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REVIEW ARTICLE

Do first-line treatments for obsessive-compulsive disorder impact brain structure and function? A systematic review

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Objective: To examine studies investigating structural and functional brain changes in individuals receiving first-line treatments for obsessive-compulsive disorder (OCD), including cognitive-behavioral therapy (CBT) or selective serotonin reuptake inhibitors (SSRIs).
Methods: This systematic review analyzed 26 neuroimaging studies involving 958 participants with OCD, using magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), resting-state functional magnetic resonance imaging (rsfMRI), and diffusion tensor imaging (DWI) to examine brain volume, cortical thickness, functional connectivity, and white-matter integrity before and after treatment.
Results: Both CBT and SSRI were associated with structural and functional brain changes in distinct neural circuits. CBT was associated with increased activation within the frontoparietal network, enhanced white-matter integrity in frontal and temporal regions, and reduced connectivity between emotional processing areas, such as the amygdala and the ventromedial prefrontal cortex. SSRIs, in contrast, were associated with increased left putamen volume, decreased activity in the insula and middle temporal gyrus, and modified white-matter properties within the striatum and midbrain.
Conclusions: Both CBT and SSRIs modulate brain networks involved in executive control, emotion regulation, and sensorimotor integration, suggesting complementary neuroplastic effects and potential biomarkers of treatment response in OCD.
Systematic review registration: PROSPERO, CRD42024545876

Keywords: Functional magnetic resonance imaging; diffusion tensor imaging; cognitive behavioral therapy; selective serotonin reuptake inhibitors; structural magnetic resonance imaging

Introduction

Obsessive-compulsive disorder (OCD) is the fourth most prevalent psychiatric disorder,[1] affecting approximately 2-3% of the global population.[2] OCD is characterized by obsessions, defined as intrusive, unwanted, and repetitive thoughts, images, impulses, or urges that often elicit significant anxiety,[3] and compulsions, which consist of repetitive behaviors or mental acts performed in response to obsessions, typically adhering to rigid rules or seeking to achieve a sense of "completeness."[3]

OCD not only impairs individual well-being but also reduces quality of life and affects family dynamics.[4] These challenges are exacerbated by high unemployment rates among individuals with OCD, which exceed 38%.[4] This far-reaching disorder requires effective treatments to mitigate symptoms and improve overall functioning. The literature identifies several therapeutic approaches for OCD.[5] Among these, the most effective are cognitive behavioral therapy (CBT)[6] and selective serotonin reuptake inhibitors (SSRIs),[7] both of which have been shown to produce significant clinical improvements.[8]

Understanding the neurobiological underpinnings of OCD is crucial to elucidating its clinical symptoms and informing treatment development.[9] A vast body of evidence from magnetic resonance imaging (MRI) studies reveals consistent brain abnormalities in individuals with OCD, including volumetric enlargements in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and thalamus – key nodes of the cortico-striato-thalamo-cortical (CSTC) circuit.[9,10] These alterations also encompass reduced cortical thickness in frontoparietal regions, white-matter integrity deficits in superior fronto-striatal tracts, and dysregulated functional connectivity within the salience, default mode, and frontoparietal networks (FPN). Such changes seem associated with disruption of core processes, including error detection, inhibitory control, habit formation, emotion regulation, and cognitive flexibility, thereby perpetuating obsessive thoughts and compulsive behaviors.[9] Recent evidence further confirms

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hyperconnectivity in limbic-cortical circuits and hypoactivation during cognitive tasks, highlighting the neurocircuitry underpinnings of OCD.[10] Despite this convergence, mechanisms remain incompletely understood, with variability attributable to symptom dimensions, comorbidities, and developmental stage.[9,10]

Emerging evidence suggests that both CBT and SSRIs can modify brain networks.[11,12] However, the putative effects of these treatments on brain structure and function are diffuse and vary significantly. Thus, this systematic review aims to examine studies focusing on brain changes observed in individuals with OCD who received treatment with either CBT or SSRIs. By exploring structural and functional changes, we aim to advance the understanding of the neurobiological mechanisms possibly associated with treatment response and to provide insights into how first-line treatments could contribute to clinical improvement.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) 2024 as CRD42024545876.

Eligibility criteria

Studies were included if: i) they were conducted in adults (age $\geqslant$ 18 years) with a diagnosis of OCD based upon the criteria of any international classification system (e.g., DSM-5); ii) they assessed the effects of first-line OCD treatments, specifically CBT and/or SSRIs/the SRI clomipramine (CMI), on brain structure or function by means of pre- and post-treatment neuroimaging using structural MRI (sMRI), functional MRI (fMRI), resting-state fMRI (rsfMRI), or diffusion tensor imaging (DWI); iii) they were based on interventional studies; iv) they compared the intervention to any control condition or to no control, including no treatment, waitlist, placebo, or another psychological intervention; v) they were primary studies published in English in peer-reviewed journals from 1995 to 2024 (Supplementary Material S1). Studies were included regardless of whether the participants were outpatients or inpatients. Any formats of CBT (either individual or group), any length of treatment (in weeks), and any treatment intensity (frequency of sessions per week) were allowed. CBT was defined as any psychotherapeutic treatment involving at least one active component of CBT, such as exposure and response prevention and/or cognitive therapy, as established in prior meta-analyses. Concurrent psychiatric medication was not considered an exclusion criterion, acknowledging that many patients with OCD in routine clinical practice receive medications.

Search strategy

In order to obtain the most up-to-date information on the topic of interest, we conducted a search across three distinct databases (PubMed, Embase, and Lilacs), covering the period from 1995 to 2024. As noted above, this review focused on two modalities of first-line OCD treatment, CBT and SSRIs, and their possible effects on the brain.

The search strategies for each treatment modality in the different databases can be found in Supplementary Table S1.

Quality assessment

To evaluate the quality of the retrieved publications, we used the Physiotherapy Evidence Database (PEDro) scale.[13] The quality of evidence from the studies is presented in Supplementary Table S2.

