# Dendritic involvement in inhibition and disinhibition of vulnerable dopaminergic neurons in healthy and pathological conditions

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## Abstract

Dopaminergic neurons in the substantia nigra pars compacta (SNc) differentially degenerate in Parkinson's Disease, with the ventral region degenerating more severely than the dorsal region. Compared with the dorsal neurons, the ventral neurons in the SNc have distinct dendritic morphology, electrophysiological characteristics, and circuit connections with the basal ganglia. These characteristics shape information processing in the ventral SNc and structure the balance of inhibition and disinhibition in the striatonigral circuitry. In this paper, I review foundational studies and recent work comparing the circuitry of the ventral and dorsal SNc neurons and discuss how loss of the ventral neurons early in Parkinson's Disease could affect the overall balance of inhibition and disinhibition of dopamine signals.

## Keywords

Dopamine; Parkinson's disease; SNc; Striatum; Inhibition; Basal ganglia; Dendrites; Disinhibition; Circuit mapping; Dendritic morphology; Substantia nigra; Striatonigral; Nigrostriatal

## 1. Introduction

Dopaminergic neurons differentially degenerate in Parkinson's Disease (PD). While dopaminergic neurons in the substantia nigra pars compacta (SNc) degenerate more severely than the dopaminergic neurons in the ventral tegmental area (VTA) (Dauer and Przedborski, 2003; Alberico et al., 2015), there is also differential degeneration within the SNc (Yamada et al., 1990; Damier et al., 1999; Kordower et al., 2013; Fearnley and Lees, 1991; Kamath et al., 2022). These findings and results from animal models of PD indicate that one subset of SNc dopaminergic neurons are more vulnerable to degeneration, while another subset is resilient. These vulnerable and resilient SNc dopaminergic neurons differ in their anatomical location, molecular identity, and projection patterns. Specifically, the vulnerable SNc dopaminergic neurons are located in the ventral region (Yamada et al., 1990; McRitchie

et al., 1997; Damier et al., 1999; Kamath et al., 2022), express aldehyde dehydrogenase 1a1 (Aldh1a1) (Liu et al., 2014; Poulin et al., 2014), do not express the calcium buffering protein calbindin (Gerfen et al., 1987a; Yamada et al., 1990; Lavoie and Parent, 1991; Aguila et al., 2021), and project to the dorsal striatum (Gerfen et al., 1987b; Matsuda et al., 2009; Poulin et al., 2018; Prensa and Parent, 2001; Wu et al., 2019), while the resilient population are located in the dorsal region of the SNc and display the opposite molecular profile (Fig. 1).

Foundational publications and recent studies comparing the vulnerable and resilient SNc populations have identified differences in intrinsic currents and synaptic connectivity, shedding light on how these subpopulations process information and how pathological conditions can cause imbalances in the basal ganglia network. The intrinsic properties of dopaminergic neurons and their relevance to Parkinson's Disease have been extensively covered (Surmeier et al., 2010; Morikawa and Paladini, 2011; Brichta and Greengard, 2014; Canavier et al., 2016; Philippart et al., 2016; Duda et al., 2016; Gantz et al., 2018; Giguère et al., 2018; Gonzalez-Rodriguez et al., 2020; Carmichael et al., 2021; Ortner, 2021). This review will focus on the inhibitory and disinhibitory circuits that modulate the activity of the vulnerable and resilient dopaminergic neurons. Understanding the differences between vulnerable and resilient dopaminergic populations is important not only for identifying factors that may increase risk of neurodegeneration, but also for defining the type of information processing that is lost early in Parkinson's Disease.

## 2. Morphology of vulnerable SNc neurons shapes their incoming synaptic input

The vulnerable dopaminergic neurons located in the ventral tier of the SNc contain two distinct types of dendrites. "SNc dendrites" project along the dopaminergic cell body layer, while "SNr dendrites" project ventrally into the GABAergic SNr nucleus (Fig. 2). This overall structure of the SNc neurons has been noted in several early studies (Björklund and Lindvall, 1975; Oertel et al., 1982; Jimenez-Castellanos and Graybiel, 1987; Triarhou and Ghetti, 1989), and one study has reported that the more ventrally-located a neuron is within the SNc, the more likely it is to have an SNr dendrite (Henny et al., 2012).

The SNr dendrites are thought to be specialized dendrites with a distinct role compared to the SNc dendrites. However, the difference in function is unclear. The dopaminergic SNr dendrite may be a site of strong dendrodendritic dopamine release (Robertson and Robertson, 1989), but direct evidence for this idea has not yet been published. Another possibility is that computations performed by the SNr dendrite are different from those performed by the SNc dendrite. One idea is that the SNr dendrite is optimized for processing inhibitory input. Inhibitory synapses are proportionally denser on the SNr dendrite than on the SNc dendrite (Henny et al., 2012), and the long, unbranching morphology of the SNr dendrite facilitates communication of slow inhibitory signals to the soma (Evans et al., 2020). On the other hand, the SNc dendrites may be optimized for processing excitatory signals. In dopaminergic neurons, the axon often comes off of a dendrite, rather than issuing from the soma (Grace and Bunney, 1983). In 70% of SNc dopaminergic neurons, the axon-bearing dendrite is an SNc dendrite, while the SNr dendrites are only axon-bearing in 18%

of cells (Evans et al., 2020). The axon-bearing dendrite is in an 'electrotonically privileged' position, meaning that it transmits incoming excitatory input more effectively than non-axon-bearing dendrites (Häusser et al., 1995), and excitatory synaptic activity on the axon-bearing dendrite can evoke action potentials that do not propagate to the non-axon bearing dendrites (Gentet and Williams, 2007). The axon-bearing dendrite has a higher expression of the hyperpolarization-activated cation current (Ih) that the non-axon bearing dendrite, which may result in increased excitability of this dendrite (Engel and Seutin, 2015). Finally, increased dendritic branches between the soma and the axon initial segment are associated with increased pacemaking frequency (Moubarak et al., 2019). The SNc dendrites branch close to the soma, resulting in more numerous small dendritic compartments (Evans et al., 2020). Small dendritic compartments can amplify excitatory synaptic inputs through supralinear integration (Spruston, 2008), and because these compartments are close to the axon and soma, they are likely to be particularly effective at generating action potential output. Therefore, even though the density of excitatory synaptic inputs onto the SNc and SNr dendrites is similar (Henny et al., 2012), the input is likely to be more effective when located on the SNc dendrite. Together, the evidence suggests that SNr dendrites readily transmit inhibitory synaptic input, while SNc dendrites are optimized to transmit excitatory synaptic input.

