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Review

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

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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.

Contents

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

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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].

This model has some weak points. One is that it doesn't take into account the role of the striatum. Most researchers in the field would almost undoubtedly agree on the striatum involvement in parkinsonian akinesia. Numerous studies have shown that locally increasing dopamine availability in the striatum diminish akinesia in animal models of the disease [62–64]. Moreover, studies performed in slices have made a strong case that chronic dopamine depletion induces marked alterations in corticostriatal synaptic plasticity [65,66], to the point of providing causal evidence linking these changes to movement impairments [67]. Finally, recent studies provided causal evidence supporting the striatal imbalance hypothesis. By using optogenetics, Kravitz et al. [68] have shown that selectively increasing the activity of striatal direct or indirect pathway neurons in normal mice has opposite effects on motor activity as predicted by rate models of basal ganglia functional organization, and that increasing activity of direct pathway neurons relieves akinesia in a mouse model of Parkinson's disease. Some studies using DREADDs have also shown opposite effects on motor output by selectively inhibiting or exciting striatal direct and indirect pathway neurons in normal rodents ([69]; but see, [70]). The other weak point of the "fast loop" model is that no clear "striatum independent mechanism" has been proposed to explain how abnormal behavior emerges in Parkinson's disease.

Thus, the striatum stands as the key to a unifying theory of basal ganglia dysfunction in Parkinson's disease. In Tseng et al. [53] we have proposed a mechanism through which the striatum may contribute to the oscillations occurring downstream in basal ganglia nuclei. Even in resting conditions, the thalamo-cortical system generates oscillations of different frequencies, whose span is usually inversely related to frequency (lower frequencies are synchronized across wider areas) [71,72]. Despite the massive cortical and thalamic projections to the striatum, thalamo-cortical rhythms are weakly represented in basal ganglia spike trains in normal conditions [24,49,50,53,56,73,74]. Our proposal was that chronic dopamine depletion allows the spreading of thalamo-cortical rhythms through more excitable striatal "medium spiny" projection neurons (MSNs), resulting in an abnormal over-representation of these rhythms across the basal ganglia circuit.

Medium spiny neurons as dopamine-dependent high pass filters: subthreshold representation of cortical oscillations in medium spiny neurons

Tseng et al. [53] have studied membrane potential oscillations in MSNs under anesthesia, in control and 6-OHDA-lesioned rats. The use of anesthesia allows the study of spontaneous network dynamics resembling those seen in physiological conditions while minimizing confounds inherent to behavioral states, like peripheral feedback. Two main resting brain states can be recorded under anesthesia: (i) a "slow wave" state characterized by 0.5–2 Hz oscillations in the cortical local field potential, reflecting synchronous oscillatory activity in a majority of cortical and thalamic neurons; and (ii) episodes of cortical "activation" during which cortical neurons fire steadily and the local field potential is dominated by higher frequency rhythms of smaller amplitude [72,75]. Recordings of cortical ensembles show that the slow waves can be dissected into epochs of pronounced and nearly absent cortical activity [72,76]. This macroscopic oscillation is produced by synchronous alternations between "up" and "down" states in cortical pyramidal neurons. On the other hand, pyramidal neurons show a persistently depolarized membrane potential in the activated state [72,75]. Importantly, it has been proposed that similar network dynamics underlie the depolarized cortical state during the slow wave up state and the activated condition [75]. Thus, anesthesia can be seen as a tool to study basal ganglia behavior under different patterns of cortical activity.

Striatal MSNs' activity is also characterized by rhythmic fluctuations in membrane potential between a highly hyperpolarized quiescent "down" state and a depolarized "up" state [77]. Since MSNs fire action potentials only during the up state, these plateau depolarizations are perceived as enabling events that allow information processing through cortex-basal ganglia circuits [78]. Importantly, besides been a hallmark of sleep and anesthesia, up states are also seen in MSNs in the awake animal, although these depolarizing events are temporally disorganized compared to slow wave sleep [79].

Several studies have demonstrated that striatal up states depend on cortical inputs. MSNs' membrane potential remains in a continuous down state in striatal slices, and up states disappear when the striatum is deprived of afferent input [77,78]. However, whether a persistent cortical input is required to sustain striatal up states [76,80–82], or intrinsic mechanisms can sustain striatal up states after cessation of cortical input [83,84] remains under debate. We have shown that MSNs' membrane potential replicates the activity of cortical ensembles [76,82]. Medium spiny neurons' membrane potential follows the activity of cortical multiunit activity, and cortical electrical stimulation induces an abrupt stop of cortical and striatal up states which is followed by a synchronized resumption of up states in both structures [76,80]. Moreover, it has been proposed that NMDA receptor endows MSNs with intrinsic bistability, but our in vivo data [81] and a computational modeling study [85] show that NMDA receptors contribute to MSN depolarization and firing during up states without changing up state duration. Overall, the data are consistent with striatal up states being a subthreshold representation of firing activity in afferent ensembles.

