Synchronized neural oscillations and the pathophysiology of Parkinson's disease

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Purpose of the review
Developments in functional neurosurgery for movement disorders and recent advances in electrophysiological techniques have allowed important insights into the role of oscillations in corticobasal ganglia circuits, both in health and in neurological disease states. Here we review recent developments in our understanding of how abnormally synchronized oscillatory activity within the corticobasal ganglia loop may play a key role in the pathophysiology of cognitive and motor phenotypes in Parkinson's disease.

Recent findings
Recent developments highlight the motor and non-motor roles of α, β and γ oscillations in the context of Parkinson's disease. They also emphasize the importance of oscillatory coupling between basal ganglia and cortex and draw attention to the importance of interactions between different frequency bands.

Summary
Oscillatory activities across multiple frequency bands and their cross-frequency interactions within spatially segregated loops of the basal ganglia-thalamo-cortical system may relate to distinct components of clinical impairment, both motor and non-motor. It is hoped that this characterization will lead to improved interventions like deep brain stimulation, tailored to specific components of clinical impairment and their associated spatial and spectral signatures.

Keywords
coherence, electroencephalography, local field potentials, magnetoencephalography, spectral analysis, subthalamic nucleus

INTRODUCTION

Growing evidence highlights the crucial role of synchronized neuronal oscillations in mediating both normal cognitive function and abnormalities observed in common neurological disease states. Here we review how abnormalities of oscillatory activity across multiple frequency bands within corticobasal ganglia circuits may play a causal role in the generation of both motor and non-motor Parkinsonian impairments.

Traditionally, motor Parkinsonian phenotypes have been viewed in the context of the classical model of the corticobasal ganglia circuit [1] (Fig. 1). Specifically, it has been argued that dopamine depletion in Parkinson's disease leads to excessive activity of the indirect pathway, which in turn has antikinetic effects. Although this model has proved an invaluable starting point, it has a number of shortcomings [1]. In this review, we will argue that the study of oscillatory activity within the corticobasal ganglia circuit can further finesse our understanding of Parkinsonian pathophysiology. An important starting point is consideration of oscillatory activity within the β band. β Band frequencies have long been thought to play an important role in the generation of voluntary movements.

β BAND ACTIVITY IS EXCESSIVELY SYNCHRONIZED ACROSS THE CORTICOBASAL GANGLIA CIRCUIT IN PARKINSON'S DISEASE

Numerous studies in patients undergoing neurosurgery for the insertion of deep brain stimulation

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KEY POINTS

- Excessively oscillatory activity in the β (15–35 Hz) band has received prominent attention in the context of motor Parkinsonian phenotypes.
- Here we review recent evidence highlighting that synchronized oscillations at multiple frequencies within spatially segregated regions of the corticobasal ganglia circuit relate to distinct components of clinical impairment.
- Characterizing how specific components of Parkinsonian clinical impairment relate to oscillatory networks may lead to improved future stimulation strategies that specifically target network abnormalities and potentially have fewer side-effects.

(DBS) electrodes have demonstrated that a hallmark of dopamine depletion in the Parkinsonian state is elevated β band (15–35 Hz) synchronization in motor areas of the basal ganglia, including the subthalamic nucleus (STN), globus pallidus interna (GPi) and striatum [2–5,6▪,7]. Within patients undergoing DBS of the STN, it has been estimated that around 95% of electrode contacts exhibit a peak at β band frequencies [6▪]. Similarly, non-invasive studies of cortical activity using magnetoencephalography (MEG) also highlight an exaggeration of β band activity over motor areas at rest in Parkinson's disease with resting levels of β correlating with motor impairment [8,9▪▪].

Evidence that β band oscillations contribute to motor impairment in Parkinson's disease also comes from several reports of levodopa-induced suppressions in local field potential (LFP) β power correlating with treatment-induced improvements in bradykinesia and rigidity, but not tremor [10–13]. Similarly, spontaneous fluctuations of β activity within the STN have been shown to correlate with clinical state [6▪,14]. Furthermore, stimulation at β frequencies, of the cortex in healthy controls, and of STN electrodes in DBS patients, results in a slowing of movement and a worsening of Parkinsonian symptoms, respectively [14–17,18▪▪]. These observations have fuelled the idea that dopamine deficiency in Parkinson's disease leads to exaggerated β band activity.

