

New insights into the relationship between dopamine, beta oscillations and motor function

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Synchronised neuronal oscillations at beta frequencies are prevalent in the human motor system, but their function is unclear. In this Opinion article, we propose that the levels of beta oscillations provide a measure of the likelihood that a new voluntary action will need to be actuated. Oscillatory beta activity is in turn modulated by net dopamine levels at sites of cortical input to the basal ganglia. We hypothesise that net dopamine levels are modulated in response to salient internal and external cues. Crucially, the resulting modulation of beta activity is predictive, enabling the appropriate prospective resourcing and preparation of potential actions. Loss of dopamine, as in Parkinson's disease, annuls this function, unless net dopaminergic activity can be elevated through medication.

Introduction

Brain activity is dominated by synchronised oscillations between populations of neurons. These oscillations appear as rhythmical fluctuations in both electroencephalographic (EEG) and local field potential (LFP) recordings (see [Glossary](#)), as well as in synchronised activity between cells. Whether these patterns have functional significance or are epiphenomenal is a major unresolved question in neuroscience. Oscillations in neuronal populations are generally characterised by the frequency at which they occur, and the past decade has seen growing interest in those oscillations occurring in the beta band (i.e. between 13 and 30 Hz). These are prominent in the human motor system, being recorded in the somatomotor cortex, the cerebellar system and basal ganglia (BG), where they behave in a task-dependent manner [1].

Nevertheless, the function of beta activity in the motor system remains unclear. Here, we will consider the possible role for beta activity in the BG–cortical motor loop, where interest has been heightened by the recent observation that beta activity is exaggerated in the BG of patients with Parkinson's disease (PD) and may contribute to their motor impairment (reviewed in [1–4]). Initially, beta oscillations were thought to be a marker of idling activity [5], but this theory has been superseded by the view that beta activity in the BG–cortical loop promotes tonic activity at the expense of voluntary movement [1,6]. This more recent hypothesis certainly captures some features of beta activity, such as its

increase during tonic contractions and its suppression during voluntary movement [2]. However, this hypothesis has also been challenged [7–9], and it is essentially phenomenal, with limited heuristic value. Here, we will critically evaluate the evidence for and against this hypothesis, before refining and developing it into a more detailed model, which places beta activity in the context of emerging ideas about dopamine function. Clear experimental predictions to test such a model are outlined.

Current status: do beta oscillations promote tonic activity?

Support for the hypothesis that beta activity promotes tonic activity at the expense of voluntary movement comes from investigations of oscillatory activity at the cortical level [10–12] and relies on the fact that the BG and cortex are connected in a functional loop. As such, cortical beta levels are likely to be functionally related to beta levels in the BG, as revealed by magnetoencephalography (MEG)

Glossary

Akinesia: paucity of voluntary movement.

Beta oscillations: oscillations between 13 and 30 Hz, evident in the discharge of single neurons and in the interactions between neurons. The latter undergo temporal and spatial summation to afford population activities such as the LFP and EEG activity.

Bradykinesia: slowness in the execution of voluntary movement.

Direct pathway: a pathway that links the BG to the cortex via the striatum, internal globus pallidus/substantia nigra and thalamus. In contrast to the indirect pathway, it acts to release the motor cortex from inhibition, thus promoting movement.

Fast-scan cyclic voltammetry: an electrochemical technique that is used to measure the level of monoamines like dopamine.

Hyperdirect pathway: a neuronal circuit through the BG that bypasses the striatum, unlike the direct and indirect pathways. Cortical input is directly received in the subthalamic nucleus and is relayed to the thalamus via the internal globus pallidus.

Indirect pathway: a neuronal circuit through the BG to the cortex via the striatum, external globus pallidus, subthalamic nucleus, internal globus pallidus/substantia nigra and thalamus in turn. Activity in the indirect pathway inhibits thalamic activity and decreases motor function.

Local field potentials (LFP): electrical potentials recorded from within the brain using low impedance electrodes. LFPs are thought to represent the synchronised input to the area from which they are recorded.

Rigidity: sustained involuntary muscle contraction. When an affected muscle is passively stretched, the degree of resistance remains constant regardless of the rate at which the muscle is stretched.

Subthalamic nucleus (STN): a small but key nucleus of the BG. The STN and pathways traversing this region are involved in several functions including the organization and control of movement. The STN is the most common target of DBS for therapeutic purposes in PD patients. During and in the few days following the implantation of stimulation electrodes, it is possible to record LFPs from the STN of such patients [85,86].

