Toward Circuit Mechanisms of Pathophysiology in Depression

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The search for more effective treatments for depression is a long-standing primary objective in both psychiatry and translational neuroscience. From initial models centered on neurochemical deficits, such as the monoamine hypothesis, research toward this goal has shifted toward a focus on network and circuit models to explain how key nodes in the limbic system and beyond interact to produce persistent shifts in affective states. To build these models, researchers have turned to two complementary approaches: neuroimaging studies in human patients (and their healthy counterparts) and neurophysiology studies in animal models, facilitated in large part by optogenetic and chemogenetic techniques. As the authors discuss, functional neuroimaging studies in humans have included largely task-oriented experiments, which have identified brain regions differentially activated during processing of affective stimuli, and resting-state functional MRI experiments, which have identified brain-wide networks altered in depressive states. Future work in this area will build on a multisite approach, assembling large data sets across diverse populations, and will also leverage the statistical power afforded by longitudinal imaging studies in patient samples. Translational studies in rodents have used optogenetic and chemogenetic tools to identify not just nodes but also connections within the networks of the limbic system that are both critical and permissive for the expression of motivated behavior and affective phenotypes. Future studies in this area will exploit mesoscale imaging and multisite electrophysiology recordings to construct network models with cell-type specificity and high statistical power, identifying candidate circuit and molecular pathways for therapeutic intervention.

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Depression is a highly heterogeneous psychiatric syndrome and the leading cause of disability worldwide (1, 2). Selective serotonin reuptake inhibitors, the psychopharmacological mainstay of treatment for over 30 years, are highly effective in some individuals but only partially effective or ineffective in up to two-thirds of patients (3–5). Efforts to develop new antidepressant drugs have been challenging, in part because our understanding of depression pathophysiology and antidepressant mechanisms is still in its infancy. Thus, there is a pressing need for a mechanistic understanding of depression pathophysiology that might open avenues to developing fundamentally new treatment strategies.

The monoamine hypothesis and other early pioneering models of depression neurobiology focused on the role of neurochemical deficits (6–8). These models found support in data showing that monoamine oxidase inhibitors are effective antidepressants and appear to function by increasing serotonergic and noradrenergic signaling (8). Later studies showed that dietary tryptophan depletion was sufficient to induce depression in patients with a family history of mood disorders (9), lending further support to the hypothesis that a serotonin deficit may play a central role in the etiology of depression. The monoamine deficit model was later expanded to emphasize the role of deficits in dopaminergic signaling in mediating anhedonia, amotivation, and cognitive symptoms in depression (10). However, important limitations of the monoamine hypothesis and other neurochemical deficit models were also apparent: not all drugs that modulate monoaminergic signaling are effective antidepressants; tryptophan depletion is not sufficient to cause depression in that it has no effect on healthy individuals without a family history; and monoamine-targeting antidepressants elicit rapid changes in serotonin and noradrenaline signaling but do not produce rapid antidepressant effects and can even be anxiogenic initially (8, 9). Furthermore, depression is widely understood to be a heterogeneous syndrome, not a unitary disease entity, with a weak correspondence to any single biological substrate (11, 12). This implies that different pathophysiological processes may be involved in different patients, as opposed to a single unifying etiology.

These observations have motivated increasing interest in developing and testing alternative models in which depression is understood to arise from dysfunctional information processing in specific brain circuits and networks (13). In these circuit-focused frameworks, monoamine neuromodulators are still key players in depression pathophysiology,

in that they exert a powerful influence on circuit function, but monoamine-targeting antidepressants are thought to achieve their therapeutic effects by engaging plasticity mechanisms, remodeling synaptic connectivity, and altering the functional properties of specific circuit elements (13). Our understanding of depression pathophysiology is still rudimentary, especially at the level of neural circuits and networks, but converging findings from functional neuroimaging in patients and neurophysiology studies in animal models—enabled by rapidly developing technologies for probing and manipulating brain circuit function with remarkable precision—have begun to identify key neuroanatomical substrates and delineate circuit-level mechanisms that may give rise to specific depression-related behaviors and symptoms.

