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Melancholy, anhedonia, apathy: the search for separable behaviors and neural circuits in depression

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Major depressive disorder can manifest as different combinations of symptoms, ranging from a profound and incapacitating sadness, to a loss of interest in daily life, to an inability to engage in effortful, goal-directed behavior. Recent research has focused on defining the neural circuits that mediate separable features of depression in patients and preclinical animal models, and connections between frontal cortex and brainstem neuromodulators have emerged as candidate targets. The development of methods permitting recording and manipulation of neural circuits defined by connectivity has enabled the investigation of prefrontal-neuromodulatory circuit dynamics in animal models of depression with exquisite precision, a systems-level approach that has brought new insights by integrating these fields of depression research.

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Introduction

Depression is a debilitating psychological disorder affecting nearly one-fifth of Americans [1]. Despite its prevalence and societal impact, we have not yet achieved the ability to successfully treat all cases of depression, and some patients remain treatment-resistant despite exhaustive attempts at resolution. It is clear that while much progress has been made in recent years, we do not fully understand the neural mechanisms underlying the entry into and exit from the depressed state, and why some are vulnerable to stressors while others are resilient. A contributing factor is that major depressive disorder is defined by a wide range of symptoms, which can include depressed mood (sadness, emptiness, or hopelessness), loss of interest or pleasure in everyday activities (anhedonia), fatigue or decreased energy, impaired concentration or decision-making, psychomotor agitation or retardation, insomnia or hypersomnia, weight loss or weight gain, and others [2]. It is unclear if biologically distinct processes underlie the presence of different symptoms in different people, or if, instead, a common dysfunction simply manifests differently in different brains.

The variability in symptoms, combined with the lack of definitive biomarkers, has presented a major challenge for modeling depression in the laboratory. Encouragingly, recent years have seen the rapid development of transformative technological developments that should accelerate progress substantially. Machine learning methods for the automated and high-throughput analysis and classification of rodent behaviors have extraordinary promise for defining distinct clusters of stress-induced behaviors in mice [3–5]. The development of methods to monitor and control specific subsets of neurons defined by genetics and connectivity [6,7], and advances in analytical methods for revealing structure in high-dimensional networks [8–10] will allow investigators to determine the contributions of distinct neural circuit elements, structural and functional network motifs, and whole-brain activity patterns [11••] to potentially separable clusters of behavioral changes. These developments will move the study of depression toward a circuit-level understanding, and may help to define new treatment targets and refine diagnostic criteria.

Features of depression: melancholia, anhedonia, apathy

Different types of depression are associated with markedly different symptoms. Depression with melancholic features is associated with anhedonia, lack of mood reactivity, sadness, weight loss, insomnia, psychomotor agitation, and worse mood in the morning. Depression with atypical features, on the other hand, is associated with a distinct cluster of symptoms, and includes leaden paralysis, fatigue, weight gain, hypersomnia, mood reactivity, sensitivity to social rejection, and worse mood in the evening. It is currently unclear whether the inclusion of such profoundly different clusters of symptoms under the umbrella of a single disorder is a help or a hindrance for the development of treatments. The association of tricyclic antidepressants with better outcomes for melancholic depression [12] and bupropion for atypical depression [13], suggests (but does not mandate) differences in the underlying biology.

Animal models of depression

A depression-like behavioral state can be induced through exposure to chronic mild stress (CMS) or chronic social defeat stress (CSDS) [14–16], immunogenic factors [17,18], or through selection for helplessness-like behavior [19], among other methods. A subset of depression-related human behaviors can be modeled more or less successfully in rodents, but debate about the meaning and relative merits of different behavioral tests continues [20]. *Anhedonia*, the lack of interest or pleasure in daily activities, is modeled by the sucrose preference task, in which rodents are given free choice of drinking water or sucrose solution; normal rats and mice show robust sucrose preference, which is reduced by stress and rescued by antidepressant drugs [14,21]. *Behavioral despair* is modeled by the forced swim test (FST), in which the amount of time spent struggling to escape a tank of water is measured [22]. There is some concern that the FST may not be specific to depression, and may instead measure changes in stress-coping strategy common to many psychiatric disorders [23] (although the same criticism could be leveled at the sucrose preference test); additionally, acute single-dose selective serotonin reuptake inhibitor (SSRI) administration improves behavioral performance much faster than remission occurs in humans [20]. The chronic social defeat paradigm, developed to model depression-related *social withdrawal*, is a better model for the delayed onset of SSRI antidepressant drugs in humans [15,16]. Tests such as the effort-related choice test [24,25] were developed to model *fatigue or reduced energy*, and attempt to differentiate between motivation (the willingness to expend effort for reward) and consummatory pleasure [26]; encouragingly, rodent and human performance seems to depend on similar neural circuits [24].

