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Effects of antidepressants on brain structure and function in patients with obsessive-compulsive disorder: A review of neuroimaging studies

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ABSTRACT

Obsessive-compulsive disorder (OCD) affects 2–3% of people worldwide. Although antidepressants are the standard pharmacological treatment of OCD, their effect on the brain of individuals with OCD has not yet been fully clarified. We conducted a systematic search on PubMed, Scopus, Embase, and Web of Science to explore the effects of antidepressants on neuroimaging findings in OCD. Thirteen neuroimaging investigations were included. After antidepressant treatment, structural magnetic resonance imaging studies suggested thalamic, amygdala, and pituitary volume changes in patients. In addition, the use of antidepressants was associated with alterations in diffusion tensor imaging metrics in the left striatum, the right midbrain, and the posterior thalamic radiation in the right parietal lobe. Finally, functional magnetic resonance imaging highlighted possible changes in the ventral striatum, frontal, and prefrontal cortex. The small number of included studies and sample sizes, short durations of follow-up, different antidepressants, variable regions of interest, and heterogeneous samples limit the robustness of the findings of the present review. In conclusion, our review suggests that antidepressant treatment is associated with brain changes in individuals with OCD, and these results may help to deepen our knowledge of the pathophysiology of OCD and the brain mechanisms underlying the effects of antidepressants.

1. Introduction

Obsessive-compulsive disorder (OCD) is a severe mental disorder characterized by unwanted and intrusive thoughts (obsessions) and repetitive behaviors (compulsions) (Ruscio et al., 2010). The lifetime prevalence of OCD ranges between 2% and 3% (Ruscio et al., 2010). The onset of OCD tends to occur earlier in males, and childhood-onset OCD is predominantly observed in males. On the other hand, OCD onset in females mostly occurs after puberty and it is often associated with depressive symptoms (Mathes et al., 2019). Blasphemous thoughts are the most common manifestations in men, while hygiene concerns are most commonly observed in women (Mathes et al., 2019). Early age at onset, low or no response to medications, long illness duration, and symptom severity are key factors associated with poor outcomes (Sharma and Math, 2019). Conventional treatments for OCD include cognitive-behavior therapy (CBT) and antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). However, evidence shows that up to 62% of patients may suffer residual symptoms (Bernstein et al., 2019; Eddy et al., 2004; Hoexter et al., 2012). Thus, understanding the underlying psychopathology and modulatory effects on the brain of pharmacological treatments is crucial to elucidate the mechanisms of action of antidepressants in these patients.

Neuroimaging studies, including structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI), have revealed numerous abnormalities in the cortico-striato-thalamo-cortical circuit (CSTC) in patients with OCD, a brain network responsible for the regulation of movement execution, reward-based learning, action inhibition, and control of impulsivity (Calzà et al., 2019; Rădulescu et al., 2017; Yoo et al., 2007). Other

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important networks in OCD include the frontoparietal network (FPN), the salience network (SN), and the default mode network (DMN), which are part of the so-called triple network (Menon, 2011). In particular, the DMN is associated with introspection, and alterations in this network can lead to excessive self-referential thinking in individuals with OCD (Beucke et al., 2014). Differently, the FPN is involved in decision-making, shifting attention, and goal-directed behavior. Dysfunctions in the FPN can cause difficulties in inhibiting repetitive behaviors and shifting attention effectively (Fornaro and Vallesi, 2023). Lastly, the SN plays a role in assigning salience to internal and external stimuli. In individuals with OCD, dysfunction in the SN can result in inappropriate attention allocation and heightened responsiveness to certain stimuli (Bernstein et al., 2019; Gürsel et al., 2020; Menon, 2011).

SSRIs increase serotonin levels in the brain by blocking the reabsorption of serotonin by neurons (Sangkuhl et al., 2009). This results in changes in the activity of the brain circuits involved in regulating mood and anxiety, including corticolimbic network and DMN (Cipriani et al., 2018; Gudayol-Ferré et al., 2015). Notably, SSRIs have been found to be effective in treating OCD by reducing anxiety and compulsions through inhibition of the CSTC circuit (Kim et al., 2019; Tang et al., 2016). Medications, especially SSRIs, have a significant impact on controlling OCD symptoms, and neuroimaging changes after treatment are important for better understanding the underlying mechanisms associated with treatment response. The effects of SSRIs on neuroimaging measures have been previously explored in other disorders. Examples include volume loss in the hippocampus after 12 months of citalopram in schizophrenia (Qi et al., 2021), increased activation of the right insula, thalamus, putamen, and left middle temporal gyrus in response to different facial expressions after two weeks of escitalopram in healthy people (Henry et al., 2013), decreased activation of amygdala-hippocampal regions in response to angry faces after single-dose fluoxetine in depression (Capitão et al., 2019), and reduced axial, mean, and radial diffusivities (AD, MD, and RD) of anterior corona radiata, corpus callosum, and external capsule after intravenous citalopram therapy in depression (Seiger et al., 2021). Long-term use of these medications has also been associated with various brain changes in patients with OCD, including reductions in gray matter volume in the anterior cingulate cortex and the orbitofrontal cortex (OFC) (Cheng et al., 2016; Hoexter et al., 2012); however, reports on the effects of SSRIs on the brain are inconsistent and inconclusive due to different treatments, study durations, and imaging modalities. In this study, we collected all available evidence on structural or functional alterations in patients with OCD treated with antidepressants to clarify the brain mechanisms underlying the clinical efficacy of these drugs.