Data extraction

Two authors (AMN and RMFS) independently evaluated the titles and abstracts based on the inclusion criteria. Following this, both authors jointly reviewed the full texts of relevant articles for eligibility. In the event of any discrepancies, a third author (DLCC) was consulted to facilitate resolution. Rayyan[14] software was employed during this stage. The article selection process considered not only adherence to the inclusion criteria but also the scientific quality of studies, taking into account their design and variables aimed at assessing study quality. More details can be found in the flowchart in Figure 1.

Results

We identified a total of 727 studies. After removing 33 duplicates, 702 studies were excluded based on title and abstract screening as they did not meet our inclusion criteria. Following a thorough full-text review, 25 studies were included, and one additional study was incorporated after a hand search of the references, bringing the total to 26 studies (Table 1).

Three studies utilized sMRI, eight used fMRI, 10 used rsfMRI, and five used DWI. Sixteen studies investigated cognitive CBT alone, six focused exclusively on SSRIs, and four examined a combination of CBT and SSRIs. A total of 958 individuals (49.6% female) with OCD participated in these 26 studies, all of which employed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) to measure symptom severity. The SSRIs used in the studies included sertraline, fluoxetine, citalopram, and fluvoxamine. CBT interventions were administered alone, as cognitive-coping therapy, and as exposure with response prevention.

Brain structure

Alterations in brain volume were a common finding across the reviewed studies, underscoring the impact of pharmacological and psychotherapeutic interventions on gray-matter structures. In a randomized clinical trial involving 36 participants, a significant increase in left putamen volume was observed after 12 weeks of SSRI treatment, while no such change was noted in the CBT group.[27] Of note, both treatment groups had smaller left putamen

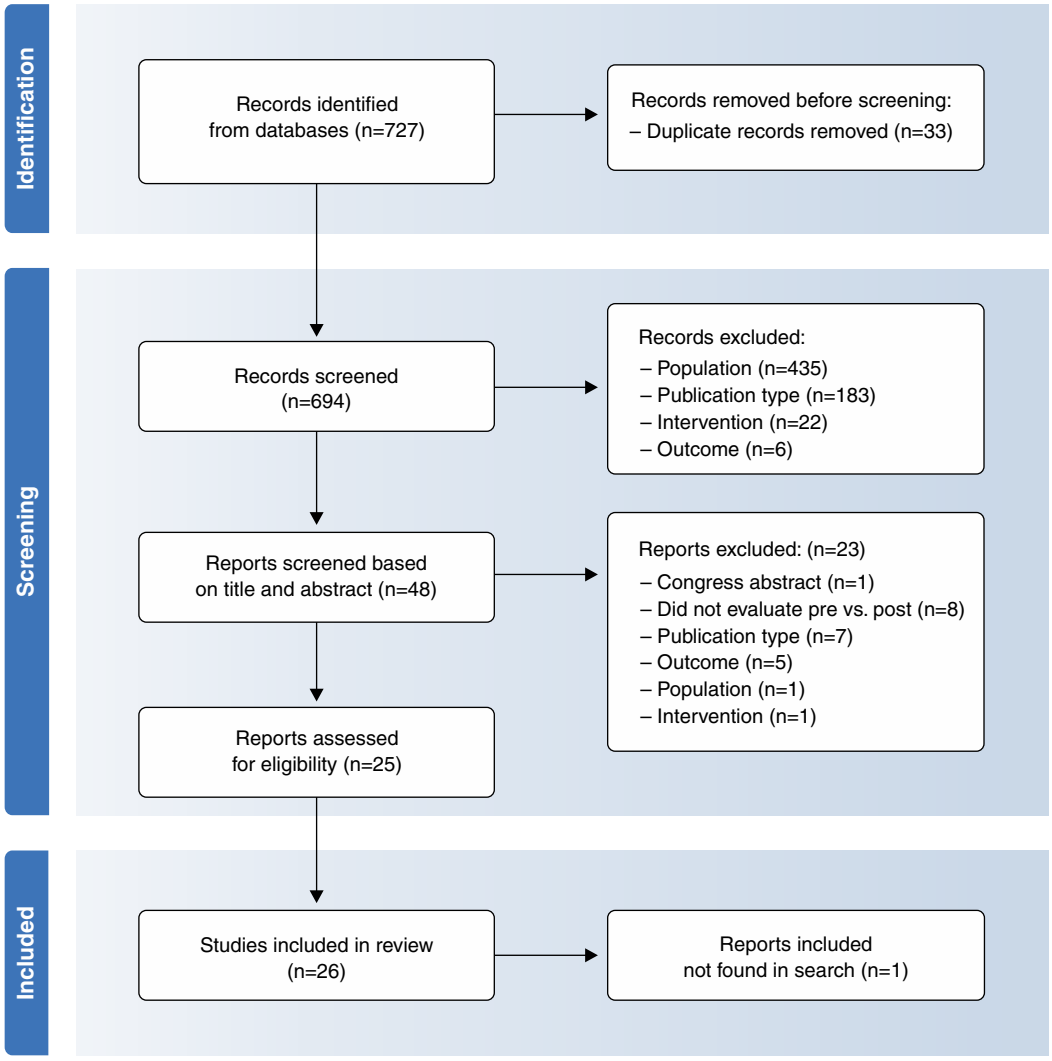


Figure 1 Flowchart of the study selection.

volumes compared to controls before treatment.[27] On the other hand, decreased thalamus volume and increased OFC volume were reported in a smaller cohort of 12 individuals with OCD treated with CBT and an equal number of controls.[15] In contrast, the same research group later observed that CBT did not alter the pituitary gland volume after 16 weeks of treatment in 81 individuals with OCD when compared to 12 controls without OCD.[16]

No studies examining the effects of CBT or SSRIs on cortical thickness in individuals with OCD were identified at the time of writing.