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recordings in PD patients that show coherent beta activity in the two structures (Figure 1a) [13–15]. Studies of cortical beta in humans suggest that raised physiological levels of activity penalize voluntary movement [10–12], while actively promoting postural activity, including tonic holding contractions [10]. The latter may be achieved through an up-regulation of relevant sensory inputs during and immediately after bursts of beta activity [10,14,16].

Related to this, there is a prospective increase in beta synchrony prior to an expected postural challenge, with this increase being associated with improved behavioural performance [17]. There is also an increase in cortical beta activity during successful stop trials in Go/NoGo-tasks in both human and non-human primates (Figure 1b), in which inhibition of a pre-potent movement is required [18,19]. Conversely, cortical beta activity is progressively suppressed with increasing likelihood of a cue requiring movement [20]. Voluntary movements are slowed if they are triggered during spontaneous bursts of cortical beta activity [10]. Moreover, movement was slowed when transcranial alternating current stimulation was used to boost beta synchrony in the sensorimotor cortex [21], providing some causal evidence that cortical beta synchrony can be antikinetic.

These data are encouraging, but the extent to which activity in the motor cortices can be assumed to reflect activity in the BG–cortical loop is not certain. Even in patients with PD, where beta activity is exaggerated within this loop, BG activity is only able to predict about 20% of the variance of the cortical signal in the beta band [13–15], therefore much of the beta activity in the cortex is probably independent of that in the BG. Experimentally, this is underscored by benzodiazepine treatment, which increases cortical beta activity without causing PD symptoms [22], presumably because the affected cortical networks are independent of those coherent with subcortical activity. Indeed, there is a good precedent for this, as benzodiazepines barely affect another cortico–subcortical system with a pre-dilection for activity in the beta band, the corticospinal tract, as evidenced by a lack of increase in corticospinal coherence [22]. The functional polymorphism of cortical beta activity may also explain why oscillatory corticospinal synchronisation in the beta band is paradoxically diminished in untreated PD (reviewed in [1]), despite the increase in beta synchrony in the BG. Ironically, treatment with levodopa or deep brain stimulation (DBS) actually restores physiological beta activity in the corticospinal system [1]. BG-related beta activity is therefore just one of several forms of synchronised oscillatory activity at the motor cortical level: this includes several in the beta band as well as others (not discussed here) in different frequency bands. Even within the BG–cortical system itself, we cannot rule out the possibility that there is more than one functionally distinct beta activity [2]. For example, the beta synchronisation following movement may relate to re-calibration of the system in the face of changed peripheral feedback [23], and furthermore, may be modulated by neurotransmitters other than dopamine [24].

To best investigate the role of BG beta activity it would be ideal to record directly from the BG of healthy subjects, but obviously this cannot be ethically justified. Rarely,

there are occasions when LFP activity is recorded from the BG of patients with diseases not thought to primarily involve these nuclei (e.g. some forms of tremor). Such recordings confirm that beta activity in the BG and cortex demonstrate similar patterns of movement-related suppression, followed by a rebound [25].

However, the major support for the hypothesis that BG–cortical beta activity promotes tonic motor activity at the expense of novel voluntary movement has come from studies in PD patients who have undergone functional neurosurgery for DBS, in whom it is possible to record directly from the BG. PD is characterised by increased tonic muscle activity (rigidity) and slowed movement (bradykinesia), and as anticipated, BG recordings demonstrate exaggerated synchronised oscillatory neuronal activity in the beta band [2]. Usually such recordings are made in the subthalamic nucleus (STN), the most common target for DBS in PD patients (reviewed in [26]). Exaggerated beta activity is suppressed by treatment with dopaminergic drugs and the degree to which bradykinesia and rigidity improve following drug treatment is correlated with the amount of suppression of beta band activity in the STN [27–31]. Furthermore, STN-DBS suppresses beta activity, and the induced improvement in bradykinesia and rigidity correlates with the degree of suppression of beta activity in the STN LFP [32–34]. Only one study has explicitly addressed whether BG oscillations in the lower and upper beta frequency band are equally related to bradykinesia and rigidity. This study concluded that although synchronisation may be more commonly manifest in the lower beta band in PD, synchronisation in the upper beta band also correlated with motor impairment [30]. Indeed, the two bands demonstrate non-linear interactions, suggestive of harmonic relationships [35].

