Minireview

Dysregulation of brain dopamine systems in major depressive disorder

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Impact statement

MDD is produced by complex and heterogeneous disruptions in brain architecture, neuroplasticity, and function, with genetic, epigenetic, and environmental contributions. In addition to other biogenic amines, the symptoms and pathophysiology of depression indicate significant involvement of dysfunction in dopamine and dopaminergic circuits. New studies are providing a much more precise and nuanced view of how depression may originate from neurodevelopmental maladaptations in dopamine-modulated processes, and suggest new targets for therapeutic intervention.

Abstract

Major depressive disorder (MDD or depression) is a debilitating neuropsychiatric syndrome with genetic, epigenetic, and environmental contributions. Depression is one of the largest contributors to chronic disease burden; it affects more than one in six individuals in the United States. A wide array of cellular and molecular modifications distributed across a variety of neuronal processes and circuits underlie the pathophysiology of depression—no established mechanism can explain all aspects of the disease. MDD suffers from a vast treatment gap worldwide, and large numbers of individuals who require treatment do not receive adequate care. This mini-review focuses on dysregulation of brain dopamine (DA) systems in the pathophysiology of MDD and describing new cellular targets for potential medication development focused on DA-modulated micro-circuits. We also explore how neurodevelopmental factors may modify risk for later emergence of MDD, possibly through dopaminergic substrates in the brain.

Keywords: Depression, major depressive disorder, receptor, neurodevelopment, anhedonia, mood

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Major depressive disorder

Major depressive disorder (MDD) is one of the world's greatest public health concerns due to its prevalence, impact, and complexity. MDD, otherwise known as depression or clinical depression, is defined as a prolonged period of time of a person experiencing a depressed mood, loss of interest, or pleasure.[1] MDD affects at least one in six people in the US population,[2] and a 2007 World Health Organization study of over 200,000 adults demonstrated that MDD results in the greatest overall reduction in health when compared with other debilitating and chronic diseases, including diabetes and arthritis.[3] MDD encompasses a variety of symptoms related to mood, cognition, and hedonic systems that implicate multiple central nervous system (CNS) circuits and neural functions.[4,5] These symptoms include anxiety, fatigue, anhedonia, changes in sleep and activity, and even suicidality. It is difficult to ascertain which CNS changes contribute to the underlying pathophysiology of MDD, rather than function as compensatory neuroplastic responses induced by the CNS to ameliorate disease processes. Early studies of the neurobiology of MDD focused largely on the neurotransmitters norepinephrine and serotonin, due to the antidepressant properties of pro-noradrenergic and pro-serotonergic agents, including the selective serotonin reuptake inhibitors (SSRIs). However, serotonergic dysfunction alone is insufficient to fully describe MDD and its treatment (for excellent reviews of this topics, please see references[6,7]). Current antidepressants are associated with only moderate efficacy, delayed therapeutic effects, and significant side effects. Approximately 30% of patients do not remit from MDD, even after several treatment attempts. Moreover, newly developed medications show a high failure rate in clinical trials, and a significant proportion of MDD patients are "treatment-resistant".[8]

Recent studies on MDD have explored several intriguing and important avenues in this regard. First, genetic studies have continued to identify multiple risk alleles and disease-modifying genes across a wide variety of neurochemical and cellular function families.[9] Important environmental,

behavioral, developmental, and epigenetic factors continue to be identified,[10–12] and a more detailed understanding of altered brain architecture is now evident.[13] There is still a pressing need for fast-acting, specific, and efficacious therapies—both pharmacological and behavioral.

