

# Psychiatry's age of enlightenment: optogenetics and the discovery of novel targets for the treatment of psychiatric disorders

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A major goal of neuroscience has been to understand the systems-level neural processes governing higher-order functions, such as perception, cognition and emotion. Until recently, however, achievement of this goal has been limited by a lack of neuromodulatory tools capable of targeting distinct populations of neurons, based on either genetic identity or circuit connectivity, in behaving animals with the temporal precision required for causality testing. Such a tool would finally enable direct linkage of distinct neural activity patterns to behaviour. Since its inception in 2005,<sup>1</sup> the field of optogenetics has been responsible for the rapid progress in our understanding of the intricate neural circuit elements driving emotive behaviours relevant to psychiatric disorders, such as schizophrenia, anxiety, depression and bipolar disorder. By using light pulses to turn specific populations of neurons on and off in awake, freely moving animals, optogenetics has finally provided science with a tool that has the spatial and temporal resolution required to causally link neural activity patterns to behaviour.

It is becoming increasingly recognized that many psychiatric disorders are better conceptualized as diseases of abnormal brain wiring and aberrant neural activity. Although in the past biological psychiatry has focused on chemical imbalance as a pathophysiological driving force, this same approach may also explain the current paucity of truly effective treatment options for many psychiatric illnesses. Innovation and novel approaches that capitalize on the latest technologic advancements are required for substantial progress. In this regard, it is an exciting time to be in the field of psychiatry, as optogenetics is leading to groundbreaking progress in our understanding of neurocircuit function in health and disease. This progress forces us to refocus and reconceptualize our understanding of the neural underpinnings of psychiatric disease and helps to identify novel targets for mechanistic-based therapeutic discovery. For basic and clinical scientists alike, an appreciation and understanding of this technology is essential in helping the field move forward. This editorial

is not meant to provide an exhaustive review of optogenetic technology (see Yizhar and colleagues<sup>2</sup> for an excellent optogenetic primer); rather, the purpose is to provide a working knowledge of the tool, to highlight key findings and to discuss the future applications, limitations and possible clinical translation of this emerging technology.

## Combining optical and genetic components to control neural activity

### *Optic-based temporal precision*

The identification of light-sensitive ion channels, called rhodopsins, in microbial organisms has proven to be the quintessential discovery providing the platform for the development of optogenetics.<sup>3</sup> Optogenetics employs 2 main classes of microbial opsins: first, the "gain-of-function" cation channel, channelrhodopsin (ChR2),<sup>4</sup> which activates neurons in response to blue wavelengths of light, and second, the "loss-of-function" chloride pump, halorhodopsin, which inactivates neurons in response to yellow light.<sup>5</sup> Variants of these microbial opsins were initially discovered almost 40 years ago,<sup>6,7</sup> but the full potential of this discovery and its application to neuroscience wasn't realized until 2005. In a seminal paper, Boyden and colleagues<sup>1</sup> reported on the feasibility of introducing a microbial opsin into mammalian neurons, without the need for additional chemicals, genes or components (opsin function is dependent on the presence of a retinoid cofactor, which mammalian neurons just happen to express). By expressing these single-component light-sensitive ion channels in mammalian neurons, the authors were the first to show that light pulses could reliably sustain control of mammalian neural firing in vitro with millisecond temporal precision owing to the inherent speed of optic-based stimulation and the rapid open and closing kinetics of ion channels (unachievable with pharmacologic manipulations). Successive tool development resulted in

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the creation of an optical–neural interface that permitted light-evoked gain or loss of function in awake, freely moving rodents. This is accomplished through the use of a permanent optical fibre implant that delivers light from a laser or light-emitting diode directly to the opsin-expressing brain region of interest.<sup>8,9</sup> A simple proof of principle experiment that illustrates and captures both the power and elegance of this technologic advancement is real-time optical control of rodent motor behaviour (Video 1, available at [www.youtube.com/user/crflleisch](http://www.youtube.com/user/crflleisch)): blue light stimulation of one side of the motor cortex in a behaving mouse constitutively expressing ChR2 causes motor rotation in the opposite direction, which immediately ceases when light stimulation is terminated.

### Genetic-based spatial targeting

A main advantage of optogenetics over other traditional approaches to neuromodulation, such as electrophysiology, is the spatial resolution that can be achieved. For instance, in a heterogeneous population of neurons, an electrode would stimulate all neurons within the vicinity, regardless of subtype. Optogenetics, however, uses genetic-based techniques to deliver opsins to distinct populations of neurons based on their genetic identity (e.g., dopamine [DA] or serotonin neurons within close proximity can be individually targeted and stimulated independently). This is accomplished in vivo using stereotaxic injection of viral vectors carrying the opsin gene of interest under the control of cell type–specific promoters. Additionally, a recombinase-dependent system can be used to attain cell-type specificity if promoters prove too large for the vector of choice or suboptimal opsin expression is achieved. With this approach, opsin expression is restricted to cells containing Cre recombinase (Cre) when delivered to transgenic mice expressing Cre. Prime examples of this are studies in which Cre-inducible virus is delivered to tyrosine hydroxylase (TH)-Cre mice.<sup>10,11</sup> This approach directs ChR2 expression to TH-containing DA neurons, thus enabling the precise temporal control of DA neural activity. Such studies have demonstrated that distinct patterns of DA cell firing in the ventral tegmental area (VTA) elicit reward-related behaviours — findings that have vast implications for addiction research.