In isolation, the above correlative evidence does not establish causality and it could be that beta oscillations are epiphenomena of the switch between functional regimes, as posited by Leblois and colleagues [7]. However, evidence of a causal link between elevated beta synchrony and motor impairment in PD comes from DBS experiments in which, rather than stimulate the STN in chronically implanted patients at therapeutic high frequency, patients are temporarily stimulated at low frequency [36–41]. Stimulation artificially induces synchronisation at the stimulation frequency in afferent and efferent fibres of the STN [36–41]. Such studies have shown that stimulation at 5–25 Hz exacerbates bradykinesia. Importantly, these deleterious effects are not apparent with stimulation at 30–50 Hz [36,37,40], suggesting that the susceptibility of BG–cortical loops to the effects of excessive synchronisation may be elevated across a relatively broad low-frequency band in PD patients. This band overlaps with the beta frequency band where spontaneous pathological synchronisation is prominent in PD (reviewed in [2]). However, the effects of direct stimulation at ~20 Hz are weak, at best (i.e. about 5–20% slowing in movement) [36,37,39]. Various explanations for this have been suggested [1], and bigger effects after 20 Hz stimulation have been seen in a rodent model of PD [42].

Nevertheless, the evidence is not yet sufficient to say whether changes in synchrony are the only or major cause