Early studies of the monoamine hypothesis of MDD also considered dopamine (DA), but interest in DA soon focused on movement disorders and drug use and abuse. Recently, the crucial role of anhedonia as an endophenotype of MDD has been re-emphasized, and indeed, this is a cardinal symptom of MDD. Anhedonia is unlikely to be a specific symptom of MDD; for example, it is also prevalent in disorders historically linked conceptually to DA dysfunction, such as schizophrenia and Parkinson's disease.[14,15] This also encompasses the complex reward-related deficits observed in MDD such as disruption of decisional anhedonia, which refers to the anticipation, motivation, and decision-making process involved in obtaining a reward.[16,17] Importantly, anhedonia is one the hallmark symptoms of MDD aside from depressed mood, and was shown nearly 50 years ago to be a sign of poor antidepressant response.[18] No treatment has been efficient in treating anhedonia; in this regard SSRIs have been shown to be ineffective for positive affect deficits.[19] In this mini-review, therefore, we focus on dysregulation of brain DA systems in the pathophysiology of MDD and propose new cellular targets for potential medication development focused on DA-modulated micro-circuits and novel cellular targets. We also explore how neurodevelopmental factors may modify risk for later emergence of MDD, possibly through DAergic substrates in the developing brain.

Dopamine and dopamine receptors

DA is a catecholamine neurotransmitter and neuromodulator that primarily acts through binding to high-affinity receptors. DA receptors (D1–D5) are G-protein coupled receptors with relatively slow effects on synaptic signaling through second messenger systems. DAergic systems modulate a wide variety of neural functions and behaviors, including motor control, motivation, reward, cognition, and maternal and reproductive behaviors. DA receptors are divided into two primary families: the D1-like and the D2-like receptors. The D1-like receptor family includes the D1 and D5 receptors, which are encoded by the DRD1 and DRD5 genes, respectively. The D2-like receptor family includes the D2, D3, and D4 receptors, which are similarly encoded by DRD1, DRD2, and DRD4, respectively. Each subtype of DA receptor has a unique regional and cellular pattern of expression, developmental ontogeny, regulatory properties, and functional roles. The two families (D1-like and D2-like) are easily distinguished pharmacologically, but development of truly specific agonists and antagonists of each molecular receptor subtype has been challenging for the field. D1 and D2 receptors are the most abundantly expressed receptors, and are rarely co-expressed in the same neurons, at least in adult animals.[20] D1-like receptor activation can contribute to either excitation or inhibition, dependent on cell type; D2-like receptor activation is usually inhibitory.[21–23] DA signaling is typically terminated by re-uptake of DA through a high-affinity presynaptic transporter (DAT).

The D1-like receptors typically stimulate adenylate cyclase to increase the intracellular concentration of the second messenger cyclic adenosine monophosphate downstream of activation of the adenylate cyclase stimulatory G proteins $G_{\alpha s/\alpha olf}$; this, in turn, stimulates the activity of protein kinase A.[24,25] D1 receptors are mostly found in the caudate and putamen (striatum), substantia nigra pars reticulata, nucleus accumbens (NAc), olfactory bulb, amygdala, and frontal cortex, with D5 receptors particularly expressed in the cerebral cortex.[26,27] On the other hand, D2, D3, and D4 receptors all couple to $G_{\alpha i/\alpha o}$-proteins to primarily inhibit adenylate cyclase.[28] This group of receptors is mainly expressed in the striatum, cerebral cortex, hippocampus, NAc, substantia nigra pars compacta, and pituitary gland.[27,29,30] D2-like receptors can also modulate the Akt-GSK3 signaling pathway which in turn regulates proliferation, differentiation, and gene transcription.[31] MAPK signaling is also modulated by both D1- and D2-like receptors, and this pathway significantly contributes to DA-mediated modulation of cell death, developmental patterning, and synaptic plasticity.[32]