2. Methods and materials

We conducted a comprehensive literature search using PubMed, Scopus, Embase, and Web of Science of papers published before December 2023. Keywords of the search included "obsessive-compulsive disorder/OCD" and "functional Magnetic Resonance Imaging or fMRI/ Magnetic Resonance Imaging or MRI/ Diffusion Tensor Imaging or DTI" in combination with "Antidepressive Agents/ Antidepressant/ Selective serotonin reuptake inhibitor or SSRI/ Serotonin-norepinephrine reuptake inhibitor or SNRI/ Fluoxetine/ Fluvoxamine/ Sertraline/ Paroxetine/ Citalopram/ Escitalopram/ Clomipramine/ Venlafaxine Hydrochloride." Data selection was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). We included any study that assessed the effects of antidepressants in patients with OCD via MRI, fMRI, or DTI. Reviews and meta-analyses, letters, case reports, case series, pre-print articles, and conference abstracts were not included. We also excluded studies in which subjects were concurrently treated with other therapies, including psychotherapy and antipsychotics. The age and sex of the subjects, publication year and language were not restricted.

3. Results

3.1. Search results

We retrieved a total of 894 studies, 161 of which were duplicates and were therefore removed. In the title/abstract screening, 687 papers did not meet our inclusion criteria and were excluded. After full-text reading, 13 studies were eligible to enter our systematic review (Fig. 1).

3.2. Overview of the studies

A total of 13 studies were included in our study (see Table 1). Of these, six were sMRI (Atmaca et al., 2016a, 2016b; Benedetti et al., 2012; Gilbert et al., 2000; Hoexter et al., 2012; Szeszko et al., 2004), two used DTI techniques (Fan et al., 2012; Yoo et al., 2007), and five were fMRI studies (Bernstein et al., 2019; Beucke et al., 2013; Bhikram et al., 2016; Kim et al., 2020; Shin et al., 2014). The 13 articles included 261 patients with OCD (sample range 8–46) and 219 healthy controls (sample range 8–36). The majority of the included studies assessed adult OCD, and only three explored brain changes in pediatric OCD (Bernstein et al., 2019; Gilbert et al., 2000; Szeszko et al., 2004). Moreover, 11 investigations had a longitudinal design, and two were cross-sectional investigations that compared medicated and unmedicated patients with OCD (Benedetti et al., 2012; Beucke et al., 2013). Symptom severity was assessed with the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Wolff and Wolff, 1991) in the studies that examined pediatric OCD, while the rest employed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989). Details about the antidepressant type, follow-up duration, and comorbidities are reported in Table 1. The majority of the employed drugs were SSRIs, including paroxetine, fluoxetine, fluvoxamine, sertraline, and citalopram. Other pharmacotherapies included TCAs, such as clomipramine, and serotonin-norepinephrine reuptake inhibitors (SNRIs). None of the participants were taking antipsychotics or were doing CBT. Participants of four studies were allowed to take benzodiazepines at the time of the study (Atmaca et al., 2016a, 2016b; Benedetti et al., 2012; Shin et al., 2014).

3.3. sMRI studies

3.3.1. Longitudinal studies

A total of five longitudinal sMRI studies were selected. Among them, two explored changes in thalamic volume and showed similar results. The first study by Gilbert et al. (2000) assessed the effects of 12-week treatment with paroxetine in children (Gilbert et al., 2000). The authors reported that thalamic volumes decreased significantly throughout the treatment period (Gilbert et al., 2000). Similarly, in another study, Atmaca et al. (2016) demonstrated a reduction in thalamic volume, whereas OFC volume did not change after treatment. In contrast to the first study, the participants underwent 12 weeks of therapy with paroxetine, clomipramine, fluoxetine, fluvoxamine, or sertraline, and they were adults. The authors also reported a significant correlation between changes in Y-BOCS scores and changes in pre-to-post-treatment left thalamic volumes of patients with OCD (Atmaca et al., 2016a). Another study with a longitudinal design assessed GM volume changes in patients with OCD going through 12 weeks of fluoxetine or 12 weeks of CBT. After treatment with fluoxetine, GM volume in the left putamen was increased, while no changes were observed in CBT-treated patients (Hoexter et al., 2012).

The remaining studies explored changes in the amygdala and the pituitary gland. The investigation by Szeszko et al. (2004) displayed left amygdala volume reductions in children with OCD after 16 weeks of paroxetine monotherapy. In this trial, all patients with OCD began paroxetine treatment at 10 mg/day, and the dosage was titrated to a maximum of 60 mg/day based on their response (mean ± standard deviation: 38 mg/day ± 16 mg/day). At last, higher paroxetine dosage