Importantly, β activity appears to be excessively synchronized not only locally, but also between

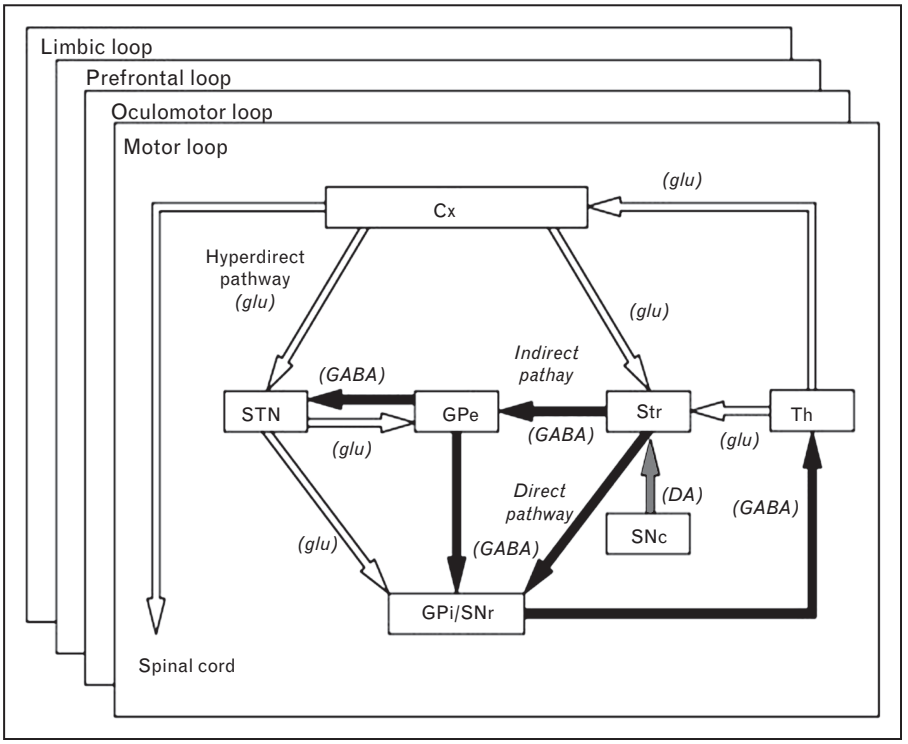

FIGURE 1. The corticobasal ganglia motor loop and its neurotransmitter modulations. A hyperdirect pathway exists between Cx-STN-GPi/SNr. The direct (Cx-Str-GPi/SNr) and indirect pathways (Cx-Str-GPe-STN-GPi/SNr) are also shown. Open arrows represent excitatory glutaminergic projections, whereas filled arrows represent inhibitory GABAergic projections. The grey arrow represents dopaminergic inputs. Cx, cortex; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Adapted with permission from ref [1].

cortical areas and the basal ganglia [5,19–23]. Resting recordings with MEG have confirmed the existence of a β band network between the STN and motor/premotor cortical areas [19,20, 24▪,25▪] (Fig. 2). Using Granger causality-based estimates of directionality of coupling between sites, it has been possible to demonstrate that β band coupling is asymmetric such that cortical β oscillations are the most likely driver of increased β band activity in the Parkinsonian basal ganglia [19,23]. A pathophysiological picture consequently emerges whereby cortical β activity drives subcortical β band activity, leading to increased synchronization between and within these sites. This model is complicated by the observation that cortical driving at rest is primarily seen in the upper β band [19,20], whereas it is the lower β band in the STN that is most exaggerated and best suppressed following the administration of levodopa in Parkinson's disease [19,26–28]. Furthermore, levodopa has not been conclusively shown to reduce cortico-STN coherence in the upper β frequency band (significant effect in [29], but not in [19,23]). One possible explanation for these paradoxes stems from the existence of nonlinear interactions between STN activities in the upper and lower β frequency bands, which are severely attenuated by dopamine [27]. Thus, maybe in the dopamine-depleted state, high cortical β activity is transformed during its subcortical relay into lower frequency activity. Direct experimental evidence for this assertion is as yet lacking, however.

