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Brittain, John-stuart; Sharott, Andrew; Brown, Peter

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The highs and lows of beta activity in cortico-basal ganglia loops

John-Stuart Brittain,¹ Andrew Sharott² and Peter Brown¹

¹Experimental Neurology Group, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford OX3 9DU, UK

²Medical Research Council Anatomical Neuropharmacology Unit, Department of Pharmacology, University of Oxford, Oxford, UK

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Abstract

Oscillatory activity in the beta (13–30 Hz) frequency band is widespread in cortico-basal ganglia circuits, and becomes prominent in Parkinson's disease (PD). Here we develop the hypothesis that the degree of synchronization in this frequency band is a critical factor in gating computation across a population of neurons, with increases in beta band synchrony entailing a loss of information-coding space and hence computational capacity. Task and context drive this dynamic gating, so that for each state there will be an optimal level of network synchrony, and levels lower or higher than this will impair behavioural performance. Thus, both the pathological exaggeration of synchrony, as observed in PD, and the ability of interventions like deep brain stimulation (DBS) to excessively suppress synchrony can potentially lead to impairments in behavioural performance. Indeed, under physiological conditions, the manipulation of computational capacity by beta activity may itself present a mechanism of action selection and maintenance.

Introduction

Rhythmic phenomena are a ubiquitous feature of the cortico-basal ganglia network. The beta rhythm (13–30 Hz) is one such occurrence that is widely observed and that has received particular interest in the motor and (increasingly) non-motor domains. It reflects the oscillatory synchronization between neurons and is manifest in the cross-correlation between pairs of single neurons, in multi-unit activity, in the coherence between single neuron discharges and the local field potential (LFP), and in the LFP itself (Hammond *et al.*, 2007). The synchronization demonstrated in the LFP is likely to be dominated by subthreshold phenomena such as synaptic activity, which are then correlated with spike activity (Belitski *et al.*, 2010; Buzsaki *et al.*, 2012). Direct beta band synchronization between spikes occurs more strongly than can be explained by the passive interaction of independent oscillators with a similar oscillation frequency (Moshel *et al.*, 2013).

Recently, beta activity has been proposed to be an immutability rhythm that promotes the current state over novel action selection (Brittain & Brown, 2014). This, it has been argued, is in line with the pathological exaggeration of such activity in PD, a condition associated with diminished or absent movement (bradykinesia) and reinforced postural contraction (rigidity). Here, we refine and develop the hypothesis still further, suggesting that beta activity helps control the computational power of neuronal populations, and that there is a degree of synchrony in this frequency band (and

hence computational power) that determines task and context-optimal population performance. By computation we mean an algorithm underpinned by neuronal interactions that assigns outputs to inputs. Thus, the 'computational power' of a given neuronal population can be assessed by evaluating the complexity and diversity of associations of inputs to outputs that can be implemented by it (see Bertschinger & Natschläger, 2004). Implicit in this is the capacity of the neuronal population to dynamically integrate the existing state with continual input, and hence demonstrate both memory and reactivity. Computationally optimal neural systems have been associated with neuronal avalanches and are characterized by a power-law scaling of their frequency spectrum (Plenz, 2012). The term 'task and context-optimal population performance' introduces a central tenet of our hypothesis that the ideal balance of neuronal interactions varies from moment to moment and between neuronal populations, as dictated by the task in hand, and the present context. Thus, neuronal ensembles can be engaged or disengaged according to task demands, providing the ideal state for behaviour given the current context. This ideal state will be a trade-off between focusing on one task (attention) and yet maintaining reactivity so that other tasks can be entertained if and when necessary. Where this trade-off occurs is dependent upon context, as the latter determines the importance of retaining reactivity. Consider the difference between standing and holding onto a handle on a bus that takes corners slowly or fast. The task is the same, but the potential demands are different. We suggest that this will be reflected in different levels of beta band synchrony in this and similar tasks, and evidence that levels of beta synchrony are modulated in anticipation and prediction of outcomes is growing (Williams *et al.*, 2003; Doyle *et al.*, 2005a; Kilner *et al.*,

Correspondence: Peter Brown, as above.
E-mail: peter.brown@ndcn.ox.ac.uk

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2005; Androulidakis *et al.*, 2007; van Wijk *et al.*, 2009; Tzagarakis *et al.*, 2010; Gould *et al.*, 2011, 2012). Critically, the above hypothesis introduces a paradox; optimality in terms of the individual's behaviour no longer implies optimality in the performance of a neuronal population in an information theoretic or computational sense. Specifically, task and context-optimal population performance need not equate to the balance of neuronal interactions that affords optimal computational power. We propose that beta band synchronization may be one of the mechanisms that dynamically control a neuronal population's computational power so that it is task and context-optimal.

To do this, beta must modulate computational power and, here, we briefly review how variations in temporal and spatial dynamics related to beta synchrony may achieve this. However, our main purpose is to suggest how similar temporal and spatial dynamics may shape treatment responses and side-effects during therapeutic deep brain stimulation (DBS) in patients with PD, and how they are likely to be important considerations in future therapeutic electrical or optogenetic circuit interventions. Our intention is not to comprehensively review the connectivity and neurophysiology of cortico-basal ganglia circuits, but to consider the role of a specific oscillatory form of synchronization, beta activity, that has been brought to general attention by its florid exaggeration in patients with PD. Ultimately, we hope to provide testable hypotheses explaining some of the paradoxical observations made in such patients, particularly during treatment. Accordingly, we will focus on data from human subjects, but drawing on findings made in other animals and disease models where relevant observations are scant or absent in our species.

What is the functional role of beta synchrony in cortico-basal ganglia motor loops?

