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Dopamine dysfunction beyond psychosis: Reevaluating its role in depression, anxiety, and obsessive-compulsive disorder

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Summary

Dopaminergic dysfunction has traditionally been associated with psychotic disorders. However, emerging evidence implicates dopamine in a broader range of psychiatric conditions. This review critically reexamines dopamine's role beyond psychosis, focusing on major depressive disorder, anxiety disorders, and obsessive-compulsive disorder (OCD)—three high-burden conditions where current treatments remain suboptimal for many patients. This review is conducted to synthesise and critically evaluate the evidence for dopamine dysfunction as a transdiagnostic mechanism underpinning core symptom domains across depression, anxiety, and OCD. Consistent patterns of dopamine dysregulation were identified in mesolimbic and mesocortical pathways, as well as the cortico-striatal-thalamo-cortical (CSTC) loop. Common symptom dimensions—such as anhedonia, apathy, compulsivity, and cognitive inflexibility—were linked to region-specific dopamine deficits. Furthermore, gene–environment interactions and inflammation-induced suppression of dopamine emerged as shared etiological factors. Dopaminergic agents (e.g., bupropion, pramipexole, aripiprazole), neuromodulatory approaches (e.g., TMS, DBS), and biomarker-guided interventions showed promise, particularly in treatment-resistant or subtype-specific presentations. Dopamine dysfunction is a core, transdiagnostic mechanism in depression, anxiety, and OCD, affecting key circuits involved in reward, motivation, and cognitive control. Integrating dopaminergic biomarkers and interventions into psychiatric care may facilitate personalised treatment and improve clinical outcomes.

Keywords: *Dopamine dysfunction, depression, anxiety, obsessive-compulsive disorder, reward processing, biomarkers, precision psychiatry, transdiagnostic model, mesolimbic pathway, CSTC circuit*

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INTRODUCTION

Dopamine has long been implicated in the pathophysiology of psychosis, particularly within schizophrenia and bipolar mania. The dopamine hypothesis emphasises subcortical hyperdopaminergia as a driver of positive psychotic symptoms such as hallucinations and delusions. Neuroimaging studies have supported this model, showing elevated presynaptic dopamine synthesis capacity and increased D_2 receptor occupancy in acutely psychotic states, as well as the efficacy of D_2 antagonists in symptom suppression (Ashok et al., 2017; Mikell et al., 2016). Growing evidence now implicates dopaminergic dysfunction in non-psychotic conditions such as major depressive disorder (MDD), anxiety, and obsessive-compulsive disorder (OCD), which involve disruptions in mood, motivation, arousal, and cognitive flexibility (Felger, 2016; Gassó et al., 2015; Nikolaus et al., 2019).

Molecular imaging, pharmacological studies, and genetic analyses suggests dopamine dysregulation contributes to symptoms like anhedonia, anticipatory anxiety, and compulsive behavior (Felger, 2016; Hamilton et al., 2018; Whitton et al., 2020). PET and SPECT studies report altered D_2/D_3 receptor binding and dopamine transporter (DAT) density in the striatum and prefrontal cortex across depression, OCD, and anxiety disorders (Gassó et al., 2015; Sekiguchi et al., 2023; Tiger et al., 2020). These patterns highlight region-specific dopaminergic dysfunction and support a dimensional framework linking dopamine tone to transdiagnostic symptom domains (Mizuno et al., 2023; Nikolaus et al., 2019). Inflammatory markers like IL-6 and TNF-α are also linked to reduced dopamine signaling in corticostriatal pathways, contributing to fatigue, psychomotor slowing, and diminished reward processing (Bekhbat et al., 2022; Felger, 2016). Dysregulated tonic-phasic dopamine balance may underlie key symptoms across depression, anxiety, and OCD, aligning with the "sickness behaviour" model of inflammation-induced dopamine suppression (Pirtošek, 2011).

Genetic evidence further substantiates dopamine's role across non-psychotic disorders. Polymorphisms in dopamine-related genes—such as SLC6A3 (DAT1),

DRD2, and COMT—have been shown to interact with early-life adversity and trauma to modulate risk for internalising symptoms, including anxiety and depression (Azadmarzabadi et al., 2018; Handley et al., 2023; Saloner et al., 2020). Polygenic analyses highlight population-specific dopaminergic profiles, with certain alleles showing greater effects in high-stress groups and underrepresented populations (Braverman et al., 2022; Malén et al., 2024).

Dopamine is increasingly understood not as a simple "pleasure" neurotransmitter, but as a dynamic regulator of prediction error, motivational salience, cognitive effort, and emotional precision. Models now emphasise dopaminergic homeostasis, in which both excesses and deficiencies can produce maladaptive behavioral states (Ang et al., 2022; Mitchell et al., 2018). Modulators such as chronic stress, gut microbiota, hormonal imbalances, and cognitive load can disrupt this balance and produce overlapping symptoms across traditional diagnoses (González-Arancibia et al., 2019; Serafini et al., 2020). These conceptual shifts carry significant translational implications. Dopamine-targeting interventions have shown efficacy in reducing anhedonia, apathy, and executive dysfunction in individuals with depression and anxiety (Gervasini et al., 2018; Whitton et al., 2020). Furthermore, dopaminergic markers have been explored as candidate biomarkers for personalised treatment and diagnosis (Liu et al., 2020; Peciña et al., 2017). Despite growing evidence implicating dopamine across non-psychotic disorders, an integrated synthesis across the affective and anxiety spectrums remains lacking. This review addresses this gap by critically examining how dopaminergic dysfunction contributes to the pathophysiology of depression, anxiety, and OCD.

DOPAMINE NEUROBIOLOGY AND ITS ROLE IN EMOTIONAL REGULATION

Dopamine (DA) is a catecholaminergic neurotransmitter synthesised in the midbrain, particularly in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). It acts via five G-protein-coupled receptor subtypes (D1–D5), classified into D1-like (D1, D5) and D2-like (D2, D3, D4) families (Butini et al., 2016; Terrón-Díaz et al., 2019). The dopaminergic system regulates cognition, emotion, motivation, motor activity, reward learning, and behavioural flexibility, central to both psychiatric and neurological pathology. Dopamine is metabolised by monoamine oxidase (MAO-A/B) and catechol-O-methyltransferase (COMT). Dysregulation in these mechanisms contributes to affective and compulsive symptoms (Chu et al., 2019; Handley et al., 2023).

