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 is a prevalent neurodegenerative disorder that primarily affects the basal ganglia, a complex group of subcortical nuclei in the brain. The basal ganglia consist of several key structures, including the striatum, globus pallidus, subthalamic nucleus, and substantia nigra (Zhang et al., 2018). These structures play crucial roles in various neurological functions such as motor control, decision-making, and reward processing (Zhang et al., 2018; Ojagbemi et al., 2013).

In the context of Parkinson's disease, the most significant impact is seen in the substantia nigra, a component of the basal ganglia (Abedini et al., 2015). The disease is characterised by the degeneration of dopaminergic neurons in the substantia nigra, leading to the motor symptoms associated with the disease (Abedini et al., 2015). These symptoms are primarily attributed to the disruption in the balance and function of the direct and indirect pathways in the basal ganglia, which play a critical role in motor control Abedini et al. (2015); Ojagbemi et al. (2013).

The conventional model of basal ganglia function posits two antagonistic pathways: the direct pathway, which promotes movement, and the indirect pathway, which inhibits movement (Isett et al., 2022). These pathways primarily consist of medium spiny neurons (MSNs) that react differently to dopaminergic inputs, influencing their role in motor control (Isett et al., 2022). Alterations in the balance and function of these pathways, specifically within these MSNs, are thought to contribute to the motor deficits seen in Parkinson's disease (Cui et al., 2013).

Notably, these pathways primarily influence voluntary movements, such as intentional motor actions, rather than involuntary movements, like reflexes. However, this binary model, which portrays the direct and indirect pathway as strictly antagonistic, has been challenged by recent evidence. Emerging studies suggest a more nuanced interaction between these pathways, with potential concurrent activation and divergence during certain motor actions. This further complicates our understanding of their roles in voluntary movement control (Perez et al., 2017).

Optogenetics has emerged as a revolutionary tool in neuroscience, allowing for precisely manipulating specific neurons using light. This technique involves the genetic modification of neurons to express light-sensitive proteins known as opsins. When exposed to certain wavelengths of light, these opsins can either activate or inhibit the neurons, providing unprecedented control over their activity (Deisseroth et al., 2006).

In the context of the basal ganglia, optogenetics has significantly advanced our understanding of the direct and indirect pathways (Kravitz et al., 2010; Cui et al., 2013). For instance, Kravitz et al. employed optogenetics to activate direct and indirect pathway medium spiny neurons (MSNs) selectively. They achieved this by introducing different types of opsins into these pathways. This allowed them to independently control the activity of the direct and indirect pathways, providing evidence for the traditional model that the direct pathway promotes movement while the indirect pathway inhibits it (Kravitz et al., 2010).

This pioneering work paved the way for other optogenetic investigations that veered away from the traditional dichotomous model. For example, Yttri & Dudman (2016) proposed that these pathways may function bidirectionally (Yttri & Dudman, 2016). Their study suggested that depending on the context, such as the specific motor be-

haviour being executed, either pathway could modulate motor activity in both facilitatory and inhibitory manners. This highlights the complexity of basal ganglia pathways beyond the traditional direct-promotes and indirect-inhibits dichotomy.

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 velocity.

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.

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. (2013) utilised optogenetic techniques, a groundbreaking method that allows the manipulation of specific neurons using light, providing precise 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.

The most significant revelation from Cui et al. (2013) 's study was the concurrent activation of the direct and indirect pathways during action initiation as shown in Figure 2.1. 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. (2021), which explored 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.

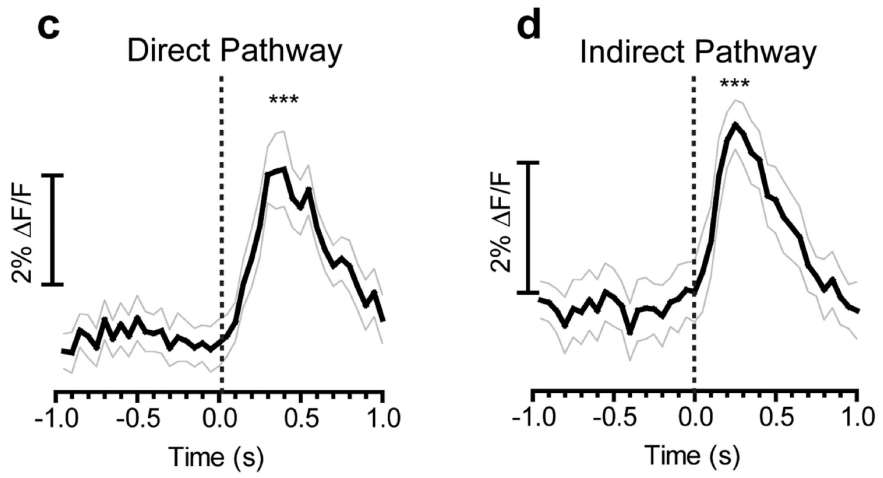

Figure 2.1: **Concurrent activation of direct and indirect pathways during action initiation.** This figure presents data from Cui et al. (2013) 's study, specifically parts c and d of their original Figure 2, demonstrating the concurrent activation of direct-pathway medium spiny neurons (dMSNs) and 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, countering the classical model's assertion of opposing activation of these pathways. This suggests a more complex interplay between the direct and indirect pathways during action initiation, challenging traditional models of basal ganglia function.

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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