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Of mice, men, and microbial opsins: how optogenetics can help hone mouse models of mental illness

Tobias F. Marton and **Vikaas S. Sohal***

Department of Psychiatry, Center for Integrative Neuroscience, and Sloan Swartz Center for Theoretical Neurobiology University of California, San Francisco, San Francisco, CA 94143-0444

Abstract

Genetic, pharmacological, and behavioral manipulations have long been powerful tools for generating rodent models in order 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 can be classified and organized using hierarchical frameworks such as the NIMH RDoC matrix.

Keywords

optogenetics; animal models; depression; obsessive compulsive disorder; anxiety

INTRODUCTION

Rodent models represent powerful tools for investigating the neural basis of both normal and pathological 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, and thus, translating these genotype-phenotype relationships into new treatments has proven challenging (3).

To whom correspondence should be addressed: vikaas.sohal@ucsf.edu.

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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 better be 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 NIMH RDoC framework (7), which advances a dimensional approach to understanding mental illness by elucidating neural pathways which 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 bio-behavioral 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 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 activated by designer drugs (DREADDs) (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 or 60Hz, but not by an equivalent amount of stimulation delivered using frequencies outside the gamma band (13). Different patterns of 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 in order 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 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 supraphysiological nature of optogenetic stimulation is not intended to precisely re-create the pathological 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 reflects dysfunction in cortical-striatalthalamo-cortical (CSTC) 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. 2013 and Burgiere et al. 2013, both 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 elucidate underlying circuit mechanisms of disease.

Ahmari et al. 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 over-grooming behavior. Accordingly, they report that daily brief sessions of optogenetic stimulation of glutamatergic OFC axonal terminals residing in VMS results in a progressively worsening over-grooming 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 pathological plasticity (hyperconnectivity) of the OFC-VMS circuit as an underlying circuit mechanism in OCD. Further, both the over-grooming phenotype and neuronal hyperactivity in OFC-VMS connections were reversed with chronic administration of fluoxetine, an evidence-based treatment for OCD in humans (28).

Burgiere et al. 2013 took a complementary approach to probing the OFC-striatal circuit using optogenetics. Illustrating the potential power of combining genetic and optogenetic approaches, they target OFC-striatal connectivity in *Sapap3*$^{-/-}$ mice, which exhibit repetitive grooming, and aimed to reverse this phenotype by optogenetically manipulating OFC-striatal circuits. They report that stimulating lateral OFC projection terminals in striatum rescues over-grooming associated with hyperactivity of medium spiny neurons (MSN) in the striatum. This optogenetic rescue was associated with increased feed-forward inhibition of these hyperactive MSNs by striatal fast-spiking (FS) interneurons, thus providing a novel target for OCD treatment.

While these two studies demonstrate seemingly opposing effects of optogenetic OFC-striatal terminal stimulation on repetitive grooming behavior, in fact these findings provide insight into the complementary uses of genetic/developmental models of disease and optogenetic circuit manipulation. Unlike the Ahmari et al. study, which models OFC-striatal dysconnectivity in an otherwise developmentally normal adult mouse, Burgiere et al. start with a model of OCD driven by genetic disruption of *Sapap3*, a synaptic scaffolding protein, then use optogenetics to probe an abnormal circuit. It is therefore not surprising that in the context of a developmentally altered OFC-striatal pathway, similar optogenetic stimulation protocols could drive divergent behavioral output. For example, it is possible that in the context of the *Sapap*3$^{-/-}$ mutation, significant re-tuning of the OFC-striatal network has occurred, resulting in altered circuit dynamics which respond differently to optogenetic stimulation, compared to the “wild-type” condition. Indeed, Burgiere et al. describe the loss of FS interneurons and subsequent loss of inhibitory tone in the striatum as a probable mechanism underlying the hyperactivity of striatal MSNs in the *Sapap*3$^{-/-}$ mice. Inhibitory tone is rescued through OFC-striatal optogenetic stimulation driving feed-forward inhibition and restoring normative MSN firing. Interestingly, Ahmari et al. also reported striatal glutamatergic neuron hyperactivity as a primary driver of repetitive behavior through optogenetic stimulation of OFC-striatal activity in a developmentally normal background. It is possible that with normal striatal inhibitory tone, optogenetic stimulation of OFC-striatal terminals does not ectopically engage feed-forward inhibition as occurs in *Sapap3*$^{-/-}$ mice. Consistent with this, acute stimulation of OFC terminals in Sapap3 WT littermates had no effect on grooming behavior, reinforcing the importance of genetic background in setting the basal state of the circuit. In this way, both approaches converge on a single underlying circuit mechanism that contributes to OCD – hyperactive connectivity in OFC-striatal networks – and illustrate the value of using optogenetics to study circuit pathology in *both* normal and genetically altered backgrounds.