Dopaminergic Pathways and Brain Circuits

There are four major dopaminergic pathways, each with distinct functions and implications in psychopathology.

Mesolimbic (VTA to nucleus accumbens/amygdala): This pathway is associated with reward processing, motivation and reinforcement.

Mesocortical (VTA to prefrontal cortex): This pathway supports executive functions and emotional regulation.

Nigrostriatal (SNc to dorsal striatum): This pathway mediates motor control.

Tuberoinfundibular (Hypothalamus to pituitary): This pathway regulates prolactin release.

Mesolimbic and mesocortical dysfunction are consistently reported in depression and anxiety. OCD-related symptoms are linked to dysregulation in the cortico-striatal-thalamo-cortical (CSTC) loops (Gassó et al., 2015; González-Arancibia et al., 2019; Nikolaus et al., 2019). Functional and structural alterations in the striatum, prefrontal cortex, and amygdala have been repeatedly involved across non-psychotic disorders. This indicates a shared circuit-level disruption (Ashok et al., 2017; Iaccarino et al., 2020)

RECEPTOR-LEVEL SPECIFICITY AND CLINICAL IMPLICATIONS

D1 receptors are excitatory and predominantly expressed in the prefrontal cortex and striatum. These receptors facilitate working memory and cognitive control. D2-like receptors, abundant in limbic regions and basal ganglia, modulate reinforcement and emotional salience. Neuroimaging studies reveal reduced D2/D3 receptor availability in the ventral striatum in depression, anxiety, and substance use disorders (Malén et al., 2024; Tiger et al., 2020). These reductions are associated with apathy and anhedonia in depression and Parkinson's disease (Costello et al., 2023; Santangelo et al., 2015). D4 receptors are located in the frontal cortex, and they have been linked to OCD and ADHD, with DRD4 polymorphisms linked to anxiety and compulsivity (Gervasini

et al., 2018; Kanarik et al., 2022). Disruption of D1–D2 heteromeric complexes may also impair mood regulation (Heyl et al., 2019).

PRESYNAPTIC FUNCTION AND TRANSPORTERS

Presynaptic dysfunction is a hallmark of dopamine-related pathophysiology. The dopamine transporter (DAT) modulates extracellular dopamine levels by reuptaking the neurotransmitter into presynaptic terminals. PET studies using DAT-selective tracers have consistently demonstrated reduced DAT binding in the striatum in patients with depression, suggesting compromised dopamine clearance and hypoactivity (Mizuno et al., 2023; Sekiguchi et al., 2023). Similar reductions are observed in OCD and generalised anxiety disorder (Lee et al., 2015). In Parkinson's disease (PD), early DAT loss in the ventral striatum predicts the emergence of apathy and anhedonia before motor symptoms. This underscored the transdiagnostic significance of presynaptic dopaminergic decline (Costello et al., 2023; Picillo et al., 2017). In comorbid conditions such as depression in PD, DAT deficits are amplified in limbic and cortical projections (Frosini et al., 2015; Yang et al., 2023).

CIRCUIT DYSFUNCTION AND CROSS-DISORDER OVERLAP

Symptoms of depression, anxiety, and OCD arise from dysregulated dopaminergic circuitry rather than single-receptor deficits. In depression, reduced striatal dopamine binding correlates with impaired connectivity between the ventral striatum and large-scale networks (e.g., default mode, salience), disrupting reward processing (Hamilton et al., 2018). Elevated or misregulated dopaminergic signalling in the caudate nucleus and anterior cingulate cortex contributes to intrusive thoughts and repetitive behaviours (Gassó et al., 2015; Murray et al., 2019). In anxiety, reduced dopamine signalling in the amygdala and rostral anterior cingulate cortex (rACC) is linked to heightened emotional reactivity and treatment resistance. Berry et al. (2019) and Hjorth et al. (2021) demonstrated that lower dopamine release in the amygdala and rACC is associated with heightened anxiety symptoms and treatment resistance (Berry et al., 2019; Hjorth, Frick, Gingnell, Hoppe, Faria, Hultberg, Alaie, Månsson, Rosén, et al., 2021).

DEVELOPMENTAL AND GENE–ENVIRONMENT MODELS

Genetic variations and environmental interactions shape the dopaminergic functions. Polymorphisms in genes such as DAT1, DRD2, DRD4, and COMT modulate vulnerability to mood and anxiety disorders (Chu et al., 2019; Handley et al., 2023). For example, polygenic risk in dopamine pathways interacts with childhood trauma to influence emotional dysregulation. Environmental stressors such as chronic stress, maternal deprivation, and early adversity can induce epigenetic modifications of dopaminergic genes (Azadmarzabadi et al., 2018; Kaitz et al., 2016). These changes may underlie the persistent dopaminergic alterations seen in treatment-resistant depression and chronic anxiety.

PLASTICITY, HOMEOSTASIS, AND TRANSDIAGNOSTIC PERSPECTIVE

Dopamine dysfunction depends on timing, location, receptor subtype, and neural context. Some models advocate for dopaminergic homeostasis, where both excess and deficiency can lead to pathology. For instance, hyperdopaminergia in the mesolimbic pathway may produce impulsivity or mania, while hypodopaminergia in the mesocortical route may cause cognitive flattening and affective blunting (Arjmand et al., 2018; Ashok et al., 2017). These circuit-based models challenge static diagnostic categories and propose a dimensional framework, where dopamine dysfunction underlies overlapping symptoms, such as apathy, compulsivity, and affective dysregulation across Depression, OCD, and anxiety (Blagotinšek Cokan et al., 2020; Nikolaus et al., 2019). This view is consistent with transdiagnostic approaches in modern neuroscience, including RDoC paradigms.