Using the 6-OHDA lesion rat model of Parkinson's disease, we have demonstrated that a subgroup of MSNs shows a more depolarized up state and an increased firing probability in rats with nigrostriatal lesions (Fig. 1) [53]. As a result, cortical slow waves are over-represented in spike trains of striatal neurons (see also [56,86]). Of note, normal MSNs show a very low firing probability, thanks to potassium voltage-dependent currents becoming active at the up state membrane potential [77] and the influence of local inhibitory circuits [87,88].

Several mechanisms may contribute to increasing the activity of MSNs projecting to the globus pallidus in the parkinsonian condition [86]. Corticostriatal neurons are not hyperactive in animal models of the disease [89,90] and indirect pathway MSNs show a lower spine density in rodents with chronic dopamine depletion [91,92], but corticostriatal synapses show a deficit in LTD [65,66] which may result in enhanced efficacy of the remaining synapses. Moreover, changes in dendritic excitability [91,93] and reduced feedback inhibition [94,95] may enhance the influence of synapses located in distal parts of the dendritic tree on firing probability. Overall, these changes may lock striatal cell assemblies into an over-synchronized state [96] with enhanced influence on downstream structures.

Over-representation of spontaneous cortico-striatal rhythms in the parkinsonian globus pallidus

As we have already stated, influential models of basal ganglia pathophysiology propose that chronic dopamine depletion induces an increased gain of the indirect pathway in the parkinsonian state [4,5]. According to this rate model, hyperactivity in MSNs expressing the D2 receptor (D2-MSNs) would lead to globus pallidus hypoactivity and subthalamic nucleus hyperactivity. However, several studies show modest modifications of globus pallidus firing rate accompanied by robust changes in firing pattern in experimental models of Parkinson's disease and in patients [22,27,28,50,97–100]. This has been considered one of the