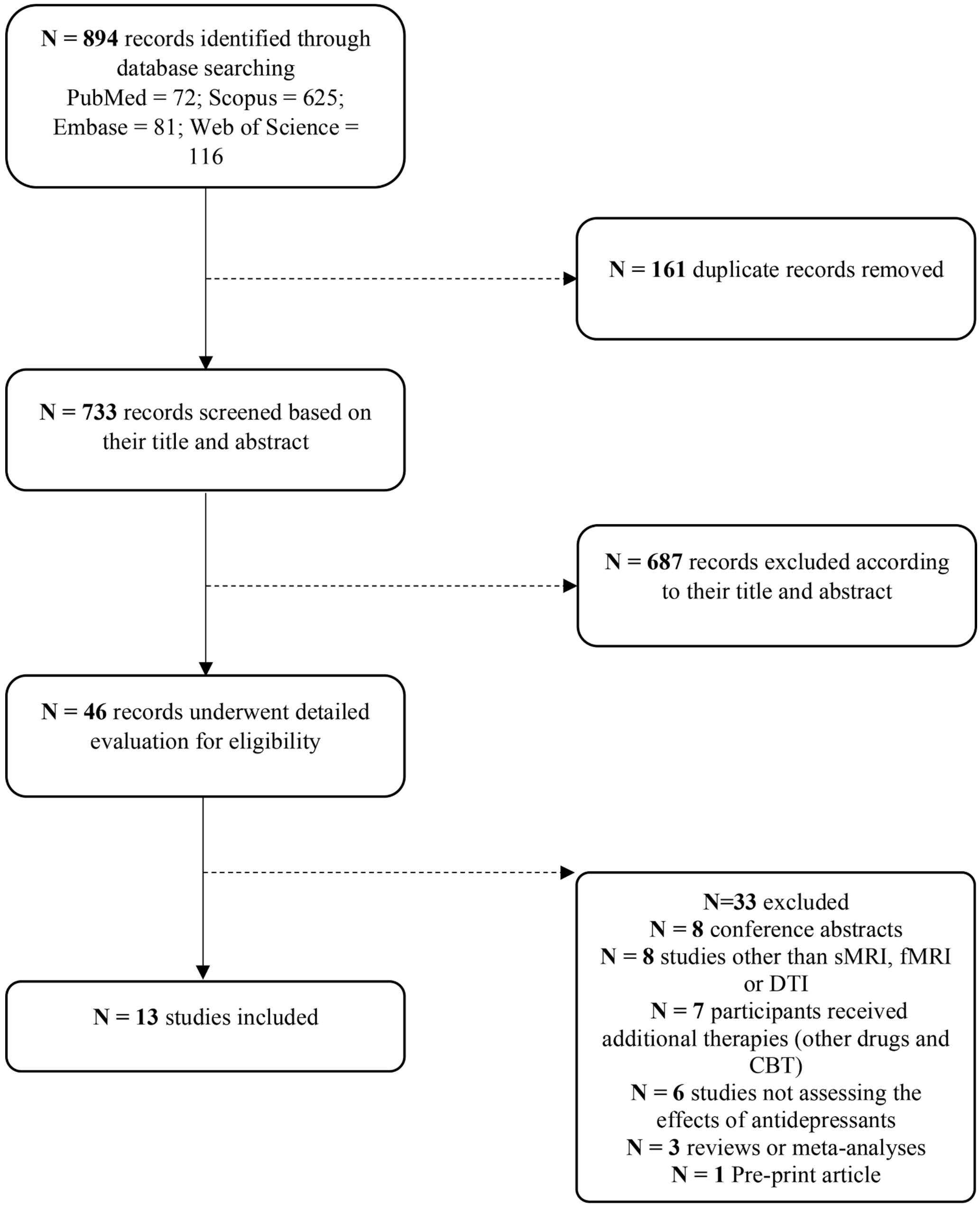

Fig. 1. Flowchart of the study selection.

at the time of the follow-up scan and total cumulative paroxetine exposure between the scans were significantly correlated with the left amygdala volume reductions (Szeszko et al., 2004). Finally, another study by Atmaca et al. (2016) showed the effects of paroxetine, clomipramine, fluoxetine, fluvoxamine, and sertraline on pituitary volume in OCD. The results showed that pituitary gland volume increased significantly after 12 weeks of treatment. The authors tested if this increase was correlated with disease severity but found no significant results (Atmaca et al., 2016b).

3.3.2. *Cross-sectional studies*

Benedetti et al. (2012) examined sMRI data in 15 unmedicated patients with OCD and 25 medicated with clomipramine, fluvoxamine, or sertraline in a cross-sectional manner. Their results showed that gray matter (GM) volume in the head of the left caudate nucleus was lower in medicated patients compared with the unmedicated group. Furthermore, patients with higher adverse childhood experiences had greater left caudate nucleus GM than those with lower adverse childhood experiences (Benedetti et al., 2012).

3.4. *DTI studies*

3.4.1. *Longitudinal studies*

Two longitudinal DTI studies were included. Yoo et al. (2007) explored fractional anisotropy (FA) changes in the patients with OCD after citalopram monotherapy. In their study, they performed a voxel-based morphometry technique using a 1.5 Tesla magnetic resonance scanner from which they derived the T1-weighted and DTI data. The authors reported an FA reduction in the posterior thalamic radiation on the right parietal lobe of the patients after 12 weeks. They also showed that mood disorder comorbidities (depressive and dysthymic disorders) and severity of OCD were not associated with FA reduction in this area (Yoo et al., 2007). In the other study by Fan et al. (2012), the investigators conducted a voxel-based analysis on patients with OCD.