DEPRESSION

Attempts to model depression in rodents rely on many behavioral assays, each capturing potentially overlapping components of the disease (e.g. forced swim or tail suspension tests for motivated behavior, sucrose preference test for anhedonia) (29–31). Optogenetics has accelerated the identification of precise neural pathways mediating each of these phenotypes which together contribute to the syndrome of depression. Optogenetic studies of depression have largely focused on manipulating mesolimbic and mesocortical pathways involving the VTA, NAC and PFC because commonly used behavioral paradigms for depression largely assay motivation, reward/anhedonia and social interaction, thought to reflect functions of these networks (32).

Covington et al. 2010 first exploited optogenetics to reversibly control depression-related phenotypes in mice by manipulating the medial prefrontal cortex (mPFC) (33). Mice subject to chronic social defeat exhibit decreases in social interaction as well as reward seeking behavior measured by the sucrose preference test (31, 34). Reductions in mPFC immediate early gene (IEG) expression are associated with the development of depression-like behavior suggesting that decreases in mPFC activity may contribute to depression. Consistent with this hypothesis, the authors were able to transiently rescue depression-related behaviors in

chronically defeated mice through optogenetic stimulation of the mPFC. Kumar et al. 2013 built on these findings, demonstrating that therapeutic effects of mPFC optogenetic stimulation in socially defeated mice correlate with increased synchrony among limbic regions (NAC, VTA, BLA) associated with depression (35).

Both studies demonstrate that optogenetic manipulation of mPFC and its downstream projections alter neuronal activity associated with therapeutic responses, thereby identifying important targets for therapeutic interventions. Finally, Warden et al. 2012 examined how in rats, specific projections from the mPFC contribute to performance during the forced swim test (FST), an alternative assay for depression-related behavior (14, 29, 30). Transient stimulation of mPFC projection terminals in the dorsal raphe nucleus (DRN) resulted in rapid, reversible and ad lib control of kicking, i.e. motivated escape behavior, in the FST. In contrast to the effects of stimulation on social interaction and sucrose preference phenotypes in susceptible socially defeated mice, Warden et al. found no effect of direct, nonspecific mPFC stimulation on the FST; Rather, the control of FST kicking behavior specifically involves the mPFC-DRN circuit. Of course, the use of rats vs. mice, and the fact that Warden et al. did not examine the effect of nonspecific mPFC stimulation during social interaction or sucrose preference assays posits an important caveat in interpreting divergent findings between these studies. That said, all three of these studies suggest that increases in mPFC activity may rescue depression-related behaviors, but also reveal important ways in which these effects depend on cell types, specific assays (social interaction and sucrose preference vs. FST), and the overall context (rats vs. susceptible socially defeated mice). This follows the RDoC framework of using distinct tasks to assess a specific behavioral domain rather than a categorical state, e.g. “depression,” and of mapping these domains onto specific neuronal circuitry.

Optogenetic manipulation of the VTA and its projections has also been the subject of studies dissecting the neural circuitry of depression, following the putative importance of the VTA in phenotypes related to anhedonia (36). Of note, given the VTA’s central role in reward processing, there is considerable overlap in optogenetic studies targeting mechanisms underlying depression (anhedonia) and those studying addiction-related behavior (reward seeking) (37). Chaudhury et al. 2013 examined the role of phasic activity within VTA dopaminergic neurons (38). Previous studies from this group suggested that increases in phasic, but not tonic, VTA neuron activity are associated with decreases in social interaction and sucrose preference in susceptible (but not resilient) mice subjected to chronic social defeat (39, 40). The authors demonstrate that phasic optogenetic stimulation of VTA dopaminergic neurons exacerbated the susceptible phenotype in mice undergoing a subthreshold social defeat paradigm, and also made previously resilient mice susceptible. Projection specific stimulation revealed that phasic stimulation of VTA-NAC, but not VTA-PFC, projections drove this effect. Interestingly, inhibiting VTA-NAC and VTA-PFC projections drove opposite effects: VTA-NAC inhibition induced resilience, whereas VTA-PFC inhibition induced susceptibility. The findings related to VTA-PFC projections are consistent with Covington et al. 2010, which found that direct PFC stimulation rescues depression-related behaviors in susceptible socially defeated mice, suggesting that the VTA represents a critical input to the PFC under these conditions. In contrast to Chaudhury et al., Tye et al. 2013 reported opposite effects of phasic VTA stimulation, namely a rescue of