Here, we provide a brief review of significant and consistent findings that have emerged from this area of research and discuss promising future directions for delineating mechanisms of depression pathophysiology at the level of neural circuits and networks. This is not intended to be a comprehensive review of findings from neuroimaging studies and animal models, which are available elsewhere, as noted below. Instead, we focus on highlighting emerging insights from efforts to understand depression pathophysiology at the neural circuit level, and we discuss especially promising avenues for future research, including new approaches to understanding depression pathophysiology using human functional MRI (fMRI) and leveraging new technologies to delineate causal mechanisms in animal models of specific behaviors and motivational states.

NOVEL NEUROIMAGING APPROACHES FOR UNDERSTANDING CIRCUIT DYSFUNCTION IN DEPRESSION

A large and rapidly expanding body of research (>2,300 studies to date) has sought to delineate brain networks that are altered in depression, using noninvasive neuroimaging tools. (Note that we use the term "depression" to refer throughout to unipolar major depressive disorder, not bipolar depression, except as otherwise noted.) Although some early studies were limited by small sample sizes—a problem that can be compounded by diagnostic heterogeneity—recent reviews and meta-analyses have identified multiple consistent findings. Structural MRI studies indicate that depression is associated with volume reductions in the thalamus, basal ganglia, hippocampus, prefrontal cortex (PFC), and orbitofrontal cortex, and in some studies, in the amygdala and anterior cingulate cortex (14). However, these differences are modest and highly variable across individuals, and it remains unclear whether these changes in volume are caused by loss of neurons, dendritic atrophy, loss of glial cells, or some other process. Task-based fMRI and positron emission tomography studies have identified functional correlates in some of the same brain regions, including increased amygdala activation in response to negative words and fearful or sad faces (15–18); decreased lateral prefrontal activity during emotion regulation and executive control tasks (18, 19); increased blood flow in the subgenual anterior cingulate cortex and anterior insula and decreased blood flow in the right dorsolateral PFC in both normal sadness and depression (20); and reduced reward responsiveness in the nucleus accumbens (21). A meta-analysis found that across a variety of tasks and experimental paradigms, depression is consistently associated with hypoactivity in the dorsolateral PFC, superior temporal cortex, insula, and cerebellum, and hyperactivity in the thalamus, caudate, visual cortex, and ventrolateral and anterior PFC (22).

More recently, investigators have turned to using resting-state fMRI to characterize functional connectivity abnormalities in depression, an appealing approach because the experimental demands are low (rendering it accessible to a larger group of patients) and because resting-state fMRI data sets from multiple sites can in principle be combined and integrated to yield much larger samples (discussed in more detail below). Early studies showed that depression is associated with increased functional connectivity involving the subgenual anterior cingulate cortex, thalamus, and default mode network (23, 24), reduced functional connectivity in frontoparietal task control networks (25), and abnormal interactions between frontoparietal control networks and the default mode network (25–27)—findings that have been consistently replicated in recent meta-analyses (28, 29).

Together, these studies define a network of brain areas that are consistently altered in depression, but they also have some important limitations and raise several unanswered questions. First, these findings are highly significant and consistent but they are also observational in nature, so it is unclear whether and how any of these structural and functional abnormalities are causally involved in driving specific depressive symptoms and behaviors, or are merely correlated with some other more important mechanism. In the following section, we discuss how human neuroimaging data can be used to formulate mechanistic hypotheses that could be tested in animal models, leveraging optogenetic and chemogenetic tools, neurophysiological recordings, and increasingly sophisticated behavioral assays. Although outside the scope of this review, it is also worth noting that promising approaches are increasingly available for testing causal mechanisms in humans. These include deep brain stimulation (DBS) (30) and concurrent transcranial magnetic stimulation (TMS) and fMRI (27, 31) for manipulating brain circuit function in vivo and sophisticated brain lesion mapping analyses for identifying brain network pathology that is necessary and sufficient for producing specific symptoms and behaviors (32–34).