## 3. Striatonigral control of dopaminergic neurons

Direct pathway spiny projection neurons in the dorsal striatum project to the midbrain (Kemp and Powell, 1971; Ribak et al., 1980; Wassef et al., 1981; Gerfen, 1985; Smith and Bolam, 1991) inhibiting both SNr GABAergic neurons (Grace and Bunney, 1985; Hikosaka et al., 1993; Connelly et al., 2010; Chuhma et al., 2011) and SNc dopaminergic neurons (Grace and Bunney, 1985; Paladini et al., 1999; Brazhnik et al., 2008; Lerner et al., 2015; McGregor et al., 2019; Evans et al., 2020). Because GABAergic SNr neurons also inhibit dopaminergic SNc neurons (Grace and Bunney, 1979; Tepper et al., 1995; Rizzi and Tan, 2019; Ambrosi and Lerner, 2021), the striatonigral connection has the potential to both inhibit and disinhibit SNc activity (Fig. 3). These findings have led to the question: Does striatal activity increase dopaminergic activity or decrease it? While this question is the subject of ongoing research (Paladini and Tepper, 1999; Mailly et al., 2003; Lobb et al., 2011; Paladini and Tepper, 2016; Yang et al., 2018; Ambrosi and Lerner, 2021), it is likely that striatal activity will inhibit dopaminergic neurons in some situations, and disinhibit dopaminergic neurons in others. There are several possible scenarios that could make sense of the striatum's ability to both inhibit and disinhibit the dopaminergic neurons of the SNc. Here I describe the current data supporting and contradicting four specific hypotheses for how striatonigral circuitry may function. These hypotheses are not mutually exclusive and all four frameworks could play a role in shaping dopamine signals.

### Hypothesis 1. Neurons located in striosomes (striatal patches) directly inhibit SNc neurons, while neurons located in the matrix disinhibit SNc neurons (Fig. 4).

The dorsal striatum can be divided into the striosome (mu-opioid receptor-positive) and matrix (calbindin-positive) compartments (Graybiel et al., 1981; Gerfen, 1984). Both compartments contain direct pathway spiny projection neurons that project to the midbrain.

The idea that striosome neurons inhibit while the matrix neurons disinihibit midbrain dopaminergic neurons first came from anatomical evidence that the striosomes send axons to the dopaminergic SNc, while the matrix sends axons to the GABAergic SNr (Gerfen, 1985; Fujiyama et al., 2011; Watabe-Uchida et al., 2012), but see (Smith et al., 2016). Striosomal axons form columns in the primate SNr (Smith and Parent, 1986; Lévesque and Parent, 2005) and tightly wrap around the SNr dendrite of the ventral dopaminergic neurons forming 'striosome-dendron bouquets' in mice (Crittenden et al., 2016; Matsushima and Graybiel, 2020). These striosome-dendron bouquets are enriched in pre-synaptic GABA release markers (GAD1/GAD2), D2 dopamine receptors, and cannabinoid (CB1) receptors (Crittenden et al., 2016; Davis et al., 2018). Electrophysiological recordings show that within this bouquet structure, the striosomes selectively inhibit the SNr dendrites of the dopaminergic neurons by recruiting local GABAA and GABAB receptors (Evans et al., 2020). *In vivo* dopamine measurements show that activation of striosomal fibers reduces dopamine release in the striatum (Nadel et al., 2021), indicating that even with local circuitry intact, the overall effect of striosome stimulation is to inhibit dopaminergic activity.

The evidence that neurons in the striatal matrix disinhibit the dopaminergic neurons is less clear. The axons from the matrix do not participate in striosome-dendron bouquets (Crittenden et al., 2016), but retrograde rabies viral tracing from dopaminergic neurons has shown both few (Watabe-Uchida et al., 2012) and many (Smith et al., 2016) labeled matrix neurons. Optogenetic stimulation of striatal matrix axons only weakly inhibits the dopaminergic SNc neurons when compared to stimulation of striosomal axons (Evans et al., 2020). Similarly, the connection from the striosomes to the SNc is of a similar strength to the connection from the entire striatum to the SNc. However, the entire striatum was more strongly connected to the GABAergic neurons of the SNr than the striosomes alone (McGregor et al., 2019). This finding suggests that the striatal matrix inhibits the SNr neurons more strongly than the striosomes do. However, the strength of the synaptic connection from the striatal matrix neurons to the SNr GABAergic neurons has not been directly tested or directly compared to the striosome-SNr connection. In addition, the relative strength of the SNr GABAergic input to the SNc dopaminergic neurons is unknown and may depend on striatal subregion (Ambrosi and Lerner, 2021). Therefore, the hypothesis that the striosomes inhibit and the matrix neurons disinhibit dopaminergic neurons is well-supported, with only a few experiments required to fully confirm it.

### Hypothesis 2.  The striatum inhibits ventral tier SNc neurons, but disinhibits dorsal tier SNc neurons (Fig 5).

The vulnerable ventral tier neurons of the SNc receive strong inhibition from the striatum. Anatomical studies show that axons from the dorsal striatum predominately project to the ventral SNc (Gerfen, 1985; Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994; Maurin et al., 1999; Haber et al., 2000; Crittenden et al., 2016; Wu et al., 2019). Calcium imaging and electrophysiological recordings show that the striatum makes stronger functional synaptic connections onto the ventral tier neurons than onto the dorsal tier SNc neurons (Evans et al., 2020). Therefore, it is clear that the vulnerable, ventral tier SNc neurons are more strongly inhibited by the striatum than the resilient, dorsal tier SNc neurons. Because the dorsal tier receives weak direct striatal inhibition, these neurons are

more likely to be disinhibited by striatal activation. In this framework, the inhibitory and disinhibitory circuit could be coming from either the same striatal neurons or separate neural populations. For example, hypothesis 1 and hypothesis 2 could both be true if the striosomes inhibited the ventral tier and the matrix disinhibited the dorsal tier. While hypothesis 2 is well-supported, a key piece of information that has yet to be experimentally determined is the relative strength of SNr GABAergic synapses onto the ventral and dorsal tier SNc neurons.

An interesting, but mostly unexplored possibility is that the dorsal tier may be disinhibited through pathways not involving the SNr. One alternative pathway is through the external globus pallidus (GPe). Striatal direct pathway neurons selectively inhibit the Lhx6-positive (Spix et al., 2021) and Npas1-positive (Cui et al., 2021) population of GPe neurons. While there is some overlap between these GPe subtypes (Abecassis et al., 2020), the Lhx6-positive neurons have been shown to inhibit both the dorsal and ventral tier SNc neurons selectively activating GABAA receptors and undergoing strong short-term synaptic depression (Evans et al., 2020). The striatal direct pathway inhibiting both the Lhx6-GPe neurons and the ventral tier SNc neurons could create a situation where the ventral dopaminergic neurons are inhibited, but the dorsal tier neurons are disinhibited (Fig. 5). Striatal activation of GABAB receptors inhibits the ventral tier neurons so strongly that it may overcome any potential disinhibition through the GPe with the overall result being inhibition of the ventral tier. However, because the striatum does not strongly inhibit dorsal SNc neurons, the overall effect on the dorsal tier would be disinhibition through the GPe. Further experiments are needed to determine the extent to which significant disinhibition of dorsal dopaminergic neurons occurs through direct pathway inhibition of Lhx6-positive or Npas1-positive GPe neurons.