resilient phenotypes (assayed by sucrose preference and tail suspension test), as opposed to generation of susceptibility, in a chronic stress paradigm (11). The authors suggest these divergent findings may arise from the fact that they used an intermittent foot-shock paradigm to induce chronic stress as opposed to the social defeat paradigm used by Chaudhury et al., and propose that these paradigms may pathologically alter neural circuits in differing ways.

A subsequent study by Friedman et al. 2014 shed additional light on these divergent findings. Prior studies found that susceptible, but not resilient, socially defeated mice showed increases in VTA DA neuron firing associated with increase in the hyperpolarization-activated cation current (Ih) (39). Unexpectedly, Friedman et al. found that in resilient mice after social defeat, Ih increases even more then in susceptible mice, and further showed that these elevations in Ih actually restore VTA DA neuron firing to normal levels by recruiting inhibitory currents. By optogenetically stimulating these neurons repeatedly in susceptible mice after social defeat, thereby increasing Ih to levels that result in dampening of activity, they rescued the susceptible phenotype, replicating the findings of Tye et al.

This mechanistic insight provides a possible explanation as to the divergent findings of the Tye et al. and Chaudhury et al. papers and the importance of timing in optogenetic rescue experiments. While Tye et al. and Friedman et al. applied optical stimulation to VTA DA neurons in susceptible mice after the depression-inducing stress paradigm (chronic defeat or CMS), Chaudhury et al. applied stimulation during the actual social defeat episodes themselves. Hence, one can imagine that Chaudhury's stimulation increased VTA DA firing and Ih sufficiently to bias naive animals towards the susceptible phenotype in the context of the stressor, while Tye and Friedman's post-stress stimulation increased Ih beyond its already elevated levels, thereby restoring balance in the circuit. Thus, different rodent models of depression may respond to stimulation of the same, or at least broadly similar, pathways in a superficially opposing manner depending on the specific timing and parameters of stimulation. This is a valuable insight which suggests that the variable effects optical manipulations exert on these pathways may not simply be "noise" but may inform meaningful variation related to the underlying pathological process. In particular, in the absence of these optogenetic findings, if one had observed opposing changes in VTA physiology in these two experimental conditions, one might have been tempted to dismiss these changes in VTA physiology as irrelevant to, and uncorrelated with, the pathophysiology of depression. But taken together, these optogenetic studies support the opposite conclusion: understanding what exactly is different about VTA physiology between these models is likely to be extremely relevant to understanding key aspects of depression.

ANXIETY

While both assays of innate anxiety, such as the open field test (OFT) and elevated plus maze (EPM), as well as conditioned fear paradigms, in which a conditioned stimulus (CS) is paired with an aversive unconditioned stimulus (US), are well established in the rodent literature, optogenetic manipulation of amygdala circuitry and its distal projections during these assays has added to our understanding of the circuitry that contributes to anxiety-like

behavior (41, 42). While upstream amygdala circuitry differs between unconditioned anxiety and conditioned fear paradigms, optogenetic studies have established the common downstream circuit mechanisms that give rise to the expression of negative valence states in both cases. In particular, previous work has identified the central nucleus of the amygdala (CEA) as the primary output nucleus of the amygdala that projects to brainstem nuclei responsible for generating the autonomic arousal associated with fear and anxiety states (43). Ciocchi et al. 2010 used optogenetics to interrogate the micro-circuitry of the CEA during a conditioned fear paradigm, reporting that the brainstem projecting centromedial nucleus (CEM) of the amygdala is under tonic inhibitory control from the GABAergic interneurons of the centrolateral nucleus (CEL) (44). This defined how a specific synaptic pathway can gate critical fear-related behaviors.

Tye et al. 2011 further elaborated this circuit in unconditioned anxiety paradigms (EPM and OFT) demonstrating reversible control of anxiety states through optogenetic manipulation of BLA projection terminals residing in the CEA (45). Specifically, optical stimulation of BLA-CEA terminals during the EPM resulted in an anxiolytic phenotype, whereas optical inhibition increased anxiety.

