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Parkinsonism-related β oscillations in the primate basal ganglia networks – Recent advances and clinical implications

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ABSTRACT

Today, the basal ganglia (BG) network can be viewed as a three-layer neural network in which the striatum and the subthalamic nucleus (STN) are the two BG input structures and together innervate BG downstream structures using GABA and glutamate, respectively. The striatum is larger than the STN and is the main site of dopamine depletion in Parkinson's disease (PD). However, STN is the prime target for deep brain stimulation (DBS) of patients with advanced PD. Traditionally, the efficacy of STN-DBS is attributed to the suppression of the pathological synchronous β oscillations along the cortico-thalamo BG network. In conventional DBS, stimulation is delivered continuously and equally influences normal and pathological neural activity. A DBS protocol would be therefore more effective if stimulation was only applied when necessary. We recently showed in the non-human primate model of PD that parkinsonism-related β oscillations resonate across the BG network through the STN, not the striatum. Moreover, we also demonstrated that BG β oscillations are episodic and albeit extended in parkinsonism also exists in the healthy condition. Thus, not all parkinsonian β oscillatory episodes are necessarily pathological. Remarkably, the duration of BG β episodes is more highly impacted than their magnitude in parkinsonism and may be more reliable metric - especially in STN - to discriminate between normal ("good") and pathological ("bad") β episodes. Thus, prolonged STN β episodes is suggested as one of the biomarkers of the pathological neuronal activity in parkinsonism that could be used as a trigger for adaptive DBS.

1. Basal ganglia model 1.0 – the D1/D2 direct/indirect pathway model of the basal ganglia

Basal ganglia (BG) are a set of interconnected subcortical nuclei involved in behavioral control whose dysfunction leads to motor (e.g., Parkinson's disease, Huntington disease and dystonia) and non-motor (e.g., obsessive compulsive disorders, depression and schizophrenia) disorders. Most of neurology and neuroscience textbooks describe the BG network as two segregated direct and indirect internal BG pathways [1,2] (Fig. 1A). Both BG pathways start in the striatum that is innervated by nearly all cortical areas (only the primary auditory and visual cortices do not project to the striatum [3], but see, e.g. Refs. [4,5]) and converge on the BG output structures (i.e., the internal segment of the globus pallidus and the substantia nigra pars reticulata or GPi and SNr, respectively). In return, these BG output structures project back to the frontal cortex, through the thalamus. Finally, the frontal cortex projects to the spinal level through the cortico-spinal and cortico-brainstem pathways and controls muscle activation and movements.

The "direct pathway" (striatum-GPi/SNr) is mono-synaptic GABAergic inhibitory, whereas the "indirect pathway" (striatum-GPe-STN-GPi/SNr) is poly-synaptic dis-inhibitory through the GABAergic projections of the striatum and the external segment of the globus pallidus (GPe) and the glutamatergic (excitatory) subthalamic nucleus (STN). Striatal medium spiny (projection) neurons (MSNs) account for the large majority of striatal neurons and receive important inputs from midbrain dopaminergic neurons [6–8]. Although the extent and relevance of co-expression of D1 and D2 dopamine receptors in MSNs is a

Abbreviations: BG, basal ganglia; DBS, deep brain stimulation; EEG, electroencephalogram; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; LFP, local field potential; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSN, medium spiny neuron; MUA, multi-unit activity; NHP, non-human primate; PD, Parkinson's disease; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; TAN, tonically active neuron; 6-OHDA, 6-hydroxydopamine