### Hypothesis 3.    Brief striatal activity disinhibits while sustained striatal activity inhibits dopaminergic neurons (Fig 6).

*In vivo* experiments stimulating the striatum and recording action potentials from dopaminergic neurons show that single pulses and trains of striatal activation result in complex responses including excitatory, early inhibitory, and late inhibitory components, with larger stimulation amplitudes and longer trains of activation associated with inhibitory responses (Grace and Bunney, 1985; Brazhnik et al., 2008). These multicomponent responses reflect the complex inhibitory and disinhibitory circuitry between the striatum and the dopaminergic neurons. To determine whether striatal activation time course influences the inhibition *vs* disinhibition state of the dopaminergic neurons, the characteristics of the synaptic connections from the striatum to the GABAergic SNr neurons and to the dopaminergic SNc neurons must be understood.

The synaptic connection from the striatum to the SNc dopaminergic neurons and from the striatum and the SNr GABAergic neurons appear to display different temporal characteristics, suggesting the possibility that distinct patterns of striatal activity would differentially cause inhibition *vs* disinhibition in the dopaminergic SNc neurons. The striatonigral synapses on the SNc dopaminergic neurons become stronger over time during sustained activity. Specifically, the striosome-SNc connection includes facilitating GABAA-

mediated currents and a slow-developing GABAB-mediated current (Evans et al., 2020). By contrast, the striosome-SNr connections show short term depression and do not include a GABAB-mediated component (Faust, 2017). This suggests that a period of brief striatal activity would only weakly inhibit the SNc dopaminergic neurons, but would strongly inhibit the SNr GABAergic neurons resulting in a brief period of dopaminergic disinhibition. On the other hand, a sustained period of striatal activity would strongly inhibit the SNc dopaminergic neurons while only weakly inhibiting the SNr GABAergic neurons, resulting in overall inhibition of dopaminergic neurons (Fig. 6). However, the evidence that the striatal input to the SNr and SNc differ in their time course has been specific to the activation of striosomes. Electrical activation of the striatonigral connection (including both striosome and matrix connections) in brain slices has been shown to cause facilitating inhibitory synaptic currents on GABAergic SNr neurons (Wallmichrath and Szabo, 2002; Connelly et al., 2010; de Jesús Aceves et al., 2011), and it is not yet known whether the striatum, as a whole, activates the GABAB receptors located on SNr neurons (Boyes and Bolam, 2003). Therefore, additional experiments are needed to conclusively determine which patterns of striatal activity will promote inhibition *vs* disinhibition of the dopaminergic neurons.

A second factor to consider is the connection between the SNr GABAergic neurons and the SNc dopaminergic neurons. For the striatum to effectively disinhibit the dopaminergic neurons, the SNr GABAergic neurons receiving striatal input must tonically inhibit the SNc. Historically, it has been difficult to isolate and characterize the direct synaptic connection between the SNr neurons and the dopaminergic neurons because many inhibitory axons from the striatum and the globus pallidus are intermixed with the SNr GABAergic cell bodies. Therefore, electrical stimulation within the SNr (Hajós and Greenfield, 1994; Saitoh et al., 2004) will not selectively activate SNr inputs to the SNc. However, recent work using optogenetics and slice electrophysiology has shown that genetically- and anatomically-defined subsets of SNr neurons selectively inhibit SNc dopaminergic neurons (Rizzi and Tan, 2019; Ambrosi and Lerner, 2021). This connection appears to be mediated by GABAA receptors and to display short term synaptic depression. However, a comprehensive analysis of the short-term plasticity and the receptors activated at this connection has not been published. Therefore, the hypothesis that brief striatal activation disinhibits while sustained striatal activation inhibits SNc dopaminergic neurons is somewhat supported, but key experiments are needed to draw a firm conclusion. These experiments include applying trains of optical stimulation to channel rhodopsin-expressing SNr neurons while recording from SNc neurons. This would determine the extent to which the SNr-SNc connection undergoes short-term synaptic depression of facilitation.

### Hypothesis 4.    Striatal inhibition promotes rebound dopamine activity (Fig. 7).

Another way that striatal input to dopaminergic neurons can cause a type of inhibitory and disinhibitory activity is by recruiting intrinsic rebound mechanisms in the dopamine neurons and causing a pause-rebound firing pattern. Dopaminergic neurons are often inhibited during aversive stimuli and rebound firing may act as a safety or relief signal after aversive events (Oleson et al., 2012; Lee et al., 2016; Schultz, 2019). Unlike the dorsal tier SNc neurons, the vulnerable ventral tier SNc neurons highly express channels recruited by inhibition such as hyperpolarization-dependent cation channels (Neuhoff et al., 2002) and T-type

calcium channels (Evans et al., 2017). Because these channels require membrane potential hyperpolarization to be engaged, they facilitate rebound firing upon release of inhibition. However, not all forms of inhibition can recruit these rebound currents. GABAA receptor activation inhibits dopaminergic neurons *via* chloride ion channels, which shunt current, but do not strongly hyperpolarize. This is because dopaminergic neurons have a high (−62 to −69 mV) reversal potential for chloride (Grace and Bunney, 1985; Gulácsi et al., 2003). By contrast, GABAB receptor activation strongly hyperpolarizes dopamine neuron membrane potential through the activation of g-protein dependent inwardly rectifying potassium (GIRK) channels (Beckstead and Williams, 2007; Koyrakh et al., 2005) and blocking sodium leak channels (Philippart and Khaliq, 2018). The striatonigral connection from the striosomes to the ventral tier SNc recruits GABAB receptors and can generate pause-rebound dopamine activity through the striosome-dendron bouquet connection (Evans et al., 2020). Because these ventral tier dopamine neurons project back to the striatum (Gerfen et al., 1987a; Jiménez-Castellanos and Graybiel, 1989; Prensa and Parent, 2001; Matsuda et al., 2009; Poulin et al., 2018; Wu et al., 2019), this circuit represents a mechanism by which the striatal neurons might control the dopamine release back onto themselves (Fig. 7). Because this dopamine signal directly follows striatal activity, it would be precisely timed with respect to striatal neuron action potentials and may serve as a plasticity signal (Yagishita et al., 2014; Shindou et al., 2019) and be critical for habit and motor skill learning (Carmichael et al., 2021). While ventral tier SNc neurons were once thought to selectively innervate striosomes (Gerfen et al., 1987a; Jiménez-Castellanos and Graybiel, 1989; Prensa and Parent, 2001), more recent work suggests that these neurons do heavily innervate striosomes, but also innervate the striatal matrix (Matsuda et al., 2009; Wu et al., 2019). However, future work is needed to determine whether dopaminergic SNc neurons connect back to the same striosomal neurons that inhibit them forming a closed loop, or to adjacent striatal regions, forming an open loop, ascending spiral, or descending spiral (Haber et al., 2000; Belin and Everitt, 2008).

