Flicking the Switch:
Optogenetics and the Interplay of Direct and Indirect Pathways in Motor Control

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Abstract

This essay presents a comprehensive synthesis of the current understanding of basal ganglia pathways, focusing on direct and indirect neural circuits. It critically evaluates the traditional dichotomous model and examines recent evidence suggesting a nuanced, dynamic interaction between the two pathways in motor control, decision-making, reward processing, and motor learning. Utilising key studies employing optogenetic techniques, the essay contributes to a deeper understanding of these pathways' concurrent activation and divergence during action initiation and execution.

Moreover, the essay delves into the implications of alterations in these pathways for the manifestation of Parkinson's disease symptoms and potential therapeutic strategies for mitigating these symptoms. It also outlines the significant contributions of optogenetics to our knowledge of these pathways, underscoring the technique's power and precision. Despite significant advancements in understanding basal ganglia circuit dynamics, the essay highlights open questions regarding the precise mechanisms coordinating pathway interactions during action selection and learning, underlining the need for continued research.

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1 Introduction

Parkinson's disease, a prevalent neurodegenerative disorder, primarily affects the basal ganglia, a group of subcortical nuclei in the brain. These nuclei, which include key structures such as the striatum, globus pallidus, subthalamic nucleus, and substantia nigra, play crucial roles in motor control, decision-making, and reward processing (Zhang et al., 2018; Ojagbemi et al., 2013).

The motor symptoms of Parkinson's disease, such as rigidity, tremors, and bradykinesia, are often attributed to the degeneration of dopaminergic neurons in the substantia nigra, a critical component of the basal ganglia (Abedini et al., 2015). The resultant disruption in the balance and functioning of the basal ganglia's direct and indirect pathways, which are primarily composed of medium spiny neurons (MSNs), has significant implications for motor control Abedini et al. (2015); Ojagbemi et al. (2013).

Traditionally, the direct and indirect pathways of the basal ganglia are thought to function antagonistically: the direct pathway facilitates movement, while the indirect pathway inhibits it (Isett et al., 2022). However, this binary model has been challenged by recent studies, which suggest a more complex interaction between these pathways. For instance, these pathways may show potential concurrent activation and divergence in certain motor actions, adding complexity to our understanding of their roles in voluntary movement control (Perez et al., 2017).

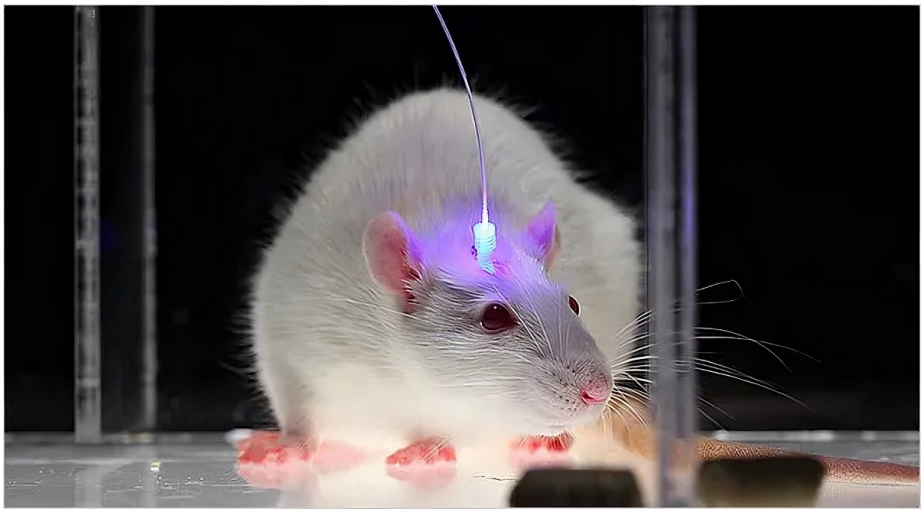

Figure 1.1: **A rat equipped with an optogenetic implant.** The probe seen here, part of an optogenetic implant, can measure or manipulate neuronal signals, offering precise control over specific neural pathways. Image credit: The New York Times (Belluck, 2016).

The advent of optogenetics, a technique allowing precise manipulation of specific neurons using light, has significantly advanced our understanding of the basal ganglia pathways (Deisseroth et al., 2006). Optogenetics involves the genetic modification of neurons to express light-sensitive proteins known as opsins. These opsins can be activated or inhibited by exposure to certain wavelengths of light via an implanted device,

as depicted in Figure 1.1. Notably, Kravitz et al. used optogenetics to activate direct and indirect pathway MSNs selectively, providing key insights into their functions and contribution to the traditional model of the basal ganglia (Kravitz et al., 2010).

