CHAPTER NINE

Optogenetically-inspired neuromodulation: Translating basic discoveries into therapeutic strategies

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Abstract

Optogenetic tools allow for the selective activation, inhibition or modulation of genetically-defined neural circuits with incredible temporal precision. Over the past decade, application of these tools in preclinical models of psychiatric disease has advanced our understanding the neural circuit basis of maladaptive behaviors in these disorders. Despite their power as an investigational tool, optogenetics cannot yet be applied in the clinical for the treatment of neurological and psychiatric disorders. To date, deep brain stimulation (DBS) is the only clinical treatment that can be used to achieve circuit-specific neuromodulation in the context of psychiatric. Despite its

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increasing clinical indications, the mechanisms underlying the therapeutic effects of DBS for psychiatric disorders are poorly understood, which makes optimization difficult. We discuss the variety of optogenetic tools available for preclinical research, and how these tools have been leveraged to reverse-engineer the mechanisms underlying DBS for movement and compulsive disorders. We review studies that have used optogenetics to induce plasticity within defined basal ganglia circuits, to alter neural circuit function and evaluate the corresponding effects on motor and compulsive behaviors. While not immediately applicable to patient populations, the translational power of optogenetics is in inspiring novel DBS protocols by providing a rationale for targeting defined neural circuits to ameliorate specific behavioral symptoms, and by establishing optimal stimulation paradigms that could selectively compensate for pathological synaptic plasticity within these defined neural circuits.

1. Introduction: Overview of optogenetics in the context of neuromodulation

"Optogenetics" is an umbrella term that refers to a biological technique that involves the use of light to control neurons that have been genetically modified to express light-sensitive ion channels, pumps or receptors (Deisseroth, 2015; Fenno, Yizhar, & Deisseroth, 2011; Nagel et al., 2005). When exposed to light in a specific wavelength range, these opsins undergo conformational changes that alter their ion conductance or coupling to intracellular signal transduction pathways. Upon activation, these opsins have either excitatory, inhibitory or neuromodulatory effects on the cells in which they are expressed. Excitatory opsins conduct positive current, which depolarizes cells and induces the firing of action potentials (AP). Activation of inhibitory opsins hyperpolarizes the neuronal membrane and ultimately inhibits neuronal firing. A third type of modulatory opsin engages second messenger signaling cascades to influence cellular activity or even localization of proteins within the neuron, which alters neuronal metabolism, activity or plasticity (Lee et al., 2017; Repina, Rosenbloom, Mukherjee, Schaffer, & Kane, 2017; Spangler & Bruchas, 2017). This chapter reviews recent advances in the use of optogenetics as a research tool for rationally designing novel neuromodulatory therapies for psychiatric disease, as well as the potential direct utility of optogenetics in the clinic.

Opsins are typically expressed in neurons via two approaches—viral-mediated delivery or generation of a transgenic rodent line. In the former case, a viral vector (e.g., adenovirus, lentivirus or adeno-associated virus) is used to package opsin transgenes, and viruses are stereotaxically injected into specific brain regions. Alternatively, opsins may be constitutively

expressed under specific genetic promoters in transgenic mouse lines to allow for cell type-specific opsin expression. To deliver light, in most studies of optogenetic neuromodulation, optic fibers are implanted into specific nuclei in the brain to restrict light delivery to opsin-expressing neurons in the vicinity of the optic fiber. Because opsins are inserted in the cell's plasma membrane, light may be directed at specific neuronal compartments to lend versatility to experimental approaches (Kim, Adhikari, & Deisseroth, 2017). For example, light activation of terminals is sufficient to induce a standing action potential and induce neurotransmitter release from axon terminals independent of somatic cell firing, which can be used to achieve activation of specific neuronal projections. In this way, light can be delivered with great spatial and temporal precision to control the activity and firing of neurons (Fig. 1).

Precise spatial and temporal control of neuron firing is of paramount importance to many treatments for psychiatric and movement disorders. For example, early investigations of Parkinson's disease (PD) showed that pathological bursting activity within the subthalamic nucleus (STN) was causally related to the motor symptoms of PD, specifically to PD-related tremor (Hutchison et al., 1998; Plenz & Kital, 1999). There was thus strong rationale for modulating STN activity with high-frequency stimulation as a therapeutic strategy for motor symptoms of PD. While commonly used to treat psychiatric disorders, classical pharmacology did not deliver the same degree of spatiotemporal resolution, as small molecules distribute throughout the brain and exert complex effects depending on the cell type and post-synaptic receptor. Deep brain stimulation (DBS), on the other hand, provided adequate spatiotemporal resolution to disrupt pathological bursting associated with motor symptoms of PD. DBS is a surgical therapy, whereby current is passed through electrodes that are chronically implanted into specific brain nuclei, most often STN. Stimulation is typically applied at high frequencies (>100 Hz) continuously for months or years at a time (Benabid et al., 1998; Starr, Vitek, & Bakay, 1998). Since its advent over 30 years for Parkinson's disease, DBS has become a mainstay therapy for movement disorders; to date, DBS is the only FDA-approved clinical treatment that can achieve a degree of circuit-specific modulation.

While not currently FDA-approved for non-motor disorders, DBS has shown promise as a treatment in clinical studies of depression (Holtzheimer et al., 2017; Johansen-Berg et al., 2008; Mayberg et al., 2005), addiction (Kuhn et al., 2014; Müller et al., 2013; Valencia-Alfonso et al., 2012), Alzheimer's disease (Laxton et al., 2010; Sankar et al., 2015;