Brain functioning

rsfMRI studies revealed several changes in brain connectivity following CBT and SSRI treatments. After 4 weeks of intensive CBT, Feusner et al.[22] demonstrated an increase in small-worldness and clustering coefficient within brain networks in 17 adults with OCD, indicating a change in connectivity patterns following treatment. Fullana et al.[24] found a significantly decreased connectivity between the basolateral amygdala (BLA) and ventromedial prefrontal cortex (vmPFC) following 12 weeks of CBT in 73 individuals with OCD. Decreased functional connectivity across multiple brain regions was noted after 12 weeks of CBT in 45 unmedicated individuals with OCD, including the connectivity between the centromedial amygdala and the left middle temporal gyrus (MTG), the right centromedial amygdala and left middle occipital gyrus, and the right BLA and left middle occipital gyrus, while increased connectivity was observed between the right inferior parietal lobule and the left centromedial amygdala.[25]

CBT was also associated with decreased functional connectivity in the left dorsolateral prefrontal cortex (DLPFC) and an increased degree of centrality in the bilateral superior occipital gyrus in 20 individuals with OCD.[29] In addition, decreased functional connectivity between the left DLPFC and right OFC was observed after CBT treatment.[29] However, a later study by the same group involving 57 individuals with OCD found no

Table 1 Summary data of included studies

Author	Mean age (years)	n	Intervention duration (weeks)	Participant characteristics	Baseline medication	Treatment	Comparators	Neuroimaging	Clinical outcomes (Y-BOCS) (mean difference)	Neuroimaging outcomes (pre vs. post)
Atmaca et al.[15]	30.2	12	12	OCD patients	Not reported	CBT	Healthy control	sMRI	-7.70	No significant change in pituitary gland volume
Atmaca et al.[16]	30.1	12	12	OCD patients	Not reported	CBT	Healthy control	sMRI	-8.30	↓ Thalamus and ↑ OFC
Becker et al.[17]	31.2	111	12	OCD adolescents and adults	SSRI	CBT	SMT	fMRI	-11.20	↑ FPN and ↓ FPN-DMN
Brecke et al.[18]	30.2	32	12	OCD patients	Not reported	CBT	Healthy control	DWI	-15.60	No significant alterations
Block et al.[19]	30.1	116	12	OCD adolescents and adults	SSRI	CBT	SMT	fMRI	-7.50	No significant alterations
Cao et al.[20]	28.5 (responders)	34	12	OCD patients	Unmedicated	CBT	Healthy control	DWI	-14.90	↓ Global network clustering and nodal clustering at the left lingual gyrus, left middle temporal gyrus, left precuneus, and left fusiform gyrus
Fan et al.[21]	25.5	27	12	OCD patients	Unmedicated	SSRI	Healthy control	DWI	-11.90	↓ RD in the left striatum and right midbrain ↓ MD in the right midbrain
Feusner et al.[22]	34.0	17	4	OCD patients	SSRI	CBT	None	rsfMRI	-9.40	↑ Small-worldness and clustering coefficient in brain networks
Freyer et al.[23]	36.1	20	8-12	OCD patients	SSRI	CBT	Healthy control	fMRI	-9.10	↑ Basal ganglia
Fullana et al.[24]	34.2	73	12	OCD patients	SSRI	CBT	Healthy control	rsfMRI	-6.70	↓ BLA - ventromedial prefrontal cortex
Gao et al.[25]	34.2	45	12	OCD patients	Unmedicated	CBT	Healthy control	rsfMRI	-13.30	↓ Left centromedial amygdala and left middle temporal gyrus, right centromedial amygdala and left middle occipital gyrus, left BLA and left middle temporal gyrus, left inferior temporal gyrus and left middle occipital gyrus, right BLA and left middle occipital gyrus, right superficial amygdala and right middle temporal gyrus↑ Right inferior parietal lobule and left centromedial amygdala, left and right superficial amygdala
Han et al.[26]	24.3	10	16	OCD patients	Unmedicated	SSRI	Healthy control	fMRI	-3.40	↑ Ventral frontal, striatal, and limbic/paralimbic regions, including the caudate, ventrolateral prefrontal cortex, rostral ACC, thalamus, insula, and hippocampus ↓ Right middle temporal gyrus
Hoexter et al.[27]	31.5	38	12	OCD patients, treatment-naive	Drug-naive	CBT/ SSRI	Healthy control	sMRI	-8.60	↑ Left putamen in SSRI group
Kim et al.[28]	26.4	17	16	OCD patients	SSRI	SSRI	Healthy control	fMRI	-9.20	↑ DAN-DMN and DAN-left FPN

Continued on next page

Table 1 (*continued*)