Subsequent optogenetic investigations have proposed that these pathways may function bidirectionally, with the specific function depending on the context or the motor behaviour being executed (Yttri & Dudman, 2016). This revelation, along with recent studies expanding our understanding of these pathways' roles in reward-based learning, motor learning, and movement velocity regulation (Hilt et al., 2016; Wang et al., 2015), underscores the complexity of basal ganglia pathways.

This essay, therefore, aims to synthesise our current knowledge of the basal ganglia pathways' role in motor control and decision-making, focusing on the insights provided by optogenetic studies. The following section will delve into significant research that has challenged the traditional model of these pathways.

2 Challenging the Traditional Model

One pivotal study that has advanced our understanding of the basal ganglia pathways is by Cui et al. (2013). The researchers proposed a more dynamic interaction between the direct and indirect pathways during action selection, a significant departure from the conventional understanding.

Cui et al. (2013) employed optogenetic techniques to explore this interaction. They focused on the medium spiny neurons (MSNs) in the dorsomedial striatum of mice, the origin points of the direct and indirect pathways, and manipulated neuronal activity precisely to study its effects on action selection.

A key revelation from their study was the concurrent activation of both the direct and indirect pathways during the initiation of a movement. As illustrated in Figure 2.1, both types of neurons increased their firing rates at the start of a lever-pressing session, contradicting the conventional model's assertion of opposing activation of these pathways.

Moreover, they observed a decrease in the activity of iMSNs during the actual movement execution, whereas the activity in dMSNs remained unchanged. This divergence in activity suggests that although both pathways are involved in action initiation, their roles may differ during action execution.

Interestingly, both types of neurons were inactive when the rats were not moving, suggesting a more nuanced interplay between the direct and indirect pathways than previously thought.

In addition to these findings, Cui et al. (2013) examined the role of these pathways in contralateral vs. ipsilateral movement control. Understanding the differences in these roles is crucial, as the basal ganglia, like many brain structures, control movements on the opposite side of the body (contralateral).

These groundbreaking findings from Cui et al. (2013) were further supported by a study conducted by Guillaumin et al. (2021). They explored the role of the direct and indirect pathways in reward-based learning, a process where an individual learns to perform certain actions based on the reward they receive. This differs from operant conditioning, where an individual learns to associate an action with a consequence.

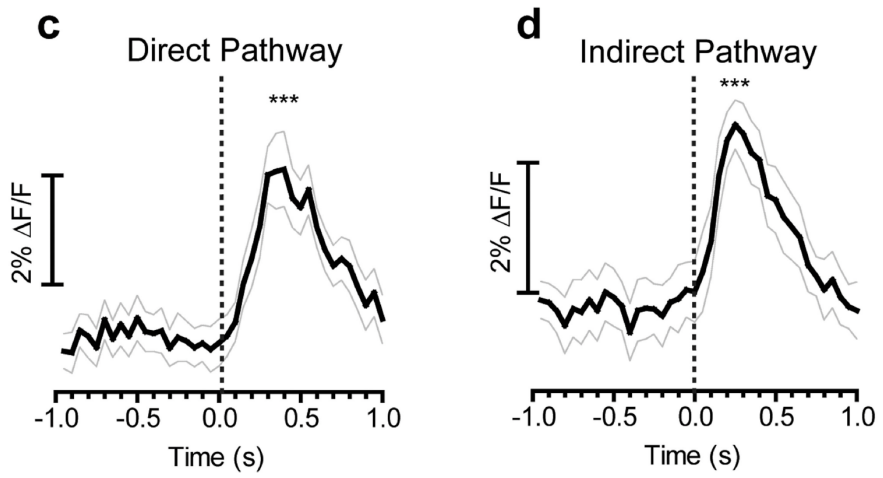

Figure 2.1: **Concurrent activation of direct and indirect pathways during action initiation.** This figure, based on data from Cui et al. (2013) 's study, demonstrates the concurrent activation of direct-pathway medium spiny neurons (dMSNs) and indirect-pathway medium spiny neurons (iMSNs) at the start of a lever-pressing session. The fluorescence traces indicate increased activity for both dMSNs and iMSNs at the session start, challenging the classical model's assertion of opposing activation of these pathways.

Their study found that activating the direct pathway enhanced reward-seeking behaviour while activating the indirect pathway suppressed it, reinforcing the view of a 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) in mice, the cell types that form the direct and indirect pathways. Their pioneering work 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.

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, providing 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 brain's complex workings.

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 the bidirectional control of movement velocity using optogenetic stimulation. Their findings provided evidence that both pathways can bidirectionally regulate movement velocity and speed, complementing Cui et al. (2013) 's finding of concurrent activation during action initiation.

In a different vein, Guillaumin et al. (2021) 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. (2013) '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 control. 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 velocity and speed regulation.

5 Conclusion

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

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.

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 complexities 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 in functions like motor control and learning. Continued research into these complex neural circuits promises exciting breakthroughs in comprehending the basal ganglia's multifaceted roles and neurologic disease.

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