DOPAMINE DYSFUNCTION IN DEPRESSION

Major depressive disorder (MDD) is increasingly understood as a condition marked not only by mood dysregulation but also by fundamental impairments in motivation, reward processing, and cognitive engagement. Traditional models have focused on serotonergic and noradrenergic systems, but dopamine dysfunction has emerged as a central mechanism, particularly regarding anhedonia, apathy,

psychomotor slowing, and treatment resistance (Ang et al., 2022; Felger, 2016). Dopaminergic dysfunction in MDD appears to affect both the mesolimbic reward system and mesocortical executive circuits, leading to impairments in reward anticipation, learning, and hedonic experience. These dysfunctions are measurable at behavioural, neurochemical, and molecular levels, reflecting a hypodopaminergic state that reduces the capacity of depressed individuals to identify environmental stimuli for rewards (González-Arancibia et al., 2019; Whitton et al., 2020).

Neuroimaging Evidence: Reduced Dopamine Availability and Connectivity

Neuroimaging studies provide compelling evidence for dopaminergic deficits in depression. Hamilton et al. (2018) reported increased ^11c-raclopride binding in the ventral and dorsal striatum, indicating reduced endogenous dopamine levels. This hypodopaminergic state was associated with altered connectivity between the striatum and large-scale networks such as the default mode network (DMN) and salience network. These findings are compounded by Sekiguchi et al. (2023) and Mizuno et al. (2023), reported reduced dopamine transporter (DAT) availability and D1 receptor binding in the striatum and midbrain, further implicating impaired dopamine synthesis and clearance (Mizuno et al., 2023; Sekiguchi et al., 2023). These abnormalities were most strongly linked to anhedonia and apathy, reinforcing the role of dopamine in goal-directed behaviour and effort valuation.

Genetic and Molecular Correlates: Dopamine-Related Vulnerabilities

Genetic polymorphisms in dopaminergic genes further induce depression. Handley et al. (2023) identified polygenic risk clusters in DAT1 and DRD2 that significantly moderated the impact of childhood trauma on emotional outcomes, supporting a gene × environment interaction model (Handley et al., 2023). Similarly, Chu et al. (2019) found that polymorphisms in SLC6A3 (DAT1) and DRD2 predicted pain sensitivity and depressive symptoms in elderly patients, suggesting that dopaminergic genes modulate both affective and somatic domains of depression (Chu et al., 2019). In contrast, Azadmarzabadi et al. (2018) reported that individuals with high stress resilience exhibited upregulated expression of dopamine synthesis and receptor genes, suggesting a neuroprotective dopaminergic profile (Azadmarzabadi et al., 2018).

Inflammation and Dopamine: The Immune-Dopamine Axis

Emerging research highlights inflammation-induced dopaminergic suppression as a contributor to treatment-resistant and atypical depression. Pro-inflammatory cytokines such as IL-6 and TNF-α inhibit tetrahydrobiopterin (BH4), a key cofactor for tyrosine hydroxylase, thereby reducing dopamine synthesis (Felger, 2016). Bekhbat et al. (2022) found that patients with elevated inflammatory markers exhibited blunted reward responsiveness and striatal dopamine signalling, which improved following L-DOPA administration (Bekhbat et al., 2022). These findings suggest that dopaminergic hypofunction may represent a final common pathway through which inflammation exerts behavioural effects. Further reinforcing this, Serafini et al. (2020) reported elevated D2/D3 receptor binding in patients with comorbid fibromyalgia and depression, potentially reflecting a compensatory response to chronic low dopamine tone (Serafini et al., 2020).

Behavioural Studies: Anhedonia, Apathy, and Decision-Making

Anhedonia is one of the most debilitating symptoms of depression, and its neurobiological underpinnings are increasingly linked to mesolimbic dopamine dysfunction. Whitton et al. (2020) demonstrated that patients with depression show impaired reward prediction error signalling and reduced ventral striatal dopamine release (Whitton et al., 2020). Treatment with pramipexole, a D2/D3 receptor agonist, was more effective in patients with lower baseline dopamine function, suggesting a potential for dopaminergic profiling in personalising antidepressant treatment. Ang et al. (2022) found that depressed patients generated fewer but more unique options in decision-making tasks, with putaminal D2 receptor availability predicting both quantity and originality of choices (Ang et al., 2022). These results suggest dopamine is involved not only in reward consumption but also in motivational exploration and action selection. Costello et al. (2023), further demonstrated that striatal DAT reductions in Parkinson's disease predicted apathy two years before motor symptoms emerged, highlighting the transdiagnostic relevance of presynaptic dopaminergic decline (Costello et al., 2023).

GUT–BRAIN AXIS AND DOPAMINERGIC REGULATION

Emerging research suggests that gut microbiota composition may influence dopaminergic tone. Gonzalez-Arancibia et al. (2019) demonstrated that alterations in gut bacteria affect dopamine availability in brain regions such as the prefrontal cortex, hippocampus, and nucleus accumbens, potentially modulating mood and reward responsiveness (González-Arancibia et al., 2019).

While still an evolving field, the gut–dopamine link offers new mechanistic pathways and therapeutic targets for depression, particularly for patients unresponsive to traditional monoaminergic drugs.

NEUROMODULATION AND DOPAMINE IN DEPRESSION

Non-pharmacological interventions also interact with dopaminergic systems. Kinney and Hanlon (2022) found that transcranial magnetic stimulation (TMS) applied to the prefrontal cortex may modulate dopamine receptor availability, contributing to its antidepressant effects (Kinney & Hanlon, 2022). However, most TMS research has focused on cortical networks rather than direct dopaminergic targets, highlighting a research gap in understanding the full scope of TMS–dopamine interactions. Additionally, Wang et al. (2024) showed that deep brain stimulation (DBS) may restore dopaminergic function in treatment-resistant depression by modulating subcortical nodes such as the nucleus accumbens and ventral striatum (Wang et al., 2024).

TOWARD A DOPAMINERGIC SUBTYPE OF DEPRESSION

These findings suggest that a subset of depression patients may experience depression primarily due to dopaminergic dysfunction, rather than serotonergic or noradrenergic imbalance. These individuals are often characterised by profound anhedonia, fatigue, apathy, cognitive slowing, and poor response to SSRIs—but may benefit from dopamine agonists, L-DOPA, bupropion, or modafinil (Peciña et al., 2017; P. Wang et al., 2023). The clinical implications are profound: rather than treating all depression as a monolithic disorder, identifying dopaminergic biomarkers, such as D2 receptor availability or striatal DAT density, could enable personalised treatment and improve remission rates.

