

## Review

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# Significance and Translational Value of High-Frequency Cortico-Basal Ganglia Oscillations in Parkinson's Disease

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**Abstract.** The mechanisms and significance of basal ganglia oscillations is a fundamental research question engaging both clinical and basic investigators. In Parkinson's disease (PD), neural activity in basal ganglia nuclei is characterized by oscillatory patterns that are believed to disrupt the dynamic processing of movement-related information and thus generate motor symptoms. Beta-band oscillations associated with hypokinetic states have been reviewed in several excellent previous articles. Here we focus on faster oscillatory phenomena that have been reported in association with a diverse range of motor states. We review the occurrence of different types of fast oscillations and the evidence supporting their pathophysiological role. We also provide a general discussion on the definition, possible mechanisms, and translational value of synchronized oscillations of different frequencies in cortico-basal ganglia structures. Revealing how oscillatory phenomena are caused and spread in cortico-basal ganglia-thalamocortical networks will offer a key to unlock the neural codes of both motor and non-motor symptoms in PD. In preclinical therapeutic research, recording of oscillatory neural activities holds the promise to unravel mechanisms of action of current and future treatments.

**Keywords:** Pathophysiology, movement disorders, bradykinesia, dyskinesia, animal models, cortex, thalamus

## INTRODUCTION

There are several clinico-pathological subtypes of Parkinson's disease (PD), but all cases share the typical motor symptoms that lead to diagnosis (poverty and slowness of movement, resting tremor, muscle rigidity, postural problems). These symptoms are mainly caused by dopamine (DA) deficiency in the striatum, which in turn depends on the degeneration of nigrostriatal DA projections. Parkinsonian

motor symptoms are greatly ameliorated by L-DOPA, a DA precursor that can cross the blood-brain barrier. Unfortunately, L-DOPA pharmacotherapy causes complications that limit its utility. Already within five years of treatment, 30–50% of the patients develop L-DOPA-induced dyskinesia (LID), abnormal involuntary movements that are often debilitating [1]. Moreover, L-DOPA (and other dopaminergic treatments for PD) can induce non-motor complications, such as psychosis (hallucinations, delusion, excitement), a complication particularly common in older PD patients and often associated with cognitive deterioration (reviewed in Cenci and Odin [2]). While LID is elicited by dysregulated DA transmission in

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the motor striatum [3], and possibly also in the sensorimotor cortex [4], the emergence of psychosis in PD has been linked to altered neurotransmission in limbic brain regions [5].

There is vast consensus that both the primary symptoms of PD and the complications of L-DOPA therapy depend on altered information processing in cortico-basal ganglia-thalamocortical pathways [3–6], but the underlying neural mechanisms remain to be elucidated. Clues of major importance came from the discovery of powerful oscillations of the local field potential (LFP) within deep basal ganglia nuclei in PD patients undergoing functional neurosurgery [7, 8]. In particular, LFP recordings in patients “off” dopaminergic medications revealed prominent oscillations in a broad beta band (8–30 Hz; reviewed in Hammond et al. [9]). Similar oscillations were detected also in dopamine-denervated animals (reviewed in [6, 9, 10]). The exaggerated activity in the beta band was found to be suppressed by dopaminergic drugs, and the degree of drug-induced improvement in bradykinesia and rigidity was found to correlate with the degree of suppression of beta band oscillations in both the STN and cortex (reviewed in [9, 10]). Based on these observations it was hypothesized that, in the untreated parkinsonian state, the basal ganglia engage in abnormally synchronised oscillatory activities in the beta band. Exaggerated oscillatory synchronisation of neuronal activity may disturb information processing in cortico-basal ganglia loops and therefore contribute to both motor and cognitive problems in PD [11].

By now, basal ganglia beta band oscillations in PD (and in animal models thereof) have been the subject of a vast scientific literature (e.g., [8–18]). The present review article primarily focuses on faster oscillations with frequencies spanning the higher end of the gamma band, in particular we discuss the high-frequency oscillations found within a narrow frequency interval of the gamma band that have recently been associated with hyperkinetic states. Our interest in this area has been fuelled by a serendipitous observation made in 6-OHDA-lesioned rats treated with L-DOPA. When L-DOPA elicits dyskinesia in this animal model, the expression of abnormal involuntary movements (AIMs) coincides with the appearance of gamma oscillations in a narrow frequency-band around 80 Hz within motor cortical and basal ganglia circuits [19, 20]. Importantly, the same type of oscillations have now been detected in motor cortex and subthalamic nucleus in PD patients affected by LID [21] (Fig. 1). Notably,

these narrowband gamma oscillations are quite distinct from the increased gamma activities detected during normal voluntary movement [22]. Indeed, the latter type of gamma-activity cannot be regarded as proper oscillations at a well-defined frequency, but rather appear to be non-rhythmic activities manifesting in a much broader range of frequencies [19–21, 23–25].