RECENT INSIGHTS ON NON-MOTOR ROLES OF β BAND OSCILLATORY ACTIVITY IN PARKINSON'S DISEASE

A defining feature of β oscillations at both cortical and subcortical sites is their reactivity upon voluntary movement (Fig. 3). Interestingly, β desynchronization – a reduction in β amplitude relative to baseline – may serve different functional roles, depending on its timing in a motor task.

The timing of perimovement β desynchronization correlates with reaction times, highlighting its importance to motor control [7,30]. In contrast,

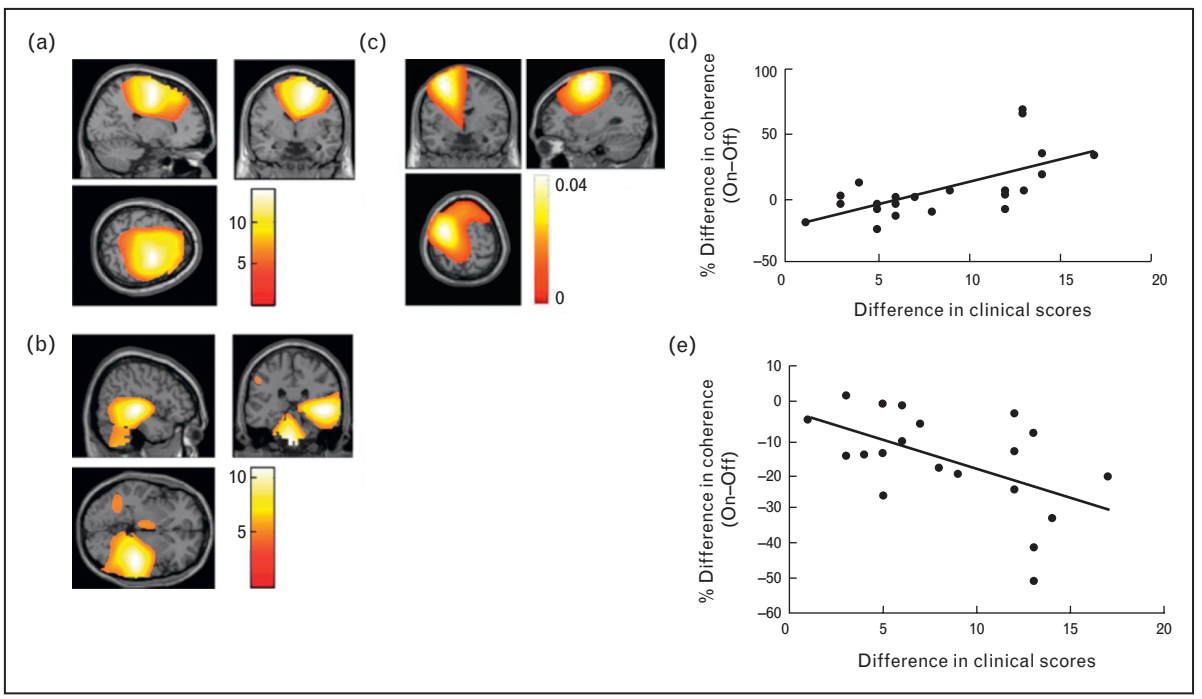

FIGURE 2. (a, b) The topography of coherence between subthalamic nucleus (STN) and cortical areas, at rest, averaged across 13 PD patients. Significant coherence was seen in the β (a; STN motor/premotor areas) and α (b; STN-temporo-parietal-brainstem areas) bands. The color bars represent *t* statistic values. Between half a second prior to and post movement, increased γ band coherence between STN and M1 is also observed (c). Here the color bar represents threshold absolute coherence values. (d, e) During movement dopamine increases coupling between STN and M1 in the γ band (d) and decreases coupling between STN and temporoparietal areas in the α band (e). Both of these features correlate across patients with drug-induced improvements in clinical scores. Note that the correlation between improvements in UPDRS motor scores and coherence changes is positive for the γ band, but negative for the α band. (a) and (b) Adapted with permission from [19]; (c) and (d) adapted with permission from [24▪]; (e) adapted with permission from [25▪].