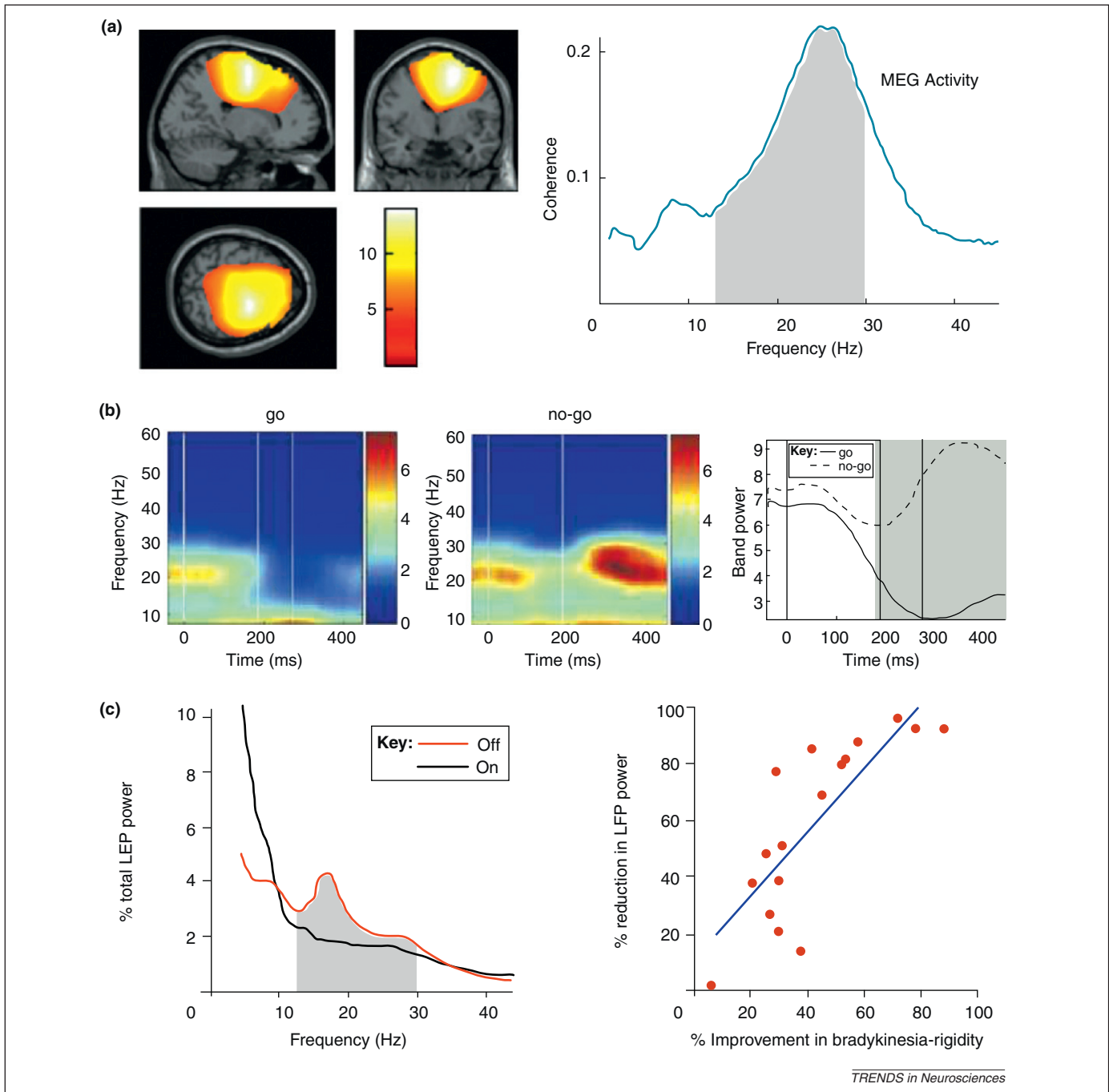


Figure 1. Functional significance of local field potential (LFP) activity in the beta frequency band. **(a)** Beta activity in the cerebral cortex and in the basal ganglia (BG) is coherent in patients with Parkinson's disease (PD). Left panel: topographic distribution of magnetoencephalography (MEG) activity coupled with simultaneously recorded LFP activity in the subthalamic nucleus (STN). The coronal, sagittal and axial sections are centred on the local maximum of MEG activity, which is anatomically located in the supplementary/premotor cortex. Images are mean data from 13 individuals with PD. Colour bar indicates t -statistic for each voxel, with white indicating the highest level of activation. Right panel: corresponding coherence spectrum of coupling between activities in supplementary/premotor cortex and ipsilateral STN. There is a peak in coupling in the beta frequency band between these two areas. Adapted, with permission, from [15]. **(b)** LFP from the sensorimotor cortices of a non-human primate (macaque) performing a go/no-go task. Left panel: time-frequency plots of average power spectra during go-trials, when a cue instructs the monkey to make a pre-prepared movement as fast as possible. Beta activity (i.e. in the 13–30 Hz range) is suppressed after cue onset (at 0 ms) and remains reduced throughout the recorded period. Middle panel: time-frequency plots of average power spectra during no-go trials, when a cue instructs the monkey to withhold the pre-prepared movement. Beta activity is also seen to decrease after cue onset but then quickly rebounds before any movement would have been executed. Right panel: average power in the beta band for go and no-go trials: grey shading represents significant statistical difference between the trials. Beta oscillations are up-regulated when voluntary movement has to be suppressed. Vertical lines represent stimulus onset, decision time and reaction time (for go-trials), respectively. Adapted, with permission, from [19]. **(c)** Effect of treatment with the dopamine produg, levodopa, on beta activity within the STN and the correlation with clinical improvement in patients with PD. Left panel: frequency spectra of the mean normalised LFP power in the STN of nine PD patients (in whom 17 STN were recorded) while on levodopa (black) and withdrawn from levodopa (red). There is a significant increase in LFP power in the beta frequency range (i.e. 13–35 Hz) off levodopa. Right panel: scatter plot showing that the greater the degree of suppression of LFP beta activity by treatment with levodopa in a given STN (red dot), the larger the improvement in slowness of movement (bradykinesia) and stiffness (rigidity) of the limbs contralateral to that STN ($r = 0.835$, $P < 0.001$). Adapted, with permission, from [28].

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of bradykinesia and rigidity in patients with PD. Likewise, it remains unclear whether beta synchrony contributes to the earliest manifestations of PD [8,43,44]. Indeed, it seems unlikely that beta synchrony could be the only pathophysiological disturbance in PD, given the diverse range of neurotransmitter systems deranged in this disease (for review, see [45]). Moreover, just as PD is a progressive neurological disease, the dominant pathophysiological mechanisms are likely to change over time [46]. In this respect, it is important to stress that most data on beta synchrony have so far been derived from patients (and animal models) in an advanced disease state.

An extended hypothesis of the function of BG–cortical beta

Although the quantitative importance of exaggerated beta synchrony in PD is still to be established, there remains some support for the general notion that BG–cortical beta activity biases against voluntary movement. This characterisation, however, fails to place beta activity in the context of other theories of BG function, and hence, its essentially phenomenal nature has limited heuristic value.

We propose that beta activity in the BG–cortical system provides an internal index of the likelihood of the need for a novel voluntary action, and, further, that this index is the direct consequence of net dopamine levels at the sites of cortical input into the BG, the striatum and STN, and, possibly, the thalamus. Specifically, we argue that within the BG–cortical system, the level of beta activity is inversely proportional to the likelihood that a new voluntary action will need to be processed and performed. At the heart of this internal index is its predictive nature, enabling appropriate anticipatory resourcing, including where probabilities are high, preparing the required action in advance of the likely voluntary movements. In effect, beta activity, or rather its suppression, determines motor readiness.

