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REGULAR RESEARCH ARTICLE

The Influence of Acute SSRI Administration on White Matter Microstructure in Patients Suffering From Major Depressive Disorder and Healthy Controls

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) are predominantly prescribed for people suffering from major depressive disorder. These antidepressants exert their effects by blocking the serotonin transporter (SERT), leading to increased levels of serotonin in the synaptic cleft and subsequently to an attenuation of depressive symptoms and elevation in mood. Although long-term studies investigating white matter (WM) alterations after exposure to antidepressant treatment exist, results on the acute effects on the brain's WM microstructure are lacking.
Methods: In this interventional longitudinal study, 81 participants were included (33 patients and 48 healthy controls). All participants underwent diffusion weighted imaging on 2 separate days, receiving either citalopram or placebo using a randomized, double-blind, cross-over design. Fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity were calculated within the FMRIB software library and analyzed using tract-based spatial statistics.
Results: The repeated-measures ANOVA model revealed significant decreases after SSRI administration in mean diffusivity, axial diffusivity, and radial diffusivity regardless of the group ($P < .05$, family-wise error [FWE] corrected). Results were predominantly evident in frontal WM regions comprising the anterior corona radiata, corpus callosum, and external capsule and in distinct areas of the frontal blade. No increases in diffusivity were found, and no changes in fractional anisotropy were present.
Conclusions: Our investigation provides the first evidence, to our knowledge, that fast WM microstructure adaptations within 1 hour after i.v. SSRI administration precede elevations in mood due to SSRI treatment. These results add a new facet to the complex mode of action of antidepressant therapy. This study was registered at clinicaltrials.gov with the identifier NCT02711215.

Key Words: Selective serotonin reuptake inhibitors, white matter, depression, diffusion tensor imaging, tract-based spatial statistics

Introduction

In line with the monoamine deficiency theory (Delgado, 2000), selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for major depressive disorder (MDD). These antidepressants exert their action by blocking the serotonin transporter, hence elevating the levels of serotonin in the synaptic cleft (Spies et al., 2015). Although under considerable

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Significance Statement

Selective serotonin reuptake inhibitors (SSRIs) are first-line treatment for major depressive disorder (MDD) by blocking the serotonin transporter (SERT), leading to elevated serotonin levels in the synaptic cleft. Whereas long-term effects of SSRIs on brain structure have already been demonstrated, acute effects on the white matter (WM) microstructure have not been investigated yet. Using a placebo-controlled, randomized, double-blind, cross-over design by applying either 8 mg citalopram or placebo (saline) to patients suffering from MDD and healthy controls, changes in diffusivity parameters in the WM were observed already within 1 hour after the start of the administration. We mainly found diffusivity decreases most pronounced in frontal brain regions and areas in and around the corpus callosum due to SSRI administration regardless of the group. Our results deliver the first evidence, to our knowledge, of rapid SSRI effects on the WM of the brain in humans.

discussion, this higher availability of serotonin in the brain is considered a main factor for the improvement of depressive symptoms. In addition to their antidepressant effects and their modulatory properties within the monoaminergic system, SSRIs are strongly linked to neuroplasticity (Kraus et al., 2017), a phenomenon responsible for shaping new connections within the brain triggered by environmental or internal (e.g., cellular) mechanisms (Pascual-Leone et al., 2005; Zatorre et al., 2012). In this regard, animal studies already demonstrated structural adaptions following SSRI administration such as increased cell proliferation and neurogenesis in the hippocampus (Malberg et al., 2000), upregulation of cAMP response element binding protein (CREB), and increased brain-derived neurotrophic factor levels (Nibuya et al., 1996). Not only within the hippocampus but also in the prefrontal cortex neuroplastic effects were shown in the form of dendritic remodeling and alterations in synaptic contacts (Bessa et al., 2009). In addition, elevated glutamate receptor expression was shown, which correlated with dendritic spine number in the rat's forebrain (Ampuero et al., 2010).

