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Unraveling the Neurobiological Underpinnings of OCD

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Abstract: Obsessive–Compulsive Disorder (OCD) is a heterogeneous psychiatric condition marked by intrusive obsessions and ritualistic compulsions that significantly impair functioning and quality of life. Advances in neuroimaging have substantially clarified its complex neurobiological basis. Structural findings frequently demonstrate morphological alterations in the orbitofrontal cortex, anterior cingulate cortex, and striatum, linked to both gray and white matter disruptions. Functional neuroimaging studies highlight hyperactivity within cortico-striato-thalamo-cortical (CSTC) loops and aberrant connectivity involving the parietal cortex, limbic structures, and cerebellum. Task-based paradigms underscore that different symptom dimensions (e.g., contamination fears, checking, hoarding) activate partially distinct yet overlapping cortical–subcortical networks. Integrating these structural and functional perspectives supports a connectome-based framework, in which OCD emerges from dysregulated interactions among diverse brain systems involved in cognitive control, emotional regulation, and habit learning. Emerging biomarkers—such as caudate volume, anterior cingulate metabolites, and orbitofrontal connectivity—show promise for predicting response to pharmacotherapy and cognitive-behavioral therapy. Future investigations may expand on these findings through larger longitudinal cohorts, inclusion of pediatric populations, and implementation of multi-omic approaches that integrate genetic, epigenetic, and neuroimaging data. This synthesis of current evidence underscores the potential for refined diagnostic stratification, personalized therapeutic interventions, and enhanced monitoring of treatment efficacy.

Keywords: Obsessive–Compulsive Disorder (OCD); Cortico-Striato-Thalamo-Cortical Loop; Neuroimaging; Structural and Functional Alterations; Connectome; Biomarkers; Personalized Medicine.

INTRODUCTION:

Obsessive–Compulsive Disorder (OCD) is characterized by intrusive, recurrent thoughts (obsessions) and repetitive, ritualized behaviors or mental acts (compulsions), which individuals feel compelled to perform in order to reduce anxiety or distress. These symptoms can substantially interfere with daily functioning, strain interpersonal relationships, and negatively impact overall quality of life [1, 2]. Epidemiological studies estimate a lifetime prevalence of OCD ranging from 1% to 3%, making it one of the more common psychiatric disorders worldwide [2, 3]. Given its prevalence and the profound burden it imposes, OCD has become an important subject for translational research aimed at refining diagnostic procedures and improving therapeutic outcomes [4].

The clinical presentation of OCD involves obsessions—unwanted, persistent thoughts, impulses, or images that generate significant anxiety—and compulsions—ritualized behaviors or mental routines performed to alleviate the distress produced by obsessions. Common obsessional themes include contamination fears, aggressive or sexual thoughts, a need for symmetry, and excessive doubts about safety. Corresponding compulsions often manifest in repetitive washing, checking, counting, ordering, or seeking reassurance. Severity can vary from mild to severe, with many individuals experiencing substantial impairment in daily activities, social interactions, and work performance [1]. Globally, OCD affects millions of individuals across diverse cultures [2, 3]. Its chronic nature, alongside early onset, often translates into prolonged distress and comorbidity with other psychiatric conditions, thereby compounding functional disability [1]. Consequently, understanding its underlying neurobiology is vital not only for accurate diagnosis but also for the development of novel, more effective treatments that can be tailored to individual clinical profiles [4, 5].

Exploring the neurobiological mechanisms of OCD has emerged as a key frontier due to advances in neuroimaging methodologies [4]. These approaches offer insights into how structural and functional alterations in specific circuits may underpin the emergence and perpetuation of obsessive–compulsive symptoms. Early and accurate identification of such neurobiological markers has the potential to optimize both preventive strategies and personalized treatment approaches, potentially enhancing remission rates and minimizing unwanted side effects [4, 6, 7]. As the integration of neuroimaging data into clinical practice continues to evolve, so does the potential for improved patient outcomes.

