The University of Manchester
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Changes of [^{11}C]DASB binding in human brain after citalopram infusion

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Introduction

Quantification of brain PET studies is commonly based on two assumptions with respect to a ***reference region***

(1) devoid of specific binding,

(2) free and nonspecifc binding of the radioligand uniform across the entire brain.

In studies of radioligand binding to the ***serotonin transporter*** (SERT), several reports suggested that these assumptions may not be met

- Szabo Z *et al*. (*JNM* **43** (2002), 678-92): changes of [^{11}C](+)McN5652 and [^{11}C]DASB binding in cerebellum after MDMA lesion or paroxetine treatment observed in baboons,
- Ikoma Y *et al*. (*JCBFM* **22** (2002), 490-501): dual injection paradigm using [^{11}C](+)McN5652 and [^{11}C](-)McN5652 to estimate regionally variable free and nonspecifically bound,
- Kish SJ *et al*. (*Nucl Med Biol* **32** (2005), 123-8): SERT concentration in cerebellar cortex and white matter approximately 20% of cerebral cortex or 5% of striatum,
- Parsey RV *et al*. (*Biol Psychiatry* **59** (2006), 821-8): in [^{11}C]DASB scans, 33% reduction of the *VD* in cerebellar grey matter after daily oral sertraline treatment.

Methods

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- **Four** healthy male volunteers underwent two PET scans.
- In a randomised design, either 5 ml saline or 10 mg **citalopram**, a selective serotonin re-uptake inhibitor (SSRI), in the same amount of saline were **infused intravenously** over 30 minutes.
- Then approximately 550 MBq of **[^{11}C]DASB** were injected as a smooth bolus.
- 90 min dynamic 3D data were acquired in list mode on the ECAT EXACT3D tomograph (Siemens/CTI).
- The **arterial plasma input function** was derived from continuous on-line whole blood monitoring and 10 discrete blood samples, in 8 of which the fraction of unmetabolised parent compound was determined.
- **Regions of interest** (ROI) were defined on the co-registered MRI with the help of a probabilistic brain atlas template.
- **Tissue time-activity curves** (TACs) were generated from sampling the grey matter voxels of those ROIs.
- Regional estimates of **total volumes of distribution** *VD* were obtained from **compartmental modelling**, from **Logan** graphical analysis of reversible binding and from **spectral analysis**.
- **Binding potential** estimates were calculated indirectly

$$BP_2 = \frac{VD_{\mathrm{ROI}}}{VD_{\mathrm{Cerebellum}}} - 1.$$

- **Occupancy** was expressed as percentage reduction of binding potential

$$Occ = \left(1 - \frac{BP_{\mathrm{Blocked\ scan}}}{BP_{\mathrm{Baseline\ scan}}}\right) \cdot 100\ \%.$$