Recent studies already observed structural grey matter (GM) alterations in the adult human brain due to SSRI administration. However, results remained inconclusive, as GM decreases and increases were shown in different brain regions. Treatment of at least 8 weeks with SSRIs in patients with social anxiety disorder showed decreases in striatal regions and the thalamus and increases in the cerebellum (Talati et al., 2015). A study with social anxiety disorder patients found only decreases in superior temporal areas and the cerebellum after a 12-week treatment period (Cassimjee et al., 2010). Ten days of SSRI administration in healthy participants showed primarily decreases in the pre- and postcentral gyri, while increases in the posterior cingulate cortex and the precuneus were found (Kraus et al., 2014). However, another study found only increased GM values in the left superior frontal gyrus after 6 weeks of escitalopram administration in remitted panic disorder patients (Lai and Wu, 2013).

Next to GM changes in the human brain, studies observing white matter (WM) alterations due to SSRI administration start to emerge. The properties of the WM microstructure within the brain are preferably measured using diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) (Basser et al., 1994). Tract-based spatial statistics (TBSS) is a frequently used approach to assess changes within the WM. Here, a skeleton of the WM pathways is constructed enabling a voxel-wise analysis of WM microstructure (Smith et al., 2006). Parameters such as axial diffusivity (AD), radial diffusivity (RD), fractional anisotropy (FA), and mean diffusivity (MD) are frequently assessed in this regard, calculated by using the 3 diffusivity parameters: λ_1, λ_2, and λ_3 (Soares et al., 2013). AD (λ_1) delivers information about the diffusion along a tract, while RD gives information about the diffusion perpendicular to the tract $[(\lambda_2 + \lambda_3)/2]$. While MD delivers information about the mean diffusion process in all directions, FA gives additional information regarding the directionality of the diffusion process, indicated by the grade of anisotropy. For further information and formulae, see Alexander et al. (2011).

However, studies investigating WM changes due to SSRI administration featured diverse patient populations and methodological approaches. For example, Yoo et al. 2007 investigated obsessive-compulsive disorder patients before and after a 12-week period of citalopram treatment using DTI and voxel-based morphometry. Their analysis showed higher FA in several areas in patients compared with controls at baseline, while SSRI treatment after 12 weeks led to decreases specifically in the posterior thalamic radiation. However, results were not corrected for multiple comparisons (Yoo et al., 2007). Increased FA metrics were also found in another investigation where remitted patients with panic disorder were assessed after 6 weeks escitalopram therapy. Changes were specifically observed in the right uncinate fasciculus and in the left fronto-occipital fasciculus using TBSS (Lai et al., 2013). Another study with obsessive-compulsive disorder patients after 12 weeks of SSRI treatment could not corroborate those FA changes. Instead, MD and RD decreases in the midbrain and exclusively RD decreases in the striatum were found (Fan et al., 2012). A voxel-based morphometry study using T1-weighted scans also indicated differences in WM areas in depressed patients compared with healthy controls, while SSRI therapy again normalized this difference. However, unspecific WM volume increases and decreases were observed across different regions of the brain (Zeng et al., 2012). No influence on the WM was observed by a recent DTI study using a region of interest approach in depressed patients and healthy controls after 8 weeks of SSRI treatment (Davis et al., 2019).

Hence, studies assessing the long-term influence on the brain's WM exist but differ significantly in results and their methodological approaches. Moreover, no acute effects of SSRI treatment in MDD patients and healthy controls have been investigated so far to our knowledge. To this end, we aimed to assess short-term changes within 1 hour on the WM microstructure in the human brain in people suffering from MDD and healthy controls using DTI and an i.v. SSRI challenge.

