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Review

Oscillations in the basal ganglia in Parkinson's disease: Role of the striatum

Mariano Andrés Belluscio, Mariela Verónica Escande, Ettel Keifman, Luis Alberto Riquelme, Mario Gustavo Murer *, Camila Lidia Zold

Neural Circuit Physiology Lab, Systems Neuroscience Group, Department of Physiology and Biophysics, School of Medicine, University of Buenos Aires, 2155 Paraguay St, Buenos Aires 1121, Argentina

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ABSTRACT

In animal models of Parkinson's disease cortical oscillations entrain abnormal synchronous rhythms in basal ganglia neurons. A mechanism accounting for these oscillations should: (i) vindicate a key role of the striatum in Parkinson's disease pathophysiology by considering how alterations in striatal physiology may gate cortico-basal ganglia oscillations; (ii) explain why abnormal basal ganglia oscillations span the whole frequency range of oscillations observed in the normal frontal cortex; and (iii) provide insight into how these oscillations may relate to akinesia. Here we update our proposal that striatal projection neurons (medium spiny neurons) behave as dopamine-dependent filters which normally do not allow the propagation of resting cortical activity through the basal ganglia circuit. After chronic dopamine depletion, cortical oscillations would spread through more excitable medium spiny neurons to entrain the whole indirect pathway. Therefore, akinesia may not be directly related to oscillations, but to the inability of medium spiny neurons to separate salient pieces of cortical information from the ongoing cortical rhythms they are embedded in. We propose that uncontrolled translation of ongoing cortical activity into no-go signals in the indirect pathway induces akinesia. Thus, oscillations would be an extreme manifestation of this excessive permeability of medium spiny neurons to cortical input in advanced stages of Parkinson's disease.

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Models trying to account for the emergence of parkinsonian symptoms can be roughly divided into two types. One type points to a failure in the signals involved in action selection and initiation, focusing on alterations in the temporal and spatial interactions between competing "go" and "no-go" signals. These alterations would make no-go signals to prevail when actions are attempted in the parkinsonian state [1–3]. The other type of model looks at changes in neuronal activity during resting behavioral states. According to this type of model, chronic dopamine depletion sets the basal ganglia network in a fixed functional status which continuously sustains akinesia and/or turns the network impermeable to environmental and internal drive [4–7]. Although these

* Corresponding author. Tel.: +54 11 5950 9500x2137.
E-mail addresses: mbellu@fmed.uba.ar (M.A. Belluscio), mvescande@gmail.com (M.V. Escande), neurofis@fmed.uba.ar (L.A. Riquelme), gmurer@fmed.uba.ar (M.G. Murer), czold@fmed.uba.ar (C.L. Zold).

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two model types are not mutually exclusive, most research in the field has taken one or the other point of view. Here we will focus on the mechanisms underlying abnormal spontaneous neuronal activity in a rodent model of Parkinson's disease, the 6-hydroxydopamine-lesioned rat.

Neuronal activity underlying parkinsonian symptoms: rate or pattern?

During the last decades, two main kinds of abnormal resting activity have been described in the basal ganglia of animal models of Parkinson's disease and in patients: (i) changes in firing pattern [4,5]; and (ii) emergence of oscillations and increased synchrony within and between structures [6,8]. These "rate" and "oscillation/synchronization" models have often been perceived as opposed to each other [9,10].

According to the rate model the symptoms of Parkinson's disease stem from opposite changes in the activity of striatal projection neurons belonging to the direct and indirect pathways. Pioneering 2-deoxyglucose studies performed by Crossman and coworkers in non-human primates revealed a hyperactivity of the indirect pathway and a hypoactivity of the direct pathway in MPTP-induced parkinsonism [11–13]. Moreover, they showed the opposite effect on the indirect pathway in a model of chorea induced by GABA receptor antagonist administration into the striatum [14,15]. Their results led them to propose a central role of the subthalamic nucleus in both conditions [15]. In parallel, the excitatory nature of subthalamic neurons [4,16] and the segregation of D1 and D2 dopamine receptors in direct- and indirect-pathway striatal projection neurons [17] were discovered. Findings showing that nigrostriatal lesions result in diminished expression of substance P and augmented expression of enkephalin in direct- and indirect-pathway neurons respectively provided further support to the striatal imbalance hypothesis [17,18]. The demonstration that lesioning the subthalamic nucleus reverses akinesia in parkinsonian monkeys provided a causal link between subthalamic nucleus activity and the symptoms of Parkinson's disease [19], further supporting the rate model.