Results: Input Function

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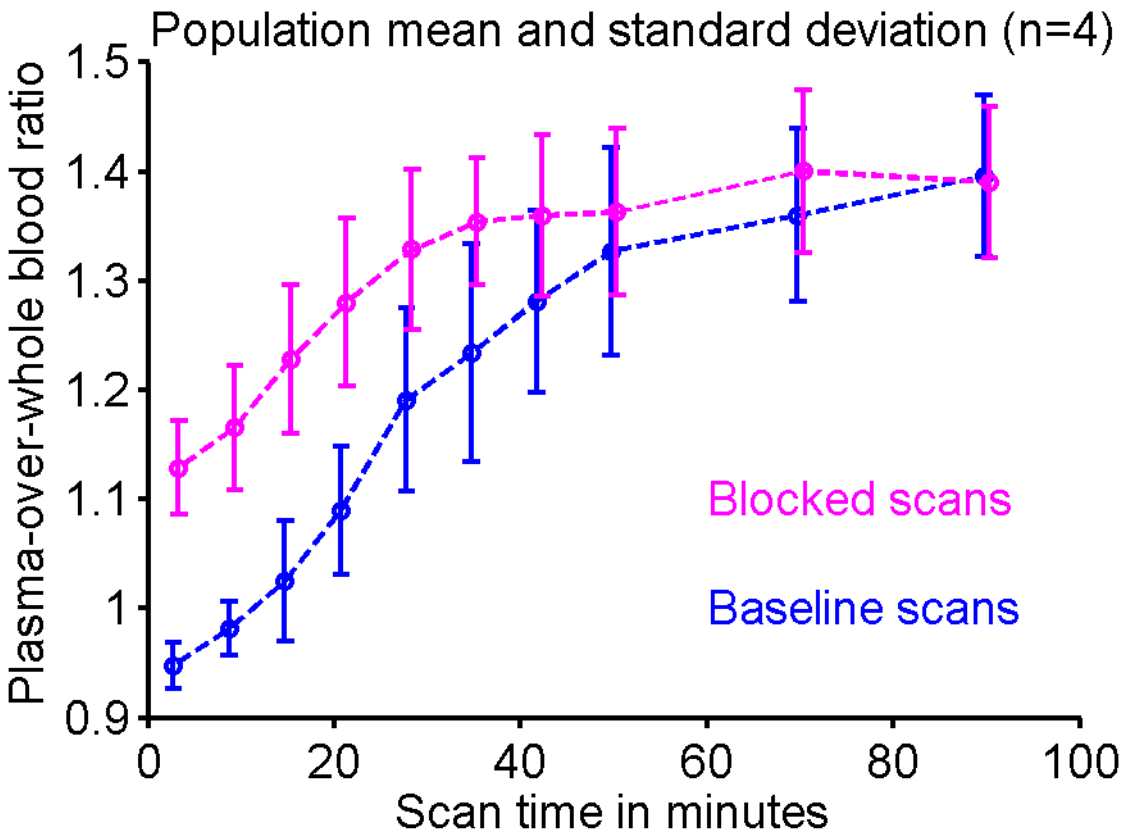
plasma-over-whole blood (POB) ratio = $\frac{\text{activity concentration in plasma}}{\text{activity concentration in whole blood}}$



Observation:

In the initial phase of the blocked scans, the POB ratio was significantly higher than in the base-line scans.

Discussion:

SERT binding sites on the platelets blocked by citalo-pram?

At later times:

- most of the activity due to radiolabelled metabolites rather than [^{11}C]DASB,
- lower concentration of citalopram than at the beginning.