Table 1
Characteristic data of included studies and their findings.

Study	Participants (F/M ratio)	Age in years (mean ± SD)	Baseline OCD severity	Comorbidities	Medication	Duration of follow-up (if longitudinal)	Imaging parameters and metrics	Outcome measures	Main findings
Gilbert et al., 2000	21 OCD (14/7) 21 HC (14/7)	12.35 ± 2.93 12.47 ± 2.64	31.30 ± 4.37 (CY-BOCS)	**OCD at the time of study:** 7 (33%) Anxiety disorders, 2 (9%) Dysthymia, 2 (9%) Oppositional defiant disorders, 1 (4%) Attention-deficit disorder without hyperactivity, 1 (4%) Trichotillomania **HC at the time of study:** None (0%)	Paroxetine	12 weeks	sMRI 1.5 T GM Volume	Thalamus volume	↓ **volume** in the thalamus in patients after treatment
Szeszko et al., 2004	11 OCD (8/3) 11 HC (8/3)	11.80 ± 3.0 13.3 ± 2.4	28.5 ± 6.4 (CY-BOCS)	Patients with a lifetime history of unipolar or bipolar disorder, psychosis, eating disorders, substance abuse or dependence, Sydenham's chorea, Tourette syndrome, other tic-related conditions, conduct disorder, significantly debilitating medical or neurological conditions, pervasive developmental disorders, mental retardation, or learning disorders were excluded.	Paroxetine	16 weeks	sMRI 1.5 T GM Volume	Amygdala volume	↓ **volume** in the left amygdala in patients after treatment
Yoo et al., 2007	13 OCD (5/8) 13 HC (5/8)	27.8 ± 7.3 26.9 ± 7.0	30.2 ± 4.6 (Y-BOCS)	**OCD at the time of study:** 2 (15%) MDD, 1 (7%) Dysthymic disorder **HC at the time of study:** None (0%)	Citalopram	12 weeks	DTI 1.5 T FA	Whole-brain microstructure	↑ **FA** in the corpus callosum extending to the temporal lobe, the WM around the lentiform nucleus, including the posterior limb and retrolenticular part of the internal capsule bilaterally, and the lateral aspect of the right caudate nucleus in patients compared to HC at baseline ↑ **FA** in the body of the corpus callosum and the right superior temporal region in patients compared to HC after treatment ↓ **FA** in the posterior thalamic radiation on the right parietal lobe in patients after treatment
Benedetti et al., 2012	15 unmedicated OCD (5/10) 25 medicated OCD (9/16)	34.4 ± 8.72 36.12 ± 10.82	31 ± 4.53 32.96 ± 4.95 (Y-BOCS)	N/A	Clomipramine, Fluvoxamine, or Sertraline	N/A	sMRI GM Volume	Whole-brain volume	↓ **volume** in the head of the left caudate nucleus medicated compared with

(continued on next page)

Table 1 (*continued*)

Study	Participants (F/M ratio)	Age in years (mean ± SD)	Baseline OCD severity	Comorbidities	Medication	Duration of follow-up (if longitudinal)	Imaging parameters and metrics	Outcome measures	Main findings
									unmedicated patients
Fan et al., 2012	27 OCD (10/17) 23 HC (8/15)	25.5 ± 7 28.8 ± 7.6	22.0 ± 4.9 (Y-BOCS)	Subjects with comorbid DSM-IV axis I psychiatric disorders and a history of neurologic disorders were excluded.	Fluoxetine, Fluvoxamine, Sertraline, or Paroxetine	12 weeks	DTI 1.5 T FA, MD, AD, and RD	Whole-brain microstructure	↓ **MD** in the right midbrain and ↓ **RD** in the left striatum and right midbrain in patients after treatment
Hoexter et al., 2012	19 OCD (12/7) 36 HC (23/13)	31.2 ± 11.1 27.8 ± 7.8	25.1 ± 5.2 (Y-BOCS)	Subjects with past/current substance abuse or dependence and a lifetime history of psychosis were excluded.	Fluoxetine	12 weeks	sMRI 1.5 T GM Volume	Orbitofrontal, anterior cingulate and temporolimbic cortices, striatum, and thalamus volumes	↓ **volume** in the left putamen, bilateral medial OFC, and left anterior cingulate cortices in patients compared to controls at baseline ↓ **volume** in the bilateral medial OFC and left anterior cingulate cortices in patients compared to HC after treatment ↑ **volume** in the left putamen in patients after treatment
Beucke et al., 2013	23 unmedicated OCD (12/11) 23 medicated OCD (14/9) 23 HC (14/9)	29.1 ± 9.1 32.2 ± 9.6 31.9 ± 8.6	20.0 ± 5.7 21.6 ± 7.2 (Y-BOCS)	**Medicated OCD lifetime diagnoses:** 12 (52%) MDD, 2 (8%) Specific phobia, 1 (4%) Hypochondria, 1 (4%) Social phobia, 1 (4%) Dysthymia, 1 (4%) Bulimia, 1 (4%) Anorexia, 4 (17%) GAD, 2 (8%) Panic disorder, 1 (4%) Agoraphobia, 1 (4%) Adjustment disorder **Unmedicated OCD lifetime diagnoses:** 12 (52%) MDD, 1 (4%) Specific phobia, 2 (8%) Hypochondria, 2 (8%) Substance abuse, 6 (26%) Social phobia, 1 (4%) Dysthymia, 1 (4%) Bulimia, 1 (4%) Anorexia, 1 (4%) GAD, 2 (8%) Panic disorder, 1 (4%) Somatoform disorder	SSRI, SNRI, and TCA (not specified)	N/A	fMRI 1.5 T rs-FC	Whole-brain rs-FC	↓ **rs-FC** in the ventral striatum in medicated compared with unmedicated patients
Shin et al., 2014	17 OCD (5/12) 21 HC (10/11)	26.4 ± 6 26 ± 5.3	21.2 ± 7.6 (Y-BOCS)	N/A	Escitalopram	16 weeks	fMRI 3 T rs-FC	Whole-brain rs-FC	↑ **rs-FC** in the right posterior cingulate cortex left posterior insula, left temporal gyrus, right ventral frontal cortex, right ventral anterior prefrontal cortex, bilateral dorsolateral