Second, most neuroimaging studies to date have relied on cross-sectional analyses, in which a group of patients who are currently depressed is compared with a group of never-depressed healthy control subjects. This approach can be powerful, but it precludes any efforts to understand how changes in brain circuit structure and function contribute to the induction and remission of depressive episodes over time. Third, depression is a highly heterogeneous syndrome, but most neuroimaging studies have tended to ignore diagnostic

heterogeneity or mitigate its effects by focusing on a more homogeneous but potentially unrepresentative subpopulation. This approach is advantageous because it increases statistical power to detect functional abnormalities that are shared by most patients at the group level, but it is also limiting in that it is not well designed to detect pathophysiological processes that are operating in only a subset of patients, and it may obscure potentially important individual differences. These problems are potentially compounded by the fact that for feasibility reasons, most depression neuroimaging studies have involved relatively small samples, typically on the order of 25–50 patients. Below, we discuss two complementary and emerging approaches in depression neuroimaging that have the potential to overcome these obstacles: large-scale neuroimaging collaborations involving hundreds or thousands of patients scanned at multiple sites and "deep sampling" studies that aim to study a small group of individuals intensively over time.

Large-Scale Neuroimaging Studies

Facilitated by technical advances and earlier models for harmonizing and integrating data acquired across multiple sites, such as the Human Connectome Project (35, 36), large-scale collaborative depression neuroimaging projects are becoming increasingly common. Extremely large samples offer multiple advantages. On the technical side, statistical power is dramatically increased, reproducibility can be systematically characterized, and more sophisticated multivariate analysis techniques can be employed. Conceptually, they have the potential to facilitate fundamentally new approaches to understanding and characterizing diagnostic heterogeneity, discovering novel subtypes of depression, investigating how genetic variants influence brain network function, and studying the impact of demographic factors such as sex and age that are critically important in depression but can be hard to study in smaller samples.

Although this is a relatively new approach in depression research, there are already some promising early successes. The UK Biobank consortium is perhaps the largest-scale example; it is tracking the health of >500,000 participants, including mental health variables and fMRI scans in >20,000 participants. As expected for an epidemiologically representative cohort, depression is highly prevalent in the sample (7%−12% with a lifetime history of recurrent unipolar depressive episodes and 1.3% with a lifetime history of bipolar depression) (37). One recent study tested for structural abnormalities in a sample of >1,000 participants with a lifetime history of depression—orders of magnitude larger than samples in many previous studies—and found a significant reduction in white matter integrity (indexed by diffusion-weighted imaging) in multiple white matter tracts (38). Interestingly, they did not observe significant reductions in volume in any subcortical structure in these patients with a lifetime history of depression, in contrast to the results of the meta-analysis discussed above. In contrast, recent results from the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) consortium, another large-scale multisite neuroimaging collaboration (39), included a significant reduction in hippocampal volume that was driven by patients with recurrent episodes, but no significant volume reductions were observed in other subcortical structures (40). Important technical considerations (e.g., differing sample sizes and methods for diagnosing depression and varying approaches to parcellating brain structures, defining statistically significant effects, and correcting for clinical heterogeneity and positive publication bias in meta-analyses) could account for these contrasting results. It is also important to note that the meta-analyses discussed above tended to focus on currently depressed individuals, whereas the UK Biobank and ENIGMA studies included both currently euthymic individuals with a lifetime history of depression and currently depressed individuals. This suggests that some of the previously observed findings may be mood-state dependent, and it further underscores the need for longitudinal studies tracking the same patients over time. Another strength of the UK Biobank and ENIGMA samples is that DNA sequencing data are available for many participants, which could enable efforts to investigate how known genetic risk variants influence brain network properties in depression. One recent report involving >322,000 participants identified 17 independent genetic loci conferring risk for depression with genome-wide significance (41). Interestingly, another study (42), involving 978 individuals, tested whether polygenic risk scores for depression predicted subcortical volumes or white matter microstructure and found no significant associations, suggesting that polygenic risk variants may not modulate brain structure, at least not in this sample with a lifetime history of depression (as opposed to a current depressive episode).

