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MEETING ABSTRACT

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Decreased white matter diffusivity metrics after acute SSRI challenge in depressed patients and healthy controls

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Background: Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to treat patients suffering from mood disorders such as major depression. These agents act by blocking the serotonin transporter (SERT), which leads to elevated serotonin levels in the synaptic cleft [1]. While gray matter changes in the brain after SSRI administration have already been investigated [2], assessments of white matter alterations are largely missing. In this study, mean diffusivity (MD), fractional anisotropy (FA), axial (AD) and radial diffusivity (RD) were calculated using *in vivo* diffusion-weighted imaging (DWI). A constant SSRI infusion was applied while patients and healthy controls underwent MRI scanning before and after the application within one scanning session to assess rapid effects of SSRI treatment on white matter microstructure.

Methods: In total, 81 subjects (controls: $n = 48$, age = 28.0 ± 8.8 years (mean ± SD); patients: $n = 33$, 29.2 ± 9.6 years) were included in this study. All participants underwent two DWI sessions twice on two separate days receiving either the study drug or placebo using a randomized, double-blind, cross-over design. Subjects were measured before and after 40 minutes after the study drug/placebo application using a constant infusion of 8 mg citalopram for 7.5 minutes. Scans were acquired with a 3-Tesla Siemens MR scanner using a single-shot diffusion-weighted echo planar imaging sequence (TR = 8800 ms, TE = 76 ms, matrix = 128×128×70, resolution = 2 mm isotropic, flip angle = 180°). Thirty diffusion encoding directions with a *b*-value of 1000 s/mm^2 and 3 non-diffusion reference images were acquired. The analysis was conducted within FSL 5.0.11 [3]. After an initial brain extraction step, data were corrected for susceptibility artefacts and eddy currents. Subsequently, the diffusion tensors were calculated with DTIFit using the rotated *b*-vectors generated during the eddy correction step. Voxel-wise analysis was conducted using tract-based spatial statistics (TBSS) [4]. Treatment effects were assessed within FSL's Randomise tool and by using the threshold-free cluster enhancement method (TFCE) [5]. A two-way mixed effects ANOVA was conducted to investigate main SSRI effects and to test for differences between the groups.

Results: No interaction between group and treatment was found. However, a significant main effect ($p < 0.05$, corrected) for treatment was observed. Specifically, our results revealed MD decreases in the tracts comprising the anterior corona radiata (ACR) and the genu of the corpus callosum (*t*-value: 4.88; MNI: −16/31/−11). In addition, reductions in the superior frontal blade (*t*-value: 3.77; MNI: −19/43/21) and the superior longitudinal fasciculus (SLF) (*t*-value: 3.50; MNI: −31/−23/41) were observed. Reductions in AD were also found in the SLF (*t*-value: 4.69; MNI: −32/−22/41) next to decreases in the external capsule (*t*-value: 4.76; MNI: −28/−9/18), while RD reductions were also most pronounced in the ACR (*t*-value: 3.77; MNI: −23/23/5), similar to the results observed for MD. However, no changes for FA were found.

Discussion: This analysis suggests that SSRI administration leads to significant decreases in diffusivity in several white matter tracts even after a short period of time, reflected by changes in MD, AD and RD. While MD decreases indicate a general reduction in diffusivity, AD and RD can be interpreted as specific decreases in diffusivity along the axon (AD) or perpendicular to it (RD). Interestingly, no increases were found and also no changes in FA were observed. Furthermore, SSRI administration did not lead to different effects between groups. These results may indicate changes in fiber bundle organization including axonal or dendritic adaptions. However, axonal swelling or changes in protein transport may also be responsible for these observations.

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Keywords: diffusion-weighted imaging – diffusion tensor imaging – tract-based spatial statistics – SSRIs – serotonin – antidepressants – depression

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