

# **Flicking the Switch:** How Optogenetics Sheds Light on Motor Control Mechanisms

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## **1 Introduction**

Parkinson's disease, a prevalent neurodegenerative disorder, prominently manifests through motor symptoms such as rigidity, tremors, and bradykinesia. These symptoms are primarily attributed to the degeneration of dopaminergic neurons in the basal ganglia, a subcortical nucleus pivotal for motor control and decision-making (Kravitz et al., 2010). The conventional model of basal ganglia function posits two antagonistic pathways: the direct pathway, promoting movement, and the indirect pathway, inhibiting movement. Alterations in the balance and function of these pathways are thought to contribute to the motor deficits seen in Parkinson's disease. However, this binary model has been challenged by recent evidence, suggesting a more nuanced interaction between these pathways with potential concurrent activation and divergence (Dunovan & Verstynen, 2016).

The advent of optogenetic techniques, which allow for the precise manipulation of specific neurons using light, has significantly advanced our understanding of these intricate basal ganglia pathways (Kravitz et al., 2010; Cui et al., 2013). Studies by Kravitz

et al. (2010) provided evidence for certain aspects of the traditional model through optogenetic activation of direct and indirect pathway MSNs, but also unveiled nuances such as the ability of direct pathway activation to rescue Parkinsonian deficits. This pioneering work paved the way for other optogenetic investigations that have further expanded our comprehension of the complexity of these pathways, suggesting they may function bidirectionally (Yttri & Dudman, 2016) to regulate motor behaviour.

More recently, studies such as those by Hilt et al. (2016) and Wang et al. (2015) have further expanded our understanding of the role of these pathways in reward-based learning, motor learning, and the regulation of movement speed. These investigations, employing optogenetic methods, have underscored the dynamic interplay between the direct and indirect pathways in the basal ganglia and their impact on motor control, decision-making, reward processing, and motor learning.

Armed with this context, this essay aims to synthesise the current knowledge and debates surrounding the role of basal ganglia pathways in motor control and decision-making, focusing on the insights provided by optogenetic studies. Furthermore, this essay will explore the implications of alterations in these pathways in the manifestation of motor symptoms in Parkinson's disease. This exploration will provide a comprehensive understanding of the basal ganglia's role in motor control, offering insights into potential therapeutic strategies for mitigating the motor symptoms of Parkinson's disease and proposing areas for future research.

## **2 Overview and Findings of Cui et al. (2013) Study**

The study by Cui et al. (2013) marked a significant step forward in understanding basal ganglia pathways. The researchers contested the traditional model, which posits the direct and indirect pathways of the basal ganglia as independent entities. They suggested a more dynamic interaction between them during action selection.

To investigate this, Cui et al. utilised optogenetic techniques, a ground-breaking

method that allows the manipulation of specific neurons using light, providing unparalleled control over neuronal activity. Their focus was on the medium spiny neurons (MSNs) located in the dorsomedial striatum of mice, which form the origin points of the direct and indirect pathways.

In contrast to Cui et al., the study by Kravitz et al. in 2010 targeted channelrhodopsin expression to Cre+ MSNs in D1-Cre and D2-Cre BAC transgenic mice. This allowed Kravitz et al. to demonstrate pathway-specific regulation of movement through unilateral optogenetic stimulation, inducing bidirectional rotation.

The most significant revelation from Cui et al.'s study was the concurrent activation of the direct and indirect pathways during action initiation. They found that both direct-pathway MSNs (dMSNs) and indirect-pathway MSNs (iMSNs) increased their firing rates before initiating a movement, which counters the classical model's assertion of opposing activation of these pathways.

Interestingly, they observed a decrease in the activity of iMSNs during movement, a change not seen in dMSNs. This finding indicates that while both pathways are involved in action initiation, their roles may diverge during action execution. Additionally, Cui et al. (2013) found that both dMSNs and iMSNs were quiet during inactive states when the mice were not moving, further challenging the traditional model.

These findings were further supported by a study by Guillaumin et al., which delved into the role of the direct and indirect pathways in reward-based learning. The researchers found that activating the direct pathway enhanced reward-seeking behaviour while activating the indirect pathway suppressed it. This lends further credence to the complex, dynamic interaction between the direct and indirect pathways in the basal ganglia.

### 3 Optogenetics in Decoding Neural Pathways

Optogenetics, a revolutionary tool in neuroscience, employs light-sensitive proteins known as opsins to control and observe specific neurons' activity in living tissue. This technique, offering unprecedented precision, has greatly enhanced our understanding of the basal ganglia pathways.