DOPAMINE DYSREGULATION IN ANXIETY DISORDERS

Anxiety disorders have been associated with dysregulation of the serotonergic and noradrenergic systems. However, emerging research has begun to challenge this paradigm, indicating that dopaminergic dysfunction particularly in mesolimbic, mesocortical, and striatal circuits plays a significant role in the onset, maintenance, and expression of anxiety symptoms (González-Arancibia et al., 2019; Nikolaus et al., 2019). While dopamine is commonly known for its role in reward, motivation, and movement, it is also deeply involved in fear conditioning, avoidance behaviour, cognitive control, and emotion regulation—core processes disrupted in anxiety disorders (Berry et al., 2019; Kwon et al., 2015). Dopaminergic abnormalities may contribute to anticipatory anxiety, hypervigilance, and maladaptive responses to uncertainty, symptoms seen across conditions such as generalised anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, and PTSD.

NEUROIMAGING EVIDENCE: STRIATAL AND LIMBIC DOPAMINE IN ANXIETY

Neuroimaging studies have identified consistent dopaminergic abnormalities in striatal and limbic regions among individuals with anxiety. Berry et al. (2019) reported that individuals with high trait anxiety exhibited reduced dopamine release in the amygdala and rostral anterior cingulate cortex (rACC), regions critical for fear processing and emotional regulation (Berry et al., 2019). This reduction was associated with heightened threat appraisal and affective rigidity. Similarly, Hjorth et al. (2021) demonstrated that dopamine transporter (DAT) availability in the striatum and thalamus predicted SAD symptom severity and placebo response to SSRIs, implicating dopamine in expectancy and stress regulation (Hjorth, Frick, Gingnell, Hoppe, Faria, Hultberg, Alaie, Månsson, Wahlstedt, et al., 2021). In line with this, Lee et al. (2015) observed significantly reduced DAT availability in patients with GAD, suggesting altered dopaminergic clearance and tone (Lee et al., 2015). These neurobiological signatures may help explain common features of anxiety such as hyperarousal, rumination, and excessive worry.

DOPAMINERGIC CIRCUITS IN FEAR AND AVOIDANCE LEARNING

Fear learning, a hallmark of anxiety, also appears dependent on dopamine. Kwon et al. (2015) found that D4 receptors in the dorsal intercalated cell mass (ITC) of the amygdala modulate long-term depression (LTD)

during fear conditioning (Kwon et al., 2015). Mice with impaired D4 function in this region showed abnormal fear extinction and exaggerated freezing responses, suggesting a failure to inhibit maladaptive fear memories—a core symptom in PTSD and phobic disorders. Beyond the amygdala, Vassena et al. (2019) noted that striatal D2 receptor binding was associated with external locus of control, which correlates with anxiety proneness (Vassena et al., 2019). This study linked dopamine function to belief updating and uncertainty processing, mechanisms that are often impaired in anxious individuals who struggle to flexibly adapt to changing threat cues.

GENETIC AND DEVELOPMENTAL RISK: DOPAMINE PATHWAY POLYMORPHISMS

Dopaminergic gene variants have been implicated in the developmental trajectory of anxiety symptoms. Handley et al. (2023) reported that individuals with high polygenic risk scores in DAT1 and DRD2 were more sensitive to childhood adversity, with significantly elevated internalising symptoms in adolescence and adulthood (Handley et al., 2023). This gene × environment interaction supports a neurodevelopmental framework for dopamine-linked anxiety. Kanarik et al. (2022) also identified polymorphisms in DRD4, COMT, MAOA, and DAT1 that interact with environmental stress to influence anxiety and ADHD phenotypes (Kanarik et al., 2022). These findings suggest that dopamine gene variants do not act in isolation but in combination with psychosocial exposures, particularly in shaping emotional reactivity and fear learning circuits.

INFLAMMATION AND DOPAMINE IN ANXIETY

Inflammation is less extensively studied in anxiety than in depression, the inflammatory modulation of dopamine is increasingly relevant in anxiety research. Cytokines such as IL-1β and TNF-α are known to impact dopamine synthesis and receptor sensitivity (Felger, 2016). Studies in Parkinson's disease and fibromyalgia show that elevated systemic inflammation is associated with increased anxiety symptoms, potentially through dopaminergic suppression in corticostriatal regions (Goltz et al., 2024; Iaccarino et al., 2020). These immune-dopamine interactions may underpin treatment-resistant anxiety, particularly in individuals who do not respond to SSRIs or benzodiazepines. Future research exploring dopamine–inflammation pathways could yield novel biomarker-guided treatments.

DOPAMINE, COGNITIVE CONTROL AND INTOLERANCE OF UNCERTAINTY

Dopamine is involved in cognitive control mechanisms, such as working memory, conflict monitoring, and task switching—all of which are impaired in anxiety. Ang et al. (2022) demonstrated that dopamine D2 receptor availability in the putamen influenced the generation of behavioural options in depression patients (Ang et al., 2022). Moreover, Mitchell et al. (2018) linked dopamine dysregulation to time perception and impulsivity, core traits in anxious individuals who experience time as elongated and threatening (Mitchell et al., 2018). These findings align with theories that dopamine modulates mental effort, expectancy violation, and motivational salience, all critical dimensions in anxiety phenomenology.