Results: Input Function

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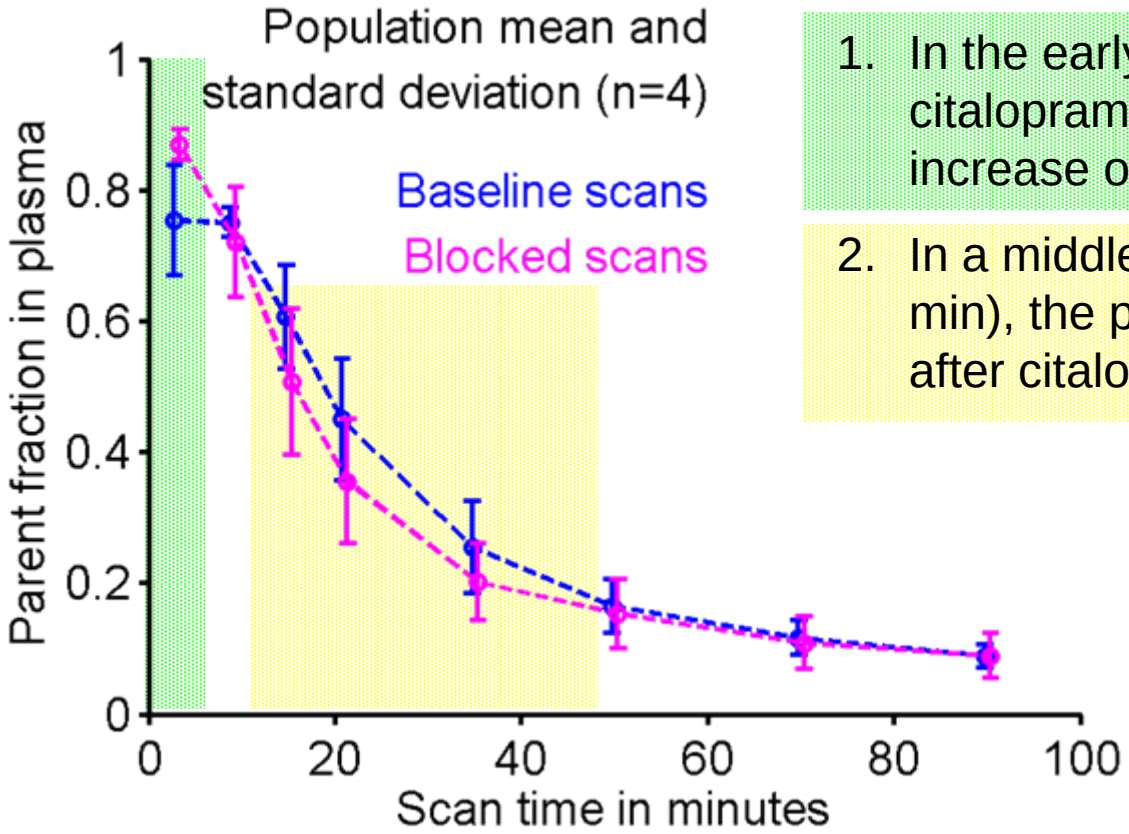
Fraction of radioactivity due to unmetabolised parent [^{11}C]DASB in plasma



Observations consistent in all four subjects:

1. In the early phase (before 5 min), citalopram administration caused an increase of the parent fraction.
2. In a middle phase (between 10 and 45 min), the parent fraction was decreased after citalopram administration.

Citalopram administration lead only to subtle systematic changes.

Results: Input Function

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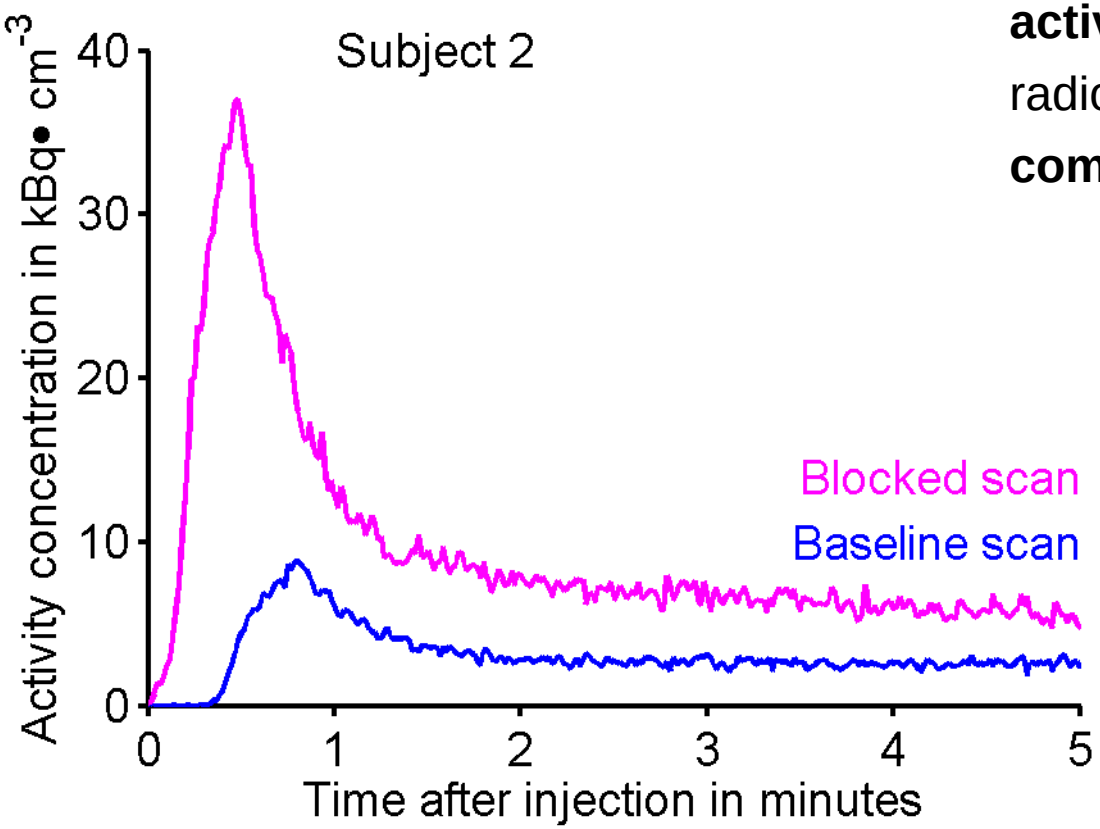
Bioavailability