Large-scale multisite samples will also facilitate efforts to understand diagnostic heterogeneity at the brain network level and to predict individual differences in treatment response based on structural and functional circuit measures. Multiple multisite collaborations have begun to investigate how abnormalities in specific circuits and functional networks predict individual differences in the antidepressant response to SSRIs (43, 44) and repetitive TMS (rTMS) (45) or differential response to antidepressant medications compared with cognitive-behavioral therapy (46). Leveraging relatively large samples, we and others have used multivariate analytical methods to discover linked dimensions of brain network dysfunction that predict individual differences in clinical symptoms in depression and related affective disorders (47–50), and clustering methods to identify putative subtypes of depression characterized by distinct patterns of abnormal connectivity (48, 50–54). Importantly, these approaches also involve several technical obstacles that warrant careful consideration, including challenges in integrating multisite neuroimaging data (55); controlling for head motion (56, 57) and other physiological artifacts (58, 59) in the MR blood-oxygen-level-dependent (BOLD) signal; optimizing the signal-to-noise ratio and test/retest reliability

(60, 61); and implementing methods to reduce overfitting and to maximize the generalizability of machine learning and other statistical models (49, 62). (For a review, see Lynch et al. [63]).

Longitudinal "Deep Sampling" Studies

A complementary but equally promising future direction involves repeated longitudinal imaging of a small group of study subjects over time. Depression is fundamentally an episodic form of mental illness, yet the mechanisms that mediate transitions into and out of depressive episodes are not well understood, especially at the neural circuit and network levels. Although relatively few studies have systematically tracked the temporal dynamics of depressive symptoms over time in individual patients, those that have indicate remarkable heterogeneity (64, 65). The mechanisms that mediate the induction of a depressive episode, its maintenance and subsequent remission, and the durability of that remission are not well defined. Why some patients experience multiple depressive episodes annually, while others may remain euthymic for years between episodes, is unknown. To date, most neuroimaging studies have involved cross-sectional analyses, but longitudinal studies will be critical for answering these questions.

Longitudinal imaging studies in healthy human subjects have already yielded several important results. First, by repeatedly imaging the same individual (60, 66) or a small group of individuals (61, 67–69) over a period of several months, these studies showed that fMRI measures of functional connectivity are stable over time within individuals, but the stability of these measures depends on the duration of the fMRI scan (60, 67, 68). Shorter scans tend to yield unstable functional connectivity measures, which may be due in part to measurement noise but may also be related to the fact that they are derived by correlating low-frequency fluctuations in the MR BOLD signal, which may not be adequately sampled in short-duration scans. This finding further reinforces the consensus that future neuroimaging studies, including fMRI studies in depression, would benefit from incorporating resting-state fMRI scans of at least 10–15 minutes. Second, although functional connectivity measures derived from longer scans are stable overall, dynamic changes in some connections are also evident over months and even days and can be influenced by arousal, caffeine intake, and whether the subject has eaten or is fasting (61, 66). Although these studies did not involve depressed patients, this result is important for depression neuroimaging because it supports the hypothesis that dynamic functional connectivity changes could be important mediators of state-dependent changes in mood symptoms as opposed to trait-like markers of depression susceptibility. Third, for the first time, they identified important individual differences in the topology of functional networks (61, 67–69). Just as human faces are individually unique while also sharing key features such as two eyes, a nose, and a mouth, functional brain networks are organized in similar ways across individuals, but there are also important individual differences in the precise shape and boundaries of these networks. Thus, group-level approaches to analysis could obscure potentially important individual differences in depression. This result also suggests that future efforts to develop personalized targeting approaches for therapeutic neurostimulation could benefit from the accounting for individual idiosyncrasies in the topological properties of these networks.