Depression and the prefrontal cortex

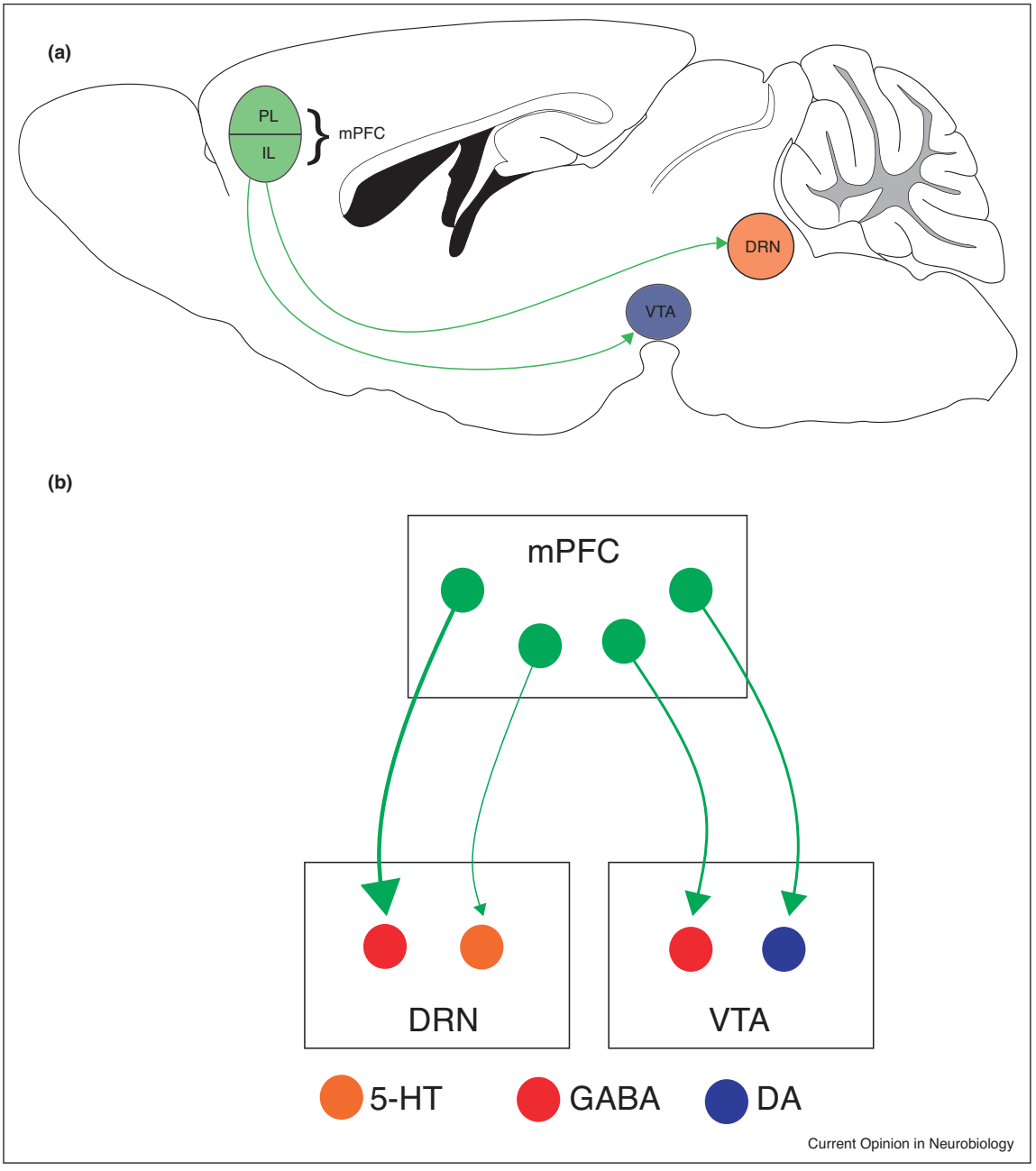
The prefrontal cortex (PFC) is well positioned to integrate behaviorally relevant information from limbic, cognitive, sensory, and motor regions [27], and medial PFC in particular is thought to play a major role in value-based decision making [28,29]. There is a growing clinical literature supporting a role for the subgenual cingulate cortex (SCC), a PFC subregion, in depression [30]. Functional neuroimaging has shown that SCC activity is elevated in treatment-resistant depressed patients and during normal sadness [31]. Additionally, high-frequency deep brain stimulation (DBS) of white matter tracts adjacent to the SCC has been shown to decrease activity in this region relative to pre-DBS baseline and to be therapeutic in a subset of patients [32]. Although large-scale clinical trials based on this initial data have had mixed results [33], the SCC continues to be a prime focus for research on the neural circuit dysfunction underlying depressive behavior, particularly in animal models [34,35].