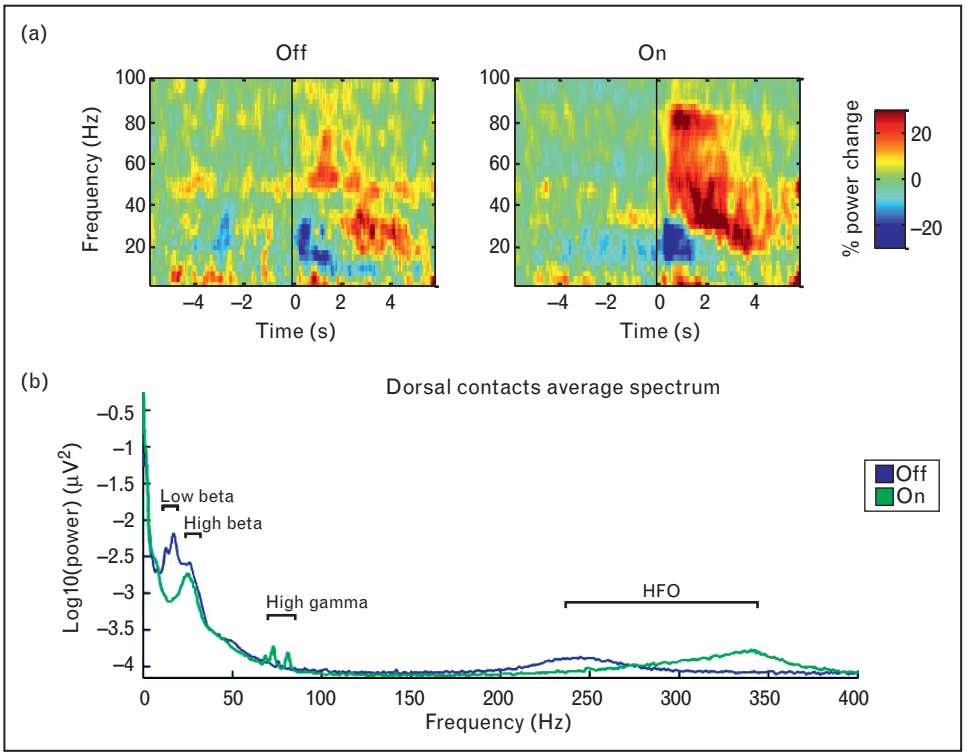

FIGURE 3. Subthalamic nucleus power spectra observed on and off dopaminergic medication in a cohort of patients with Parkinson's disease. (a) Time–frequency plots, showing time evolving spectra as percentage power change from baseline, centered at the onset of a cue instructing movement ($t = 0$ s). Beta activity desynchronizes during movement, particularly on medication. This is accompanied by a concurrent broad increase in γ band activity. (b) The resting spectrum shows a reduction in low, but not high, frequency β power on medication. There are also distinct peaks in the theta/α, γ and high-frequency (250–350 Hz) bands. (a) Shows our own unpublished data, whereas (b) is adapted with permission from [26].

early or anticipatory β desynchronization follows cues indicating that a forthcoming action, be it motor or cognitive, will need to be performed. Hence, this type of activity is independent of motor processing and is proposed to signal the likelihood of a forthcoming action [31▪,32]. It has been proposed that impairments of such facilitatory β reactivity may contribute to both motor and cognitive slowing, as observed in Parkinson's disease [31▪].