Area under the curve (AUC) of the **activity concentration** (corrected for radioactive decay) **due to parent compound [^{11}C]DASB in plasma**

in kBq · cm^{-3} · min

minutes		5	30	90
subject	1	27.1	86.1	122.9
		56.4	107.4	137.0
	2	15.5	77.0	124.9
		48.7	113.5	161.5
	3	13.9	81.9	134.5
		64.2	136.2	185.6
	4	23.7	74.7	104.5
		47.9	94.8	120.6

The blockade of peripheral SERT binding sites by citalopram led to a substantial increase of [^{11}C]DASB availability in plasma.

Results: Tissue Response

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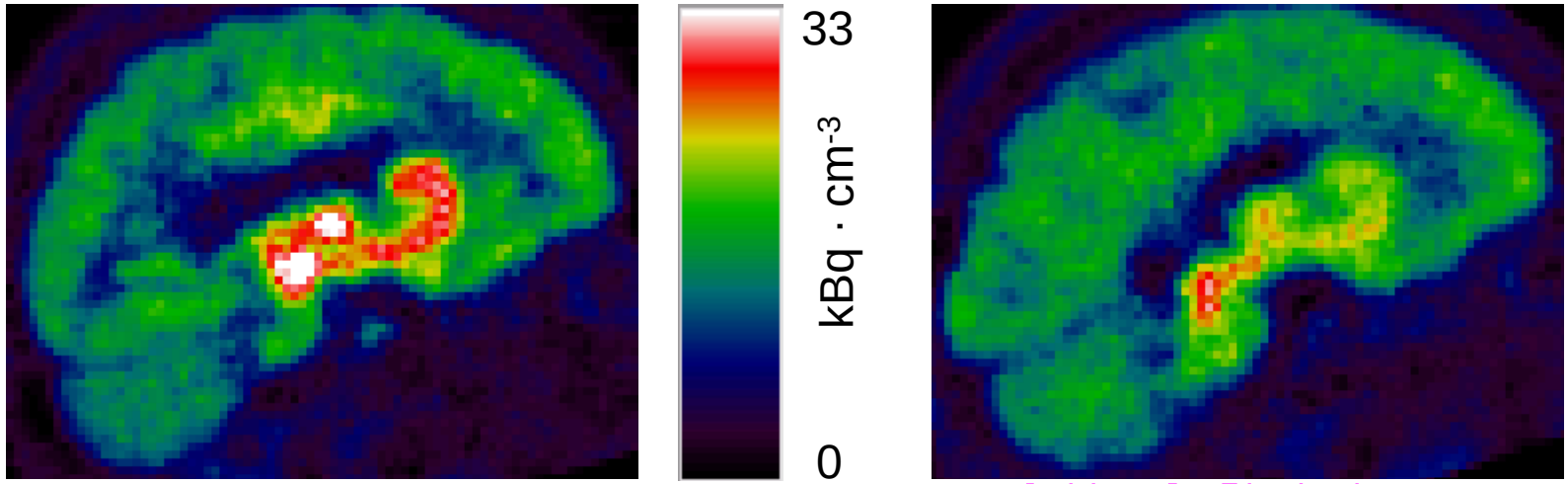