TRANSDIAGNOSTIC EVIDENCE: DOPAMINE ACROSS AFFECTIVE CONDITIONS

While dopamine dysfunction in anxiety is less overt than in depression, the two often co-occur and share underlying circuitry. For instance, studies in Parkinson's disease have shown that reduced DAT uptake in the ventral striatum predicts both anhedonia and anxiety, suggesting shared mesolimbic dysregulation (Picillo et al., 2017; Santangelo et al., 2015). Costello et al. (2023) extended this by demonstrating that striatal dopamine deficits predicted motivational symptoms like apathy and anhedonia (Costello et al., 2023). These findings emphasise that dopaminergic dysfunction in basal ganglia and limbic structures manifests across psychiatric spectra, not just in psychosis or movement disorders. Additionally, the interaction between serotonin and dopamine systems may be critical. For example, imbalances in this interaction may explain why some patients respond poorly to serotonergic drugs alone and may benefit from dopaminergic augmentation (Hjorth, Frick, Gingnell, Hoppe, Faria, Hultberg, Alaie, Månsson, Rosén, et al., 2021).

THERAPEUTIC IMPLICATIONS AND RESEARCH GAPS

Despite growing evidence, dopamine remains under-targeted in anxiety treatment. Most current interventions focus on GABAergic and serotonergic modulation. However, preliminary evidence supports the use of dopamine agonists, such as bupropion and modafinil, in individuals with co-occurring apathy, fatigue, or treatment resistance (Kinney & Hanlon, 2022; H. Wang et al., 2023). Neuromodulatory approaches such as TMS and DBS have also shown promise. Kinney and Hanlon (2022) noted that TMS can alter dopamine receptor availability in the prefrontal cortex, yet few studies have explored its potential in GAD, SAD, or panic disorder (Kinney & Hanlon, 2022). Expanding the scope of dopamine-based therapies may open doors for treating refractory cases or those with atypical symptom presentations. A critical barrier remains the lack of biomarkers for dopaminergic activity in anxiety. Developing reliable measures such as PET-based DAT imaging or peripheral dopamine metabolites could facilitate patient stratification and guide treatment selection in clinical settings.

THE ROLE OF DOPAMINE IN OBSESSIVE-COMPULSIVE DISORDER (OCD)

Obsessive-Compulsive Disorder (OCD) has traditionally been conceptualised as a serotonergic dysfunction, with selective serotonin reuptake inhibitors (SSRIs) constituting first-line treatment. However, the partial or non-response in many patients, the clinical benefit of dopamine-modulating agents (e.g., antipsychotics), and the frequent co-occurrence of motor tics and compulsive behaviours suggest a deeper involvement of dopamine systems than previously acknowledged (Gassó et al., 2015; Nikolaus et al., 2019). Emerging evidence supports dopaminergic dysregulation within the cortico-striato-thalamo-cortical (CSTC) loop as a core mechanism in OCD pathophysiology.

NEUROANATOMY OF CSTC LOOPS AND DOPAMINE'S ROLE

The hallmark neural substrate in OCD is the hyperactivation of the CSTC loop, particularly involving the orbitofrontal cortex, anterior cingulate cortex, caudate nucleus, and thalamus. Dopamine modulates activity in these circuits by influencing goal selection, response inhibition, and error monitoring—all disrupted in OCD symptomatology. Murray et al. (2019) demonstrated that OCD patients exhibit heightened negative prediction error signals in the ACC during reward tasks, which could be attenuated by both dopaminergic stimulation and blockade (Murray et al., 2019). This bidirectional response points to a dysregulated, unstable dopaminergic tone rather than a simple excess or deficit, possibly contributing to obsessive doubt and the urge for compulsive correction.

NEUROIMAGING STUDIES: DAT AND D2/D3 RECEPTOR DYSREGULATION

PET and SPECT studies of OCD have revealed alterations in both dopamine transporter (DAT) availability and dopamine receptor binding. Gassó (2015) identified white matter microstructure abnormalities in dopaminergic pathways associated with polymorphisms in DAT1 (SLC6A3) and DRD3 (Gassó et al., 2015). Similarly, studies have observed increased striatal dopamine turnover in OCD patients, potentially reflecting compensatory upregulation due to deficient dopamine release or post-synaptic receptor sensitivity (Butini et al., 2016; Nikolaus et al., 2019). These abnormalities are particularly evident in the caudate nucleus, underscoring the role of basal ganglia dysfunction in repetitive, habitual behaviour characteristic of OCD.

GENETIC FINDINGS: DOPAMINE RECEPTOR AND TRANSPORTER POLYMORPHISMS

Genetic studies have consistently confirmed dopamine-related genes in OCD. Gervasini et al. (2018) reported that polymorphisms in the DRD4 gene were associated with increased severity of obsessive-compulsive, anxiety, and phobic symptoms in individuals with eating disorders. This suggests a shared dopaminergic vulnerability across obsessive and compulsive spectra. Fraporti et al. (2019) examined DRD2 gene variants in children with anxiety and ADHD and found overlapping genetic markers with OCD, particularly involving dopamine D2 receptor function and its interaction with adenosine A2A

receptors (Fraporti et al., 2019). Interestingly, a study on alcohol-dependent patients revealed a significant association between the ANKK1 Taq1A polymorphism and sucrose preference, with A1 alleles being more prevalent among sweet likers (p=0.00161) (Jabłoński et al., 2013). These findings support the notion that dopaminergic genetic variants may modulate reward sensitivity, which is observed in depression and OCD. While DRD2 polymorphisms themselves did not show a significant effect, the involvement of ANKK1 underscores the importance of considering indirect modulators of the dopamine system when exploring transdiagnostic mechanisms of anhedonia and compulsivity. These genetic insights support the hypothesis that OCD arises from dopaminergic signaling abnormalities in inhibitory control networks, leading to deficits in response suppression and overvaluation of intrusive thoughts.

PHARMACOLOGICAL EVIDENCE: DOPAMINE ANTAGONISTS AND AUGMENTATION STRATEGIES

The clinical efficacy of dopamine-targeting medications in OCD supports the biological relevance of the dopaminergic system. Low-dose antipsychotics—particularly risperidone and aripiprazole—are effective in augmenting SSRIs in treatment-resistant OCD, especially in patients with comorbid tics or impulsivity (Gassó et al., 2015; Nikolaus et al., 2019). These medications act primarily on D2 receptors, reducing striatal overactivity and modulating reward feedback loops. However, dopamine antagonists are not uniformly effective, and some patients worsen with excessive dopamine blockade, suggesting that dopamine imbalance in OCD may be bidirectional. Murray et al. (2019) found that both stimulation and inhibition of dopamine transmission could reduce OCD symptoms depending on baseline function, implicating a U-shaped or homeostatic response curve (Murray et al., 2019). Additionally, DRD2 polymorphisms have been associated with differential treatment response to dopamine antagonists, hinting at the potential for personalised dopamine-modulating therapies based on genetic and neuroimaging profiles (Dretsch et al., 2016).