Beta activity (13–30 Hz) in cortico-basal ganglia loops is now widely associated with static motor control such as tonic or postural contraction (Jenkinson and Brown, 2011). Normal voluntary movements are preceded and accompanied by a relative suppression in beta activity. Equally, cues that predict the need for and form of voluntary movement are associated with beta suppression. Are these changes in beta activity epiphenomena of network activity or are they causally important in determining motor behaviour? Recent evidence would suggest the latter. Thus, stimulation of the motor cortex at beta frequencies in healthy subjects slows the development of force during motor responses (Pogosyan *et al.*, 2009; Joundi *et al.*, 2012) and slows tapping (Wach *et al.*, 2013). In these studies, stimulation probably entrains and promotes intrinsic beta activity in susceptible circuits (Ozen *et al.*, 2010; Ali *et al.*, 2013). A similar behavioural effect is seen with stimulation of the basal ganglia at beta frequencies, although here we can only assess patients who have undergone surgery for DBS therapy. Most of these patients have PD, but direct stimulation of the subthalamic nucleus (STN) at 20 Hz still slows tapping (Chen *et al.*, 2007) and the development of force during motor responses, especially in those subjects who perform particularly well without stimulation at the time of study. In the latter case, slowing in force development reaches over 20% (Chen *et al.*, 2011). An even more pronounced exacerbation of parkinsonian impairment has been reported during optogenetic driving of subthalamic nucleus afferents at 20 Hz in the 6-hydroxydopamine mouse model of Parkinsonism (Gradinaru *et al.*, 2009).

The degree of beta suppression has been associated with the likelihood that a new voluntary action will need to be actuated (Jenkin-

son & Brown, 2011; Wyart *et al.*, 2012). Suppression in beta activity therefore reflects a response to the demands of action selection and acts to release task-relevant neural circuits to encode and process incoming activity. But how might such a schema be realized in the basal ganglia? Systems-level suppression in beta activity would release the striatum to receive and process current and future states from the cortex, including stimulus properties. One proposition posits that, whereas the striatum lacks the required circuitry to perform action selection itself, it is instead ideally suited to act as an information reservoir, dynamically integrating the ongoing flow of activity from the cortex (Bertschinger & Natschläger, 2004; Ponzi & Wickens, 2013). Such integration is possible only as the system approaches the 'critical boundary' between noise and determinism, where recurrent networks promote the resident memory and remain flexible to the integration of new information (see Bertschinger & Natschläger, 2004). Modular interference of this activity in the striatum by beta band synchronization conceivably helps to focus action selection through attention (Courtemanche *et al.*, 2003), with propagation or selection of the desired action set occurring downstream (e.g. Bar-Gad *et al.*, 2000; Ponzi & Wickens, 2013).

How might beta synchronization be mechanistically important?

As we have detailed elsewhere (Brittain & Brown, 2014), beta activity can demonstrate phase synchrony over extensive neuronal populations, both locally and between connected regions or nuclei. This constrains neural activity to temporally predictable and spatially amorphous low-entropy signalling that impedes the response to novel demands. In particular, with a frequency that is approximately double or quadruple that of other potentially pervasive rhythms like theta and alpha, the effect of beta synchrony will be more to 'fix' local interactions, without any of the potential benefits of temporal scaffolding that might be provided by these other rhythms, whereby there is still an opportunity for local processing given the long cycle periods (as, for example, in the phenomenon of phase precession seen in the hippocampus). Put more simply, pervasive beta band oscillatory synchronization will act to limit the computational power of the neuronal population as a whole (Mallet *et al.*, 2008; Schneidman *et al.*, 2011; Hanslmayr *et al.*, 2012). In line with this, there is good evidence for a reciprocal relationship between beta synchronization and rate coding, in both the primary motor cortex (Baker *et al.*, 2003; Spinks *et al.*, 2008) and basal ganglia (Courtemanche *et al.*, 2003).

However, the precise level of synchronization and hence computational power that will be optimal for a given neuronal population will vary according to task and context, and synchronization that is stronger or weaker than this will degrade the behavioural performance of the individual. This follows as excessive synchronization will degrade computational power in a neuronal population, whereas weak levels of synchrony result in a loss of focused attention and hence do not benefit from dimensionality reduction, just as entertaining several responses slows the selected response in choice reaction as opposed to simple reaction time paradigms (Williams *et al.*, 2003, 2005). The performance of a neuronal population with respect to behaviour in different tasks and contexts will then be described by a family of inverted U-shaped functions relating synchronization to behavioural performance (Fig. 1). By synchronization (x-axis in Fig. 1) we include correlations in both time (where the same pattern is repeated in time) and space (where the same pattern is repeated across processing channels). For example, during fast voluntary movements, significant computational power may need to be liber-

ated, and synchronization in the beta band lessened (Fig. 1B). At other times it may actually be beholden to the animal to have a given neuronal population's computational power clamped down. This could arise in the motor system when a certain motor response becomes inappropriate or has to be cancelled (Fig. 1C). In accordance with this, relative or absolute increases in beta activity occur at both cortical and basal ganglia levels in no-go and stop signal paradigms (Kühn *et al.*, 2004; Zhang *et al.*, 2008; Swann *et al.*, 2009; Ray *et al.*, 2012; Alegre *et al.*, 2013). Similar changes occur in the Stroop task (Brittain *et al.*, 2012) and the orienting of attention paradigm (Pastötter *et al.*, 2008). Likewise, the deleterious effects of imposing extrinsic beta band synchronization through stimulation during movement are replaced by an improvement in behaviour during circumstances in which motor inhibition is desirable (Joundi *et al.*, 2012). Note that if beta synchronization is to be considered as a means of gating computational power and controlling the balance between history (status quo) and reactivity, then increases should be graded and not binary, and there is evidence for this at both cortical (Spinks *et al.*, 2008) and subcortical (Tan *et al.*, 2013) levels. Finally, although we invoke findings in the motor domain, the role of beta activity need not be exclusively motoric (Engel & Fries, 2010). In this regard, it is interesting to recall the inverted U-shaped function attributed to the effect of dopamine on cognitive performance (Vaillancourt *et al.*, 2013). Given the clear evidence of dopaminergic influence on the extent and reactivity of beta band synchrony, it is therefore tempting to consider the suppression of beta synchronization as a possible mediator of the effect of dopamine on motoric and cognitive function, although this remains to be tested (Jenkinson & Brown, 2011).

