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

Pia Baldinger¹, Georg S. Kranz¹, Markus Savli¹, Wolfgang Wadsak², Daniela Haeusler², Andreas Hahn¹, Markus Mitterhauser², Cécile Philippe², Siegfried Kasper³, Rupert Lanzenberger¹

¹ Department of Psychiatry and Psychotherapy, ² Department of Nuclear Medicine, PET Center, Medical University of Vienna, Austria
http://www.medunwien.ac.at/neuroimaging/pia.baldinger@medunwien.ac.at

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 thereby 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 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 and PET 3 for both subcortical and cortical brain regions.

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 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$_{cont}=65.66$ and M$_{unc}=72.99$ for PET 2, and M$_{cont}=63.82$ and M$_{unc}=78.54$ 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: