Optogenetic approaches to evaluate striatal function in animal models of Parkinson disease

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Introduction

The advent of optogenetic technologies has advanced the field of neuroscience by allowing the manipulation of specific neuronal populations with millisecond resolution using light. Optogenetics allows researchers to stimulate or inhibit brain cells defined by a specific promoter and to specifically target a particular brain region. Opsins, or light-sensitive proteins, are genetically expressed in the neurons of a model organism and can then be activated with ~1-ms tempo-
Clinical research

porally precise delivery of specific wavelengths of light (Figure 1).

Optogenetic viruses, constructs, and equipment are now readily available, making this technology accessible for various applications.

The first light-sensitive protein was isolated in the 1970s from *Halobacterium halobium*, though it took many years for its bioengineering potential to be realized. In 2003, initial work was published by Ernst Bamberg, describing the use of Channelrhodopsin-2 (ChR2) to drive neuronal activity with light. In a 2005 paper, Boyden et al from Karl Deisseroth’s laboratory further characterized ChR2’s potential for fast, precise, and dynamic stimulation of neurons and made significant improvements in the ease of genetic expression and efficacy. Furthermore, optogenetic stimulation has almost no measurable side effects for the host tissue, proving to be minimally invasive for use in vivo in mammals. Optogenetic proteins have also been engineered for the targeted inhibition of neuronal populations (Figure 1). The two primary inhibitory opsins are NpHR, a halorhodopsin, and Arch, an archaerhodopsin. NpHR, a chloride pump, requires constant light to move through its photocycle and has slower dynamics than Arch, a proton pump, which has more potent inactivation effects.

Genetic technology facilitates cell-type specificity for targeting optogenetic proteins to individual classes of neurons. Lentiviruses or the more commonly used adeno-associated viral (AAV) vectors can be used to express a given construct in all neurons, excitatory pyramidal neurons, inhibitory interneurons, astrocytes, or oligodendrocytes, depending on the genetic promoter used. The use of transgenic Cre-recombinase mouse lines affords definitive cell-type specificity. In combination with Cre-dependent AAV vectors or transgenic mice, robust expression can be attained in a cell type restricted by a chosen Cre-driving promoter.

This technique allows researchers to use various existing transgenic Cre mouse lines and to ask precise, directed questions that can be used to gather information about the actions of neuronal subclasses. Another advantage presented by optogenetic technologies is the ability to target not only a specific cellular class, but also modulate the projections of that cell type to a structure of interest. Optical cannulae can be implanted in downstream structures receiving projections from the injection location as a way to target only efferent projections (Figure 2).

Because of their versatility, the various optogenetic proteins and stimulation techniques present a rich tool-

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**Selected abbreviations and acronyms**

- **ChR2** Channelrhodopsin-2
- **DBS** deep brain stimulation
- **MFB** medial forebrain bundle
- **MSN** medium spiny neurons
- **PD** Parkinson disease
- **STN** subthalamic nucleus
- **VTA** ventral tegmental area

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**Figure 1.** Optogenetic tools for modulating membrane voltage potential. Stimulating the neurons expressing the nonselective cation channel Channelrhodopsin-2 (ChR2) using blue light immediately depolarizes the neuron and triggers an action potential. Sometimes it is desirable to inhibit neuronal signaling instead of triggering it. Light stimulation of halorhodopsin (NpHR), a chloride pump, hyperpolarizes neurons and inhibits spikes in response to yellow light. Recent variants (named eNpHR2.0 and eNpHR3.0) exhibit improved membrane targeting in mammalian cells and consequently, photocurrents. Light-driven proton pumps such as archaerhodopsin-3 (Arch), Mac, bacteriorhodopsin (eBR), and rhodopsin-3 (GtR3) can also be used to hyperpolarize neurons and block signaling. Ca++, calcium; ChETA, channelrhodopsin-2 mutant E12ET; mV, millivolts; Na+, sodium; nm, nanometer; SFO, step-function opsin; VChR1, Volvox-derived channelrhodopsin-1.

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box for a multitude of research questions. For comprehensive reviews on the use of optogenetics for a wide range of applications, see Yizhar et al.20 Zhang et al.21 and Deisseroth.1 Manipulating neuronal activity with the high level of temporal and spatial precision, cell-type specificity, and control that optogenetics allows has led to major advancements in our understanding of basic neural circuitry. Additionally, pairing these methods with multichannel and multisite neuronal recordings has the potential to reveal how these circuits are disrupted in neuropsychiatric diseases such as Parkinson disease (PD).

**Parkinson disease neural circuitry and current treatments**

PD is a neurodegenerative disorder characterized by the gradual death of midbrain dopaminergic neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA).22-24 The cardinal symptoms of PD in humans are resting tremor, muscle rigidity, and akinesia (difficulty in initiating movements)—of note, PD can also lead to nonmotor symptoms.25,26 PD symptoms result from striatal dysfunction. The striatum integrates projections from the cortex and thalamus to promote action selection (Figure 3).27,29 It mainly consists of medium spiny neurons (MSNs) expressing two main types of dopamine receptors: D1-type and D2-type.30-33 These populations are expressed in two main output pathways: D1 in the striatonigral “direct” pathway, and D2 in the striatopallidal or “indirect” pathway.31,32 The striatonigral pathway directly inhibits the globus pallidus interna (Gpi) and substantia nigra pars reticulata (SNr). The striatopallidal pathway indirectly excites the Gpi/SNr via disinhibition (Figure 3).29,34 The striatonigral (direct) pathway has been speculated to pro-

![Figure 2](image_url)
mote motor actions, whereas the striatopallidal (indirect) pathway suppresses actions. Imbalances between neural activities in the direct and indirect pathways in the basal ganglia caused by a loss of dopaminergic input result in profound motor deficits among patients with PD.\textsuperscript{35,36}

Optogenetics to probe striatal circuits and motor symptoms in animal models of PD

In animal models of PD, optogenetic approaches have been applied to answer a variety of fundamental research questions. There are two primary toxin-based animal models of PD, both of which are induced by toxic pharmacological lesion. The first involves a 6-hydroxydopamine (6-OHDA) injection into the substantia nigra, medial forebrain bundle (MFB), or striatum. The second requires repeatedly administering 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intraperitoneally.\textsuperscript{37-40} Although 6-OHDA and MPTP animal models do not replicate the progressive loss of dopaminergic neurons, they model catecholamine dysfunction in PD. Other models involve $\alpha$-synuclein overexpression or mutations; to our knowledge, optogenetics has not been explored in these models.\textsuperscript{41-43}

Optogenetics has provided details of striatal MSNs, interneurons, and afferents that could have implications for PD and other neuropsychiatric diseases (for complete review, see ref 44). As a result of the efficacy of subthalamic nucleus (STN) deep brain stimulation (DBS) on the motor symptoms of PD, Gradinaru et al\textsuperscript{12} investigated STN optogenetic inhibition and excitation as a method to mimic the effects of DBS in animals with 6-OHDA injections in the MFB (Figure 4).\textsuperscript{12,19,45} While optogenetic excitation and inhibition of STN neurons had no effect, high-frequency stimulation of afferent fibers projecting from the motor cortex to the STN ameliorated motor symptoms. It is important to note that infusions of muscimol and lidocaine in the STN have been demonstrated to relieve some PD symptoms in monkeys treated with MPTP.\textsuperscript{46} Changes in STN activity following stimulation could influence downstream structures, including the striatum. These results illustrate how optogenetics can be used to precisely define neural circuitry and describe the influence of stimulation and inhibition on behavioral measures.

As previously described, it is thought that hyperactivity in the indirect pathway and insufficient activity in the direct pathways contribute to the motor symptoms of PD.\textsuperscript{35} To investigate this hypothesis, Kravitz et al\textsuperscript{45} used optogenetics to selectively probe these pathways in mice expressing D$_1$-Cre or D$_2$-Cre recombinase-dependent ChR2 in MSNs. They found that bilateral stimulation of the D$_2$ neurons of the indirect pathway...
induced freezing and bradykinesia and decreased locomotion, whereas stimulation of the D₁ neurons of the direct pathway reduced freezing and increased locomotion. Additionally, they reported that optogenetic stimulation of the direct pathway rescued motor abnormalities induced by 6-OHDA lesions in the MFB (Figure 4). These data indicate the importance of the opposing influences of the direct and indirect pathways and indicate potential therapeutic strategies to ameliorate the motor deficits associated with PD.45

Figure 4. A schematic diagram (top panel) shows key neural projections that are involved in parkinsonian behavior and treatment. Data in the bottom left panel are from a study that used a constitutively expressing ChR2 mouse line (Thy1::ChR2) to identify a mechanistic explanation for the therapeutic effects of deep brain stimulation. By illuminating and recording in the subthalamic nucleus, this paper showed that afferent fibers entering the subthalamic nucleus, rather than local cell bodies themselves, are likely to be the direct target of deep brain stimulation in the correction of parkinsonian motor activity. High-frequency stimulation of the afferent fibers into subthalamic nucleus potently silenced the structure as shown and reversibly abolished the parkinsonian symptoms. By contrast, low-frequency stimulation of the afferents simply added spikes on top of endogenous spikes and worsened parkinsonian symptoms.12 Data in the bottom right panel are from a study that used a Cre-AAV to selectively express ChR2 in either D1 dopamine receptor (D1R)::Cre or D2 dopamine receptor (D2R)::Cre mice to examine the differential contributions of the direct and indirect pathways with respect to motor output. Activation of D1R-expressing neurons silenced local basal ganglia activity and increased ambulation, whereas activation of D2R-expressing neurons increased this activity and enhanced immobile or bradykinetic (slow) behavior.45 Black bars indicate the duration of illumination. AAV, adeno-associated viral; ChR2, Channelrhodopsin-2; HFS, high-frequency stimulation; LFS, low-frequency stimulation; M1, primary motor cortex; μV, microvolts; D1, D1-type dopamine receptor; D2, D2-type dopamine receptor; GABA, γ-aminobutyric acid; GP, globus pallidus; Hz, hertz; ms, milliseconds; s, seconds; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus. Reproduced from reference 19: Tye KM, Deisseroth K. Optogenetic investigation of neural circuits underlying brain disease in animal models. Nat Rev Neurosci. 2012;13(4):251-266. © 2012, Nature Publishing Group. Bottom left image group originally published in reference 12: Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. Science. 2009;324(5925):354-359. © 2009, American Association for the Advancement of Science. Bottom right image group originally published in reference 45: Kravitz AV, Freeze BS, Parker PRL, et al. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature. 2010;466(7306):622-626. Copyright © Nature Publishing Group, 2010.
Optogenetics has also been used to probe the mechanisms underlying the efficacy of grafting human pluripotent stem cell-derived dopaminergic neurons in disease models. Animals with striatal 6-OHDA lesions exhibit motor impairments that are robustly reversed following engraftment of dopaminergic neurons in the lesioned area. To probe the mechanisms underlying the efficacy of this effect, Steinbeck et al optogenetically inhibited engrafted dopamine stem cells after motor recovery. They report that inhibiting dopamine neurons resulted in the reappearance of motor deficits, indicating the essential role of dopaminergic neurons at the lesion site. The studies described here provide evidence for the importance of optogenetic exploration of striatal function in animal models of PD. These results could inform the design of novel drug- and stimulation-based therapies to rescue dopaminergic dysfunction and motor symptoms in PD.

**Optogenetics to probe neural circuitry and cognitive dysfunction in animal models of PD**

In addition to the characteristic motor symptoms, non-motor symptoms are also present in PD including depression, psychosis, and cognitive dysfunction. Cognitive impairment is a serious component of PD for many patients. Though initially controversial, cognitive deficits are now an integral part of PD symptomatology. These cognitive symptoms can be diverse, including visuospatial dysfunction, working-memory deficits, and executive dysfunction. Despite its prevalence, the underlying basis of cognitive dysfunction in PD is poorly understood. Whereas treatments exist that successfully alleviate motor symptoms of PD, their cognitive benefits are not established. Cognitive dysfunction in PD patients may involve the prefrontal cortex, a key input structure to the striatum. Frontostriatal circuits are the primary neural pathways responsible for cognitive dysfunction in PD. The frontal cortex receives dopaminergic projections from dopaminergic neurons in the VTA. Dopaminergic neurons in the VTA also die during PD and therefore could play a role in disease-related cognitive abnormalities. Given the critical role of the dopaminergic system in the development of PD, its significance in cognitive symptoms of PD has also been studied.

As described earlier in this review, animal models are a critical component of PD research. However, the relevance of animal models is less obvious when dealing with complicated internal processes like “cognitive dysfunction.” When trying to approach cognitive deficits of PD in an animal model, it is essential to find a behavioral assay that is simple, relies on the structures involved in the disease, and is translatable to human patients. Temporal processing tasks meet these criteria. Interval-timing tasks require subjects to make a motor estimation of the passage of an interval of time. Interval timing can be studied in both rodents and humans. Tasks that rely on time estimation are known to rely on dopaminergic systems. Our group has shown that interval-timing tasks are impaired in PD and in rodents administered 6-OHDA injections in the VTA or in the frontal cortex. Specifically, we found that disrupting dopamine synthesis also impaired interval timing. We used optogenetics to specifically implicate prefrontal D1 dopamine receptors and demonstrated that stimulating prefrontal D1 neurons could enhance performance of timing tasks. Additionally, PD patients and rodent PD models had diminished frontal, low-frequency, cue-related activity and single-neuron ramping activity, indicating conserved mechanisms for timing and cognitive function.

Optogenetics provides a novel way to probe frontostriatal interactions in animals performing the interval-timing task and can be tailored specifically to D1 dopamine receptors using Cre-dependent expression of ChR2 or other opsins. These techniques can be used in animal models of PD with depleted D1 dopamine to try to ameliorate aberrant frontal and striatal neuronal activity and rescue performance on behavioral tasks. The same techniques could be used to probe cognitive flexibility and frontostriatal circuitry in other paradigms including reversal learning, attentional set-shifting, and task switching. These tasks are impaired in PD and can all be explored in animal models. Elucidating the neural mechanisms of cognitive impairment in neuropsychiatric disease may identify novel sites for DBS or transcranial magnetic stimulation in PD, schizophrenia, and other neuropsychiatric diseases that share dysfunctional D1-dopamine and striatal abnormalities. Results from these proposed studies have the potential to illuminate the neural mechanisms of cognitive impairment and help identify novel biomarkers and novel therapeutic targets for the D1-dopamine system.
Future directions

This review summarizes the powerful contribution that optogenetics has made to our understanding of striatal circuitry, abnormalities in PD, and the potential for striatal modulation as a novel therapeutic target in PD. Yet, it is clear that if we aim to inspire new treatments for PD, there is a great need for further optogenetic exploration of striatal circuitry and function in animal models. Looking forward, optogenetics can be used to pave the way for emerging technologies to adaptively stimulate brain circuitry in diseases of impaired motor and cognitive function. If we can map specific neuronal abnormalities and show that optogenetic stimulation or inhibition successfully rescues motor and/or cognitive impairments in animal models of PD, an online, closed-loop design could be used to stimulate aberrant circuits. In patients with PD, cognitive and motor function could be restored using concomitant electroencephalography to detect neural abnormalities and deep brain or transcranial stimulation to adaptively rescue specific patterns of neuronal activity.29

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Estrategias optogenéticas para evaluar la función estrial en modelos animales de la Enfermedad de Parkinson

La optogenética se refiere a la capacidad de controlar células que han sido modificadas genéticamente para expresar canales iónicos sensibles a la luz. La introducción de las estrategias optogenéticas ha facilitado la disección de los circuitos neurológicos. La optogenética permite precisar la estimulación e inhibición de conjuntos específicos de neuronas y sus proyecciones con una alta especificidad temporal. Estas técnicas idealmente están adaptadas para investigar los circuitos neurológicos que subyacen a la disfunción motora y cognitiva en modelos animales de la enfermedad humana. Este artículo se enfoca en cómo se ha empleado la optogenética durante la última década para explorar los circuitos neurológicos que están involucrados en la Enfermedad de Parkinson, una condición neurodegenerativa que incluye alteraciones motoras y cognitivas resultantes de la degeneración de neuronas dopaminérgicas del mesencéfalo. Aunque las estrategias optogenéticas están algo alejadas del empleo clínico, el conocimiento a partir de estos estudios puede ayudar a identificar nuevos blancos terapéuticos y puede inspirar nuevos tratamientos para la Enfermedad de Parkinson. Es esclarecer cómo las mediciones neurológicas y conductuales son influidas y potencialmente recuperadas por la manipulación optogenética podría llegar a ser traducible a los humanos. Estos conocimientos pueden ser empleados para guiar futuras estrategias de estimulación cerebral para anormalidades motoras y cognitivas en la Enfermedad de Parkinson y otras enfermedades neuropsiquiátricas.

L'optogénétique et son utilisation pour évaluer la fonction striatale dans des modèles animaux de la maladie de Parkinson

L’optogénétique est une méthode permettant de contrôler des cellules qui ont été préalablement génétiquement modifiées pour exprimer des canaux ioniques sensibles à la lumière. Son utilisation a ouvert la voie à l’analyse des circuits neuronaux car elle permet la stimulation et l’inhibition précises de groupes spécifiques de neurones et de leurs projections avec une excellente spécificité temporelle. Ces techniques sont parfaitement adaptées à l’examen des circuits neuronaux sous-tendant une dysfonction motrice et cognitive dans des modèles animaux de pathologies humaines. Cet article met l’accent sur la façon dont l’optogénétique a été utilisée ces 10 dernières années pour examiner les circuits striataux impliqués dans la maladie de Parkinson, une maladie neurodégénérative dont les troubles moteurs et cognitifs résultent d’une dégénérescence des neurones dopaminergiques du mésencéphale. Les mécanismes précis sous-tendant la contribution du striatum au dysfonctionnement moteur et cognitif de la maladie de Parkinson sont encore méconnus. Bien que l’optogénétique soit quelque peu éloignée de l’usage clinique, les connaissances issues de ces études peuvent aider à identifier de nouvelles cibles thérapeutiques et suggérer de nouveaux traitements pour la maladie de Parkinson. Une fois élucidés, les mécanismes par lesquels les manipulations optogenétiques peuvent influencer et potentiellement restaurer les fonctions neuronales et comportementales pourraient être transposés chez l’homme. Ces connaissances pourraient alors être utilisées pour mener de futures stratégies de stimulation cérébrale dans les anomalies motrices et cognitives de la maladie de Parkinson et d’autres maladies neuropsychiatriques.

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Cognitive deficits and striato-frontal dopamine release in Parkinson's disease.

Cognitive slowing in Parkinson's disease is related to frontostriatal dopaminergic dysfunction associated with frontostriatal circuitry in Parkinson's disease.

Activity in frontostriatal neural circuitry.

Cognitive symptoms of Parkinson's disease are accompanied by reductions in dopaminergic modulation of high-level cognition in Parkinson's disease.

ES cells efficiently engraft in animal models of Parkinson's disease.

Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease.

Lateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow multiple clocks?

Cognitive deficits in Parkinson's disease.

Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment.

Cognitive fysfunction in Parkinson's fisease: The role of dopaminergic pathophysiology and treatment.

Dopaminergic pathophysiology and treatment.

Dopamine-related dysfunction.

Dopaminergic regulation of attention and motor performance.

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