DOPAMINE AND COMPULSIVITY: CIRCUIT-LEVEL INTERPRETATIONS

Compulsivity in OCD can be interpreted as a maladaptive reward prediction error loop, where actions meant to prevent harm (e.g., checking, cleaning) are not sufficiently reinforced or corrected by internal cues. The striatum may fail to appropriately register the non-occurrence of threat leading to repetitive behavior. This theory aligns with studies by Ashok et al. (2017) and Mikell et al. (2015), who describe dopaminergic disruption in the ventral striatum and anterior hippocampal circuits—regions overlapping in OCD, depression, and anxiety (Ashok et al., 2017; Mikell et al., 2016). Nikolaus (2018) further emphasises that OCD patients show unique patterns of regional dopamine receptor desensitization, with differences from both schizophrenia and depression. For example, while psychosis involves generalised dopaminergic hyperactivity, OCD shows region-specific dysregulation, particularly involving D2 receptor hypoactivity in striatal regions and D1-D2 balance in the prefrontal cortex (Nikolaus et al., 2019). Aberrant salience attribution may also explain symptom patterns in OCD where neutral stimuli are imbued with pathological significance. Moreover, the balance between tonic and phasic dopamine activity offers a unifying framework for understanding dopaminergic contributions to both hypoactive and hyperactive states observed across these conditions (Branković, 2015).

DOPAMINE, COGNITIVE CONTROL, AND REWARD DEVALUATION

OCD is not merely a motor or fear-based disorder—it also involves distortions in value attribution, conflict resolution, and cognitive control. Dopamine is centrally involved in these processes. Ang et al. (2022) demonstrated that dopamine D2 receptor availability modulates the flexibility and originality of behavioral options,(Ang et al., 2022) while Whitton et al. (2020) showed impaired reward prediction error signaling in OCD and depression alike Murray et al. (2019) demonstrated that patients with OCD overestimate the value of potential negative outcomes and demonstrate impaired extinction learning, possibly due to disrupted dopaminergic feedback loops. (Murray et al., 2019) These findings support the concept of OCD as a disorder of impaired cognitive gating and outcome reappraisal, processes that are tightly modulated by dopaminergic tone in fronto-striatal pathways.

TRANSDIAGNOSTIC FEATURES: DOPAMINERGIC OVERLAP WITH DEPRESSION AND ANXIETY

There is substantial symptom and circuit overlap between OCD, depression, and anxiety disorders, all of which share dopaminergic dysregulation in reward and salience networks. For instance, apathy and anhedonia, once thought exclusive to depression, are increasingly reported in OCD and linked to ventral striatal dopamine dysfunction (Costello et al., 2023; Wang et al., 2024). Studies argue for a dimensional understanding of psychiatric disorders, where dopamine dysfunction is a shared mechanism underlying impulsivity, rigidity, and reward misprocessing across diagnoses (Belkacemi & Darmani, 2020; Blagotinšek Cokan et al., 2020). These findings justify the use of dopaminergic agents in OCD subtypes, particularly those with comorbid ADHD, tic disorders, or affective dysregulation.

SHARED MECHANISMS AND OVERLAPPING PATHOPHYSIOLOGY

As psychiatric neuroscience is shifting from categorical to dimensional models. Depression, anxiety, and OCD share symptom domains like cognitive inflexibility, anhedonia, and avoidance, which are increasingly tied to dysfunction in dopaminergic circuits (González-Arancibia et al., 2019; Nikolaus et al., 2019; Whitton et al., 2020). Evidence from neuroimaging, genetics, and molecular studies converges on the striatum, particularly the nucleus accumbens and caudate, as a central hub integrating reward processing, cognitive control, and motor behaviour. Table 1 demonstrates the regions involved in depression, OCD and anxiety disorders. When these identified polymorphisms in dopamine-related genes are taken into patient care, it could assist I genomic profiling of patients with treatment resistance depression and OCD. For instance, DRD2 variants may predict response to dopaminergic augmentation in OCD, whereas DAT1 could help identify individuals at risk for hedonic impairments in depression.

Table 2 shows several core symptoms of dopamine dysfunction and brain regions.

Table 1: Depression, OCD and Anxiety and Brain Regions Involved

Disorder	Dopamine Dysfunction	Associated Symptoms/ Effects	Brain Regions Involved	References
Depression	Reduced dopamine binding	Anhedonia, Motivational blunting	Ventral striatum	(Hamilton et al., 2018; Whitton et al., 2020)
OCD	Altered dopamine dynamics	Habit formation, Compulsivity, Impaired action updating	Caudate	(Gassó et al., 2015; Murray et al., 2019)
Anxiety Disorders	Striatal dopamine abnormalities affecting anticipatory salience	Disrupted threat appraisal, reduced behavioural flexibility	Striatum	(Hjorth, Frick, Gingnell, Hoppe, Faria, Hultberg, Alaie, Månsson, Wahlstedt, et al., 2021; Lee et al., 2015)

Table 2: Symptoms and Brain Regions

Symptom/Behaviour	Dopamine Dysfunction	Brain Regions Involved	References
Anhedonia and Apathy	Low dopamine tone	Ventral striatum	(Costello et al., 2023; Peciña et al., 2017)
Compulsivity and Habitual Behavior	Dysregulated dopamine	Dorsal striatum, Prefrontal cortex	(Nikolaus et al., 2019)
Cognitive Inflexibility and Rumination	Dysfunction in D2 receptor systems	Caudate, Anterior cingulate cortex (ACC)	(Murray et al., 2019)
Avoidance and Emotional Rigidity	Blunted dopamine release	Amygdala, Rostral anterior cingulate cortex (rACC)	(Berry et al., 2019; Vassena et al., 2019)
Reduced Reward Anticipation and Exploration	Mesolimbic hypodopaminergia	Broad mesolimbic regions (including nucleus accumbens, VTA, etc.)	(Ang et al., 2022; Whitton et al., 2020)

THERAPEUTIC IMPLICATIONS AND FUTURE DIRECTIONS

SSRIs remain the first-line treatment for OCD, depression, and anxiety, but their limitations in patients with anhedonia, apathy, or compulsivity point to the need for broader dopaminergic strategies (Felger, 2016; Whitton et al., 2020). Dopamine's role in motivation, reward valuation, and action selection positions it as a promising target in future therapeutic models. Medications targeting dopamine transmission is shown in Table 3.