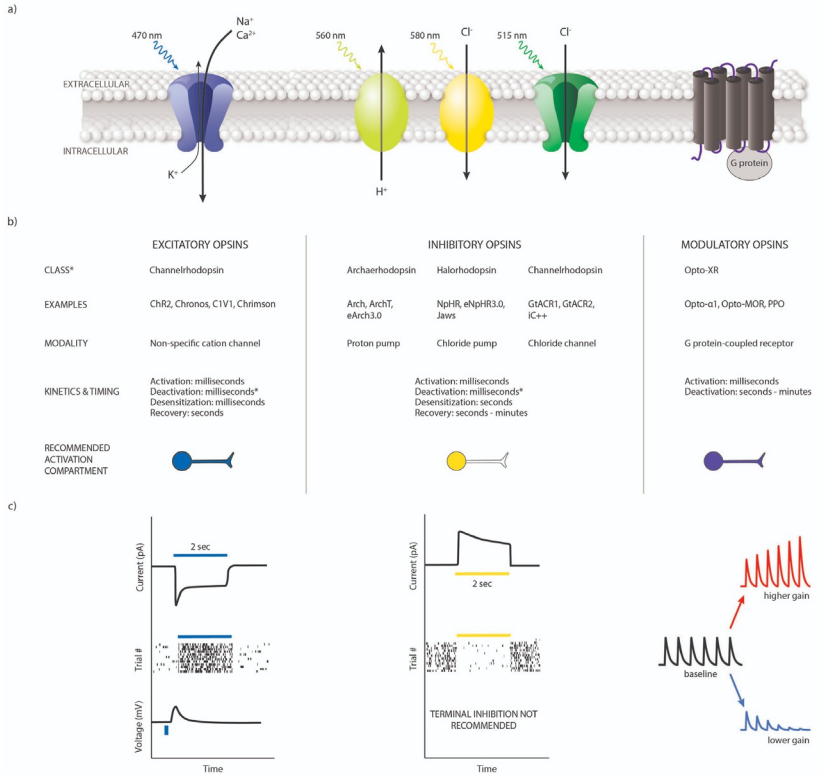

Fig. 1 Summary of classes of optogenetic effectors. Currently used opsins can be classified as excitatory, inhibitory or modulatory, depending on the biophysical effects they induce on opsin-expressing neurons when activated. (A) Schematic of ion permeability and activation wavelength of commonly used optogenetic effectors. (B) Examples, description and key implementation considerations of broad classes of optogenetic effectors. (C) Excitatory channelrhodopsins induce depolarizing currents in response to light activation when applied at the cell body, which increases depolarization and neuronal firing. Activation of channelrhodopsin-expressing terminals depolarizes axons and induces neurotransmitter release (left). Conversely, inhibitory opsins produce hyperpolarizing currents when activated at the cell body, which inhibits neuronal firing. Existing inhibitory opsins are not recommended for efficient inhibition of axon terminals, due to ineffective shunt inhibition, changes in intracellular pH and rebound excitation (middle). (D) Modulatory opsins couple to g-protein coupled receptors to either increase or decrease neuronal excitability (when activated at the cell body) or probability of neurotransmitter release (when activated in axon terminals).

Scharre et al., 2018), eating disorders (Lipsman et al., 2013; McClelland, Bozhilova, Campbell, & Schmidt, 2013; Treasure & Ashkan, 2013), obesity (Formolo et al., 2019), and chronic pain (Farrell, Green, & Aziz, 2018; Gopalakrishnan et al., 2018; Pereira et al., 2007; Rasche, Rinaldi,

Young, & Tronnier, 2006). Also promising have been the results of DBS for the treatment of OCD (Bewernick et al., 2010; Denys et al., 2010; Goodman et al., 2010), which has been granted approved by the FDA under a humanitarian device exemption (HDE). However, in contrast to well-established parameters for the successful treatment of movement disorders, the rationale for both stimulation target and stimulation parameters in psychiatric disorders is much less clear. Neuroimaging studies that localize altered blood oxygenation or metabolic activity in disease states to specific brain regions can help identify potential targets for neuromodulation. However, the mechanisms underlying changes in activity and functional connectivity between brain regions cannot be determined with imaging approaches alone. Moreover, altering the stimulation parameters, specifically frequency, temporal pattern, amplitude and pulse width has complex effects on target tissue, which can lead to important differences in the effects of DBS on local cell bodies and fibers of passage, and thus circuit function. As we will discuss below, pre-clinical models are particularly useful to address this mechanistic gap, because they allow invasive functional investigation of the disease pathology and effects of DBS with cellular resolution.

To this end, the impact of optogenetics on the field of neuroscience cannot be overstated. We review recent advances with the goal of providing insights into how optogenetic investigations can be leveraged to reverse-engineer and optimize existing deep brain stimulation protocols, and to develop novel neuromodulation strategies to treat neurological and psychiatric disorders.

2. Optogenetics as a unique research tool

A neuronal circuit refers to a functional ensemble of neurons connected via synapses. While neuronal death or degeneration is a hallmark of disorders such as Parkinson's disease, Alzheimer's disease or stroke, many psychiatric disorders such as depression, obsessive-compulsive disorder, schizophrenia and addiction are instead characterized by dysfunction of neural circuits. Since there are no characteristic gross anatomical changes in these circuit disorders, structural imaging methods are limited in their diagnostic potential. Moreover, while imaging techniques such as PET and fMRI can elucidate metabolic activity and functional connectivity changes associated with a given disorder, they cannot be used to determine the molecular or synaptic basis of this altered activity or functional connectivity. To address this mechanistic gap, pre-clinical models are particularly

powerful. Not only do pre-clinical models allow invasive functional investigation of the disease pathology, but they afford a versatile array of investigatory tools that can be used with cellular resolution. To this end, the advent of optogenetics has been especially consequential. Light activation of specific cell populations allows for the dissection of discrete components of neural circuits underlying complex behaviors, and provides insight into alterations of these circuits in mouse models of brain diseases. Stereotaxically-targeted injection of a cell type-specific viral construct may be combined with precise focusing of the optical fiber, such that activation of light-sensitive opsins is restricted to a distinct cell type, brain area, or projection. These approaches have been strategically combined with behavioral analyses and in vivo electrophysiology to yield unprecedented insight into how coordinated activity within defined neural circuits mediates complex behaviors. In a complementary approach, in vivo manipulations may be paired with ex vivo patch clamp electrophysiology to interrogate the molecular mechanisms of synaptic transmission and plasticity withing genetically-defined neural circuits. In this way, optogenetics lends remarkable versatility—from the synaptic to the circuit level—to investigation of neural signatures associated with psychiatric disorders. In the sections below, we give an overview of the most commonly used optogenetic inhibitors and optogenetic activators used in preclinical studies of neuropsychiatric disorders.

2.1 Classical optogenetic manipulation: Inhibition

Over the past decade, optogenetic approaches have yielded enormous insight into the neural-circuit basis of maladaptive behaviors in preclinical models of neuropsychiatric disease. Gain or loss of function experiments are particularly powerful approaches used by preclinical researchers to establish necessity and/or sufficiency of a specific neural population in a given behavior, optogenetic inhibition is frequently used. Activation of inhibitory opsins effects an essentially "reversible" lesion. Decades of preclinical behavioral neuroscience studies have used physical lesion of a brain structure or local infusion of $GABA_{A/B}$ receptor agonists (i.e., muscimol and baclofen, respectively) to inactivate target structures. However, these manipulations do not allow for cell-type selectivity, and the region of tissue affected is difficult to control. Moreover, lesions are non-reversible, and the effects of chemical inactivation reverse only over slow timescales. As a more selective and temporally robust alternative, optogenetic tools allow for reversible loss of function studies with cell-type specificity, and corresponding effects on

behavior can be observed in real time. Inhibitory opsins ultimately suppress neuronal activity either by lowering the probability of action potential initiation or by attenuating synaptic vesicle release. However, the cellular mechanisms by which each class of inhibitory opsins exerts its effects are diverse.

