Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Cells, pathways, and models in dyskinesia research

M. Angela Cenci[1] and Arvind Kumar[2]

Abstract

L-DOPA-induced dyskinesia (LID) is the most common form of hyperkinetic movement disorder resulting from altered information processing in the cortico-basal ganglia network. We here review recent advances clarifying the altered interplay between striatal output pathways in this movement disorder. We also review studies revealing structural and synaptic changes to the striatal microcircuitry and altered cortico-striatal activity dynamics in LID. We furthermore highlight the recent progress made in understanding the involvement of cerebellar and brain stem nuclei. These recent developments illustrate that dyskinesia research continues to provide key insights into cellular and circuit-level plasticity within the cortico-basal ganglia network and its interconnected brain regions.

Addresses

[1] Basal Ganglia Pathophysiology Unit, Department Experimental Medical Science, Lund University, Lund, Sweden

[2] School of Electrical Engineering and Computer Science, KTH Royal Institute of Technology, Stockholm, Sweden

Corresponding author: Cenci, M. Angela (angela.cenci_nilsson@med.lu.se)

(Kumar A.)

(Cenci M.A.)

Current Opinion in Neurobiology 2024, **84**:102833

This review comes from a themed issue on **Motor circuits in action 2023**

Edited by **Dawn Blitz** and **Sten Grillner**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.conb.2023.102833

Introduction

L-DOPA-induced dyskinesia (LID) consists of abnormal involuntary movements and postures that interfere with or replace normal motor sequences. It is a frequent complication of dopamine (DA) replacement therapy in Parkinson's disease (PD), affecting up to 90% of patients after 10 years of L-DOPA treatment [1]. Beside its medical significance, LID provides a paradigm for investigating cellular and circuit mechanisms underlying the generation of abnormal motor sequences by the cortico-basal ganglia network. The interest of basic scientists in this topic has rapidly increased since rodent models of LID have become available. To this day, the best-characterized LID models are obtained in rats or mice that first sustain unilateral 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal dopamine (DA) pathway and then receive systemic injections of L-DOPA (typically combined with the DOPA decarboxylase inhibitor benserazide), once or twice daily, for a few days or weeks (reviewed in [2]). The treatment rapidly leads to the development of abnormal involuntary movements (AIMs) including both fast (hyperkinetic) and slow (dystonic) features. These AIMs have a time course analogous to peak-dose LID in PD patients and are modulated by clinically effective antidyskinetic drugs (reviewed in [2]). The dyskinetic features affect mainly the side of the body contralateral to the lesion, being particularly evident in the upper trunk/neck (axial AIMs), the forelimb (limb AIMs), and the orofacial and masticatory muscles (orolingual or orofacial AIMs). Dyskinetic motor sequences can be distinguished from stereotypic exaggerations of otherwise normal movements, which differ from LID in their response to pharmacological agents [3] and moreover occur in a variety of neuropsychiatric conditions unrelated to PD.

In general terms, LID is attributed to a dysregulated state of dopaminergic transmission involving large rapid fluctuations in brain DA levels on one hand and abnormal signaling at post-synaptic DA receptors on the other hand. Both mechanisms also affect non-dopaminergic transmitters in the cortico-basal ganglia network. Reviews covering different levels of the pathophysiological cascade can be found elsewhere [2,4–7]. Here we review recent progress on some topics of central importance to the field, while highlighting open questions and future research directions.

Striatal output pathways and dopamine receptors

Many studies on the pathophysiology of LID have been inspired by the so-called dual-pathway model originally proposed by Albin, Young, and Penney [8]. Briefly, the model posits that both hypokinetic and dyskinetic states depend on an imbalanced activation of two pathways linking the striatum with the basal ganglia output nuclei and acting like a push-pull system in movement control. Thus, a monosynaptic pathway originating from D1 receptor-positive striatal projection

neurons (dSPNs) would promote movement (direct pathway), whereas a polysynaptic pathway originating from D2 receptor-positive striatal projection neurons (iSPNs) would exert the opposite effect (indirect pathway). This theory was mainly based on clinical, neurochemical, pharmacological, and pathological findings in patients with PD or Huntington's disease (HD). In particular, hypokinesia in PD and chorea in HD were attributed to excessive or diminished activity, respectively, of iSPNs [8]. During the past decade, the availability of transgenic rodent lines expressing Cre recombinase in specific cell groups has made it possible to test the dual-pathway theory experimentally.

Using 6-OHDA-lesioned mice with SPN type-specific Cre expression, studies have shown that selective stimulation of dSPNs via chemogenetic [9] or optogenetic approaches [10–12] elicits dyskinetic movements. These data have established a causal link between dSPN overactivity and LID. However, using one approach or another may lead to somewhat different conclusions. A chemogenetic approach that increased dSPN excitability without directly inducing action potentials reproduced the full severity of LID only when accompanied by the administration of a D2 receptor agonist, thus mimicking the action of L-DOPA on both pathways [9]. On the contrary, optogenetic dSPN stimulation was reportedly capable to fully mimic LID without any additional pharmacological challenge [10–12]. The results obtained using dSPN optostimulation do not overrule an implication of the indirect pathway in LID. Indeed, LID severity can be substantially reduced by increasing the activity of iSPNs via chemogenetic [9] or optogenetic stimulation methods [13–15].