There are several major DAergic pathways in the brain.[33,34] The main brain regions containing DA-containing cell bodies are in the midbrain and consist of the substantia nigra pars compacta (SN) and the ventral tegmental area (VTA). Axons arising from the DA cells in the SN pars compacta form the nigro-striatal tract and provide DA innervation to the dorsal striatum, arranged in a topographical manner. The striatum is part of the basal ganglia, a group of forebrain structures involved in motor control, motivation, and cognition. Degeneration of the nigrostriatal DA neurons is the main pathology of the movement disorder Parkinson's disease, but Parkinson's disease is also characterized by dysfunctions in affect, mood, and reward. The mesolimbic and mesofrontocortical DA systems arise from the medially localized VTA. The mesolimbic system provides DA innervation to subcortical regions including the NAc, septum, olfactory tubercle, hippocampus, and amygdala. The NAc (sometimes also referred to as the ventral striatum) is an important interface for functional output related to motivation and motor systems. The NAc consists of two subregions containing largely GABAergic medium spiny neurons, the core and the shell, and it is a vital component of brain reward systems. The mesofrontocortical system provides dopaminergic afferents to specific cerebral cortical areas, including the orbitofrontal and medial prefrontal cortex (PFC). Disruption of DA neurotransmission within the mesofrontocortical system has been associated with mental health conditions, including schizophrenia, bipolar depression, substance use disorders, and MDD. The PFC is involved in complex cognitive functions including motor planning, attention, and behavioral inhibition and is highly stress-sensitive (see below). The PFC sends glutamatergic projections to forebrain structures including the striatum, midbrain, and hippocampus. Lastly, the tuberoinfundibular DA system is an important hypothalamic pathway,

which connects the hypothalamus and pituitary gland to control prolactin secretion in the anterior pituitary.

Dopamine, stress, and MDD

Roles for the dopamine system in modulating stress and depression-related circuits have been posited for some time (for reviews, see references[35–38]). Mesolimbic and mesocortical DA neurons are activated by acute behavioral stressors, as well as by other behaviorally salient stimuli.[39–42] Mesocortical DA neurons are especially sensitive to acute stressful stimuli such that relatively mild stressors induce marked activation of these neurons and of DA neurotransmission in the PFC. Functional heterogeneity is observed within the mesolimbic projections to the NAc in that behavioral stressors activate DAergic activity to a greater extent in the NAc shell than in the NAc core or dorsal striatum.[43] Studies of conditioned fear also implicate mesolimbic DA pathways as a key controller of fear-related learning, and DA-recipient cell targets in the NAc have been directly implicated in animal models of depression.[36,44] Acute exposure to stress has been shown to increase DA synthesis activity in terminal regions and the rank order of this effect again reflects differential responses across DA circuits (PFC greater than NAc; NAc greater than dorsal striatum). Stress also serves as a crucial potential of drug self-administration and relapse. Collectively, these data demonstrate that region and cell-specific increases in DA neurotransmission and downstream signaling activation occur during exposure to acute stress. Studies in humans reveal that blocking or decreasing DA using pharmacological interventions resulted in induction and deepening of depression.[35] Conversely, antidepressants increase brain DAergic mechanisms[45] and D2-like receptor antagonists are often efficacious successful adjuvants to SSRIs in the treatment of MDD.[46] For example, lurasidone and aripiprazole/brexpiprazole are new agents with DA receptor modulating effects that are both effective in treating depressive symptoms.[46–49]

Rodent models of MDD also implicate and replicate DAergic contributions to MDD-induced cellular and regional pathologies and maladaptations (Table 1; see also the following excellent reviews focused on this topic[50–52]). Anhedonia, again, takes center stage, and this can be assessed through a variety of assays with distinct strengths and limitations, ranging from simple sucrose consumption assays to complex operant models of decisional anhedonia.[5,17,53–58] Because MDD has a such a complex etiology across individuals, animal models similarly utilize a number of induction agents, including acute and chronic stress exposure, early life stress and/or maternal neglect, exogenous administration of glucocorticoids, chronic inflammatory conditions, and genetic manipulations[59–61] (Table 1). Chronic mild unpredictable stress, social defeat stress, and resident-intruder chronic social stress appear to have particularly strong validity and alter a wide variety of neural circuits and behaviors, including CNS DA systems and their targets.[62–69] However, others have argued that laboratory rodents do not encounter the adaptive evolutionary social pressures required for the development of depression, and thus all rodent models of MDD may be irrevocably flawed.[70]