What if the functional effects of bursts of beta outlast the duration of synchronization?

Under physiological conditions, beta activity comes in bursts (Murthy & Fetz, 1996; Courtemanche *et al.*, 2003; Spinks *et al.*, 2008). Hitherto, the implication has been that beta activity influences circuits directly and instantaneously through synchronization. However, some studies report that the functional effects of beta synchrony may outlast bursts, albeit for short, subsecond periods (Gilbertson *et al.*, 2005; Androulidakis *et al.*, 2006). This has prompted speculation that beta bursts may have additional short-lived plastic effects (Androulidakis *et al.*, 2006). Alternatively, although the cessation of beta synchronization liberates computational power, the reconfiguration of circuits may incur delays. The effects of discrete bursts of beta may be further smoothed out by delays due to the knock-on reorganization of other neuronal ensembles necessary for behaviour. Perhaps beta bursts have emerged as an efficient means of gating computational power, achieving this in a rolling window, rather than continuously over time, given time constants that may exist in the system as a whole.

The flipside of a slow time constant of functional change following beta bursts would be a delay in effect onset. Thus, anticipatory changes in beta synchrony would be necessary to achieve optimal behaviour. There is growing evidence for such anticipatory and predictive modulation of beta synchrony (Williams *et al.*, 2003; Doyle *et al.*, 2005a; Kilner *et al.*, 2005; Androulidakis *et al.*, 2007; van Wijk *et al.*, 2009; Tzagarakis *et al.*, 2010; Gould *et al.*, 2011, 2012). Indeed, the beta suppression that may occur at 1–3 s before a self-paced voluntary movement may also be an example of this phenomenon, given that this is of similar magnitude to, but far exceeds the duration of, beta suppression preceding a cued movement (Pfurtscheller, 1981).

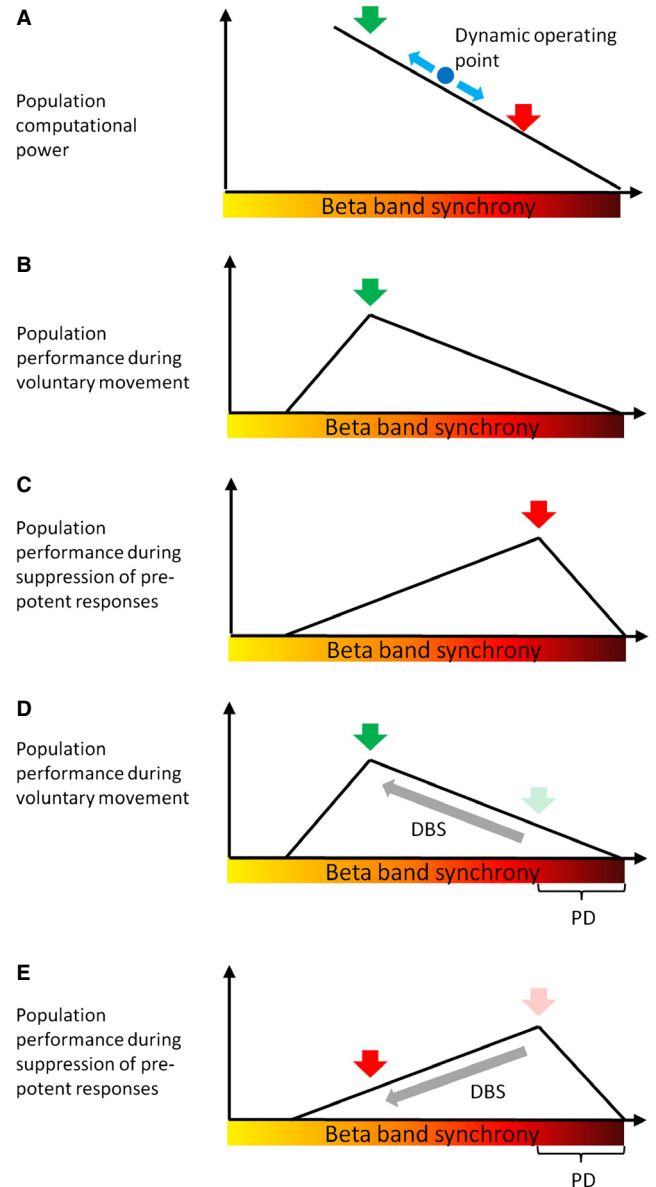


FIG. 1. Schematic relationship between beta band synchrony, computational power and population performance. (A) Dependency of computational power on the level of beta band synchrony. (B) Voluntary response. (C) Suppression of prepotent response. (D) Effect of DBS when elevated synchronization is task inappropriate, as when voluntary movement has to be made. Suppression of beta synchronization leads to less impaired movement. (E) Effect of DBS when elevated synchronization is task appropriate, as in the suppression of a prepotent response. Suppression of beta synchronization leads to impulsive action. Population performance is with respect to optimal behaviour for the given context. Green and red arrows denote task and context-optimal population performance in each case. DBS, deep brain stimulation; PD, Parkinson's disease.

Is synchronization sufficient in health to limit encoding space?