The infralimbic cortex (IL) in rodents is thought to share some features with the human SCC, a correspondence based on similarities in connectivity with brainstem, limbic, and striatal regions, and on similarities in function [36,37]. Some studies do not differentiate IL from the adjacent prelimbic cortex (PL); in these cases, we will refer to medial PFC (mPFC; Figure 1). DBS of the SCC may induce its antidepressant effects via white matter tracts, altering its communication with downstream targets (for a full review on the proposed mechanisms of DBS, see Veerakumar and Berton [38]). Chronic electrical stimulation of the rat mPFC has been shown to increase swimming in unstressed mice on the FST [39] and can reverse anhedonia in a rodent model of depression [40]. Similarly, high-frequency optogenetic stimulation of a mixed population of excitatory and inhibitory neurons in the mPFC has been shown to exert an antidepressant-like effect, increasing both social interaction and sucrose preference [41]; a potential caveat to this result is the existence of long-range cortical GABAergic projections, which raises the possibility of behavioral changes driven by distal inhibition [42]. Stimulation of all cells in the region at supraphysiological frequencies (perhaps resulting in disconnection or net inhibition) appears to be key, as optogenetically stimulating excitatory mPFC neuronal cell bodies at a lower frequency intended to maximize glutamate release at the terminal does not have an antidepressant-like effect on the FST [43].

Supporting the correlation between increased mPFC activity and depression-like behavior, Ferenczi *et al.* [44••] chronically elevated the activity of excitatory pyramidal cells in the rat mPFC using a stabilized step-function opsin that increased spontaneous firing rate [45], and found that this intervention decreased sucrose preference and sociability, a pro-depressant-like behavioral effect. Additionally, elevating mPFC activity decreased the striatal blood-oxygen level dependent (BOLD) imaging response to dopamine (DA) neuron stimulation [44••]. Coherence has been detected between mPFC neural activity and multiple downstream regions in normal animals [46•,47], and elevated mPFC activity may disrupt coherence, leading to changes in mood and behavior. Indeed, it has been shown in mice that short-term stimulation of descending pyramidal mPFC cells at endogenous, slow frequencies synchronizes the nucleus accumbens, amygdala, and ventral tegmental area, and that this synchronization has an antidepressant and anxiolytic effect [47]. Conversely, chronic stress desynchronizes these areas and elicits social aversion, a depression-like symptom [46•].

The model derived from rodent studies — that chronically increased mPFC activity typical of the depressed state disrupts normally synchronous activity within and between subcortical regions — is supported by recent clinical evidence. Drysdale *et al.* [11••] found multiple distinct neurophysiological patterns that correlate with