Author	Mean age (years)	n	Intervention duration (weeks)	Participant characteristics	Baseline medication	Treatment	Comparators	Neuroimaging	Clinical outcomes (Y-BOCS) (mean difference)	Neuroimaging outcomes (pre vs. post)
Li et al.[29]	30.3	20	12	OCD patients, treatment-naive	Drug-naive	CBT	Healthy control	rsfMRI	-11.95	↓ Left DLPFC and right OFC, ↑ occipital gyrus
Li et al.[30]	20.1	41	8	OCD patients	Not reported	CBT	Healthy control	rsfMRI	-11.95	No significant alterations
Ma et al.[31]	32.3	59	4	OCD patients	None	CBT + SSRI	SSRI	rsfMRI	-21.60	↓ Insula, putamen, and postcentral gyrus in left cerebrum↑ Occipital medial gyrus, occipital inferior gyrus, and lingual gyrus in right hemisphere in CBT and CBT + SSRI groups
Moody et al.[32]	33.4	43	4	OCD patients	SSRI	CBT	Healthy control	rsfMRI	-8.50	↑ Bilateral frontal pole, cerebellum, caudate, and thalamus, right dorsal anterior cingulate, precuneus, middle frontal gyrus, inferior frontal gyrus, precentral gyrus, superior frontal gyrus, intracalcarine cortex, left lingual gyrus, posterior cingulate, superior lateral occipital, posterior insula, and parietal operculum
Nabeyama et al.[33]	32.3	11	12	OCD patients	SSRI	CBT	Healthy control	fMRI	-23.00	↑ Cerebellum and parietal lobe↓ OFC, middle frontal gyrus, and temporal
Nakao et al.[34]	30.7	10	12	OCD patients	Unmedicated	CBT or SSRI	Healthy control	fMRI	-6.70	↑ Cerebellum and parietal cortex↓ OFC, DLPFC, and ACC
Shin et al.[35]	26.4	25	16	OCD patients	Drug-free	SSRI	Healthy control	rsfMRI	-9.20	↑ Frontoparietal module
Van der Straten et al.[36]	30.6	34	12	OCD patients	SSRI	SSRI	None	fMRI	-8.00	↑ Cerebellum, posterior insula, caudate nucleus, hippocampus, and occipital and prefrontal cortex↓ Insula
Yang et al.[37]	31.0	22	12	OCD patients	Unmedicated	CBT	Healthy control	rsfMRI	-12.10	↓ Right OFC, bilateral DLPFC, left cerebellum, and vermis↑ Left caudate
Yoo et al.[38]	27.8	13	12	OCD patients	Drug-naive	SSRI	Healthy control	DWI	-13.60	↓ FA in the internal capsule, corpus callosum, and right caudate
Zhao et al.[39]	29.9	31	4	OCD patients	SSRI	CBT + SSRI	Healthy control	rsfMRI	-15%	No significant alterations
Zhong et al.[40]	29.9	85	12	OCD patients	Unmedicated	CBT	Healthy control	DWI	-5.80	↓ FA right putamen nucleus↑ FA right middle frontal gyrus, left OFC, right cerebellum, and left middle temporal gyrus

ACC = anterior cingulate cortex; BLA = basolateral amygdala; CBT = cognitive behavioral therapy; DAN = dorsal attention network; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; DWI = diffusion tensor imaging; FA = fractional anisotropy; fMRI = functional magnetic resonance imaging; FPN = frontoparietal network; MD = mean diffusivity; MPFC = medial prefrontal cortex; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; RCT = randomized controlled trial; RD = radial diffusivity; rsfMRI = resting-state functional MRI; sMRI = structural MRI; SMT = standard medical treatment; SSRI = selective serotonin reuptake inhibitor; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

significant changes in brain function after 8 weeks of CBT.[30]

Ma et al.[31] reported a decreased amplitude of the low-frequency fluctuation (ALFF) in the insula, putamen, and postcentral gyrus of the left hemisphere, while an increase in ALFF was observed in the medial occipital gyrus, inferior occipital gyrus, and lingual gyrus of the right hemisphere after 4 weeks of treatment with either CBT or CBT combined with SSRIs in 59 individuals with OCD. No significant changes were observed in the SSRI-only group.[31] Increased connectivity in the right dorsal anterior cingulate, caudate, precuneus, middle and inferior frontal gyri, precentral gyrus, and superior frontal gyrus was demonstrated after 4 weeks of CBT.[32]

Enhanced small-world efficiency in the frontoparietal module was observed after 16 weeks of SSRIs treatment in 25 individuals with OCD.[35] Following treatment, patients with OCD exhibited reduced regional homogeneity (ReHo) in the right OFC, bilateral DLPFC, left cerebellum, and vermis. In contrast, an increase in ReHo was observed in the left caudate following 12 weeks of CBT in 22 individuals with OCD.[37] Zhao et al.[39] did not observe changes in low-frequency fluctuations after 4 weeks of CBT + SSRIs in 31 individuals with OCD.

Task-based fMRI studies also revealed distinct patterns of brain activation following treatment. Becker et al.[17] found increased FPN density and decreased FPN-default mode network (DMN) density after 12 weeks of CBT in 111 individuals with OCD. In contrast, no significant differences were observed in a randomized clinical trial with 116 individuals with OCD compared to healthy controls after CBT.[19]

Freyer et al.[23] demonstrated increased basal ganglia activation following 8-12 weeks of CBT in 20 individuals with OCD. Han et al.[26] reported increased task-switching activity in the ventral frontal, striatal, and limbic/paralimbic regions, including the caudate nucleus, ventrolateral prefrontal cortex, rostral ACC, thalamus, insula, and hippocampus. Decreased activity was observed in the right MTG after 16 weeks of SSRI treatment in 10 unmedicated individuals. Additionally, using the Tower of London planning task, increased connectivity between the dorsal attention network (DAN)-DMN and DAN-left FPN was observed after 16 weeks of SSRI treatment in 17 individuals with OCD.[28] Following 12 weeks of CBT treatment, during the Stroop task (executive control), the cerebellum and parietal lobe showed increased activation, whereas the OFC, middle frontal gyrus, and temporal regions showed decreased activation.[33] Provocation-related activation decreased in the orbitofrontal, DLPFC, and anterior cingulate cortices, whereas the Stroop task-related activation increased in the parietal cortex and cerebellum after 12 weeks of SSRIs or CBT treatment in 10 previously unmedicated individuals.[34] After 12 weeks of fluoxetine treatment in 25 individuals with OCD, a reduction in insula activity was observed during symptom provocation. Comparisons between treatment groups revealed widespread and distinct neural changes across several brain regions, including the cerebellum, posterior insula, caudate nucleus, hippocampus, and both the occipital and prefrontal cortices. These changes were associated with tasks involving emotional processing, such as emotional face matching and symptom provocation, as well as response inhibition assessed through the stop-signal task.[36]

Diffusion tensor imaging (DWI)