BEYOND THE β BAND IN PARKINSON'S DISEASE: INSIGHTS FROM SIMULTANEOUS MAGNETOENCEPHALOGRAPHY AND SUBTHALAMIC NUCLEUS LOCAL FIELD POTENTIAL RECORDINGS

It has become evident that oscillatory activity across multiple circuits and frequency bands may be important in the pathophysiology of Parkinson's disease. This is perhaps best exemplified by recent simultaneous MEG and STN LFP experiments in patients undergoing DBS surgery, which demonstrate the existence of multiple spatially and spectrally segregated STN-cortical oscillatory networks. At rest, a β band network exists between the STN and motor/premotor areas as previously mentioned, in addition to a diffuse α band network between the STN and temporoparietal as well as brainstem areas [19,20]. A γ band network between the STN and motor/premotor cortical areas also develops or intensifies around the time of movement, particularly following dopaminergic therapy (Fig. 2, see also the next section, The γ frequency band: a prokinetic signal) [24▪].

With regard to the identified α network, it is interesting to note that activities in this frequency band have been linked to orienting attention at a cortical level [33] and also that the directionality of this network is predominantly in the direction of cortex to STN [19]. Although formal confirmation of a putative role for the STN-cortico-brainstem α band network in orienting attention is awaited, it is interesting to note that movement-related reductions in coherence in this network on and off levodopa correlate with clinical motor improvement [25▪]. Given the above findings, one possibility is that coupling changes within the STN-cortico-brainstem

α network in Parkinson's disease may relate attentional deficits to motor impairments. This hypothesis is supported by previous correlations of attentional deficits in Parkinson's disease with motor impairment such as gait freezing and falls [34,35]. As yet, to our knowledge, no correlations between attentional deficits and more common motor symptoms such as either rigidity or bradykinesia have been demonstrated.

The observation of multiple STN-cortical oscillatory networks raises the possibility of each of these uniquely contributing to specific components of motor and non-motor Parkinsonian impairment. To this extent, it is interesting to note the levodopa dependence of frequency selective changes in the reactivity of STN-cortical coupling during voluntary movement. The degree of reactivity correlates across the α and γ bands with treatment-related improvement in motor performance [24▪,25▪]. However, analysis suggests that changes in coupling in the two frequency bands explain the same portion of the variance in the clinical response to treatment [25▪]. Interestingly, this is the case despite frequency-dependent differences in the cortical topography of the coherences. This would imply that the dopamine-dependent disengagement of the STN from its locking to temporal cortex at α band frequencies and the engagement of STN locking to motor cortex in the γ band are two related and partially dependent processes (Fig. 2).

THE γ FREQUENCY BAND: A PROKINETIC SIGNAL?

Several studies have demonstrated finely tuned, narrow frequency, 60–90 Hz γ activity – termed finely tuned gamma (FTG) activity – in the spectra of LFPs recorded in the GPi, STN and thalamus of patients at rest [5,26,36,37]. This activity is contralaterally enhanced during voluntary movement, so that the direction of change is opposite to that of activity in the β band. Akin to the β rhythm, however, subcortical FTG is coherent with motor/frontal cortical activity. It is also enhanced by therapy with the dopamine prodrug levodopa [3,5,23,24▪,37]. Unlike β, however, the available evidence points to FTG driving, or at least, leading cortical activity in this band [5,24▪]. It has been suggested that the role of oscillations in this frequency band may be to contribute to the vigor or effort (and hence influences the scaling) of a motor response, which partly relates to the level of phasic arousal. Impairment of motor vigor may be an important feature of the dopamine depleted Parkinsonian state [38▪].

Patients with Parkinson's disease also demonstrate broad-band γ synchronization perimovement, even in the absence of FTG in the resting spectrum [24▪,36,39]. It is therefore likely that although FTG can contribute to this broad-band reactivity, this is not the only factor. Whether broad-band γ reactivity also helps encode motor effort or vigor, rather than specific biomechanical movement parameters like force, remains unclear. Studies that demonstrate a correlation between both drug-related increases in STN γ activity and STN-cortical γ band coherence and motor improvement do not really address this point [24▪]. Similarly, studies that show γ amplitude around movement correlating with the speed and scale of voluntary movements cannot disambiguate vigor from force [40▪–42▪]. Indeed, whether γ activity actually encodes anything and is causally relevant is uncertain. Nevertheless, some evidence of a causal role comes from cortical stimulation studies in healthy volunteers, demonstrating that stimulation at γ frequencies does increase the rate of development of grip force although only by less than 10% [18▪▪].