Figure 1



(a) Projections of the medial prefrontal cortex. The medial prefrontal cortex (mPFC), and the prelimbic (PL) and infralimbic cortex (IL) specifically, send excitatory projections widely throughout the brain. This review focuses on projections to two subcortical regions: the serotonergic dorsal raphe nucleus (DRN) and the dopaminergic ventral tegmental area (VTA). IL, infralimbic prefrontal cortex; mPFC, medial prefrontal cortex; VTA, ventral tegmental area; DRN, dorsal raphe nucleus. **(b)** Projections of the medial prefrontal cortex. The medial prefrontal cortex innervates the DRN and VTA. Projections to the DRN preferentially synapse onto GABA neurons, while projections to the VTA are divided between DA and GABA neurons. mPFC, medial prefrontal cortex; VTA, ventral tegmental area; DRN, dorsal raphe nucleus.

unique clinical profiles; hyperconnectivity in frontostriatal networks was associated with anhedonia and psychomotor retardation, and reduced fronto-amygdala connectivity was associated with anxiety. In both cases, the functional relationship between the PFC and subcortical regions was disturbed, suggesting that this may be a hallmark of depression.

In the remainder of this review, we will consider two of these subcortical regions: the dorsal raphe nucleus

(DRN), and the ventral tegmental area (VTA), source of the majority of forebrain serotonin (5-hydroxytryptamine; 5-HT) and DA neurons, respectively. We will review how these areas respond to stress, and how activity in these regions is controlled by the mPFC.

Prefrontal control of the dorsal raphe nucleus

The DRN has long been a prime focus of depression research, spurred by the monoamine hypothesis and the clinical efficacy of antidepressant drugs — initially monoamine oxidase inhibitors and tricyclic antidepressants, then rationally designed selective serotonin reuptake inhibitors (SSRIs) [48]. The temporal dynamics of synaptic 5-HT following SSRI administration are complex, and the net effect of this intervention on circuit operation is still unclear [48].

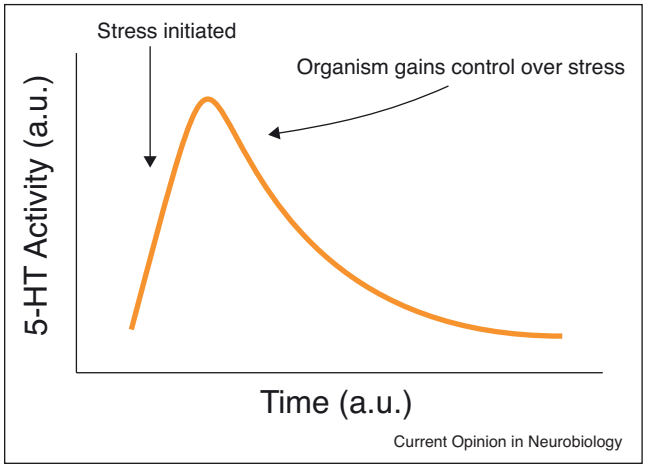
Exposure to an uncontrollable stressor such as a tail shock strongly activates 5-HT neurons and induces a helpless state, but if an animal can control the stressor (e.g. by spinning a wheel to escape a shock), 5-HT activity rapidly returns to baseline [49]. Foundational work by Maier *et al.* demonstrated that the mPFC is necessary for this reduction in 5-HT activity; when the mPFC is pharmacologically inhibited, the animal learns and performs the escape behavior, but serotonin remains elevated [50]. Because the mPFC preferentially synapses onto inhibitory GABA neurons in the DRN (Figure 2), mPFC activity may serve to decrease serotonin release [51,52].

The development of optical tools for neural circuit intervention [53,54] has enabled the functional role of the projection from the mPFC to the DRN to be directly investigated in behaviors relevant to depression in rodents. Acute optogenetic stimulation of mPFC terminals in the DRN was shown to increase escape-related behaviors in the FST without increasing generalized locomotor activity, pointing toward a specific role of this projection in motivated response to challenge [43]. Interestingly, activating this circuit during exposure to an aggressor's cues was shown to decrease later social interaction [51], a pro-depressant-like effect that suggests the possibility of a role for this circuit in enhancing stress learning. A major remaining challenge is understanding how mPFC input to DRN GABA neurons differs from similar habenular and retinal inputs that may promote negative states [55–57].