In addition to the LID-associated oscillations, narrowband high-frequency oscillations in the 100–200 Hz range have recently been observed in limbic nodes of the cortico-basal ganglia system upon pharmacologic treatment with psychotomimetic drugs and in disturbed cognitive states [26, 27]. These recent data suggest a more general pathophysiological role of high-frequency oscillations in conditions involving cortico-basal ganglia dysfunction [23]. In addition to these two types of high-frequency oscillations, dopamine-dependent oscillatory activity of even higher frequencies (above 200 Hz) have been reported in the STN [28] and the GPi [29] in PD patients.

Mechanistically, narrowband oscillations of the LFP are thought to reflect rhythmic synchronizations of transmembrane currents among a local population of neurons. Synchronization appears spontaneously in neural networks even without rhythmic external input. This is a consequence of resonances that naturally appear in any dynamic system endowed with feedback mechanisms when the feedback tends to amplify certain frequencies and suppress others. Feedback mechanisms exist at the level of individual neurons (e.g., voltage-dependent ion channels), at the microcircuit level (e.g., reciprocally connected interneurons), in the interaction between cell populations (e.g., the excitation-inhibition balance between glutamatergic and GABA-ergic cells), and in the interaction between connected brain structures (e.g., the cortico-basal ganglia-thalamic loop). Since resonances are readily and spontaneously appearing in any feedback-controlled system, it is possible that some LFP oscillations are merely epiphenomena without significant consequences to neural information processing, even when they are strongly correlated to specific behavioral states. However, there is considerable and growing support for the notion that LFP oscillations play an important role in both normal brain function and brain pathologies [23, 30–33].

In this review article, we discuss cortico-basal ganglia high-frequency narrowband oscillations from the following perspectives: 1) methodological aspects

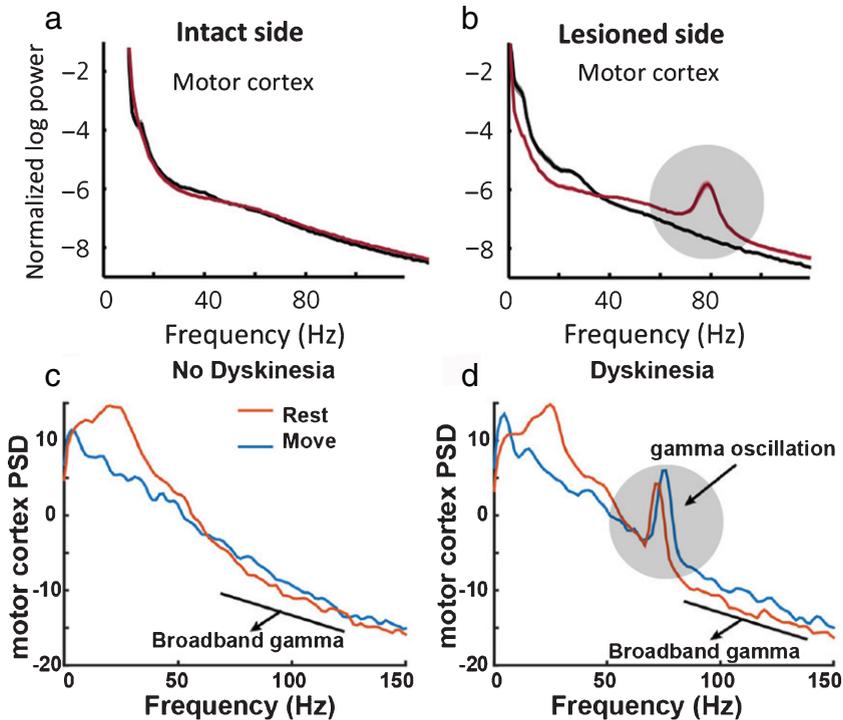


Fig. 1. Levodopa-induced dyskinesia is strongly associated with 80Hz cortical oscillations in both Parkinson's disease patients and in rodent models of the disease. This gives unique opportunities to search for the network mechanism underlying motor symptoms. (a-b) Rat data (ON/OFF levodopa denoted in red/black). (c-d) Human data (ON and OFF levodopa represented in (c) and (d), respectively). Note the striking similarity of the high-frequency oscillations associated with dyskinesia in rats/humans and the difference of these narrowband resonant oscillations compared to physiological broadband gamma. Figures adapted from Halje et al. and Swann et al. [19, 21]).

and taxonomy, 2) principal experimental findings, 3) possible underlying mechanisms, and 4) translational importance.

#### *On how to measure oscillatory activities in the brain*

Measures of oscillatory neuronal activities can be obtained using a range of techniques offering different spatiotemporal resolutions and sensitivities.

Scalp electroencephalography (EEG) is the most widely used method to probe oscillatory electrical activities in the human brain. For steady-state oscillatory activity in the cortex/thalamocortical system, EEG can be regarded as a spatially and temporally smoothed version of the local field potential [34]. This smoothing arises mainly because the signal in each EEG electrode correspond to the integrated LFPs over several  $\text{cm}^2$ , but also because of the electrical filtering properties of the tissues located between the electrodes and the brain [34].