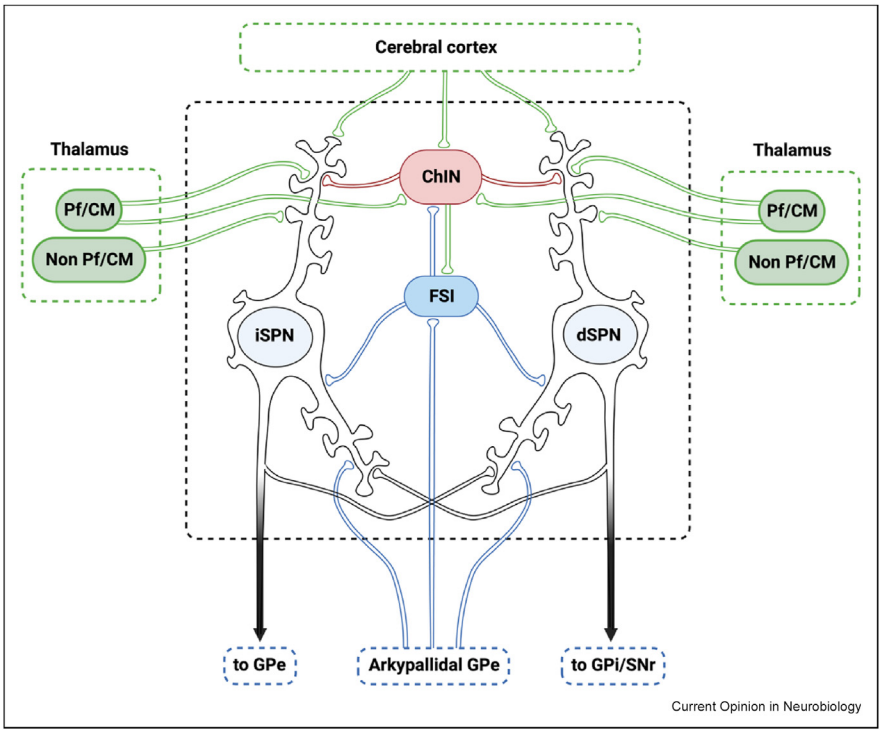
Taken together, the above studies provide experimental support to the classical dual-pathway model, which attributed dyskinesia to an imbalanced pathway activation favoring dSPNs over iSPNs [8]. The imbalance can be partly explained by the fact that dSPNs and iSPNs express different DA receptor types, where the G_{α}olf-coupled D1 and the G_{α}i-coupled D2 mediate facilitatory versus inhibitory effects on these neurons during the L-DOPA-on state (reviewed in [7,16]). However, this level of explanation cannot account for the plasticity of LID, which increases in both prevalence and severity during the course of clinical PD, and during the course of low-dose L-DOPA treatment in animal models [2]. As reviewed below, additional and more complex factors are in play.

Patterns of SPN activity and the striatal microcircuitry

The advent of cell type-specific *in vivo* calcium imaging methods has led to the realization that spatially coordinated ensembles of dSPNs and iSPNs are active during the execution of specific movements [17,18]. Application of the same methodology to 6-OHDA-lesioned mice has revealed altered and diametric patterns of dSPN-iSPN activation under both untreated and L-DOPA-treated conditions [19]. In the untreated parkinsonian state, iSPNs lose their ability to form spatially compact activity clusters, while dSPNs do form such clusters although their activity is reduced. Conversely, in the L-DOPA-on dyskinetic state, dSPNs become largely hyperactive seemingly without spatial coordination, while iSPNs do form spatial clusters but their overall activity is largely reduced [19]. Using single-unit recordings from optogenetically labeled striatal neurons, Ryan and colleagues verified that, during LID, the average dSPN firing rate was more than double the rate in healthy controls, while iSPN firing was decreased below rates typically recorded in healthy mice. However, only the activity of dSPNs that showed exceedingly high firing rates was correlated with the L-DOPA-induced AIM scores [12]. While supporting the dual-pathway model, these observations reveal complex changes in the spatial and temporal interactions between SPN ensembles that are not explained by the existing theories. These changes are likely to depend on a reorganization of synaptic connections at the level of the striatal microcircuitry.