2.1.1 Inhibitory ion pumps

The most common inhibitory effectors that have been applied in models of psychiatric disease are ion pumps halorhodopsin (NpHR) and archaerhodopsin (Arch). Halorhodopsin, a chloride pump activated by yellow light, was the first optogenetic tool used for neuronal silencing (Zhang et al., 2007). Activation of halorhodopsin and its variants transports chloride (a monovalent anion) ions into the cell to directly hyperpolarize the membrane potential. Similarly, archaerhodopsin, a green light-activated proton pump, transports protons from the cytosol to the extracellular space to similarly hyperpolarize neurons (Chow et al., 2010). Light activation of either halorhodopsin or archaerhodopsin results in an inward-going negative or outward-going positive transmembrane current (respectively), hyperpolarizing the membrane potential and decreasing the probability of action potential generation.

The use of inhibitory opsins for neuronal silencing is not without its caveats, however. Optically-activated ion pumps transport only one ion across the plasma membrane for each photocycle. As such, halorhodopsins and archaerhodopsins are relatively inefficient and often require high constant delivery of light power over prolonged periods of time to achieve their desired effects. This is especially problematic for loss of function experiments, which often require inhibition of target cell populations for multiple minutes at a time intermittently throughout hours-long experiments. Light application on the scale of seconds or minutes may be potentially disruptive to cellular homeostasis and normal physiological function. Furthermore, high light powers delivered through an optical fiber can warm brain tissue enough to directly alter neuronal firing properties (Owen, Liu, & Kreitzer, 2019; Stujenske, Spellman, & Gordon, 2015), which is a major caveat for interpreting optogenetic silencing experiments. Moreover, because ion pumps operate independently of electrochemical gradients, their persistent activation results in the disruption of intracellular ion concentrations. For example, the resulting accumulation of intracellular chloride from halorhodopsin activation dramatically increases the reversal potential of the $GABA_A$ receptor (Raimondo, Kay, Ellender, & Akerman, 2012) and render it temporarily excitatory after only seconds of activation. Changes

in ion concentrations also contribute to attenuation of induced photocurrents over time (Berndt et al., 2011; Mattis et al., 2011), rebound spiking upon light offset (Chuong et al., 2014; Mahn, Prigge, Ron, Levy, & Yizhar, 2016), and unanticipated synaptic dynamics during light-off periods (El-Gaby et al., 2016).

Due to the sensitive machinery at pre-synaptic terminals and the variability in ion concentrations across cellular compartments, the adverse effects described above are exacerbated in axons and axon terminals. Indeed, the inevitable photocurrent-induced increase in pH following archaerhodopsin activation promotes pH-dependent increases in pre-synaptic calcium and increased spontaneous vesicle release from axon terminals. Similarly, intracellular concentrations of chloride are often higher in axonal compartments, making effects of chloride pumps and channels on excitability unpredictable at axon terminals (Mahn et al., 2016).

Interestingly, each of the unintended secondary effects described here results in the exciting of targeted cells, rather than inhibiting them as intended. Therefore, validation of inhibitory opsins in specific experimental applications is recommended.

2.1.2 Opto-modulators

Opsins that employ intracellular signaling cascades have also been used to modulate neuronal activity. Rather than the opsin behaving as a pump or a channel itself, rhodopsin GPCRs (opto-XRs) are engineered to use light to engage G protein-mediated signaling cascades. Optical activation of a G protein complex, which occurs via its transmembrane receptor, triggers the dissociation of α- and $\beta\gamma$-subunits from the membrane-bound receptor and releases each to the cytosol. Each subunit complex may then act as an effector to alter the activity of myriad intracellular processes, including altering ion conductances of excitable cells.

While opto-XRs exist in excitatory and inhibitory variants, their intrinsic properties are particularly well-suited for neuronal inhibition. Contrary to optically-activated ion pumps, opto-XRs are highly photosensitive and remain in their active state for timescales ranging from minutes to hours (Ernst et al., 2014). Thus, with brief, periodic pulses of light, opto-XRs may be activated indefinitely. These properties are particularly beneficial for loss of function studies, which often require persistent inactivation, potentially hours at a time. Recent advances in opto-XR development have optimized these G protein-coupled opsins further by introducing an on-off switch to their functionality; light delivered in one wavelength activates the

opsin, while a different wavelength inactivates the opsin (Spoida et al., 2016; Tichy, Gerrard, Sexton, & Janovjak, 2019).

The nature of GPCRs—and, therefore, opto-XRs—allows them to *modulate* activity rather than directly influence neuronal outputs. In this way, opto-XRs operate against the backdrop of existing circuit functionality. This gain control functionality acts as a potentiometer (rather than a switch) for neuronal activity, where the opsin increases or decreases the probability of neuronal output, without directly evoking an action potential or hyperpolarizing current itself. Used in conjunction with existing DBS paradigms, for example, modulating circuit activity and plasticity over long periods of time with optogenetics has tremendous investigatory and therapeutic potential. Being able to "turn down" distinct components of neuronal circuits or cellular populations provides insight into how and where DBS-induced plasticity occurs. Moreover, as opto-XR technology continues to be optimized, photo-switchable opto-XRs will allow investigators to demonstrate causality between circuit plasticity and behavior, adding dimension to the therapeutic potential of optogenetics.

2.2 Classical optogenetic manipulation: Activation

In the majority of the published studies using optogenetic effectors to dissect circuit function, effectors are used to activate bulk populations of neurons that share a common genetic promoter. Expression of opsins can be further limited to specific brain regions, allowing for activation of distinct projections. The effects of acute activation of targeted neuron populations on behavior are measured in real time during light stimulation. A caveat of this common approach is that optogenetic stimulation is inherently non-physiological, inducing synchronized firing of neuronal populations at a constant frequency. Coordinated firing of large neural populations does not faithfully mimic endogenous activity of neural populations, which often show heterogeneity in their firing patterns and activity, even when defined by a common genetic promoter. Further complicating matters is the choice of stimulation frequency for a given experiment. Frequently, a constant stimulation frequency, ostensibly in the physiological range of neuronal activity, is delivered, and the acute effect of stimulation on behavior is monitored. However, single neurons and populations of neurons are capable of firing at a range of frequencies, often as a function of behavioral state, making the choice of a single stimulation frequency difficult. To circumvent this limitation, a minority of studies have linked neural activity to given

behaviors by systematically varying stimulation frequency while examining the acute effects on behavior. In this way, establishing a frequency-response curve can determine the level of synchronized neural activity necessary to elicit a given behavioral state. An alternative strategy to overcome this limitation has been to record endogenous activity of neuronal populations during behavior, and then mimic endogenous firing frequencies within that population to establish causality between stereotyped neural activity and a given behavioral state. However, at a given time during behavior, a "population" of neurons can still exhibit considerable heterogeneity in firing rates, which cannot be captured with a single stimulation frequency.

