Review

Biological Psychiatry

Of Mice, Men, and Microbial Opsins: How Optogenetics Can Help Hone Mouse Models of Mental Illness

Tobias F. Marton and Vikaas S. Sohal

ABSTRACT

Genetic, pharmacologic, and behavioral manipulations have long been powerful tools for generating rodent models to study the neural substrates underlying psychiatric disease. Recent advances in the use of optogenetics in awake behaving rodents has added an additional valuable methodology to this experimental toolkit. Here, we review several recent studies that leverage optogenetic technologies to elucidate neural mechanisms possibly related to depression, anxiety, and obsessive-compulsive disorder. We use a few illustrative examples to highlight key emergent principles about how optogenetics, in conjunction with more established modalities, can help to organize our understanding of how disease-related states, specific neuronal circuits, and various behavioral assays fit into hierarchical frameworks such as the National Institute of Mental Health Research Domain Criteria matrix.

Keywords: Animal models, Anxiety, Depression, Obsessive-compulsive disorder, Optogenetics

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Rodent models represent powerful tools for investigating the neural basis of both normal and pathologic behavior. The fact that genetic and/or developmental manipulations can elicit enduring phenotypes that model important aspects of psychiatric disorders has fundamentally transformed our understanding of these disorders by linking them to specific biological causes (1). Nevertheless, elucidating the detailed pathophysiological mechanisms through which genetic or developmental lesions elicit specific phenotypes has proven more difficult (2). In many cases, it has been difficult to identify the specific physiological loci on which these lesions act; thus, translating these genotype-phenotype relationships into new treatments has proven challenging (3).

These difficulties may reflect, in part, the imperfect mapping that exists between genes or developmental events and categorical diagnoses such as depression or anxiety, which comprise clinical heterogeneity across broad clusters of symptoms. As a result, multiple behavioral assays developed to probe the same categorical diagnosis may yield contradictory or inconsistent results when applied to a single putative disease model (4–6). These inconsistencies reflect the lack of precision inherent in both the current diagnostic system and established behavioral protocols and limit our ability to leverage rodent model systems as platforms for drug discovery.

There is increasing appreciation that psychiatric illnesses may be better understood as disorders of neural network function, i.e., single psychiatric disorders likely arise from multiple, multifactorial molecular and cellular lesions distributed throughout large-scale circuits, leading to multifaceted and heterogeneous clinical presentations. Conversely, clinically distinct psychiatric diseases likely share functional deficits across the same neural circuits, as reflected in the overlap of symptoms across categorical diagnoses. This concept has been recognized as a limitation of the historical categorical-based approach to studying psychopathology and is reflected in the recent development of the National Institute of Mental Health Research Domain Criteria (RDoC) framework (7), which advances a dimensional approach to understanding mental illness by elucidating neural pathways that underlie behavioral constructs (e.g., motivation, attention, fear, etc.), which, taken together, comprise the complex phenomenology observed in the clinic. This hierarchical framework establishes five primary biobehavioral domains (negative valence, positive valence, cognitive, arousal, and social neural systems) under which the above constructs are grouped. Elucidating molecular, cellular, circuit, and systems-level mechanisms that engender these behavioral constructs may represent a more tractable route to understanding the pathophysiology of psychiatric disorders.

The recent development of optogenetics, which allows real-time, region and cell type specific manipulation of neural pathways in awake behaving rodents, has started to address some of the issues raised above (8–10). Specifically, the acute manipulation of targeted neural circuits via optogenetics can yield phenotypes that are highly specific and yet shared across categorical diagnostic domains. For example, optogenetic inhibition of dopamine-expressing neurons in the ventral tegmental area (VTA) drives reduced reward-seeking behavior in rodents analogous to the anhedonic states observed in both

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depression and schizophrenia, suggesting that dysfunction in a common neural pathway may potentially be shared between these distinct categorical syndromes (11).

Of course, other acute manipulations, e.g., electrical stimulation and localized drug infusion, have been used for decades to probe neural circuits involving psychiatric disorders. Recent advances allowing acute circuit manipulation also include designer receptors exclusively activated by designer drugs (12). While these approaches continue to be powerful techniques for manipulating neural circuits in freely moving animals, the specific advantage of optogenetics is the ability to manipulate activity in a cell type and temporally precise manner, making it possible to drive circuits at specific frequencies of interest (8,9). Of course, as a result, interpretations of optogenetic manipulations must take into account the pattern and frequency of optical stimulation, as these determine the specific patterns of neuronal firing that ultimately determine circuit output and behavior. For example, a recent study from our group demonstrated that deficits in cognitive flexibility in mice with abnormal parvalbumin interneuron development can be rescued by optogenetically stimulating prefrontal interneurons at gamma frequencies of 40 Hz or 60 Hz but not by an equivalent amount of stimulation delivered using frequencies outside the gamma band (13). Different patterns of medial prefrontal cortex (mPFC) stimulation also elicit divergent effects on immobility in the forced swim test (FST) (14). These studies highlight the unique ability of optogenetics to deliver temporally precise stimulation to test hypotheses about how specific patterns of activity can drive behavior, as well as the importance of choosing these patterns appropriately (13).