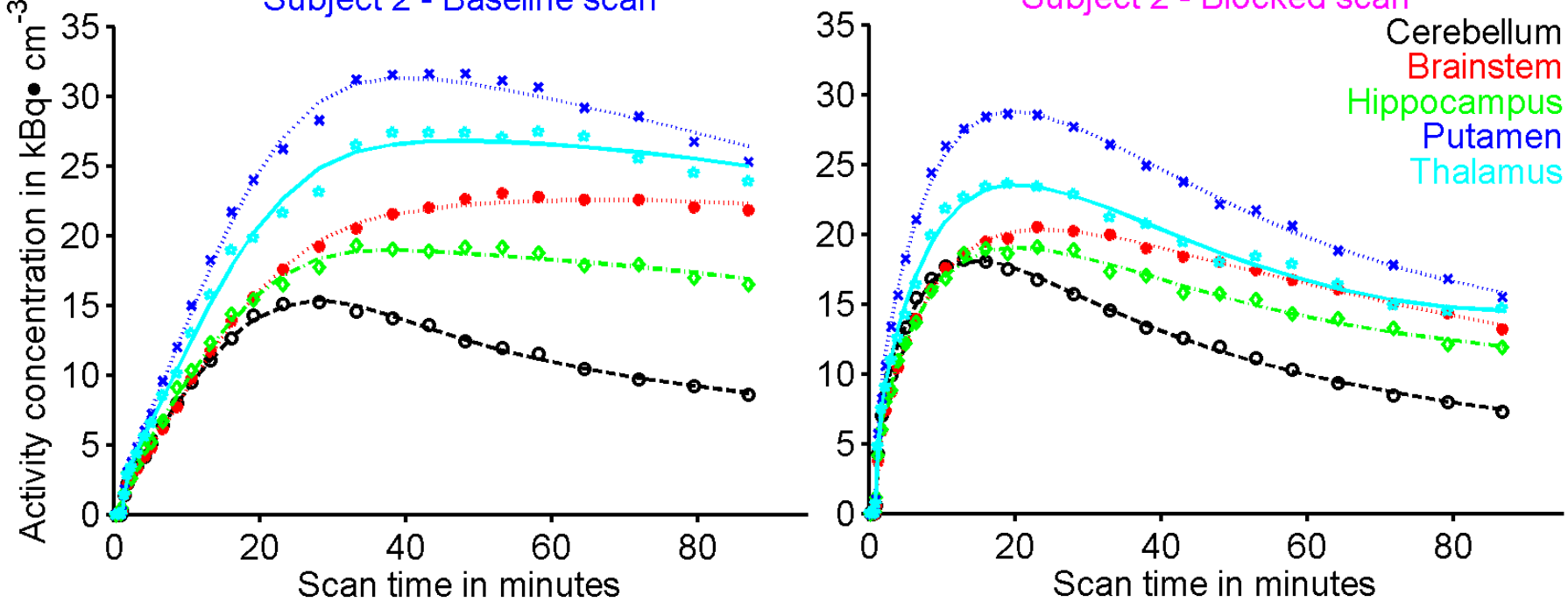
Summed images from 9 to 90 min p.i. (oblique slices)





Results: Parameter Estimates

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Compartmental models:

- Two-tissue, four rate constants: difficulties with convergence, negative k_4 and sometimes also k_3 estimates
- One-tissue, two rate constants: always converges two a solution. However, the quality of the fit, particularly in the regions with lower uptake, is not good (high residual sum of squares).

