Optogenetics and Psychiatry: Applications, Challenges, and Opportunities

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Achieving circuit-level insight into the fundamental nature of psychiatric symptoms has long proven elusive. Technological limitations have traditionally prevented cell type-targeted and temporally precise interventions into intact mammalian neural circuitry to elicit or ameliorate expression of disease symptom-related phenotypes. However, recent years have seen a growing wave of applications of optogenetics to questions in neuropsychiatric disease, with the deployment of millisecond-precision optical excitation or inhibition of specific circuit elements within behaving mammals. Indeed, optogenetic technology now exists in a special relationship with psychiatry because one of the unique and most versatile features of optogenetics (modulation of defined neural projections) is well aligned with what may be a core feature of psychiatric disease (altered function along pathways of neural communication). In this special issue, we collect perspectives from leading researchers at the convergence of psychiatry and optogenetics, highlighting the fundamental questions that have been addressed and many of the opportunities that remain.

The convergence of optogenetics (1–3) and psychiatry has occurred rapidly over the last few years, with enough complexity that a review and update of the core technology is useful in this venue before review of the psychiatry applications. Therefore, this special issue opens with a detailed summary of optogenetic technology itself from an optogenetics pioneer. Mei and Zhang (4) lead with a detailed and concise introduction to the diversity of microbial opsin-based optogenetic tools, the basic principles of operation, and the suite of enabling technologies that have been developed.

Most important among the associated enabling technologies (especially from the perspective of psychiatry) was the fiber optic neural interface, which overcame the depth limitation caused by light scattering and allowed access to (and optogenetic control of) any brain region even in freely moving mammals. This device debuted in 2007 (5) and was first applied (also in 2007) to address questions relevant to narcolepsy and sleep-wake transitions (6). Specific activity patterns were played into targeted hypocretin neurons in the lateral hypothalamus in freely moving mice; certain patterns but not others were found to favor sleep-wake transitions, providing the first casual understanding of specific activity patterns in well-defined cells underlying mammalian behaviors (6). Here Adamantidis *et al.* (7) provided a review and update from this field, describing not only the initial studies but also the rapid progression of the field since 2007, extending beyond sleep itself to questions of arousal and interactions among different relevant neuromodulatory systems in the brain.

For the initial hypocretin work in 2007, a fragment of DNA called a cell type–specific promoter was fused to the opsin gene, and the resulting construct was packaged within an injected lentivirus that infected or transduced all the cells in the target brain region, but because of the promoter, the virus successfully manufactured opsin only in the hypocretin neurons (and not adjacent cells of other types) (6). However, in general, it is difficult to identify promoter fragments that are specific but also small enough to be efficiently packaged within a virus particle. A more versatile approach involves mouse Cre-driver lines in which the enzyme Cre-recombinase is expressed across generations as a genetically transmitted transgene, only in targeted cells. In this case the DNA conferring specificity does not have to fit within a virus particle, allowing for greater specificity. Cre-dependent viruses are constructed and injected that will therefore express opsin only in the targeted (Cre-expressing) cells. This trick led to the control of specific populations in freely moving mice via selective opsin expression in tyrosine hydroxylase-expressing (dopaminergic) neurons in the ventral tegmental area, to probe reward and conditioning (8, 9); this approach was later extended to freely moving rats with the generation of Cre-driver rats (10). Stuber *et al.* (11) provided a detailed review of this avenue of work, which has recently extended beyond dopamine neurons to probing the causal role of cholinergic neurons in reward-related behaviors (including cocaine conditioning) (12).

The same targeting trick was later used by Anderson (13), as reviewed in this issue, to selectively control defined populations of hypothalamic cells with pronounced effects on the interplay between aggressive/violent and sexual impulses (14). The study of neurobiologic underpinnings of aggression and violence is underexplored, despite the pressing importance of this topic in our world. It is encouraging that optogenetic interventions have now provided a highly precise foothold for neuroscientists in this important realm of mental health and behavior, which we hope will spark further research.

Cre targeting was also (in separate studies) used to control the intriguing parvalbumin or fast-spiking inhibitory neurons (15,16). Prior pioneering work had shown that these neurons are altered in schizophrenia and had long been suggested to be involved in modulating certain kinds of brain rhythmicity such as gamma oscillations, which are also known to be abnormal in schizophrenia. Sohal (17) here provide a review of the optogenetic studies that were able to ascribe a causal role of these neurons in the modulation of gamma oscillations, which in turn were found to modulate information flow within neocortical circuitry.