Following 12 weeks of CBT, increased fractional anisotropy (FA) values were found in the right middle frontal gyrus, left OFC, right cerebellum, and left MTG, as well as reduced FA values in the right putamen, in 85 individuals with OCD.[40] On the other hand, Fan et al.[21] demonstrated a reduction in radial diffusivity (RD) in the left striatum and right midbrain, as well as a reduced mean diffusivity (MD) in the right midbrain, following 12 weeks of SSRI treatment in 27 unmedicated individuals with OCD. Yoo et al.[38] reported decreased FA in the internal capsule, corpus callosum, right caudate, and right posterior thalamic radiation after 12 weeks of SSRI therapy in 13 individuals with OCD. In addition, Cao et al.[20] found a decrease in global network clustering and nodal clustering at the left lingual gyrus, left MTG, left precuneus, and left fusiform gyrus after 12 weeks of CBT in a sample of 34 unmedicated individuals with OCD. Brecke et al.[18] found no significant changes in FA, MD, or RD after 12 weeks of CBT in 32 individuals with OCD as compared to healthy controls.

Discussion

This systematic review synthesizes neuroimaging evidence showing how first-line treatments for OCD (CBT and SSRIs/CMI) target core abnormalities in the CSTC circuit and associated networks that underpin obsessive-compulsive symptomatology. CBT consistently elicited structural normalization (thalamus volume reduction, OFC expansion), enhanced network topology (increased small-worldness/clustering), frontotemporal white matter remodeling (increase in FA), and amygdala-prefrontal decoupling, suggesting that CBT strengthens inhibitory control to disrupt compulsive loops. SSRIs, conversely, promoted striatal volumetric growth (left putamen), DMN/DAN connectivity normalization, and fronto-striatal task-related hyperactivation, reflecting serotonergic restoration of salience processing and habit suppression. Convergent effects across modalities on error monitoring circuits suggest shared therapeutic mechanisms, while distinct signatures highlight the heterogeneity of OCD neurobiology and offer precision psychiatry potential.

Regarding CBT, sMRI studies showed a reduction in thalamus volume and an increase in OFC volume. rsfMRI findings revealed significant alterations in connectivity, such as reduced functional connectivity between the left DLPFC and right OFC, and increased connectivity in regions such as the right inferior parietal lobule and left centromedial amygdala. Additionally, CBT promoted enhanced network organization, reflected in increased small-worldness and clustering coefficients. fMRI findings demonstrated increased activation in regions such as the prefrontal cortex, basal ganglia, and ventral frontal-striatal circuits. DWI studies revealed increased FA in the right

middle frontal gyrus, left OFC, right cerebellum, and left MTG, while FA was reduced in the right putamen. Furthermore, CBT modulated lower-frequency brain activity, as evidenced by changes in ALFF and ReHo in cortical and subcortical regions.

As for SSRIs, sMRI revealed an increase in left putamen volume, with no other significant changes in brain volume. In rsfMRI, SSRIs normalized connectivity within networks such as the DMN and DAN. fMRI findings showed increased activation in regions like the basal ganglia, thalamus, prefrontal cortex, and ventral frontal-striatal circuits. DWI indicated decreased FA in the internal capsule, corpus callosum, and right caudate, as well as reduced RD and MD in the left striatum and right midbrain. While SSRIs influenced lower-frequency activity, findings were less consistent compared to CBT. Notably, SSRIs did not alter ALFF in the same way as CBT, and no significant changes in ReHo were reported in the SSRI groups.

It is important to note that several studies did not report significant neuroimaging alterations following CBT or SSRI/CMI treatment, highlighting the variability in treatment response across individuals. Differences in methodology, sample sizes, and imaging protocols likely contributed to this variability. Furthermore, studies that combined CBT with SSRIs/CMI suggested that the combination of these treatments may lead to different neural responses. The results of tasks involving cognitive control, such as the Stroop and Tower of London tasks, further supported the involvement of brain regions responsible for executive control and decision-making. For instance, increased activation in the cerebellum and parietal lobes was observed during executive tasks after CBT, while SSRI treatment altered activation in emotional processing regions.

Overall, both CBT and SSRIs/CMI consistently modulated key neural circuits involved in executive control, emotional regulation, and sensorimotor integration, underscoring their role in OCD symptomatology. However, the presence of inconsistent findings warrants further investigation, preferably with larger samples and harmonized data collection. Below, we address the most prominent findings regarding brain structure and function before and after first-line treatments for OCD, as demonstrated by each imaging modality.

Structural magnetic resonance imaging (sMRI)

The volumetric changes observed in this review are consistent with prior research emphasizing the role of gray-matter alterations in the neurobiology of OCD. Atmaca et al.[15] reported that individuals with OCD had larger bilateral thalamus and OFC volumes compared to a control group. After CBT, there was a reduction in bilateral thalamus volume and an increase in the left OFC volume. Although left OFC volume reductions are frequently observed in OCD patients, the authors proposed that sample size (n=12) may have influenced these findings.[15] This suggests that CBT may promote structural adaptations that enhance emotional regulation and reward processing, potentially improving psychological well-being. However, despite observing thalamic reductions and increased left OFC volume, the same research group noted no significant changes in pituitary volume post-CBT.[16] This indicates that CBT may induce region-specific brain volume changes, suggesting that neuroplasticity may vary across brain regions. Such variability could be influenced by pharmacological dosages[41] and clinical factors like cortisol levels, which are linked to brain structural changes.[42]

Hoexter et al.[27] observed a significant reduction in the left putamen volume in an SSRI-treated group after 12 weeks, a change not mirrored in the CBT-treated group. Both groups showed smaller left putamen volumes compared to controls, but these reductions were not significant post-intervention. Despite these structural changes, both groups exhibited significant clinical improvement. Furthermore, Hoexter et al.[43] found that clinical improvement in SSRI-treated patients was associated with changes in the right middle lateral OFC, while CBT-related improvement was linked to the right mPFC. These findings underscore that CBT and SSRIs elicit distinct volumetric changes in regions implicated in OCD. Considering these sMRI findings, both interventions seem to induce brain volume changes associated with clinical improvement.