Additionally, there is also a much higher-frequency event-related synchronization upon movement extending up to 600 Hz in the STN [24▪]. So far, it is unclear, however, whether this activity is the product of multiple, dynamic, phase-coupled neuronal clusters spanning this broad frequency range, or reflects the brief and asynchronous burst of activity hypothesized to be an LFP correlate of population firing [43–45]. It is interesting to note that reciprocal movement-related activities in the β and γ bands have also been observed in the basal ganglia of patients with dystonia [46].

Finally, it is noteworthy that oscillatory activities in the β and γ frequency bands are impaired in the dopamine-deficient state and are reciprocally responsive to levodopa (Fig. 3). This raises the important question of whether patterns of alterations in the β and γ frequency bands occur simultaneously in the disease process or in a staged manner. With this in mind, recent work demonstrates that increases in γ band activity may actually increase during repetitive movement in order to compensate for higher levels of β activity [47▪]. However, we await the results of studies formally relating the evolution of oscillatory features of the disease with clinical progression.

OSCILLATIONS AND COGNITIVE FEATURES OF PARKINSON'S DISEASE

Cognitive impairments in patients with Parkinson's disease may also be associated with changes in oscillatory activity in the cortex and in non-motor

regions of the STN. A global phenomenon in Parkinson's disease is the slowing of background oscillatory activity in cortical electroencephalography (EEG) and MEG, manifest as a diffuse increase in theta and α band power [48,49]. However, in Parkinson's disease dementia, this slowing becomes even more marked so that there is an increase in the power of delta rhythms at the expense of a relative reduction in α power [50]. Reversal of oscillatory slowing in Parkinson's disease dementia by acetylcholine esterase inhibitors highlights that the spectral changes may be the result of cholinergic neuron loss [51]. Although the functional consequences or associations of such oscillatory changes remain to be elucidated, their demonstration in other primarily cognitive disease states such as Alzheimer's disease [48] suggests an important relationship with cognitive processing.

At the level of the basal ganglia, theta activity in the STN has been reported to be particularly elevated in Parkinson's disease patients with impulse control disorders [52]. Similarly, it has been suggested that STN α band reactivity to emotional stimuli may be an important marker of depressive symptoms in Parkinson's disease [53–55] and that impaired β reactivity within the STN has cognitive effects [31▪].Finally, γ activity in the STN has also been implicated in cognitive processing. In particular, studies suggest that STN γ activity may underlie executive processes such as suppression of habitual or prepotent responses and switching from automatic to controlled processing in cognitive tasks [56▪,57]. Therefore, it is plausible that dopamine deficiency-induced impairments of γ band activity and reactivity in Parkinson's disease may in part be responsible for some cognitive features, such as cognitive inflexibility.

OSCILLATIONS AND TREMOR IN PARKINSON'S DISEASE

Tremor dominant types of Parkinson's disease have traditionally been considered distinct to bradykinesia–rigidity dominant subtypes [58,59] and it is, therefore, of little surprise that dopamine depletion in the striatum and β band activity has not been shown to correlate with the severity of Parkinsonian tremor [60,61]. A key difficulty in understanding the neural basis of tremor has been the fact that tremor displays marked spatiotemporal patterning, such that the tremor activities of different limbs in a Parkinson's disease patient are almost never coherent [60,62].

MEG studies have allowed characterization of the brain regions coherent with Parkinsonian resting tremor, hence revealing functional tremor networks. These studies demonstrate the presence of strong electromyogram (EMG) coupling with contralateral primary motor cortex (M1) and also coupling between M1 and other premotor, supplementary motor and somatosensory areas as well diencephalic and cerebellar sites [63].

Investigation of tremor frequency activity at subcortical sites in Parkinsonian patients has revealed oscillatory peaks at tremor frequency and tremor harmonics within the STN, GPi and thalamus [3,64–67] in addition to coherence between these sites and EMG activity [68,69▪▪]. Recent work has shown that in both the STN and VIM, distinct spatially segregated tremor clusters may relate to tremor activity in specific muscle groups, pointing to multiple tremor-related subloops within subcortical structures [68,69▪▪]. The above lines of evidence point to the possible existence of multiple tremor oscillators within basal ganglia-thalamo-cortical circuits.