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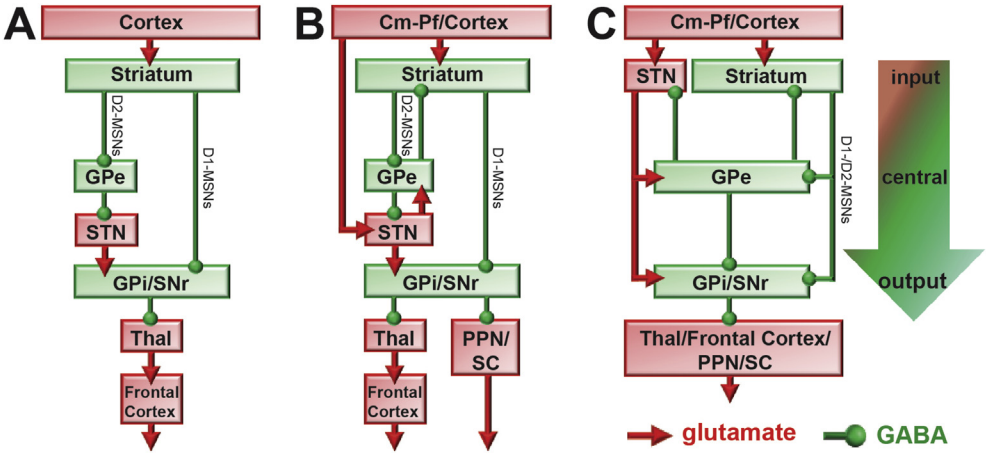

Fig. 1. Many ways to "box&arrow" the BG network. (A) The D1/D2 direct/indirect pathway model. **(B)** The updated functional connectivity of the BG. **(C)** The three-layer neural network. Input, central and output indicate the three different stages of the BG network. Red and green arrows indicate the glutamatergic or GABAergic nature of the connection. Abbreviations: *Cm*-Pf: Centromedian and parafasiscular intralaminar thalamic nuclei; D1-/D2-MSNs: striatal medium spiny (projection) neurons expressing D1/D2 dopamine receptors; GPe-i: external and internal segments of the globus pallidus; PPN: pedonculopontine nucleus; SC: superior colliculus; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus; Thal: thalamus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

matter of debate, especially in the ventral striatum [9,10], the consensus is that MSNs that predominantly express D1 dopamine receptors give rise to the "direct pathway", whereas MSNs predominantly expressing D2 dopamine receptors project to GPe and constitute the origin of the "indirect pathway" (Fig. 1A). This D1/D2 direct/indirect pathway model of the BG network has been very useful for the understanding of the computational physiology and pathophysiology of the BG network, as well as for the development of surgical treatments of common BG disorders [11]. However, it does not reflect the extreme complexity of the BG circuitry as revealed by numerous recent anatomical and electrophysiological studies (Fig. 1B).

2. Basal ganglia model 2.0 – the three-layer basal ganglia network

Both the striatum and STN receive considerable glutamatergic inputs from diverse areas of the cortex and the thalamus [12,13] (Fig. 1B). Although cortical projections to the STN originate mostly from motor, premotor and prefrontal areas [14,15], the importance of these (hyper) direct projections from the cortex to the STN [15–18] indicate that STN should no longer be considered a relay station of the BG "indirect pathway". Like the striatum, the STN is a BG input structure. The striatum and STN provide major inhibitory GABAergic and excitatory glutamatergic drive respectively to the GPe and the GPi/SNr [12,13]. In return, the GPe emits feedback GABAergic projections to the STN [19,20] and to the striatum [21–26] as well as massive feedforward GABAergic projections to the GPi/SNr [13,27] (Fig. 1B). Thus, the GPe is a central nucleus in the BG network, which is reciprocally connected to the striatum and the STN (the BG input structures), and is a major source of innervation of the BG output structures – the GPi and the SNr [28]. Finally, projections from BG output structures to brainstem motor centers such as the pedunculopontine nucleus and the superior colliculus [29,30] have been identified and can no longer be neglected in the current BG models (Fig. 1B).

In light to these additional anatomical, as well as new physiological findings, the BG can be viewed as a three-layer neural network that connects thalamo-cortical areas to cortical and brainstem motor centers (Fig. 1C). In this revised BG model, the striatum and STN are the two BG input structures and together innervate the BG central (GPe) and output (GPi/SNr) structures using GABA and the glutamate, respectively (Fig. 1C).

3. STN vs. striatum in the control of the activity of BG downstream structures

Despite evidence of subthalamic dopamine depletion in PD and its role in the pathophysiology of the disease [31–33] the striatum remains the main site of dopamine depletion in PD patients and animal models of PD. In addition, the striatum is much larger than the STN (10^7 vs. 10^5 neurons in non-human primates (NHPs), respectively [34]). Nevertheless, the STN, not the striatum, is the prime target for deep brain stimulation (DBS) of patients with advanced PD [35,36]. Moreover, it has been shown that STN-DBS abolishes abnormal synchronized oscillations in the BG network of animal models of PD [37] and PD patients [38,39]. These findings suggest that STN plays a pivotal role in the release of commands by BG output structures. In line with this conflicting evidence, the respective influence of the striatal and subthalamic activity on the activity of the BG central and output structures in PD is still debated and controversial.

