Escitalopram Administration, Neuroplastic Effects and Relearning: A Diffusion Tensor Imaging Study in Healthy Individuals

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Abstract

Background Neuroplastic processes are influenced by selective serotonergic reuptake inhibitors, while learning in conjunction with the administration of serotonergic agents alters white matter microstructure in humans. The goal of this double-blind, placebo-controlled imaging study was to investigate the influence of escitalopram on white matter plasticity during (re)learning.

Methods Seventy-one healthy individuals (age = 25.6±5.0, 43 females) underwent 3 diffusion magnetic resonance imaging sessions: at baseline, after 3-weeks of associative learning (emotional/non-emotional content) and after relearning shuffled associations for an additional 3 weeks. During the relearning phase, subjects received daily escitalopram 10 mg or placebo orally. Data were analyzed using the FMRIB Software Library (FSL) and the implemented Tract-Based Spatial Statistics (TBSS) approach.

Results The TBSS analysis revealed widespread decreases in fractional anisotropy metrics in subjects that received escitalopram. In addition, axial diffusivity decreases were mainly found in the corpus callosum and in areas within the internal capsule. In subjects receiving placebo, we did not find such effects, nor did our results show diffusivity changes related to learning or relearning.

Conclusion Diffusivity changes were found within several tracts in the escitalopram group, while we observed no changes in the placebo group. Although previous studies examining the effects of SSRIs on white matter tracts in humans are underrepresented, our results suggest a relationship between serotonergic agents and diffusivity parameters. The findings of this study implicate that escitalopram may directly or indirectly impact white matter microstructures in healthy subjects. Nevertheless, we did not find a relationship between serotonergic modulation, neuroplastic effects and relearning.

Introduction

Antidepressants and in particular selective serotonin reuptake inhibitors (SSRIs) present a well-established and frequently applied treatment option for patients with mood and anxiety disorders (Bauer et al., 2013). Therapeutic agents modulating monoaminergic neurotransmission have been found to restore well-being with regard to different symptom complexes including depression, anxiety or obsessions and compulsions. According to the monoamine deficiency theory (Delgado, 2000), treatment-induced changes in mood following SSRI administration are physiologically related to a blockage of the serotonin transporter and subsequent up-regulated serotonin levels in the synaptic cleft that stimulates auto- and hetero-receptors located at serotonergic neurons and projection areas (Spies et al., 2015).

Throughout the last decade the influence of SSRIs on brain structure has been primarily investigated by exploiting T1-weighted magnetic resonance imaging (MRI). Most structural imaging investigations were conducted in patients with receiving SSRIs as a study and treatment intervention and results are partly heterogeneous. (Kraus et al., 2017). SSRI studies in healthy subjects and patients using MRI predominantly examine drug-induced changes in neuronal activation and functional connectivity (Dichter et al., 2015). Pharmacological studies on SSRI in healthy individuals and structural MRI are astonishingly scarce (Kraus et al., 2014; Shively et al., 2017). In longitudinal studies, cognitive or physical training and learning as well as administered SSRIs were found to impact brain morphology (Kristensen et al., 2018; Knorr et al., 2019). Also, SSRI intervention studies demonstrated treatment-associated changes in white matter integrity in different clinical samples with diverse methodological approaches (Yoo et al., 2007; Fan et al., 2012; Seiger et al., 2021).

Although SSRIs have been comprehensively studied on a cellular level in animal models and humans *in-vivo*, the mechanisms underlying their therapeutic potential in neuropsychiatric disorders are not well understood. Due to the partly insufficient and yet unexplained remission and response rates of approximately 40% to 60% following antidepressant treatment, respectively (Trivedi et al., 2006), the

notion that SSRIs do not directly improve mood and thus cause depression to resolve, but instead enable susceptibility to change irrespective of direction has been increasingly studied and propagated (Chiarotti et al., 2017). SSRIs and fast-acting antidepressants as ketamine have been demonstrated to facilitate neuroplasticity (Alboni et al., 2017; Casarotto et al., 2021). According to this hypothesis, the brain is then suggested to be more prone to the quality and amplitude, implicating that the outcome of an SSRI treatment is dependent on encouraging or stressful influences one experiences (Branchi and Giuliani, 2021).