Neurobiological inquiries into OCD can be traced back to the 1980s, when pioneering studies utilized positron emission tomography (PET) to detect metabolic hyperactivity in frontal-striatal circuits [6, 8]. These foundational investigations helped establish the now-classic model involving cortico-striato-thalamo-cortical (CSTC) circuits as a framework for understanding OCD's neurobiological underpinnings [4, 6]. Over subsequent decades, research expanded to encompass various neuroimaging modalities. Magnetic Resonance Imaging (MRI) enabled detailed structural analyses, highlighting gray and white matter abnormalities in cortical and subcortical regions [9, 10]. Functional MRI (fMRI), particularly in resting-state paradigms, shed light on atypical connectivity patterns, while PET and Single Photon Emission Computed Tomography (SPECT) continued to reveal valuable data on cerebral metabolism and neurotransmitter function [11, 12]. More recent methods such as diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) have further enriched understanding of white matter integrity and metabolic deviations in brain networks pivotal to obsessive–compulsive symptoms [4, 13]. These technological strides, supported by improved computational and analytic techniques, underscore that multiple neurocircuits beyond the fronto-striatal loop contribute to OCD's heterogeneous presentations [4, 9, 14].

Against this background, the principal aim of this review is to synthesize up-to-date findings regarding structural and functional aberrations underlying OCD, emphasizing how various neuroimaging methods converge to elucidate the pathophysiology of the disorder [4, 10]. A related goal involves illustrating how evidence from structural and functional perspectives intersects, with particular attention paid to cortico-striato-thalamo-cortical pathways and broader networks. Finally, this integration of data paves the way for clinical applications, from facilitating early detection and guiding individualized interventions to identifying neurobiological markers that might predict treatment responses [4, 8, 11]. By disentangling the neurobiological foundation of OCD, the discussion aims to advance the drive toward precision medicine while pointing to forthcoming interdisciplinary investigations that bridge fundamental neuroscience and clinical psychiatry.

1.Structural alterations in OCD: a neuroanatomical perspective

Obsessive–compulsive disorder (OCD) has repeatedly been linked to morphological changes in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and the basal ganglia (especially the caudate

nucleus and putamen). Voxel-based morphometry (VBM) meta-analyses highlight decreased gray matter volumes in orbitofrontal and cingulate areas, along with variable findings in the striatum, where volumetric increases or relative preservation have been reported [4, 13, 15]. Surface-based morphometry (SBM) builds upon these insights by revealing cortical thinning in frontal, parietal, and temporal cortices, while some deep gray matter structures may exhibit volumetric enlargement [16, 17].

Several factors can moderate these structural findings. First, age of onset may shape the extent of frontostriatal abnormalities, with early-onset OCD sometimes showing more pronounced differences [9]. Second, medication status appears critical: samples comprising medication-naïve or drug-free patients have documented marked frontal and striatal alterations, whereas chronically treated individuals may display comparatively attenuated changes [15, 18]. Third, psychiatric comorbidities, including depressive or anxiety disorders, potentially influence gray matter volumes by introducing overlapping neurobiological alterations [9].

White matter integrity also emerges as a key component of the disorder's neuroanatomical profile. Diffusion tensor imaging (DTI) studies show microstructural disruptions in the genu of the corpus callosum, the cingulum bundle, and the superior longitudinal fasciculus, which connect frontal, striatal, and limbic structures [4, 19, 20]. These changes often correlate with scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), suggesting that severe disruptions in frontostriatal and frontal-limbic connections may underlie more pronounced obsessive–compulsive symptoms [21]. Furthermore, partial normalization of white matter abnormalities has been reported following pharmacological or cognitive-behavioral therapy, underscoring the dynamic nature of these neural pathways [19, 22].