Pause-rebound activity has been observed in dopamine neurons *in vivo* (Brischoux et al., 2009; Wang and Tsien, 2011) and in fluorescent measurements of dopamine release in the striatum (Gut et al., 2022). Pause-rebound activity is particularly strong in ventral SNc neurons in monkeys (Fiorillo et al., 2013a, 2013b). However, additional experiments are needed to determine whether striatal activity causes this pause-rebound *in vivo.* Because multiple striatal neurons are likely to synapse on each dopaminergic neuron (Lévesque and Parent, 2005), striatal activity would likely need to be synchronized to generate pause-rebound firing. Future work is required to determine the extent to which striatonigral connectivity governs the pause-rebound activity observed in the ventral SNc *in vivo.*

## 4.  Potential importance of the bouquet structure

The striatonigral connection may communicate information in a highly specialized way due to the unique striosome-dendron bouquet structure. This structure is characterized by tightly packed dopaminergic dendrites with thin striatal axons wrapping around them. The parallel dopaminergic dendrites in close proximity to each other may facilitate dendrodendritic communication between SNc neurons, while the high-density striatal axons may facilitate dopamine signaling from the SNc neurons to the pre-synaptic striatal terminals.

Dendrodendritic communication between SNc dopaminergic neurons has been observed for over 40 years (Groves et al., 1975; Cheramy et al., 1981). When depolarized, midbrain dopaminergic neurons can release dopamine from their dendrites and activate D2 dopamine receptors on nearby neurons (Beckstead et al., 2004; Gantz et al., 2013) and on themselves (Hikima et al., 2021). This D2 receptor activation inhibits the dopaminergic neuron through the activation of G-protein coupled inwardly rectifying potassium (GIRK) channels (Beckstead and Williams, 2007; Koyrakh et al., 2005), and through the inhibition of the sodium leak channel (NALCN) (Philippart and Khaliq, 2018), similar to GABAB activation. An early study evaluating dopaminergic dendrites with electron microscopy postulated that different dendrites would serve different roles, specifically hypothesizing that there were 'presynaptic dendrites' which receive few axodendritic contacts and whose role would be primarily to release dopamine (Groves and Linder, 1983). Recent work shows that the dopaminergic SNr dendrites contain the mRNA necessary for local translation of dopamine transmission machinery (Hobson et al., 2022). Another recent study using dopamine-sensitive nanofilm and cultured dopaminergic neurons observed that some dopaminergic dendrites released dopamine, while others did not (Bulumulla et al., 2022). Because dendrodendritic communication between dopaminergic neurons depends on dopamine transporters, but does not depend strongly on dopamine diffusion (Ford et al., 2010; Condon et al., 2021), the D2 dopamine receptors activated by somatodendritic release of dopamine must be in close proximity to the release sites. In the bouquet structure, the dopaminergic dendrites can run parallel to each other for long distances (100 s of microns) and each dendrite is within a few microns of several others (Crittenden et al., 2016). Not only are these bouquet-participating dendrites in close proximity, but their long, unbranched nature can facilitate slow inhibitory signals reaching the soma to inhibit action potential firing (Evans et al., 2020). Therefore, the dendron bouquets may be sites of particularly effective dendrodendritic inhibition between SNc dopaminergic neurons.

The bouquet structure may also facilitate dendroaxonic communication between the dopaminergic dendrites and presynaptic striatal terminals. Striatal axons express presynaptic D1 dopamine receptors at their synaptic connections with both dopaminergic and non-dopaminergic neurons (Caillé et al., 1996; Hattori et al., 1979). When activated, these D1 receptors potentiate GABA release (Cameron and Williams, 1993; Radnikow and Misgeld, 1998). In the striosome-dendron bouquet, dendritically released dopamine has the potential to enhance striatal GABAergic inhibition onto the bouquet-participating ventral tier SNc neurons. The axonal configuration of the bouquet may also shape the way that the striatum inhibits the dopaminergic neurons. Striatonigral axons are fine processes with minimal boutons and are densely packed in striosome-dendron bouquets (Crittenden et al., 2016; Evans et al., 2020; Matsushima and Graybiel, 2020). Multiple striatal neurons are likely to participate in each bouquet (Lévesque and Parent, 2005). Striato-nigral axons have a slow conduction velocity (~0.7 m/s) (Connelly et al., 2010), and their synaptic signal builds up over time (Evans et al., 2020). These characteristics may facilitate the transmission of sustained signals to the dopaminergic neurons and may enhance the extra-synaptic activation of GABAA and GABAB receptors on dopaminergic dendrites. However, more studies are needed to understand how the bouquet structure affects neurotransmitter release dynamics and the degree of synchronization in striatonigral axons.

## 5. Inhibition and disinhibition in pathological conditions

In pathological conditions, the circuitry controlling inhibition and disinhibition of dopaminergic neurons can be disrupted. In Parkinson's Disease when the ventral, more vulnerable SNc neurons begin to degenerate, the striosome-dendron bouquet structure and the striatonigral connection may be disrupted. The evidence for dendritic disruption in PD includes human and model animal studies. In PD patients, dopaminergic dendrites in the SNr are truncated and display reduced spine density (Patt et al., 1991). The MitoPark mouse model shows morphological disruptions to dendritic arbors (Lynch et al., 2018), and mutations in the leucine-rich repeat kinase (LRRK2), implicated in inherited Parkinson's Disease, alter dendritic morphology in culture (MacLeod et al., 2006). A 6-hydroxydopamine (6-OHDA) lesion model of PD shows that the ventral tier, calbindin-negative SNc neurons with SNr dendrites are selectively lost compared to unlesioned controls (Gerfen et al., 1987a). Importantly, the SNr dendrites of the dopaminergic neurons appear to be lost in the LRRK2 (R1441G) mutation mouse model of PD (Li et al., 2009) and in an alpha-synuclein seeding model of PD (Paumier et al., 2015). These studies did not determine whether the SNr dendrites were selectively degenerated relative to the SNc dendrites or examine the extent to which the SNr dendrite loss was simply due to the loss of ventral tier SNc neurons. Regardless of whether the SNr dendrites are lost because the cells containing them are lost or because SNr dendrites degenerate relative to the other dendrites, these findings suggest that the dendrite-selective striatonigral connection would be disrupted in Parkinson's Disease.

The degeneration of the dopaminergic dendrites in the SNr may have additional consequences due to the reduced dendritic release of dopamine within the SNr. Dopamine release in the SNr can directly modulate SNr GABAergic output (Zhou et al., 2009), and acute blockade of dopamine receptors within the SNr results in a bursting pattern similar to that observed in Parkinsonian conditions (de Jesús Aceves et al., 2011). Dopamine neuron loss results in an upregulation of D1 receptors on striatonigral terminals which increases their sensitivity to dopamine and enhances their dopamine-dependent inhibitory output (Ding et al., 2015). A recent study selectively knocked out *Ndufs2* from dopaminergic neurons to model progressive degeneration in PD and showed that the loss of dendritic dopamine release was critical for the development of Parkinsonian motor symptoms in the experimental animals (González-Rodríguez et al., 2021). Previous work has shown that the dopamine precursor commonly used to treat PD *L*-dihydroxyphenylalanine (L-DOPA) increases dopamine release in the striatum of dopamine depleted (6-OHDA) mice for only a short time, but increases dendritic dopamine release in the midbrain for the duration of the behavioral effects (Robertson and Robertson, 1989). Similarly, these behavioral effects (L-DOPA induced rotational behavior) were more effectively reduced by dopamine receptor antagonists infused into the SNr than by the same antagonists infused into the striatum. Together these results implicate dendritic dopamine release in the symptoms in PD, and suggest that the loss of dopaminergic dendrites in the SNr could directly impair basal ganglia function by disrupting midbrain dopamine signaling.