Several key recent studies have brought a focus back to dopaminergic systems, and DA D1 receptors specifically, in considering the underlying pathophysiology of mood disorders. Optogenetic initiation of phasic firing patterns in VTA dopaminergic neurons projecting to the medial PFC induced increased susceptibility to social defeat stress.[65] Another group instead optogenetically inhibited VTA neurons in awake, behaving mice and observed that this instantly reduced struggling in the tail suspension test and induced anhedonia in a sucrose preference test.[71] Within the cerebral cortex itself, overexpression of D1 receptors only slightly increased sucrose preference, but termination of the overexpression (to normal D1 levels) produced profound depression-like behaviors across several paradigms.[72] Several additional studies also implicate dopaminoceptive circuits within the PFC, hippocampus, and amygdala in altering responses to challenges and stressors.[73–75] Beyond MDD, alterations in dopaminergic circadian activity may contribute to rapid mood-cycling in bipolar disorder.[76] A newly identified population of D1 receptor-expressing neurons within a subregion of the medial amygdala determines approach-avoidance conflict in the face of threatening stimuli.[77] A previously neglected population of DA neurons in the dorsal raphe nucleus, the brain region usually associated with 5-HT neurons and the actions of many antidepressant drugs, has recently been demonstrated to functionally contribute to aspects of mood regulation.[78] A newly identified DA-modulated circuit involving D1 receptor-containing neurons in the interpeduncular nucleus contributes vitally to the regulation of anxiety behaviors.[79] In this newly identified circuit, VTA projections to the interpeduncular nucleus activate D1 receptors to modulate a specific subtype of GABAergic neuron, which then differentially excite or inhibit two additional specific subpopulations of neurons to drive anxiety-related behavior. Perhaps most strikingly, D1 receptor-mediated changes in the structure and function of PFC neurons can suppress stress susceptibility.[80] Emerging data from our group indicate that cerebral cortical interneuron deletion of D1 receptors produces mice who have strong antidepressant and stress resilient phenotypes at baseline (Delva and Stanwood, unpublished observations). These data suggest that cell-specific neuropharmacology strategies are needed, location- and signaling-biased ligands may be particularly useful.[81] For example, a ligand that blocks D1 receptors expressed on cortical interneurons, but not D1 receptors expressed by excitatory neurons, striatal medium-spiny neurons, or interpeduncular nucleus neurons would represent a new and exciting mechanism to treat MDD. These studies are also summarized in Table 2.

Individuals with MDD also exhibit changes in markers of DAergic circuits and neurochemical regulation. For example, *in vivo* availability of DAT, as studied with a PET tracer, is reduced both in the putamen and VTA, bilaterally.[82] Reduced DAT levels after stressor exposure have been observed in animal studies as well, and this effect is typically interpreted as reflecting compensatory DAT

Table 1. Animal models, especially rodent models, are a crucial step in understanding the pathophysiology and treatment of MDD and other depression-related disorders, but also have limitations.[a]

