - k_{off} \cdot [RL]$$

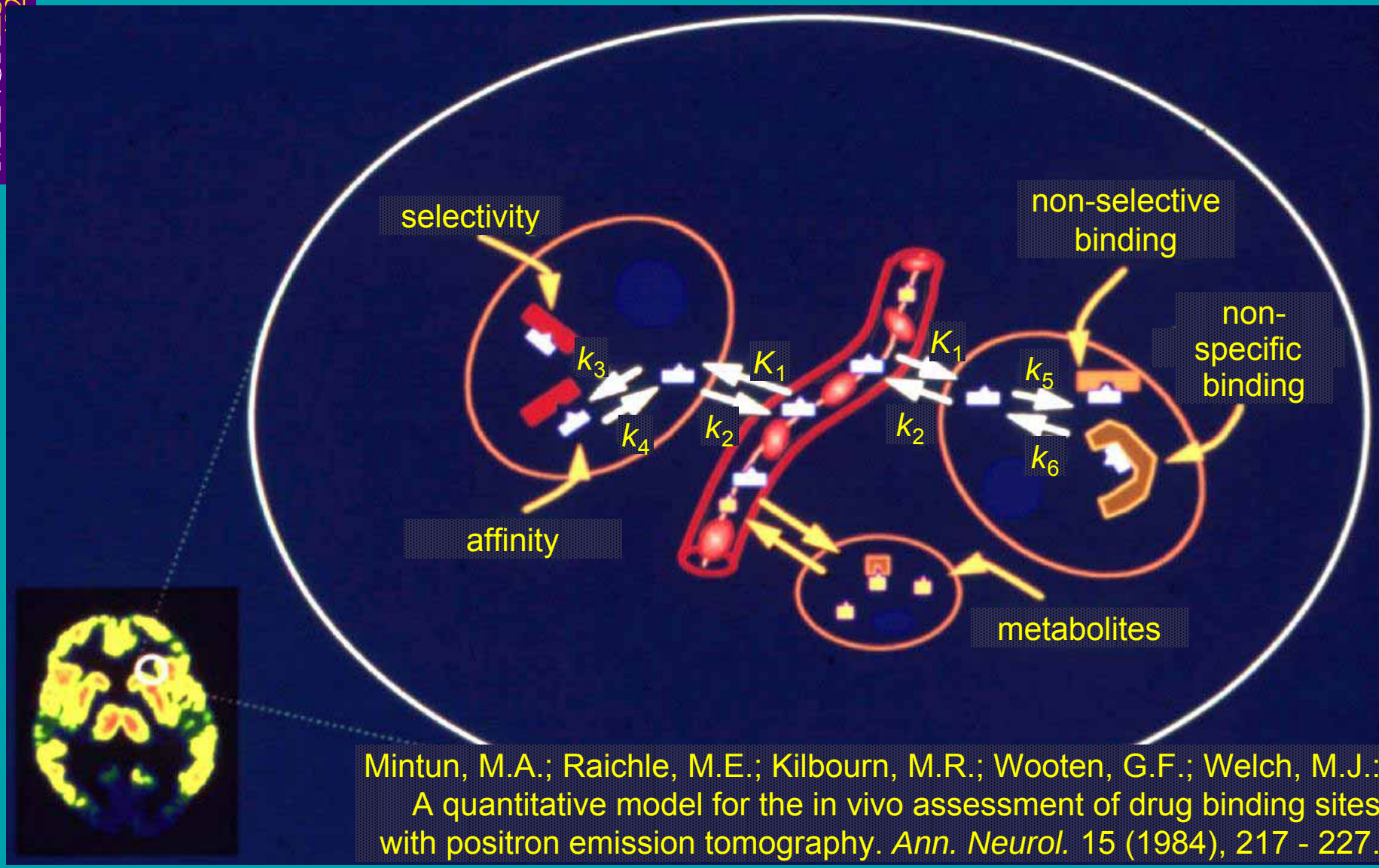
dissociation constant: $K_D = \frac{k_{off}}{k_{on}}$

maximum binding capacity (total number of receptors): $B_{max} = [R] + [RL]$

$$\frac{d\,[RL]}{d\,t} = k_{on} \cdot [L] \cdot (B_{max} - [RL]) - k_{off} \cdot [RL]$$