Non-pharmacologic interventions, including transcranial magnetic stimulation (TMS), cognitive training, and behavioural activation, may also influence dopaminergic circuits and warrant further research. While included studies revealed efficacy of dopamine-modulating agents, but these findings are derived from retrospective analyses or small-scale interventions (Costello et al., 2023; H. Wang et al., 2023; Whitton et al., 2020). Future research should prioritize randomised clinical trials targeting specific symptom clusters such as anhedonia, apathy, and compulsivity.

THE CASE FOR DOPAMINERGIC BIOMARKERS IN PSYCHIATRY

A major limitation in psychiatry is the lack of objective biomarkers to guide diagnosis and treatment. Several studies suggest that dopaminergic markers could be used to stratify patients into treatment-responsive subtypes, as shown in Table 4.

PET-based measures of DAT binding and D2/D3 receptor availability have shown promise (Martinez et al., 2010). However, it is limited to research settings. Large-scale studies are needed to assess their clinical feasibility, cost-effectiveness, and predictive value, including integration into health records and care algorithms. Figure 1 outlines the interplay between environmental triggers, dopamine dysregulation, neural circuits, symptoms, and treatments across mood, anxiety, and OCD, offering a transdiagnostic framework.

Environmental factors such as stress, inflammation, and gut microbiota dysbiosis can trigger dopaminergic dysfunction (Azadmarzabadi et al., 2018; Felger, 2016; González-Arancibia et al., 2019). This impacts key neurocircuits leading to clinical outcomes such as anhedonia,

Table 3: Dopamine Targeting Medication

Medication	Mechanism of Action	Clinical Use	Dopamine-Related Effects	References
Pramipexole	D2/D3 receptor agonist	Treatment-resistant depression, Bipolar depression (low hedonic tone)	Restores reward responsiveness in ventral striatal circuits	(Whitton et al., 2020)
Bupropion	Norepinephrine-dopamine reuptake inhibitor (NDRI)	Depression (fatigue, anergia, attention), Off-label use in anxiety and OCD	Enhances dopamine signaling, particularly in energy and attention regulation	(H. Wang et al., 2023)
Aripiprazole	Partial D2 receptor agonist	Augmentation in MDD and OCD, especially SSRI non-responders	Modulates prefrontal dopamine and serotonin; reduces intrusive thoughts and compulsivity	(Costello et al., 2023; Gassó et al., 2015)

Table 4: Dopaminergic Biomarkers

Biomarker/Measure	Clinical Significance	Associated Conditions/ Symptoms	References
Striatal DAT binding (via SPECT/PET)	Predicts treatment response	Depression, OCD	(Picillo et al., 2017; Sekiguchi et al., 2023)
D2/D3 receptor availability (nucleus accumbens)	Correlates with motivational and compulsive traits	Apathy, Anhedonia, Compulsivity	(Costello et al., 2023)
Inflammation-dopamine interaction markers (e.g., IL-6, CRP + imaging)	May guide personalised dopamine-augmenting therapies	Depression, Inflammation-related anhedonia or treatment resistance	(Bekhbat et al., 2022)