4. Striatal projections neurons do not express parkinsonism-related β oscillations as do the STN and BG downstream structures

In PD, the degeneration of midbrain dopaminergic neurons leads to substantial dopamine depletion throughout the BG (especially in the striatum) which provokes abnormal BG neuronal activity and notably the emergence of synchronized β oscillatory activity in the BG network [40,41]. Abnormal synchronized β oscillatory activity has been found at multiple levels of the BG network, within and between BG nuclei, in both PD patients and animal models of PD (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP-treated monkeys and 6-hydroxydopamine or 6-OHDA lesioned rodents) [40–42]. These β oscillations have been detected in various neurophysiological signals, such as single-unit activity, multi-unit activity (MUA) and local field potential (LFP) [42–45] and are generally defined over an extended range of 8–30 Hz [42,46–48]. The β frequency range varies across species [48] and in MPTP-treated monkey generally spans a narrower 8–15 Hz frequency band, also referred to as the low β band [49–53]. In any case, these pathological synchronous β oscillations are thought to disturb information flow through the BG network and significantly reduce the information coding capacity of the BG neurons, thus resulting in the release of abnormal motor commands by BG output structures [40,54,55]. Moreover, recent human [56] and NHP [57] studies have shown that low frequency β oscillations (< 20 Hz) are better correlated with the clinical motor symptoms of PD and are also more sensitive to dopaminergic medication [58].

Remarkably, in our last two major studies, we showed that this pathological synchronous β oscillations, at least at the level of spiking activity, is not shared by all BG neuronal components in NHP model of PD [52,53] (Fig. 2, first and second columns). Even though rodent [59] and primate [60,61] studies have shown that MSN activity patterns are