In rodents, SPNs constitute ~95% of the total striatal neuronal population. The remaining 5% consists of cholinergic interneurons (ChINs) and several types of GABAergic interneurons (reviewed in [20]). Fast-spiking interneurons (FSIs) are particularly important because they receive cortical input and mediate strong feedforward inhibition onto all SPNs [16,20] summarized in Figure 1). Striatal SPNs and ChINs receive excitatory inputs from both cortical and thalamic afferents, which form abundant synaptic contacts on their dendrites and spines according to specific ultrastructural patterns (reviewed in [16,21]; Figure 1). The structural-functional properties of both cortico-striatal and thalamo-striatal synapses are profoundly altered in the DA-depleted state [22–25]. Prominent changes also affect striatal interneurons that potently modulate SPN activity, i.e. ChINs and FSIs [26–28]. In addition, the loss of DA afferents causes dendritic regression, changes in spine density, and altered intrinsic excitability to both dSPNs and iSPNs [29–31]. Experimental studies and post-mortem observations in human striatal tissue indicate that standard DA pharmacotherapies are overall ineffective at restoring the dendritic structure of SPNs. Even though chronic L-DOPA treatment increases dendritic spine density in iSPNs [29,32], the reduced dendritic length inevitably results in a net loss of spines and synaptic inputs also in these neurons [25]. Patterns of GABAergic synaptic connectivity are affected as well. The SPN dendrites are densely innervated by GABAergic synapses originating from striatal interneurons, arkypallidal neurons, and axon collaterals of other SPNs (Figure 1). A recent study found that the number of perisomatic contacts formed by FSIs on both SPN types

Figure 1



Schematic representation of the synaptic inputs to SPNs and their topology. Due to graphic constraints, synaptic inputs from glutamatergic afferents and cholinergic interneurons (ChIN) versus GABAergic inputs are represented on the upper and lower dendritic segment, respectively (in reality all of these inputs coexist on the same dendrite). Also due to space constraints, synaptic and non-synaptic axonal boutons from dopaminergic neurons and other neuromodulatory systems (e.g. cholinergic PPN projections) have been omitted. Scholarly reviews on each of the mentioned neuronal systems and afferent pathways can be found in [62]. A recent review on the striatal microcircuitry can be found in [20]. *Abbreviations:* FSI, fast spiking interneurons; GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; Pf/CM parafascicular and centromedian thalamic nuclei; SNr, substantia nigra pars reticulata.

were reduced after DA denervation, and treatment with L-DOPA did not reverse this change [27]. In addition, the loss of DA input strongly weakens the lateral inhibition mediated by SPN axon collaterals, disrupting the ability of a neuronal pool to arrest the firing of another neuronal pool [33]. The latter finding can perhaps be explained by considering that most of the SPN-to-SPN synapses are formed on distal dendrites [34]. Although the functional consequences of these microstructural rearrangements are poorly understood, *in silico* models of DA-denervated striatal neurons are linking changes in SPN dendritic structure to an altered pattern of distance-dependent connectivity and a reduction in higher-order activity motifs (those involving 3 or more neurons in the striatum) [35]. Indeed, a change in the spatial connectivity structure among SPNs may underlie the altered spatial structure of striatal activity in movement disorders. This interesting possibility might be demonstrated using *in silico* models of the striatal microcircuitry in PD and LID.

Cortico-striatal activity dynamics

The cerebral cortex strongly regulates the activity of striatal neurons and striatal output pathways, and an altered interplay between cortex and striatum is ascribed a central pathophysiological role in LID [5,36,37]. Although multiple cellular mechanisms are certainly involved, large importance has been attributed to an altered plasticity of cortico-striatal synapses, which is known to be governed by post-synaptic D1 and D2 receptors [5,22]. In particular, LID has been linked to an inability to reverse activity-dependent cortico-striatal long-term potentiation, which has in turn been linked to a supersensitive activation of D1-dependent signaling pathways by L-DOPA [38,39]. It seems plausible that the loss of downscaling at cortico-striatal synapses

observed in brain slices goes hand in hand with a stronger glutamatergic synaptic drive to dSPNs *in vivo*, thus contributing to the high activity levels of this neuronal population during the expression of AIMs.

Functional brain imaging studies in PD patients have revealed that cortical activity in primary and supplemental motor areas is increased in LID (reviewed in [37]), which is consistent with classical models of cortico-basal ganglia interactions in movement disorders [8]. Several recent studies have addressed the interplay between cortex and striatum in LID by measuring the generation and transmission of local field potential (LFP) oscillations. In general terms, oscillations of the LFP are thought to reflect rhythmic synchronizations of transmembrane currents among populations of neurons in the recorded brain region (reviewed in [40]). Rhythmic synchronization plays an important role in the communication of spiking activity from one brain region to another [41]. A seminal study in the rat model of LID reported that the expression of AIMs is temporally locked with the appearance of strong narrowband gamma oscillations of the LFP in the primary motor cortex [42]. Interestingly, narrowband gamma LFP oscillations specifically correlated with LID were later detected in PD patients on L-DOPA [43]. We have recently characterized this pathophysiological rhythm using *in vivo* multiscale recordings in L-DOPA-primed dyskinetic rats treated with different dopaminergic agents (L-DOPA vs selective D1 or D2 receptor agonists [44]). The dyskinesia-associated narrowband gamma oscillations were strongest in cortical motor areas compared to subcortical structures, and a phase analysis revealed that the primary motor cortex (forelimb area) was leading a supplementary motor area and the striatum [44]. We also found that both the detection rate and the absolute power of narrowband gamma oscillations were larger after treatment with a D1 agonist compared to both a D2 agonist and L-DOPA, although the anatomical location of the involved D1 receptor pool could not be established [44].