On the basis of imaging studies, convincing evidence points towards a relation between white matter integrity, plasticity and intellectual development of the central nervous system during child- and adulthood (Wang and Young, 2014; Bells et al., 2019). Apart from age-related changes of white matter throughout lifespan, which peak in the third and decline from the fifth decade onward (Dvorak et al., 2021), longitudinal neuroimaging studies revealed an effect of experience on white matter that can be traced with diffusion weighted imaging (Zatorre et al., 2012). Investigations in animals and humans show that white matter changes dynamically and dependent of the standardized study-experience *in vivo* following training (Keller and Just, 2009; Blumenfeld-Katzir et al., 2011). For instance, motor exercise learning as juggling increased fractional anisotropy (FA) in the right posterior intraparietal sulcus, an area associated with hand-eye co-ordination, and prevailed for at least 4 weeks following training (Scholz et al., 2009). The majority of white matter studies examined an increase in FA, and positive effects working memory on FA in parietal tracts (Takeuchi et al., 2010). In addition, perceptual learning such as texture discrimination learning or Braille reading training altered white matter, reflected in elevated FA (Yotsumoto et al., 2014; Debowska et al., 2016).

Within the last decade, diffusion tensor imaging (DTI) emerged as a reliable and frequently applied imaging approach to non-invasively investigate white matter microstructure. Although water diffusivity metrics are too coarse to comprehensively relate those findings to specific cellular mechanisms that are involved in white matter neuroplasticity, multimodal investigations in rodents have identified a significant overlap of molecular and cellular changes and white matter plasticity

measured by diffusion MRI (Sampaio-Baptista et al., 2020). Several diffusion metrics have been found useful to describe differences between groups or over time (Smith et al., 2006). Among these metrics, FA provides information on the directionality of the diffusion process, hence, reflecting the grade of anisotropy and myelination. Axons allow water molecules to diffuse quickly along the direction of organization (axial diffusivity; AD), but constraining radial diffusivity (RD) meant to perpendicular travel along the direct axis. Mean diffusivity (MD) estimates the average water diffusion across all directions.

To reveal potential neuroplastic effects that SSRIs have on white matter during relearning, we performed a longitudinal placebo-controlled interventional learning study. Healthy subjects performed an associative learning task either with or without emotional content, where face pairs or pairs of Chinese characters and unrelated German nouns had to be memorized. After 21 days, subjects had to learn shuffled associations (i.e. relearning) within the same group for another 21 days. During the relearning period, subjects received either escitalopram 10 mg/day, or placebo. DTI models were estimated before and after associative learning and relearning periods.

Methods

Subjects and study design

Data from 71 healthy subjects (age = 25.6 ± 5.0) measured at three time points in a randomized, double blind, placebo-controlled manner were included in this DTI analysis. All participants were randomly assigned to one of four groups prior to study inclusion as follows: SSRI: 17 character-group, 16 faces-group; Placebo: 15 character-group, 23 faces-group. The design has been described in detail in previously published studies (Reed et al., 2021; Spurny et al., 2021). In brief, diffusion MRI scans were carried out before and after an associative learning period of 3 weeks as well as after a subsequent 3-week associative relearning under SSRI/placebo treatment. During the associative relearning period subjects received daily escitalopram 10 mg (Cipralex® Lundbeck A/S, provided by the Pharmaceutical

Department of the Medical University of Vienna) orally or placebo. To ensure compliance, venous blood was drawn from the cubital vein to assess citalopram plasma through levels 1 week and 2 weeks into drug administration and before the third MRI. The therapeutic reference range for escitalopram it is 15-80 ng/mL (Hiemke et al., 2011).

The learning paradigm was divided into 2 groups (with or without emotional valence), where participants had to learn either face pairs or pairs of Chinese characters and unrelated German nouns. During the relearning phase the learning content was shuffled. During each phase, 200 image-pairs per group had to be learned or relearned with a daily subset of 52 image pairs. All faces were derived from the "10k Adult Faces Database" (Bainbridge et al., 2013).