Non-invasive recordings of brain electrical activity can also be obtained using magnetoencephalography

(MEG), which records magnetic fields generated by the electrical currents in the brain. By measuring the magnetic rather than the electric component of the field created by neuronal currents, MEG is expected to improve both the spatial and temporal resolution of the recorded signals, although this is not always the case [35].

Electrocorticography (ECoG) utilizes high-density subdural electrodes to record electrical activity directly from the surface of the cerebral cortex. This technique can enable recordings of higher frequency components with a high spatial resolution and a significantly improved signal-to-noise, essentially resembling the signal of cortical LFPs [36]. Compared to non-invasive approaches, ECoG recordings are also less susceptible to muscle artefacts.

To record from deep brain nuclei, invasive recording techniques are however required. The shape and size of the recording probe, as well as the electronics used for signal acquisition, can be optimized for the study of single unit activity or LFPs, and trade-off solutions are needed to record both phenomena [37]. Local field potentials (LFPs) are often the preferred

measure to assess the degree of neuronal synchronization in a certain volume of brain tissue. Despite being a scalar quantity, the LFP is the potential difference between two points in space, and therefore depends on the length and direction of the vector going between the two measuring points. Hence, the measured LFP crucially depends on the spatial arrangement of the electrodes. The LFP is thought to mainly reflect the local synchronization of dendritic currents induced by excitatory and inhibitory synaptic inputs to the population of cells surrounding each electrode [38]. Spiking events in the nearby cell population are considered to give only a minor contribution to the recorded LFP signal in most situations, but because action potentials of cells are in many cases entrained to the LFP, field potentials are nevertheless frequently used as proxy for local cell activity [39]. However, this approximation may not always be valid because LFPs can also be generated by very large networks of sparsely connected neurons [23, 40]. Because all neuronal activity that influences the potential difference between the electrode pair will contribute to the signal, it is of key importance to use electrode pairs that are arranged in a meaningful way with respect to the cytoarchitecture (for a detailed discussion see [40]). A good strategy is to implant multiple electrodes into the structure of interest, and then create differential measures between all possible pairs of electrodes. With this approach, one can make sure that the current sources creating the field are indeed local (in which case, different pairs of electrodes would show different signals) [41]. Even when LFPs are recorded with the best possible methods, it will be difficult to interpret the significance of differences in LFP amplitudes between structures, since differences in the cytoarchitectonic arrangement of neurons in relation to the recording electrodes, and properties of the extracellular space, will ultimately define the recorded signal [40].

When the same microelectrodes are used to record both unit activity and LFP, the recorded voltage signal is split into a high-frequency and low-frequency part to separate the two signals. Note however, that this separation is not perfect and for higher frequencies of LFP-oscillations a spectral leakage of spiking activity may occur [42]. Although less explored in the context of dyskinesia, unit activity has been shown to provide an independent state description even when restricting the analysis to firing rate changes [20]. Large differences in the physical size of the electrode (e.g., macroelectrodes used for deep-brain stimulation

vs. microelectrodes) could influence the capacity to detect certain high-frequency oscillations that are spatially more confined. This could for example explain why 110–160 Hz oscillations are a common finding in micro- but not macroelectrode recordings. For a more extensive discussion on extracellular recording methods we refer the reader to more specific reviews on this subject (e.g., [39, 43]).

#### *On the taxonomy of high-frequency oscillations*

The classical EEG nomenclature was established in the 1930s to describe the dominant, slow waves below  $\sim 35$  Hz that are directly visible in unprocessed EEG traces (delta, theta, alpha, and beta). The term gamma was instead applied to indistinct fluctuations faster than 35 Hz [44]. Gamma oscillations are orders of magnitude weaker than the lower-frequency oscillations and their existence in the neocortex was established first in the 1990s, with the discovery of 40 Hz oscillations in visual cortex. In the last two decades, a plethora of even faster oscillations have been found in EEG and LFP recordings, and these are often collectively called high-frequency oscillations (HFOs) or fast/high gamma oscillations. There is unfortunately no consensus on how to classify and name these phenomena either within or beyond the classical gamma band, or where the border to the “high” gamma range lies. Thus, for the purpose of this review, we need to clarify the definitions and classifications applied to different types of HFOs. First, we exclude phenomena that are not proper oscillations. A proper oscillation has a well-defined frequency, like an auditory tone, as opposed to a non-rhythmic signal, which is more comparable to a hissing sound (there are methods that can reliably distinguish between the two cases, see for example Wen et al. [45]). Second, we distinguish between different HFO phenomena based on the following questions, which we suggest may serve as a good basis for an HFO taxonomy in this context: (1) Is the oscillation transient or is it continuous? (2) In which anatomical structures does it occur? (3) Is it related to or modulated by a specific behavioral, pathological or pharmacological state? (4) In what frequency range does it occur?