Ongoing investigations are pursuing the main "cellular generators" of these narrowband gamma oscillations, while also trying to determine whether they play a direct causal role in the production of dyskinetic movements. We can however expect that the cortical narrowband gamma rhythms can strengthen the interaction between motor cortex and striatum either by entraining striatal activity (communication through resonance [45]) or by a phase synchrony-mechanism (communication through coherence [46]). In both cases, cortical rhythms would enable transmission of excessive cortical activity to the striatum, which is already profoundly affected due to microcircuit rearrangements entailing weaker SPN-to-SPN inhibition (discussed above).

Beyond striatum and cortex

Treatment of PD with L-DOPA can potentially affect any brain structure containing DA receptors, and rodent models of LID do display changes in immediate-early gene expression in a large number of brain regions, also beyond the classical motor systems [47]. Although specific investigations are needed to elucidate how different brain structures contribute to LID, important novel insights have recently emerged from the study of cerebellar and brainstem nuclei involved in motor control.

Prompted by reports that transcranial cerebellar stimulation has antidyskinetic effects in PD (for a review see [36]), Coutant and colleagues have examined the impact of Purkinje cell optostimulation in the mouse model of LID [48]. Optogenetic theta stimulation applied to the orolingual region of the cerebellar cortex was found to both improve already established AIMs and prevent their occurrence during L-DOPA treatment, with the clearest effects observed on the orolingual AIM subscore. While pursuing the mechanisms behind this effect, it was found that treatment with L-DOPA increased firing irregularity in the cerebellar output nuclei, and that Purkinje cell stimulation prevented the irregularity of neural discharges at this level [48]. Furthermore, it was found that the antidyskinetic effect of Purkinje cell optostimulation could be prevented by inhibiting a projection from the cerebellar output nuclei to the parafascicular thalamus, whereas the motor thalamus did not appear to play a role [48]. Although we are still far from understanding how the cerebellum is involved in PD and LID, this study provides the first indication that the activity of cerebellar output nuclei is dysregulated during the L-DOPA-on state in animals exhibiting dyskinesia, and moreover points to the parafascicular thalamus as a crucial link between cerebellum and striatum in this movement disorder.

The substantia nigra pars reticulata (SNr) is one of two main output nuclei of the basal ganglia, and regulates neuronal activity in thalamic and brainstem targets. Multiple pathophysiological changes have been detected in SNr neurons both under DA-depleted conditions [49,50] and after L-DOPA treatment in dyskinetic animals [49,51]. Moreover, protocols of dSPN optostimulation that induce AIMs have been reported to profoundly inhibit neuronal activity in SNr [11]. A causal role of altered SNr activity in LID has been recently demonstrated using optogenetic interventions in the 6-OHDA-lesion mouse model [52]. Thus, while optoinhibition of SNr GABAergic neurons significantly improved forelimb akinesia, optostimulation of the same neurons at 50–100 Hz strongly inhibited forelimb and axial AIMs, as mice rapidly transitioned from severe dyskinesia to nearly normal locomotion during the stimulation [52]. Interestingly,

optostimulation of SNr GABAergic projections to the pedunculopontine nucleus (PPN) recapitulated the effects of direct SNr stimulation [52]. These results will hopefully stimulate further investigations into the pathophysiological role of specific SNr projections and their long-range connectivity.

Conclusions and future research directions

Research on animal models of LID has spearheaded the discovery of pathophysiological principles that have proven useful to understand a vast range of movement disorders, including primary dystonia, Huntington's disease, and tardive dyskinesia [5,53]). More research is now needed to shed light on important pending questions, exemplified in the following.

Besides striatum, we are learning that cortex, cerebellum, and brain stem nuclei also show aberrant activity in LID, and that the chronic loss of DA alters the cortico-striatal, thalamo-striatal, and striato-striatal connectivity. Thus, the dopaminergic treatment of PD acts on a highly abnormal network that is driven by pathological inputs. New detailed *in silico* models are therefore needed to investigate the interplay of altered striatal network, aberrant inputs, and fluctuating DA levels in shaping the pathological spatiotemporal dynamics of dSPN and iSPN activity in LID.

On the experimental level, rather than considering dSPNs and iSPNs as homogeneous cell categories, future studies will need to characterize the spatial and temporal structure of SPN ensemble activity in relation to different types of dyskinesia. It is noteworthy that the motor manifestations of LID can vary between PD patients and between different phases of the L-DOPA dosing cycle [54]. In the mouse model too, LID includes orofacial, axial, and limb AIMs that are variably represented [55], and map onto functionally distinct striatal domains [56] having different transcriptional profiles [57]. Orofacial, axial, and limb AIMs are differentially expressed when dyskinetic behaviors are elicited using selective D1 or D2 receptor agonists [55] or via different methods of chemogenetic dSPN stimulation [9], suggesting an involvement of distinct neuronal networks. Therefore, dissecting complex dyskinetic motor patterns into topographically distinct components appears necessary to guide future spatiomolecular investigations of the striatal network in LID.