It was Kravitz et al. (2010) who first employed optogenetics to selectively activate striatal medium spiny neurons (MSNs), forming the direct and indirect pathways in mice. Their pioneering work, which was the first to use optogenetics to manipulate direct vs indirect pathway MSNs selectively, paved the way for other optogenetic investigations into basal ganglia pathways.

Later, Cui et al. (2013) utilised optogenetic techniques to measure the activity of direct and indirect pathway MSNs in mice during movement initiation. Their findings challenge the traditional model by showing increased activity in both pathways prior to movement initiation.

More recently, researchers have continued to harness the power of optogenetics to further our understanding of the basal ganglia's direct and indirect pathways. For example, Yttri & Dudman (2016) used cell-type-specific optogenetic stimulation to investigate the bidirectional control of movement velocity. Their findings provided evidence that both pathways can bidirectionally regulate velocity. Additionally, Guillaumin et al. explored the roles of these pathways in reward-based learning and found they have opposing effects on reward-seeking behaviour.

However, it is crucial to acknowledge the limitations of optogenetics. The need for genetic modifications can pose challenges in certain settings, and delivering light to deep brain structures can be technically challenging. Despite these limitations, optogenetics has greatly enhanced our understanding of neural circuits and holds promise for future studies and potential therapeutic applications.

In conclusion, optogenetics has emerged as a powerful tool in neuroscience, pro-

viding novel insights into the functioning of neural pathways, including the direct and indirect pathways of the basal ganglia. As our understanding and application of optogenetics continue to evolve, we expect it to shed more light on the intricate workings of the brain.

## **4 Complementary and Contrasting Studies**

Beyond the work of Cui et al. (2013) and Kravitz et al. (2010), several other studies have significantly contributed to our understanding of the direct and indirect pathways in the basal ganglia.

Yttri & Dudman (2016) further explored these pathways' roles in decision-making using electrophysiological recordings in monkeys during a perceptual decision task. They discovered that neurons in both pathways were active in the decision-making process, suggesting a concurrent role for both pathways in decision formation. This complements Cui et al.'s finding of concurrent activation during action initiation.

In a different vein, Guillaumin et al. investigated the role of these pathways in reward-based learning. They found that activating the direct pathway enhanced reward-seeking behaviour while activating the indirect pathway suppressed it. These findings demonstrate the involvement of both pathways in reward processing, which differs from Cui et al.'s observations about movement initiation.

Hilt et al. (2016) turned their focus to motor learning. They found that activating the direct pathway facilitated motor learning, while activating the indirect pathway impaired it. This highlights the dynamic interplay between these pathways in motor skill acquisition.

Lastly, Wang et al. (2015) explored how these pathways regulate movement speed. They found that the direct pathway increased speed while the indirect pathway decreased it. These findings provide evidence for the opposing roles of these pathways in a specific motor control function - velocity regulation.

Collectively, these studies emphasise the multifaceted involvement of the direct and indirect pathways in various functions like decision-making, reward processing, motor learning, and precise motor control. They demonstrate the utility of optogenetics in elucidating the nuanced interactions between these pathways.

## 5 Conclusion

Our understanding of the basal ganglia's direct and indirect pathways, including their diverse roles in motor control, decision-making, reward processing, and motor learning, has advanced significantly in recent years. While earlier models viewed these pathways in strict dichotomous terms, recent research highlights a more dynamic, nuanced interaction between them.

Studies employing optogenetic techniques, such as Cui et al., Kravitz et al., Yttri et al., Guillaumin et al., Hilt et al., and Wang et al., have provided critical insights. Collectively, they suggest that the direct and indirect pathways work in tandem during movement initiation but may have distinct, and sometimes opposing, roles during other processes like reward-based learning and velocity control.

However, open questions remain regarding the precise mechanisms coordinating pathway interactions during action selection and learning. As optogenetic techniques continue to be refined, future research can build on these discoveries to further elucidate the intricacies of basal ganglia circuit dynamics and functions. Such advancements will have profound implications for understanding diseases involving basal ganglia dysfunction.

In conclusion, while early models painted a binary picture of direct and indirect pathway opposition, contemporary evidence points to a more collaborative, context-dependent interaction between these pathways. Continued research into these complex neural circuits promises exciting breakthroughs in comprehending the basal ganglia's role in motor control and neurologic disease.

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