In this review, we will also consider any oscillation faster than the classical 40 Hz gamma oscillation to be an HFO. Note that this definition deliberately includes so called finely-tuned gamma (FTG) below 100 Hz as an HFO phenomenon (cf. [46]).

## EXPERIMENTAL FINDINGS

In conjunction with neuromodulatory treatment applying deep-brain stimulation (DBS), recordings of LFPs have been obtained from implanted brain structures in human patients during the early postoperative period. This procedure offers an unusual opportunity to obtain invasive recordings from deep structures in the human brain. Under such conditions, a number of studies involving different patient groups have characterized neuronal activity, e.g., in GPi [8, 29, 47–49], STN [8, 28, 48–52], pedunculo-pontine nucleus (PPN) [53], and thalamus [54, 55]. HFOs were observed in several of these recordings, and broadly, the observed HFOs can be placed in three categories based on their frequency: 60–90 Hz, 120–160 Hz and >200 Hz.

### *60–90 Hz oscillations*

Basal ganglia LFP oscillations in the 60–90 Hz range was first reported by Brown et al. [8], who found a ~70 Hz peak in STN and GPi of PD patients after levodopa treatment. This phenomenon was further investigated in follow-up studies (see e.g., [49, 50–56]). Interestingly, in a limited number of studies, recordings from deep structures were also combined with EEG/MEG. These recordings suggested the presence of cortical oscillations in this frequency range that emerges after L-DOPA treatment, and which may be functionally coupled to oscillations in deeper structures since the recorded LFP signals were reported to be coherent and displaying relatively constant phase differences over prolonged time periods [48, 49, 57, 58]. From these studies in patients, it has however been difficult to establish whether 60–90 Hz oscillations are associated with the beneficial pro-kinetic effect of L-DOPA therapy or if they instead indicate the transition to a pathological hyperkinetic state, manifesting as dyskinetic movements [56]. In general, it has been concluded that increased HFO amplitude – at least in the deep basal ganglia nuclei – is primarily associated with increased motor activity and/or a state of arousal that may enable motor activity (for a review on this subject see [46]).

In motor cortex, on the other hand, evidence for a physiological role of HFOs in this frequency range is not as convincing. While investigations using non-invasive recording technologies, such as electroencephalography and magnetoencephalography (EEG/MEG; [59–61]), or intracranial electrocorticography (ECoG) recordings in epilepsy patients

[62–64] have shown that high-frequency oscillations in the 60–90 Hz frequency band can indeed be found in the motor cortex in association with movements, these findings relate only to brief episodes of movement-related increases in gamma power rather than sustained oscillatory activity. Thus, in healthy individuals, activity in this band does not seem to be characterized by clear sustained rhythms with a well-defined frequency but rather by a transient gamma band power increase that occur during movement onset.

In an alternative view, a pathological role of this HFO in motor cortex was instead first proposed by Halje et al. [19], based on experiments using microwire recordings from motor cortex and dorsal striatum in unilaterally 6-OHDA lesioned rats. The authors found prominent HFOs around 80 Hz that were only present in the lesioned hemisphere during levodopa-induced dyskinesia (LID) [19]. In this seminal study, it was also found that the topical application of an antagonist to dopamine type 1 receptor (D1R) onto the cortical surface was sufficient to break the oscillation and concomitantly suppress dyskinesia.

The relevance of this finding to PD was recently demonstrated by Swann and colleagues as a result of the first long-term recordings performed in dyskinetic patients using a combined DBS-electrocorticography (ECoG) device [21]. Importantly, chronically implantable bidirectional electrodes help circumvent experimental caveats associated with the early postoperative phase following DBS-electrode implantation. This phase is not ideally suited for brain recordings, as symptoms are often significantly reduced following electrode implantation (i.e., even when no current is passed through the electrode) – indicating that the symptomatic relief in this case is primarily related to the lesion inflicted by the electrode [65]. By recording neuronal activity over motor cortical areas and in the STN for 12 months, Swann and colleagues could present convincing evidence that, in PD patients, dyskinesia goes hand in hand with the same type of motor cortical HFOs observed in the rat model of LID. A detailed analysis of HFOs was also performed in the STN, prompting the conclusion that this narrow-band HFO is principally pathological rather than pro-kinetic. More specifically, the oscillation was found to be minimally affected by voluntary movements while its presence proved to be a reliable biomarker of dyskinesia. This result is at variance with previous studies

that have associated gamma oscillations with the beneficial pro-kinetic effect of levodopa therapy [50, 56]. Such an interpretation likely stems from the increased oscillation amplitude often observed in the STN following levodopa-treatment, and sometimes also in other parts of the cortico-basal ganglia-thalamic loop (also in non-PD subjects) in direct association with motor actions, taking the form of a transient event-related synchronization of neuronal activity (reviewed in Jenkinson et al. 2013, [46]; see also [66]). However, these movement-modulated oscillations may not be functionally equivalent to the long-lasting oscillations found in dyskinetic states, even if the two phenomena may have similar spectral contents. Indeed, such a distinction has been proposed also for beta-band oscillations by a recent study in parkinsonian monkeys, showing that the duration of oscillatory episodes in the beta-band is critical to predict pathological motor states [18].