From a translational perspective, future studies should consider that PD patients with motor complications are often cotreated with L-DOPA and D2/3 receptor agonists, and not just with L-DOPA as done in animal studies. Recent findings from both PD patients [58–60] and rodent models of LID have highlighted that the addition of D2/3 agonists to L-DOPA shifts the action of the therapy towards D2 receptors, having a profound impact on the patterns of LID-related cellular plasticity in the striatum [61]. Finally, it is hoped that recent experimental discoveries on the role of extrastriatal regions will inspire the exploration of novel approaches to antidyskinetic treatment based on brain stimulation. In this regard, non-invasive strategies able to suppress or desynchronize cortical narrowband gamma rhythms seem to represent an interesting topic for future investigations.

Authors' roles

M. Angela Cenci: Writing – original draft; Writing – review & editing; Visualization.

Arvind Kumar: Writing – review & editing.

Declaration of competing interest

The Authors (M. Angela Cenci and Arvind Kumar) do not have any conflict of interest to declare in relation to this submission.

Data availability

No data was used for the research described in the article.

Acknowledgments

M. Angela Cenci acknowledges partial funding from the Swedish Research Council, the Swedish Government Funding for Clinical Research, the Lundbeck Foundation, the Swedish Brain Foundation, the Swedish Parkinson Foundation, and the Strategic Research Area MultiPark. Arvind Kumar acknowledges partial funding from the Swedish Research Council, and the Strategic Research Area Neuroscience (StratNeuro). The Authors warmly thank Valentina Cesaroni for the artwork in Figure 1 and Yoland Smith for valuable discussion.

References

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Manson A, Stirpe P, Schrag A: **Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life**. *J Parkinsons Dis* 2012, **2**:189–198.

2. Cenci MA, Crossman AR: **Animal models of l-dopa-induced dyskinesia in Parkinson's disease**. *Mov Disord* 2018, **33**: 889–899.

3. Breger LS, Dunnett SB, Lane EL: **Comparison of rating scales used to evaluate L-DOPA-induced dyskinesia in the 6-OHDA lesioned rat**. *Neurobiol Dis* 2013, **50**:142–150.

4. Bastide MF, Meissner WG, Picconi B, Fasano S, Fernagut PO, Feyder M, Francardo V, Alcacer C, Ding Y, Brambilla R, *et al.*: **Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease**. *Prog Neurobiol* 2015, **132**:96–168.

5. Calabresi P, Pisani A, Rothwell J, Ghiglieri V, Obeso JA, Picconi B: **Hyperkinetic disorders and loss of synaptic downscaling**. *Nat Neurosci* 2016, **19**:868–875.

6. Solis O, Moratalla R: **Dopamine receptors: homomeric and heteromeric complexes in L-DOPA-induced dyskinesia**. *J Neural Transm* 2018, **125**:1187–1194.

7. Spigolon G, Fisone G: **Signal transduction in L-DOPA-induced dyskinesia: from receptor sensitization to abnormal gene expression**. *J Neural Transm* 2018, **125**:1171–1186.

8. Albin RL, Young AB, Penney JB: **The functional anatomy of basal ganglia disorders**. *Trends Neurosci* 1989, **12**:366–375.

9. •• Alcacer C, Andreoli L, Sebastianutto I, Jakobsson J, Fieblinger T, Cenci MA: **Chemogenetic stimulation of striatal projection neurons modulates responses to Parkinson's disease therapy**. *J Clin Invest* 2017, **127**:720–734.
Using chemogenetic stimulation methods, combined or not with pharmacological challenges, this study shows that both the untreated parkinsonian state and the L-DOPA-treated dyskinetic state are bidirectionally controlled by the two striatal output pathways. Different methods of chemogenetic dSPN stimulation resulted in different AIMs pattern, and the full spectrum and severity of LID was obtained only when dSPN stimulation was combined with a D2 receptor agonist, thus mimicking the action of L-DOPA on both pathways.

10. Girasole AE, Lum MY, Nathaniel D, Bair-Marshall CJ, Guenthner CJ, Luo L, Kreitzer AC, Nelson AB: **A subpopulation of striatal neurons mediates levodopa-induced dyskinesia**. *Neuron* 2018, **97**:787–795 e786.

11. Keifman E, Ruiz-DeDiego I, Pafundo DE, Paz RM, Solis O, Murer MG, Moratalla R: **Optostimulation of striatonigral terminals in substantia nigra induces dyskinesia that increases after L-DOPA in a mouse model of Parkinson's disease**. *Br J Pharmacol* 2019, **176**:2146–2161.

12. •• Ryan MB, Bair-Marshall C, Nelson AB: **Aberrant striatal activity in parkinsonism and levodopa-induced dyskinesia**. *Cell Rep* 2018, **23**:3438–3446. e3435.
Using *in vivo* SPN recordings in the mouse model of LID, this is the first study to show that not all dSPNs respond in the same way to L-DOPA. Authors identified a subpopulation of dSPNs with abnormally high L-DOPA-evoked firing rates that correlated specifically with the expression of dyskinesia. These results highlight the importance of future studies revealing the specific SPN ensembles that encode specific motor abnormalities.