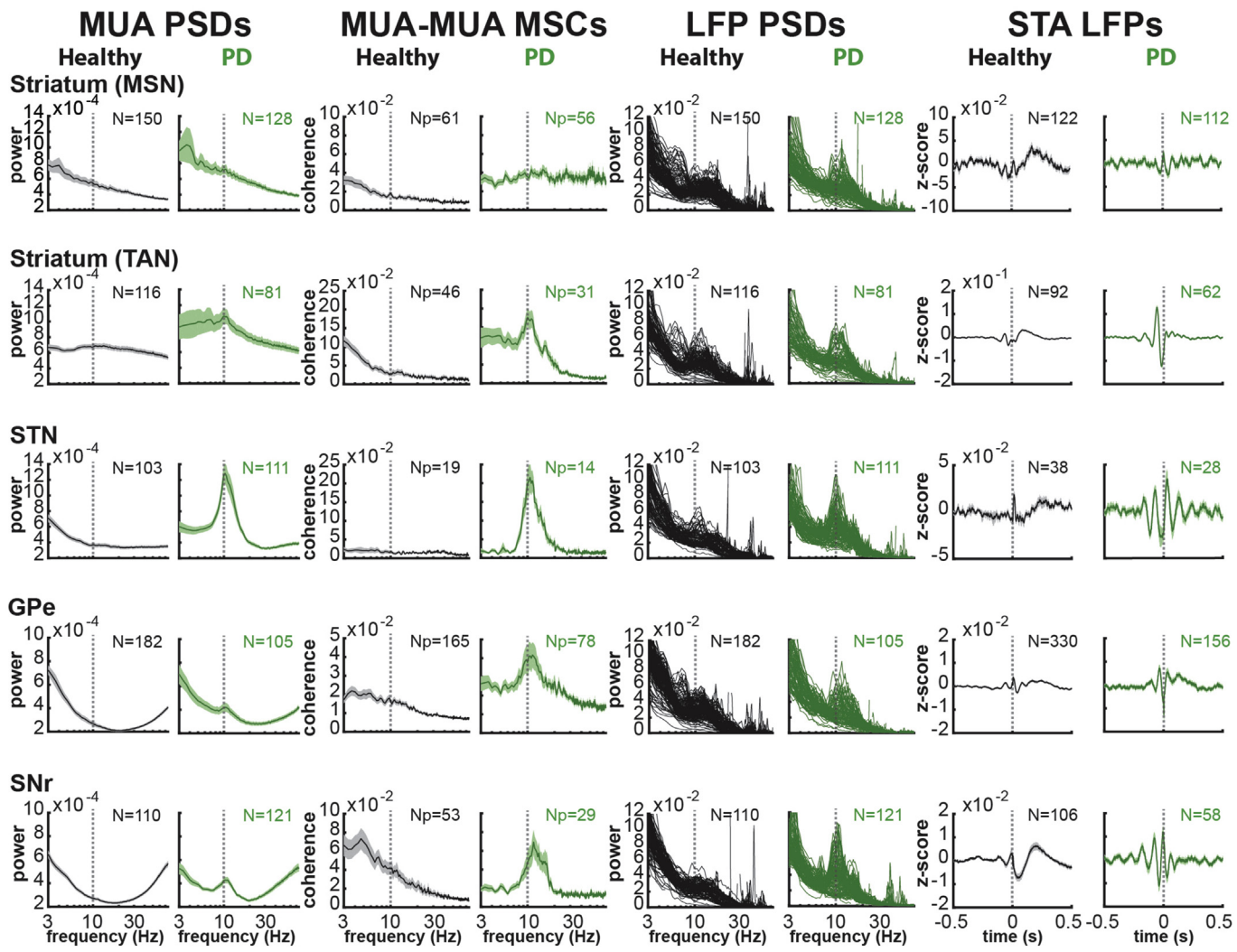

Fig. 2. Materialization of parkinsonism-related β oscillations in the BG network of the MPTP primate model. First and second columns, mean power spectral densities (PSDs) and magnitude-squared coherences (MSCs) of the MUAs and MUA-MUA pairs recorded in the vicinity of the striatal (MSNs and TANs), STN, GPe, SNr neurons in the healthy and parkinsonian states. Third column, superimposed PSDs of the LFPs recorded in the different BG nuclei (Striatum, STN, GPe and SNr) in the healthy and parkinsonian states. Fourth column, population spike-triggered averages of the LFPs (STA LFPs) recorded in the striatum, STN, GPe and SNr. Spike train (i.e., single-unit activity) and LFP (i.e., online 1–250 Hz band-pass filtered signal) were simultaneously recorded from different microelectrodes in the same BG structure. In the first, second and third columns, abscissas are in log scale, the shaded areas mark SEMs, and N and Np indicate the number of MUA and MUA-MUA pairs, respectively. In the fourth column, time = 0 indicates the time of the spikes, the shaded areas mark SEMs, and N is the number of STA LFPs averaged. *Adapted from Deffains* et al. *(2016) and Deffains* et al. *(2018)*.

altered in parkinsonism, we did not find any significant change in the discharge properties of the striatal MSNs. This lack of significant change in the discharge properties of the striatal projection neurons is in sharp contrast with the robust changes found in the discharge properties (rate, pattern and synchronization) of the projection neurons of the STN, GPe and GPi/SNr [52,53]. The demonstration that changes in the discharge rate and pattern of the MSNs in the MPTP-treated monkeys are weak, if not actually nonexistent, is consistent with our unpublished observations of no evident modification of the spiking activity in the striatum of parkinsonian patients undergoing DBS procedures. Given MSNs fire at low rate (if not silent) at rest, one might argue that MSN spiking activity, albeit on the frontline of the initial insult of striatal dopamine depletion in parkinsonism, is inherently less indicative of PD physiopathology than the spiking activity of STN, GPe and GPi/SNr neurons that fire at higher rate. Population oscillatory phenomena can emerge in networks of neurons that fire irregularly at a low rate [62,63]. Using the MUA of the recorded cells that contains the unsorted spiking activity of hundreds of neighboring cells and the single-unit activity of the recorded cell itself, we minimized the possible confounding effects of the low discharge rate and spatial under-sampling of the striatal MSNs on our results [52,53]. Indeed, we did not find population oscillatory phenomena in the striatal MSN MUAs of our MPTP-treated NHPs.