Here we need to consider whether the dynamic range of beta band synchronization under physiological conditions may be sufficient to affect computational power across neuronal populations. The necessary evidence is difficult to come by, as mesoscopic and macroscopic signal data are confounded by volume conduction. However, this issue can be addressed by considering the percentage of neurons

whose suprathreshold activity is locked to beta activity in the LFP. This affords a more sensitive assessment of synchronization than the direct correlation between the discharges of pairs of neurons. In the motor cortex of awake non-human primates this is estimated to be from 30 to 80% of spiking neurons (Murthy & Fetz, 1996; Baker *et al.*, 1997, 2003), and in the striatum this is almost 60% of spiking neurons (Courtemanche *et al.*, 2003). However, these estimates may be compromised by sampling bias and do not capture subthreshold phase coupling. Moreover, the reported phase synchronization of neurons with LFP beta is never perfect, just significant. Indeed, from Baker *et al.* (2003) we can estimate that only about 5% of the variance in spike timing could be predicted by LFP oscillations in the beta band. Synchronization may be even weaker in the pallidum, where the firing of neurons is dominated by autonomous currents (Surmeier *et al.*, 2005), and some cell types have inhibitory axon collaterals (Falls *et al.*, 1983; Sadek *et al.*, 2007) that may act to decorrelate firing (Wilson, 2013). In patients with dystonia, for example, assuming that there is no pathological alteration in the synchronization of activity in the beta band in this condition, about 10% of spiking neurons are coherent with LFP beta activity, with no more than about 20% of the variance in spike timing of each neuron predicted by LFP oscillations in this frequency band (Weinberger *et al.*, 2012). Intuitively, these levels of synchronization, particularly those in the pallidum, would seem to lie to the left of Fig. 1A. However, the dynamic increase in beta power in population signals upon tasks involving motor inhibition may be sufficient to temporarily move the operating point to the right of Fig. 1A. Context- or task-dependent changes in circuit resonances, including those in the beta band, are increasingly reported (Joundi *et al.*, 2012; Feurra *et al.*, 2013).

Implications for disease

Where excessive beta activity is present in motor circuits this will impair processing related to new voluntary movements and, judging from the effects of extrinsic driving of beta synchrony (Pogosyan *et al.*, 2009; Joundi *et al.*, 2012; Wach *et al.*, 2013), slow force generation and hence movement. Consistent with this, in untreated PD where movement is slowed, there is now considerable evidence of excessive synchronization in cortico-basal ganglia loops in the beta band (Hammond *et al.*, 2007; Pollok *et al.*, 2012). Within non-striatal nuclei in particular, decorrelation mechanisms appear to break down following dopamine depletion, and there is strong external modulation of the firing pattern, where previously there was very little (Magill *et al.*, 2001; Wilson, 2013). This could be a consequence of a down regulation of hyperpolarization-activated cyclic nucleotide-gated channels or network plasticity, with both potentially reducing the influence of autonomous firing. Whatever the mechanism, moving synchronization to the right of the normal range in neurons of the globus pallidus externa (GPe) in particular could be very disruptive for the basal ganglia network, as these neurons are extensively connected to virtually every other basal ganglia structure (Bevan *et al.*, 1998). This change in GPe function may also be important for increasing the sensitivity of STN neurons to beta oscillatory input from the cortex (Baufreton *et al.*, 2005). About 34% of spiking pallidal neurons in patients with PD are coherent with LFP beta activity in this frequency band, a significant change from the state in dystonic patients (Weinberger *et al.*, 2012). Moreover, the spatial extent and density of beta synchrony are inappropriately increased in PD (Weinberger *et al.*, 2006; Pogosyan *et al.*, 2010; Zaidel *et al.*, 2010; Moshel *et al.*, 2013) and the reactivity of beta synchronization, whether task-

related or seemingly spontaneous, is diminished (Devos *et al.*, 2004, 2006; Doyle *et al.*, 2005b; Little *et al.*, 2012). These features correlate with the degree of motor impairment (Devos *et al.*, 2004; Doyle *et al.*, 2005b; Pogosyan *et al.*, 2010; Zaidel *et al.*, 2010; Little *et al.*, 2012).

Correlations are not limited to bradykinesia, but also include another hallmark of PD, i.e. rigidity (Kühn *et al.*, 2006; Ray *et al.*, 2008). At first glance it might be thought that a reduction in computational power in motor circuits would just lead to the maintenance of existing normal posture and tone rather than the development of a positive sign like rigidity. However, a secondary reinforcement of postural tone, and hence rigidity, could emerge through the suppression of competing anticipatory processes in an external and internal environment rich in cues with motor significance (Oswal *et al.*, 2012). In other words, the normal postural state is one in which tone is relatively suppressed due to a prevailing expectancy of the need for movement. Preventing the latter will increase tone. This leads to a testable prediction – parkinsonian rigidity should be associated with impaired anticipatory modulation of beta synchrony and, consequent to this, diminished effects of warning cues in terms of reaction time shortening.

We have posited that some of the motor impairment in PD is the consequence of excessive, task-inappropriate beta synchronization, which preserves or even reinforces existing processing streams and precludes others by limiting the number of independent processing channels. But what if the existing state is a sustained action like a grip, rather than a less active posture? The motor-related suppression of beta synchrony in PD is relatively attenuated, so our schema leads to the paradoxical prediction that patients should also be slowed in discontinuing tasks like a grip. This turns out to be a well-established, if poorly understood, feature of the disease (Corcos *et al.*, 1996).

The insights to be gained from PD are heightened by the fact that dopaminergic therapy reduces pathological beta synchrony, with commensurate improvements in bradykinesia and rigidity (Kühn *et al.*, 2006, 2009; Weinberger *et al.*, 2006; Ray *et al.*, 2008). The latter focuses attention on dopaminergic input as one of the key modulators of beta synchrony, and this is further reinforced by the observation that beta activity can show an anticipatory and predictive modulation in PD that is similar to normal, but only in the presence of dopaminergic therapy with the dopamine prodrug levodopa (Oswal *et al.*, 2012). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates that are given optimal dopamine replacement therapy (e.g. without dyskinesia), oscillatory correlations between GPe neurons in the OFF state are reduced towards normal levels in the ON state (Heimer *et al.*, 2006).