To further clarify the neurophysiological role of narrow-band HFOs in LID, several studies have further explored this phenomenon in rodents [20, 24, 67, 68]. A study by Dupre and colleagues showed that the oscillations develop together with dyskinetic symptoms with daily levodopa administration during a one-week priming period [24]. During this period, the abnormal involuntary movements became gradually more severe. They also showed that similar oscillations can be induced in L-DOPA-primed rats by independently stimulating dopamine receptors of the D1 or D2 type [24]. At the level of LFPs, these oscillations are particularly strong in corticostriatal circuits and are also observed both in the globus pallidus (corresponding to the external pallidal segment in primates) and in motor nuclei of the thalamus, but are typically somewhat less pronounced in the STN compared to the findings obtained in patients [21]. Overall, LFP oscillatory activities, including HFOs around 80 Hz, can be used as very robust electrophysiological biomarkers to classify parkinsonian and dyskinetic states in the 6-OHDA rodent model, as shown in Tamte et al. [20]. In this study the authors quantitatively compared the spectral components in eight different brain structures to assess which components most reliably predicted brain states associated with untreated parkinsonism versus dyskinesia, with or without additional pharmacological treatment. Classification performance (as estimated by fitting of a Gaussian mixture model to the data [20]) improved steadily with inclusion of a broader spectral content and/or addition of brain structures. Interestingly, HFOs around 80 Hz in the rostral

forelimb area (a premotor/supplementary motor area in rodents) were a particularly useful physiological marker of LID [20] (which also appears consistent with the findings by Swann et al. [21]).

#### *110–160 Hz oscillations*

HFOs in the 110–160 Hz range have been studied intensely in the hippocampus of healthy animals (for a review, see [69]). Recently, similar HFOs were shown by Brys et al. to be widespread in the basal ganglia and motor cortex of unilaterally 6-OHDA lesioned animals, being present on both sides of the brain (and with relatively increase in power following L-DOPA treatment) [70]. A general feature of these oscillations is that their amplitude is modulated by the phase of a much slower oscillation in the theta range (5–10 Hz) as indicated by measurements of phase-amplitude coupling. In the hippocampus literature, an increase of theta-HFO coupling has been shown to correlate with higher cognitive demands and brain states associated to memory processing [42, 71]. The role of theta-HFO coupling in this PD model is currently unknown, but both L-DOPA and antidyskinetic treatment with 5-HT<sub>1A</sub> agonists alter the amplitude and frequency of this type of HFO, as well as its coupling to lower frequencies [70].

Intriguingly, a separate line of research has shown that acute administration of psychotomimetic/psychedelic drugs to healthy animals often induce similar HFOs in the prefrontal cortex and the nucleus accumbens [26, 27], structures belonging to the limbic part of the cortico-basal ganglia-thalamic loop. It is therefore tempting to speculate that psychotic symptoms can arise as a consequence of aberrant HFOs (or the brain state associated with these oscillations) in the cognitive and limbic loops of the cortico-basal ganglia network in a similar way as motor symptoms may result from oscillations in sensorimotor loops. This could also explain why some PD patients experience episodes of psychotic symptoms as a side effect of levodopa treatment (reviewed [2]). Therefore, these HFOs may be important to further study in the context of non-motor PD symptoms and neuropsychiatric side effects of current medications [70].

#### *Oscillations above 200 Hz*

LFP oscillations above 200 Hz were first observed in the parkinsonian brain by Foffani et al. [28], who reported distinctive peaks at  $319 \pm 33$  Hz in

the STN of levodopa-treated PD patients. Moreover, Wang et al. [72] detected HFOs above 200 Hz in part of the STN in PD patients off medications, reporting that the power of such oscillations was negatively correlated with akinesia and rigidity scores [54]. Importantly, although HFOs above 200 Hz are often disregarded as leaked spiking activity of a few neurons, Wang et al. [72] were able to show that this oscillation was not directly caused by spiking activity (since the high-frequency power increase remained also after subtraction of all visible unit activity) and could thus be regarded as a proper LFP phenomenon generated by a large population of neurons.

The frequency of these HFOs is strongly modulated by dopamine, with a slowing by about 60 Hz in the dopamine-depleted state ( $265 \pm 33$  Hz; [73]). The amplitude is positively correlated to dopamine tone and it is also enhanced during voluntary movement, especially in the L-DOPA-treated state [28, 73]. This pattern of amplitude modulation is very similar to the modulation pattern of the 70–80 Hz HFOs observed in the STN of PD patients [48]. Several studies have also reported modulation of the HFO amplitude by the phase of beta oscillations (phase-amplitude coupling; [15, 73, 74]) and to other frequencies below the beta band [72]. An oscillation with very similar characteristics has also been reported in GPi [29].