Magnetic resonance spectroscopy (MRS) complements the above measures by quantifying neurometabolites that reflect neuronal viability (N-acetylaspartate, NAA), astroglial function (myo-inositol), and excitatory neurotransmission (glutamate/glutamine). Multiple studies describe reduced NAA/creatine (Cr) ratios in the OFC, ACC, and striatum, implying compromised neuronal integrity in these regions [4, 23, 24]. Conversely, investigations have also reported lower glutamate or glutamate–glutamine levels in the frontal cortex and thalamus, indicative of disturbed excitatory balance [25]. The magnitude of these metabolic abnormalities frequently shows positive or negative relationships with Y-BOCS severity, suggesting that neuronal health and excitatory–inhibitory balance may both contribute to symptom intensity [26, 27].

Table 1. Structural findings in OCD: key regions, representative results, and clinical correlations

Region or Tract	Representative Finding	Association with Y-BOCS	Key Studies
Orbitofrontal Cortex (OFC)	Reduced gray matter volume and cortical thickness in symptomatic patients	Greater volume reductions often correlate with symptom severity	[4, 13]
Anterior Cingulate Cortex (ACC)	Volumetric reductions and lower NAA levels; altered WM connectivity	Metabolite levels and white matter integrity may track severity	[15, 24]
Caudate Nucleus	Increased or decreased volume; lower NAA/Cr in unmedicated samples	Mixed results; some findings show volume changes linked to Y-BOCS	[17, 23]
Corpus Callosum (Genu)	Reduced fractional anisotropy indicating disrupted interhemispheric	Pronounced deficits often map onto worse obsessions/compulsions	[20, 22]

Region or Tract	Representative Finding	Association with Y-BOCS	Key Studies
	connectivity		
Cingulum Bundle	Lower fractional anisotropy, particularly in anterior sections	Changes in tract integrity frequently correlate with symptom load	[19, 21]
Glutamate/Glutamine (MRS)	Decreased concentrations in medial frontal and thalamic regions	May reflect dysregulated excitatory neurotransmission	[4, 25]
N-Acetylaspartate (MRS)	Reduced levels in the OFC, ACC, and striatum, suggesting impaired neuronal health	Lower NAA typically corresponds to greater clinical severity	[23, 24]

Although the precise direction and extent of structural changes can vary, the collective data underscore the involvement of cortico-striato-thalamo-cortical networks in OCD. Disrupted white matter tracts appear to exacerbate communication deficits, while metabolic anomalies in frontal–subcortical circuits may potentiate specific clinical manifestations. These multilayered findings lay the groundwork for subsequent functional imaging analyses, which further clarify how structural alterations intersect with dynamic brain activity and symptom expression.

2. Functional alterations and the network perspective

Research employing resting-state functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) has consistently linked obsessive–compulsive disorder (OCD) to hyperactivity within the cortico-striato-thalamo-cortical (CSTC) loop. Studies using PET often detect excessive glucose metabolism in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and striatum, findings that correlate with symptom severity and sometimes normalize following successful therapy [4, 6, 11]. Resting-state fMRI adds to this knowledge by revealing elevated functional connectivity between OFC, ventral striatum, and thalamus, alongside aberrant activity in related regions such as the parietal cortex, amygdala, hippocampus, and cerebellum [28, 29]. This broader network perspective suggests that OCD symptoms may reflect maladaptive interactions across diverse circuits implicated in emotion processing, habit formation, and cognitive control [9, 14]. Patterns of hyperactivation or hypoactivation in these regions often correlate with the severity of obsessive–compulsive symptoms, reinforcing the view that pathophysiological disruptions extend beyond a single frontostriatal loop [12, 30].

Task-based fMRI studies, including paradigms such as Stroop tasks, N-back working memory, Tower of London, and exposure to symptom-provocative stimuli, indicate that specific obsessions and compulsions activate distinct but overlapping regions. Washers commonly exhibit pronounced medial prefrontal and striatal reactivity when confronted with contamination-related stimuli, whereas checkers display stronger dorsal frontal and subcortical engagement in response to potential threat cues [31, 32]. Hoarding behaviors elicit unique neural activity in orbitofrontal and sensorimotor areas, while ordering or symmetry obsessions often involve heightened activation in premotor and parietal regions [9, 31]. Pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) or psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), can modulate these neural response patterns. For instance, successful SSRI or CBT treatment has been associated with reduced OFC and caudate hyperactivation, decreases in ACC overactivity, and partial normalization of frontoparietal connectivity [4, 11, 19, 33].