DBS is another effective treatment for PD and this too suppresses circuit synchrony (Moran *et al.*, 2012). In patients, this is particularly noticeable in the beta band where the degree of suppression correlates with clinical improvement (Kühn *et al.*, 2008; Eusebio *et al.*, 2011; Rosa *et al.*, 2011; Whitmer *et al.*, 2012). Nevertheless, the efficacy of DBS potentially challenges the hypothesis that increases in beta synchrony can compromise the information-coding capacity and hence computational power. After all, high-frequency stimulation (around 130 Hz), as practiced during therapy, should itself compromise these phenomena through somal inhibition and the driving and pacing of axons (McIntyre *et al.*, 2004). The answer to this paradox may lie in the propensity of DBS to reduce synchronization across the extended network (Wilson *et al.*, 2011; Moran *et al.*, 2012), and in its frequency selectivity. The latter can arise through a non-linearity introduced at the level of the thalamus. Here, information transmission is com-

promised by synchronized inputs from the basal ganglia at frequencies in and below the beta band, but not by those at higher frequencies driven by DBS (Rubin & Terman, 2004; Guo *et al.*, 2008; Cagnan *et al.*, 2009; Moran *et al.*, 2012). Alternatively, frequency selectivity may relate to the potential plastic effects associated with beta band synchrony that we have previously alluded to. In a coupled oscillator model, low-frequency stimulation not only drove the neural population to heightened beta band synchronization, but also actively reinforced the rhythm through long-term potentiation (Tass & Majtanik, 2006). High-frequency stimulation in the same model had little effect on plasticity, with synaptic weights remaining fixed (Tass & Majtanik, 2006).

Implications for treatment

The hypothetical scheme proposed here implies that the effects of treatments should, at least to some extent, depend on the baseline levels of beta band synchronization. Thus, a treatment that reduces synchrony may lead to net motor improvement in patients in whom most local neuronal populations exhibit pathologically exaggerated beta, but may worsen function in those subjects in whom these populations exhibit more physiological levels of synchronization. Indeed, this is what has been reported. Conventional DBS improves tapping performance in those patients who, at the moment of study, demonstrate poor performance (and presumably high levels of beta synchrony) off-stimulation, whereas stimulation in those subjects with good baseline performance (and presumably less synchronization) leads to a paradoxical slowing of tapping (Chen *et al.*, 2006) (Fig. 2). Similar observations have been made with respect to paradoxical deterioration in other cognitive-motor behaviours in patients with PD performing within the normal range (Brown *et al.*, 2006; Ray *et al.*, 2009). Equally, patients with dystonia who have no disturbance of limb function may develop motor impairment in the upper limbs or gait disturbance during pallidal high-frequency stimulation that otherwise improves their dystonia (Ostrem *et al.*, 2007; Berman *et al.*, 2009; Schrader *et al.*, 2011). Under these circumstances, high-frequency stimulation may be reducing beta activity to an inappropriate level for the tasks undertaken.

Interventions like high-frequency DBS may also compromise shifts in the level of synchronization necessary to ensure optimal performance under different task and contextual conditions. Thus, a treatment that drives beta synchronization down, and biases the operating point to the left, may improve limb bradykinesia in PD (Fig. 1D) but may lead to impulsive action when inhibition of limb movement is more behaviourally relevant (Fig. 1E). Indeed, impulsive responding is often a by-product of conventional DBS that is otherwise very effective in improving bradykinesia (Frank *et al.*, 2007). The dynamic nature of circuits may also help to explain why closed-loop DBS can be paradoxically more effective than continuous DBS (Rosin *et al.*, 2011; Little *et al.*, 2013). Closed-loop DBS, by focusing stimulation at the time of bursts in beta activity, preferentially suppresses periods of particularly extensive beta synchronization, leaving undisturbed other periods in which the degree of synchrony, and hence neuronal population performance, is closer to task optimality (Little *et al.*, 2013). Continuous high-frequency DBS is less discriminating, so that some of the benefits of suppressing spatially extensive beta synchrony may be off-set by driving less marked degrees of synchronization down so that population performance is compromised (Fig. 3). Clinically, the effect of continuous DBS at times of diminished beta synchronization will not manifest as sudden, brief periods of worsening as the effects of high-frequency

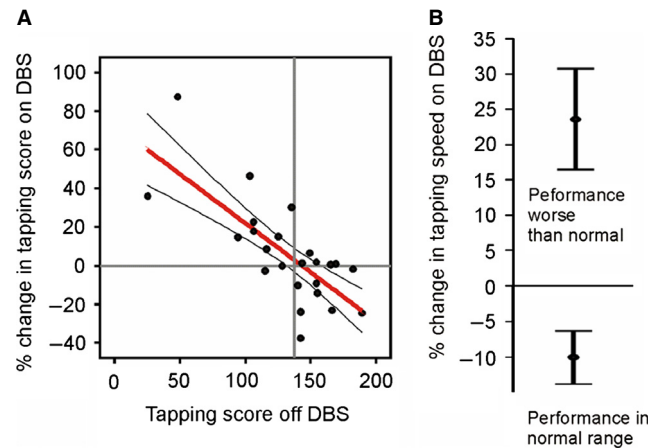


FIG. 2. Dependency of DBS effects on baseline performance. Conventional DBS improves performance in those patients who at the moment of study have poor tapping performance and presumably high levels of beta synchrony across populations of motor-related neurons, whereas stimulation in those subjects with good baseline performance and presumably less synchronization leads to a paradoxical slowing of tapping. (A) Negative correlation and 95% confidence limits between percentage change in tapping rate of each hand with DBS and tapping rate prior to onset of DBS. Positive percentage change indicates improvement with DBS. Vertical grey line demarcates the lower limit of tapping scores in healthy age-matched subjects. (B) Mean (\pm SEM) percentage change in tapping rate with DBS in hands with baseline tapping performance within or less than the normal range ($P < 0.001$ for difference between groups, unpaired two-tailed t -test; $P = 0.019$ and $P = 0.008$ for each group differing from zero, two-tailed one-sample t -tests). Adapted with permission from Chen *et al.* (2006). DBS, deep brain stimulation.

DBS are low-pass filtered, as demonstrated by the time-course of clinical response to stimulation, which builds up (and down) over seconds or more.