DELINEATING CIRCUIT-LEVEL MECHANISMS OF DEPRESSION PATHOPHYSIOLOGY IN ANIMAL MODELS

As reviewed above, human neuroimaging studies have defined a consistent and reproducible neuroanatomical substrate of depression at the network level, and emerging approaches have the potential to yield new insights into the mechanisms that mediate transitions between depressive states over time, the neurobiological basis of diagnostic heterogeneity, and the influence of genetic risk variants on depression-related circuit function. However, testing causal mechanisms can be challenging in human neuroimaging studies, especially those involving a level of spatial or temporal resolution beyond what is currently possible using fMRI. Neurophysiology studies in animal models have the potential to complement these approaches by providing experimentally tractable opportunities to test mechanistic hypotheses—which could be derived from human neuroimaging data—by recording and manipulating the activity of specific circuits and cell types with remarkable precision.

The past decade has seen a rapid expansion of techniques for probing the circuit-level physiology underlying depression-related behavioral states in animal models. The impact of this work has been magnified by an increasing focus in recent years on the utility of rodent models for studying specific depression-relevant behaviors and motivational states, as well as the inevitable limitations of modeling other aspects of depression (70), discussed in greater detail below. A convergence of new molecular tools, optical hardware, and computational methods has allowed researchers to parcellate brain regions and long-range connections whose aggregate activity underlies depression-associated behaviors. The emergence of in vivo optogenetics (71) and chemogenetics (72) has enabled researchers to access new dimensions of specificity in modulating and measuring brain activity.

Among the earliest demonstrations of in vivo optogenetics to control mammalian behavior was a study published by the Deisseroth group in 2009 (73). The researchers reported a behavioral rescue of movement in hemi-parkinsonian rats by excitatory stimulation of layer V motor cortex pyramidal neurons. While nonspecific stimulation of these neurons failed to rescue motor movement in these animals, stimulation of their axon terminals in the subthalamic nucleus rescued the motor impairment (73). The result confirmed a principle that had long been presumed and may be important in depression, and that would guide the design of many

optogenetic experiments over the subsequent decade, namely, that the specificity of long-range connectivity is critically important in controlling circuit-level dynamics.

In the ensuing years, numerous high-impact findings elucidated the circuit-level physiology underlying depression-related behaviors by focusing on the control of motivated reward-seeking behaviors, with an emphasis on the basal ganglia and associated structures. Tye et al. (74) demonstrated bidirectional modulation of anhedonia and escape behaviors resulting from up- and down-modulation of activity in dopaminergic neurons of the ventral tegmental area (VTA) and showed that such behaviors were regulated by VTA projections to the nucleus accumbens (NAcc). Ferenczi et al. (75) then showed, in a study that combined fMRI and optogenetics in mice, that the powerful excitatory drive provided to the NAcc by the VTA could be blocked by increasing the excitability of the medial PFC. Further studies showed that activation of projections from the basolateral amygdala to the NAcc controlled reward-seeking behavior bidirectionally (76) and that prefrontal projections to the dorsal raphe nucleus drove motivated escape behavior (77), acting through circuit-level mechanisms that are modulated by environmental threats (78).

The most common approach for inducing and studying depression-related behaviors in rodents is through chronic stress. The chronic social defeat stress (CSDS) paradigm has been especially useful in studying the neurobiological mechanisms mediating the induction of depression-related behaviors and for identifying mechanisms that determine stress susceptibility and resilience. In this paradigm, a mouse is repeatedly attacked and dominated by an aggressor mouse and then is housed in close proximity to the aggressor, over 5–10 days. This experience produces anhedonic behavior (assessed as reduced preference for sucrose solution over water), social avoidance (assayed by a social interaction test), and reductions in motivated escape behavior (quantified as amount of movement during tail suspension or forced swim). Depending on their responses to such assays, mice undergoing a CSDS protocol may be classified as resilient or susceptible to the stress protocol (79).