While still an emerging technology, simultaneous optical imaging paired with holographic stimulation has the potential to interrogate neural circuit function. Holographic illumination refers to computer-generated holography offers an enormous flexibility to sculpt the excitation light in three-dimensions, particularly when combined with two-photon light sources. By projecting holographic light patterns on the sample, the activity of multiple neurons across a 3D brain volume can be simultaneously imaged or manipulated with single-cell resolution (Zhang, Russell, Packer, Gauld, & Häusser, 2018). With this strategy, activity of individual neurons is recorded during behavior, and the same activity patterns are played back to individual neurons to precisely emulate endogenous activity. As we discussed above, this approach is especially powerful since even neighboring neurons from the same genetic class can exhibit vastly different activity patterns, which are masked by bulk or whole-field optogenetic stimulation. However, holographic imaging and stimulation can only potently be achieved with two photon microscopy (Yang, Carrillo-Reid, Bando, Peterka, Yuste, 2018), which introduces some important limitations. Firstly, achieving imaging and stimulation with two-photon light sources requires head-fixation, which limits the range of behaviors rodents can engage in during imaging and stimulation. Moreover, while cortical structures lend themselves to widescale 2P imaging, sculpting light for delivery to deep brain structures poses additional challenges. The biophysical properties of brain tissue make it prone to scattering light that penetrates beyond 80 μM especially at shorter wavelengths typically used for optogenetic stimulation (Cheong, Prahl, & Welch, 1991). Solutions that address the consequent optical aberrations are highly invasive, such as ablation of tissue columns dorsal to the brain area of interest to implant specialized gradient index lenses.

Despite these caveats, classical optogenetics studies have been used to perform loss- and gain-of-function studies which have yielded important insights into neural circuit control of behavior. Understanding how distinct neural circuits control behaviors relevant to psychiatric disease (i.e., avoidance behaviors, reward learning, seeking and processing, fear expression), is the first step in identifying neural circuit that could be targeted with neuromodulation therapies in the context of treating psychiatric disease. A comprehensive review of classical optogenetic studies dissecting behaviors relevant to psychiatric disease is beyond the scope of this chapter. However, we refer the readers to contemporary reviews of optogenetic interrogation of neural circuits in preclinical models of mood (Fox & Lobo, 2019; Knowland & Lim, 2018; Lobo, Nestler, & Covington, 2012), substance use (Creed & Lüscher, 2013; Farrell, Schoch, & Mahler, 2018; Lüscher, 2016), anxiety (Ahmari, 2016; Allsop, Vander Weele, Wichmann, & Tye, 2014), and movement disorders (Gittis & Yttri, 2018; Parker, Kim, Alberico, Emmons, & Narayanan, 2016; Sizemore, Seeger-Armbruster, Hughes, & Parr-Brownlie, 2016).

3. Optogenetic neuromodulation of the basal ganglia in disease models

The prior section pointed out caveats and the non-physiological nature of classic "circuit-cracking" optogenetic manipulations (Packer, Roska, & Häusser, 2013). In the field of neuromodulation, alternative optogenetic strategies have emerged for studying neural circuits, which embrace the supraphysiological nature of optogenetic stimulation. In the first approach, optogenetic stimulation is delivered acutely at specific physiological frequencies to induce long-term plasticity within neural circuits. In the case where induction of synaptic plasticity causes long-term physiological changes in circuit function, the resulting long-term effects on behavior are examined to establish causal links between function of specific nodes in a neural circuit and emerging behavior. A second strategy uses optogenetics to probe the mechanisms underlying effective neuromodulation therapies, specifically deep brain stimulation (DBS). DBS is a surgical therapy whereby current is passed through electrodes chronically implanted into specific brain nuclei, and is currently a mainstay treatment for movement disorders. Optogenetics has been used to emulate or abolish the effects of DBS on behavior, in order to reverse-engineer which DBS-induced changes in neuronal activity are causally related to its therapeutic effects. In the discussion

below, we will focus on a subset of optogenetic studies that either induce long-term circuit changes to inspire novel DBS paradigms, or that have been used to reverse engineer the effects of deep brain stimulation.

In this section, we discuss a subset of optogenetic studies that have explicitly attempted to induce plasticity and thus alter neural circuit function, or to reverse-engineer the therapeutic effects of DBS, or to inspire novel neuromodulation paradigms to improve behavioral symptoms of neurological and psychiatric disorders. We focus on disorders of the basal ganglia, which is a collection of subcortical nuclei whose coordinated activity mediates action selection, reinforcement learning and motivational processing (Kimura, Yamada, & Matsumoto, 2003; Nicola, 2007; Nieoullon & Coquerel, 2003). Several basal ganglia targets, such as the globus pallidus, ventral pallidum, subthalamic nucleus and nucleus accumbens are already established or promising DBS targets. The subthalamic nucleus and internal segment of the globus pallidus have been leading DBS targets for movement disorders including PD for decades. Indications for STN-DBS have expanded to include OCD and potentially addiction, while the nucleus accumbens (NAc), has emerged as a potential target for depression (Bewernick et al., 2010; Grubert et al., 2011; Ressler & Mayberg, 2007), addiction (Creed, 2018; Kuhn et al., 2014; Müller et al., 2013), obesity (Formolo et al., 2019), and obsessive-compulsive disorder (Ahmari & Dougherty, 2015; Denys et al., 2010; Greenberg et al., 2003). Specifically, the studies below have provided pre-clinical validation of which neural subcircuits within the basal ganglia are promising targets for neuromodulation in a given disease state, or have inspired novel plasticity-inducing stimulation paradigms that could be adapted for DBS.

3.1 Movement disorders

One of the earliest applications of optogenetics to the field of DBS was seminal work from Gradinaru and colleagues, which used cutting-edge optogenetic effectors to determine whether modulation of discrete basal ganglia afferents or populations of STN neurons could emulate the effects of STN-DBS. The paper used the 6-hydroxy dopamine model of PD, in which motor symptoms of bradykinesia and akinesia emerge due to degeneration of dopaminergic neurons projecting from the substantia nigra to striatum (Gradinaru, Mogri, Thompson, Henderson, & Deisseroth, 2009). Competing hypotheses of DBS mechanisms suggested that motor symptoms of PD could be due to (a) functional inhibition of the STN, (b) stimulation of STN efferents and (c) antidromic activation of afferents or fibers of passage through the STN.

This investigation first tested the hypothesis that the motor effects of STN-DBS were due to local inhibition. Arguing against this hypothesis, optogenetically silencing cell bodies of the STN with halorhodopsin was unable to rescue motor deficits in a 6-OHDA model of PD. However, it should be noted that investigations from a separate group also using halorhodopsin reported that optogenetic inhibition of the STN had no effect on forelimb use asymmetry in the same 6-OHDA model (Yoon et al., 2014) but had more subtle effects on improving forelimb akinesia as well as axial dyskinesia in a model of L-Dopa induced dyskinesia (Yoon et al., 2016). One explanation for the motor effects of inhibitory opsins on dykinesias but not akinesias is that silencing STN neurons prevents aberrant bursting activity which is causally related to dyskinesia and tremor symptoms, but is not to akinesia (Hutchison et al., 1998).