With respect to motor signs, it has been reported that UPDRS scores of akinesia/rigidity were negatively correlated with HFO amplitude, i.e., the more impaired patients had weaker HFOs [72]. It is however not clear if HFOs may have a direct impact on the genesis of parkinsonian motor features or are, instead, modulated by them.

Recently, this very high frequency HFO has been proposed as a marker for resting tremor. In particular, Hirschmann et al. [75], showed that HFOs above 200 Hz are positively correlated with tremor at rest (i.e., HFOs are stronger during tremor), although in this study it was not possible to reliably distinguish between resting tremor and voluntary movement.

### **POSSIBLE MECHANISMS UNDERLYING THE GENERATION OF HIGH-FREQUENCY OSCILLATIONS**

In the parkinsonian brain, dopaminergic denervation results in a multitude of neurochemical, physiological, and cellular changes that could potentially make both cortex and striatum prone to produce oscillations at a network-level, leading to the emergence

of different types of HFOs. Oscillations can however emerge in a wide range of highly interconnected networks and it remains to be explored which cellular components are predominantly responsible for the tuning of network oscillatory properties. Thus, while it is at present not possible to pinpoint the key drivers of HFOs, some general candidate mechanisms appear worth mentioning.

First, the excitability of certain groups of neurons may change because of altered expression levels of voltage-sensitive or shunting ion channels, or other changes in intrinsic membrane properties [76], which can in turn alter oscillatory properties (akin to what has been reported for lower oscillation frequencies [17]). Second, the synaptic weight of critical connections may change [77, 78]. This increased coupling can facilitate synchronization of independently oscillating neurons, similar to how coupled oscillators synchronize in mechanical systems. Third, the electrical coupling between neurons, in particular fast-spiking interneurons, may change because of altered gap-junction protein composition and/or gap-junction density [13, 79, 80]. Fourth, the interaction between principal cells and interneurons and/or the balance of excitatory/inhibitory activity may alter the resonance properties of the network [81–83].

For HFOs in the 110–160 Hz range, information regarding the underlying mechanisms may also be obtained from characterizing the pharmacological profiles of different drugs known to induce HFOs of this type. A particularly interesting aspect is that psychotomimetic drugs known to act on different receptor systems—for example on either 5-HT<sub>2A</sub> or NMDA receptors have been found to induce very similar HFO activities in animals [26, 84]. It has been proposed that a partial depression of NMDA-receptor function could be a common underlying mechanism [85]. According to some reports based on local pharmacological manipulations, it is sufficient to interfere with NMDA signaling in one node of the network to induce high-frequency oscillations throughout the limbic loop. Thus, applying an NMDA-antagonist in PFC, hippocampus or nucleus accumbens [86, 87] induces the same LFP oscillations as does a systemic administration of the same drug [84, 88]. Interestingly the extended amygdala network has also been shown to have an intrinsic propensity to oscillate at these frequencies (typically 130–160 Hz), indicating that broadly distributed limbic circuits may be involved in the phenomenon [89]. Relatively few recordings of LFP oscillations in this frequency range have been reported involving non-limbic circuits

following pharmacological NMDA-depression, but at least primary motor cortex and parts of the basal ganglia circuitry have been shown to also display this type of activity [70, 90], whereas, for example visual cortex, does not seem to share this propensity (at least in rodents) [91]. For a more extensive overview on the effects of NMDA-antagonist treatment on oscillatory activity, we would like to refer the reader to the review by Hunt and Kasicki [92].

**POSSIBLE MECHANISMS UNDERLYING THE PROPAGATION OF HIGH-FREQUENCY OSCILLATIONS**

While intrinsic network changes induced by the disease and its pharmacotherapy, may contribute to pushing the network towards a state that can uphold HFOs in certain brain structures, changes in inter-structure connectivity could, in parallel, facilitate the transmission of oscillations of certain frequencies between different brain structures, [68, 93, 94]. It

has, however, proven difficult to establish if oscillatory activity can indeed spread from one structure to another and which structures would be the principle drivers in this scenario. We here limit our discussion to three alternative models. These conceptual viewpoints are not entirely mutually exclusive but each emphasize somewhat different mechanistic components.

*The flowchart model*

It is often presumed that the physiological signaling within the basal ganglia can be directly deduced from the anatomical connectivity in the sense that activity in one structure will directly influence the next downstream brain structure via synaptic excitation or inhibition. According to this view, oscillatory activity is expected to be passed on from one structure to the next in a step-wise chain of events (Fig. 2a). Indeed, in studies of gamma oscillations in cortico-basal ganglia circuits, cross-structure interactions