13. Castela I, Casado-Polanco R, Rubio YV, da Silva JA, Marquez R, Pro B, Moratalla R, Redgrave P, Costa RM, Obeso J, *et al.*: **Selective activation of striatal indirect pathway suppresses levodopa induced-dyskinesias**. *Neurobiol Dis* 2023, **176**, 105930.

14. Liu K, Song M, Gao S, Yao L, Zhang L, Feng J, Wang L, Gao R, Wang Y: **The dynamics of dopamine D(2) receptor-expressing striatal neurons and the downstream circuit underlying L-dopa-induced dyskinesia in rats**. *Neurosci Bull* 2023, **39**:1411–1425.

15. Saez M, Keifman E, Alberquilla S, Coll C, Reig R, Murer MG, Moratalla R: **D2 dopamine receptors and the striatopallidal pathway modulate L-DOPA-induced dyskinesia in the mouse**. *Neurobiol Dis* 2023, **186**, 106278.

16. Gerfen CR, Surmeier DJ: **Modulation of striatal projection systems by dopamine**. *Annu Rev Neurosci* 2011, **34**:441–466.

17. Barbera G, Liang B, Zhang L, Gerfen CR, Culurciello E, Chen R, Li Y, Lin DT: **Spatially compact neural clusters in the dorsal striatum encode locomotion relevant information**. *Neuron* 2016, **92**:202–213.

18. Klaus A, Martins GJ, Paixao VB, Zhou P, Paninski L, Costa RM: **The spatiotemporal organization of the striatum encodes action space**. *Neuron* 2017, **95**:1171–1180 e1177.

19. •• Parker JG, Marshall JD, Ahanonu B, Wu YW, Kim TH, Grewe BF, Zhang Y, Li JZ, Ding JB, Ehlers MD, *et al.*: **Diametric neural ensemble dynamics in parkinsonian and dyskinetic states**. *Nature* 2018, **557**:177–182.
This is the first publication using *in vivo* calcium imaging to compare SPN ensemble activity in healthy, parkinsonian, and L-DOPA-treated dyskinetic states. Results show that both the untreated parkinsonian condition and the L-DOPA-treated condition with dyskinesia entail major changes to the spatial structure of dSPN and iSPN activation patterns. This data takes us beyond the classical theories that attributed movement disorders to differences in average firing rates between pathways.

20. Burke DA, Rotstein HG, Alvarez VA: **Striatal local circuitry: a new framework for lateral inhibition**. *Neuron* 2017, **96**:267–284.

21. Galvan A, Villalba RM, Wichmann T, Smith Y: **The thalamostriatal systems in normal and diseased states**. *Handb Behav Neurobiol* 2016, **24**:477–493.

22. Shen W, Zhai S, Surmeier DJ: **Striatal synaptic adaptations in Parkinson's disease**. *Neurobiol Dis* 2022, **167**, 105686.

23. Tanimura A, Du Y, Kondapalli J, Wokosin DL, Surmeier DJ: **Cholinergic interneurons amplify thalamostriatal excitation of striatal indirect pathway neurons in Parkinson's disease models**. *Neuron* 2019, **101**:444–458 e446.

24. Tanimura A, Shen W, Wokosin D, Surmeier DJ: **Pathway-specific remodeling of thalamostriatal synapses in a mouse model of Parkinson's disease**. *Mov Disord* 2022, **37**:1164–1174.

25. Villalba RM, Smith Y: **Loss and remodeling of striatal dendritic spines in Parkinson's disease: from homeostasis to maladaptive plasticity?** *J Neural Transm* 2018, **125**:431–447.

26. Choi SJ, Ma TC, Ding Y, Cheung T, Joshi N, Sulzer D, Mosharov EV, Kang UJ: **Alterations in the intrinsic properties of striatal cholinergic interneurons after dopamine lesion and chronic L-DOPA**. *Elife* 2020, **9**.

27. Gomez G, Escande MV, Suarez LM, Rela L, Belforte JE, Moratalla R, Murer MG, Gershanik OS, Taravini IRE: **Changes in dendritic spine density and inhibitory perisomatic connectivity onto medium spiny neurons in L-dopa-induced dyskinesia**. *Mol Neurobiol* 2019, **56**:6261–6275.

28. Paz RM, Tubert C, Stahl AM, Amarillo Y, Rela L, Murer MG: **Levodopa causes striatal cholinergic interneuron burst-pause activity in parkinsonian mice**. *Mov Disord* 2021, **36**:1578–1591.

29. Fieblinger T, Graves SM, Sebel LE, Alcacer C, Plotkin JL, Gertler TS, Chan CS, Heiman M, Greengard P, Cenci MA, *et al.*: **Cell type-specific plasticity of striatal projection neurons in parkinsonism and L-DOPA-induced dyskinesia**. *Nat Commun* 2014, **5**:5316.

30. Li C, Elabi OF, Fieblinger T, Cenci MA: **Structural-functional properties of direct-pathway striatal neurons at early and chronic stages of dopamine denervation**. *Eur J Neurosci* 2023, e16166.