Nevertheless, recent studies in rodents reported, as predicted by the classical D1/D2 direct/indirect pathway model, a significant imbalance in the discharge rate and calcium dynamics of D1 and D2 MSNs in the dopamine-depleted striatum [64,65]. Also, Sharott and colleagues [64] reported that striatal D2, not D1, MSNs are prone to being entrained to parkinsonian β oscillations, suggesting that striatal D2 MSNs might be a principle generator of exaggerated β oscillations in BG network in the dopamine-depleted state [66]. To date, experimental approaches in PD patients and NHP model of PD do not allow us to discriminate between the spiking activity of the striatal D1 and D2 MSNs. Therefore, technical advances and further studies in PD patients and NHP model of PD should be made in order to validate or refute the results obtained in the rodent model of PD.

In any case, not all the neuronal populations in the striatum are deprived of parkinsonism-related β oscillatory activity. Indeed, striatal

tonically active neurons (TANs, presumably the striatal cholinergic interneurons) exhibit 10 Hz synchronized oscillatory spiking activity after striatal dopamine depletion and induction of parkinsonism [52,67] (Fig. 2, second row of the first and second columns). Moreover, earlier studies by our and other groups showed exaggerated β LFP oscillations in all BG structures, including the striatum, in the parkinsonian state [52,68,69] (Fig. 2, third column). BG LFP represents sub-threshold (e.g., synaptic input) activity at best [70,71] and might be largely contaminated by volume conductance of cortical electroencephalogram (EEG) activity if recorded by monopolar electrodes [72,73]. Therefore, one might posit that BG LFPs do not accurately reflect local cellular activity and should be at best interpreted with caution. Even if BG LFPs are volume conducted from cortex (EEG), the aggregate of cortical activity still represents one of the major synaptic inputs to the BG network. Indeed, we also demonstrated that abnormal parkinsonian oscillating LFPs (synaptic inputs) recorded in the vicinity of the BG neurons (i.e., from the same microelectrode [52]) or by a different microelectrode than the one that recorded the spiking activity (Fig. 2, fourth column) entrain the spiking activity of STN, GPe, SNr neurons and even striatal TANs, but do not entrain the spiking activity of striatal MSNs. In contrast, although weak, increased MSN spike-field coherence has been already reported in the dopamine-depleted striatum of free-moving rodents [68]. The discrepancy in the oscillatory features of the striatal MSNs in parkinsonian condition between our and other studies might be due to differences in experimental approaches, such as species (obviously), the methods of parkinsonism induction (idiopathic disease vs. experimental induction, MPTP vs. 6-OHDA), the time elapsed between the onset of parkinsonism and neuronal recordings, the severity of the parkinsonian symptoms and the dopamine replacement therapy history etc. Moreover, very special attention should be paid to the animals' behavioral state. In our study [52] the MPTP-treated monkeys were passive and seated quietly in a primate chair, as opposed to free-moving rodents. Further studies should be conducted to determine the importance of the animal's behavioral state during electrophysiological recordings when studying the oscillatory features of BG neuronal activity, especially in the dopamine-depleted striatum. Nevertheless, parkinsonism-related β oscillatory spiking activity of the MSNs has not yet been reported in PD patients and the NHP model of PD. In line with the view that STN is the driving force behind BG physiology and pathophysiology [74,75], one might posit that abnormal oscillations observed in PD resonate across the closed loop of the cortico-BG network through the STN, not the striatum. This idea is also supported by the fact that STN is such an effective site for DBS of patients with advanced PD [35,36] and that the efficacy of STN-DBS for advanced PD is commonly attributed to the suppression of pathological synchronous β oscillations along the cortico-thalamo-BG network [37–39].