Although fMRI, PET, and SPECT remain primary methods to investigate functional alterations, near-infrared spectroscopy (fNIRS) constitutes a promising adjunct, particularly for task-based assessments. fNIRS gauges oxygenated hemoglobin fluctuations to infer localized neuronal activity during cognitive or behavioral tasks [34]. Portable fNIRS setups allow for

ecologically valid testing scenarios and potentially more accessible longitudinal studies, although they often have shallower penetration depth relative to fMRI and thus provide a narrower field of view [35]. In OCD, initial fNIRS data suggest atypical lateral prefrontal activation during tasks taxing executive control, but a limited number of studies precludes definitive conclusions [4, 36]. Future research could capitalize on fNIRS portability to broaden participant recruitment (e.g., child/adolescent populations) and include real-time biofeedback paradigms.

Table 2. Overview of functional neuroimaging modalities in OCD: main findings and target brain regions

Method	Key Findings	Relevant Brain Regions	References
Resting-state fMRI	Heightened connectivity within CSTC loops; network-level dysregulations involving parietal, limbic, and cerebellar areas	OFC, striatum, ACC, parietal cortex, cerebellum	[4, 28, 29]
PET/SPECT	Elevated metabolic activity correlating with symptom severity; partial normalization post-therapy	OFC, ACC, basal ganglia, thalamus	[6, 11, 30]
Task-based fMRI	Distinct patterns linked to specific obsessions/compulsions; therapeutic interventions alter hyper/hypoactivation	Dorsal/ventral PFC, striatum, parietal cortex, limbic system	[19, 31, 32]
fNIRS	Emerging modality for cortical activation measurements in more flexible settings; limited data in OCD	Primarily lateral PFC (due to measurement constraints)	[4, 35, 36]

In summary, functional neuroimaging highlights that OCD is driven by abnormal interactions within and beyond the classic orbitofronto-striatal circuitry. The involvement of parietal regions, limbic structures, and the cerebellum, along with evidence for treatment-induced neural plasticity, underscores a network approach to understanding obsessive–compulsive symptoms. Continued advances in imaging technologies, including fNIRS, promise to refine these insights by enabling a broader range of experimental designs, ultimately guiding more precise therapeutic strategies.

3.Integration of data: clinical and therapeutic implications

Findings from structural imaging, such as gray matter abnormalities in orbitofrontal and cingulate cortices, and functional investigations, including hyperconnectivity within the cortico-striato-thalamo-cortical (CSTC) loop, collectively point to a multidimensional pathophysiology of obsessive–compulsive disorder (OCD). Morphological alterations in key regions appear tightly interlinked with aberrant functional connectivity patterns, implying that disrupted structural networks may predispose individuals to the dysregulated activation dynamics observed in functional imaging studies [4, 9]. This convergence underlines the utility of a connectome-oriented perspective, wherein OCD is interpreted as a network-level disturbance rather than an isolated fault

in any single cortical or subcortical node [14]. By examining how interactions among multiple systems—encompassing executive control, emotional processing, habit formation, and sensorimotor coordination—converge to drive compulsive behaviors, researchers can better elucidate the heterogeneity in symptom profiles and treatment responses [16].

Neuroimaging biomarkers increasingly serve as predictors of treatment outcomes. Studies suggest that variations in caudate volume, anterior cingulate metabolism, and orbitofrontal connectivity may forecast the efficacy of selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT), potentially aiding in tailoring personalized interventions [11, 12]. Some evidence indicates that reduced metabolic activity or normalization of hyperactivity in these regions correlates with better clinical improvement, while persistent hyperactivation may predict poorer treatment response [30]. Shifts in neurometabolites, such as elevated N-acetylaspartate in the anterior cingulate cortex or altered glutamate levels in the striatum, also show promise as quantifiable indices of therapeutic success [24, 27]. Such imaging-based markers could be integrated into longitudinal monitoring protocols, allowing clinicians to refine pharmacological dosages or modify psychotherapeutic strategies in a more targeted, data-driven manner [4].