Rodent model	Strengths	Weaknesses	Evidence for DA involvement
Chronic social and/or physiological stress	Introduction of salient stressors is an important risk factor for MDD; in rodents, these include temperature, tail- or foot-pinch, isolation, restraint, and defeat during social confrontations; high apparent translational relevance, especially for social stressors; physiological stressors such as temperature and restraint are easily quantifiable and reproducible	Stress is used to induce depression-like traits in rodents, but this has poor specificity and does not specifically induce MDD—instead, elements of anxiety disorders, substance use disorders, and psychosis are also all induced; species-appropriate social stressors are not always utilized	Nearly all external stressors activate at least some central DA neurons and pathways; social defeat and resident intruder social stress alter molecules, cells, circuits, physiology, and behavior related to DA, both as a source of risk but also as substrates for behavioral resiliency; altered phenotypes responsive to DAergic drugs
Unpredictable chronic mild stress (UCMS)	Introduction of chronic low-intensity stressors is an important risk factor for MDD; high translational relevance; reproduces anhedonia (and other) symptoms of MDD	Inconsistent responsiveness across species, strains, and laboratories; unclear how sensitivity to these stressors is offset by neurobiological resilience mechanisms	Mild stress is a risk factor not just for MDD but also for relapse to drug abuse, accompanied by modifications in DA-related circuitry; UCMS-induced changes in DA systems relatively poorly studies to date, but changes in receptor expression
Early life stress (pre- or postnatal) and/or maternal neglect	Encompasses neurodevelopmental risk factors; adverse early-life experiences are important risk factors for MDD and suicide, among other disorders	Complex methodologically and difficult interpretation—parental care and units are very species-specific and resultant phenotypes are sometimes inconsistent; maternal neglect is typically intermittent in rodent models, but chronic in human scenarios; timing of brain development across species varies—for example, early postnatal life for a rodent is equivalent to late prenatal stage in humans	Alterations in DA receptor expression patterns and signaling; genetic and epigenetic changes in DA-related genes; altered differentiation, synaptic structure and morphology in DA neurons and dopaminoceptive brain regions
Olfactory bulbectomy	Simple and reproducible model	Poor face and construct validity and lack of clinical population	Some documented changes in brain DA levels and NAc circuitry; depression-related deficits reversed by some DAergic drugs
Learned helplessness	Learned helplessness induces behaviors that align well with several MDD symptoms from the DSM-V; fairly simple and reproducible; can also be used as a readout for helplessness behavior induced by other paradigms/models	Complex experimental protocols and equipment are required; paradigm likely only mimics a subset of the heterogenous disorder; relatively poor predictive validity for efficacy of antidepressants	
Glucocorticoid/Corticosterone administration	Aberrant hypothalamic–pituitary–adrenal axis activity is a clinical feature of MDD; simple, quantitative, and reproducible insult in animals; can be used in a variety of species, including nonhuman primates	Differential metabolism patterns, regional activation differences, timing between exogenously administered corticosterone, and endogenous; reduces the complex experience of MDD to a single molecule; many patients with MDD have normal cortisol levels	Both DA neurons and their targets express glucocorticoid receptors which respond to stress both acutely and chronically to regulate cognition and motivation
Genetic models (inbred vs. outbred lines; selective breeding for sensitive or resilient traits; targeted gene knockouts, knockins, and transgenics	There are important genetic risk factors for MDD; relatively easy to implement targeted mutations in rodents, especially with current CRISPR techniques	MDD is genetically complex; no single gene mutations produce the disorder in most patients; ignores the crucial role of environmental risk factors unless combined with other paradigms	Depending on the gene mutation under study and the cell-type and developmental timing of the alterations in gene expression patterning and/or function—but many alter specific aspects of DA circuitry

(continued)

Table 1. Continued.

Rodent model	Strengths	Weaknesses	Evidence for DA involvement
Immune system/ Inflammatory-based models	A link between MDD and inflammation (both central and peripheral) has been widely established; immune molecules also have indispensable functions during brain development	Exogenous immune activation strategies are unlikely to mimic the wide-ranging low-grade auto-immune activation observed in MDD	DA systems appear to be a crucial node in dysregulation of brain structure and function following chronic inflammatory insults

[a]Also see the following excellent reviews focused on this topic.[50–52]

Table 2. Summary table of recent key animal studies establishing new specific roles for dopaminergic mechanisms in mood-related circuits and phenotypes.