Data acquisition

The diffusion-weighted images (DWI) were acquired with a 3 Tesla Siemens MR scanner (MAGNETOM, Prisma, Siemens Medical, Erlangen, Germany) using a 64-channel head coil. 57 diffusion encoded images, with a b-value of 800 s/mm^2 along with 13 non-diffusion (b=0) images were recorded (TR=9400 ms, TE=76 ms, slice thickness=1.6 mm, resolution=1.6x1.6 mm, matrix size=128x128x75, flip angle=90°, acquisition time=11:45 min). Subjects were instructed to keep their head as still as possible during the entire scan to minimize movement artifacts. Additionally, their heads were stabilized with foam cushions.

Data processing

Data processing was conducted within the FMRIB software library (FSL, v. 5.0.11) (Smith et al., 2004) with the standard TBSS pipeline (Smith et al., 2006). All data outside of the brain were masked out (Smith, 2002), corrected for movements, geometric distortions and eddy currents as well as for outliers in the form of signal dropout (J. L. R. Andersson et al., 2016; J. L. R. Andersson and Sotiropoulos, 2016). The diffusion tensors were fitted using the dtifit command as well as the rotated b-vectors gained from the prior eddy current correction step. For the TBSS analysis, FA maps were eroded and brought into

standard space using FNIRT (J. L. R. Andersson, Jenkinson, M., and Smith, S., 2007a; J. L. R. Andersson, Jenkinson, M., and Smith, S. M., 2007b). The data from each subject was then projected onto the FMRIB58_FA mean FA image and skeleton. The skeletonized images of all subjects were further used for voxel-wise statistics. In addition, the tbss_non_FA command was utilized to generate the skeletonized maps for the remaining parameters, AD, MD and RD.

Statistical analysis

To test the following hypotheses, the respective models were set up and subsequently run within FSLs *randomise* using 5000 permutations analyzing AD, FA, MD and RD. First, we tested whether there is an influence of SSRIs compared to placebo over time on DTI metrics. Here, difference maps between time point (TP) 2 and TP3 were calculated using data from both learning groups combined followed by a 2-sample t-test between the SSRI and the placebo condition. To test for the main effect of substance, a subsequent paired t-test between TP2 and TP3 was conducted for the SSRI group. This was also calculated for the placebo group. As next step, we tested for differences between the learning groups under the influence of SSRIs. Again, difference maps were calculated for the SSRI condition for TP2-TP3 and a 2-sample t-test between the faces and the character groups was conducted. The same statistical model was set up for the placebo condition. To test for differences in the relearning vs. learning effect on the brain without the influence of SSRIs, differences were calculated between the two time periods. As for this data a paired design was applicable, we again calculated the difference between the above generated maps: [(TP3-TP2) – (TP2-TP1)]. This data was then entered into a one-sample t-test. We further investigated if the two learning groups are differently affected by the relearning period. Therefore, the same statistical model was carried out for both learning groups separately.

Results

The analysis of the SSRI influence did not reveal statistically significant results for the entire model, when we tested for differences between time and group. However, subsequent analysis showed significant decreases in FA and AD for the SSRI group between TP2 and TP3 in several white matter tracts. Results indicated widespread effects for FA, but most pronounced in a cluster comprising the splenium of the corpus callosum and the retrolenticular part of the internal capsule (peak MNI coordinate of cluster: x=-25, y=-56, z=18, t-value=5.00). In addition, strong decreases were evident in the anterior corona radiata (x=-18, y=16, z=30, t=3.86) and in the genu of the corpus callosum (x=17, y=24, z=22, t=2.12). Decreased diffusivity for AD was predominantly found in the posterior limb of the internal capsule (x=-23, y=-17, z=5, t=4.73), splenium of the corpus callosum (x=1, y=-35, z=14, t=2.51), anterior limb of the internal capsule (x=23, y=-2, z=15, t=4.98) and in the retrolenticular part of the internal capsule (x=24, y=-24, z=4, t=3.38). All results reported at $p<0.05$ threshold-free cluster enhancement (TFCE), FWE-corrected. In general, AD and FA changes overlapped to a great extent (see Figure 1). We further compared the placebo condition (TP2 vs TP3) as well as the same group of subjects between TP1 vs TP2 before they started their intake of medication. No, significant results were found for those observations, supporting the SSRI-related effect on the white matter. However, this indicates that learning as well as relearning did not lead to significant alterations.