Altered gamma oscillations are also seen in autism, another disorder (like schizophrenia) in which information processing and social function deficits are seen, although with a markedly different quality. A long-standing hypothesis in the field had been that elevated excitation-inhibition imbalance could give rise to social dysfunction of the kind seen in autism, but the physiology (unlike the genetics) had been difficult to test in causal, temporally precise fashion. Yizhar (18) here provides a review of optogenetic work that has now directly and causally implicated excitation-inhibition balance changes (19) in setting up abnormal social function as well as giving rise to abnormal information processing and gamma oscillations of the kind seen in autism and schizophrenia.

Memory deficits (notably in working memory but also in aspects of long-term episodic or declarative memory) are seen in autism and schizophrenia but more prominently in cognitive impairment and dementia. The persistence of episodic memories is also highly relevant to posttraumatic stress disorder (PTSD) and other anxiety

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disorders, in which the memory can be a contextual fear memory. Recent work using optogenetics has now found that long-term contextual fear memories surprisingly involve both hippocampus and neocortex, even in the remote phase (20); this work may help inform our understanding of PTSD and attempts to ameliorate the debilitating consequences of this disease. Johansen *et al.* (21) here provide a broad review on the now-extensive set of optogenetic studies focused on fear memory formation and expression, involving amygdala, hippocampus, neocortex, and other neural circuits, in freely moving mammals (20, 22–24).

Anxiety disorders are a broad category, including both conditioned (such as PTSD) and unconditioned (such as generalized anxiety disorder) forms. Optogenetics has also been used to probe unconditioned anxiety, and a specific intraamygdala pathway has been optogenetically resolved that appears to bidirectionally set anxiety expression level in real time as mammals behave (25). Anxiety is also cormorbid with, and likely causally linked to, major depression; Lobo *et al.* (26) here provide a review on optogenetic technology application to depression-related behaviors in rodent models (27).

One of the remarkable features of depression is the complexity of the symptoms seen that span many different domains of brain function (including anhedonia, hopelessness, and psychomotor changes). Yet despite such complexity, many of these symptoms can resolve with a single kind of intervention, perhaps most strikingly in the case of focal deep brain stimulation or DBS (28). Prior optogenetic work had provided a clue to DBS mechanism; Gradinaru *et al.* (29) found that the likely direct initial target of DBS (at least in the case of Parkinson's disease) (30) is not local cell bodies but afferent axons to the region (in this case, subthalamic nucleus), which may arise from globally distributed brain regions (29). An optogenetic method that may enable unbiased global assessment of these neural circuits upstream and downstream of focal stimulation is optogenetic functional magnetic resonance imaging or ofMRI (31); Lee *et al.* (31) initially brought these two technologies together in the context of a rodent system, and numerous opportunities for psychiatric disease model work now arise from ofMRI.

By no means do optogenetic technologies stand alone; instead this approach must be integrated well with existing sophisticated psychiatric disease-model research methods spanning behavior, psychology, imaging, electrophysiology, pharmacology, and genetics. Additional technologies also need to be developed further for this approach to reach its full potential, and we describe three such technologies here. First, efficient methods must be developed for determination of global (brainwide) wiring diagrams and molecular phenotypes of cells that are controlled by specific optogenetic interventions in vivo. Second, volumetric (3D), genetically targeted, and simultaneous (i.e., nonscanning) methods are needed to visualize neural activity patterns (e.g., synchrony and oscillations) responding to optogenetic control within intact brain tissue, in models of neuropsychiatric disease. Finally, because even light-based imaging methods encounter fundamental limitations of resolution because of scattering in mammalian brain tissue, nonoptical methods that leave a recoverable trace of activity history within individual cells will be useful. To sidestep the light scattering problem, here I suggest and describe a novel possible strategy, which could involve (like optogenetics) only a single exogenous component: a gene encoding an error-prone polymerase transduced into all (or a genetically targeted subset) of neurons in vivo. If the polymerase were engineered for increased error rate in the setting of elevated Ca^{2+} concentrations, which can track neural activity patterns at high speeds, even in the nucleus (32,33), long transcripts such as neurofibromin (or a designed transcript) could be recovered or assessed from cells throughout the brain that would thereby carry an effective millisecond-precision activity record over times long enough to report on behaviors or experiences in mammalian subjects, with no limitations in scope or resolution because of light scattering. Experimenter-provided stimulation would provide a barcode-like time stamp so that experimental time could be synchronized across all the transcripts within a cell and throughout the brain, thereby dovetailing well with optogenetic control.

While many exciting challenges such as these remain, we have provided here an overview of investigations into psychiatric disease that use optogenetic tools and point the way toward future opportunities. In these avenues of investigation, optogenetic tools provide experimental leverage leading to insights into neural circuit function and dysfunction that are impossible to establish by other means. Extension of these studies to additional classes of symptoms, with identification of unifying themes, will very likely continue to be an exciting and productive avenue of research into neurological and psychiatric disease.

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