(*continued on next page*)

Table 1 (*continued*)

Study	Participants (F/M ratio)	Age in years (mean ± SD)	Baseline OCD severity	Comorbidities	Medication	Duration of follow-up (if longitudinal)	Imaging parameters and metrics	Outcome measures	Main findings
									prefrontal cortex, and right dorsal frontal cortex in patients after treatment ↓ **rs-FC** in the left posterior cingulate cortex and bilateral occipital cingulate cortex in patients after treatment
Atmaca et al., 2016	14 OCD (8/6) 14 HC (7/7)	33.02 ± 3.76 30.35 ± 4.09	26.4 1 ± 4.22 (Y-BOCS)	Subjects with psychiatric comorbidities (except depression) were excluded.	Paroxetine, Clomipramine, Fluoxetine, Fluvoxamine, or Sertraline	12 weeks	sMRI 1.5 T GM Volume	Orbitofrontal cortex and thalamus volumes	↑ **thalamic volume** in patients compared to HC at baseline ↓ **OFC volume** in patients compared to HC at baseline **No changes in thalamic volume** in patients and HC after treatment ↓ **OFC volume** in patients compared to HC after treatment ↓ **thalamic volume** in patients after treatment **No changes in OFC volume** in patients after treatment
Atmaca et al., 2016 (2)	14 OCD (8/6) 14 HC (7/7)	33.02 ± 3.76 30.35 ± 4.09	26.4 1 ± 4.22 (Y-BOCS)	Subjects with psychiatric comorbidities (except depression) were excluded.	Paroxetine, Clomipramine, Fluoxetine, Fluvoxamine, or Sertraline	12 weeks	sMRI 1.5 T GM Volume	Pituitary gland volume	↑ **pituitary gland volume** in patients after treatment
Bhikram et al., 2016	8 OCD (4/4) 8 HC (4/4)	27.6 ± 2.3 25.5 ± 2.9	21.8 ± 4.4 (Y-BOCS)	**OCD lifetime diagnoses:** 2 (25%) MDD, 1 (12%) Panic disorder **HC lifetime diagnoses:** None (0%)	Citalopram	2 weeks	fMRI 3 T Provocation task	Whole-brain neural activation	↓ **activation** in the OFC in patients after treatment
Bernstein et al., 2019	14 OCD (6/8) 14 HC (9/5)	13.4 ± 2.6 13.4 ± 2.9	24.7 ± 6.6 (CY-BOCS)	**OCD at the time of study:** 4 (26.7%) ADHD, 4 (26.7%) MDD, 12 (80%) GAD, SAD, and/or social anxiety **HC at the time of study:** None (0%)	Sertraline	12 weeks	fMRI 3 T rs-FC	Whole-brain rs-FC	↑ **rs-FC** in the right putamen with left frontal cortex/ insula and the left putamen with the left frontal cortex and the pre- and post-central cortices in patients after treatments
Kim et al., 2020	17 OCD (5/12) 21 HC (10/11)	26.4 ± 6 26 ± 5.3	30.4 ± 4.1 (Y-BOCS)	**OCD at the time of study:** 9 (52.9%) depressive disorder **HC at the time of study:** None (0%)	Escitalopram	16 weeks	fMRI 3 T Tower of London planning task	DAN, CON, LFPN, RFPN, and DMN neural activation	**No changes in activation** in all networks of patients before and after treatment

Abbreviations: AD: axial diffusivity; ADHD: attention-deficit/hyperactivity disorder; CON: cingulo-opercular network; CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale; DAN: dorsal attention network; DMN: default mode network; DSM: Diagnostic and Statistical Manual of Mental Disorders; DTI: diffusion tensor imaging; F/M: female/male ratio; FA: fractional anisotropy; fMRI: functional magnetic resonance imaging; GAD: generalized anxiety disorder; GM: gray matter; HC: healthy control; LFPN: left frontoparietal network; MD: mean diffusivity; MDD: major depressive disorder; N/A: not applicable; OCD: obsessive-compulsive disorder; OFC: orbitofrontal cortex; RD: radial diffusivity; RFPN: right frontoparietal network; rs-FC: resting-state functional connectivity; SAD: separation anxiety disorder; SD: standard deviation; sMRI: structural magnetic resonance imaging; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; WM: white matter; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.