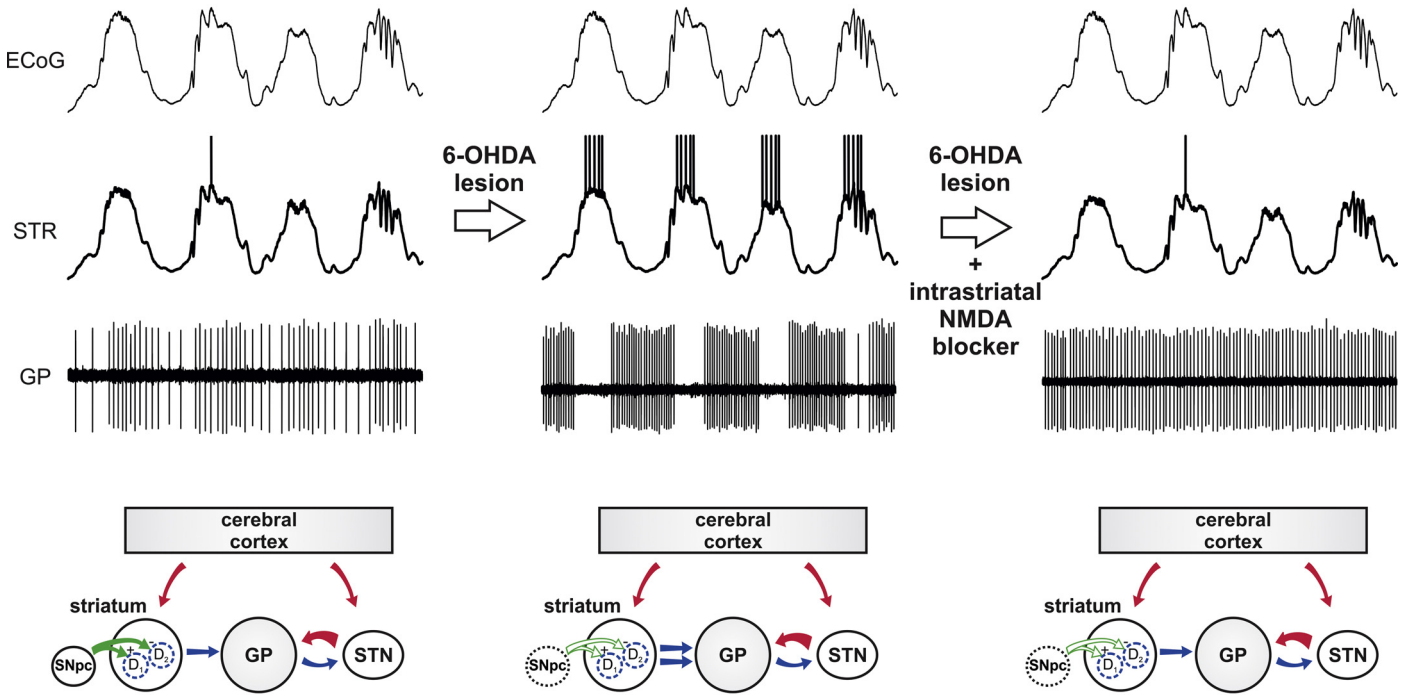

Fig. 1. Effect of an intrastriatal NMDA receptor blocker on the abnormal low frequency oscillations induced by chronic dopamine depletion in the cortico-striato-pallidal circuit. Diagram of the activity recorded in the cortex (ECoG), striatum (STR) and globus pallidus (GP) under slow wave activity. Under normal conditions, MSNs' membrane potential oscillates between up and down states mimicking cortical activity, but globus pallidus neurons show a slight increase in firing during the cortical up state (left). In contrast, up states become more depolarized and MSNs become hyperactive in 6-OHDA lesion rats. Synchronously to the striatal activation, globus pallidus neurons decrease their activity under cortical slow waves thus inducing abnormal low frequency oscillations in chronic dopamine depletion (middle). This abnormal oscillations can be abolished by administrating an NMDA antagonist in the striatum, which restores striatal activity to its normal levels and eliminates globus pallidus inverse phase relationship to the cortical slow waves (right).

main drawbacks of the classical basal ganglia model, and has lead to questioning the functional significance of the indirect pathway [2,97,101,102].

Previous studies have shown that in Parkinson's disease models, anomalous low frequency oscillations are coordinated along striatal, pallidal, subthalamic and basal ganglia output neurons [50,51], and between neurons in all these structures and the frontal cortex [24,49,50,53]. Because our results suggested an over-representation of cortical oscillations in MSNs' spike trains after chronic dopamine depletion, we investigated whether the spontaneous firing pattern of globus pallidus neurons is shaped by cortico-striatal oscillations in the parkinsonian condition.

In control animals, cortical output increases are accompanied by a rise in pallidal activity [50,100,103]. In contrast, a high proportion of pallidal neurons exhibits periodic inhibitions of spiking activity coupled to the activation of striatal and cortical neurons during slow waves in the 6-OHDA rats (Fig. 1) [50,51]. We have proposed that this abnormal cortico-pallidal coupling induced by dopamine depletion is due to a switch in cortical control over the pallidum, from excitatory (cortico-subthalamo-pallidal) to inhibitory (cortico-striato-pallidal) [50,100,104] (Fig. 1).

To provide causal evidence linking striatal activity to pallidal inhibition during slow waves, we investigated whether enhanced firing of MSNs during the up state promotes the anomalous synchronization between the cortex and globus pallidus in the parkinsonian condition. We first determined the NMDA receptor contribution to striatal spiking activity in control and dopamine depleted animals. Using reverse microdialysis combined with intracellular recordings in vivo, we demonstrated that NMDA receptors blockade reduces up states amplitude inducing a lower firing probability of individual neurons in normal animals [81]. Furthermore, local infusion of an NMDA antagonist reduced striatal hyperactivity in 6-OHDA rats, suggesting that tonic stimulation of NMDA receptors contributes to sustain an increased striatal output activity in rats with chronic nigrostriatal lesion (Fig. 1) [56]. Then, we tested whether intrastriatal administration of an NMDA antagonist blocked anti-phase synchronization of pallidal spike trains with cortical rhythms in 6-OHDA rats, and found that it completely abolished low frequency oscillations in the globus pallidus neurons showing inverse phase relationship with cortical slow waves (Figs. 1 and 2).

