Prediction of SSRI treatment response in major depression based on serotonin transporter binding ratios

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Objective:
Recent simulation studies in the wake of the serotonin hypothesis suggest that a down-regulation of serotonin transporters (SERT) in terminal regions predispose the antidepressant effect of SSRIs [1,2]. Since SERT down-regulation under SSRI treatment may depend on SERT expression both in the raphe and in terminal regions, we investigated the predictive power of terminal SERT adjusted to raphe SERT availability before and during drug intake on antidepressant treatment response. This work has been accepted for publication in NeuroImage on July 14, after acceptance of the abstract to the 25th ECNP Congress on June 26. The poster therefore contains data already recently published [3].

Methods:
Study design and medication: Longitudinal pooled study. Subjects received an equivalent amount of the enantiomer S-citalopram, i.e., they were administered oral treatment.

Measurements: [123I]CIT PET was performed before and after a single oral dose, as well as after three weeks (mean ± 3.3 days) of continuous treatment.

Study population: 19 outpatients (13F, 42±7.8 yrs) suffering from major depression (HAM-D score ≥16). Subjects were medication-free for three months prior scanning.

SERT quantification: SERT binding potential (BPND) was quantified within a voxel-wise whole-brain (projection areas) and regions of interest approach (for the median and dorsal raphe nuclei, MRN and DRN, resp.) [4].

SERT drug occupancy was derived using the equation: Occupancy(%) = [1–BPND treatment/BPND baseline]x100.

Data analysis: Associations between treatment efficacy (reduction in HAM-D values) and SERT pre-treatment BPND ratios (SERT BPND in projection areas divided by SERT BPND in raphe nuclei) were evaluated using voxel-wise linear regression analyses. ANOVA was used to compare SERT BPND ratios between remitters, responders and non-responders. Resulting t maps were corrected for multiple comparisons (p < 0.05 voxel-level) using the false discovery rate (FDR).

Results:
Pre-treatment terminal SERT BPND, adjusted to pre-treatment SERT BPND in the MRN, predicted treatment response (t=5.8, all p<0.05 FDR corr., Fig1 and 4). That is, the more SERT BPND in terminal regions such as the bilateral amygdala–anterior hippocampus complex, habenula, putamen, orbitofrontal cortex (OFC), subgenual and anterior cingulate cortex (sgACC and ACC, resp.) in relation to SERT BPND in the MRN, the better was treatment outcome (reduction in HAM-D scores). Comparing SERT BPND ratios in remitters (n=7, HAM-D final scores ≤7) and responders (n=11, 50% reduction in HAM-D scores) to non-responders (n=8, see Fig2) revealed significant clusters in sgACC and OFC, habenula, amygdala, anterior insula, striatum and midbrain (Fig2). No associations were found for the ratio terminal BPND/DRN BPND. No associations were found between SERT occupancy after a single dose, or after three weeks of treatment with treatment response.

Conclusions:
The results of this study provide a first proof-of-concept for recent simulation studies and further underline the importance of key regions including habenula and subgenual cingulate cortex in the etiology of and recovery from major depression. Our findings may indicate a promising molecular predictor of treatment response and stimulate new treatment approaches based on regional differences in SERT function.