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Current Opinion in Neurobiology

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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Current Opinion in Neurobiology 2018, **49**:192–200

This review comes from a themed issue on **Neurobiology of behavior**

Edited by **Kay Tye** and **Nao Uchida**

https://doi.org/10.1016/j.conb.2018.02.018

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