Similarly, optogenetic activation of STN cell bodies also did not rescue motor deficits, arguing that STN-DBS does not exert its effects through driving action potentials in efferent STN fibers. However, these experiments stimulated at 130 Hz, while kinetics of the variants of ChR2 available at the time were not able to faithfully follow high stimulation frequencies (Gunaydin et al., 2010). More recent studies with mutated opsins (i.e., Chronos, which is capable of following frequencies over 100 Hz (Saran, Gupta, & Roy, 2018) have suggested that activation of cell bodies at frequencies relevant to DBS may indeed rescue motor deficits in a PD model (Yu, Cassar, Sambangi, & Grill, 2020). This underscores that exploring the parameter space of optogenetic stimulation can yield important insights into the potential neural mechanisms underlying the therapeutic effects of DBS.

Instead, using ChR2 to selectively activate terminal fields of cortical afferents into the STN rescued unilateral motor deficits in the PD model (Gradinaru et al., 2009), suggesting a critical role of antidromic activation of "hyperdirect" cortico-STN pathway in the motor effects of DBS. This result has been repeated in subsequent studies, confirming that selective activation of afferents from motor cortex to STN is sufficient to improve motor symptoms in a PD model, and to partially reverse pathological synchrony of neural activity between these two structures that emerges following dopamine depletion (Fraix, Pollak, Vercueil, Benabid, & Mauguière, 2008; Li, Arbuthnott, Jutras, Goldberg, & Jaeger, 2007). This dissociation of antidromic activation of afferents from alternative mechanisms of DBS is prohibitively challenging with electrical stimulation, and emphasizes the utility of optogenetics for parsing therapeutic mechanisms.

The goal of the above studies was to apply optogenetics to reverse-engineer effective therapies of DBS. A feature of DBS is that the effects

are largely transient, and reappear after stimulation offset. This suggests that conventional DBS temporarily modulates circuit function, but is not reversing disease-related adaptations in neural circuits. An alternative approach is to delivery stimulation in such a way as to induce long-term plasticity within basal ganglia circuits, to reverse disease-induced adaptations and have long-lasting effects on motor symptoms. Optogenetics has been critical for informing such optogenetically-inspired DBS protocols.

Specifically, an optogenetic stimulation protocol was developed by Gittis and colleagues, where modulation of neurochemically-defined subpopulations of GPe neurons efficiently reversed locomotor deficits in a 6-OHDA model of PD (Mastro et al., 2017). The GPe is a common DBS target for movement disorders, although the mechanisms underlying the effects of DBS here are no better understood than with STN-DBS. Prototypical GPe projection neurons can be dissociated into two largely distinct populations, based on their expression of either parvalbumin (PV) or the transcription factor Lim hox 6 (LHX6;(Mastro, Bouchard, Holt, & Gittis, 2014). While these neuronal populations are both GABAergic and both project downstream to SNr, manipulation of these circuits have dramatically different effects on motor behavior. Specifically, optogenetic activation or inhibition of the whole GPe failed to modulate motor symptoms in a 6-OHDA model of PD. By contrast, pulsatile activation of PV population, but not the Lhx6 population induced a progressive increase in mobility and normalized GPe burst activity, which outlasted the cessation of stimulation. Interestingly, these two populations are interconnected, and inhibition of Lhx6 population mimicked these effects, revealing reciprocal roles of these populations on basal ganglia circuit function. This cell-type specific dissection would have been incredibly challenging to arrive at without the use of optogenetics, which allows genetic access to each subpopulation for manipulation and monitoring. Going forward, leveraging differences in biophysical properties or afferent connectivity of these two neuronal populations could lead to refined, optogenetically-inspired deep brain stimulation protocols to effectively restore circuit function. Critically, because this stimulation is inducing plasticity within the basal ganglia, these motor benefits substantially outlast the duration of stimulation.

3.2 Compulsivity-related disorders

In addition to movement disorders, dysfunction of basal ganglia circuits have also been implicated in compulsive disorders, specifically obsessive compulsive disorder and addiction. While human neuroimaging studies have

consistently reported altered functional connectivity between prefrontal cortex and striatum across these disorders, establishing causality between this altered connectivity and behavioral symptoms, or the neural mechanisms underlying this altered connectivity cannot be established by human neuroimaging. However, optogenetic tools have established links of causality between altered cortico-striatal connectivity and compulsive behavior in disease models. Moreover, while the ventral striatum (including the nucleus accumbens, NAc) has emerged as potential DBS target in both OCD and addiction, clinical efficacy is mixed, and the mechanisms of action are largely unknown. In this respect, leveraging optogenetic tools to dissect the mechanisms underlying DBS could be a necessary step in the optimization of DBS.

3.2.1 Obsessive compulsive disorder

Evidence supporting corticostriatal dysfunction in OCD comes from human neuroimaging studies, which demonstrate hyperactivity of striatal-projecting cortical areas at baseline and during symptom provocation (Mataix-Cols et al., 2004; Rauch et al., 1994; Rotge et al., 2008), including OFC. This is accompanied by abnormal functional connectivity between OFC and dorsal and ventral striatum (Abe et al., 2015; Anticevic et al., 2014; Posner et al., 2014). Optogenetic studies have provided mechanistic support for the hypothesis that these changes are causally related to emergence of OCD symptoms in animal models.

By inducing plasticity specifically within lateral orbitofrontal (lOFC) inputs to ventral striatum, optogenetics has established that altered function of this circuitry is causally related to compulsive behaviors in animal models of OCD. In the first investigation by Ahmari et al. (2013), channelrhodopsin was expressed in the lOFC and terminals were stimulated over the ventral striatum. The hypothesis was that acutely activating of this pathway (to mimic hyperactivity observed in functional imaging studies) would increase compulsive behaviors. However, compulsive grooming behavior emerged only after repeated daily sessions of optogenetic activation. Interestingly, stimulation was delivered at 10 Hz, which is efficient at inducing LTD at cortical synapses onto dorsal and ventral striatal neurons (Hoffman, Oz, Caulder, & Lupica, 2003; Robbe, Kopf, Remaury, Bockaert, & Manzoni, 2002). Moreover, the differences in grooming were most pronounced during the habituation phase prior to the optogenetic stimulation, further arguing that long-term plasticity in these circuits, and not acute activation per se is the driver of compulsive behavior.