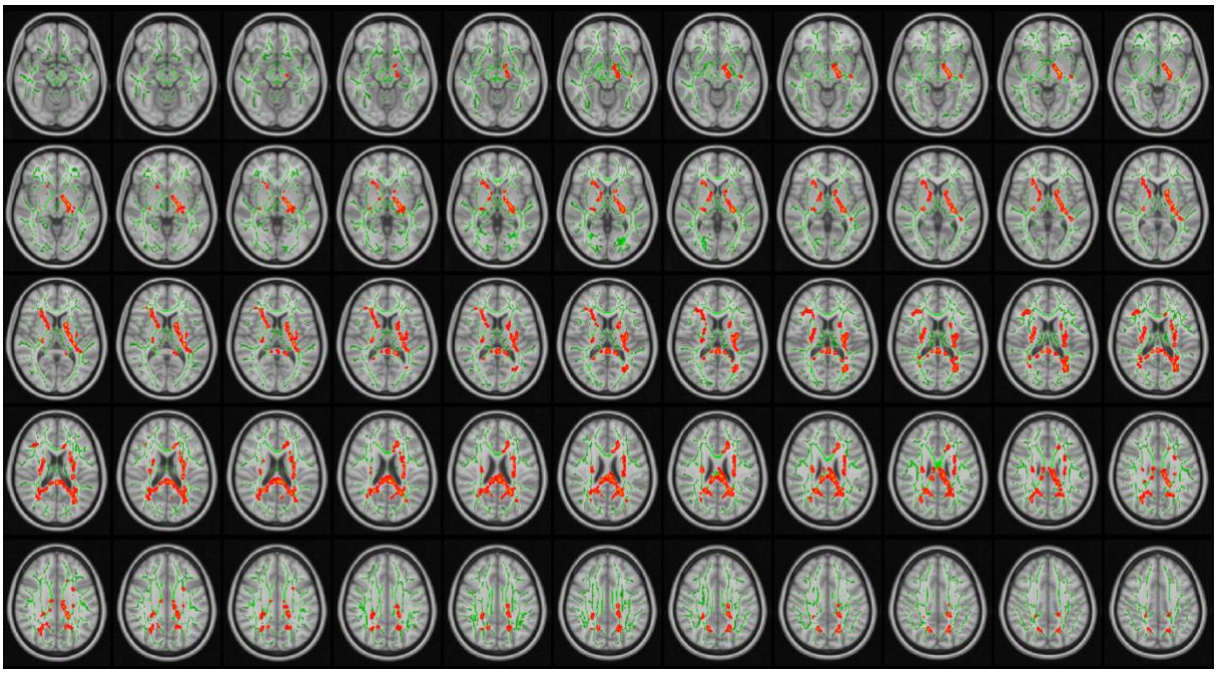

Figure 1: Significant decreases in diffusivity parameters after 3-weeks of SSRI administration. Red areas indicate changes were axial diffusivity (AD) and fractional anisotropy (FA) showed both significant changes (TFCE FWE-corrected p<0.05). Hence, AD results were masked with statistical FA maps before using the "tbss_fill command" within FSL. Statistical maps are overlayed over the mean_FA_skeleton and the MNI152_T1_1mm template provided within the FMRIB Software Library (FSL), Radiological convention, left = right, TFCE: Threshold-free cluster enhancement, FWE: Family-wise error.

