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Chapter 3

# Changes in the Striatal Network Connectivity in Parkinsonian and Dyskinetic Rodent Models

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http://dx.doi.org/10.5772/intechopen.70601

**Abstract**

In Parkinson's disease, there is a loss of dopaminergic innervation in the basal ganglia. The lack of dopamine produces substantial changes in neural plasticity and generates pathological activity patterns between basal ganglia nuclei. The treatment to relieve Parkinsonism is the administration of levodopa. However, the treatment produces dyskinesia. The question to answer is how the interactions between neurons change in the brain microcircuits under these pathological conditions. Calcium imaging is a way to record the activity of dozens of neurons simultaneously with single-cell resolution in brain slices from rodents. We studied these interactions in the striatum, since it is the nucleus of the basal ganglia that receives the major dopaminergic innervation. We used network analysis, where each active neuron is taken as a node and its coactivity with other neurons is taken as its functional connections. The network obtained represents the functional connectome of the striatal microcircuit, which can be characterized with a small set of parameters taken from graph theory. We then quantify the pathological changes at the functional histological scale and the differences between normal and pathological conditions.

**Keywords:** Parkinson's disease, L-DOPA induced dyskinesia, striatal microcircuit, functional connectome, network properties

## 1. Introduction

Idiopathic Parkinson's disease (PD) was first described by James Parkinson in 1817 and it is the second most common neurodegenerative disease after Alzheimer's disease. PD prevalence is lower in African, Asian, and Arabic countries than in North America, Europe, and South America [1, 2]. In the USA, the incidence of PD by ethnicity is highest among Hispanic people, followed by non-Hispanic white people, Asian people and black people [1, 2]. Gender

is another risk factor with a male to female incidence ratio around 3:2 [1, 2]. However, age is the greatest risk factor to develop PD: the incidence is low before the age of 50 years but increases quickly peaking around 80 years [1, 2]. In addition, there are several environmental risk factors for PD: pesticide exposure, head injury, rural living, etc.; but also there are some factors that help to decrease the risk: tobacco smoking, coffee drinking, alcohol consumption, etc. [1, 2].

The main characteristics of PD are the motor symptoms: resting tremor, rigidity, postural instability, bradykinesia, among others [3]. The motor symptoms of PD are the result of dopaminergic denervation of the basal ganglia (BG). This loss of dopamine is due to the death of dopaminergic neurons in the *substantia nigra pars compacta* (SNc). Dopamine is essential for the proper functioning of the BG [4]. The causes of PD are still unknown. Some neurotoxic animal models have been developed to mimic and study its pathophysiology. In rodents, the most used is the hemiparkinsonian model: the unilateral lesion of the SNc with the 6-hidroxidopamine toxin (6-OHDA). It is commonly evaluated by turning behavior induced by dopaminergic agonists [5–7]. In this chapter, recent results to study pathophysiology at the microcircuit level will be disclosed together with their theoretical framework [8, 9]. The best treatment to relieve some signs and symptoms of PD is the administration of dopaminergic agonists, mainly L-DOPA. However, the long-term administration of L-DOPA produces other movement disorders: L-DOPA-induced dyskinesias (LIDs). There are three well-characterized types of LID [10]. (1) Peak dose dyskinesia, which is the most common, occurs in 80% of patients at peak of dopamine concentrations derived from L-DOPA ("on" time). (2) Diphasic dyskinesia, that occurs at the rising and falling of L-DOPA's clinical useful concentrations. (3) Early morning dystonia, that occurs when dopamine levels are very low, commonly after patients spent nighttime without L-DOPA.

LID is characterized by abnormal and involuntary movements which seem to appear randomly. It is often extremely disabling. 50% of the patients present it between 4 and 5 years after starting treatment and 75% after 10 years of treatment [11, 12]. To study this kind of dyskinesia, the 6-OHDA rodent model is treated with high doses of L-DOPA during several days and it is evaluated by counting abnormal involuntary movements (AIMs): locomotive, limb, axial, and orolingual [13]. Here, this model was used to study the dyskinetic pathophysiology at the microcircuit level [9]. We propose the study of the BG at the microcircuit level in order to better understand the detailed pathophysiology of these movement disorders.