Besides the over-representation of low frequency oscillations under chronic dopamine depletion, several studies have found abnormal cortico-pallidal oscillatory synchronization spanning a broad frequency range in animal models of Parkinson's disease and in patients [41,45,50,56,57]. We then asked if striatal hyperactivity was responsible for the spreading of these higher frequency oscillations observed downstream in the basal ganglia circuit in 6-OHDA lesion rats. To do this, we broke down frontal cortex activity in complementary frequency bands and investigated the effect of an intrastriatal NMDA receptor blocker on the emergence of these oscillations and on pallidal neuron coupling to these rhythms [56]. It is important to mention that the NMDA receptor contribution to striatal hyperactivity was observed both in the slow wave and the activated cortical states. Blocking NMDA receptor-dependent striatal output had distinct frequency dependent effects on the abnormal oscillatory activity observed in the globus pallidus. As we have already mentioned, the NMDA antagonist completely abolished inverse phase relationship of pallidal neurons to the cortical slow waves. In addition, 2.5–5 Hz rhythms became non significant and 10–20 Hz oscillations were clearly attenuated (Fig. 2). On the other hand, high beta oscillations (20–40 Hz) were only slightly reduced (Fig. 2). These results show that resting cortical rhythms spread abnormally to downstream basal ganglia nuclei through the striatum in dopamine depleted animals. It is

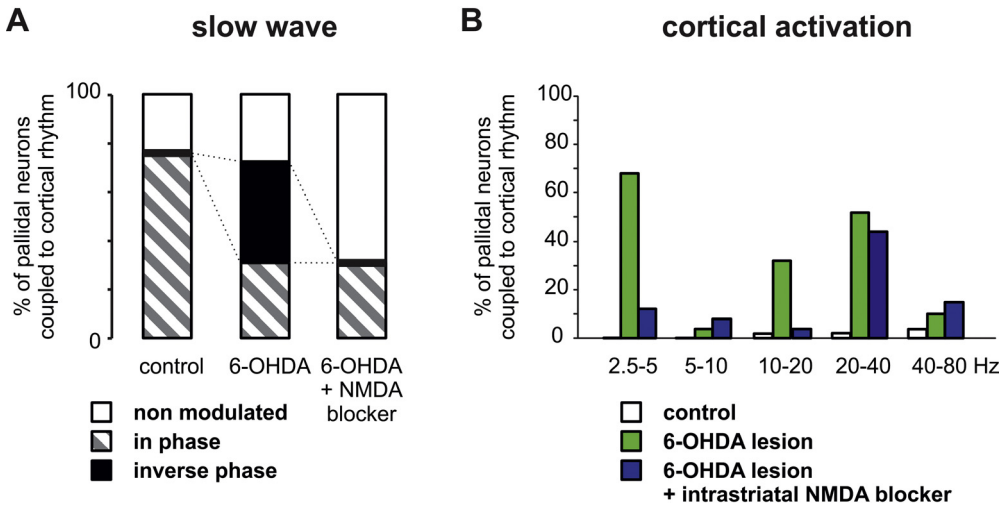

Fig. 2. Frequency dependent effect of striatal NMDA receptor blockade on anomalous cortico-pallidal synchronization under different brain states. (A) Pathological inverse phase synchronization between cortex and globus pallidus during slow waves is significantly decreased after intrastriatal administration of an NMDA antagonist in parkinsonian rats. (B) Control animals show no significant synchronization to cortical rhythms during episodes of cortical activation. Chronic dopamine depletion induces abnormal synchronous cortico-pallidal activity in a wide frequency range. Intrastriatal NMDA receptor blocker had a frequency dependent effect on these abnormal synchronized activity. An NMDA antagonist clearly attenuated 2.5–5 Hz and 10–20 Hz oscillations in 6-OHDA lesion rats.

important to mention that the NMDA receptor blocker had no effect on globus pallidus spontaneous activity in control animals [56]. This suggests that spontaneous pallidal activity depends on intrinsic pacemaker mechanisms and on excitatory influence from the subthalamic nucleus in the intact brain (Fig. 1).

Overall, these results demonstrate that an increased gain of the cortico-striato-pallidal axis drives functional changes in globus pallidus spontaneous activity in experimental parkinsonism. Rather than a decreased firing rate, as predicted by the rate model, the main change induced by dopamine depletion is an exaggerated transmission of cortical information in a wide range of frequencies to downstream structures. This spreading of abnormal oscillations would stem from a reduced "filtering" striatal capacity in dopamine depleted animals. The fact that an NMDA receptor blocker had distinct frequency dependent effects suggests that low and high frequency oscillations stem from partially different mechanisms. This view partially reconciles the rate and oscillation/synchronization models since the abnormal oscillations observed downstream the striatum would be the result of striatal hyperactivity.