Prefrontal control of the ventral tegmental area

Unlike 5-HT, dopamine (DA) neurons in the ventral tegmental area (VTA) do not project widely and diffusely, but rather concentrate on two primary targets: the striatum and frontal cortex [58]. Ventral striatum-projecting DA neurons signal reward prediction error — outcomes that are better than predicted result in phasic DA bursts, while those that are below expectation lead to transient

Figure 2



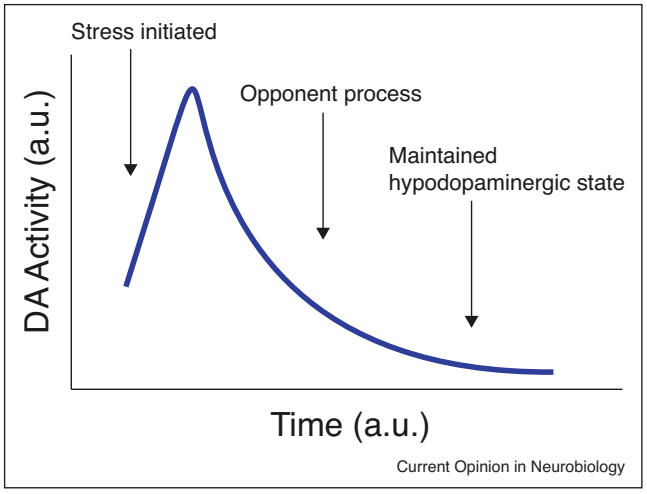
Serotonin dynamics under stress. Upon the initiation of stress, 5-HT activity rises. It recedes to baseline when the animal learns that it can control its environment; otherwise, if stress is inescapable and prolonged, 5-HT level remains elevated.

firing rate decreases [59,60,61••]. The role of DA signaling in the PFC has been somewhat less clear. Stimulation of inputs to mPFC-projecting DA neurons has been shown to elicit chronic place aversion [58], but direct stimulation of mPFC-projecting DA neurons did not produce this effect [62••]. Instead, mPFC DA may function as a modulator of cognitive strategy [63], enabling animals to switch between exploration (random choice) and exploitation (perseveration) [62••].

Two of the hallmark symptoms of depression — anhedonia and decreased motivation — may be partially attributable to dysfunction in the DA system. DA activity increases with the onset of stress and decreases as the stressful environment becomes chronic, and a subset of DA neurons transiently increases their activity in response to stressful events [64–68] (Figure 3). Like 5-HT, DA levels remain high in the mPFC during inescapable shock [69]. Exposure to chronic mild stress (CMS) decreases both the number of spontaneously active DA neurons [70] and the mean firing rate and bursting duration of DA neurons relative to the same neural population in unstressed controls [71]. DA neurons exhibit functional diversity along the medial–lateral axis in the VTA [72], but it appears that at least a subset of DA neurons undergo an opponent process: acute activation brought on by intense stress is followed by a much longer-lasting compensatory decrease in activity [73,74]. It should be noted that there is some disagreement in the field regarding electrophysiological classification of dopaminergic neurons, and that not all of the studies cited above used the same criteria [60,75].

In addition to gradually decreasing spontaneous dopaminergic activity, CMS elicits decreases in sucrose

Figure 3



Dopamine dynamics under chronic stress. During acute stress, DA activity rises. Hours later, an opponent process occurs in which DA levels recede below baseline. If chronic stress is maintained, a hypodopaminergic state arises in which tonic DA activity is significantly lower than pre-stress baseline.

preference and in the FST and the analogous tail suspension test (TST), in which a mouse is suspended from its tail and cannot climb to safety. Optogenetically stimulating VTA DA neurons of CMS-exposed mice in a phasic pattern increases sucrose preference and struggling on the TST to the levels of unstressed controls [71]. These results demonstrate that increasing dopaminergic firing in chronically stressed mice can rescue depression-like behaviors in these tests.