## 2. Striatal microcircuit

The BG contains subcortical nuclei involved in motor coding: selection, generation, learning, and control of movements [14]. The nuclei of the BG are the striatum, the external and internal segments of the *globus pallidus* (GPe & GPi), the subthalamic nucleus (STN), and the *substantia nigra pars compacta* (SNc), and *substantia nigra pars reticulata* (SNr). The main input of the BG is the striatum, which receives glutamatergic afferents from the cortex and the thalamus, and dopaminergic terminals from the SNc [15]. The striatal microcircuit contains different neural classes. A general classification separates the spiny projection neurons (SPNs) from the

interneurons. The SPNs are the 95% of the striatal neural population and they have collateral synapses between them at distances less than 100 μm [16–18]. The SPNs are divided in two populations: direct pathway SPNs (dSPNs) that connect monosynaptically to the BG output nuclei, GPi and SNr, and the indirect pathway SPNs (iSPNs) that send synaptic terminals to the GPe. Normally, SPNs have little spontaneous activity until they are activated by an excitatory drive, defined as afferents, neurotransmitter agonists, or modulators that induce the microcircuit to produce alternant neural activity [19]. When SPNs are activated, they show particular temporal patterns with oscillations between two distinct states: one with a hyperpolarized membrane potential or downstate at around −80mV, and the second with membrane potential depolarizations that last hundreds of milliseconds or seconds, the upstate, at around −50 mV [20]. It is during the upstate that SPNs fire action potentials, better respond to synaptic inputs and concert their firing with other SPNs conforming active neuronal ensembles.

On the other hand, the interneurons conform the remaining 5% of the population [15]. One class of interneuron expresses choline acetyltransferase (ChAT) with axons extending more than 1 mm. Other classes of interneurons are GABAergic and they are divided in numerous types: the fast spiking interneurons, which express parvalbumin (PV) and/or serotonin receptors (5-HT3); the low threshold spike interneurons (LTS), which could be further subdivided and may express or coexpress neuropeptide Y (NPY), somatostatin (SOM), nitric oxide synthase (NOS), or else, serotonin receptors (5-HT3), or calretinin, there are also neurogliaform interneurons (NGF), and other types still being studied [21–23]. The axonal arborizations of most interneurons may reach up to 1 mm. The exact combination of connections between these neuronal classes is still under study using electrophysiological recordings and optogenetics. There may be several valid combinations depending on function or context and further research is necessary to find out each of them.

The traditional model of the two pathways [24–25] propose that in control conditions there is an equilibrium between the activity of the direct pathway (dSPNs), which promotes movement, and the indirect pathway (iSPNs) which inhibits movement. Therefore, the balanced activation of both pathways produce coordinated movements. It is posited that in PD there is an imbalanced activity between these pathways: the activity of iSPNs becoming more important producing greater inhibition of movements. In contrast, during LID there is more activity in the direct pathway producing more involuntary movements. Unfortunately, these explanations are not supported by some experiments in monkeys, where these differences in activity were not observed [4]. Therefore, instead of staying at cellular level descriptions, in this work, we describe the interactions or functional connections between neuronal ensembles of the striatal microcircuit at the functional histological level in living brain tissue. This approach may help to identify what changes characterize control and pathological microcircuits to then ask, in future experiments, what cellular elements produce them.

## 3. Striatal cell assemblies

In the history of neuroscience, ideas about how neural activity is organized, one of them stands out: the cell assembly hypothesis. This hypothesis was formally proposed in its modern form

by Hebb in 1949 [26] and defines a cell assembly as a group of interconnected neurons dedicated to code motor processes or to store and maintain neural representations. This hypothesis is based on long-term synaptic plasticity and has been modified to include both long-term potentiation and depression (LTP and LTD). It postulates that the changes in synaptic weights due to synaptic plasticity produce preferential connections and circuits for the flow of activity within and between neuronal ensembles, making up neural circuits. Experiments in small areas of tissue have shown these ensembles, which exhibit recurrence and alternation in their activity. The flow of activity generates spatiotemporal sequences and reverberations that correlate with behavior [27–34].