Citation	Manipulation	Findings	Implications
DeGroot *et al*.[79]	Expressed a genetically encoded G protein-couple receptor activation-based DA sensor in mouse midbrain. Used anatomical, neurochemical, and behavioral techniques to demonstrate a functionally important DA input from the VTA to the interpeduncular nucleus.	DA was detected in the interpeduncular nucleus. Two distinct D1R-dependent subpopulations circuits were identified, which contribute to anxiety responses.	Adds an additional level of necessary complexity to DA-dependent neural micro-circuits in the midbrain.
Freund *et al*.[72]	An inducible lentiviral vector was used to manipulate the expression of D1 receptors in prefrontal glutamatergic neurons in rats.	Elevated D1R expression increased hedonic behavior, and the termination of over-expression produced depression-related behavior.	These findings support a significant role for prefrontal cortical D1R expression in the regulation of mood and hedonic reward.
Miller *et al*.[77]	This research team isolated a specific subpopulation of D1R-expressing neurons in the posteroventral medial amygdala. They used viral tracing, optogenetics, pharmacology, and cell imaging to define effects on conflict-related behaviors.	Distinct subpopulations of the D1R-expressing posteroventral medial amygdala neurons innervate the bed nucleus of the stria terminalis and the ventral hypothalamus. These two projections have opposite effects on approach versus avoidance of threatening stimuli.	Distinct approach and avoidance micro-circuits exist within the medial amygdala and are potently modulated by DA innervation and postsynaptic D1Rs.
Shinohara *et al*.[80]	The authors altered D1R expression in the medial PFC using viral methods and quantitatively examined the effects on behavioral stress responsiveness, as well as changes at the biochemical, neurochemical and neuroanatomical levels.	Repeated social defeat stress reduces D1R expression in the PFC of susceptible mice. D1R knock-down promotes the induction of social avoidance by social defeat. D1Rs also contribute to stress-induced structural synaptic changes in the PFC.	D1R in the dopaminoceptive PFC appear to play a key role in determining sensitivity and resiliency to the behavioral and neuroanatomical effects of stress.
Sidor *et al*.[76]	Examined *Clock*Δ19 mutant mice for circadian cycle-influenced mood-related phenotypes and phenocopied phenomemon in wildtype mice using a novel optogenetic stimulation paradigm of select DA neurons.	Documented rapid mood-cycling across the light-dark cycle in the mutant mice and linked these time-dependent changes in VTA DA neuronal firing and DA synthesis across the light–dark cycle.	These findings document a novel mechanism for regulation of DA synthesis and firing by CLOCK and underscores the importance of normal patterns of DAergic activity in mood-related behaviors.
Tye *et al*.[71]	Used a combination of electrophysiological, optogenetic, and pharmacological methods to examine the impact of VTA DA neurons on stress and depression-related behavior and cell responses.	Identified bidirectional control of specific midbrain dopamine neurons and bidirectionally inducing or relieving multiple independent depression symptoms. For example, optogenetic inhibition of VTA neurons in awake, behaving mice immediately reduces struggling in the tail suspension test and induces anhedonia in a sucrose preference test.	Activation/inhibition of specific midbrain DA neurons modifies the neural encoding of depression-related behaviors in the NAc, suggesting that processes affecting depression symptoms may involve alterations in the processing of action commands in limbic circuitry.

downregulation following blunted DA neurotransmission. Postmortem Western blot analyses confirm the reduction in DAT in the putamen and VTA, but not in the caudate or NAc, and further demonstrate reduced tyrosine hydroxylase, the rate limiting enzyme in DA synthesis.[82] Moreover, the number of depressive episodes and specific symptom presentation within individuals was predictive of the decreases in DAT availability. Individuals with MDD who reported feeling trapped in perceived inescapable circumstances showed the lowest DAT availability in the VTA, suggesting that DAergic impairment might be more prevalent in a subset of people with severe and specific MDD symptoms. Replication of these findings are needed. Importantly, this study focused on unmedicated individuals with MDD and minimal comorbidity with other conditions; these issues have made it difficult to find consistency of findings in human MDD patients. Additional studies have documented reduced reward-related neural fMRI signals in the caudate and NAc,[83] and alterations in both striatal and cerebral cortical responses to positive mood states.[84] Notably then, significant heterogeneity has been observed among studies, with some changes localized to DA cell body-containing regions, and other to terminals and/or dopaminoceptive targets. In addition, some changes localize more strongly to different striatal subdivisions; it is unclear whether this reflects differences in study subjects, in circuit-related neuroadaptations, or in the specific brain mechanisms interrogated by different measurements. Of additional interest, expression of the gene CHRNA7, which encodes a subunit of the nicotinic acetylcholine receptor and regulates cognition through interneuron modulation of DA signaling, is increased in the PFC of patients with MDD.[85] Conversely, protection from MDD following stress can be conferred through resiliency mechanisms. Recent studies of the neurobiology of resiliency indicate that the function of the mesolimbic DA system contributes to adaptive behavioral responses to stress.[86]