Of note, those results were observed for both learning groups combined. We then also investigated putative changes only due to learning. Here, both time periods were compared to assess influences of relearning compared to learning on the white matter. This was calculated for both learning groups combined, as well as for each learning group separately. However, no significant results were found for neither of those investigations.

Discussion

Given numerous reports on the neuroplastic effects of SSRI and its relevancy for neuropsychiatric disorders, we aimed to investigate the influence of escitalopram on white matter microstructure *in vivo* during relearning. We examined no influence when testing between substance and relearning intervention over time and also no effect when comparing separately the escitalopram to the placebo group or relearning groups (with regards to emotional or semantic content). Since we hypothesized an SSRI effect on DTI metrics, we further compared white matter measures pre-post SSRI administration and found widespread FA and AD decreases, but most prominent in the internal capsule, bilaterally and in the corpus callosum. We did not detect such changes in the placebo group nor between time point 1 and 2 for the SSRI group during the learning period before the start of SSRI intake.

Work by our group demonstrated immediate changes in diffusivity parameters following intravenous SSRI-administration. In a PET/MRI study, patients with depression and healthy controls received

citalopram 8 mg, which was found to sufficiently occupy the serotonin transporter (Gryglewski et al., 2019). Citalopram led to attenuated MD, AD and RD in the anterior corona radiata, corpus callosum, external capsule and frontal blade in patients and controls, without affecting FA or increasing any DTI metric (Seiger et al., 2021). Also, short and intensive learning has been found to affect white matter microstructure (Hofstetter et al., 2013), suggesting that cellular rearrangement in this tissue occurs rapidly (Sagi et al., 2012). In comparison to these short-time effects of SSRI, in this study we administered escitalopram for 3 weeks, a timespan which is found reasonable for SSRIs to prompt neuroplasticity and to unfold efficacy in clinical settings (Bauer et al., 2013; Alboni et al., 2017). We found similar results, since FA and AD decreased over time in subjects that received escitalopram. Also, when we tested for the influence of substance over time between both groups, we examined no significant changes in diffusivity measures. Although group comparisons did not yield findings, it is suggested that a decrease in FA and AD is related to the administration of escitalopram, since no such findings appeared in the placebo group or following a learning period (first 3 weeks). In a DTI study in patients with obsessive-compulsive disorder, decreased MD and RD in midbrain regions and striatum were observed, while changes in FA were not detected (Fan et al., 2012). Area specific changes in white matter following SSRI administration overlap only partly, but these findings link SSRI to diminished FA and AD, indicating a reduction in longitudinal water diffusion. Disorder-specific symptoms decreased significantly following 12 weeks of citalopram treatment in patients with obsessive-compulsive disorder in comparison to controls, while FA was higher before treatment initiation and diminished over time in the corpus callosum, internal capsule and adjacent structures to the right caudate (Yoo et al., 2007). Then, decreased FA following learning has previously been associated with learning-related surges of cell density or restrained diffusivity due to axonal branching (Taubert et al., 2010). A recently published multimodal study aimed to reveal the neurobiology of environmental-dependent white matter changes and found a relationship of diffusivity measures and transcription levels of proteins critical for myelination (Sampaio-Baptista et al., 2020). Morphological measures of myelinated axons underly ongoing optimizations, which are essential for precisely timed depolarization, as shown in rodents, where region-specific myelin architecture determines accurate temporal processing for

acoustic processing and localization (Ford et al., 2015). Overall, study findings suggest an effect of escitalopram on white matter tracts, while it is challenging to ascribe white matter changes directly to specific cellular processes (Jones et al., 2013).