In cerebral slices, the activity of some neural circuits may be facilitated by an excitatory drive [19]. In striatal slices of rodents, microcircuits are almost silent, therefore to induce their activation one may use an excitatory drive such as N-methyl-D-aspartate (NMDA) [35]. However, circuits may also be activated by an adequate electrical stimulus in the cortex or the thalamus without the use of any chemical transmitter (unpublished). Recording the activity of dozens of neurons in the striatum using calcium imaging, the alternation and recurrence of so-called "network states," conformed by coactive sets of neurons or neurons that have correlated firing between them as expected for cell assemblies or ensembles [36], have been observed. It has also been shown that this activity could also depend on the short-term plasticity of the synaptic connections [37] and their ever-changing mutual innervation.

In tissue from the Parkinsonian rodent model, the striatal microcircuit is observed as overactive, not quite silent or with little activity as in control conditions. This excess in activity occurs without any excitatory drive or stimulus. However, a network state becomes dominant during the alternation of activity between neuronal ensembles attracting most active neurons and being more recurrent [8]. In this way, the circuit is metaphorically trapped by one network state, decreasing alternation and resembling what is seen in the patient who has trouble in changing or initiating a movement. Pharmacological bioassays in the striatum have been performed while observing the Parkinsonian overactivity. Adding L-DOPA [38] or nicotine [39] to the Parkinsonian striatal circuit reduced this activity and returned the circuit to resemble control conditions. To go beyond alternation and recurrence of network states, the dynamics of transitions between these states has been analyzed [9, 40], and a temporal sequence of these transitions was constructed using Eulerian paths—where every transition is traveled once—the paths that form the dynamics were then analyzed. In control conditions, more than a half of the sequences are closed forming reverberations. But in Parkinsonian and dyskinetic conditions, most transitions conformed open Eulerian paths [9]. In addition to the temporal dynamics of cell assemblies, neural network analysis was performed to compare control and pathological conditions.

## 4. Network analysis in neuroscience

Network analysis is a branch of discrete mathematics known as graph theory, which started in 1736 thanks to the mathematician Leonard Euler. Basically, a graph is a set of nodes and the links or edges between them. Nodes could be people, brain areas, neurons, etc., and links

could be some relation between them: friendship, anatomical connections, synapses, action of modulators, etc. In the last 15 years, the interest included complex networks, which are characterized by irregular and complex structures evolving in time [41]. Complex networks may maintain their properties despite changes in scale: temporal or spatial [42]. To study cerebral connectivity, anatomical and functionally, this theoretical framework is being used in many areas of neuroscience: neuroanatomy, neurodevelopment, cognitive neuroscience, etc. [43, 44]. Sporns and Hagmann, simultaneously and independently, called "connectome" to the network of connections that make up a brain [45, 46]. This concept has been extended to include functional connectivity of any kind, obtaining functional connectomes [47]. Functional connectivity refers to the associations that relate the activity between the elements of the cerebral network, not necessarily anatomical, for example, the coactivity between cerebral areas, nucleus or neurons [9], their correlations [48] or coherence [49]. Network analysis in neuroscience has shown a hierarchical organization and scale-free connectivity at different scales: microcircuits [9, 50], larger circuits [51, 52], and the whole brain [49]. The characterization of functional connectomes using quantitative parameters allows compare the complexity of the neuronal interactions between control, pathological or pharmacological treated conditions.