Evidence that beta activity provides an internal likelihood index of the need for a novel voluntary action

What is the evidence that beta activity in the BG–cortical system provides an internal index of the likelihood of the need for a novel voluntary action? Imperative cues demanding voluntary movement are well established to suppress beta activity [2]. More significantly, in warning-go paradigms tested in healthy and Parkinsonian subjects, beta activity at both BG and cortical levels is suppressed by warning cues and the degree of suppression correlates with how predictive cues are with regard to required action [47–49]. Accordingly, the latency of beta suppression correlates with reaction time across and within subjects [47,48,50,51]. Similarly, beta activity in the STN and motor cortex is suppressed in line with the temporal expectancy of an imperative cue, something that is again associated with shortened reaction times [20,50]. In the motor cortex, beta activity is also progressively suppressed as evidence accumulates to allow a response in a perceptual detection task [52]. Conversely, if a cue signals that a pre-prepared action must be suppressed then this is followed by an increase in beta activity in humans and monkeys [18,19,50]. Importantly, the relationship between beta activity, the evidence in

favour of action and motor readiness may not be limited to external cues, and beta suppression is seen prior to internally generated voluntary movements, presumably reflecting the salience of internal cues with respect to action [25]. These data from self-paced movements are also important in highlighting that the beta suppression is not directly related to motor processing. Thus, the beta suppression prior to a self-paced movement can precede the movement itself by as much as 2–3.5 s, well before the onset of any motor processing [53]. In summary, beta activity in the BG–cortical system, in effect, provides a running index of the extent to which internal and external cues predict the need for action.

Evidence that the changes in beta activity are underpinned by net dopamine levels

What is the evidence that the changes in beta activity are underpinned by net dopamine levels at the sites of cortical input into the BG? There is good evidence that the prevailing level of beta activity in the BG can be altered by drugs that manipulate dopamine and its receptors, both in patients with PD [2] and those without PD [54]. Midbrain dopaminergic (DA) neurons operate in tonic and phasic modes under physiological circumstances. Ordinarily, they fire at low frequencies (i.e. tonic mode), but, every so often, and particularly in response to a salient cue, they discharge a burst of action potentials (i.e. phasic mode). These higher frequency bursts induce greater extracellular dopamine compared to tonic, single-spike firing activity [55]. This is likely to be exacerbated at the population level, where many DA neurons may be synchronously activated, either through electrical coupling in phasic bursts or common afferent input related to a given cue [56].

The seminal studies of Shultz and colleagues have spawned many investigations in rat and primate experimental models focused on the role of phasic dopamine release from the ventral tegmental area (VTA) in response to reward [57,58]. However, DA neurons within the substantia nigra respond with phasic bursts to salient auditory, visual, somatosensory and olfactory stimuli without these necessarily having to have primary or conditioned reward or aversive properties [59,60]. Fast-scan cyclic voltammetry can detect the presumed consequences of such phasic activity as ‘dopamine transients’ in both the dorsal and ventral striatum of rats. These transients may be precipitated by novel odours, unexpected noises or cues in a cued lever-press task for food reward. Alternatively, they may appear spontaneous, when they increase in frequency during exposure to novel environments and social interaction, suggesting that they are related to salient cues in the environment [61]. We propose that salient events cause the release of dopamine in motor regions of the striatum and STN, and that this summates with dopamine released in other recent phasic bursts and with background dopaminergic levels (Figure 2a). Increases in extracellular dopamine in the striatum last about 200 ms after a single discharge of DA neurons, and 500–600 ms after multiple discharges at 20–100 ms intervals over 100–200 ms [62,63], as is typical of phasic bursts. Thus, as salient events in the environment build up, so will dopamine, so that net dopamine levels afford a rolling index of the likelihood of motor action