Possible mechanisms leading to the strengthening of the cortico-striato-pallidal network

The effect of dopamine over MSNs varies depending on the currents available at the up or down state [105]. Under normal conditions, dopamine D2 receptors impede up state transitions and inhibit NMDA dependent currents reducing the positive feedback loop between NMDA receptors activation and up state amplitude in MSNs [106,107]. Furthermore, D2 receptor activation favors endocannabinoid release and long term depression through multiple mechanisms, including the inhibition of striatal cholinergic interneurons [65,108]. Therefore, under normal conditions, D2 receptor signaling favors feedback loops opposing depolarization and excitatory synaptic drive (Fig. 3).

Chronic dopamine depletion induces severe alterations in cortico-striatal plasticity. In parkinsonian animals, long term depression is absent in indirect pathway MSNs and experimental protocols that normally induce long term depression induce potentiation instead [65,66]. Moreover, when D2 receptor stimulation is reduced in the parkinsonian condition, the positive feedback between the NMDA receptor and up state depolarization gets freed from dopamine control (Fig. 3). Thus, the lack of dopamine in parkinsonian animals would lead to a cascade of events resulting in a more depolarized membrane potential, increased long term potentiation and consolidation of fixed routes of information flow through the cortico-strtiato-pallidal axis (Fig. 3).

Changes in local inhibitory mechanisms may also contribute to enhance transmission of cortical oscillations through D2-MSNs after dopamine depletion. Feedback inhibition among MSNs, which is subject to dopamine regulated short term plasticity [109,110], is markedly reduced after dopamine depletion [94,95]. On the contrary, inhibition by striatal GABAergic interneurons is conserved or enhanced in rodent models of Parkinson's disease [111].

Additional hypothesis about how the striatum may contribute to the emergence of oscillatory synchronization in Parkinson's disease

Alternative views regarding striatal contribution to the emergence of oscillatory synchronization in Parkinson's disease point to: (i) local generation or exacerbation of oscillations and (ii) striatal triggering of oscillations in non-striatal circuits.

In normal conditions, the striatum presents oscillatory local field potential activity in a wide range of frequencies, from slow to fast rhythms [112–115]. The proposed role for those oscillations is to facilitate the interactions between cell assemblies. There is an increase in oscillatory activity in the striatum after acute dopamine depletion in mice [116], after pharmacological blockade of dopamine receptors with haloperidol in rats [117], and after chronic nigrostriatal lesion in rats [54,118], across a wide frequency range, including delta, theta, beta and low gamma frequencies (see citations above).

Different studies have addressed how the striatum itself could generate abnormal oscillatory activity. Using a computational model, McCarthy et al. [119] proposed that a local circuit of interconnected MSNs can generate beta activity in the striatum. The locally generated rhythm displayed by the striatal network specifically acquired a frequency in the beta range because of the interaction between the M-current (a non-inactivating potassium