## 5. Functional connectome of the striatal microcircuit

Network analysis at the microcircuit level started recently [9, 43, 51]. Here, we describe the analysis of the striatal microcircuit. The first step to get a functional connectome is to define the nodes and a specific functional connection between them. In the striatum, cell assemblies were analyzed at histological level by taking the neurons as the nodes and the coactivity between neurons as the functional links [9]. However, other functional links are being assayed and a consistency between different approaches is being observed (unpublished). In the present case, each neuron is functionally connected with other neurons when they are active during the same minimal time window. At the end of the recording the neural network or, more specifically, the functional connectome is obtained. The next step is to measure the parameters of the connectome to answer what kind of topology the network has and whether there are neurons with particular connections. To determine whether the network has random connectivity or regular connectivity, two main parameters are used: the characteristic path length (L) and the clustering coefficient (C) [41]. These two metrics were then compared with models of random and regular networks. A main observation was that the striatal connectome has neither random nor regular connectivity, but has properties of both at an intermediate point [9] known as "small-world" networks, which belong to the set of complex networks [53]. Other property found for the striatal microcircuit was free-scale, i.e., the same properties are maintained at different temporal and spatial scales. This property seen in the striatal microcircuit [9], has also been found in somatosensory, auditory, and primary motor cortices microcircuits [50, 51]. To determine the scale-free property, the distribution of connections P(k) was obtained. Next, we observed that this distribution could be fitted to a power law function indicating that it is a scale-free network [54]: there are few neurons with many connections and many neurons with few connections. In other words, there are some particular neurons that have the most connections in the network, so-called "hub neurons," that play

a key role in the connectivity: they provide the physical substrate to have mutual innervation and connect different ensembles. Since Sherrington description, this property is necessary to alternate activity between ensembles. Even if a network is scale-free, it does not mean that has a modular organization as hypothesized for brain microcircuits [55–57]. Thus, a next question to answer was whether the connectome is constituted hierarchically, in a modular way. This was shown to be the case because the distribution of clustering coefficients C(k) of the nodes were also well fitted to a power law function [58]. Thus, a modular architecture has been seen in the striatal microcircuit [9], as well as in the somatosensory and auditory cortices microcircuits [51]. In summary, the striatal microcircuit connectome is a complex network, with "small-world" and scale-free properties forming hierarchical modules. In addition, network analysis allowed to describe with single neuron resolution some particular neurons identified by their connectivity as "hub neurons."

## 6. Key role of hub neurons

Since some neurons can be identified by their particular connectivity as hub neurons, the next step is to know what class of neurons they are. There are evidences that some hub neurons are interneurons (unpublished). The functional connectome in the striatum was observed in an area of about 1 $mm^2$ with hub neurons connecting many neurons at distances larger than 500 μm, while synapses between projection neurons can only be found at a distances less than 100 μm [16–18]. Indeed, only interneurons can extend their axons to connect neurons at distances up to 1 mm. This inference was confirmed by whole cell patch clamp recordings of some hub neurons identifying fast-spiking (PV), low-threshold spiking (LTS) and cholinergic interneurons (ACh) [9, 36]. Transgenic mice in which optogenetic stimulation activates a particular neural population [59] shows that hub neurons connect with different groups of neurons perhaps inducing the coactivity that underlies network states, and therefore, are responsible for their alternation. However, further experiments using transgenic animals and optogenetics are needed to identify the classes of neurons that form striatal modular circuits and under what conditions.

## 7. Pathological changes in the functional connectome

To know the role of cortical afferents in the striatal microcircuit, we used decorticated striatal slices. The decorticated striatal microcircuit preserves some active network states conforming temporal sequences, albeit alternation between ensembles is greatly reduced. In fact, network analysis revealed a loss of active hub neurons [9]. This result suggested that cortical afferents maintain privileged connections with striatal hub neurons, probably interneurons, to organize striatal activity.

Similarly, in the rodent model of Parkinson's disease, there is a significant loss of hub active neurons. Not strangely, the Parkinsonian striatal microcircuit shows less transitions between network states, confirming that one larger neuronal ensemble becomes dominant [8, 38],

recruiting the majority of active neurons [9]. These results indicate that the majority of hub neurons are functionally eliminated during dopamine deprivation and a remaining set of hub neurons help to maintain the dominant state. This is supported by studies that suggest a breakdown of corticostriatal connectivity during Parkinson's disease [60, 61]. Other studies show potentiation of synaptic currents of some classes of interneurons [62, 63]. It is also known that drugs as L-DOPA or nicotine could return the microcircuit to control conditions [38, 39], implying that hub neurons are not physically eliminated during dopamine deprivation. The role of the interneurons has been recently addressed [9], since previous studies did not consider them [64].