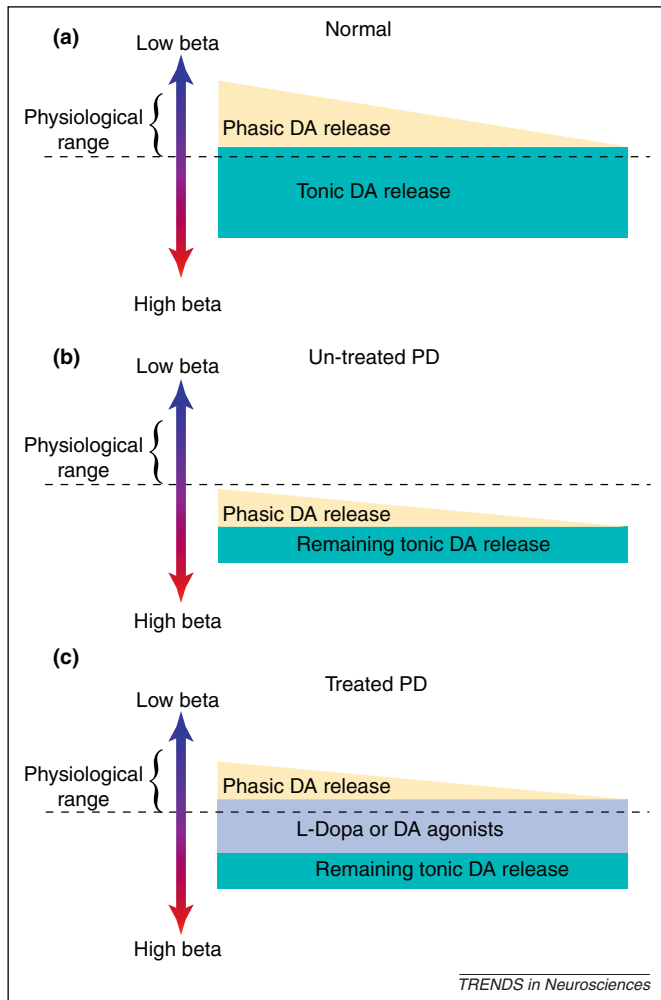


Figure 2. Schematic model of the proposed relationship between dopaminergic activity in the basal ganglia (BG) and beta activity, in health and in untreated and treated Parkinson's disease (PD). **(a)** In the normal state, tonic and phasic dopamine release combine to give high levels of dopamine and beta oscillations are driven down into the physiological range. **(b)** In PD, loss of nigral dopaminergic (DA) neurons means that there is less presynaptic dopamine for release in the striatum and STN. Without treatment, net dopamine (i.e. the sum of tonic and phasic release modes), is at a low level. Beta oscillations are consequently elevated and vary with levels outside of the physiological range. **(c)** Treatment of PD patients with levodopa or dopamine agonists changes the set-point of the system. Boosting tonic dopamine activity brings variations in net dopamine owing to phasic release back within the physiological range. Consequently, beta oscillations are driven back to normal levels.

becoming necessary. Net dopamine levels are then predicted to suppress beta synchrony, which in turn might mediate dopaminergic involvement in the determination of behavioural saliency. In line with the above, spontaneous beta activity recorded from the BG of patients with PD has an intermittent and scalloped nature [64], consistent with its suppression by dopamine transients following phasic bursting in DA neurons.

Implicit in our notion that net dopamine, through its effects on beta, provides a running index of the likelihood of new processing demands is some degree of spatiotemporal integration of dopamine release. This raises the possibility that it is higher affinity dopamine D2 receptors, and consequently the indirect pathway, that have the dominant influence over beta, consistent with their purported importance in extra-synaptic DA transmission [65]. Interestingly, then, the predominant D2 receptor agonist apomorphine is able to

suppress beta activity in patients [58] and a rodent model of PD [66,67].

What happens in the untreated PD state?

Overall, due to the loss of midbrain DA neurons, there is less presynaptic dopamine for release. This may particularly compromise the effects of extracellular dopamine release in the less efficient tonic mode of discharge. The dynamic range of dopamine variation therefore begins from a lower level than in the healthy state, so that net dopamine (i.e. the sum of tonic and phasic modes) is in a low range (Figure 2b). These changes translate into a high level of background beta, which can still be suppressed in response to salient cues, except perhaps when presynaptic loss is at its most severe. The low net dopamine and high beta activity at any given time means that the likelihood of a change in current processing requirements is underestimated and processing of voluntary movement, when it becomes necessary, under-resourced and unanticipated. Movements are slow, but also have prolonged reaction times compared to healthy subjects. The relative lengthening of reaction times is most prominent when subjects should benefit from prospective information, such as that provided by warning cues and temporal expectation [67,68].

How does simply elevating background levels of dopamine with levodopa improve motor dysfunction in PD? One possibility is that levodopa increases synaptic dopamine, and hence, has an effect through movement-related phasic synaptic release. But the evidence for this after treatment with levodopa is relatively sparse, and in any case, this does not explain how dopamine agonists can suppress beta and ameliorate motor impairment. It is more likely that treatment with the dopamine pro-drug, levodopa, or with dopamine agonists, restores net dopaminergic activity to its normal dynamic range (Figure 2c), attenuating beta activity and improving movement. Indeed, drug-induced changes in the overall level of beta activity appear much more robustly correlated with motor impairment than levodopa-induced changes in beta reactivity, which probably relate more directly to acute synaptic release. Previous reports have varied with regard to whether dopaminergic therapy increases movement-related beta suppression and whether this correlates with motor improvement [24,27,69] or not [70]. By contrast, drug-induced suppressions in average tonic beta power in STN more consistently correlate with motor improvements [27–31]. The implication of these findings is that it is net extrasynaptic dopamine levels that, through their modulation of levels of beta synchrony, largely dictate motor state, rather than any short-lived increment in synaptic dopamine.