Here, we review several recent studies using optogenetics in awake behaving mice to link specific neural pathways to distinct behavioral endophenotypes that together comprise the clinical diagnoses captured in the DSM. Notably, we will not critique rodent behavioral assays or disease models themselves—that would exceed the scope of this review; rather, we will attempt to glean what optogenetics can add to these assays. Finally, this is not intended to be a comprehensive review of all optogenetic studies related to psychiatric disorders—there have been several excellent reviews on these subjects, e.g. (15,16). Indeed, we have omitted discussion of the numerous optogenetic studies targeting reward/addiction pathways, choosing rather to constrain our focus to depression, anxiety, and obsessive-compulsive disorder (OCD) to highlight a few studies demonstrating key principles (17–19).

We find several emergent themes that illustrate the current shift in our conceptualization of the pathologic mechanisms underlying psychiatric disease, thereby informing how reductionist rodent models can be better leveraged moving forward. Manipulating discrete neural pathways can drive highly specific, and sometimes opposing, effects on established behavioral assays. Conversely, manipulating specific neural pathways can sometimes elicit differential effects on distinct behavioral assays putatively designed to test the same categorical disease construct (e.g., the forced swim test and sucrose preference test for depression). Consistent with these findings, optogenetic studies appear to validate the approach of the RDoC framework, whereby psychiatric disease is re-conceptualized in terms of dysfunction within specific neural networks driving specific cognitive or affective endophenotypes cutting across traditional diagnostic categories (7). Finally, optogenetic strategies alone cannot uncover the developmental or neurodegenerative processes that lead to psychiatric illness and are the focus of genetic modeling in rodents. Indeed, the supraphysiologic nature of optogenetic stimulation is not intended to precisely recreate the pathologic circuit changes likely present in psychiatric disease, which are often manifest physiologically through more subtle changes in neuronal firing rates or patterns. Rather, the power of optogenetics is to provide a complementary network down approach that aims to establish causal links between specific neural pathways and complex behaviors and assay how manipulating these pathways might lead to more specific circuit-based treatments. The possibility that such supraphysiologic stimulation might elicit effects that differ qualitatively, rather than quantitatively, from the endogenous effects of these pathways, remains a vexing caveat for the field.

OBSESSIVE-COMPULSIVE DISORDER

Evidence from both humans and animals reveals that the repetitive and compulsive behaviors characteristic of OCD reflect dysfunction in cortico-striato-thalamocortical circuitry (20). Specifically, hyperactive connectivity between the orbitofrontal cortex (OFC) and striatum has been implicated as an important circuit mechanism underlying compulsive/repetitive behavior (21,22). Moreover, reversal of hyperactivity in this circuit is associated with treatment response in humans (23). According to the RDoC framework, abnormal connectivity involving the OFC may be conceptualized as an underlying circuit mechanism driving the construct of compulsive behavior rather than OCD per se (7). Indeed, similar functional and anatomical abnormalities involving OFC are also observed in the setting of compulsive behaviors related to stimulant addiction (24,25).

Two recent studies, Ahmari *et al.* (26) and Burgiere *et al.* (27), exploited optogenetics to manipulate OFC-striatal pathways to investigate the role of this circuit in repetitive behavior (26,27). While these two studies report seemingly opposite effects on repetitive grooming behavior by optogenetically stimulating glutamatergic projections from OFC to striatum, these divergent findings illustrate several important concepts regarding the application of optogenetic strategies to model psychopathology, as well as to elucidate underlying circuit mechanisms of disease.

Ahmari *et al.* (26) hypothesized that repetitive optogenetic stimulation of projections from OFC to ventral medial striatum (VMS) would model the hyperactivity in this circuit reported in the human imaging literature and drive overgrooming behavior. Accordingly, they reported that daily brief sessions of optogenetic stimulation of glutamatergic OFC axonal terminals residing in VMS resulted in a progressively worsening overgrooming phenotype. Notably, increases in grooming behavior were not seen during the stimulation sessions themselves. Rather, they only manifested in the hours following stimulation, taking several days of repeated stimulation to achieve significance. Importantly, worsening of this behavioral phenotype over several days was associated with increases in stimulation-evoked firing in VMS, effectively modeling