In the L-DOPA-induced dyskinesia model, the microcircuit keeps showing a significant increase in activity with respect to the controls. In fact, more functional connections and even more hub neurons, and more transitions between network states correlate with the increase of prokinetic gamma rhythms described in dyskinetic subjects [65]. The "return" of hub neurons confirmed that they were not physically but only functionally removed during the Parkinsonian state. Their reappearance during dyskinesia indicates that they are necessary in the striatal microcircuit to produce movements. Nevertheless, the dyskinetic striatal microcircuit exhibited a loss of hierarchical modules [9]. This finding could be seen as a correlate of the excessive disordered movements present in dyskinetic subjects.

## 8. Primitive process in the striatal microcircuit

It is well known that pyramidal neurons connect preferentially to interneuron pools and not to the projections neurons or motoneurons in the spinal cord [66]. Thus, the present findings suggest a principle of general organization, which can explain how the same cell assemblies could be used in different behaviors depending on the activation of certain hub neurons by the cortical commands. According to Huyck [31, 67], any neural model at the microcircuit level should fulfill a primitive process: to have an input that selects the operators, apply operators on the operands, store results, and generate an output. In the striatum, the working hypothesis would be that input coming from the cortex selects the interneurons—operators—and apply their operations on the projections neurons—operands—the information is stored and striatal output is generated, the result of the whole operation: activation and inhibition of agonist and antagonist muscles in sequence (**Figure 1**). This hypothesis implies that cortical afferents organize groups of interneurons to induce the activity in a similar way as in the processes described by the cognitive theory of Allen Newel [31, 67]. Being the hub neurons the operators and the projections neurons the operands, the process of alternating network states, the sequences and the reverberations could underlie the actions of minimal motor routines [29]. Each microcircuit could be associated with others to produce different actions, depending on the group of operators activated by the cortex. This would explain the changes in the dynamics of the microcircuit and the functional relations between their neurons [68]. Now, there is technology to record several simultaneous neurons *in vivo* at the microcircuit level to study the functional connectome under different behaviors. Thus, the multiple combinations of connections being described at the cellular level may make sense.