As with the studies discussed above, the use of optogenetic stimulation in mice undergoing CSDS has identified projection-specific pathways mediating the induction of depression-related behaviors. Chaudhury et al. (80) showed that activation of VTA-NAcc projections increased the likelihood of susceptibility to the CSDS protocol, while inhibition of axon terminals from this projection increased stress resilience. Bagot et al. (81) subsequently found that projections from the ventral hippocampus to the NAcc, but not inputs originating in the medial PFC or basolateral amygdala, modulate the behavioral effects of CSDS. This model has also proven useful for studying antidepressant mechanisms. For example, Covington et al. (82) found that nonspecific activation of medial PFC neurons in a manner designed to mimic therapeutic DBS (83) rescued social interaction and sucrose preference in defeated animals, suggesting that inducing hyperactivity in the medial PFC may be sufficient to suppress some depression-related behaviors.

LIMITATIONS AND FUTURE DIRECTIONS

Together, optogenetic studies of the circuit-level mechanisms regulating motivation and reward-seeking behavior and of their dysfunction in chronic stress states have produced several promising candidate network models that are relevant for understanding depression pathophysiology and are centered on the VTA, NAcc, and medial PFC (74–77, 80, 84), with potentially critical nodes in the lateral habenula, dorsal raphe nucleus, ventral hippocampus, basolateral amygdala, and ventral pallidum (77, 81, 85, 86). We conclude by reviewing several important limitations and promising future directions.

First, one important limitation of translational work in animal models is that it can be challenging to integrate findings in rodents and nonhuman primates with those acquired using fundamentally different tools in human subjects and clinical patient populations. The studies reviewed above have built a foundation for understanding how specific circuits and network nodes drive reward-seeking behavior and regulate motivation. As our understanding of neuroimaging correlates of specific depressive symptoms and behaviors in humans matures, a key next step will be to formulate testable hypotheses based on human neuroimaging results and to evaluate them in appropriate animal models (49). While several brain circuits that have been implicated in human neuroimaging studies have been the focus of extensive optogenetic dissections in animal models (e.g., medial PFC, ventral striatum, amygdala, and ventral hippocampus), others have not been studied as extensively. For example, it is unclear how dysfunction in the anterior insula, cerebellum, thalamus, and visual cortex—all consistently implicated in human neuroimaging studies—might contribute to depression-related behavior.

Second, translational studies of depression pathophysiology are limited by the fact that there are no mouse models of depression that faithfully recapitulate all aspects of the syndrome (70). It goes without saying that some depressive symptoms that are core features of the illness in many individuals, such as sadness, low mood, suicidal thinking, guilty rumination, and low self-esteem, simply are not empirically accessible in rodents. In contrast, animal models can be used productively to test hypotheses about how dysfunction in specific circuits contributes to other behaviors that play an important role in depression and are well modeled in mice, such as reward-seeking behavior, social interactions, fear learning, locomotor activity, and control of sleep/wake states, to name a few. This might mean developing new behavioral assays that are tailored to testing a specific hypothesis, an approach that would benefit from carefully considering the extent to which a given behavior and its circuit-level substrates are well conserved across species. Care must be taken not to overgeneralize the results of such assays, and any new

assay must be rigorously established in the light of construct validity, face validity, and predictive validity (70).