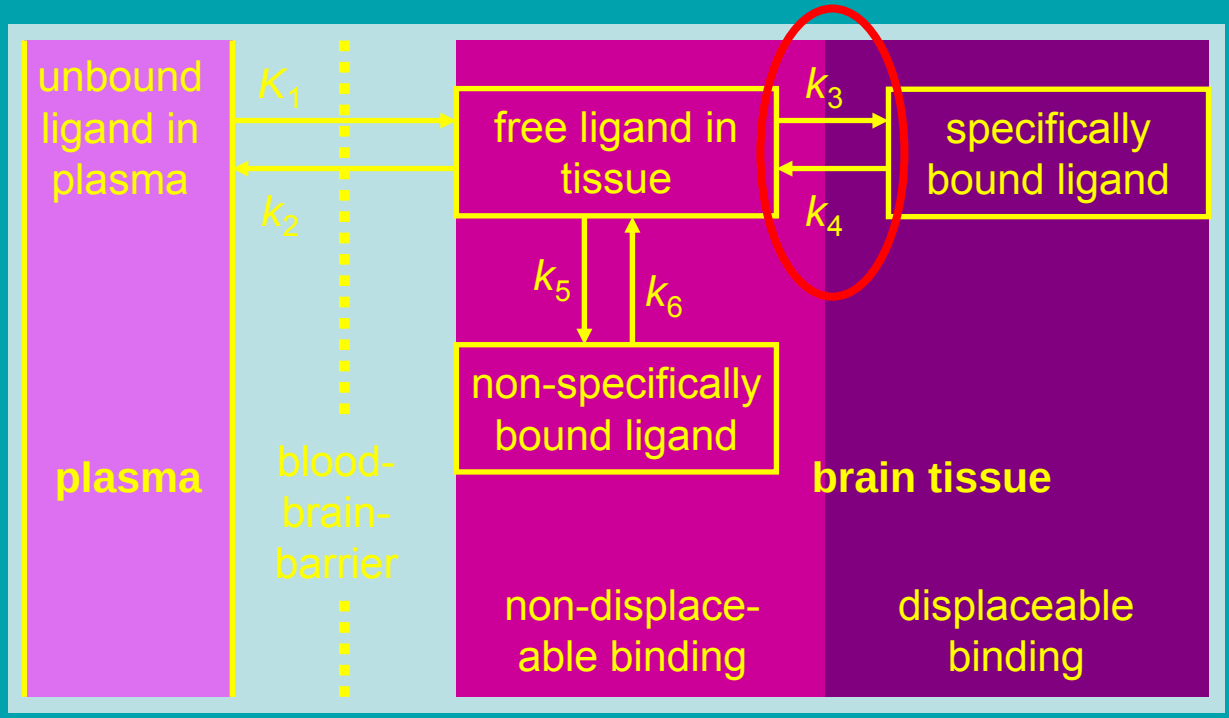
in PET: k_3 in PET: k_4

The standard model for receptor studies with PET



Mintun, M.A.; Raichle, M.E.; Kilbourn, M.R.; Wooten, G.F.; Welch, M.J.: A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann. Neurol.* 15 (1984), 217 - 227.