However, neuronal recordings performed in rat and primate models failed to convincingly demonstrate the expected rate changes in basal ganglia neurons. Instead, studies have consistently found more irregular or bursty firing patterns, excessive oscillatory activity and enhanced interneuronal correlations both in MPTP-lesioned monkeys and 6-OHDA-lesioned rats. Burbaud et al. [20] reported an increase in firing rate and burstiness in the substantia nigra pars reticulata (the main basal ganglia output nuclei in rats) of rats with nigrostriatal lesions induced by 6-OHDA, while others showed changes in firing pattern without any modification in firing rate [21]. Similarly, firing rate may increase, decrease or remain unchanged in the globus pallidus (the rodent homologous to the external pallidum of primates) of 6-OHDA rats, while firing pattern is severely disturbed [22–24]. Parallel results were obtained in striatal projection recipient neurons of parkinsonian monkeys (i.e., internal and external pallidal segments), where a rate change in the direction predicted by the rate model is reported by some studies but not others, whereas changes in firing pattern are almost invariably reported [25–30]. Consistently with the rate model, an increased firing rate has been reported in the subthalamic nucleus in rat and primate models of Parkinson's disease. However, this hyperactivity is also accompanied by profound changes in firing pattern [31,32]. Furthermore, presumably abnormal firing patterns have been reported in the subthalamic nucleus and both pallidal segments in parkinsonian patients [33–40]. Though, to what extent changes observed in patients are truly abnormal is debatable given the unavailability of appropriate controls. Overall, the view that firing pattern alterations are more pronounced and more consequential than firing rate changes prevails.

Several studies have examined in more detail these firing pattern alterations. Some investigations focused their attention on spatial aspects of neuronal activity organization, like interneuronal correlations, while others emphasized the importance of changes occurring in the time domain. Correlated activity is very limited in neurons downstream of the striatum in normal animals, but it increases dramatically in the parkinsonian state, both in rats [32,41] and non-human primates [28,29,42–45], and has also been reported in patients [37,46]. In the time domain, oscillatory activity has been detected in spike trains in patients [35–39,46,47], and found to be increased in both rat [24,48–52] and primate [29,42,45] models of the disease. These oscillations span a wide band of frequencies ranging from <2 Hz, through rhythms similar to tremor frequency in patients (3–8 Hz), to beta (13–30 Hz) (see citations above). Though it is important to mention that some frequency bands seem more represented than others and this seems to depend on the behavioral state.

Correlated activity can be computed directly from spike trains corresponding to pairs of neurons, or can be inferred from examining the temporal relationship between spiking activity in individual neurons and oscillations in the local field potential (phase locking). Because local field potential oscillations speak about the degree of organization of afferent activity, synchronization of spike trains to local field potential oscillations provides information about both the temporal and spatial organization of neuronal activity, i.e., oscillatory synchronization. Exaggerated oscillatory synchronization has been reported in animal models and patients, at different frequency bands, in the globus pallidus, subthallamic nucleus, and basal ganglia output nuclei [32,37,40,41,45,47,51,52]. Importantly, spike trains recorded in one of these structures (i.e., subthalamic nucleus) may show an enhanced synchronization with local field potential oscillations recorded in another structure (i.e., globus pallidus), which means that widespread neuronal networks are oscillating synchronously. Indeed, oscillatory synchronization extends beyond the basal ganglia nuclei since spike trains are abnormally entrained to cortical local field potential oscillations in 6-hydroxydopamine-lesioned rats [24,32,49,50,52–56], MPTP-lesioned primates [45,57] and patients [39].

Models about the origin of these observed abnormal patterns of activity need to take into account the widespread temporal and spatial organization of neuronal activity in cortico-basal ganglia networks.

Oscillatory synchronization in Parkinson's disease: basal ganglia pacemaker or basal ganglia entrainment by external oscillators?

Different models have been put forward to explain the origin of excessive oscillatory synchronization in the basal ganglia in Parkinson's disease. An early model suggested that the isolated globus pallidus – subthalamic nucleus network may behave as an abnormal pacemaker under chronic dopamine depletion. Organotypic cultures containing globus pallidus and subthalamic nucleus display low frequency locally generated synchronous oscillations [58]. Although some acute slice physiology studies suggested that the isolated globus pallidus and subthalamic nucleus may generate oscillations in certain conditions, the fact that oscillations in these structures are synchronized to cortical oscillations in vivo (see citations above) led the field to update the internal basal ganglia pacemaker viewpoint. In this context, oscillations in the pallido-subthalamic network are proposed to spread and amplify thanks to a "fast loop" involving basal ganglia output to thalamus and cortex, and direct cortical projections to the subthalamic nucleus ("hyperdirect pathway") [59–61].