Regional differences of SERT occupancy in major depression: An in vivo PET study using [^{11}C]DASB

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INTRODUCTION:

The blockade of serotonin transporters (SERT) responsible for serotonin reuptake from the synaptic cleft into the presynaptic neuron is the primary mechanism of action of selective serotonin reuptake inhibitors (SSRIs). One might assume that the selective affinity of an SSRI for SERT and hereby its antidepressant effectiveness might be similar throughout the brain. However, SERT activity mediated via various factors may differ between regions as SERT is a priori not equally distributed in the brain. Furthermore, as the internalization process of SERT and thereby its availability in a distinct area depends on its activity, SERT occupancy by an SSRI might vary throughout the brain [1]. **Here, we investigated whether SERT occupancy by SSRIs is equally distributed in brain areas known to play a role in major depression using positron emission tomography (PET).**

RESULTS:

Injected doses, masses, and specific activities for [^{11}C]DASB did not differ between groups (escitalopram/citalopram) and time points. Regarding PET2, SERT occupancies significantly differ from mean cortical values in the posterior cingulate, subgenual cingulate cortex, the middle and the inferior temporal gyrus. Subcortically, significant deviations from mean SERT occupancy levels were detected in the amygdala, the dorsal raphe and the putamen. Similarly, for PET3 this was the case for the posterior cingulate, the subgenual cingulate cortex, the middle and inferior temporal gyrus. Subcortically, SERT occupancy levels significantly differ from mean subcortical values in the amygdala, the dorsal and median raphe and the putamen. All results are subsumed in the table.
Results were mostly reflected within the voxel-wise approach at PET 2 und PET 3 for both subcortical and cortical brain regions.

	PET 2					PET 3				
	mean	**SD**	**t**	**df**	**p**	**mean**	**SD**	**t**	**df**	**p**
cortical ROI	**test value = 65.66**					**test value = 63.82**				
middle temporal gyrus	43.53	18.09	-5.19	17	<0.001*	41.84	18.34	-5.09	17	<0.001*
inferior temporal gyrus	47.4	20.67	-3.76	17	0.002*	43.53	20.65	-4.17	17	0.001*
posterior cingulate	78.49	11.65	4.12	13	0.001*	78.55	16.27	3.51	14	0.003*
subgenual cingulate	82.16	7.36	9.51	17	<0.001*	84.12	9.16	9.14	16	<0.001*
subcortical ROI	**test value = 72.99**					**test value = 78.54**				
putamen	66.71	5.27	-5.19	18	<0.001*	71.1	6.32	-5.12	18	<0.001*
median raphe	78.14	6.16	3.641	18	0.002*	85.13	4.75	6.04	18	<0.001*
amygdala	81.78	6.48	5.909	18	<0.001*	87.58	6.74	5.69	17	<0.001*
dorsal raphe	81.88	4.52	8.57	18	<0.001*	88.78	3.56	12.56	18	<0.001*

Table. Regional SERT occupancy levels compared to mean cortical and subcortical SERT occupancies (test values given in the table) in 14 cortical and 8 subcortical regions of interest. *p<0.05 Bonferroni corrected.