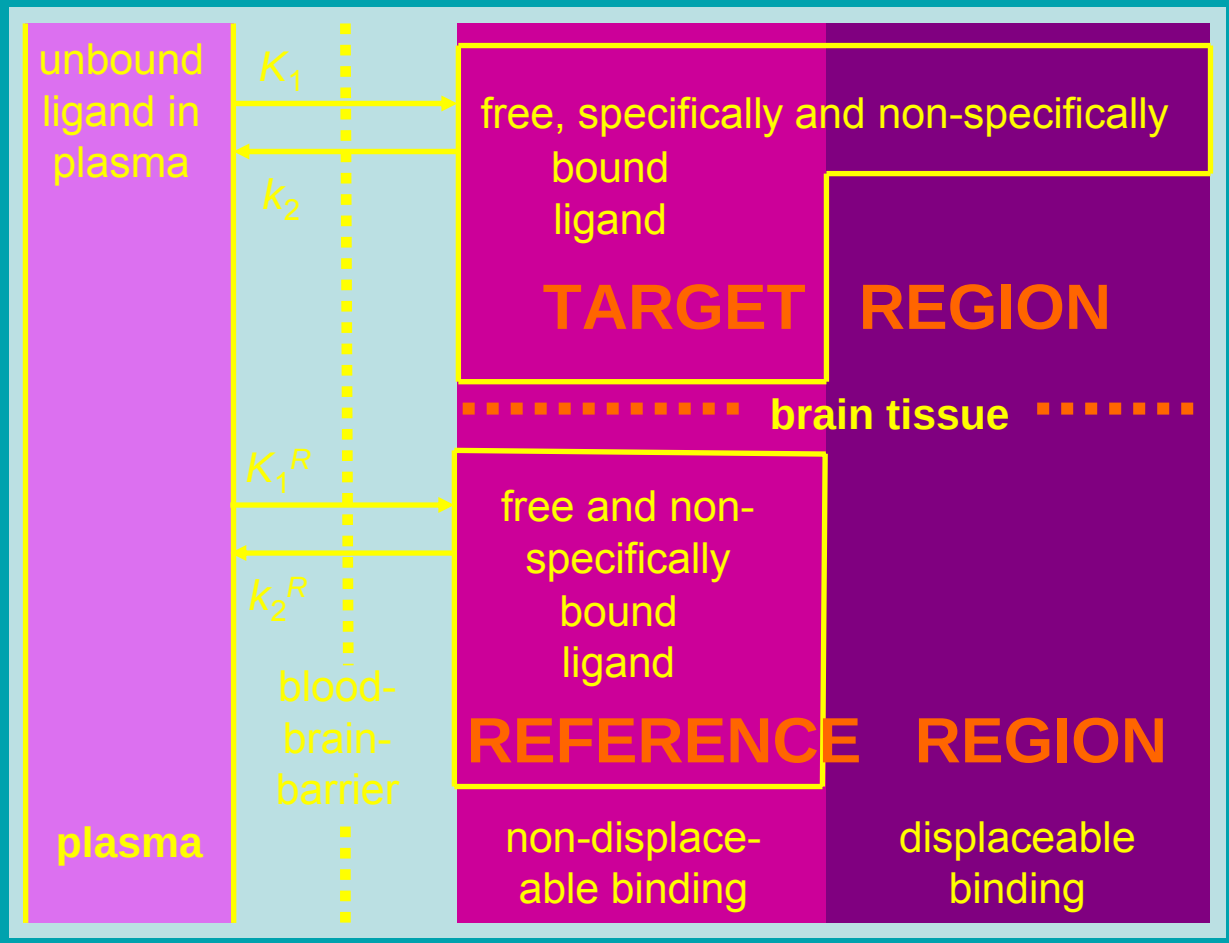
The standard model for receptor studies with PET



binding potential:

$$BP = \frac{B_{max} - [RL]}{K_D} = \frac{k_3}{k_4}$$

The simplified reference tissue model



Lammertsma, A.A.; Hume, S.P.: Simplified Reference Tissue Model for PET Receptor Studies. *NeuroImage* 4 (1996), 153 - 158.