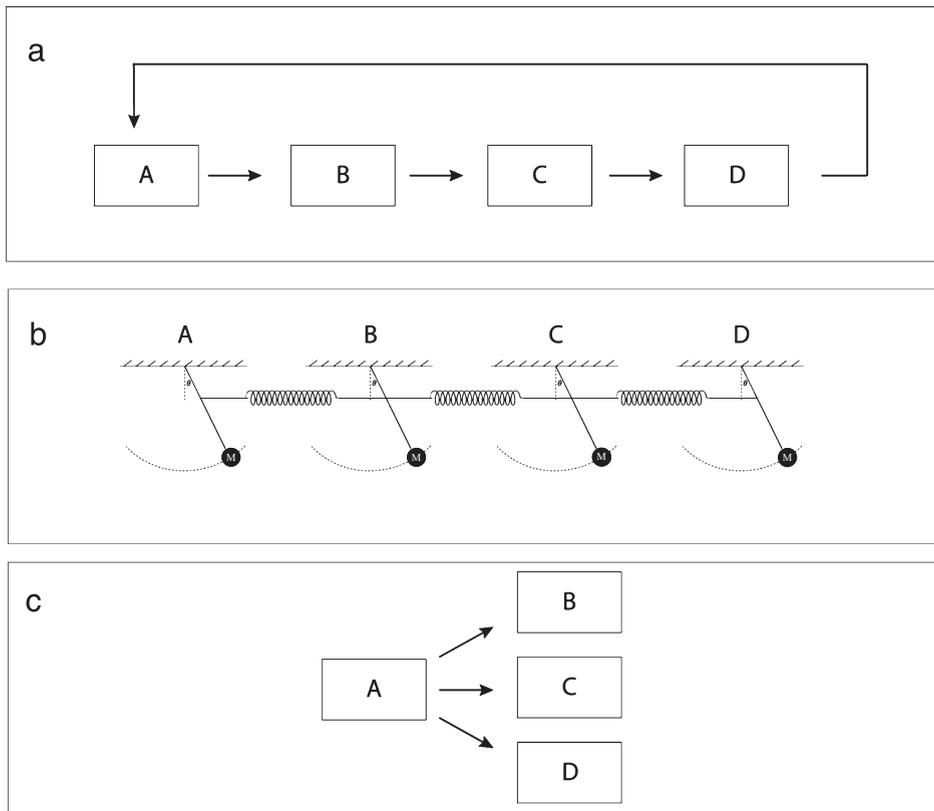


Fig. 2. Hypothetical models for the propagation of high-frequency cortico-basal ganglia oscillations in Parkinson’s disease. a) Stepwise feed-forward propagation of oscillatory activity. b) A system of independent oscillators that are weakly coupled via direct or indirect anatomical links. c) Thalamus (marked ‘A’ in diagram) acting as a central pacemaker.

have often been inferred based on this assumption (see e.g., [46, 49]; however, see also [58]). The pattern of gamma oscillations observed in the rodent model of LID do not however comply with connectivity rules in a straightforward manner. For example, narrowband gamma oscillations associated with LID are detected in motor cortex and striatum in the lesioned hemisphere, but they are never observed in the contralateral striatum, despite the bilaterality of corticostriatal projections [95]. Thus, the existence of direct anatomical connections does not seem to be sufficient for cortical gamma oscillations to be transferred to the contralateral striatum.

#### *Coupled oscillators*

A related but somewhat different view is to consider the interconnected brain structures as a system of coupled oscillators (Fig. 2b). It is possible that several brain structures could have an independent propensity to oscillate in a relatively narrow part of the frequency range under certain conditions, such as during LID [20, 70]. In this situation, even a relatively weak coupling of the oscillators could result in prominent coherent oscillations in multiple structures [96, 97]. On the other hand, structures that do not share the network properties needed to sustain oscillations of the same type would be relatively resistant to rhythmic input of this frequency from upstream structures. This could for example explain why narrowband gamma is not observed in the intact striatum, if the striatal network of an intact brain has different electrophysiological properties that do not uphold narrowband gamma oscillations. It is, however, not clear why brain structures with significant differences in neuronal microcircuitry would become tuned to similar resonance frequencies. In future studies it will therefore be important to clarify the conditions needed for the cortical and striatal microcircuitry to maintain oscillatory activities of high frequencies over extended time periods.

#### *Thalamus as a pacemaker*

Because cortex and the basal ganglia are under strong influence of thalamic input, rhythmic thalamic activity has the potential to directly drive fast oscillations in several parts of the circuit, in parallel, via a first-order synaptic connection (Fig. 2c). Indeed, in the visual system, the thalamocortical system has been shown to be a key driver of narrowband cortical gamma oscillations (~60 Hz) [98]. If narrowband

gamma oscillations in cortico-basal ganglia circuits are induced by a similar mechanism, they should be observed only in brain structures that have direct input from thalamic nuclei of the lesioned hemisphere. This notion is supported by preliminary experimental findings suggesting that diffusely projecting nuclei in thalamus, which are known to affect cortical states [99], do in fact display coherent oscillations with cortex during dyskinesia [100]. A pharmacological suppression of this thalamic activity will eliminate high-frequency oscillations also in motor cortex (although this suppression was reported to be insufficient to alleviate LID in preliminary experiments; [100]). Clearly, the role of thalamus in the induction of narrowband gamma oscillations represents quite an important topic for future studies.