Methods

Participants and Study Design

Overall, 81 individuals were included for analysis in this interventional longitudinal study (see flowchart in supplementary Figure 1): 33 patients suffering from MDD and 48 healthy controls (see Table 1 for demographical and clinical information). All participants were scanned 4 times in 2 sessions, before and after receiving either the study drug or placebo using a randomized, double-blind, cross-over design (Figure 1). The i.v. administration of either 8 mg citalopram (Seropram, Lundbeck)

Table 1. Demographics and Clinical Information

Participants	HC	Patients	Statistics	P-value
n	48	33		
Age (y ± SD)	28.0 ± 8.8	29.2 ± 9.6	0.56[a]	.58
Sex (F/M)	27/21	16/17	0.47[b]	.49
Age of onset current episode[c]	—	25.8 ± 12.0		
No. of episodes[d]	—	1.8 ± 1.1		
Length of current episode (mo)[e]	—	16.0 ± 16.3		
Past medication exposure (yes/no)	—	15/18		
HAM-D_{17}	—	22.6 ± 5.1		
BDI	—	28.5 ± 7.8		
MADRS	—	31.2 ± 6.3		

Abbreviations: BDI, Beck Depression Inventory; HAM-D_{17}, Hamilton Depression Rating Scale (17 items); HC, healthy control participants; MADRS, Montgomery-Åsberg Depression Rating Scale.
[a]Two-sample *t* test.
[b]Chi-squared test.
[c]Information not available for 6 patients.
[d]Information not available for 10 patients.
[e]Information not available for 11 patients.

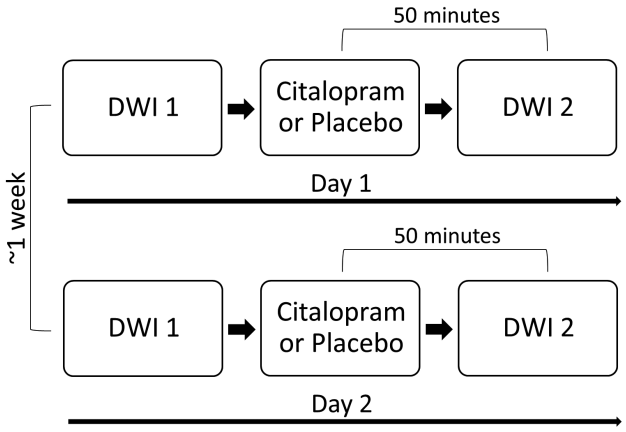

Figure 1. Study design. Healthy controls and people suffering from major depression underwent the same randomized, cross-over, placebo-controlled procedure. DWI, diffusion-weighted imaging.

diluted in 8 mL saline or placebo (saline only) was carried out over 8 minutes using a constant infusion after the baseline scan was acquired. Dosage and timing of citalopram administration were chosen to approximate a previous study investigating citalopram effects (McKie et al., 2005). Another scan was performed 50 minutes after the drug challenge. All participants were examined for general health based on physical examination, medical history, and a structured clinical interview (SCID I and II) for DSM-IV. MDD patients suffered from a moderate to severe depressive episode (Hamilton Scale 17-items [HAM-D] ≥ 18). Participants were medication free for 3 months prior to the measurements and did not receive any psychopharmacological treatment. Exclusion criteria comprised any medical, psychiatric (for healthy controls) or neurological illness, pregnancy, psychopharmacological treatment within the last 3 months, current or former substance abuse, any MRI contraindications, as well as psychiatric comorbidities among MDD patients such as anxiety disorder, bipolar affective disorder, schizoaffective disorder, or schizophrenia. A urine drug screen was performed at the day of inclusion. Participants were recruited through flyers at the Department of Psychiatry and Psychotherapy at the Medical University of Vienna. All participants provided written informed consent prior to participation, and the study was approved by the Ethics Committee of the Medical University of Vienna and was performed according to the Declaration of Helsinki.

DWI Data Acquisition

DWI data were acquired with a 3 Tesla Siemens Biograph mMR 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°). Three nondiffusion reference images (b = 0) were recorded along with the diffusion weighted images (2 before, 1 afterwards) with 30 diffusion encoding directions and a b-value of 1000 s/mm^2. An initial distortion correction was performed automatically on the scanner. The overall scan time for each DWI sequence was 7:03 minutes. Participants were instructed to avoid any kind of movement during the scanning session. In addition, foam pads were used to prevent any form of residual head movement. All scans were visually inspected and data were discarded prior to analysis if data quality was deemed insufficient (see results).