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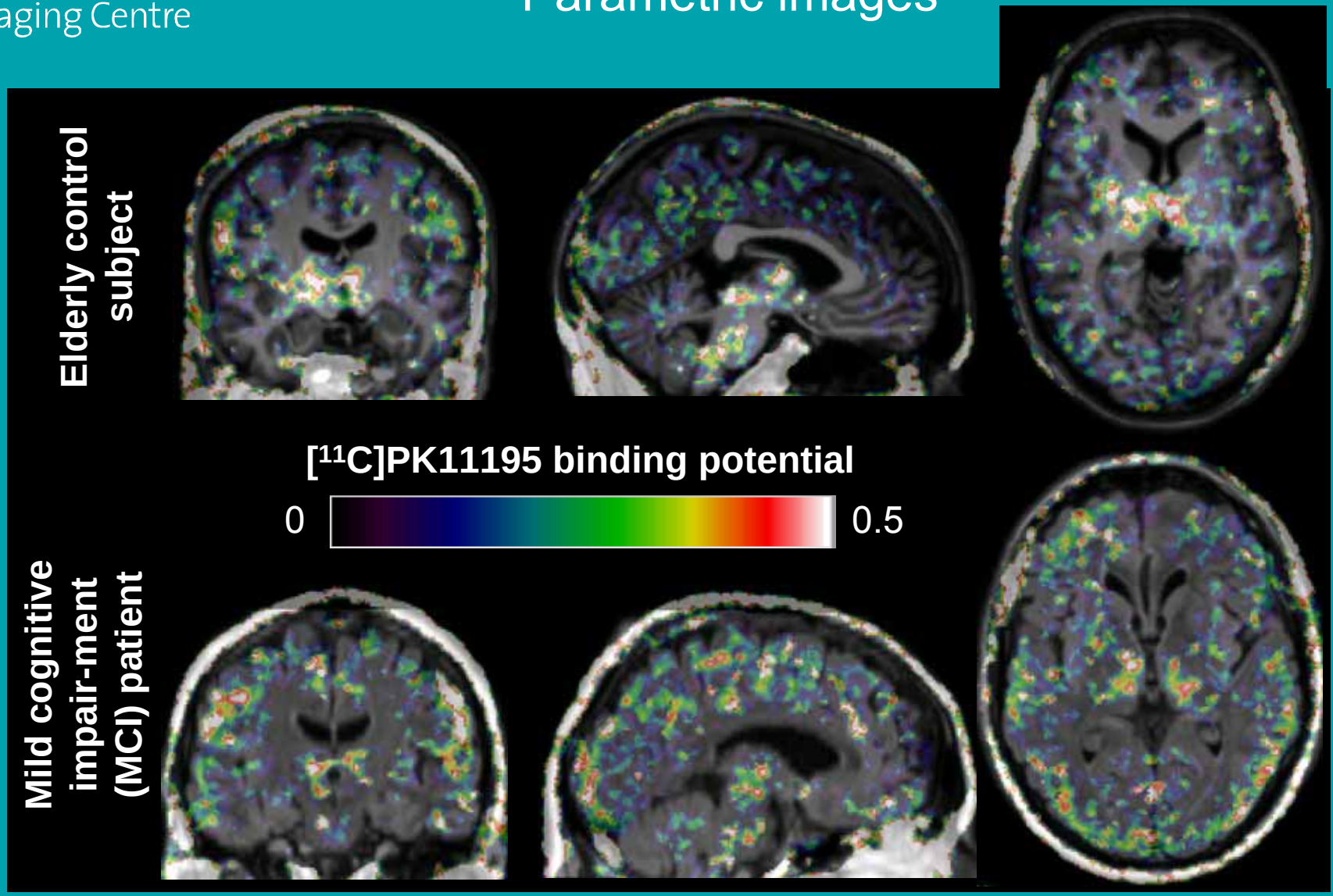
Parametric images



Simplified reference tissue model with cerebellar input function

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Extraction of reference tissue kinetics

Why?

- Anatomically defined reference region (cerebellum) contains contribution from specific binding.
- Inconsistent BP estimates plasma vs. cerebellar input function.

How? Supervised clustering

Normalise each frame of the dynamic image by subtracting its mean and dividing it by its standard deviation to create a unit input.

Database of six kinetic classes extracted from control subjects
1. Normal grey matter
2. White matter
3. Blood pool
4. Muscle
5. Scull / bone
6. High density PBR binding

Describe every pixel $P_i(t)$ as a weighted linear combination of the kinetic classes as:

$$P_i^n(t) = \sum_{j=1}^{6} w_{ij} K_j^n(t),$$

with $w_{ij} \geq 0$

$P_i^n(t)$ … normalised kinetic at voxel i

$K_j^n(t)$ … normalised kinetic class j ($j = 1, \ldots, 6$)

Non-negative least squares (NNLS) algorithm to determine the set of weights w_{ij} per pixel.
Use the map w_{i1} of the normal grey matter kinetics to calculate the reference tissue kinetics.

Turkheimer, F.E. et al., *J. Nucl. Med*. 48 (2007), 158 – 167.

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An investigation to detect central nervous system inflammation in individuals at increased risk of stroke with elevated levels of inflammatory markers and controls using position emission tomography.

Cohort 1	Cohort 2
Subjects at increased risk of stroke	Age matched control subjects

Between group comparison

The role of inflammation in the causation of mild cognitive impairment and Alzheimer's disease.

Scan 1

Scan 2

Within subject comparison

Neuropsychological tests and measurement of peripheral inflammatory markers are performed in parallel

Future projects on neuroinflammation in schizophrenia, depression, brain tumours.

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Physics team

Validation team

Radiochemistry team

Information systems team

Project managers


Quality Control team

Blood lab and bioanalysis team

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Clinical team, Matt Jones and David Coope

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