A simultaneous study from Burguière and colleagues provided further evidence of orbitofrontal-cortical activity in compulsive grooming behavior (Burguière, Monteiro, Feng, & Graybiel, 2013). In this assay, authors used a genetic model of OCD, the SAPAP3 knock-out model which shares genetic risk factors observed in human OCD patients (Bienvenu et al., 2009, p. 3; Züchner et al., 2009) and exhibits corticostriatal transmission deficits and pathological compulsive grooming phenotype (Welch et al., 2007). In a conditioned grooming assay, SAPAP3-mutant mice showed elevated striatal activity and conditioned grooming response to tones predicting delivery of a water droplet to the snout, which was not observed in wildtype mice. By optogenetically activating the lOFC-DMS pathway, while simultaneously recording both structures, the authors determined that acute activation of this pathway both suppressed the maladaptive conditioned grooming response, and elevated striatal activity. Further analysis of striatal neuronal firing revealed that this lOFC-mediated inhibition of striatal activity was due to activation of striatal fast-spiking interneurons, inducing lateral inhibition of surrounding medium spiny neurons.

Together, these results point to a model whereby reduced excitatory drive from lOFC to striatum is causally related to inhibitory control of grooming. This interpretation is further bolstered by subsequent ex vivo observations that used optogenetics to isolate excitatory transmission from lOFC to striatal neurons (Corbit, Manning, Gittis, & Ahmari, 2019; Hadjas et al., 2020). Combining ex vivo electrophysiology and optogenetics revealed that lOFC to striatal synapses are significantly depressed relative to wildtype mice. This bidirectional manipulation of activity highlight the potential benefit of modulating lOFC-striatal synapses in maladaptive repetitive behaviors in OCD models. It's critical to keep in mind that in the two aforementioned studies, the grooming behaviors were both learned conditioned responses: in the case of optogenetic induction of plasticity, grooming occurred in response to a conditioned environment, or to a conditioned tone in the case of the suppression of grooming in the SAPAP3 model. This further underscores the role of OFC-striatal synapses in behavioral flexibility.

As a therapy that received CE mark and is approved by the FDA under a humanitarian device exemption, DBS of the anterior limb of the internal capsule and ventral striatum has been applied to treat severe OCD in the clinic (Denys et al., 2010; Goodman et al., 2010). While promising, the mechanisms of action are still poorly understood. To date, no published preclinical studies have directly sought to use optogenetics to elucidate the therapeutic effects of DBS in animal models. However, a single study applying

DBS to the ventral striatum in SAPAP3 mice found no efficient reduction of grooming symptoms (Pinhal et al., 2018). However, the internal capsule was modulated and efficiently reduced grooming in the same study. By analyzing immediate early gene induction as a proxy for neural activity, the proposed mechanism of effective DBS was antidromic activation of prefrontal cortex. Future work using optogenetic tools could establish whether activation of prefrontal cortical inputs to striatum is indeed necessary for the therapeutic effects of DBS, and whether alternative DBS parameters could more efficiently alter plasticity in prefrontal cortico-striatal circuits and more efficiently reduce behavioral symptoms of OCD.

3.2.2 Addiction

A myriad of studies have reported altered metabolic activity in prefrontal cortical subregions (comprised of orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC)) in patients with substance use disorder (Asensio et al., 2010; Goldstein et al., 2007; Koob, 2020; Tang, Posner, Rothbart, & Volkow, 2015). These regions are critical for executive function such as attribution of salience, inhibitory control, behavioral flexibility and decision making, which are all disrupted in addiction and lead to compulsive drug seeking. Preclinical studies employing optogenetics have yielded further insight into how altered function of cortico-striatal circuits mediates maladaptive drug seeking and sensitization in animal models of addiction, which has informed neuromodulation therapies aimed at reversing drug-induced neural circuit dysfunction.

Addiction is a complex disorder made up of a constellation of behavioral symptoms; these symptoms can be modeled in rodents using several behavioral paradigms. For example, increased incentive salience of drug associated contexts can be modeled with locomotor sensitization, while craving and relapse behaviors can be modeled by context- and cue-evoked drug seeking in extinction (Bossert, Marchant, Calu, & Shaham, 2013; Di Chiara, 1999; Lüscher, Robbins, & Everitt, 2020; Robinson & Berridge, 2000). Finally, compulsive drug seeking, arguably the hallmark of addiction, is modeled by drug seeking despite punishment or aversive consequences. Optogenetic circuit dissection has implicated drug-induced aberrant plasticity at cortico-striatal synapses in all of these addiction-relevant behaviors.

Exposure to addictive drugs such as psychostimulants (Boudreau & Wolf, 2005; Famous et al., 2008; Pierce, Bell, Duffy, & Kalivas, 1996; Thomas, Beurrier, Bonci, & Malenka, 2001) or opioids (Hearing et al., 2016;

Madayag et al., 2019; Zhu, Wienecke, Nachtrab, & Chen, 2016) increase excitatory drive onto nucleus accumbens neurons. Addictive drugs share the property of increasing dopamine release in the nucleus accumbens (Di Chiara & Imperato, 1988; Willuhn, Wanat, Clark, & Phillips, 2010), which in turn induces plasticity at corticostriatal synapses. This plasticity is known to be dopamine dependent, since optogenetically driving dopamine neurons directly is sufficient to mimic drug-evoked plasticity and induce addiction-relevant behavior in the absence of addictive drugs (Pascoli, Terrier, Hiver, & Lüscher, 2015). Moreover, it was not until the application of optogenetic circuit dissection that plasticity could be attributed to specific nucleus accumbens cell types and synapses. By transfecting neurons in the PFC and performing patch-clamp recordings downstream in the nucleus accumbens, multiple groups have reported that exposure and withdrawal from cocaine and opioids potentiate excitatory synapses from PFC onto NAc neurons (Boudreau & Wolf, 2005; Creed, Pascoli, & Lüscher, 2015; Ma et al., 2014; Pascoli et al., 2014; Pascoli, Turiault, & Lüscher, 2011; Roberts-Wolfe, Bobadilla, Heinsbroek, Neuhofer, & Kalivas, 2018). This was observed with experimenter administered drugs and with self-administration.

Critically, optogenetic experiments have established that this cortical potentiation arises from driving insertion of AMPARs to the synapse, and this plasticity is causally related to behavioral symptoms of addiction. Specifically, stimulating terminal fields of mPFC neurons projecting to ventral striatum at either 1 or 12–13 Hz is known to induce long-term synaptic depression at this pathway. 1 Hz stimulation is thought to induce LTD according to classic Hebbian mechanisms, while stimulation between 10 and 15 Hz is thought to reduce synaptic strength through an mGluR1-dependent mechanism that leads to phosphorylation and internalization of AMPA receptors from the synapse. If these same LTD-inducing stimulation protocols are applied in vivo to mice that have been exposed to addictive drugs, behavioral sensitization and preference for drug-paired environments is abolished (Creed et al., 2015; Hearing et al., 2016; Pascoli et al., 2011). Further implicating mPFC to accumbens synapses in drug seeking behavior, in vivo optogenetic depotentiation of this pathway following cocaine self-administration abolished cue-induced drug seeking (Pascoli et al., 2014). Interestingly, only 13 Hz LTD, not 1 Hz LTD, was able to abolish drug seeking behavior in this paradigm. The interpretation is that while 1 Hz LTD induces homosynaptic LTD only at the stimulated synapse, 13 Hz stimulation evokes a form of LTD that involves signaling through

extra-synaptic mGluR receptors, which induces a form of heterosynaptic plasticity affecting neighboring glutamatergic inputs to the NAc. Together, this optogenetic induction of plasticity provides mechanistic insight into the mechanism of altered cortico-accumbal functional connectivity in patients with addiction, and argue that modulating this circuitry may be a therapeutic target for neuromodulation in addictive disorders.