5. BG β oscillatory activity is episodic and not necessarily pathological

An earlier study on PD patients showed that STN neurons exhibit long, non-continuous, 8–20 Hz oscillatory spiking activity that is coherent with their background MUA [76]. Similarly, examination of the dynamics of the β oscillatory spike-LFP synchrony in the STN of PD patients revealed that synchronized β oscillatory activity in human parkinsonian STN is interrupted by irregular short de-synchronization events [77]. Recently, β bursts have also been detected in the LFPs recorded in the STN of PD patients [78,79]. Also, a recent study reported an elongation of episodic LFP β oscillations in the parkinsonian-like striatum (after inducible ablation of the striatal D2 dopamine receptors) of freely moving mice with a locomotion deficit [80]. In our last study [53], we found that parkinsonism-related episodic synchronized β oscillatory activity is not limited to LFP, but could also be detected at the spiking activity scale in the STN (BG input, Fig. 3A), as well as in the central (GPe) and output (SNr) structures of the BG network. In line with the previous studies, these parkinsonism-related BG β oscillations consist of synchronized time-limited episodes, rather than a continuous stretch, of β oscillatory activity [53,78,79].

In research on patients [78,79], healthy control groups are obviously not available for comparison. Examination of the oscillatory features of the BG spiking (output) activity in NHPs before and after induction of severe parkinsonism via MPTP systemic intoxication showed that episodic BG β oscillatory activity, although extended in parkinsonism, is not necessarily pathological, since short β episodes can be detected in the healthy state [53] (Fig. 3A). In normal behavioral control, β oscillatory activity probably contributes to the maintenance of the current sensorimotor or cognitive state - the status quo hypothesis [81,82]. Consistent with this hypothesis, accentuation of brief β bursts has been observed in the cortical-BG network of healthy rodents during post-performance periods once the animals' behavior becomes habitual [83] and when a change in the animals' state is unlikely [84,85]. In addition, high levels of synchrony in LFP β oscillations have also been observed in the striatum of healthy monkeys during hold periods [86].

6. Prolonged STN β oscillatory episodes are a reliable biomarker for parkinsonism –discriminating between normal and pathological β oscillatory activity

Conventional (i.e., continuous high-frequency) STN-DBS, by influencing pathological but also physiological neural activity, can worsen motor functioning or induce side-effects in PD patients [87,88]. The DBS protocol may be more effective when stimulation is applied only when necessary as in a closed-loop adaptive DBS strategy [89–92]. For optimal adaptive DBS to be achieved, stimulation should be triggered by the most relevant biomarker of the pathological neuronal activity in parkinsonism.

In earlier studies, adaptive STN-DBS was delivered whilst the magnitude of STN β oscillatory activity exceeded a certain threshold [91,93], thus suggesting that healthy and abnormal β oscillatory activity could be distinguished based on their magnitude. Another recent study by the same group has shown that the magnitude of the β oscillatory LFP activity in the STN of PD patients increases proportionally to the duration of the β oscillatory bursts [78]. We also reported similar positive (linear) relationships between the magnitude and the duration of the β oscillatory episodes in the STN (Fig. 3B), GPe and SNr of both healthy and parkinsonian monkeys [53]. Therefore, such linear relationship between these two features of the BG β episodes cannot be considered an electrophysiological hallmark of the pathological neuronal activity in parkinsonism. However, the magnitude and the duration of the BG β oscillatory episodes significantly increase in parkinsonian monkeys compared to healthy monkeys. Remarkably, prolongation of the BG β episodes is more pronounced than their intensification in the parkinsonian state - especially in the STN (Fig. 3C) - indicating that episode duration might be a better differentiating marker of the normal and pathological STN β oscillatory episodes in the parkinsonian state [53]. Moreover, although recording of the "output" spiking activity is technologically more demanding (e.g., higher sampling rate, higher sensitivity to electronic noise due to high-impedance microelectrodes), it represents a possible alternative to the commonly used BG LFP (that reflect at best the aggregate synaptic current occurring around extracellular recording electrodes). In the same study [53], it has been reported that the best discriminations between healthy and parkinsonian episodes occur in the STN (in comparison with the GPe and the SNr). Moreover, episode duration-based discrimination is better than episode magnitude-based discrimination to identify normal and pathological episodes within the parkinsonian STN. Accordingly, numerical deletion of longer β episodes appears to be more effective than deletion of stronger β episodes in reducing parkinsonian STN synchronized oscillatory activity [53]. Therefore, at least in the parkinsonian STN, the prolonged β episodes might reliably be considered pathological. Taking advantage of this discrimination, we suggest that