Their results showed that patients with OCD treated with 12 weeks of fluoxetine, fluvoxamine, sertraline or paroxetine had reduced MD in their right midbrain and reduced RD in their left striatum and right midbrain. These microstructural alterations were not associated with clinical symptoms of the patients. Similarly to the previous study, they used a 1.5 Tesla magnetic resonance scanner from which they gathered the data of T1-weighted and DTI (Fan et al., 2012).

3.5. fMRI studies

3.5.1. Longitudinal studies

Four longitudinal fMRI studies were selected, two of which assessed the resting-state functional connectivity (rs-FC) in patients with OCD. The study by Bernstein et al. (2019) highlighted rs-FC changes in children after 12 weeks of sertraline monotherapy. These changes included increased rs-FC in the right putamen with the left frontal cortex/insula and the left putamen with the left frontal cortex and the pre- and post-central cortices in patients (Bernstein et al., 2019). The authors also showed that elevated rs-FC in the left putamen was significantly correlated with clinical improvement in CY-BOCS scores (Bernstein et al., 2019). Similarly, the study by Shin et al. (2014) assessed rs-FC of patients with OCD before and after 16 weeks of escitalopram therapy (Shin et al., 2014). They observed elevated rs-FC of various regions, including the right posterior cingulate cortex, left posterior insula, left temporal gyrus, right ventral frontal cortex, right ventral anterior prefrontal cortex, bilateral dorsolateral prefrontal cortex, and right dorsal frontal cortex in medicated patients with OCD compared to their baseline. Moreover, the rs-FC of the left posterior cingulate cortex and the bilateral occipital cingulate cortex decreased after treatment. They also showed a negative correlation between the percentage of connectivity degree changes in the right ventral frontal cortex and the percentage changes in all obsession, compulsion, and total Y-BOCS scores (Shin et al., 2014).

Two other longitudinal fMRI studies assessed the activation of brain regions in OCD. Bhikram et al. (2016) employed a provocation task-based fMRI to explore the potential effects of a single dose of intravenous citalopram in OCD (Bhikram et al., 2016). The provocation-task runs included two pre-infusion, two mid-infusion, and two post-infusion runs. Each run lasted six minutes and consisted of seven picture blocks presenting aversive, neutral, or scenes corresponding to common OCD symptoms (i.e., checking, washing, or hoarding). Patients with OCD exhibited reductions in OFC activity after the citalopram infusion compared with their baseline (Bhikram et al., 2016). Finally, Kim et al. (2020) employed the Tower of London planning tasks to assess brain network activation changes before and after 16 weeks of monotherapy with escitalopram (Kim et al., 2020). In brief, this task comprised three conditions: in the first condition, participants were shown ball tower pictures and had to calculate the minimum number of moves necessary for the first set to become the second set of ball towers; in the second condition, participants were asked to count the number of balls presented in a picture series; and in the last condition, participants had to count the moved balls across the pictures. The authors included two study groups, 17 patients with OCD and 21 matched healthy controls, in this trial, and their study showed no significant group-by-time interaction effects at baseline and follow-up (Kim et al., 2020).

3.5.2. Cross-sectional studies

Only one cross-sectional fMRI study was retrieved. Using rs-FC as outcome measure, Beucke et al. (2013) compared two groups of unmedicated and medicated patients with OCD with SSRIs, SNRIs, or TCAs and observed lower levels of rs-FC in the ventral striatum in medicated patients compared to unmedicated patients (Beucke et al., 2013).

4. Discussion

Our results, although not consistently replicated, suggest that the use of antidepressants could be associated with structural brain changes in patients with OCD, located mostly in the thalamus, striatum, amygdala, OFC and midbrain. Furthermore, functional studies showed evidence that the antidepressant effect may be reflected in OFC activity and rs-FC in the ventral striatum, FPN, DMN, and CSTC circuit. In the following paragraphs, we will discuss the individual areas that presented structural or functional changes after antidepressant treatments in patients with OCD.

4.1. Thalamus

The thalamus is a core region in the pathophysiology of OCD, as shown by the increased volume and metabolism of the thalamus in patients with OCD before treatment (Atmaca et al., 2007; Baxter, 1992; Kim et al., 2001), which is reversible in response to SSRI therapy (Saxena et al., 2002). The dysfunction of this sensory-motor gateway to the cortex, which plays a role in information filtering, is a key factor in compulsive-like behaviors and anxiety in OCD (Gonçalves et al., 2011; Nakao et al., 2014; Ward, 2013). Previous studies showing the role of partial thalamotomy in OCD treatment also emphasized the importance of thalamic changes in the pathophysiology of OCD (Chiocca, 1990). A growing body of evidence indicates that the thalamus is a highly serotonergic region (Chugani et al., 1998; Oke et al., 1997). Given the fundamental role of serotonergic pathways in thalamo-cortical activity and development, it is not surprising to observe volumetric changes in the thalamus in response to SSRIs (Rhoades et al., 1994). Interestingly, a study investigating the effect of CBT on the thalamus in pediatric patients with OCD found that the reductions in thalamic volume were likely due to effective SSRI treatment rather than spontaneous improvement or general response to treatment (Rosenberg et al., 2000). Furthermore, an analysis of local cerebral metabolic rates of glucose in adult patients with OCD using fluorodeoxyglucose positron emission tomography (FDG-PET) showed a reduction in left thalamus metabolism after successful SSRI treatment (Baxter et al., 1992). Importantly, the FA values of drug-naïve patients with OCD are typically higher in areas with thalamic radiation. The observed FA changes in these patients may indicate thalamus excitation or disinhibition, as higher FA values are correlated with increased density and myelination of fibers (Yoo et al., 2007). This deficit in the modulation of cortico-striato-thalamic pathways may explain intrusive thoughts, which are a core psychopathological feature of OCD (Modell et al., 1989; Mori et al., 2006; Rauch and Jenike, 1993). However, there was no association between the severity of symptoms and changes in DTI parameters in patients with OCD in the studies included in our review, possibly due to their small sample size (Fan et al., 2012; Yoo et al., 2007).