Indeed, DBS of the nucleus accumbens has been tested in case studies of patients with substance use disorders. While results are still preliminary due to low numbers of patients enrolled in case studies, high-frequency DBS of the NAc was shown to reduce subjective ratings of craving, and attenuated ventral striatal activation in response to images of drug-associated cues (Kuhn et al., 2007, 2009, 2011). While, the mechanisms underlying the effect of DBS (applied at 130 Hz) to the NAc are not well understood, preclinical models have mimicked this main finding that DBS applied to the NAc reduces drug sensitization (Creed et al., 2015; Nona, Creed, Hamani, & Nobrega, 2015), as well as cue- and drug-primed seeking for heroin (Schippers et al., 2017) and cocaine (Guercio, Schmidt, & Pierce, 2015; Vassoler et al., 2008, 2013) after protracted withdrawal. In one study by Vassoler and colleagues, using lidocaine to dissociate the contribution of fibers of passage to the NAc and measuring immediate early gene induction provided circumstantial evidence that modulating of PFC to NAc inputs was necessary for the behavioral effects of DBS. Similar circuits are implicated in diet-induced obesity (Matikainen-Ankney & Kravitz, 2018), thus obesity-linked accumbal plasticity changes present an attractive target for chronic circuit manipulation through DBS. Though clinical reports of accumbal-targeted DBS are early (with only six patients) all six NAc DBS patients lost weight after ongoing DBS manipulation, and three of the six patients showed reductions of between 8 and 40% of their body weight maintained after 14 months (Formolo et al., 2019). However, to date, there are no published studies using optogenetics to reverse engineer the mechanisms underlying the ability of NAc-DBS to transiently attenuate drug or food seeking. However, as we discuss in the next section, optogenetics has been applied to develop novel DBS stimulation protocols that has long-lasting effects on drug-adaptive behavior.

In summary, optogenetic tools have yielded unprecedented insight into understanding the neural circuit bases of behavioral symptoms relevant to motor and compulsive symptoms arising from basal ganglia dysfunction. These optogenetic circuit dissection studies have revealed that brain nuclei such as the NAc, STN or GPe could be targeted with neuromodulation to

treat behavioral symptoms of these disorders. Moreover, understanding the mechanisms underlying the therapeutic effects of DBS is a necessary step in its optimization. In this respect, applying optogenetics to reverse-engineer mechanisms underlying the therapeutic effects of DBS—and disentangle these effects from mechanisms underlying adverse DBS side effects—can yield important insights necessary for optimizing DBS in the clinic.

4. Optogenetics as a clinical therapy: Current barriers and future directions

The previous sections focused on optogenetics as a research tool, and the true value of optogenetics is informing the development of treatment strategies. However, there are few cases where DBS has been applied directly in patients as a therapeutic strategy. To date, these cases are limited to Retinitis pigmentosa, where a genetically encoded red-shifted ChR2 variant is delivered to the retina via viral vectors. Coupled with a visual device that translates visual scenes into red-shifted light to activate the ChR2 and compensate for advanced degeneration of cone photoreceptors (Busskamp, Picaud, Sahel, & Roska, 2012; Soltan et al., 2018). Beyond this case application, there are significant and impressive efforts underway to optimize optogenetics for use in patients. In this section, we briefly outline the main developments that would be required for applying optogenetics clinically, and suggest that using optogenetically-inspired DBS (OiDBS) is a promising approach that can bridge optogenetic insights with clinical applications in the shorter term.

4.1 Advances that need to occur before optogenetics can be applied clinically

While optogenetic investigations have yielded insight into neural circuit dysfunction underlying behavioral symptoms of psychiatric disease, several issues preclude the immediate application of optogenetics for disorders of the central nervous system. These obstacles have been comprehensively reviewed elsewhere, but briefly, they include safety of viral vector delivery, safety and efficiency of long-term viral expression, and adequate light delivery through tissue of interest (Shen, Campbell, Côté, & Paquet, 2020). Given that the therapeutic opsin would need to be delivered to and expressed in the central nervous system over long timescales, it is paramount that delivery and expression of the opsins occurs without immunogenicity or inducing degeneration of the target cells. To overcome the

inherent limitations of stereotaxic targeting, there are efforts to develop novel viral serotypes that are suitable for peripheral delivery, either through the CSF or intranasally (Chan et al., 2017), although these have not yet been tested in human patients, and a stereotaxic surgery would still be required for targeting light delivery systems to deep brain structures.

Light delivery poses another engineering problem; the scattering of light through heterogeneous tissue is difficult to estimate due to variability in tissue absorption and scattering properties (Cheong et al., 1991), but it is unlikely that a single point source of light (akin to how optogenetics is achieved in rodents) would be sufficient to ensure light delivery over more than a 1 mm^3, making efficient targeting challenging. Increasing light power is not a viable strategy, as thermal effects of light delivered to the brain would be expected to change neural capacitance via heating, leading to unintended induction of neural activity or tissue damage. An alternative approach is to use red-shifted opsins, which are activated by light in the 600 nm range. Using a longer wavelength is estimated to increase the volume of tissue penetrance up to 1 cm^3 (DePaoli et al., 2020). While this range may be sufficient for targeting some nuclei (i.e., subthalamic nucleus), arrays or lattices of implanted fiberoptics may be required to achieve coordinated activation of opsins across larger volumes of brain tissue.