Above, we ascribe beta synchrony to a lack of dopaminergic activity at the sites of cortical input to the BG. For example, dopamine suppresses transmission of hyper-synchronous cortical events to the STN–globus pallidus network in rodent models of PD [71], in line with dopamine's inhibition of activity at the corticostriatal synapses of D2-medium spiny neurons of the indirect pathway [72]. We propose that dopamine release attenuates the propagation of cortical beta activity, and a deficit of dopamine allows the propagation of this beta around the BG–thalamo-cortical circuit. This is further amplified by the circuit's

natural resonance frequency of about 20 Hz, as shown in clinical [73] and rodent [74,75] studies. This hypothesis is consistent with evidence from patients that cortical oscillations in the beta band overall phase lead and drive those in the BG [14,15]. It also helps explain the paradoxical lack of increase in cortical beta power in PD, except perhaps in those with the most advanced disease [46], or in animal models of PD with severe dopamine depletion [44].

As mentioned above, most of the relevant data has been collected from the STN of patients with PD, and at least in these cases, the posited running index of the likelihood of new processing demands is unlikely to afford representations of multiple probabilities. This is because recordings from DBS electrodes sample from extensive areas in the target region, the dorsolateral ‘motor’ STN, and yet cue-induced LFP changes are considerable. For example, the bilateral beta suppression induced by a predictive warning or imperative cue may be 20–40% of baseline beta power [48,50], whereas that preceding a self-paced movement is ~50% [25]. Spatiotemporal integration of phasic dopamine bursts that lead to such large and bilateral responses will leave little room for signalling an increased likelihood of other actions. As such, anticipatory resourcing and pre-processing will be biased in favour of only one action at a time, perhaps explaining the difficulty PD patients have in performing two movements at a time, even if these involve different limbs, or in rapidly executing sequences of movements [76]. However, whether the reactivity of the beta rhythm is also spatially extensive at other BG sites and in healthy subjects is unknown. In the striatum of the healthy rhesus monkey, for example, it seems that beta reactivity is much more focal, so that representations of the likelihood of multiple possible actions could be maintained [77].

Finally, the previously highlighted failure of beta synchrony to rise at the cortical level despite florid BG oscillations in PD needs further consideration, for it brings into question the role of cortical areas in bradykinesia and rigidity. Indeed, thalamic lesions, even those involving

pallidal receiving areas, fail to abolish bradykinesia and rigidity in PD [78]. This is in contrast to pallidotomy [79] and STN lesions [80,81], which can both have major effects on these cardinal features of PD, and suggests, instead, that beta synchrony may exert its effects through the BG’s brainstem projections rather than through the thalamo-cortical route. Indeed, studies in non-human primates suggest that the pallido-thalamo-cortical projection acts as a steep low-pass filter that would attenuate the return input of beta oscillations to the cortex [82]. Rather, the pedunclopontine nucleus (PPN), which is connected to the STN and pallidum, could be implicated, and lesions of the PPN in experimental animals can induce akinesia and rigidity [83]. Still, there is an important distinction to be made here: although cortical areas may not play a major role in mediating the effects of beta synchrony in bradykinesia and rigidity, beta activity in the cortex is still essential because cortical input to the BG, under circumstances of diminished dopamine, is able to penetrate and entrain the BG, which in turn amplifies the oscillatory input [75]. Thus an alternative therapeutic strategy to supplementing dopaminergic activity may be to suppress this essential cortical input through high frequency stimulation of cortical afferents or of the cortex itself [32,42].

What is needed by way of experimental support?

We have refined and expanded upon the hypothesis that considers beta activity antikinetic. The arguments outlined above serve to explain several observations, particularly how pharmacological treatments can improve motor dysfunction in PD. The stage is now set for a direct demonstration that beta activity is dynamically suppressed by elevations in net dopamine, together with an explicit demonstration that motor-salient cues, whether external or internal, modulate tonic dopamine levels in the striatum and STN (Figure 3). Equally, a core prediction of the hypothesis developed here is that the dopaminergic suppression of beta activity prior to a related sequence of movements