By combining optogenetic stimulation of BLA-CEL terminals with whole cell recordings in the CEL, Tye et al. showed that BLA projection neurons selectively excite inhibitory interneurons in the CEL which then provide feed-forward inhibition to the CEM, thereby suppressing outputs that elicit anxiety-related behaviors (45). In this way, optogenetic manipulation of narrowly defined connections within a circuit of interest can elucidate specific mechanisms controlling the expression of pathological behaviors that may be targets for treatment interventions.

Two studies from Felix-Ortiz et al., (2013 and 2014) used optogenetic strategies to dissect the functional connectivity between the BLA and ventral hippocampus (vHPC) in the EPM and OFT (46, 47). Based on prior literature that a BLA-vHPC circuit is activated during the expression of anxiety, as well as the observation from Tye et al. 2011 that optogenetic stimulation of BLA somata resulted in an anxiogenic phenotype (opposite of BLA-CEA terminal stimulation), the authors speculated that optogenetic stimulation of BLA-vHPC projections may increase anxiety (48, 49). Indeed, the authors found opposing effects of BLA-CEA (anxiolytic) and BLA-vHPC (anxiogenic) optical stimulation demonstrating that neurons within a single nucleus can drive opposing behaviors via projections to discrete targets.

The diverse behavioral roles of BLA projections were further elaborated by Felix- Ortiz at al. 2014 which showed that optogenetic stimulation of BLA-vHPC connections could reduce social behavior, in addition to the increase in anxiety-related behaviors reported previously. The authors speculated that the dual behavioral function (social and anxiety) of the BLA-vHPC circuit may represent a unified functional and anatomical mechanism underlying social anxiety as well as the high comorbidity between anxiety and autism spectrum disorders.

Kim et al. 2013 examined the role of bed nucleus of the stria terminalis (BNST) in the expression of anxiety-related behaviors, reporting that stimulation within this structure elicited opposing behavioral effects by acting on specific anatomically-defined projections, similar to what was seen in the BLA (50). In addition, these sub-circuits within the BNST appear to drive separable aspects of behavior and physiology which together comprise the RDoC domain of "negative valence systems." Specifically, optogenetic stimulation of anterodorsal BNST (adBNST)-lateral hypothalamus projections reduced anxiety in the EPM and OFT, but did not affect respiratory rate (RR) or real time place preference (RTPP). Conversely, stimulation of adBNST projections to the parabrachial nucleus (PB) resulted in specific reduction in RR (without affecting EPM, OFT or RTPP), while stimulation of adBNST-VTA projections specifically drove an anxiolytic phenotype in the RTPP, with no effect on the other aspects of anxiety-related behavior or physiology.

These studies illustrate how optogenetic manipulations can enhance our understanding of neural circuit mechanisms underlying constructs within the single RDoC domain of "negative valence systems" (7). In some cases, projections from one structure may exert opposing behavioral effects by acting on different targets. In other cases, assays that might be loosely grouped together under a single domain, may actually reflect dissociable aspects of that domain, in line with the hierarchical RDoC framework of domains, constructs, and sub-constructs. Finally, in some cases, superficially disparate behaviors might be modulated in similar ways by stimulation of a single set of projections, validating the grouping of these behaviors within single RDoC domains or even single DSM diagnoses.

CONCLUSIONS

Here, we presented a few examples to show how optogenetics can elucidate the specific neural mechanisms underlying particular RDoC domains as well as advance our understanding of these domains themselves. As these examples illustrate, optogenetic studies by no means supplant studies of transgenic or mutant animals. Rather, optogenetics can be most informative when combined with these approaches to probe how the function of particular neuronal pathways is altered by these manipulations. Furthermore, superficially divergent findings from optogenetic studies can serve to validate the idea that various manipulations or assays intended to model a single disease process are actually engaging distinct pathophysiological mechanisms or measuring different constructs. Finally, optogenetic manipulations can serve to link a single neuronal pathway to multiple behaviors, or conversely demonstrate how multiple pathways contribute to separable aspects of pathological states such as depression or anxiety, helping refine the RDoC framework. Thus, whereas genetic and developmental manipulations serve to link specific etiological factors with syndromes that resemble forms of mental illness, optogenetic manipulations are well suited to pull these syndromes apart, in order to identify the circuit mechanisms driving these phenotypes.

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