Because the ventral tier SNc neurons degenerate first in PD and these neurons preferentially receive direct inhibition from the striosomes, the connection between the striatum and the

SNc dopaminergic neurons may undergo a functional shift from inhibition to disinhibition in PD (Fig. 8). The early degeneration of the ventral tier and the loss of the SNr dendrites would reduce direct inhibition from the striatum. However, based on hypothesis 2, the remaining dopaminergic neurons in the dorsal tier could continue to be disinhibited by striatal activity. Therefore, in this pathological condition, the disinhibited neurons would outnumber the inhibited neurons, shifting the overall balance of the striatonigral connection to disinhibition. Interestingly, in rodent models of PD, striatonigral neurons show increased excitability (Fieblinger et al., 2014), the striatonigral connection to the GABAergic SNr neurons shows a higher probability of GABA release due to the loss of GABAB-mediated presynaptic inhibition (Borgkvist et al., 2015), and the frequency and amplitude of spontaneous inhibitory post-synaptic currents (IPSCs) are increased in SNr GABAergic neurons (Faynveitz et al., 2019). Therefore, striatal disinhibition of the dopaminergic neurons through the SNr could be enhanced under dopamine-depletion conditions. Together, the disrupted inhibition pathway and the potentially-enhanced disinhibition pathway could play a role in the progression of PD pathology, resulting in hyper-excitability of the remaining dopaminergic neurons (Kovacheva et al., 2021) and potentially increasing their susceptibility to neurodegeneration.

The information processing that is lost early in PD as a result of the selective degeneration of the ventral tier is just beginning to be understood. A study selectively lesioning the ventral tier, Aldh1a1-positive, SNc neurons showed that lesioned mice did not appear clearly Parkinsonian and could walk around an open field without significant impairment, but had severe impairments in motor learning as assessed by the accelerating rotarod task (Wu et al., 2019). Similarly, selective lesions of the striosomes (the striatal structures that selectively inhibit the ventral tier SNc neurons) do not cause movement impairments, but do impair stimulus-response and habit learning (Jenrette et al., 2019; Nadel et al., 2020). These studies suggest that the striatum-nigrastriatum loop involving the striosomes and ventral tier SNc neurons is critical for habit and motor learning, and predict that such learning would be impaired early in the time course of PD. However, addition studies using progressive models of PD are critical because compensatory mechanisms might develop as the ventral SNc neurons degenerate and these compensatory mechanisms could alter the inhibition and disinhibition circuitry over the course of the disease.

## 6.  Summary

In this review, I have summarized the previous findings supporting four distinct hypotheses for the striatonigral control of dopaminergic signaling and have outlined some of the key experiments needed to fully confirm them. These four hypotheses are not mutually exclusive. Indeed, all four modes of inhibition and disinhibition could act in concert to govern dopaminergic output. The morphological characteristics of the SNc neurons and the distinct striosome-dendron bouquet structure shapes the dopaminergic response to striatal activity. The degeneration of the ventral tier SNc neurons in Parkinson's Disease may disrupt the balance of inhibition and disinhibition from the striatum to the SNc, resulting in increased activity of the surviving dopaminergic neurons. This increase in activity could exacerbate the neurodegenerative processes occurring in Parkinson's Disease.