31. Suarez LM, Alberquilla S, Garcia-Montes JR, Moratalla R: **Differential synaptic remodeling by dopamine in direct and indirect striatal projection neurons in Pitx3(-/-) mice, a genetic model of Parkinson's disease**. *J Neurosci* 2018, **38**:3619–3630.

32. Suarez LM, Solis O, Aguado C, Lujan R, Moratalla R: **L-DOPA oppositely regulates synaptic strength and spine morphology in D1 and D2 striatal projection neurons in dyskinesia**. *Cerebr Cortex* 2016, **26**:4253–4264.

33. Lopez-Huerta VG, Carrillo-Reid L, Galarraga E, Tapia D, Fiordelisio T, Drucker-Colin R, Bargas J: **The balance of striatal feedback transmission is disrupted in a model of parkinsonism**. *J Neurosci* 2013, **33**:4964–4975.

34. Yung KK, Smith AD, Levey AI, Bolam JP: **Synaptic connections between spiny neurons of the direct and indirect pathways in the neostriatum of the rat: evidence from dopamine receptor and neuropeptide immunostaining**. *Eur J Neurosci* 1996, **8**:861–869.

35. Carannante I, Scolamiero M, Hjorth JJ, Kozlov A, Bekkouche B, Guo L, Kumar A, Chachólski W, Hellgren Kotaleski J: **The impact of Parkinson's disease on striatal network connectivity and cortico-striatal drive: an in-silico study**. *bioRxiv* 2023. 2023-09.

36. Cenci MA, Jorntell H, Petersson P: **On the neuronal circuitry mediating L-DOPA-induced dyskinesia**. *J Neural Transm* 2018, **125**:1157–1169.

37. Meder D, Herz DM, Rowe JB, Lehericy S, Siebner HR: **The role of dopamine in the brain - lessons learned from Parkinson's disease**. *Neuroimage* 2019, **190**:79–93.

38. Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, Fisone G, Cenci MA, Calabresi P: **Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia**. *Nat Neurosci* 2003, **6**:501–506.

39. Shen W, Plotkin JL, Francardo V, Ko WK, Xie Z, Li Q, Fieblinger T, Wess J, Neubig RR, Lindsley CW, *et al.*: **M4 muscarinic receptor signaling ameliorates striatal plasticity deficits in models of L-DOPA-induced dyskinesia**. *Neuron* 2015, **88**:762–773.

40. Petersson P, Halje P, Cenci MA: **Significance and translational value of high-frequency cortico-basal ganglia oscillations in Parkinson's disease**. *J Parkinsons Dis* 2019, **9**:183–196.

41. Hahn G, Ponce-Alvarez A, Deco G, Aertsen A, Kumar A: **Portraits of communication in neuronal networks**. *Nat Rev Neurosci* 2019, **20**:117–127.

42. Halje P, Tamte M, Richter U, Mohammed M, Cenci MA, Petersson P: **Levodopa-induced dyskinesia is strongly associated with resonant cortical oscillations**. *J Neurosci* 2012, **32**: 16541–16551.

43. Swann NC, de Hemptinne C, Miocinovic S, Qasim S, Wang SS, Ziman N, Ostrem JL, San Luciano M, Galifianakis NB, Starr PA: **Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in Parkinson's disease**. *J Neurosci* 2016, **36**:6445–6458.

44. • Skovgard K, Barrientos SA, Petersson P, Halje P, Cenci MA: **Distinctive effects of D1 and D2 receptor agonists on cortico-basal ganglia oscillations in a rodent model of L-DOPA-induced dyskinesia**. *Neurotherapeutics* 2023, **20**:304–324.

Using large-scale multisite recordings, this study revealed that the narrowband gamma rhythm associated with LID is strongest in animals treated with D1 agonists compared to D2 agonists or L-DOPA. Moreover, the rhythm is strongest in the motor cortex, which leads the corresponding striatal rhythm. These data suggest that both direct pathway and motor cortex are implicated in generation of these pathological oscillations.

45. Hahn G, Bujan AF, Fregnac Y, Aertsen A, Kumar A: **Communication through resonance in spiking neuronal networks**. *PLoS Comput Biol* 2014, **10**, e1003811.

46. Fries P: **Rhythms for cognition: communication through coherence**. *Neuron* 2015, **88**:220–235.

47. Bastide MF, Dovero S, Charron G, Porras G, Gross CE, Fernagut PO, Bezard E: **Immediate-early gene expression in structures outside the basal ganglia is associated to l-DOPA-induced dyskinesia**. *Neurobiol Dis* 2014, **62**:179–192.

48. •• Coutant B, Frontera JL, Perrin E, Combes A, Tarpin T, Menardy F, Mailhes-Hamon C, Perez S, Degos B, Venance L, *et al.*: **Cerebellar stimulation prevents Levodopa-induced dyskinesia in mice and normalizes activity in a motor network**. *Nat Commun* 2022, **13**:3211.