Unlike CMS-exposed mice which show fewer spontaneously active DA neurons, mice susceptible to chronic social defeat stress (CSDS) have elevated DA neuron firing rates relative to resilient and unstressed mice [76]. This occurs via an upregulation of the hyperpolarization current (I_h) which depolarizes the dopaminergic neurons above threshold after CSDS; resilient mice have normal dopaminergic firing rates as the increased I_h is compensated for by an upregulation in repolarizing potassium channels [77]. In mice that have been exposed to a subthreshold, three-day CSDS paradigm, phasic stimulation of dopaminergic neurons in the VTA either during the sensory period post-defeat or during the social interaction test elicits a susceptible phenotype, decreasing social interaction and sucrose preference [78]. At first glance, these results may appear irreconcilable with the finding that phasic DA stimulation in CMS-exposed mice is antidepressant [71]; however, more recent results have shown that the pro-depressant effects of activating the DA projection to the striatum is dependent on brain-derived neurotrophic factor (BDNF), and not DA, release from VTA axons [79]. Other explanations for these apparent inconsistencies in DA activity in the CMS and CSDS models include the idea that DA stimulation during a stressful event (the sensory period post-defeat or during interaction with the confined aggressor) could act to reinforce the aversiveness of these situations, and the possibility that differences in the timing of the stimulation relative to stress may be critical.

The extent to which the mPFC controls DA activity in states of stress remains understudied. Anatomical evidence indicates a sparse [80] projection from mPFC to the VTA [37,81,82]. Unlike the mPFC-DRN projection in which there is preferential innervation of DRN GABAergic neurons, mPFC innervation of the VTA includes relatively equal proportions of synapses onto VTA dopaminergic and GABAergic cells [81,83]. Functionally, pharmacological excitation of the mPFC inhibits DA firing in the medial VTA, and pharmacological inhibition of the mPFC in CMS-exposed rats recovers DA firing to the levels of unstressed rats [84•]. Additionally, pharmacological inhibition of the mPFC increases DA phasic firing [85]. This work suggests that the functional relationship between the mPFC and the VTA is similar in form to the mPFC-DRN circuit — in both cases, mPFC activity may serve to inhibit the firing of neuromodulatory projections [50].

Behavioral activation and inhibition systems

An imbalance or dysfunction in the systems mediating behavioral activation (BAS) and behavioral inhibition (BIS) has been proposed as a potential underlying mechanism for major depressive disorder [86], but this theory has not been tested at the neural circuit level. A functional opponency between DA and 5-HT has been suggested [87,88], based partially on DA facilitation of movement [24,89–91] and 5-HT suppression of movement [92–94], but also inspired by the roles of these systems in reward and aversion. Dorsomedial prefrontal cortex (prelimbic and anterior cingulate cortex) and ventromedial frontal cortex (infralimbic and orbitofrontal cortex) are other potential candidates for brain regions mediating behavioral activation and inhibition, respectively; indeed, recent work has demonstrated a gradient of zones in the PFC that suggests a role for these areas in proactive and reactive behavior [95••]. Subjective reactions induced by DBS in dorsomedial PFC include the feeling of rising to challenge and persevering toward a goal even though there are obstacles in the way [96], while reactions provoked by DBS in ventromedial PFC include a sense of calmness, heightened perception, and lightness [32], effects that raise the possibility of energizing and pacifying roles for these circuits, respectively. Several recent papers have utilized rabies tracing methods to characterize brain-wide inputs to VTA DA and DRN 5-HT neurons [80,83,97,98]; unfortunately, inconsistencies between studies preclude firm conclusions about the relative strengths of dorsomedial and

ventromedial PFC inputs to the VTA and DRN at this time, but the functional roles of these circuits suggests the possibility for synergy and a mapping onto distinct symptoms of depression.

Concluding remarks

Major depressive disorder is associated with a wide range of symptoms, some shared by other psychiatric disorders, and progress toward treatment and resolution will likely accelerate as separable neural circuits for different symptoms are discovered. Methods for automated, high-throughput behavioral classification will allow the detection of behavioral clusters that emerge following stress exposure, and optical methods such as endoscopic calcium imaging, fiber photometry, and optogenetics now allow researchers to investigate the neural dynamics and functional roles of depression-relevant circuits with unprecedented specificity. We are poised to explore and shape the vast terrain of dynamic interactions between brain regions during normal and pathological states, and the discoveries that emerge from these studies will provide greater translational power and deeper insight into the neural underpinnings of depression and will likely have relevance for understanding the roles of these circuits in adaptive behavior.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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This paper demonstrates that elevating vmPFC activity increases depression-like behaviors, and additionally decreases the striatal response to dopamine — perhaps a neural mechanism underlying anhedonia.

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