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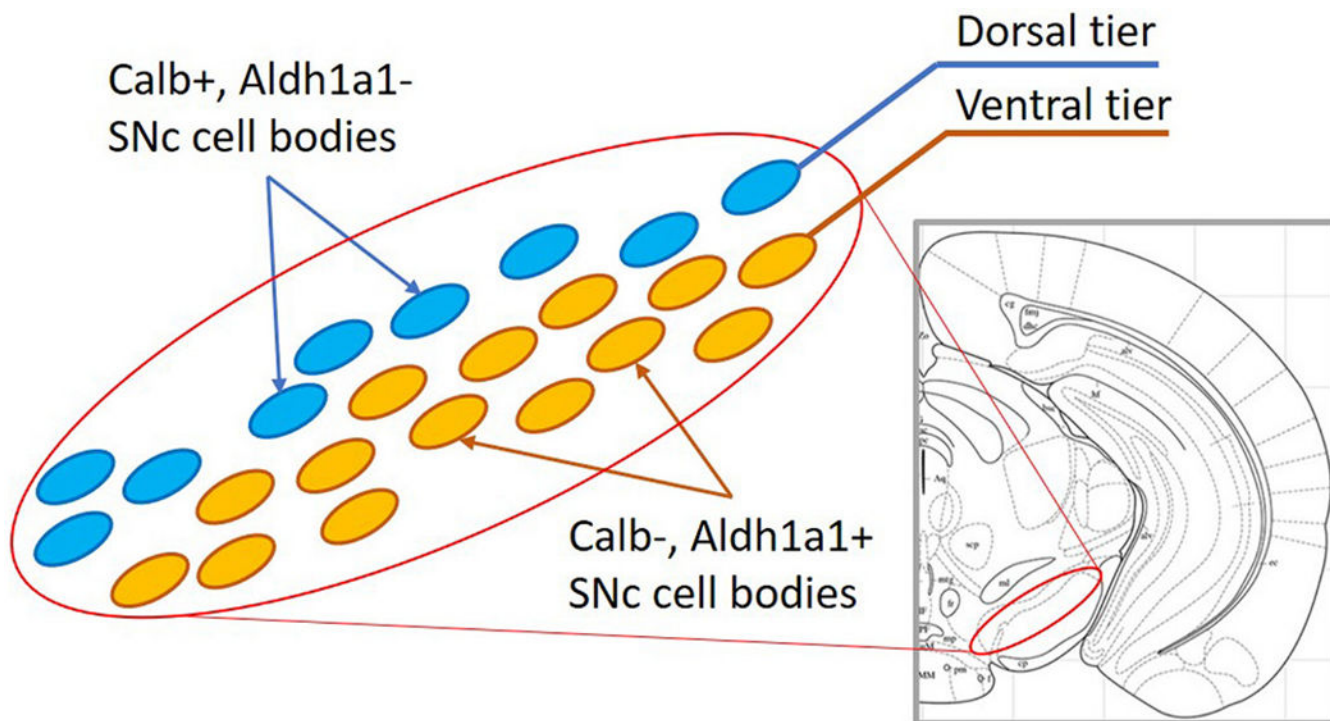
**Fig. 1. Diagram of the ventral and dorsal tier of the substantia nigra pars compacta (SNc).**
Yellow ovals represent the calbindin-negative, Aldh1a1-positive ventral tier dopaminergic neurons that are more vulnerable to degeneration. Blue ovals represent the dorsal tier calbindin-positive, Aldh1a1-negative dopaminergic neurons that are more resilient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
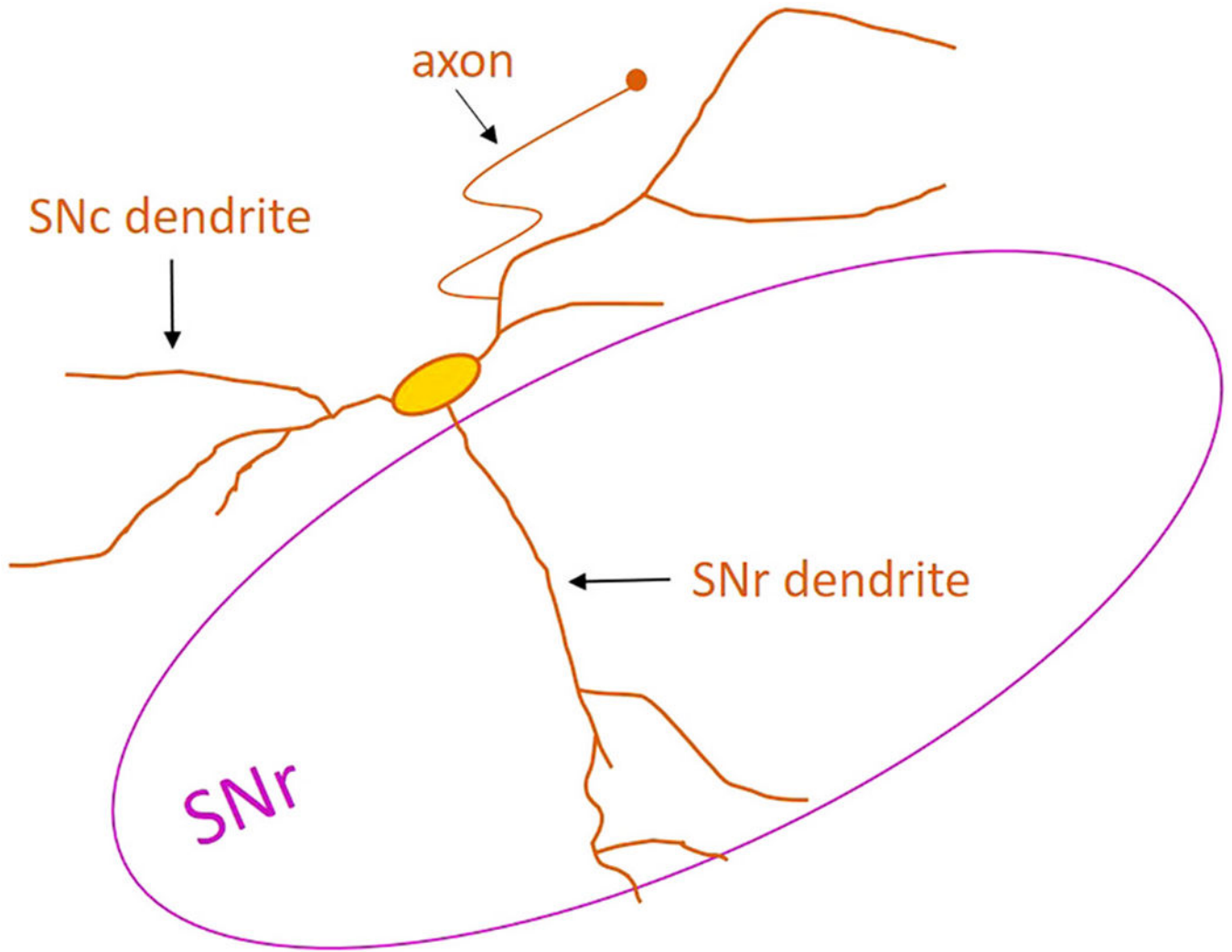
**Fig. 2. Dendritic morphology of ventral SNc neurons.**
The ventrally-located SNc dopaminergic neurons have two distinct dendrite types: SNc
dendrites projecting along the substantia nigra pars compacta cell body layer and SNr
dendrites projecting ventrally into the GABAergic substantia nigra pars reticulata. The
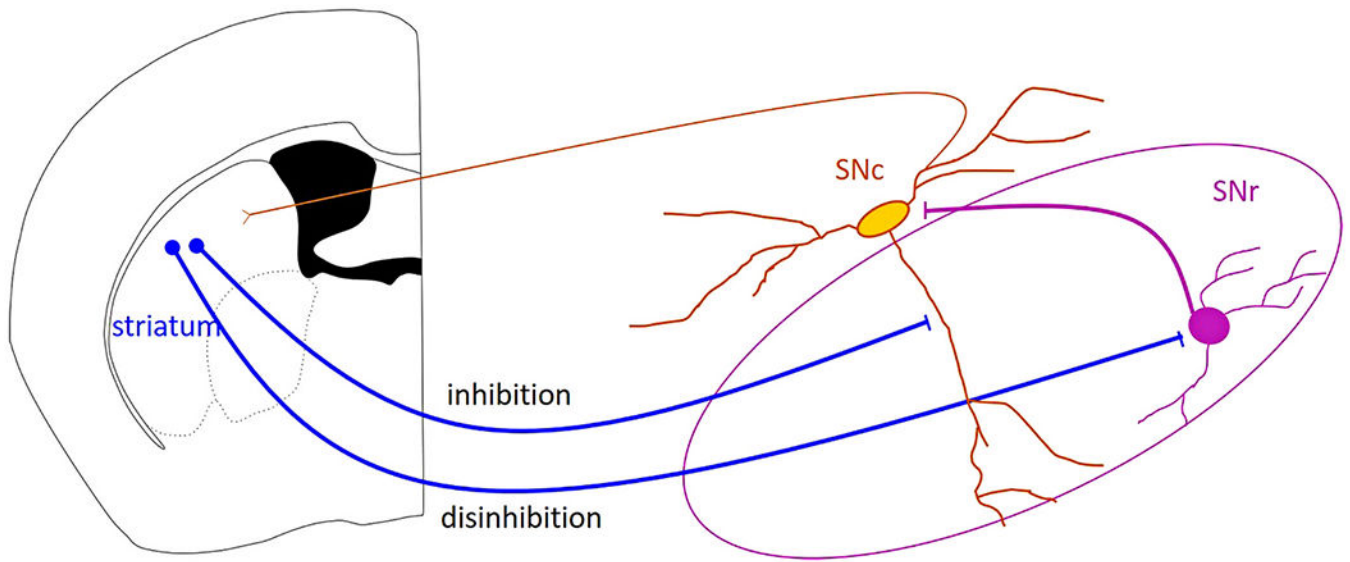axon-bearing dendrite is most often an SNc dendrite.