Cortical thickness

OCD is associated with reduced cortical thickness in frontoparietal regions.[44] Previous findings from our group indicated that variations in OFC thickness distinguish between responders and non-responders to first-line treatments for OCD.[45] Additionally, OFC thickness was identified as a predictor of treatment response for both CBT and SSRIs, highlighting the importance of this region in regulating emotional responses and decision-making.[45] This predictive capability aligns with the growing body of evidence supporting precision psychiatry approaches aimed at optimizing therapeutic outcomes in OCD.

Similarly, Yang et al.[46] demonstrated that larger right entorhinal cortex thickness could predict symptom improvement in OCD patients. These findings further emphasize the significance of cortical thickness as a biomarker for treatment response. However, the current literature is largely limited to predictive models and has not directly assessed how CBT or SSRIs influence cortical thickness over time.[46] To address this gap, future studies using sMRI should investigate potential treatment-induced changes in cortical thickness to gain a deeper understanding of the neuroplasticity underlying therapeutic interventions in OCD.

Resting-state functional magnetic resonance imaging (rsfMRI)

Research using rsfMRI has shed light on the neural mechanisms underlying OCD and how first-line treatments influence brain network reorganization. Fullana et al.[24] showed that decreased connectivity between the BLA and the vmPFC predicted better CBT outcomes in OCD patients. This reduced connectivity was specific to

those who responded to CBT, consistently linking it to positive treatment outcomes. Interestingly, no similar patterns were observed with BLA-ACC connectivity, and only partial replication occurred with centromedial amygdala-vmPFC connectivity under continuous outcome measures.[24] These findings suggest that decreased BLA-vmPFC connectivity may serve as a marker for CBT responsiveness.[24]

Gao et al.[25] further explored amygdala-cortical connectivity changes in OCD, identifying reduced functional connectivity between several amygdala subregions and cortical areas, such as the left centromedial amygdala and the MTG. However, they also noted increased connectivity between regions such as the right inferior parietal lobule and the left centromedial amygdala.[25] These patterns highlight the amygdala's role in OCD and suggest that CBT may facilitate emotional regulation through altered connectivity with the visual and associative cortices.[25]

Li et al.[24] observed significant changes in functional connectivity of the DLPFC following CBT, along with increased resting-state functional connectivity between the left DLPFC and the right OFC. In addition, changes in DMN functional connectivity were associated with clinical improvement of OCD symptoms.[29] These neural changes, seen without medication, were linked to improvement of obsessive symptoms.[29] Additionally, heightened connectivity in regions such as the precuneus and cuneus was associated with symptom improvement. This suggests that CBT affects not only the classic CSTC circuit but also other regions critical for emotional processing and cognitive control.[29] On the other hand, Li et al.[30] found no significant changes in brain function after 8 weeks of CBT, highlighting the need to explore more nuanced neural mechanisms underlying treatment response. Their study further clarifies the relationship between resting-state functional connectivity in the amygdala subregion and the long-term effectiveness of CBT in people with OCD.[30] It was observed that patients exhibited reduced functional connectivity between the left BLA and the left superior temporal gyrus at baseline.[30] Notably, this attenuated functional connectivity was associated with improvement in clinical symptoms following CBT treatment, and this association persisted at the 4-month follow-up.[30] These findings suggest that the left BLA-superior temporal gyrus connectivity pattern could serve as a potential biomarker for predicting both the short- and long-term efficacy of CBT.

Ma et al.[31] found that CBT and combined CBT + SSRI treatment led to decreased ALFF in regions such as the insula, putamen, and postcentral gyrus, which were associated with reductions in fear processing and Y-BOCS scores. Conversely, increased ALFF in the occipital medial gyrus and lingual gyrus correlated with symptom improvement, indicating that these occipital regions may play a role in regulating fear responses and supporting the effects of psychotherapy.[31] Interestingly, Zhao et al.[39] reported that the Y-BOCS scores in OCD patients showed a significant reduction after 4 weeks of treatment, with no notable difference between the CBT and SSRI + CBT groups. At baseline, resting-state brain activity in OCD patients differed from that of healthy controls; however, these differences were not associated with the severity of OCD symptoms. After 4 weeks of either CCT or pCCT treatment, the differences in resting-state brain activity between OCD patients and healthy controls were no longer evident.[39] The normalization of these abnormalities may reflect neural changes that contribute to symptom improvement.

Moody et al.[32] used network-based statistical analysis to demonstrate increased connectivity between the cerebellum, caudate/putamen, and dorsolateral/ventrolateral prefrontal cortices following CBT. These connectivity enhancements were associated with greater resistance to compulsions, suggesting that CBT promotes cross-network integration and the development of non-compulsive, goal-directed behaviors.[32] Shin et al.[35] showed that SSRI treatment improved small-world efficiency and modular organization in OCD patients. These findings indicate that, prior to pharmacological treatment, individuals with OCD exhibit abnormal topological features in their functional brain networks, both globally and locally, with the most notable differences occurring in the frontoparietal regions. These abnormalities suggest a disruption in the brain's network. Following SSRI treatment and corresponding symptom improvement, a normalization of these topological characteristics was observed, pointing to a restoration of the functional network.[35] Yang et al.[37] identified at the initial assessment that individuals with OCD exhibited altered ReHo not only within the CSTC network but also in areas such as the precuneus, calcarine cortex, MTG, and cerebellum. The findings suggested that symptom relief was accompanied by changes in ReHo in cognitive neural circuits, including the right OFC, bilateral DLPFC, left caudate, left cerebellum, and the vermis. Lastly, the study identified a correlation between ReHo in the right OFC and left cerebellum and a reduction in OCD symptoms.[37] These findings emphasize how neural reorganization underlies CBT's therapeutic effects.