Graphical analysis:

- Logan plots, $t^* = 35$ min

ROI	Subject 1			Subject 2			Subject 3			Subject 4		
	Baseline	Blocked		Baseline	Blocked		Baseline	Blocked		Baseline	Blocked	
	VD	BP_2	*VD* BP_2 *Occ*	*VD*	BP_2	*VD* BP_2*Occ*	*VD*	BP_2	*VD* BP_2*Occ*	*VD*	BP_2	*VD* BP_2 *Occ*
Cerebell	**9.2**		**9.2**	**9.9**		**7.9**	**12.7**		**9.6**	**9.3**		**6.4**
Amygdala	26.3	1.85	15.3 0.66 65	30.6	2.08	13.5 0.70 66	41.5	2.27	14.7 0.54 76	29.5	2.17	11.9 0.85 61
Brainstem	26.9	1.92	15.3 0.66 66	30.1	2.03	13.3 0.68 66	34.5	1.71	14.4 0.50 71	25.4	1.74	11.3 0.75 57
Caudate	23.7	1.57	13.5 0.46 71	23.4	1.35	12.9 0.62 54	31.7	1.49	14.5 0.51 66	22.5	1.42	9.9 0.54 62
Hippocam	17.0	0.84	12.1 0.31 64	19.6	0.97	11.7 0.48 51	26.5	1.08	13.7 0.44 60	17.4	0.87	10.0 0.57 35
Putamen	29.1	2.15	16.2 0.75 65	29.5	1.97	15.7 0.99 50	34.6	1.72	16.3 0.71 59	28.5	2.06	13.4 1.09 47
Thalamus	28.7	2.11	14.4 0.55 74	28.6	1.88	13.9 0.75 60	30.5	1.40	15.6 0.63 55	28.4	2.06	12.6 0.96 54
Mean ± stand dev			**67 ± 4**			**58 ± 7**			**64 ± 8**			**52 ± 10**

Negative bias?

Mean reduction in cerebellar *VD*: 19 ± 13 % (n= 4).

Results: Parametric images

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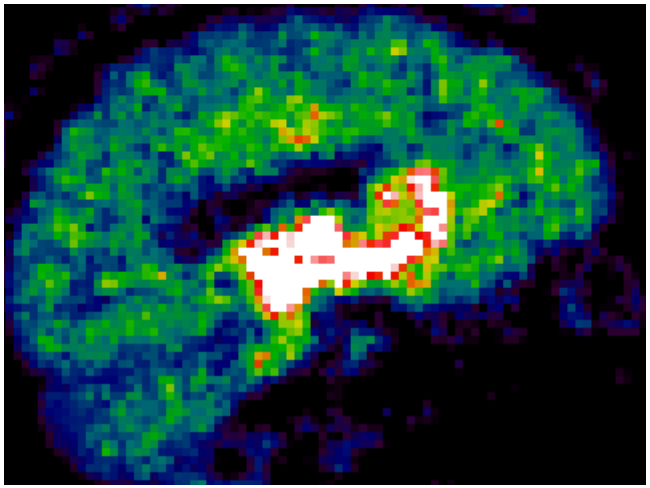
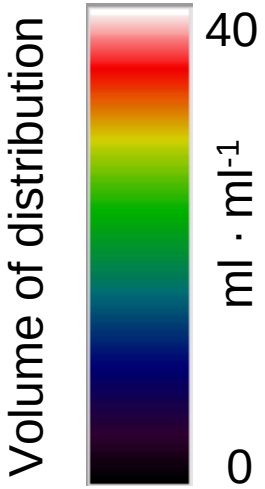
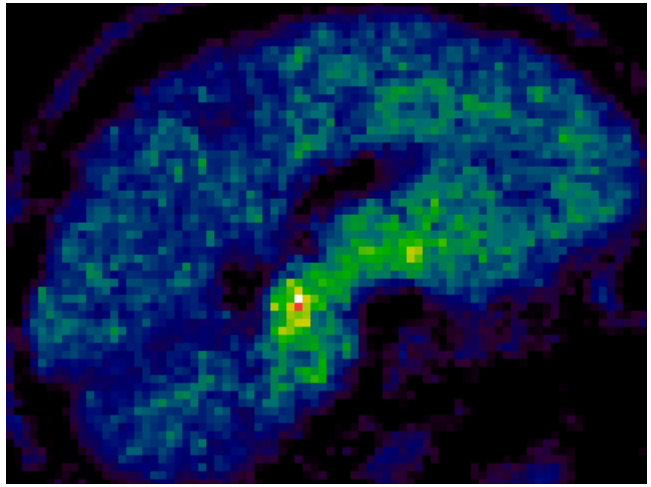
Spectral analysis using basis functions
logarithmically spaced between β_{min}= 0.0007 s^{-1} and β_{max}= 0.1 s^{-1}.