DTI Data Processing

FA, MD, AD, and RD maps were analyzed with the FMRIB software library (FSL) (Smith et al., 2004), version 5.0.11, using the default parameters if not stated otherwise. After an initial brain extraction step (Smith, 2002) with a fractional intensity threshold of 0.1, diffusion data were processed using the *eddy_cuda* command to correct for movements between frames, distortions, and eddy current artefacts (Andersson and Sotiropoulos, 2016). In addition, the newly implemented outlier replacement approach was deployed to account for putative signal dropout due to head movement (Andersson et al., 2016). Subsequently, the diffusion tensors were calculated with *dtifit* using the rotated b-vectors generated during the eddy current correction step. The DTI data were analyzed using TBSS (Smith et al., 2006). FA maps are then brought into standard space using FNIRT (Rueckert et al., 1999; Andersson et al., 2007a, 2007b), and a mean FA skeleton was created including the common tracts of the group. Afterwards, individual aligned FA data from each participant was projected onto the skeleton. Subsequently, this was also applied for the non-FA images (MD, AD, and RD) based on the FA-derived

transformation parameters. To rule out any effects of the participant's head movement between the conditions, we calculated the frame-wise displacement based on the 6 movement parameters and took the median for the analysis.

Statistical Analysis

Acute SSRI effects were assessed within FSL's Randomise tool (Winkler et al., 2014) using 5000 permutations and the Threshold-Free Cluster Enhancement method. This approach is similar to cluster-based thresholding but without the specification of a prior cluster-forming threshold (Smith and Nichols, 2009). Substance and group effects were assessed for FA, MD, AD, and RD. To this aim, the 3-factor design (group: healthy control/MDD, substance: placebo/SSRI, time point: pre-/postinfusion) was first reduced to 2 factors by subtracting the baseline scans from the scans acquired after the drug/placebo challenge within each session. This resulted in 2 datasets per participant, which were entered into a repeated-measures ANOVA model in FSL. In a first run, the group-by-substance interaction was tested and in a second one (after removing the nonsignificant interaction term, see Results), the main effect of substance. To test whether treatment response in patients is associated with DTI parameter changes, correlational analyses were performed. To mitigate the chance that results were driven by motion artefacts, the median framewise displacement (FD) (Power et al., 2012) was calculated for the realignment parameters produced by FSL's eddy function and assessed using a linear mixed-effects model (fitlme in MATLAB 2018a). Group and substance were entered as fixed effects, random intercepts were defined for the participants and the post-pre difference of the median FD was entered as dependent variable. Again, in a first run, the interaction effect was tested and removed afterwards for an unbiased inference on the main effects in a second run. Since the residuals were strongly right-skewed, the dependent variable was rank-transformed (Conover and Iman, 1981) to achieve a more reliable estimation of the significance. Even though the Friedman test is commonly employed in similar scenarios, it was not used here due to major concerns regarding its power and appropriateness (see Zimmerman and Zumbo, 1993 for a comprehensive discussion), which could have yielded false-negative results.

Results

Initially, 88 participants underwent diffusion MRI; however, due to poor data quality or technical problems during the substance application phase, data from 4 patients and 3 control participants had to be eliminated prior to statistical analysis. Hence, data from 81 participants (33 patients and 48 healthy controls) could be used for subsequent analyses. The patient cohort showed a mean HAM-D score of 22.6 ±5.1, a Beck Depression Inventory score of 28.5±7.8 and a Montgomery-Åsberg Depression Rating Scale mean value of 31.2±6.3. Patients and controls did not significantly differ regarding age as revealed by the 2-sample t test ($P = .58$). A chi-squared test did also not show significant differences regarding gender distribution between the 2 groups ($P = .49$) (see Table 1).

The ANOVA model of the TBSS analysis did not reveal a significant interaction effect between group (patients, controls) and substance (citalopram, saline) ($P > .05$). This result indicates that the diagnosis of MDD did not modulate the effect of the study drug.