Functional magnetic resonance imaging (fMRI)

Task-based fMRI findings emphasize the significant impact of treatment on brain function in OCD patients. Becker et al.[17] observed substantial increases in the density of the FPN and decreases in FPN-DMN network density following CBT treatment. These changes were consistent across various age groups, highlighting the CBT-specific alterations in task-based connectivity in OCD patients.[17] The findings suggest that these changes might signal a restoration of healthy FPN and DMN development, which could offer potential targets for improving responses to CBT.[17] Additionally, CBT produced a greater symptom reduction compared to stress management training, with selective response to CBT associated with decreased connectivity between the vmPFC and subcortical regions (caudate, thalamus) in unmedicated participants. Increased connectivity in cognitive- and motor-control circuits was also linked to greater symptom improvement.[19] However, these results should be interpreted with caution, as combining data

from adolescents and adults may obscure age-related differences in brain maturation.[19] The distinct neural maturation processes in these age groups could significantly influence connectivity and treatment responses. Therefore, it is essential to consider these variables when analyzing treatment outcomes.

Freyer et al.[23] found broad frontal network activity during strategy changes in the reversal learning task, with no significant group differences in the whole-brain analysis. However, reanalysis with a more lenient threshold revealed reduced responsiveness in the OFC and right putamen in patients before treatment compared to healthy controls.[23] A significant group-by-time effect was observed in the caudate nucleus, where activity increased over time in patients.[23] This increase was linked to clinical improvement, suggesting that psychotherapy may influence key brain regions involved in behavioral rule acquisition and OCD pathophysiology, such as the caudate nucleus and pallidum.[23]

Han et al.[26] investigated the impact of pharmacotherapy on cognitive flexibility in OCD patients using a task-switching paradigm. The study found a partial normalization of ventral fronto-striatal activation associated with clinical symptom improvement; however, dysfunctional activation persisted in the dorsal frontoparietal regions. These findings highlight the potential of pharmacotherapy to improve cognitive flexibility in OCD, with task performance improving in both task-switch and task-repeat conditions.[26] Kim et al.[28] showed that OCD patients had reduced internetwork connectivity between the DAN and DMN at baseline, which normalized after 16 weeks of SSRI treatment. This suggests that OCD may be characterized by an imbalance between brain networks during goal-directed planning, and that improved internetwork connectivity could serve as a biomarker for treatment effects.[28] Nabeyama et al.[33] found that OCD patients showed reduced activation in the anterior cingulate gyrus and cerebellum compared to controls, with increased activation in these regions following symptom improvement. These findings indicate that dysfunction in posterior brain regions, particularly the cerebellum, may play a role in OCD pathogenesis, and that normalization of function occurs with symptom improvement.[33] Similarly, Nakao et al.[34] reported that imaging prior to treatment revealed activation in the left DLPFC, left parietal cortex, and right cerebellum during the Stroop task. These findings suggest distinct neural responses to different cognitive and emotional challenges in individuals with OCD. The decrease in provocation-related activation in the OFC, DLPFC, and anterior cingulate cortices following SSRI or CBT treatment may reflect a reduction in the intensity of symptom-specific processing, particularly related to obsessive thoughts and compulsive urges. In contrast, the increased activation observed during the Stroop task in the parietal cortex and cerebellum may indicate enhanced cognitive control and attentional regulation, possibly as a compensatory mechanism or treatment-related improvement in executive function. It is important to note that Stroop tasks typically assess general cognitive interference and control, whereas provocation-related tasks are designed to trigger OCD-specific emotional and cognitive responses. Therefore, the differential activation patterns likely reflect the distinct nature of these paradigms – one targeting broader executive functioning and the other directly engaging the neural circuits implicated in OCD symptomatology.[34]

Van der Straten[36] found that both CBT and SSRIs were effective in reducing OCD symptoms. Compared to healthy controls, treatment was associated with a reduction in insula activity during symptom provocation in OCD patients. However, a comparison between the treatment modalities revealed widespread and divergent patterns of brain activity, particularly in the cerebellum, posterior insula, caudate nucleus, hippocampus, and occipital and prefrontal cortices. These differences were characterized by relative increases in neural activity following CBT and relative decreases following SSRIs treatment.[36] Notably, although both approaches led to improvements, they produced largely opposite effects on brain function, converging only in the common reduction of insula activity during symptom provocation. These results highlight both shared and distinct neural mechanisms involved in treatment response, suggesting that CBT and SSRIs facilitate recovery from OCD through partially independent neurobiological pathways.[36]

Diffusion tensor imaging (DWI)

White matter abnormalities identified through DWI have emerged as essential tools for elucidating the neurobiological basis of OCD and the effects of various treatments.[47] Brecke et al.,[18] however, did not observe significant alterations in FA, RD, axial diffusivity, or MD after 12 weeks of CBT. The authors attributed this lack of findings to the study's small sample size and to the limitations of DWI in distinguishing intra- and extracellular diffusion in regions with complex fiber crossings, which may obscure treatment-related effects.[18]

Cao et al.[20] provided evidence of global network changes in OCD patients who responded to CBT. Baseline assessments revealed a heightened clustering coefficient across the entire brain structural network compared to healthy controls, which normalized after CBT. Additionally, at the nodal level, regions such as the left lingual gyrus and left fusiform gyrus demonstrated significant CBT-related changes.[20] These nodal clustering alterations also correlated with symptom improvements, suggesting that CBT may restore abnormally heightened network segregation in OCD patients. However, this analysis was based on the responders' group, and identifying these alterations is important to elucidate the factors that contribute to responsiveness.[20] Zhong et al.[40] corroborated these findings by reporting increases in FA values in the right middle frontal gyrus, OFC, right cerebellum, and left MTG, alongside decreased FA values in the right putamen. These results underscore the potential neuroplastic effects of CBT on white-matter tracts implicated in OCD. Notably, the percent change in FA values in the left MTG correlated positively with the percent reduction in scores on the Compulsions subscale. In contrast, changes in FA values in the left OFC and right

putamen correlated negatively with reductions in the Obsessions and Compulsions subscales, respectively. These findings highlight the presence of white-matter microstructural abnormalities in unmedicated OCD patients and suggest that CBT may partially reverse these alterations.