Subject 2 – Baseline scan

Subject 2 – Blocked scan

ROI	Subject 1		Subject 2		Subject 3		Subject 4	
	Baseline	Blocked	Baseline	Blocked	Baseline	Blocked	Baseline	Blocked
	VD BP_2	*VD* BP_2 *Occ*	*VD* BP_2	*VD* BP_2 *Occ*	*VD* BP_2	*VD* BP_2 *Occ*	*VD* BP_2	*VD* BP_2 *Occ*
Cerebell	**11.8**	**10.8**	**13.5**	**10.3**	**17.1**	**11.5**	**11.7**	**8.4**
Amygdala	30.4 1.58	18.4 0.71 55	32.0 1.36	16.4 0.59 57	37.3 1.18	18.5 0.61 48	33.8 1.88	15.0 0.80 58
Brainstem	30.3 1.57	18.1 0.68 57	31.6 1.33	16.0 0.54 59	35.0 1.04	17.3 0.51 51	29.5 1.51	13.8 0.66 57
Caudate	30.4 1.58	15.1 0.40 75	30.1 1.22	14.7 0.43 65	39.5 1.30	17.3 0.51 61	27.6 1.35	11.7 0.40 70
Hippocam	21.9 0.86	14.1 0.30 65	23.6 0.74	13.8 0.33 55	31.1 0.82	16.8 0.46 43	21.3 0.81	11.9 0.43 48
Putamen	36.1 2.06	18.2 0.69 67	37.1 1.74	18.1 0.75 57	43.1 1.51	19.0 0.65 57	34.5 1.94	15.5 0.85 56
Thalamus	35.8 2.03	16.5 0.53 74	35.3 1.61	15.9 0.54 66	38.5 1.25	18.5 0.61 51	34.5 1.94	14.5 0.73 62
Mean ± stand dev		**65 ± 8**		**60 ± 5**		**52 ± 6**		**58 ± 8**

Mean reduction in cerebellar *VD*: 24 ± 11 % (*n*= 4).

Summary and Conclusions

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- Citalopram infusion led to a substantial increase of [^{11}C]DASB availability in plasma.
- Observed reductions in cerebellar *VD* are in line with previous reports.
- Occupancy estimates are fairly homogeneous across the SERT-rich regions. ROIs with low SERT density (e.g. cortical areas) could not be reliably quantified.
- Mean occupancy in 4 subjects: about 60 % with ROI-based Logan graphical analysis or 59 % with parametric maps generated by spectral analysis.
- However, occupancies expressed as reduction of indirectly calculated binding potentials are underestimations.
- Why is the reduction of the cerebellar *VD* in the blocked scans greater than expected from the reported SERT concentration?
- Did citalopram alter the [^{11}C]DASB transfer across the blood-brain barrier?
- Which is the right strategy for quantification? Must reference region approaches be avoided?
- High-affinity SERT radioligand for cortical regions???
- Can SERT imaging in the brain be improved by co-administration of a SSRI that is unable to cross the blood-brain barrier?