Hitherto we have considered that the dynamic range of beta synchrony and hence its effects on computational power are relatively fixed across populations of neurons, even though the optimal point within this range may change at any given instant as different populations are called upon to execute different tasks. However, we should also acknowledge that the dynamic range of beta synchrony may also vary between different functional populations. This may be particularly true when striatal and non-striatal neuronal populations of the basal ganglia are considered. Striatal neurons have a very low resting potential and need co-ordinated excitatory input to fire action potentials (Wilson & Kawaguchi, 1996). In contrast, neuronal populations in the globus pallidus, substantia nigra and STN have combinations of voltage-gated sodium and hyperpolarization-activated cyclic nucleotide-gated channels that allow them to fire autonomously at high frequencies (20–100 Hz) across different brain states and behavioural tasks (Surmeier *et al.*, 2005; Goldberg & Bergman, 2011). Both these intrinsic properties and some of the network characteristics of non-striatal regions tend to decorrelate activity (Bar-Gad *et al.*, 2003; Goldberg & Bergman, 2011; Wilson, 2013). The neurons of the STN may operate somewhere in the middle of the range between striatal and pallidal neurons, as they have strong autonomous firing, but have integrative properties that are different to pallidal neurons (Goldberg & Bergman, 2011). Such potential variety in the dynamic range of beta synchrony between neuronal populations might explain why treatments can improve some features but worsen others within the same subject. Conventional DBS of the STN, for example, runs the risk of worsening speech, even though limb function improves (Tripoliti *et al.*, 2011). It may be that speech is optimal when synchronization in the rele-

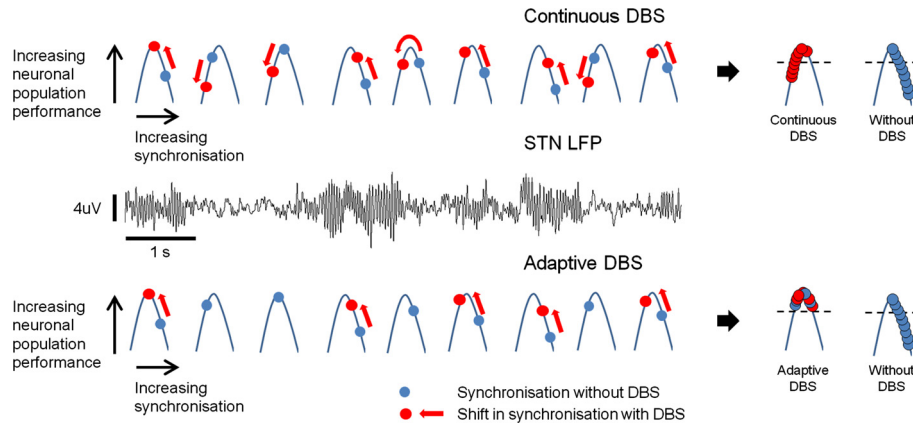


FIG. 3. Dynamic nature of synchronization may underlie the superior benefit of adaptive DBS over continuous DBS. DBS desynchronizes circuits. Without DBS, neuronal population performance is compromised by exaggerated beta activity (right-hand descending edge of the inverted U-shaped performance curve). Conventional (continuous) DBS causes the neural population to desynchronize, forcing population performance to the left-hand side of the performance curve. Adaptive DBS desynchronizes the population only when exaggerated synchronization is detected. As such, the system sits about the peak of the performance curve. Middle trace is LFP from the STN of a patient with PD showing discontinuous bursts of beta activity over time. DBS, deep brain stimulation; PD, Parkinson's disease; STN, subthalamic nucleus.

vant subcircuits is more pronounced, whereas optimal limb control is normally achieved with lower degrees of synchrony. Again, this needs to be empirically tested.

Evidence gap and future considerations

Our proposed schema may explain several clinical observations and paradoxes, yet it remains hypothetical and general. Further empirical and modelling studies are necessary to confirm or refute some of the assertions made here, and to provide further mechanistic detail. One feature that remains particularly unclear is whether beta synchrony *per se* also carries information or whether information is exclusively carried by spared processing channels, which are free to engage in oscillatory synchronization in other frequency bands, stochastic synchronization and/or rate coding. Moreover, there remains an open issue as to the quantitative importance of beta band synchronization; in effect the gradient of the slopes in Fig. 1. This has been partially explored by considering the limitation of the information-coding capacity exerted by pathological beta band synchronization in the GPe in the 6-hydroxydopamine midbrain-lesioned rodent model of Parkinsonism (Cruz *et al.*, 2009). Here, even following extrapolation to the level of large neuronal populations, the impairment of coding capacity due to synchronization was much less than that ascribable to changes in discharge rates and autocorrelation within this nucleus in the parkinsonian state. However, these experiments were performed in resting (anaesthetized) animals and beta synchrony extends beyond single nuclei, as demonstrated by the prominent coherence between levels in the parkinsonian cortico-basal ganglia circuit (Brown *et al.*, 2001; Hirschmann *et al.*, 2011; Litvak *et al.*, 2011), and so it is possible that the relative importance of excessive synchronization could increase further if its impact is considered across the extended system and during movement. This remains to be explored.

Nevertheless, the above considerations highlight that computational power is best thought of as relying on several factors, one of which is beta band synchronization. The hypothetical scheme proposed here serves to illustrate how this particular factor may impact on function and also serves to stress some critical features of neuronal populations that may dictate their response to experimental or therapeutic manipulation. Chief amongst these is that neuronal popu-

lations can differ in how much synchronization is necessary for optimal performance, and that the optimal level of synchronization within a population is also dynamic, and context- and task-dependent. One of the limitations of pharmacological therapies in the nervous system is their relative failure to allow for this variation across neuronal populations and in time. This is one potential advantage of control through neural interface technologies, although the scaling of these to the level of local populations of neurons is an immense challenge. Meanwhile, there may remain much to be gained from adapting existing DBS interventions in responding dynamically to changes in circuit requirements, and to deliver stimulation patterns that are optimized for interaction with pathological circuits in a disease- and phenotype-specific manner.

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Abbreviations

DBS, deep brain stimulation; GPe, globus pallidus externa; LFP, local field potential; PD, parkinson's disease; STN, subthalamic nucleus.