4.2. Striatum

Previous FDG-PET studies showed a decline in striatal activity in response to antidepressant therapy in patients with OCD, which is in line with our results (Baxter et al., 1992; Saxena et al., 1999). Furthermore, Fan et al. (2012) reported that SSRI therapy reversed abnormal myelin integrity in the left striatum and right midbrain of patients with OCD (Fan et al., 2012). This could be partially explained by the neuroprotective effect of SSRIs through the brain-derived neurotrophic factor (BDNF), which stimulates oligodendrocytes and improves central nervous system myelination (Hunsberger et al., 2022; Xiao et al., 2010). Data show that compulsive symptoms result from an imbalance between the goal-directed and habitual corticostriatal connectivity, which relates to caudate and putamen, respectively (Peng et al., 2022). It is thought that dysfunctions in the striatum, predominantly in the caudate nucleus, impair thalamic gating, causing hyperactivity within the OFC and leading to intrusive thoughts (Del Casale et al., 2011). Previous evidence reported that OCD is associated with an increase in the caudate's head volume, with greater GM volumes in the basal ganglia associated with more severe OCD (Radua and Mataix-Cols, 2009; Scarone et al., 1992).

As previously demonstrated in FDG-PET studies, changes in caudate morphology appear to be linked to abnormal functional responses and an increase in metabolism, which is reduced by treatment (Benkelfat et al., 1990; Linden, 2006). Studies reported that alterations in putamen are even more likely to be involved in OCD pathophysiology than caudate abnormalities (Gilbert et al., 2000). Interestingly, despite Bernstein et al. (2019) reported an enhanced rs-FC between the right putamen and the left frontal cortex/insula following SSRIs (Bernstein et al., 2019), Saxena et al. (2002) found a reduction in the metabolism of the right caudate and putamen after the administration of paroxetine hydrochloride in patients with OCD (Saxena et al., 2002). Methodological differences, heterogeneous and small samples of OCD cases, and matching criteria could partially explain these inconsistencies.

Although serotonergic dysfunction is the focus of the majority of current hypotheses about neurotransmitter abnormalities in OCD, impairment of the dopaminergic system may also be linked to the observed neuroanatomical alterations (Korsgaard et al., 1985; Szechtman et al., 1999). Given the indirect effect of serotonin on dopamine inhibition and the evidence from animal studies that dopamine systems are involved in the development of OCD, these systems may also contribute to the observed striatal volumetric changes after SSRI administration.

4.3. Amygdala

A study carried out by Szeszko et al. (2004) reported significant alterations in another core area of OCD psychopathology, the amygdala (Szeszko et al., 2004). Due to its central role in emotional processing and fear and anxiety conditioning, abnormalities in this structure contribute to compulsive behaviors associated with OCD (Bechara et al., 1995; Davis, 1992, 1997; Szeszko et al., 1999). It has been shown that decreased inhibitory tone due to an impaired OFC, combined with excessive input of sensory stimulation due to a weak operculo-insular system, results in hyperactivation of the amygdala in OCD (Pujol et al., 2004). As serotonin is believed to be involved in amygdala function, SSRIs would be effective in treating OCD by targeting the amygdala (Kawahara et al., 1993; Sommer et al., 2001; Zangrossi Jr et al., 1999). Furthermore, SSRI administration is associated with reduced stress-induced Fos-like immunoreactivity in the medial amygdala, suggesting alterations in neuronal activation (Lino-de-Oliveira et al., 2001). On the other hand, the link between the amygdala and other serotonergic areas involved in the pathophysiology of OCD, such as the thalamus, may also contribute to explaining the observed change (Gilbert et al., 2000; Goodman et al., 1989; Oke et al., 1997).

4.4. OFC

Multiple studies have supported the role of OFC abnormalities in the pathophysiology of OCD in both children and adults (Lázaro et al., 2009; Pujol et al., 2004; Valente Jr et al., 2005). OFC plays a role in emotion, reinforcement learning, and flexible behavior, all strongly modulated by serotonin (Noonan et al., 2012; Wilson et al., 2014). Existing literature shows that low levels of serotonin in OFC lead to the development of OCD obsessions (Maia and Cano-Colino, 2015). Additionally, the pathophysiology of OCD appears to be associated with excessive glutamatergic neurotransmission in the OFC and its projections to the striatum (Maia and Cano-Colino, 2015). Consistent with the finding of reduced OFC activity after citalopram infusion in patients with OCD (Bhikram et al., 2016), an FDG-PET study reported reduced local cerebral glucose metabolism in OFC after clomipramine treatment in patients with OCD, as evidenced by no difference in glucose metabolic rates in this region compared to controls (Benkelfat et al., 1990).