CROSS-FREQUENCY INTERACTIONS

Several lines of evidence point to the fact that activity in a particular frequency band may influence activity in other frequency bands or interact with other frequency bands to influence behavior. Such interactions may be either linear or nonlinear [70].

Studies adopting a multivariate approach to correlating activities in multiple frequency bands with behavioral performance during maximal grip demonstrate that effects in the α and γ bands best predict behavioral performance, when other features are held constant. Thus, the relationship hitherto reported between β activity and bradykinesia–rigidity might be tightly locked with or even secondary to effects at both lower and higher frequencies [40▪,41▪].

Another striking feature demonstrated in a variety of physiological studies is the ability of the phase of a low-frequency signal, typically in the delta, theta or α, range to drive the amplitude of a higher frequency oscillation, usually in the γ range or above [71,72]. Such phase-amplitude coupling has been demonstrated in a number of brain areas including neocortex, hippocampus and basal ganglia and has been shown to be involved in a variety of cognitive processes such as learning, memory and attention [73–75] – leading to the suggestion that it may play an important role in both local computation and long-range communication in large-scale brain networks [72].

Recently, phase-amplitude coupling has been proposed as a mechanism for motor impairment in Parkinson's disease. STN LFP recordings in

Parkinson's disease patients have demonstrated coupling between the phase of β band oscillations and the amplitude of high-frequency oscillations in the off-medicated state. This coupling is reduced by dopamine and by movement, with movement-related modulations correlating negatively with bradykinesia and rigidity scores [26]. Furthermore, recent electrocorticography studies have demonstrated coupling of β phase in the STN and in the motor cortex with broad band γ amplitude over the motor cortex in Parkinson's disease. Such exaggerated coupling appears specific to Parkinson's disease, as it is not observed in patients undergoing neurosurgery for other conditions such as dystonia or epilepsy. It is also suppressed by DBS of the STN. Moreover, in accordance with previous studies demonstrating the cortical driving of STN β oscillations is the finding that the peak modulation of high-frequency band amplitude over motor cortex precedes the peak modulation of β phase in the STN [76▪▪]. This would be consistent with the premise that high-frequency activity is related to multiunit activity in the cortex [43–45]. Thus, bursts of cortical multiunit activity at β rhythms drive STN LFP β oscillations, in line with the known directionality of cortical EEG/MEG functional coupling with STN LFP in the β band [19–23].

CONCLUSION

Growing evidence suggests that synchronized neural oscillations at discrete frequencies play a key role in neural communication and information processing both locally and within long-range brain networks. Furthermore, direct evidence of oscillatory activity being causal to behavior rather than simply being an epiphenomenon of neural processing is beginning to be provided by experiments studying the behavioral consequences of directly manipulating oscillatory activity.

In Parkinson's disease, oscillatory activity has been classically considered as either antikinetic (β band) or prokinetic (γ band), with the balance between these contributing to the motor symptoms of bradykinesia and rigidity. However, this simplistic heuristic neither captures the full functional roles of activity within these frequency bands and their cross-frequency relations, nor explains non-motor Parkinsonian phenotypes. Here we have attempted to illustrate that the tonic and phasic reactivity of oscillations across multiple-frequency bands and their cross-frequency interactions within spatially segregated loops of the basal ganglia-thalamo-cortical circuit may relate to relatively distinct components of clinical impairment, both motor and non-motor. Crucially, a number of important questions remain to be answered, perhaps the most important of which will be to clarify more precisely the relationship between groups of symptoms and their associated oscillatory abnormalities. Encouragingly, the translational benefits of an improved understanding of the role of oscillatory activity in contributing to the symptoms of Parkinsonism are already beginning to be realized. This is suggested by proof-of-principle studies demonstrating that, by specifically focusing on oscillatory activity, closed loop DBS and phase cancelling cortical stimulation may control symptoms in Parkinson's disease [77,78▪▪].

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Conflicts of interest

There are no conflicts of interest.

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