References

- Alegre, M., Lopez-Azcarate, J., Obeso, I., Wilkinson, L., Rodriguez-Oroz, M.C., Valencia, M., Garcia-Garcia, D., Guridi, J., Artieda, J., Jahanshahi, M. & Obeso, J.A. (2013) The subthalamic nucleus is involved in successful inhibition in the stop-signal task: a local field potential study in Parkinson's disease. *Exp. Neurol.*, **239**, 1–12.
- Ali, M.M., Sellers, K.K. & Fröhlich, F. (2013) Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J. Neurosci.*, **33**, 11262–11275.
- Androulidakis, A.G., Doyle, L.M., Gilbertson, T.P. & Brown, P. (2006) Corrective movements in response to displacements in visual feedback are more effective during periods of 13–35 Hz oscillatory synchrony in the human corticospinal system. *Eur. J. Neurosci.*, **24**, 3299–3304.
- Androulidakis, A.G., Doyle, L.M., Yarrow, K., Litvak, V., Gilbertson, T.P. & Brown, P. (2007) Anticipatory changes in beta synchrony in the human corticospinal system and associated improvements in task performance. *Eur. J. Neurosci.*, **25**, 3758–3765.

- Baker, S.N., Olivier, E. & Lemon, R.N. (1997) Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J. Physiol.*, **501**, 225–241.
- Baker, S.N., Pinches, E.M. & Lemon, R.N. (2003) Synchronization in monkey motor cortex during a precision grip task. II. Effect of oscillatory activity on corticospinal output. *J. Neurophysiol.*, **89**, 1941–1953.
- Bar-Gad, I., Havazelet-Heimer, G., Goldberg, J.A., Ruppel, E. & Bergman, H. (2000) Reinforcement-driven dimensionality reduction – a model for information processing in the basal ganglia. *J. Basic Clin. Physiol. Pharmacol.*, **11**, 305–320.
- Bar-Gad, I., Heimer, G., Ritov, Y. & Bergman, H. (2003) Functional correlations between neighboring neurons in the primate globus pallidus are weak or non-existent. *J. Neurosci.*, **23**, 4012–4016.
- Baufreton, J.I., Atherton, J.F., Surmeier, D.J. & Bevan, M.D. (2005) Enhancement of excitatory synaptic integration by GABAergic inhibition in the subthalamic nucleus. *J. Neurosci.*, **25**, 8505–8517.
- Belitski, A., Panzeri, S., Magri, C., Logothetis, N.K. & Kayser, C. (2010) Sensory information in local field potentials and spikes from visual and auditory cortices: time scales and frequency bands. *J. Comput. Neurosci.*, **29**, 533–545.
- Berman, B.D., Starr, P.A., Marks, W.J. Jr. & Ostrem, J.L. (2009) Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia. *Stereot. Funct. Neuros.*, **87**, 37–44.
- Bertschinger, N. & Natschläger, T. (2004) Real-time computation at the edge of chaos in recurrent neural networks. *Neural Comput.*, **16**, 1413–1436.
- Bevan, M.D., Booth, P.A., Eaton, S.A. & Bolam, J.P. (1998) Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. *J. Neurosci.*, **18**, 9438–9452.
- Brittain, J.S. & Brown, P. (2014) Oscillations and the basal ganglia: motor control and beyond. *NeuroImage*, **85**, 637–647.
- Brittain, J.S., Watkins, K.E., Joundi, R.A., Ray, N.J., Holland, P., Green, A.L., Aziz, T.Z. & Jenkinson, N. (2012) A role for the subthalamic nucleus in response inhibition during conflict. *J. Neurosci.*, **32**, 13396–13401.
- Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P. & Di Lazzaro, V. (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.*, **21**, 1033–1038.
- Brown, P., Chen, C.C., Wang, S., Kühn, A.A., Doyle, L., Yarrow, K., Nuttin, B., Stein, J. & Aziz, T. (2006) Involvement of human basal ganglia in off-line feed-back control of voluntary movement. *Curr. Biol.*, **16**, 2129–2134.
- Buzsáki, G., Anastassiou, C.A. & Koch, C. (2012) The origin of extracellular fields and currents – EEG, ECoG, LFP and spikes. *Nat. Rev. Neurosci.*, **13**, 407–420.
- Cagnan, H., Meijer, H.G., van Gils, S.A., Krupa, M., Heida, T., Rudolph, M., Wadman, W.J. & Martens, H.C. (2009) Frequency-selectivity of a thalamocortical relay neuron during Parkinson's disease and deep brain stimulation: a computational study. *Eur. J. Neurosci.*, **30**, 1306–1317.
- Chen, C.C., Brucke, C., Kempf, F., Kupsch, A., Lu, C.S., Tseng Lee, S., Tisch, S., Limousin, P., Hariz, M. & Brown, P. (2006) Deep brain stimulation of the subthalamic nucleus: a two-edged sword. *Curr. Biol.*, **16**, R952–R953.
- Chen, C.C., Litvak, V., Gilbertson, T., Kühn, A., Lu, C.S., Lee, S.T., Tsai, C.H., Tisch, S., Limousin, P., Hariz, M. & Brown, P. (2007) Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. *Exp. Neurol.*, **205**, 214–221.
- Chen, C.C., Lin, W.Y., Chan, H.L., Hsu, Y.T., Tu, P.H., Lee, S.T., Chiou, S.M., Tsai, C.H., Lu, C.S. & Brown, P. (2011) Stimulation of the subthalamic region at 20 Hz slows the development of grip force in Parkinson's disease. *Exp. Neurol.*, **231**, 91–96.
- Corcos, D.M., Chen, C.M., Quinn, N.P., McAuley, J. & Rothwell, J.C. (1996) Strength in Parkinson's disease: relationship to rate of force generation and clinical status. *Ann. Neurol.*, **39**, 79–88.
- Courtemanche, R., Fujii, N. & Graybiel, A.M. (2003) Synchronous, focally modulated β -band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. *J. Neurosci.*, **23**, 11741–11752.