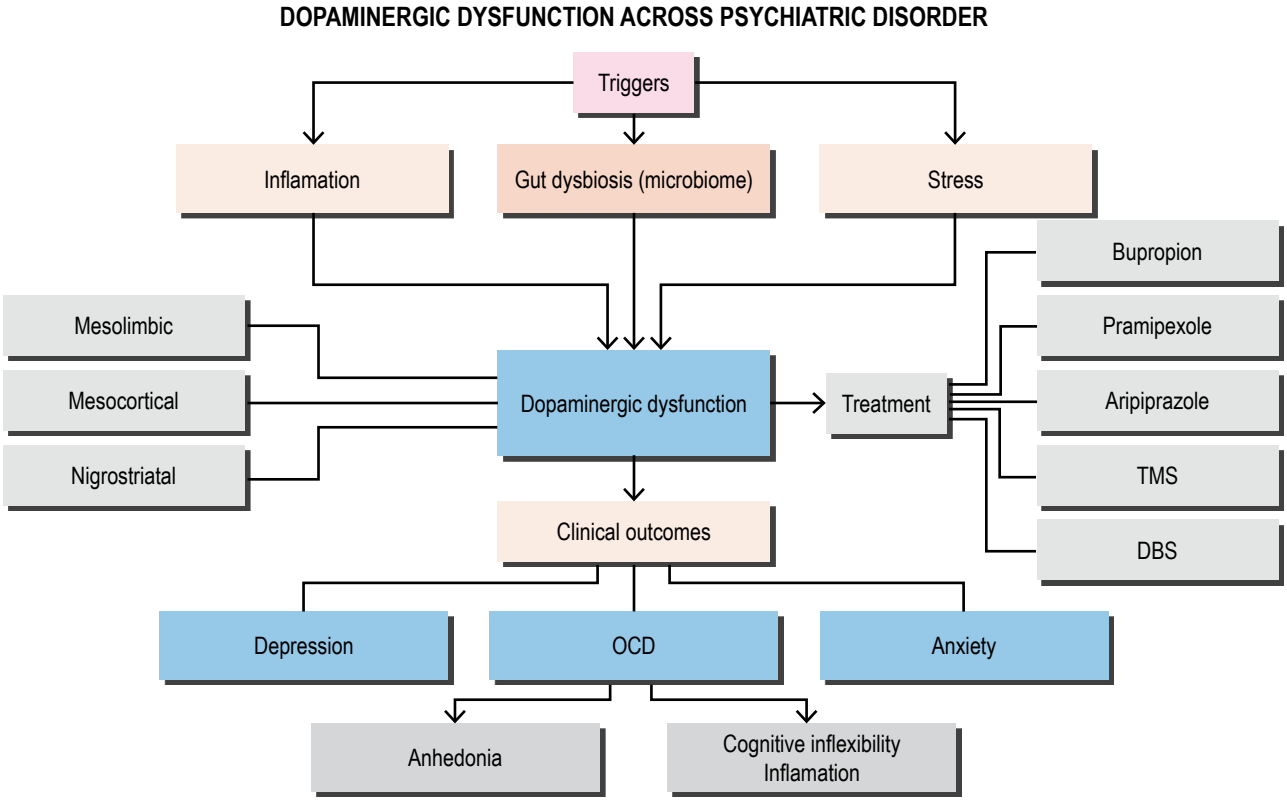

Figure 1. *Integrated model of dopaminergic dysfunction across psychiatric disorders.*

anxiety, cognitive inflexibility, and depression (Bekhbat et al., 2022). Treatments such as bupropion, pramipexole, aripiprazole, transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) aim to restore dopaminergic signaling (D'Onofrio et al., 2023; Uher et al., 2020; Whitton et al., 2020).

CONCLUSION

This review critically reexamines the role of dopamine dysfunction beyond psychosis. Contrary to the long-standing view of dopamine as primarily relevant to psychotic disorders, mounting evidence now demonstrates its central role in the pathophysiology of depression, anxiety disorders, and obsessive-compulsive disorder (OCD). Across these conditions, dopaminergic dysfunction converges on a shared set of symptom domains, including anhedonia, apathy, motivational disengagement, compulsivity, cognitive inflexibility, and avoidance behaviour. These symptoms are linked to disruptions in core brain circuits such as mesolimbic, mesocortical, and cortico-striatal-thalamo-cortical (CSTC) loops where dopamine regulates reward processing, salience attribution, emotional regulation, and behavioural control.

One central mechanism is mesolimbic hypodopaminergia, which plays a crucial role in the development of anhedonia and apathy, particularly in depression and anxiety. In parallel, striatal dopaminergic dysfunction has been strongly implicated in compulsive and habitual behaviors characteristic of OCD. Another shared feature across these disorders is impaired reward prediction error signaling, which disrupts adaptive learning and motivational processes. Additionally, gene–environment interactions involving dopamine-related polymorphisms appear to moderate the impact of early life adversity, increasing vulnerability to psychopathology across diagnostic categories. Finally, inflammation-induced dopaminergic suppression has emerged as a compelling explanation for treatment resistance, fatigue, and motivational deficits seen across these conditions.

Together, these findings support a dimensional, circuit-based framework of psychiatric illness in which dopamine plays a foundational role across diagnostic categories. This perspective aligns with emerging transdiagnostic models in neuroscience and psychiatry, including the NIMH's Research Domain Criteria (RDoC), and challenges reductionist approaches that prioritize single-neurotransmitter or categorical views of mental illness.

CLINICAL AND RESEARCH IMPLICATIONS

Understanding dopamine's multifaceted role in psychiatric disorders paves the way for more personalised and targeted treatment approaches in precision psychiatry. One promising avenue is treatment stratification based on dopaminergic biomarkers, such as dopamine transporter (DAT) imaging, inflammatory markers (e.g., CRP, IL-6), and genetic variants related to dopamine function (Sekiguchi et al., 2023). These biomarkers can help identify patient subgroups most likely to benefit from specific interventions. Pharmacologically, dopaminergic agents like pramipexole, bupropion, and aripiprazole have shown particular efficacy in individuals exhibiting motivational and cognitive deficits, offering tailored options beyond traditional antidepressants (Uher et al., 2020). Additionally, neuromodulation strategies, including transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), are being refined to target dopamine-rich circuits, especially for treatment-resistant cases (D'Onofrio et al., 2023). For individuals with immune–dopamine dysregulation, inflammation-targeting interventions may enhance treatment response by restoring dopaminergic tone. Complementing these approaches, cognitive and behavioral tools—such as reward-based cognitive behavioral therapy (CBT) and metacognitive training—aim to indirectly boost dopamine signaling through experiential and learning-based pathways. Together, these innovations signal a shift toward more nuanced and biologically informed models of mental health care.

LIMITATIONS AND FUTURE DIRECTIONS

While this review offers a comprehensive synthesis of dopamine dysfunction across depression, anxiety, and OCD, several limitations must be acknowledged. Many of the included studies are cross-sectional, which restricts the ability to draw causal inferences about the relationship between dopaminergic abnormalities and psychiatric symptoms. The reviewed studies lack causality and need to be validated through longitudinal and experimental studies. Additionally, there is substantial heterogeneity in methodologies, including differences in sample characteristics, imaging techniques, and analytical approaches, which complicates cross-study comparisons and generalisability. It's also important to note that dopaminergic dysfunction may not be uniformly present across all subtypes or severity levels of depression, anxiety, or OCD, suggesting a need for more nuanced subgroup analyses. Furthermore, biomarkers of dopaminergic activity, such as PET imaging or inflammatory assays, remain expensive and are not yet widely integrated into clinical practice, limiting their utility in routine care.

Future research should prioritize longitudinal, multimodal investigations that combine neuroimaging, genetic, and immunological data. Validating biomarkers in real-world clinical settings will be critical to moving from theoretical insights to practical applications. Moreover, clinical trials should shift focus from categorical diagnoses to symptom dimensions, incorporating biological stratification strategies to improve treatment matching and overall outcomes in precision psychiatry. Most of the findings included in this review relied on cross-sectional data despite strong associative evidence. Longitudinal studies using multimodal imaging and dopaminergic biomarkers are needed to establish causal relationship between dopamine dysfunction and symptom emergence. Future randomized trials should assess the safety and efficacy of dopamine-augmenting agents in patients with confirmed dysregulation. Multi-center studies and pragmatic trials are also needed to test the reproducibility, diagnostic value, and clinical impact of these biomarkers across diverse settings.

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