SSRIs have also been shown to induce white-matter changes. Fan et al.[21] observed reductions in RD in the left striatum and right midbrain, along with decreased MD in the right midbrain, following SSRI treatment. Importantly, these DWI changes correlated positively with clinical symptom improvements. At baseline, OCD patients exhibited white-matter abnormalities in several brain regions, including the left medial superior frontal gyrus, temporo-parietal lobe, occipital lobe, insula, right frontal lobe, midbrain, and white matter surrounding the left striatum.[21] These findings underscore the role of fronto-striato-thalamocortical circuits in OCD pathophysiology and suggest that SSRI treatment may restore white-matter integrity in these circuits.

Further evidence of SSRI-induced neuroplasticity was reported by Yoo et al.,[38] who found that increased FA in the internal capsule, corpus callosum, and right caudate normalized after treatment with these drugs. Additionally, a decrease in FA was observed in the right posterior thalamic radiation, which may reflect dysfunction in the CSTC circuit.[38] Feusner et al.[22] demonstrated that higher small-world network efficiency prior to treatment was associated with a greater risk of relapse, suggesting that functional network efficiency may serve as a biomarker for both response and relapse. This study also highlighted neuroimaging predictors of the longitudinal clinical course after OCD treatment and was among the first to use graph theory to analyze CBT effects on brain network connectivity.[22] While CBT typically enhances small-world network efficiency, patients with higher pre-treatment efficiency may be more prone to relapse. Additionally, a brain organization characterized by fewer dense local functional connections (lower clustering coefficient and small-worldness) before CBT appears to promote better maintenance of treatment gains, as CBT alleviates symptoms by enhancing network efficiency.

Clinical implications

The neuroimaging changes following first-line treatments for OCD, including increased left putamen volume with SSRIs[27] and reduced thalamus volume alongside increased OFC volume with CBT,[15] highlight potential biomarkers for tracking neuroplasticity and treatment response over time. Task-based and rsfMRI results, such as normalized fronto-striatal connectivity, enhanced small-world network efficiency, and reduced BLA-vmPFC coupling post-CBT,[23,24] offer opportunities for patient stratification to prioritize psychotherapy vs. pharmacotherapy based on baseline network profiles. Collectively, these findings advance precision psychiatry by leveraging baseline imaging markers such as OFC cortical thickness to predict individual outcomes,[44,46] guide decisions on combined CBT-SSRIs regimens for partial responders, and, ultimately, enhance symptom relief and functional recovery.

Despite the evidence of brain changes following first-line treatments for OCD, several limitations of this review must be acknowledged. The heterogeneity in study designs, sample characteristics, and imaging modalities hinders direct comparisons across studies. Many of the included studies, for example, were not randomized controlled trials (RCTs), lacked placebo groups, had short periods of follow-up or small sample sizes, and often analyzed only responder groups, offering limited details on prior medication use. Furthermore, while some studies focused solely on pharmacological interventions, others explored psychotherapeutic approaches, which limits the ability to differentiate shared vs. distinct mechanisms. The variability in sample sizes and the absence of standardized imaging protocols also may have influenced the results. Additionally, the lack of comparisons between CBT and selective SSRIs/CMI within the same study complicates our understanding of their unique effects. Future research should aim to address these gaps by utilizing larger, more homogeneous samples, longer follow-up, standardized neuroimaging techniques, and more rigorous study designs, such as RCTs. Although adding data from youth samples could increase the breadth and impact of this study, developmental neuroimaging data indicate that OCD in youth presents age-dependent trajectories of brain structure and connectivity that differ from those observed in adults, and combining these groups in a single synthesis could obscure age-specific treatment effects.[48,49] Moreover, available neuroimaging studies in youth samples treated for OCD are still scarce and methodologically heterogeneous (e.g., sample size, imaging metrics, and treatment protocols), which could reduce internal validity and lead to misleading inferences about treatment-related brain changes if analyzed together with adult data.[50] In addition, lack of explicit test-retest data for the specific imaging pipelines and time frames used in the included studies represents an important limitation of our review, and, more broadly, the scarcity and variability of test-retest information is a well-recognized limitation of neuroimaging studies in general, which constrains the degree of confidence with which longitudinal changes in brain structure and function can be interpreted as true treatment effects rather than measurement variability.[51]

In conclusion, this review addresses the neurobiological underpinnings of the response to first-line treatments for OCD. It is expected that the specific changes observed in brain structure and function after CBT and SSRI/CMI treatments are related to clinical improvement and to the overall effectiveness of these interventions. Nevertheless, there remains a need for further studies. Overall, evidence from sMRI, rsfMRI, and diffusion-weighted imaging studies highlights that both CBT and SSRIs/CMI produce significant but distinct neuroplastic changes in individuals with OCD, impacting brain structure, functional connectivity, and white matter integrity. To advance this field, future research should carefully consider methodological factors such as sample size, previous medication exposure, and the inclusion of

placebo-treated control groups, in order to minimize confounding effects and better isolate treatment-specific neural changes. The ultimate goal would be to identify neural biomarkers that could help us personalize treatment strategies for OCD, optimizing treatment outcomes for individual patients.

Data availability statement

The data that support this study are available from the authors upon request.

Disclosure

The authors report no conflicts of interest.

Author contributions

AMN: Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing.
RMFS: Conceptualization, Methodology, Software, Writing – review & editing.
DLCC: Data curation, Methodology, Writing – review & editing.
JFAN: Data curation, Project administration, Writing – review & editing.
ME: Data curation, Methodology, Writing – review & editing.
ECM: Methodology, Writing – review & editing.
MQH: Methodology, Writing – review & editing.
RGS: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.
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