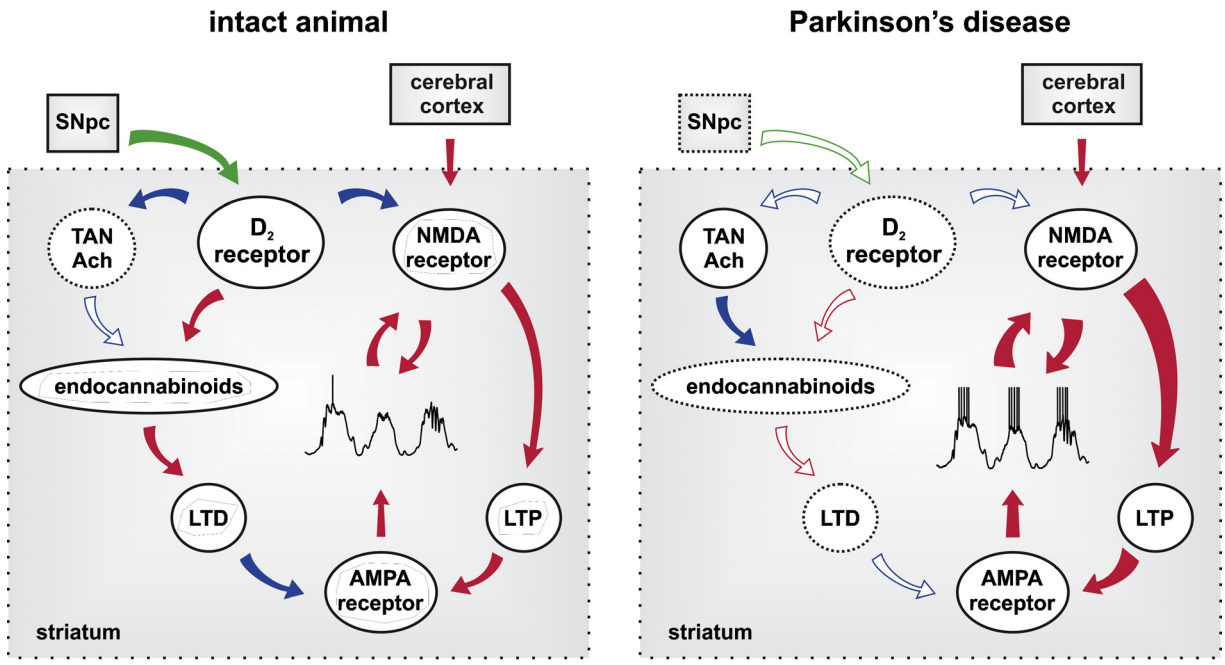

Fig. 3. Proposed mechanisms for striatal circuit changes induced in Parkinson's disease. NMDA receptor activation promotes a positive feedback loop leading to MSNs depolarization directly, and through LTP processes. Under normal conditions D2 receptors regulate this positive loop by: (i) reducing glutamate release from corticostriatal terminals; (ii) decreasing NMDA receptor currents; and (iii) promoting endocannabinoid release and LTD directly and through inhibiting cholinergic interneurons (left). Lack of D2 receptors activation, as in Parkinson's disease, leads to an imbalance of these control loops resulting in a higher membrane potential and increased firing of D2-MSN, presumably through excessive NMDA receptor activation and LTP (right) (see also [133]).

current) and $GABA_A$ currents. Oscillations were generated when the inhibitory GABAergic currents reduce the potassium M-current, inducing a post-inhibitory increase in excitability. The strength of the oscillations depended on the magnitude of the M-current, which is known to be regulated by acetylcholine in MSNs [120]. Importantly, striatal cholinergic interneurons display reduced autoinhibition through M4 receptors [121], are intrinsically more excitable [122] and show enhanced synchrony [43] in animal models of Parkinson's disease, resulting in an increased local cholinergic tone [123]. Thus, the authors modeled dopamine depletion as an increase in local cholinergic tone, which resulted in increased beta power and a more persistent oscillation pattern over time. Coincident with the changes in beta activity they also show an increase in firing rate in the MSN population, which through enhanced local GABAergic inhibition further potentiated beta power in the network. A shortcoming of this model is that the