For long, human behavior and perception was understood as an effector of neuronal activity, with the synapse as the primary location for cell communication and thus neuroplasticity, while white matter was reduced to a (in-)homogeneous structure serving as a medium for proper information transfer. Intervention studies led to the conception that the plasticity phenomena not only occurs in grey matter, where environmental stimuli are known to shape synaptic organization (Draganski et al., 2004), but are relevant for the reorganization of white matter likewise (Sampaio-Baptista and Johansen-Berg, 2017). Activity-dependent changes of myelination architecture are found to affect neuronal networks (Hartline and Colman, 2007; Ford et al., 2015). Non-pharmacological interventions as motor skill learning or cognitive training have been found to be associated with DTI-changes in healthy subjects and patients with mental disorders. These effects were demonstrated to be time-dependent, since interventions with an interval less than 8 weeks did not generate pre-post differences in white matter (Kristensen et al., 2018). Here, we examined no effects of learning or relearning intervention on DTI measures, indifferent if learning groups with emotional or semantic content were compared or learning groups were pooled together. In the same study sample, metabolic and functional changes have demonstrated after relearning and escitalopram administration. In a task-based fMRI analysis, neuronal activation was found to be decreased in the insula after relearning in subjects that were administered escitalopram (Reed et al., 2021). Further, we found a relationship between escitalopram and relearning when comparing glutamate levels in the hippocampus and thalamus before and after associative relearning (Spurny et al., 2021). These findings underline the effects of escitalopram and learning on various brain measures. Nevertheless, it is probable that learning intensity and duration were designed as insufficient to cause adaptations in the white matter compartment.

Within the group that received escitalopram during reversal learning, half of the subjects developed citalopram blood levels beneath the therapeutic range. In clinical studies, patients receiving SSRIs have generally not been found to significantly benefit from dose escalation strategies, since response rates are found similar for therapeutic dose and high-dose treatment, but less tolerability and acceptability occurred in treatment with higher doses (Adli et al., 2005; Furukawa et al., 2019). Also, already very low doses of citalopram, the racemic precursor substance of escitalopram, lead to a serotonin transporter occupancy of 50 %, while 80 % occupancy was depicted at therapeutic citalopram dosing, that is equivalent to the applied dose of escitalopram (i.e. 10 mg daily) in our study (Meyer et al., 2004; Shapiro, 2018). However, antidepressants are shown to induce brain plasticity in dependence of drug dose. Also, socioeconomic factors were relevant for treatment response, where level of socioeconomic status, which represented an environmental variable, amplified SSRIs efficiency on mood symptoms (Chiarotti et al., 2017; Viglione et al., 2019). Taken together, therapeutic doses of escitalopram 10 mg should have sufficiently stimulated serotonergic neurotransmission and prevented from higher drop-out rates, though mediocre citalopram blood levels across our study individuals could have affected study outcomes.

We aimed to reveal a relationship between SSRI treatment, neuroplastic effects on white matter properties and reversal learning in humans *in vivo*. Results show no effect between chronic escitalopram administration and emotional or semantic relearning on DTI measures. The duration and intensity of study interventions, i.e. administration of escitalopram and learning as the relearning task, might have been chosen insufficiently to induce detectable effects. We demonstrate decreased FA and AD predominantly in several parts of the internal capsule, in the corpus callosum and in the anterior corona radiata following escitalopram administration, though findings of statistical tests that were applied for various hypotheses, did not survive correction for multiple testing for different hypotheses, but survived correction for multiple testing within each run performed with FSL when including numerous brain regions, but have to be interpreted with caution.

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Conflicts of Interest

There are no conflicts of interest to declare regarding the present study. R. Lanzenberger received travel grants and/or conference speaker honoraria within the last three years from Bruker BioSpin MR and Heel and has served as a consultant for Ono Pharmaceutical. He received investigator-initiated research funding from Siemens Healthcare regarding clinical research using PET/MR. He is a shareholder of the start-up company BM Health GmbH since 2019. C. Kraus received travel grants from Roche and AOP Orphan Austria, speaker honoraria from Janssen. D. Winkler received lecture fees/authorship honoraria within the last three years from Angelini, Lundbeck, MedMedia Verlag, and Medical Dialogue.

Ethics approval

This study is part of a larger project that has been approved by the ethics committee of the Medical University of Vienna (EK Nr.: 1739/2016) and performed in accordance with the Declaration of Helsinki (1964). The project is registered at clinicaltrials.gov with the identifier NCT02753738.

Availability of data and material

The full data can be made available upon reasonable request to the corresponding author.

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