Neurodevelopmental origins of MDD and DA dysregulation during brain development

MDD and other neuropsychiatric disorders are increasingly being viewed from a neurodevelopmental perspective, with an understanding that early alterations in neuronal migration, differentiation, and circuit formation provides an altered CNS substrate on which additional deleterious factors in childhood and adolescence can further dysregulate to produce disease.[87,88] Recent studies in animal models and humans strongly implicate cortical GABAergic neuronal development in mood regulation and the pathophysiology of major depression.[89–93] But as is the case with most neuronal substrates, GABAergic interneurons in the cortex are embryonically, structurally, and functionally diverse, regulating a very delicate balance across cortical networks.[94–97] Of note, PFC interneurons receive synaptic input from dopaminergic axons, and express DA D1 and D2 receptors.[90,98–101]

In addition to being a neurotransmitter in the adult CNS, DA has important modulatory roles during pre- and postnatal development.[102] Conversely, altering neural circuits and behavioral experiences during neurodevelopment can dramatically alter the stabilizing and adaptive influences of central DA systems in the adult. For example, pre- or early postnatal exposure to stressors, drugs of abuse, or environmental toxins enduringly alter the neuroanatomical organization, cellular responsiveness, and adaptive plasticity of both DA neurons themselves and their forebrain targets.[103,104] Direct neurodevelopmental roles for genetic and environmental modulation of DA receptors and signaling components have been described by multiple laboratories and in multiple mammalian species.[105–113] The quality of parental care has also been observed to alter these mechanisms in multiple animal species/models, as well as in people. For example, repeated epochs of maternal separation during early postnatal development decrease DAT activity and increase systemic and CNS DA responses to subsequent stressors.[114–116] DA systems are also extremely sensitive to genetic, environmental, and drug-induced modifications during adolescent development.[117,118] Thus, elucidation of these risk factors, their varied but specific effects on neurodevelopmental trajectory, and the development of therapeutic methods to stabilize brain maturation and adaptive plasticity even in the face of such risk factors, are all vital areas of future study in the pathophysiology of MDD and its associated phenotypes.

Delayed DA maturation, connectivity, and plasticity during adolescence may be involved in amplifying the risk to developing mental disorders, particularly in the PFC.[38,119,120] Consequently, environmental influences may disturb adolescent prefrontal dopamine development which eventually either worsen or render individuals to become resistant to certain psychiatric conditions, including MDD and schizophrenia.

Summary

MDD is produced by complex and heterogeneous disruptions in neurobiology with genetic, epigenetic, and environmental contributions. CNS biogenic amines, including DA, have important stabilizing, integrative, and plasticity-related influences on brain circuits. Biogenic amine disruptions are certainly a component of the pathophysiology of MDD, although it remains poorly understood which of these are causal and which may be consequence. Based on emerging studies from animal models and clinical studies, we propose that the brain DA system may be crucially involved in underlying both neuropathological processes and in promoting adaptive mechanisms contributing to resilience, particularly during sensitive periods of development. New technologies and understanding are allowing researchers to frame much more specific hypotheses than ever before. The creation of neuronal cell-type specific pharmacological ligands, coupled with a modern understanding of underlying sub-circuits and neuroplastic mechanisms, has the ability to allow us to take the management of this disabling disorder to the next level. Ultimately, the heterogenous spectrum of clinical MDD requires a diversity of therapeutic options and specific modulation of DA sub-circuits within the CNS will add measurably to our pharmacological treatment repertoire.

AUTHORS' CONTRIBUTIONS

All authors participated in the writing and review of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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