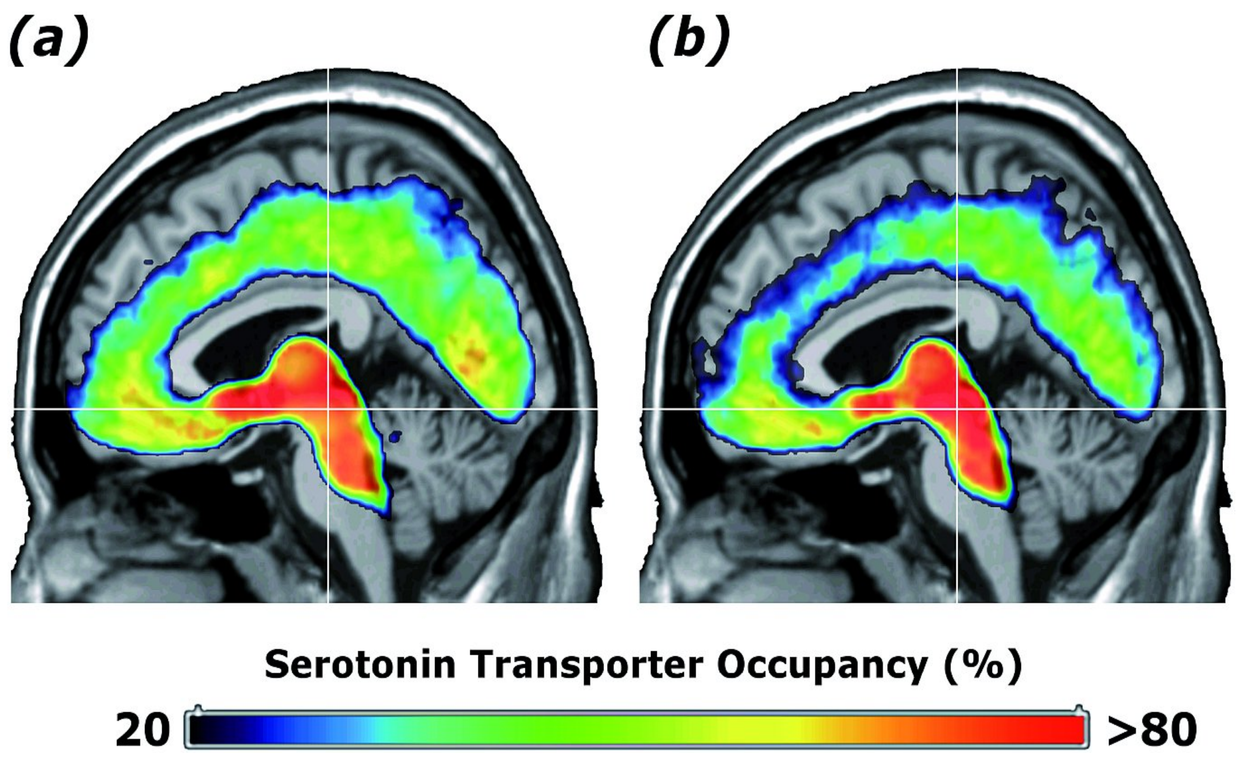

Figure. Sagittal views of voxel-wise maps representing the averaged SERT occupancies after *(a)* single dosage (PET 2) and *(b)* steady state (PET 3) escitalopram or citalopram intake, overlaid onto structural MRI planes. Occupancy values are given in the color table.

METHODS:

19 outpatients (13 female aged 42.3±7.8 years (mean±SD)) suffering from major depressive disorder (17-item HAMD ≥ 16, no pharmacological treatment 3 months prior scanning) were included in this longitudinal study. Subjects received oral doses of either escitalopram (10mg/day, 10 subjects) or citalopram (20mg/day, 9 subjects) and underwent three [^{11}C]DASB PET scans: before treatment (PET1), 6h following the first SSRI dose (PET2) and 6h after the last dose (PET3), which was administered daily for a minimum of 3 weeks (24.73±3.3 days) as described previously [2]. Quantification of SERT binding potential (BP_{ND}) was performed using MRTM2. PET images were spatially normalized to a template in MNI space using SPM8. SERT BP_{ND} was computed using both a regions of interest (ROI), where 22 ROIs were selected from a customized template based on the AAL atlas, and a voxel-wise approach. Cerebellar grey was used as reference region. Using SPSS subcortical and cortical SERT occupancy values across subjects for each ROI were tested against mean subcortical (8 ROIs) and cortical occupancy (14 ROIs) levels, respectively. One-sample t-tests were performed using M_{cort}=65.66 and M_{subc}=72.99 for PET 2, and M_{cort}=63.82 and M_{subc}=78.54 for PET 3 as test values. These values were also used to evaluate regional occupancy differences within the voxel-wise approach in SPM8.

CONCLUSIONS:

SERT occupancy was shown to vary throughout the cortex in several subcortical and cortical brain areas, e.g. the subgenual cingulate cortex and the amygdala, brain regions known to be involved in the pathogenesis of depression. This is in accordance with previous preclinical studies showing that SSRI concentrations differ between brain regions and might therefore impact on occupancy values in a various degree [3] cortically and subcortically. This region-specific modulation by escitalopram and citalopram might be of major clinical relevance in the treatment of major depression.

References:

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