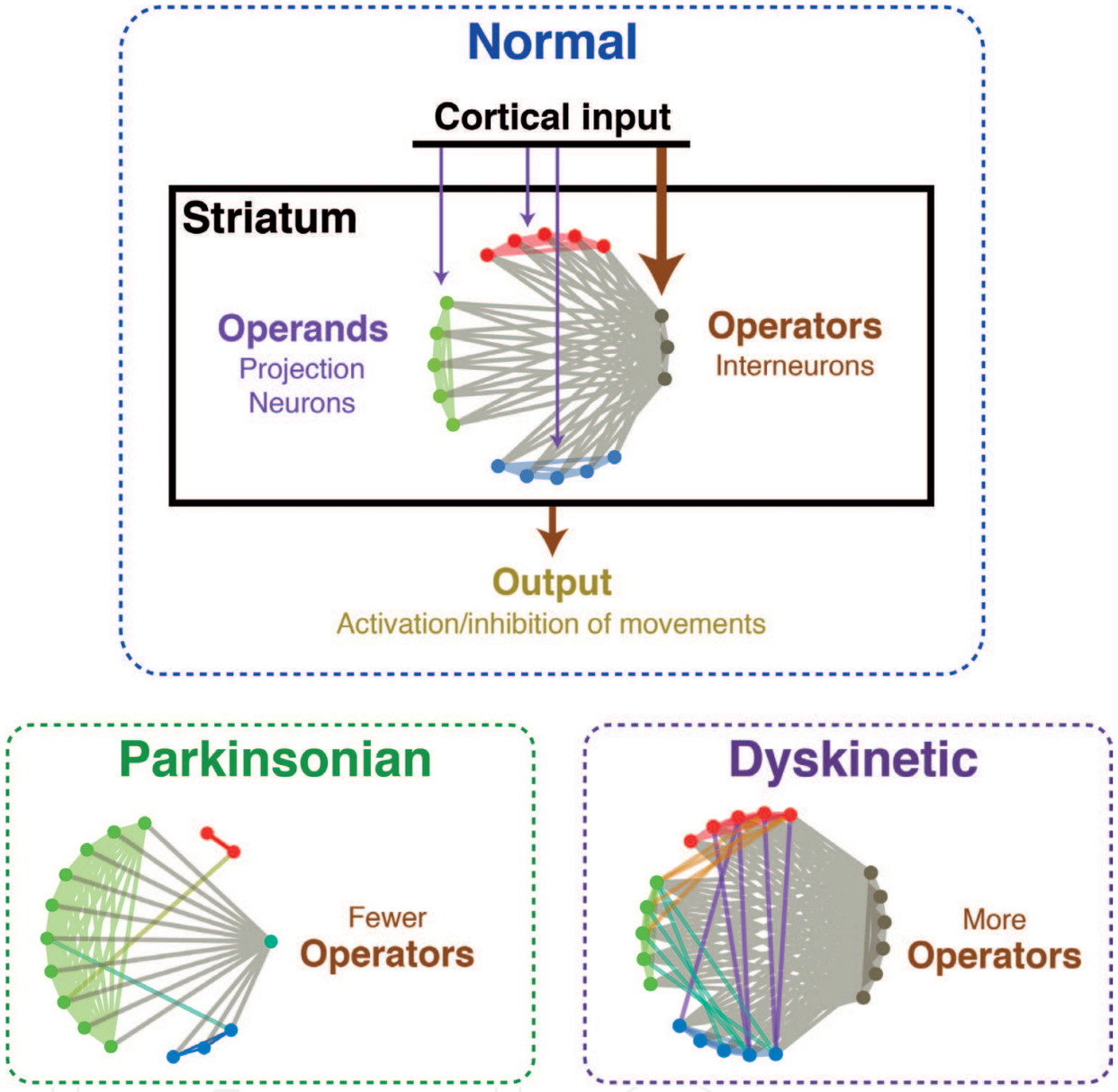


**Figure 1.** New model of cell assemblies activation in the striatal microcircuit.

## 9. Final conclusions

In this chapter, studies at the microcircuit histological level are remarked. There are many problems when jumping from the cellular/molecular level to the systems level without knowing what happens at microcircuit level when trying to understand how the brain works. The output seen at the systems level is the product of the microcircuits specific to each area, not of particular neurons or synapses; assumed in the cellular/molecular paradigm. To bridge the gap, analysis and perspectives from the microcircuit level are necessary [43, 69].

Using network analysis at the microcircuit level, it is observed that the striatal microcircuit has a set of highly connected hub neurons, which communicate efficiently with different neural

groups. These groups underlie the neural states that alternate and reverberate. The structure of the striatal connectome has "small-world" properties, is scale-free and has a hierarchical modular organization, as other complex networks seen in nature. The cortical commands use the hub neurons to organize the dynamics of the circuit and given the distances between the neurons that conform a neuronal ensemble, it can be inferred that hub neurons should be long axon neurons, that is, interneurons. After striatal decortication or during the 6-OHDA model of Parkinson's disease hub neurons decrease significantly and as a consequence, the transitions between ensembles and circuit dynamics decrease, reflecting metaphorically hypokinesia and rigidity, and supporting previous studies that show a breakdown of corticostriatal communication in Parkinsonian subjects. In L-DOPA-induced dyskinesia, the opposite happens: the number of hub neurons and the transitions between ensembles increase. However, this occurs together with a loss of the hierarchical architecture. This also is reminiscent of the signs seen in dyskinetic subjects: uncoordinated involuntary movements. Finally, we conclude that the pathophysiology and pharmacology of the nervous system can be studied in living tissue at histological scale by using simultaneous recording and network analysis.

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