**Fig. 3. Canonical pathway for striatonigral inhibition and disinhibition.**
Striatal projection neurons can directly inhibit substantia nigra pars compacta (SNc) dopaminergic neurons, and can disinhibit them by inhibiting substantia nigra pars reticulata (SNr) GABAergic neurons. The inhibition and disinhibition of the SNc neurons will shape the dopamine signal sent to the striatum through SNc dopaminergic axons.
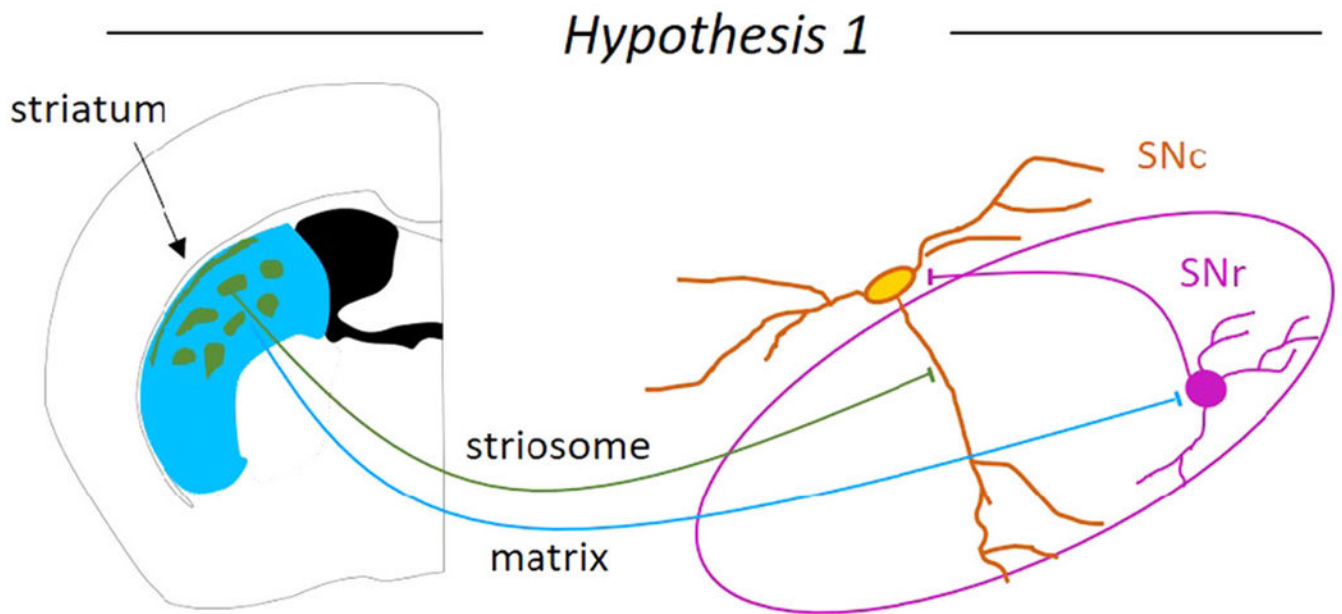
## Hypothesis 1



**Fig. 4. Hypothesis 1: Striosome inhibits and matrix disinhibits dopaminergic neurons of the substantia nigra pars compacta (SNc).**

The two striatal compartments, the striosomes and the matrix may exert opposing control of the SNc dopaminergic neurons. The striosomes are thought to directly inhibit the SNc dopaminergic neurons on the SNr dendrite, while the matrix is thought to disinhibit the SNc dopaminergic neurons through inhibition of substantia nigra pars reticulata (SNr) GABAergic neurons.
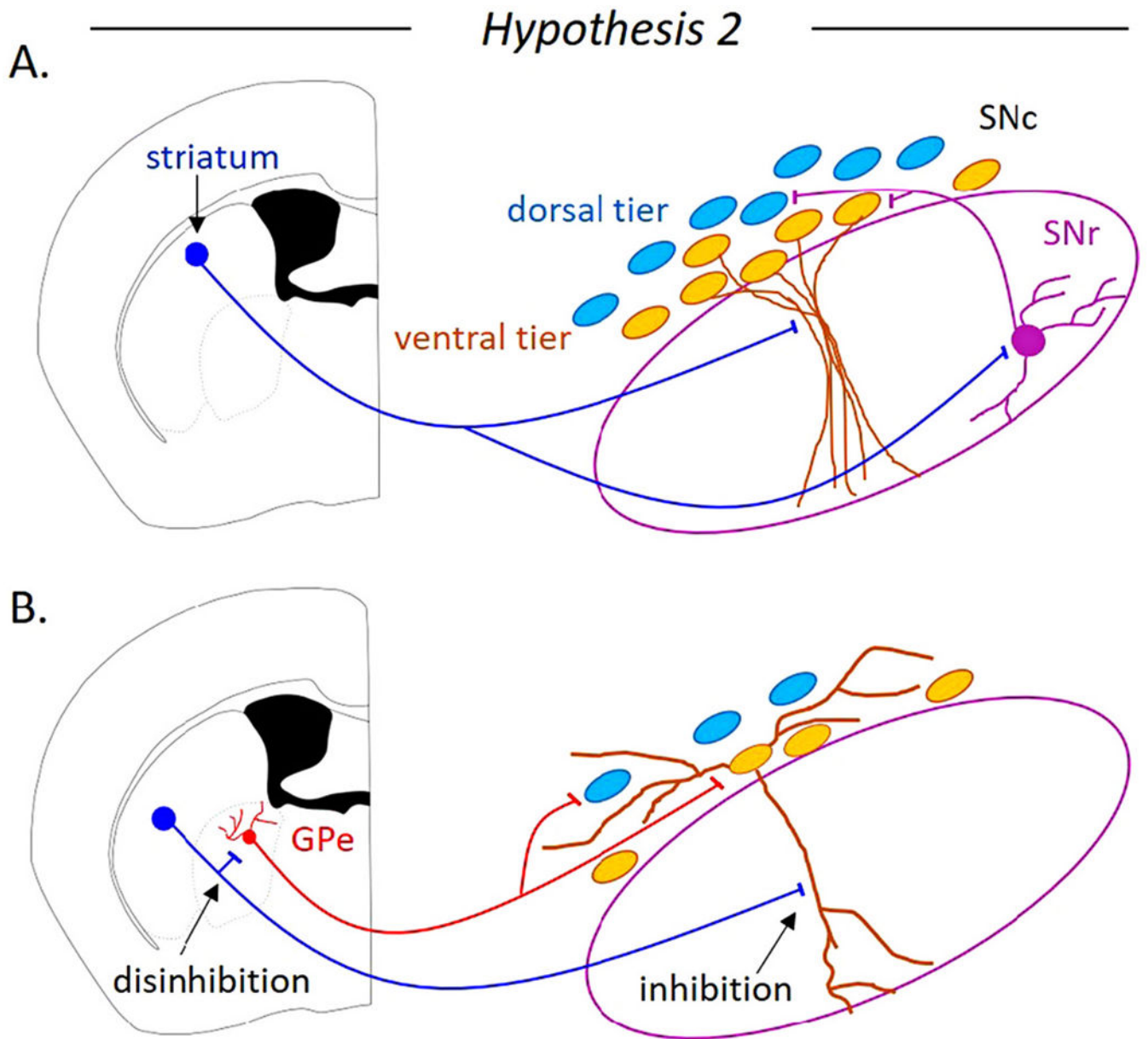
**Fig. 5. Hypothesis 2: the ventral tier neurons of the substantia nigra pars compacta (SNc) are inhibited by the striatum, while the dorsal tier neurons of the SNc are disinhibited.**
**A.** The striatal direct pathway may inhibit the ventrally-located SNc neurons and disinhibit the dorsally-located SNc neurons through the GABAergic neurons of the substantia nigra pars reticulata (SNr). **B.** A non-canonical pathway for striatonigral disinhibition is through the globus pallidus external segment (GPe). The striatal direct pathway spiny projection neurons inhibit a subpopulation of GPe neurons known to directly inhibit dopaminergic SNc neurons.
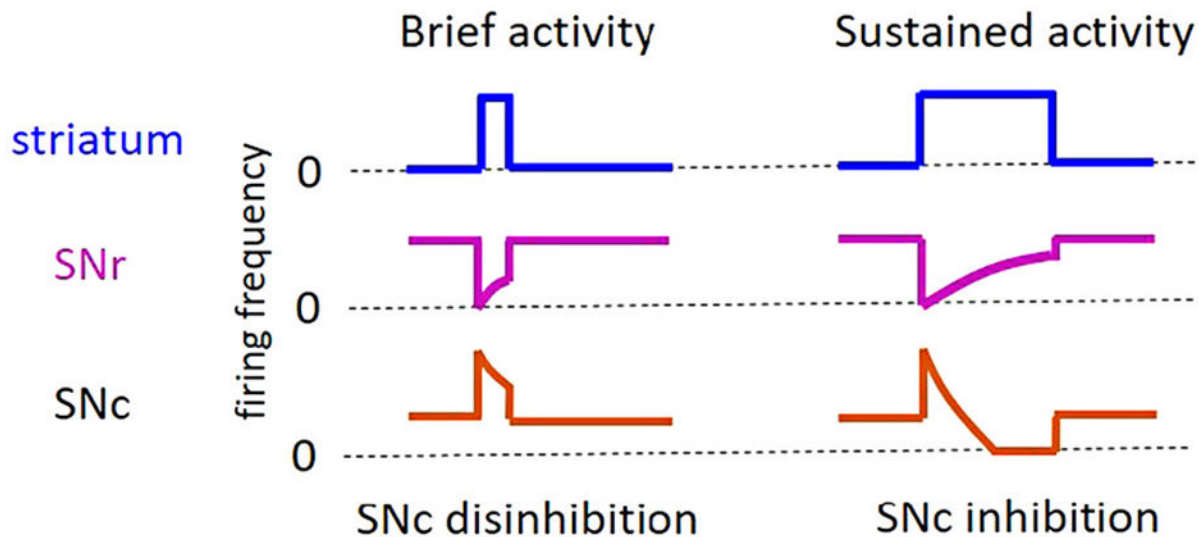
## Hypothesis 3