This is the first study revealing that cerebellar output nuclei exhibit altered firing patterns in LID. Optogenetic stimulation of the cerebellar cortex normalized these aberrant neuronal discharges while also improving LID. Chemogenetic inhibition of the cerebello-parafascicular pathway counteracted the beneficial effects of cerebellar cortex stimulation. These findings highlight the therapeutic potential of cerebellar stimulation and its capacity to restore the function of a wide motor network in LID.

49. Dwi Wahyu I, Chiken S, Hasegawa T, Sano H, Nambu A: **Abnormal cortico-basal ganglia neurotransmission in a mouse model of l-DOPA-induced dyskinesia**. *J Neurosci* 2021, **41**:2668–2683.

50. Willard AM, Isett BR, Whalen TC, Mastro KJ, Ki CS, Mao X, Gittis AH: **State transitions in the substantia nigra reticulata predict the onset of motor deficits in models of progressive dopamine depletion in mice**. *Elife* 2019, **8**.

51. Chen J, Wang Q, Li N, Huang S, Li M, Cai J, Wang Y, Wen H, Lv S, Wang N, *et al.*: **Dyskinesia is closely associated with synchronization of theta oscillatory activity between the substantia nigra pars reticulata and motor cortex in the off L-dopa state in rats**. *Neurosci Bull* 2021, **37**:323–338.

52. •• Hu Y, Ma TC, Alberico SL, Ding Y, Jin L, Kang UJ: **Substantia nigra pars reticulata projections to the pedunculopontine nucleus modulate dyskinesia**. *Mov Disord* 2023, **38**: 1850–1860.

This study demonstrates that 50–100 Hz optostimulation of SNr GABAergic neurons rapidly interrupts ongoing LID and restores a normal locomotion patterns in mice. Moreover, optostimulation of SNr GABAergic projections to the PPN recapitulated the effects of direct SNr stimulation. This study provides the first indication that the SNr may provide a neuromodulation target for the treatment of LID.

53. Abe Y, Yagishita S, Sano H, Sugiura Y, Dantsuji M, Suzuki T, Mochizuki A, Yoshimaru D, Hata J, Matsumoto M, *et al.*: **Shared GABA transmission pathology in dopamine agonist- and antagonist-induced dyskinesia**. *Cell Rep Med* 2023, **4**, 101208.

54. Espay AJ, Morgante F, Merola A, Fasano A, Marsili L, Fox SH, Bezard E, Picconi B, Calabresi P, Lang AE: **Levodopa-induced dyskinesia in Parkinson disease: current and evolving concepts**. *Ann Neurol* 2018, **84**:797–811.

55. Andreoli L, Abbaszadeh M, Cao X, Cenci MA: **Distinct patterns of dyskinetic and dystonic features following D1 or D2 receptor stimulation in a mouse model of parkinsonism**. *Neurobiol Dis* 2021, **157**, 105429.

56. Foster NN, Barry J, Korobkova L, Garcia L, Gao L, Becerra M, Sherafat Y, Peng B, Li X, Choi JH, *et al.*: **The mouse cortico-basal ganglia-thalamic network**. *Nature* 2021, **598**:188–194.

57. • Roman KM, Dinasarapu AR, VanSchoiack A, Ross PM, Kroeppler D, Jinnah HA, Hess EJ: **Spiny projection neurons exhibit transcriptional signatures within subregions of the dorsal striatum**. *Cell Rep* 2023, **42**, 113435.

This study applied RNA profiling-in situ hybridization to identify molecular signatures of dSPNs and iSPNs within dorsomedial, dorsolateral, and ventrolateral striatum in intact mice. The results reveal a remarkable regional heterogeneity in the expression of genes mediating synaptic function, neuronal plasticity, and neurotransmitter receptors in both SPN populations. This data suggests that striatal subregions topographically related to different body parts may respond differently to altered states of DA transmission, calling for new investigations to directly test this hypothesis.

58. Espinosa-Cardenas R, Arce-Sillas A, Alvarez-Luquin D, Leyva-Hernandez J, Montes-Moratilla E, Gonzalez-Saavedra I, Boll MC, Garcia-Garcia E, Angeles-Perea S, Fragoso G, *et al.*: **Immunomodulatory effect and clinical outcome in Parkinson's disease patients on levodopa-pramipexole combo therapy: a two-year prospective study**. *J Neuroimmunol* 2020, **347**, 577328.

59. Grigoriou S, Espa E, Odin P, Timpka J, von Grothusen G, Jakobsson A, Cenci MA: **Comparison of dyskinesia profiles after L-DOPA dose challenges with or without dopamine agonist coadministration**. *Neuropharmacology* 2023, **237**, 109630.

60. Kim MS, Park DG, Gil YE, Shin IJ, Yoon JH: **The effect of levodopa treatment on vascular endothelial function in Parkinson's disease**. *J Neurol* 2023, **270**:2964–2968.

61. Espa E, Song L, Skovgard K, Fanni S, Cenci MA: **Dopamine agonist cotreatment alters neuroplasticity and pharmacology of levodopa-induced dyskinesia**. *Mov Disord* 2023, **38**: 410–422.

62. Steiner H, Tseng KYE: *Handbook of basal ganglia structure and function*. Edn Second. Elsevier B.V.; 2017.