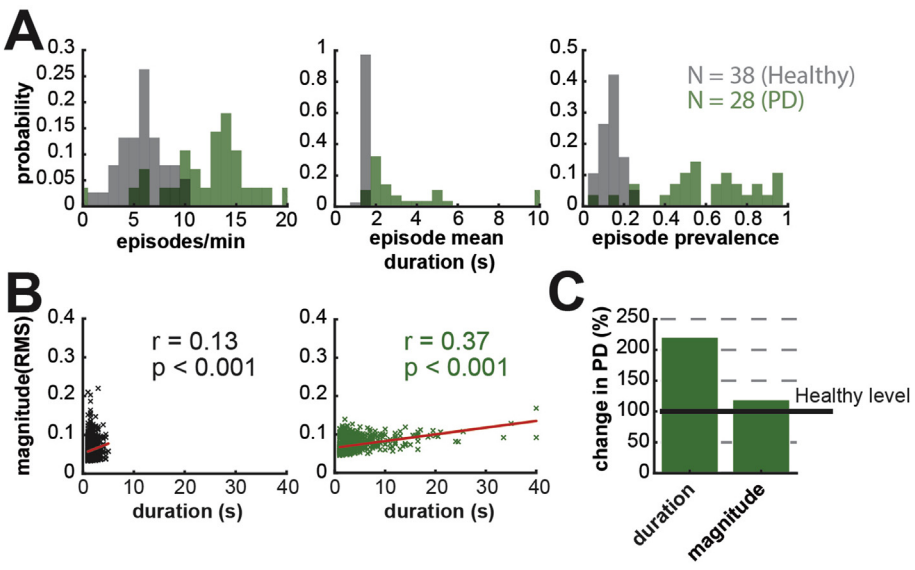

Fig. 3. Characterization of the STN β oscillatory episodes in the healthy and parkinsonian states. **(A)** Distribution of the frequency, mean duration and prevalence of the STN β episodes in the healthy and parkinsonian states. For each MUA, the frequency (left) represents the number of β episodes over the entire MUA recording span divided by the recording span, the mean duration (middle) represents the average duration of all the β episodes detected over the entire MUA recording span, and the prevalence (right) represents the probability that MUA is oscillatory in the β (8–15 Hz) range. N is the number of recording sites. Gray - healthy state; light green - parkinsonian state; dark green - overlapping bins. **(B)** Scatter plots of the magnitude and the duration of the β episodes in the healthy (left) and parkinsonian (right) states. Red line represents the linear regression line between the features (magnitude and duration) of these episodes. r is the Pearson's correlation coefficient and p indicates the probability that r = 0. **(C)** Percentage of change in the duration and the magnitude of the parkinsonian β episodes. 100% represents the duration and the magnitude of the healthy β episodes (i.e., Healthy level). *Adapted from Deffains* et al. *(2018)*. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the prolonged STN β episodes would be one of the appropriate triggers for future adaptive DBS applications [94].

7. Concluding remarks

Binary ON/OFF approach for adaptive DBS may provoke side-effects (e.g., paresthesia) caused by the rapid increase of stimulation voltage [94]. However, this important issue can be resolved by incorporating a soft-start (ramping) stimulation. We posit that the success of early studies on adaptive stimulation in PD patients [78,79,90,91,93] could be due to the soft-start (ramping) nature of the stimulation following detection of the STN β episodes, leading exclusively to effective stimulation at the time of the prolonged (i.e., pathological) epochs. Further experiments should be conducted to confirm this claim and also to determine the optimal stimulation pattern (in terms of geometry, intensity, frequency and pulse width/shape). Moreover, other potential feedback signals, such as cortical β-γ phase-amplitude coupling could be relevant for adaptive DBS in PD patients [95].

DBS treatments are also effective in other BG motor disorders, such as dystonia and essential tremor and are currently being tested for mental disorders such as obsessive compulsive disorder and depression. Therefore, adaptive DBS approaches that use the neural activity in the BG network, the objective telemetry and home-monitoring of the patient's symptoms, and the subjective evaluation by the patient and care givers of quality of life should be developed for PD patients, as well as for patients suffering from other BG-related disorders.

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