However, we found a significant main effect of substance on MD, AD, and RD (Figure 2). More specifically, widespread decreases in diffusivity were observed after SSRI administration, most pronounced in frontal brain regions and areas in and around the corpus callosum. These decreases were evident in all 3 parameters, which indicate a reduction in diffusivity following short-term SSRI administration. Main clusters for MD were found for the anterior corona radiata (t = 4.75; MNI: x = −16, y = 31, z = −11), external capsule (t = 3.43; MNI = −28, −9, 18), and the corpus callosum (t = 3.23; MNI = −18, −25, 34). Decreases in AD were also observed in the external capsule (t = 4.35; MNI = −28, −9, 18) and in the genu (t = 4.20; MNI = −12, 32, 9) and the splenium of the corpus callosum (t = 3.51; MNI = −18, −34, 31) and in several clusters in the inferior frontal blade (main cluster: t = 3.66; MNI = −33, 24, 18), while for RD reductions were present in the anterior corona radiata (t = 3.99; MNI = −24, 30, 6) and the superior frontal blade (t = 3.61; MNI = −18, 31, −10). The results were found predominantly in the left hemisphere. For detailed results, please see Table 2. No significant increases in diffusivity and no overall changes for FA were evident. All results reported were family-wise error (FWE) corrected ($P < .05$) using the Threshold-Free Cluster Enhancement approach.

The clusters showing significant decreases in MD, AD, and RD were then correlated with treatment response (absolute HAM-D changes between the 2 time points) assessed after at least 6 weeks of treatment with escitalopram (Cipralex, Lundbeck) in the patient cohort. No significant correlations were found that survived the correction for multiple comparisons. Regarding putative movement artefacts, neither the interaction nor the main effects of the median FD difference were significant ($P > .05$).

Discussion

In this investigation, a randomized cross-over, placebo-controlled design was used to assess the acute effects of 8 mg i.v. administered SSRI citalopram on the WM in depressed patients and healthy controls. The dosage of 8 mg was chosen based on a previous study to minimize the occurrence of side effects that might impair the interpretation of results (McKie et al., 2005). While prior studies demonstrated good tolerability, higher dosages entail the risk of side effects such as nausea (Kapitany et al., 1999). In addition, sufficient occupation at the SERT has been demonstrated using the same dosage of citalopram (Gryglewski et al., 2019). Our results suggest rapid effects within 1 hour on the brain's WM microstructure regardless of the group. We found significant decreases in almost the same WM regions for MD, AD, and RD, with strongest effects in the anterior corona radiata, corpus callosum, and external capsule and in distinct areas of the frontal blade. Overall, most of the observed changes were found in frontal regions of the brain. Interestingly, no increases due to SSRI administration were found and no significant changes were evident for FA. These results are in line with the study conducted by Fan et al. (2012), where after 3 months of SSRI treatment decreases for MD and RD were observed. However, their results showed changes located predominantly around the area of the striatum and the midbrain. The observed MD reductions indicate an overall diminished grade of diffusion along and perpendicular to the tracts. Although RD was slightly diminished, major results were found for AD, which suggests that our observations were mainly driven by the reduction in diffusivity along the main axis of the tract. SSRI administration did not show different effects in depressed patients compared with healthy controls. Although, SSRIs are prescribed for MDD, it seems that they do not exert differential acute effects on WM between groups, which would manifest in different changes in diffusivity. In addition, our results also indicated that changes in