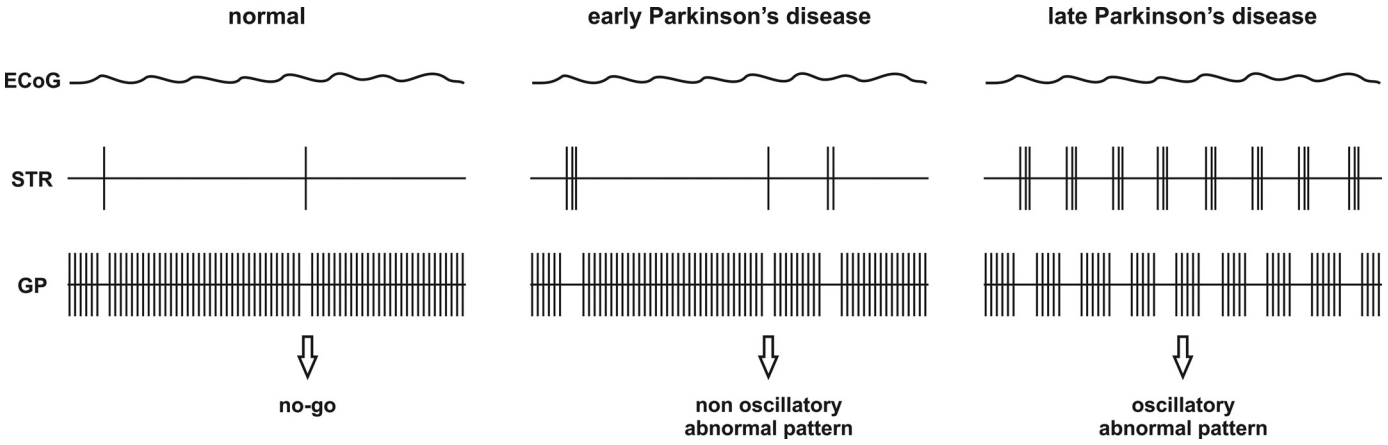

Fig. 4. Schematic representation of the emergence of altered firing patterns and oscillatory synchronization in the basal ganglia according to the "spreading" model. Left: In normal conditions the firing of D2-MSNs is tightly controlled and does not clearly follow specific events in the cortical local field potential (ECoG), which is mainly represented as subthreshold modulations of the MSN membrane potential [76,82]. Firing in D2-MSNs would produce short interruptions in the tonic activity of globus pallidus neurons, which are currently believed to stop unwanted actions [1,3]. Middle: the excitability of D2-MSNs is proposed to increase even after partial degeneration of the nigrostriatal pathway. This would increase the probability of translating into striatal firing cortical events which are unrelated to current environmental signals and internal needs. Pallidal activity would show more frequent interruptions resulting in altered firing patterns, especially when attempting actions, but the temporal and spatial organization of these interruptions would not necessarily result in widespread oscillatory synchronization. Importantly, due to the vast convergent/divergent nature of the striatopallidal projection it is proposed that, even a small change of excitability in D2-MSNs may alter pallidal firing pattern. Right: In advanced stages of the disease D2-MSNs would translate into firing the ongoing oscillatory activity of the cortex. Although the increase in firing in individual MSNs may be small even after complete ablation of the nigrostriatal pathway, the vast convergence of the striatopallidal pathway may warrant a tight coupling between pallidal firing and cortical oscillations. Of note, in this scheme the spike train is mean to represent a cluster of MSNs rather than a single neuron. The frequency and properties of the abnormal oscillations are proposed to depend on behavioral state. Because there is an inverse relationship between frequency and spatial span of oscillations in the cortex, clusters of pallidal and subthalamic neurons may oscillate synchronously at different frequencies when high frequency rhythms dominate [47].

chloride equilibrium potential should be around −80 mV for the inhibition to have a significant effect on the M-current. To support the model, they experimentally show that infusion of carbachol into the striatum increases striatal beta oscillations in normal rodents. Moreover, others have found that cholinergic stimulation enhances synchronization of striatal neurons in slices [124]. However, whether an enhanced cholinergic tone is necessary and sufficient to sustain synchronous oscillation in animal models of Parkinson's disease has not been proved yet.

Another model focusing on striatal generation of abnormal synchrony relayed on changes induced by chronic dopamine depletion on feed-forward inhibition mediated by fast spiking interneurons [125]. Fast spiking interneurons inhibit both direct- and indirect-pathway MSNs but they are more likely to synapse on direct-pathway MSNs in normal animals. After chronic dopamine depletion there is an increase in the connectivity between fast spiking interneurons and D2-MSNs, demonstrated both functionally and structurally, which elevates GABAergic input onto these cells. Based on these data, Gittis et al. [125] developed a computational model which suggests that increased inhibition by fast spiking interneurons is sufficient to increase the level of synchrony in the D2-MSN population. However, direct experimental evidence implicating fast spiking interneurons in oscillatory synchronization in Parkinson's disease has not been provided yet. Fast spiking interneurons show enhanced phase locking to low gamma local field activity in 6-OHDA rats, but not to other frequency bands (delta, theta, low beta), which are also enhanced after dopamine depletion [118]. Moreover, fast spiking interneurons do not show changes in excitability or spontaneous activity after dopamine depletion [111]. According to Dehorter et al. [111] enhanced inhibition of MSNs in parkinsonism stem from the "low threshold spike" striatal GABAergic interneurons, which display an abnormal, intrinsically generated bursting activity in slices from 6-OHDA rats. Further studies are necessary to determine whether enhanced inhibition from low threshold spike interneurons can induce oscillations in striatal output.

Alternative computational models suggest that the degree of tonic striatal inhibition over the globus pallidus determines whether the pallido-subthalamic network will show irregular asynchronous firing or rhythmic synchronous activity patterns. Terman et al., [126] have simulated a non-patterned striatal inhibition as a hyperpolarizing current in pallidal cells, and examined the effects of changing this tonic inhibition on pallido-subthalamic interactions. Based on their simulations, they proposed that elevated striatal tonic inhibition accompanied by reduced local intrapallidal inhibition make the pallido-subthalamic network enter into a synchronous oscillatory mode. However, intrapallidal inhibition is not decreased, but increased, in rat 6-OHDA rats [127]. Another model developed by Kumar et al., [128] explored whether oscillations can be induced in a large scale pallido-subthalamic network without changing intrapallidal or pallido-subthalamic connectivity. Each pallidal neuron received input from hundreds of striatal neurons, which were independently simulated as a Poisson spike train generator. In this network an increase in firing rate of the striatal population is sufficient to induce oscillations in the pallido-subthalamic network. Thus, non-patterned striatal inhibition can trigger oscillations in the pallido-subthalamic network even in the absence of local changes in synaptic connectivity.