4.5. FPN-DMN

In addition to cortico-striato-thalamic dysfunctions, growing evidence suggests that more brain circuits are involved in OCD, particularly the FPN (Stern et al., 2012; Zhang et al., 2011) and the DMN (Stern et al., 2012). The interactions between the brain regions within these networks facilitate disengagement from internal thoughts in healthy individuals (Greicius et al., 2003; Stern et al., 2012). Therefore, disrupted correlation between FPN and DMN at rest in patients with OCD could lead to an imbalance between internally-focused processes and external information, resulting in excessive focus of patients on internal scenarios that are incompatible with external stimuli (Stern et al., 2012). If OCD is a network disease, SSRI treatment could restore the proper balance between brain networks in these patients (Shin et al., 2014).

4.6. Midbrain

Increasing evidence indicates decreased availability of the serotonin transporter in the brainstem components of patients with OCD (such as the midbrain), which could change significantly with the use of SSRIs (Hesse et al., 2005; Stengler-Wenzke et al., 2006). Of note, Kim et al. (2019) proposed the raphe nucleus as a potential biomarker in OCD, as they observed higher functional connectivity of the right nucleus-left middle temporal gyrus in SSRI non-responders in comparison with SSRI responders in a group of patients with OCD (Kim et al., 2019). Studies showed close connections between the raphe nuclei and the serotonin system along the brainstem (Fan et al., 2012). It is noteworthy that the raphe nuclei mainly innervate another key region involved in OCD pathophysiology, the OFC, with dense projections from the dorsal raphe nucleus and fewer projections from the median raphe nucleus (Roberts, 2011).

4.7. The overall effect of medications on neuroimaging findings

In this study, we summarized the alterations of neuroimaging metrics in patients with OCD treated with antidepressants. Large-scale studies have been conducted by the ENIGMA consortium assessing differences between medicated and unmedicated patients with OCD. For example, in one study, the authors found no difference between unmedicated patients and healthy controls by conducting a shape analysis of the subcortical structures. Differently, medicated patients had a lower shape thickness of the putamen, thalamus, and hippocampus and a higher thickness of the pallidum and caudate nucleus compared to healthy controls (Fouche et al., 2022). Moreover, in an fMRI study, the authors assessed the whole-brain and regional functional connectivity of patients with OCD and controls, aiming to find a diagnostic biomarker through machine learning analysis. Among all models discriminating medicated, unmedicated, and healthy controls, the best classification performance was achieved in the classification of medicated subjects versus healthy controls (Bruin et al., 2023). All these findings imply a significant effect of medications on neuroimaging findings, and that some of the alterations originally attributed to OCD itself could be the result of the medications used.

4.8. Limitations

This review presents several limitations. In most studies, the sample size was relatively small, which may have negatively affected the results. The included studies were small in number (i.e., 13) and most were not conducted recently. Additionally, the patients were heterogeneous in terms of age, duration and severity of the disease, type of administered antidepressants, and duration of treatment. There were also differences among studies in terms of methodological approaches, such as study design, pre- and post-processing imaging methodologies, and imaging techniques. Finally, the regions of interest of the included studies varied considerably, ranging from a single brain region to the entire brain. The accompanying publication bias could also have significantly affected our findings. All of these limitations question the generalizability of our findings.

Despite these limitations, sMRI, fMRI and DTI imaging showed evidence of structural and functional changes in response to antidepressants in brain regions such as the thalamus, striatum, amygdala, OFC, and midbrain, suggesting that there may be a potential role for neuroimaging techniques to clarify the brain mechanisms underlying the effect of antidepressant medications in OCD.

5. Conclusions

The reported alterations in brain structure and function may be a general consequence of treatment with antidepressants or an epiphenomenon of the pathogenesis of OCD itself. For example, an increase in connectivity of the left temporal gyrus, insula, and putamen has been reported in healthy people after SSRIs (Henry et al., 2013), similar to the findings in patients with OCD (Bernstein et al., 2019; Shin et al., 2014). Moreover, alterations in prefrontal cortex activation have been consistently reported in depression after SSRI treatment (Wessa and Lois, 2015), similar to what has been observed in OCD (Bhikram et al., 2016; Shin et al., 2014). Overall, future studies on different populations, including people with OCD and other psychiatric disorders, along with healthy controls, are needed to clarify the disorder-specific effects of antidepressants on the brain. Moreover, future neuroimaging studies on populations with larger sample sizes are required to gain a deeper understanding of structural and functional brain alterations and their relationship with clinical symptoms following antidepressant treatment in patients with OCD.

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CRediT authorship contribution statement

Homa Seyedmirzaei: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Nikoo Bayan:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Mohammad Amin Dabbagh Ohadi:** Writing – review & editing, Writing – original draft. **Giulia Cattarinussi:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Fabio Sambataro:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are available from the corresponding author (FS) upon reasonable request.

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