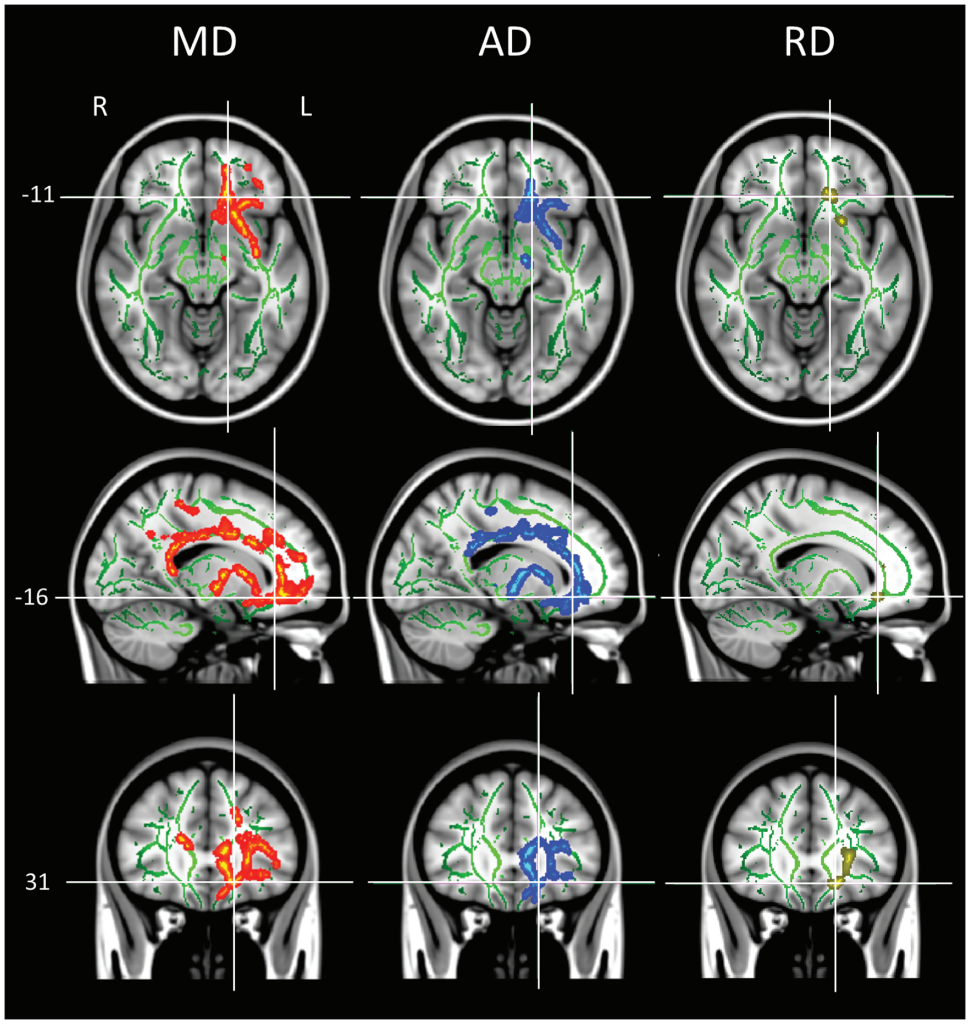

Figure 2. Significant decreases (FWE-corrected, $P<.05$) after SSRI administration in mean diffusivity (MD, red), axial diffusivity (AD, blue), and radial diffusivity (RD, yellow). Crosshair points at the anterior corona radiata (x=−16, y=31, z=−11 in MNI space). Filled significant TBSS results are overlaid on the mean FA skeleton and a standard T1-weighted image. Radiological convention, left=right. FWE, family-wise error; MNI, Montreal Neurological Institute; TBSS, tract-based spatial statistics.

diffusion after SSRI application is independent of treatment response in patients. It is still a matter of discussion how the different diffusion parameters can be interpreted regarding their underlying neurobiology (Jones et al., 2013). This is especially important when no patients with neurological deficits or WM impairments are investigated. Nevertheless, it is known that WM disintegration leads to increases in isotropy due to possible axonal loss and diminished grades of myelination, which is reflected by increases in MD and RD and decreases in FA and to some extent in AD (Soares et al., 2013; Winklewski, 2018). In addition, early landmark studies in animals demonstrated that alterations of axonal properties are tightly linked to AD, while changes in RD are related more closely to myelin alterations (Song et al., 2002, 2003). Our results suggest that acute SSRI administration leads to changes in both parameters. Overall, decreases in these metrics can be coarsely attributed to neural or glial cell alterations comprising astrocytes, oligodendrocytes, or microglia (Beaulieu, 2014). While elevated serotonin levels have been predominantly associated with dendritic spine formation (Ampuero et al., 2010), SSRIs may further elicit changes in axonal quantity, including branching, sprouting, and pruning as well as alterations in axonal density, size, and diameter (Zatorre et al., 2012; Beaulieu, 2014). However, as these processes are rather observed after long-term SSRI administration, other physiological influences, such as axonal swelling (Costa et al., 2018), protein transport (De Vos et al., 2008), or alterations in vascularity (McKie et al., 2005), seem to be more likely to contribute to the observed acute decreases in diffusivity. Recently, it has been shown that even 1 hour of neurofeedback training can induce alterations in WM microstructure and diffusivity parameters (Marins et al., 2019). However, the underlying cellular mechanism of such fast changes are still an ongoing matter of debate and remain a matter of speculation.