Future work will benefit from larger, longitudinal cohorts that capture the developmental trajectory of OCD and its clinical subtypes. Incorporating pediatric, adolescent, and adult samples is crucial for resolving how neurobiological processes evolve over time [9]. Equally important is leveraging multi-omic approaches that blend imaging data with genetic, epigenetic, and transcriptomic profiles to enable the creation of precision medicine frameworks [5]. By identifying specific molecular and neural circuit signatures, interventions can be designed with heightened specificity, potentially reducing refractory cases and enhancing remission rates [4]. Although substantial methodological challenges persist—such as managing the high dimensionality of integrated datasets—advances in computational modeling and machine learning offer robust strategies for extracting clinically relevant biomarkers from complex neurobiological information [14].

Table 3. Potential imaging biomarkers and clinical relevance: implications for personalized treatment

Domain	Potential Biomarker	Clinical Relevance	Key Evidence
Structural Imaging	Caudate nucleus volume, gray matter in OFC/ACC	Larger or more preserved caudate volume and reduced orbitofrontal abnormalities can predict better SSRI response	[4, 11]
Functional Connectivity	Hyperactivation of CSTC loops, resting-state DMN disruptions	Normalization of frontostriatal activity correlates with symptomatic improvements	[14, 30]
Metabolite Profiles (MRS)	N-acetylaspartate, glutamate in ACC or striatum	Changes in neuronal health or excitatory balance may serve as dynamic markers of treatment efficacy	[24, 27]
Integrated Multi-omics	Genetic or epigenetic markers combined with imaging measures	Aids in personalized interventions by linking molecular profiles to specific neurobiological alterations	[5]
Longitudinal Neuroimaging	Repeated MRI, fMRI, MRS assessments across treatment course	Captures brain plasticity over time, helping to adjust interventions and predict remission or relapse	[4, 16]

Integrating data from diverse imaging modalities thus enables a more comprehensive understanding of OCD's pathophysiology. The connectome framework situates local structural or functional abnormalities within large-scale networks, offering richer insights into how complex symptom domains emerge. Ongoing research aimed at validating neuroimaging-based biomarkers and forging multi-omic strategies will likely advance the efficacy and precision of OCD treatments, shaping future directions in both clinical care and translational neuroscience.

CONCLUSION

The collected body of neuroimaging research affirms that OCD cannot be reduced to isolated frontal or subcortical anomalies; rather, it involves an intricate interplay of multiple neural circuits. Structural findings indicate volumetric and microstructural changes in frontal, cingulate, and striatal regions, which appear interdependent with altered functional connectivity patterns observed in resting-state and task-based paradigms. This shift toward a network-centric understanding allows for more nuanced interpretations of how different obsessional themes and compulsive rituals emerge and persist.

Clinically, the search for reliable neuroimaging biomarkers has begun to yield tangible results, including correlations between specific brain alterations and therapeutic outcomes. Identifying factors such as caudate volume or metabolic shifts in the anterior cingulate cortex can potentially guide clinicians in predicting medication response or tailoring psychotherapeutic protocols. Incorporating repeated neuroimaging assessments during the course of treatment also opens avenues for personalized management, where interventions may be adapted based on objective neurobiological indicators of change.

Nonetheless, bridging these insights to routine clinical practice demands further large-scale, longitudinal investigations that account for various OCD subtypes and comorbid conditions. Multi-omic approaches, uniting imaging, genetic, and epigenetic data, promise to refine our grasp of the disorder's pathophysiology and enhance therapeutic precision. By harnessing these integrative strategies, the field moves closer to an era of truly individualized OCD care, in which treatment decisions and prognostic estimations can be anchored in robust neurobiological and molecular evidence.

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