Third, while early optogenetic studies in this area focused on the role of specific brain regions such as the VTA, nucleus accumbens, and amygdala, there is increasing interest in understanding how specific cell types interact within a given brain region and how these regions are organized into neuroanatomically distributed functional networks. For example, recent studies have shown how specific interneuron subtypes contribute to depression-related behavior (87) and how topologically defined projection neuron subtypes in the basolateral amygdala (88) and PFC (84) play distinct roles in learning about environmental cues that predict aversive or rewarding outcomes. Projection-defined neuronal populations are themselves functionally and topologically heterogeneous, particularly in higher-order association areas. They can exhibit diverse cognitive task–related responses, which can vary by precise anatomical location, such as cortical layer (89). Efforts to investigate how specific neuronal subtypes interact within these circuits to mediate relevant behaviors, and to understand how these interactions are disrupted in chronic stress states and how they are modulated by antidepressants, have an increasingly important role to play in understanding depression pathophysiology.

Likewise, at the network level, new imaging approaches promise to expand our understanding of how regions such as the VTA, nucleus accumbens, and amygdala interact with neocortical areas to regulate behavior at the network level. Just as optogenetics enabled translational researchers to map the contributions of long-range connections to depression-related behaviors, new methods for large-scale, high-resolution imaging are enabling researchers to examine neural dynamics across states in ways not previously possible. Whole-cortex calcium imaging allows for co-registration of brain-wide dynamics observed in fMRI data with the improved temporal and spatial resolution of dynamics defined by calcium events, allowing for more precise circuit-level interpretation of fMRI data (90). In another especially compelling example of this approach, McGirr et al. (91) used whole-cortex imaging and optical glutamate and voltage sensors to characterize network-level alterations in chronic stress states. They showed that CSDS induced widespread, globally correlated glutamatergic release events across the cortex, which was abolished by subanesthetic ketamine in a dose-dependent manner. Newer developments in mesoscale imaging promise still greater spatial resolution, allowing for the creation of cortex-wide network maps that could potentially detect more reliable signatures of depression-associated states in cortical dynamics (92). Network-level analyses of multisite electrophysiological recordings have also begun to reveal complex spatiotemporal patterns of activity that confer susceptibility to stress in rodents (93) and predict specific depressive symptoms in humans (94).

Finally, as our understanding of depression pathophysiology at the circuit and network levels progresses, translational studies may begin to play an increasing role in developing new treatments and optimizing existing ones. Therapeutic neurostimulation interventions such as rTMS and DBS are obvious candidates. Whereas antidepressant medications require optimization of two key variables—dosing and timing—neurostimulation treatments like rTMS and DBS involve a much larger parameter space, including decisions regarding neuroanatomical targeting, stimulation strength, duty cycle, and duration of stimulation, among many other factors. Animal models could provide a neurobiological rationale for optimizing these parameters as well as experimentally tractable opportunities for testing them empirically in a high-throughput way. A more comprehensive understanding of the ways in which neural dynamics shift across brain regions in depression-related behavior states could also offer new targets for neuromodulatory therapeutics like rTMS and DBS.

In the longer term, translational neurophysiology studies in animal models could identify fundamentally new treatment strategies. With this goal in mind, there is increasing interest in the use of animal models to identify new transcriptionally defined cell types through single-cell RNA sequencing, which could provide new avenues for treatment targeting. Depending on sequence clustering methods, these studies suggest that there may be hundreds of transcriptionally distinct cell types in the cortex alone (95). If particular transcriptionally defined cell types are found to play distinct roles in mediating specific depression-related behaviors, they could in principle be differentially targeted based on unique surface molecules, either through G protein-coupled receptor (GPCR)–based pharmacology or, eventually, through viral vector targeting.