After i.v. administration, SERT blockage can be measured almost immediately after SSRI application, while the timing and amplitude of changes in serotonin levels are less clear (Gryglewski et al., 2019). However, the antidepressant effect of SSRIs and an associated improvement in mood is frequently observed with a delay of several weeks (Harmer et al., 2009). This is thought to be linked to downregulation of 5-HT_{1A} autoreceptors due to elevated serotonin stimulation, which takes place over a longer period of time (Gray et al., 2013). After downregulation, a disinhibited neuron releases more serotonin into the extracellular space (Ferrés-Coy et al., 2013). This downregulation is coupled to genomic effects and takes days to weeks; hence, it is probably not related to the observed decreases in diffusivity

Table 2. White Matter Structures With Significant Decreases in MD, AD, and RD.

Structure	Abbreviation	Cluster size	Peak *t*-value	MNI coordinates (mm)		
				x	y	z
MD						
Anterior corona radiata L	ACR-L	2559	4.75	−16	31	−11
		81	3.22	−25	34	−2
External capsule L	EC-L	488	3.43	−28	−9	18
Body of corpus callosum	BCC	272	3.23	−18	−25	34
		61	2.88	−2	3	25
Posterior limb of internal capsule L	PLIC-L	195	3.41	−26	−18	15
Superior frontal blade L	SFB-L	181	3.95	−19	43	21
		103	3.51	−17	26	35
		76	2.95	−13	58	12
Genu of corpus callosum	GCC	159	2.91	13	30	13
Inferior frontal blade L	IFB-L	137	3.57	−31	35	−3
		122	3.39	−28	49	−5
Anterior limb of internal capsule L	ALIC-L	65	2.43	−19	5	12
AD						
External capsule L	EC-L	881	4.35	−28	−9	18
Genu of corpus callosum	GCC	852	4.20	−12	32	9
Splenium of corpus callosum	SCC	420	3.51	−18	−34	31
Inferior frontal blade L	IFB-L	292	3.66	−33	24	18
		189	3.85	−31	35	−1
		142	2.94	−18	19	−12
		118	3.75	−27	28	−10
		54	3.40	−36	27	−8
Superior corona radiata L	SCR-L	107	3.27	−18	9	39
Body of corpus callosum	BCC	105	3.14	5	9	24
		73	2.95	−6	−8	27
		59	3.37	−5	−18	25
		54	3.57	−12	17	25
Anterior limb of internal capsule L	ALIC-L	91	2.69	−16	10	7
Inferior fronto-occipital fasciculus L	IFO-L	43	2.18	−26	10	−12
RD						
Anterior corona radiata L	ACR-L	106	3.99	−24	30	6
Superior frontal blade L	SFB-L	40	3.61	−18	31	−10

Abbreviations: AD, axial diffusivity; MD, mean diffusivity; MNI, **Montreal Neurological Institute**; RD, radial diffusivity; TFCE, **threshold-free cluster enhancement**. Peak *t* values, cluster size, and MNI coordinates are indicated. Only clusters sized ≥ 40 are listed. All clusters withstood correction for multiple comparisons using TFCE at $P < .05$.

in this investigation. Another important and considerably discussed aspect of SSRIs are their neurotrophic properties, stimulating receptors at the postsynaptic neuron, activating second messenger systems (Cassimjee et al., 2010), and even leading to neurogenesis and long-term potentiation (Alboni et al., 2017). The rise of serotonin in the brain generally triggers intracellular signal chains, stimulating CREB activation and leading to increased brain-derived neurotrophic factor levels. There are several possibilities of how CREB can be expressed and activated, for example, by cAMP-dependent protein kinase A, calcium ion-dependent protein kinases, and by mitogen-activated protein kinase cascade (Fossati et al., 2004). However, increases in CREB have been predominantly observed after long-term SSRI administration.