Finally, according to a computational model proposed by Leblois et al. [2], cortico-basal ganglia oscillations may result from an imbalance between the opposite influences of the direct pathway and the hyperdirect pathway on basal ganglia output nuclei neurons. Striatal dopamine depletion would result in a diminished activity in the direct pathway, which by itself would impair action selection capacity. Oscillatory synchronization in the "fast loop" would only emerge after extreme dopamine depletion, when activity in the direct pathway is too small to counterbalance the effect of the excitatory hyperdirect pathway on basal ganglia output. One prediction of this model is that decreasing the activity in the striatum would trigger oscillations in the pallido-subthalamic network in normal animals. However, but reducing striatal activity in normal animals does not induce abnormal oscillations in the globus pallidus [56]. Because at the time of the publication the degree of segregation between the direct and indirect pathways was under debate, the role of the indirect pathway was not analyzed. It remains to be determined whether silencing of the direct pathway interacts with other factors like a strengthening of the cortico-striato-pallidal axis to induce oscillatory synchronization in the basal ganglia.

Concluding remarks

Hypotheses about the mechanisms underlying the emergence of abnormal oscillatory synchronization in the basal ganglia in Parkinson's disease need to take into account the role played by the striatum, whose involvement in the pathophysiology of Parkinson's disease remains undisputed. Our findings show how hyperactive striatal neurons may allow the propagation of cortical rhythms through the cortico-striato-pallidal axis. Spreading through the striatum involves oscillations of up to 20 Hz, thus encompassing most of the over-represented frequencies observed in animal models and patients. Importantly, we propose an explanation about how alterations in synaptic plasticity and excitability in indirect pathways MSNs [65,66,91,93] may account for this exaggerated spreading of cortical oscillations (Fig. 3). Thus, our hypothesis grounds on well established striatal adaptations and partially reconciles rate and oscillation/synchronization models of Parkinson's disease.

Alternative hypotheses based on computational modeling have addressed how adaptations in the striatal circuit may specifically generate beta oscillations [119,125,128]. However, cortico-pallidal coupling in the high beta range (>20 Hz) is partially resistant to interventions reducing striatal hyperactivity [56]. The fact that high beta cortico-pallidal coupling is limited to neurons showing abnormal oscillations in lower frequency ranges [56] points to a common causal mechanism. Chronic striatal hyperactivity may induce long term adaptations in the pallido-subthalamic network which may turn it into a beta pacemaker. Additionally, decreased activity in the direct pathway may contribute to beta rhythm generation [2]. Further interventions on striatal hyperactivity allowing a more profound and widespread control of indirect pathway MSNs than that obtained in our studies [56] is necessary to fully understand striatal contribution to high beta oscillations.

Whether oscillations are causally related to akinesia is under debate [2,129,130]. The dominant frequency of abnormal oscillations varies across species and in the same individual/animal it varies along time [29,42,47,55,100,131]. Moreover, oscillatory synchronization seems to appear late during the course of the disease as indicated by experiments in animal models [100,131,132]. Hypotheses dealing with the origin of oscillatory synchronization in Parkinson's disease should be able to explain the apparent dissociation between the symptoms of the disease and the frequency of oscillations or even their presence. We propose that it is not the specific frequency of oscillations but the general mechanism underlying them what produces akinesia. Striatal medium spiny neurons behave as dopamine-dependent filters which normally don't allow the propagation of resting cortical activity through the basal ganglia. We propose that it is the uncontrolled translation of ongoing cortical activity into no-go signals in the indirect pathway what induces akinesia (Fig. 4). This uncontrolled propagation takes the form of alterations in firing

pattern in nuclei located downstream the striatum, whose specific properties may depend on how much has advanced the degenerative process [2,100]. In this context, oscillations would be an extreme manifestation of this excessive permeability of MSNs and the specific frequency of oscillations would depend on the frequency content in afferent ongoing activity.

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