A final consideration that is more difficult to remedy is achieving cell-type specific expression of opsins. In many optogenetic studies, the potent effects of optogenetic stimulation on behavior arise because opsin expression (and thus optogenetic manipulation) is restricted to genetically-defined subpopulations of neurons within a target nucleus. Typically, this is achieved via transgenic rodents, which express Cre-recombinase under the control of cell-type specific promoters (Deverman et al., 2016). Combining this technology with Cre-dependent virus ensures that only Cre-positive cells are modulated by opsins. While this system leads to a powerful research tool, it is not possible in human patients. An emerging potential solution to this problem is the use of engineered viral capsids that preferentially or selectively infect only the cell types of interest. The development of the Cre-recombination-based AAV targeted evolution (CREATE) platform has allowed for improved identification of capsid variants capable of cell-type selective infection, and thus viral expression (Chan et al., 2017; Deverman et al., 2016). Briefly, this approach applies positive selective pressure for capsid variants that transfect Cre-expressing cells (which reflect the desired target population). By incorporating amplification and genetic sequencing of capsids which successfully infect Cre-expressing cells after successive rounds of selection, this platform enables

the identification of capsid variants that can efficiently infect a population of neurons defined by Cre-expression. These capsids could then be used for packaging virus encoding opsins, and would target viral delivery to genetically-defined cell types without the need for Cre expression.

Overall, the immediate clinical application of optogenetics for the treatment of CNS disorders is limited by potential safety issues related to viral delivery and expression, the need for light activation across large areas of heterogeneous tissue, as well as cell-type selective expression of opsins. Neuroscientists and engineers are making significant progress in all these areas, and it is entirely feasible that with further advances, optogenetics will become a mainstay neuromodulation therapy for a variety of CNS disorders. However, for the time being optogenetics cannot immediately translated to the clinic, and an intermediate strategy is required to leverage optogenetic insights into translational therapies.

4.2 Optogenetically-inspired DBS: Refining DBS to emulate optogenetic manipulations

As mentioned above, an intermediate strategy is required to leverage insights from optogenetic circuit dissection studies into clinically relevant therapies for neurological and psychiatric disorders. We and others have proposed that using optogenetics to inform novel DBS protocols, so called optogenetically-inspired DBS protocols, could bridge this gap. As a case study, we discuss an optogenetically-inspired DBS protocol that selectively reverses cocaine-evoked plasticity and induces long-lasting reduction in drug-adaptive behavior.

As discussed above, exposure to cocaine or morphine potentiates excitatory inputs from the mPFC onto neurons in the NAc (Thomas et al., 2001; Wolf, 1998). This potentiation has been causally related to drug sensitization and drug seeking behavior, and is driven by synaptic insertion of AMPA receptors. These AMPA receptors can be efficiently removed by mGluR-dependent signaling (Martin, Chen, Hopf, Bowers, & Bonci, 2006), which can be induced by optogenetically stimulating these mPFC projections to the NAc at 10–15 Hz (Mangiavacchi & Wolf, 2004a; Robbe et al., 2002). We and others have shown that optogenetically driving PFC projections to the NAc at these frequencies induce synaptic depotentiation and have long-lasting effects of reversing drug sensitization, seeking and conditioned place preference (Creed et al., 2015; Pascoli et al., 2014, 2011). We thus tried to emulate these effects by applying DBS at low frequencies (12 Hz) to induce LTD in vivo. However, low-frequency DBS (12 Hz)

applied to the NAc or to the upstream cell bodies in the mPFC had no effects on accumbal plasticity, and did not alter drug-related behavior (Creed et al., 2015).

Using ex vivo brain slices from cocaine-treated animals, we were able to dissect the mechanistic differences between optogenetic and electrical stimulation relevant for their divergent effects on synaptic plasticity. Specifically, we found that while optogenetics selectively released glutamate from transfected cortical afferents, electrical DBS, due to its non-specific nature, induced release of multiple neurotransmitters. Crucially, the release of dopamine would be predicted to further exacerbate cocaine-evoked plasticity, by stimulating dopamine D1-receptors and further driving AMPARs into the synaptic membrane (Mangiavacchi & Wolf, 2004b; Sun, Zhao, & Wolf, 2005; Wolf, Mangiavacchi, & Sun, 2003). We tested this prediction in the ex vivo slice preparation, and found that when electrical DBS was applied in the presence of a dopamine receptor antagonist, to preclude dopamine signaling in accumbal neurons, DBS was now able to induce an LTD comparable to what was induced by optogenetic stimulation. When we next applied this optogenetically-inspired DBS in vivo (which refers to acute, 12 Hz DBS in combination with a systemic dopamine D1 receptor antagonist), we found that we were able to mimic the effects of optogenetic stimulation: behavioral sensitization to cocaine was abolished for up to 7 days following the acute DBS protocol. Moreover, synaptic examination determined that optogenetically-inspired DBS efficiently depotentiated excitatory synapses onto NAc neurons. Critically, the antagonist used (SCH-39166, Ecopipam) is already FDA approved for the treatment of Tourette's syndrome and addictive disorders, which further reduces the barrier to translation.

Together, these results establish that deep brain stimulation, inspired by optogenetic stimulation strategies, can restore neural circuit function in disease states, and can have long-lasting effects on behavior. While this proof of concept used a model of cocaine exposure, similar potentiation of glutamatergic inputs into the nucleus accumbens have been observed in animal models of opioid addiction (Hearing et al., 2016; Madayag et al., 2019; Zhu et al., 2016), chronic pain (Goffer et al., 2013; Vekovischeva et al., 2001; Xu, Su, Lin, Manders, & Wang, 2015) and obesity (Alonso-Caraballo et al., 2020; Brown et al., 2017; Hryhorczuk et al., 2016; Oginsky, Goforth, Nobile, Lopez-Santiago, & Ferrario, 2016), raising the possibility that optogenetically-inspired DBS could normalize circuit function and treat symptoms of these disorders as well. Finally, a key advantage is that this

optogenetically-inspired DBS protocol works through a known mechanism, which may be useful for reducing adverse side effects, or screening patients that may be candidates for successful neuromodulation.

5. Conclusion

This is an exciting time for the field of optogenetics, from the perspectives of both basic and clinical science. We outlined the breadth of optogenetic effectors that can be used to achieve precise activation or inhibition of genetically-defined neuronal subpopulations, either through direct time-locked stimulation with light-gated ion channels or slower modulation of neuronal gain through diverse versions of opto-RXs (Fig. 1). We argue that while optogenetic circuit dissection has led to a myriad of insights into the neural basis of behaviors relevant to neurological and psychiatric disorders, optogenetic manipulations are inherently non-physiological, and that a real strength of optogenetics has been in suggesting novel neuromodulation targets or stimulation paradigms by probing disease-related plasticity within defined neural circuits. Finally, while exciting advances in biotechnology are reducing the barriers to the use of optogenetics in the clinic, for the immediate future, optogenetic manipulations are not feasible to treat CNS disorders in the clinic. Instead, developing optogenetically-inspired DBS protocols is a promising strategy to bridge the gap between optogenetic circuit dissection and clinical neuromodulation protocols. These optogenetically-inspired DBS protocols are unique, in that they seek to achieve targeted reversal of disease-induced plasticity within neural circuits, and thus induce long-lasting reduction in behavioral symptoms that result from this circuit dysfunction. This approach could fill the urgent need for disease-modifying therapies for chronic pain-, mood-, movement-, substance use- and mood disorders.

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