Studies already suggest that depression is reflected in the WM of the brain, as several areas differed between depressed patients and healthy controls (Jenkins et al., 2016; Coloigner et al., 2019). Interestingly, among these regions, diffusion properties seem to be altered in the anterior corona radiata and the corpus callosum. Hence, changes due to acute SSRI administration observed in this study take place partially in those brain regions where previously differences between patients and controls were found. Main diffusivity decreases were observed in frontal regions of the brain, predominantly in the left hemisphere within the anterior corona radiata. A lateralization in this region was already reported in a prior study, where differences in this tract between a bipolar patient cohort and healthy controls were found (Karababa et al., 2015). This specific WM pathway comprises fibers from the thalamus, coming from the internal capsule and finally connecting to prefrontal regions in the cortex (Olivo et al., 2017). As part of the limbic-thalamo-cortical circuitry, brain areas connected by this fiber tract are thought to be involved in processes related to emotion, cognition and attention (Sanjuan et al., 2013) and have also been linked to depression and anxiety (Coloigner et al., 2019), which are targeted by antidepressant therapy. Our results suggest that even the acute administration of SSRIs alters the diffusion properties in this tract. To account for any form of artefacts and given the fact that movements are a major challenge in diffusion studies (Le Bihan et al., 2006), heads of participants were fixated with foam pads during the scanning sessions and the data were thoroughly checked and visually inspected after each processing step. As we could not rule out greater head movement during the SSRI condition compared with placebo, we statistically tested for those differences using the provided movement parameters of each participant. The results revealed

no significant differences between the 2 conditions, indicating no higher degree of movement during the SSRI application compared with placebo. Cardiac activity may also have an influence on MRI results. However, heart rate was not monitored in our study and therefore not included as a covariate in the statistical model. Finally, we cannot conclude and generalize that the results observed in this study also apply to other SSRIs with different molecular profiles. However, it has been shown that citalopram is very specific for the SERT. We assume that SSRIs sharing a similar degree of specificity will induce comparable changes in diffusivity metrics.

In summary, here we provide the first evidence, to our knowledge, for fast WM alterations within 1 hour due to i.v. SSRI administration in a relatively large cohort of 81 participants. The neurobiological underpinnings of depression are still not known, and monoamine reuptake inhibitors seem to alleviate symptomology only after prolonged chronic treatment. This investigation, however, demonstrates SSRIs' effects on the WM immediately after administration in patients and healthy controls, adding a new facet to the action of antidepressant treatment.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Supplementary Figure 1. Flow diagram showing all participants considered for diffusion weighted imaging (DWI) analysis of a multimodal PET/MR project with several imaging branches. A total of 81 participants with available DWI data were included in the final statistical analysis. The study was conducted as a randomized, cross-over, placebo-controlled trial, where patients and healthy controls received selective serotonin reuptake inhibitors (SSRIs) either at measurement day 1 or 2, respectively. As recruitment and measurements are still ongoing, cut-off date for inclusion in this DWI investigation was April 2019.

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Statement of Interest

With no relevance to this work, R. Lanzenberger received travel grants and/or conference speaker honoraria within the last 3 years from Bruker and support from Siemens Healthcare regarding clinical research using PET/MR. S. Kasper received grants/research support, consulting fees, and/or honoraria within the last 3 years from Angelini, AOP Orphan Pharmaceuticals AG, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd., and Takeda. T. Vanicek received speaker honoraria with no relevance to this work and within the last 3 years from Shire. The remaining authors have nothing to disclose.

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