Another promising avenue for developing better treatments will involve defining the circuit-level mechanisms mediating the therapeutic effects of newly emerging antidepressants and understanding how they differ from conventional monoamine-targeting drugs. Rapid-acting antidepressants like ketamine are especially appealing in this regard in that they offer experimentally tractable opportunities to investigate how changes in neural circuit function induce rapid behavioral state transitions. For example, recent findings indicate that ketamine induces synaptogenesis in prefrontal circuits (96–98) and that these new synapses are required for maintaining ketamine's antidepressant effects over time, but not for initially inducing them (98). In contrast, rapid effects on other functional properties of prefrontal cortical circuits—including inhibition of somatostatin interneurons and restoration of multicell ensemble events (98, 99)—may be involved in initiating ketamine's antidepressant effects acutely. These findings point to at least two complementary avenues for developing new therapeutic strategies targeting specific functions and processes at the neural circuit level. Other emerging and rapidly acting antidepressants likewise warrant further investigation at the circuit level. Especially promising examples include sleep deprivation, which elicits rapid antidepressant effects through mechanisms that are not well understood (100, 101); tianeptine, an atypical antidepressant that may relieve depressive

symptoms over a period of days instead of weeks and, like ketamine (102), may act in part through effects on mu-opioid receptor signaling (103, 104); and accelerated rTMS protocols, which deliver 5–6 weeks worth of magnetic pulses in a few days (105, 106).

CONCLUSIONS

The circuit-level mechanisms underlying depression pathophysiology are not well understood, but the studies reviewed above suggest that the field is poised to make rapid progress in this area, facilitated and accelerated by new technologies. Meta-analyses of neuroimaging studies have identified a network of brain regions that are consistently altered at the group level in depressed patients, including the dorsolateral PFC, orbitofrontal cortex, anterior cingulate cortex, anterior insula, amygdala, hippocampus, basal ganglia, thalamus, and cerebellum. However, it is not well understood how dysfunction in these brain areas contributes to specific depression-related behaviors and symptoms at the neural circuit level, and the mechanisms that give rise to dysfunction in these circuits are unknown. Optogenetic and chemogenetic tools and other new technologies for recording and manipulating the activity of specific circuits and cell types have the potential to fill this gap. They have already identified important circuit-level mechanisms regulating reward-seeking behavior, stress responsiveness, motivation, and aversion, and involving the VTA, nucleus accumbens, amygdala, and medial PFC. Future studies in at least four areas are poised to transform our understanding of depression pathophysiology:

1. *Large-scale neuroimaging studies:* Collaborative multisite studies are enabling investigators to pool data and generate much larger data sets encompassing hundreds or even thousands of patients. Large sample sizes, in turn, enable new approaches, including multivariate models for understanding diagnostic heterogeneity; efforts to develop diagnostic and prognostic biomarkers for informing treatment selection; and integration with genomic data sets.

2. *Longitudinal deep sampling studies:* Depression is a fundamentally episodic mental illness, but the mechanisms driving behavioral state transitions over time are not well understood. Longitudinal imaging studies have the potential to advance our understanding of how functional changes in specific circuits mediate the induction, maintenance, and remission of a depressive episode and determine the durability of recovery. They may also inform efforts to optimize neurostimulation interventions by accounting for individual variability in the organization of functional networks.

3. *Integrating human neuroimaging studies and neurophysiology studies in animal models:* Future studies may benefit from efforts to formulate hypotheses based on human neuroimaging data and test them in animal models, with the goal of understanding how dysfunction in specific circuits gives rise to specific depression-related behaviors and symptoms. Such studies will benefit from careful consideration of limitations of the animal model and the conservation of behaviors and circuits across species. Some brain areas have been consistently implicated in human neuroimaging studies but have been less extensively studied in animal models, and it is unclear how dysfunction in these circuits might contribute to depression-related behavior. These include the anterior insula, cerebellum, thalamus, and visual cortex. New technologies will also enable investigators to define roles for mesoscale network-level interactions and for cellular subtypes within circuits.

4. *Translational models for developing novel therapeutics:* Finally, neurophysiology studies in animal models have the potential to accelerate efforts to enhance existing neurostimulation therapies (especially DBS and rTMS), by providing an experimentally tractable means of optimizing stimulation parameters, and to identify and develop new drug targets by integrating single-cell sequencing technologies with circuit-based neurophysiology studies.

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