Ultimately, because changes at many different levels (ranging from cellular to systems) likely act together, computer modelling will become an indispensable approach to help us understand how cellular processes can induce network dysfunctions, reflected in aberrant oscillatory phenomena and altered effective connectivity between the involved structures [68, 101–104]. At present, however, more detailed experimental data are needed to allow for meaningful modelling, highlighting the importance of joint interdisciplinary efforts by experimentalists and theoreticians.

### **TRANSLATIONAL IMPORTANCE OF HIGH-FREQUENCY OSCILLATIONS AND FUTURE OUTLOOK**

#### *A window into circuit dysfunctions in basal ganglia disorders*

Elucidating pathophysiological phenomena at both cellular and systems levels requires studying animal models that mimic central aspects of the disease of interest. Consequently, the generation of valid animal models of basal ganglia disease remains a high research priority [105, 106]. However, even for conditions where reliable and well-characterized models exist, the development of new treatments for neurologic and psychiatric conditions has often been hampered by an insufficient understanding of how to link molecular and pathophysiological processes that ultimately lead to disabilities. In this perspective, high-frequency oscillations in cortico-basal ganglia circuits in PD could provide valuable cues. The striking similarities between rats and humans in the characteristics of certain HFOs strongly suggests that

shared underlying mechanisms are at work in both species. This opens up unique opportunities to test hypotheses and investigate candidate mechanisms in valid models that are amenable to multiple levels of experimental investigation. Moreover, the differential manifestations of HFOs in cognitive and limbic circuits as compared to motor circuits observed in animals may provide important clues to the multi-faceted symptomatology of PD.

#### *A biomarker for developing novel therapies*

Importantly, even without a full understanding of the underlying mechanisms, HFOs can be used as reliable biomarkers of pathological brain states with which candidate pharmacological treatments can be evaluated and benchmarked against each other. Because of the great similarity of several of these phenomena across species, the effects produced by therapeutic interventions on HFOs are mostly likely to be translationally relevant. In this way, behavioral and neurochemical assessment techniques that are already in use can be complemented with electrophysiological readouts of changes in the brain, providing not only a much richer description [107] but also a biomarker of drug action that is directly translatable. The added value of electrophysiological recordings is exemplified by a couple of recent studies aimed at evaluating a number of putative antidyskinetic compounds in hemiparkinsonian rats [20, 70]. In some cases, neurophysiological signals can be the only available readout since not all pharmacological treatments affecting brain states give rise to detectable changes in motor behavior [70]. In particular, HFOs in limbic circuits (which are associated with psychotic-like states) could offer an exciting new opportunity to evaluate new antipsychotic treatments in animals.

#### *A feedback signal for closed-loop neuromodulation*

DBS is a well-established neuromodulation therapy for the advanced stages of PD, although it is an invasive method with several contraindications and some unwanted side-effects [108]. The widespread use of DBS for the symptomatic treatment of PD is therefore prompting a quest for technological developments that can improve efficacy while avoiding troublesome side-effect. In particular, it is argued that adjusting the stimulation parameters to the moment-to-moment needs

of the patient ('adaptive stimulation') could greatly improve the therapeutic application of DBS [18, 109–113]. Adaptive neuromodulatory stimulation is also referred to as 'closed-loop' stimulation because an adaptive system needs to encompass a physiological read-out of selected biomarkers which are used in the feedback control of the stimulation electrodes thus closing the control-loop. To this end, different electrophysiological signals are being considered, derived from LFPs, electrocorticograms (ECoG), EEG, MEG, or indirect measures of brain activity reflected in blood-flow changes (as detected using near-infrared spectroscopy or functional magnetic resonance imaging). Alternatively, one may simply use physical movement parameters, detected using wearable sensors. Despite this wide variety of options, electrophysiological measurements will most likely be needed for more detailed characterizations of brain states. For this reason, most studies have so far been designed to improve electrical stimulation paradigms based on simultaneously recorded neuronal activity using invasive techniques [14, 110, 111]. With respect to HFOs as a potential biomarker to be used in closed-loop DBS to treat LID, the study by Swann and co-authors provided several important insights on how neurophysiological recordings in a closed-loop arrangement could be used to adjust the stimulation parameters to the patients' symptom fluctuations [21]. In particular, the authors present data that indicate how problems with stimulation-induced dyskinesia could potentially be overcome by feedback control of the stimulator based on the ECoG/STN on-line recordings [21], and have also subsequently confirmed in two patients that significant energy savings can be achieved using this type of adaptive DBS approach [114].

In conclusion, the high-frequency cortico-basal ganglia oscillations discussed in this article have significant translational and scientific implications that deserve to be thoroughly explored. Further research efforts in this area are clearly worthwhile, both for gaining a deeper understanding of basal ganglia disorders and for developing improved therapies.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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