**Fig. 6. Hypothesis 3: The timing of the striatal activity determines whether the dopamine neurons of the substantia nigra pars compacta (SNc) are inhibited or disinhibited.**
Brief increases in striatal projection neuron firing frequency briefly inhibits the substantia nigra pars reticulata (SNr) GABAergic neurons to disinhibit SNc dopaminergic neurons (left). Sustained increases in striatal projection neuron firing could result in short term synaptic depression between the striatum and the SNr neurons or between the SNr neurons and the SNc, resulting in a short disinhibition followed by a period of inhibition in the SNc dopaminergic neurons.
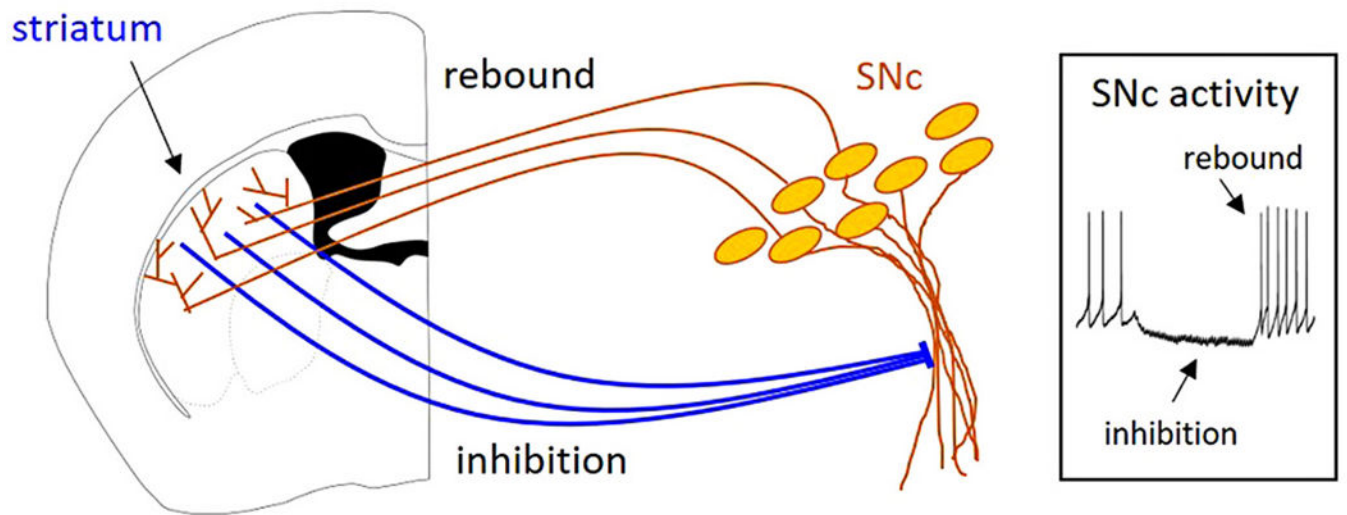
**Fig. 7. Hypothesis 4: Striatal inhibition of substantia nigra pars compacta (SNc) dopaminergic neurons generates rebound activity.**

Striatal inhibition of SNc neurons recruits intrinsic rebound mechanisms in the ventral SNc

neurons, causing increased dopaminergic neuron activity when inhibition is released.

## Healthy: balance of inhibition and disinhibition

A.

striatonigral neurons

GPe

SNr

## Parkinsonian: biased toward disinhibition

B.

striatonigral neurons

GPe

SNr

**Fig. 8. Hypothetical imbalance between inhibition and disinhibition of SNc dopaminergic neurons under pathological conditions.**
**A.** In the healthy condition, the balance of inhibition and disinhibition of the substantia nigra pars compacta (SNc) dopaminergic neurons is intact. **B.** Under Parkinsonian conditions, when the ventral SNc neurons have degenerated, direct striatonigral inhibition onto the SNc neurons is reduced, while disinhibitory pathways may be strengthened.