### Shedding light on neurocircuitry relevant to psychiatric illnesses

Although the use of optogenetics in animal models of psychiatric disease is in its infancy, its use in uncovering the neurocircuit elements of emotive behaviour is yielding promising avenues for delineating the neuronal underpinnings of various disorders that have been challenging to study at the pre-clinical stage. The field is expanding rapidly, so only a few key studies will be highlighted to illustrate the important advances in our understanding of the neurocircuit elements driving anxiety, addiction, depression and bipolar disorder.

Anxiety disorders are highly prevalent and comorbid with a number of psychiatric illnesses. Although the amygdala has been implicated, the specific amygdala microcircuitry driving anxiety remains to be fully elucidated. This, in part, is because

of the highly heterogeneous population of functionally distinct subnuclei within the amygdala and their complex interconnectivity, which has made attempts to functionally dissect these distinct populations methodologically challenging. In a recent paper, Tye and colleagues<sup>12</sup> used the spatial and temporal precision of optogenetics to target basolateral amygdala (BLA) neurons and optically stimulate them based on their connectivity to other amygdala subnuclei. Optical stimulation of BLA terminals (and not somata) within the central nucleus of the amygdala exerted an acute anti-anxiety phenotype in mice that was rapidly reversed during optical inhibition of this same pathway. This elegant study highlights the precision that can be obtained using optogenetic approaches to study highly complex microcircuits and has identified a key circuit for future therapeutic targeting.

In a paper studying loss-of-function in vivo, Witten and colleagues<sup>13</sup> examined the role of a small population of cholinergic neurons within the nucleus accumbens that, owing to their rarity, have been difficult to study. They reported that optical inhibition of cholinergic neurons in the nucleus accumbens was sufficient to prevent cocaine-induced conditioning in mice. The fact that cholinergic neurons constitute less than 1% of the nucleus accumbens neuronal population highlights the high spatial resolution imparted by optogenetics. Using this tool, scientists have now further elucidated the unique role of this small population of neurons, which may ultimately serve as a potential novel therapeutic target for addiction.

In terms of depressive behaviours, it has been recently shown that optogenetic stimulation of the medial prefrontal cortex exerted a potent antidepressant effect in mice susceptible to the effects of chronic social defeat stress,<sup>14</sup> suggesting that lower prefrontal cortex (PFC) activity mediates depressive-like behaviours. Indeed, clinically depressed patients also exhibit indicators of lower PFC activity,<sup>14</sup> offering up the tantalizing possibility that interventions aimed at increasing PFC neural activity could prove to be a novel antidepressant. Of all psychiatric disorders, however, bipolar disorder remains one of the most challenging to study at a pre-clinical level.<sup>15</sup> We have yet to develop a rodent model that exhibits spontaneous cycling between depression and manic-like behaviours and are, therefore, left to investigate these mood states independently. In Dr. Colleen McClung's lab at the University of Pittsburgh, my colleagues and I use the *ClockΔ19* mutant mouse, which exhibits a behavioural profile that is strikingly similar to the manic phase of human bipolar disorder.<sup>16</sup> Under baseline conditions, *ClockΔ19* mutant mice exhibit increased bursting and firing of DA neurons in the VTA concurrent with desynchronous neural communication across multiple brain regions.<sup>17,18</sup> We have just begun to use optogenetics to dissect the exact neurocircuitry underlying features of manic behaviours and hope to determine the neural adaptations that occur with prolonged photoperturbation of circuit function in an attempt to recapitulate the chronic nature of bipolar disorder.

### Translational applicability

Although optogenetics does not appear to be readily and

immediately applicable to human psychiatric disease, this is not necessarily an insurmountable task. There has been much discussion surrounding the potential application of combined optical and genetic technology for a more targeted and cell-specific form of deep brain stimulation.<sup>19</sup> Safe use of viral-mediated gene therapy in humans has already been established, and optogenetic manipulation of ex vivo human retinal tissue has been achieved.<sup>20</sup> Furthermore, much effort is being directed toward developing an optogenetic toolbox designed specifically for primates.<sup>21</sup> To this end, neural prosthetics have been implanted and are functionally capable of activating specific neurons in nonhuman primates.<sup>22</sup> Although highly speculative at the moment, a more indirect application of this technology involves combining optogenetic techniques with imaging, as in opto-functional magnetic resonance imaging,<sup>23</sup> where neurocircuit dysfunction within an individual patient can be visualized and treatment tailored based on a unique pathophysiological signature. Collectively, these are key steps in the translational applicability of this technology to the clinic.<sup>22</sup> For the time being, however, the greatest realized potential of optogenetics lies in shedding light on the neurocircuit elements underlying health and disease with direct applicability to designing therapeutic agents targeted to these novel pathways.

## Conclusion

In a field where drug discovery can be considered serendipitous at best and where the rate of pharmaceutical development is slow, optogenetics is providing a resurgence of hope with its potential to identify novel mechanistic-based therapeutic targets. Moving forward, it is essential for both basic and clinical scientists to become familiar with this groundbreaking and innovative technology to appreciate and fully understand its applications to, and implications for, the field of psychiatry.

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