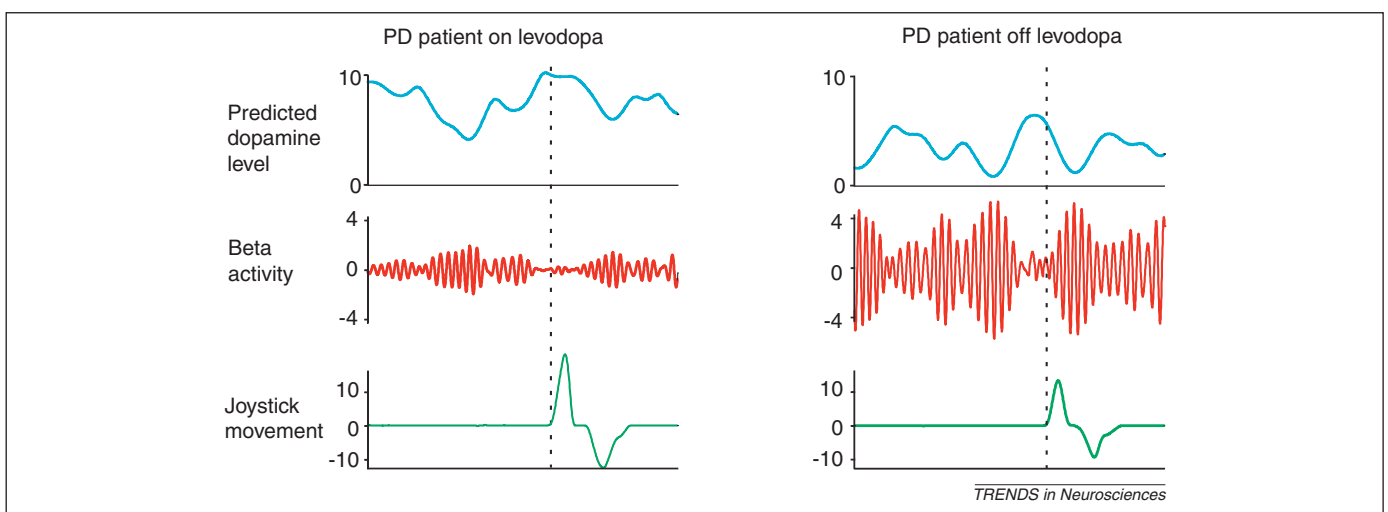


Figure 3. Hypothetical model showing the predicted dynamics of the relationship between net dopamine and beta activity in the basal ganglia (BG). Left panel: patient on the dopamine prodrug, levodopa. Background levels of dopamine are elevated but are expected to increase further before the onset of the voluntary movement. Right panel: patient withdrawn from levodopa. Dopamine levels are predicted to be low but fluctuating, with an increase before the self-paced joystick movement. Beta activity is high, but is still relatively suppressed prior to the voluntary movement (onset of latter given by dashed vertical line). The higher beta activity is associated with smaller movements off levodopa. Note that all signals are illustrative and in arbitrary units. Nevertheless, this schema could be tested by simultaneous recordings of local field potential (LFP) in the BG and fast scan cyclic voltammetry during voluntary movement.

Box 1. Outstanding questions

- Does BG–cortical beta activity alone provide an internal index of the likelihood of the need for a novel voluntary action or are oscillations at other frequencies also involved?
- Exaggerated beta activity has been related to paucity and slowness of movement [28–30], but does excessive suppression of beta activity predispose the motor system to hyperkinesias?
- Does beta activity in non-motor systems provide an internal index that predicts the likelihood of new processing demands?
- How can we better separate other activities in the beta band that may not be modulated by dopamine (e.g. as discussed in [1]) and relate to separate processes such as corticomuscular interaction?
- Do other neurotransmitters, such as acetylcholine [84], modulate the link between dopamine and beta oscillations?

will persist up to the end of the sequence rather than rebound between components. At the same time, it will be important to establish whether beta suppression is spatially more extensive in PD than in healthy animals. In parallel, there is now a rationale for testing the posited susceptibility of BG beta oscillations to D2 agonists (and their possible persistence after D1 agonists), as well as further studies to establish the relative roles of the hyperdirect and indirect pathways in sustaining beta oscillations.

It will also be instructive to contrast 20 Hz stimulation of the subthalamus with that of the pallidal receiving areas of the thalamus, to explore whether beta synchrony really does influence movement through the brainstem rather than cerebral cortex. Although this hypothesis raises further questions (Box 1), the hope is that definition of the functional anatomy of beta synchrony in BG–cortical circuits will reveal potential new therapeutic targets. Moreover, the principles established with respect to beta activity in the motor system may also be relevant in cognitive domains where beta activity may have a comparable function in predicting the likelihood of new processing demands within diverse functional systems [6].

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