- Cruz, A.V., Mallet, N., Magill, P.J., Brown, P. & Averbeck, B.B. (2009) The effects of dopamine depletion on network entropy in the external globus pallidus. *J. Neurophysiol.*, **102**, 1092–1102.
- Devos, D., Labyt, E., Derambure, P., Bourriez, J.L., Cassim, F., Reyns, N., Blond, S., Gaiue, J.D., Destée, A. & Defebvre, L. (2004) Subthalamic nucleus stimulation modulates motor cortex oscillatory activity in Parkinson's disease. *Brain*, **127**, 408–419.
- Devos, D., Szurhaj, W., Reyns, N., Labyt, E., Houdayer, E., Bourriez, J.L., Cassim, F., Krystkowiak, P., Blond, S., Destée, A., Derambure, P. & Defebvre, L. (2006) Predominance of the contralateral movement-related activity in the subthalamo-cortical loop. *Clin. Neurophysiol.*, **117**, 2315–2327.
- Doyle, L.M.F., Yarrow, K. & Brown, P. (2005a) Lateralization of event-related beta desynchronization in the EEG during pre-cued reaction time tasks. *Clin. Neurophysiol.*, **116**, 1879–1888.
- Doyle, L.M., Kühn, A.A., Hariz, M., Kupsch, A., Schneider, G.H. & Brown, P. (2005b) Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. *Eur. J. Neurosci.*, **21**, 1403–1412.
- Engel, A.K. & Fries, P. (2010) Beta-band oscillations – signalling the status quo? *Curr. Opin. Neurobiol.*, **20**, 156–165.
- Eusebio, A., Thevathasan, W., Doyle Gaynor, L., Pogosyan, A., Bye, E., Foltyniec, T., Zrinzo, L., Ashkan, K., Aziz, T. & Brown, P. (2011) Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. *J. Neurol. Neurosurg. Ps.*, **82**, 569–573.
- Falls, W.M., Park, M.R. & Kitai, S.T. (1983) An intracellular HRP study of the rat globus pallidus. II. Fine structural characteristics and synaptic connections of medially located large GP neurons. *J. Comp. Neurol.*, **221**, 229–245.
- Feurra, M., Pasqualetti, P., Bianco, G., Santarnecchi, E., Rossi, A. & Rossi, S. (2013) State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters. *J. Neurosci.*, **33**, 17483–17489.
- Frank, M.J., Samanta, J., Moustafa, A.A. & Sherman, S.J. (2007) Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science*, **318**, 1309–1312.
- Gilbertson, T., Lalo, E., Doyle, L., Di Lazzaro, V., Cioni, B. & Brown, P. (2005) Existing motor state is favored at the expense of new movement during 13–35 Hz oscillatory synchrony in the human corticospinal system. *J. Neurosci.*, **25**, 7771–7779.
- Goldberg, J.A. & Bergman, H. (2011) Computational physiology of the neural networks of the primate globus pallidus: function and dysfunction. *Neuroscience*, **198**, 171–192.
- Gould, I.C., Rushworth, M. & Nobre, A.C. (2011) Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. *J. Neurophysiol.*, **105**, 1318–1326.
- Gould, I.C., Nobre, A.C., Wyart, V. & Rushworth, M.F. (2012) Effects of decision variables and intraparietal stimulation on sensorimotor oscillatory activity in the human brain. *J. Neurosci.*, **32**, 13805–13818.
- Gradinaru, V., Mogri, M., Thompson, K.R., Henderson, J.M. & Deisseroth, K. (2009) Optical deconstruction of Parkinsonian neural circuitry. *Science*, **324**, 354–359.
- Guo, Y., Rubin, J.E., McIntyre, C.C., Vitek, J.L. & Terman, D. (2008) Thalamocortical relay fidelity varies across subthalamic nucleus deep brain stimulation protocols in a data-driven computational model. *J. Neurophysiol.*, **99**, 1477–1492.
- Hammond, C., Bergman, H. & Brown, P. (2007) Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci.*, **30**, 357–364.
- Hanslmayr, S., Staudigl, T. & Fellner, M.-C. (2012) Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. *Front. Hum. Neurosci.*, **6**, 74.
- Heimer, G., Rivlin-Etzion, M., Bar-Gad, I., Goldberg, J.A., Haber, S.N. & Bergman, H. (2006) Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of Parkinsonism. *J. Neurosci.*, **26**, 8101–8114.
- Hirschmann, J., Özkurt, T.E., Butz, M., Homburger, M., Elben, S., Hartmann, C.J., Vesper, J., Wojtecki, L. & Schnitzler, A. (2011) Distinct oscillatory STN-cortical loops revealed by simultaneous MEG and local field potential recordings in patients with Parkinson's disease. *NeuroImage*, **55**, 1159–1168.
- Jenkinson, N. & Brown, P. (2011) New insights into the relationship between dopamine, beta oscillations and motor function. *Trends Neurosci.*, **34**, 611–618.
- Joundi, R.A., Jenkinson, N., Brittain, J.-S., Aziz, T.Z. & Brown, P. (2012) Driving oscillatory activity in the human cortex enhances motor performance. *Curr. Biol.*, **22**, 403–407.
- Kilner, J., Bott, L. & Posada, A. (2005) Modulations in the degree of synchronization during ongoing oscillatory activity in the human brain. *Eur. J. Neurosci.*, **21**, 2547–2554.
- Kühn, A.A., Williams, D., Kupsch, A., Dowsey-Limousin, P., Hariz, M., Schneider, G.H., Yarrow, K. & Brown, P. (2004) Event related beta de-

- synchronization in human subthalamic nucleus correlates with motor performance. *Brain*, **127**, 735–746.
- Kühn, A.A., Kupsch, A., Schneider, G.-H. & Brown, P. (2006) Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur. J. Neurosci.*, **23**, 1956–1960.
- Kühn, A.A., Kempf, F., Brücke, C., Doyle, L.G., Martinez-Torres, I., Pogosyan, A., Trottenberg, T., Kupsch, A., Schneider, G.-H., Hariz, M.I., Vandenbergh, W., Nuttin, B. & Brown, P. (2008) High-frequency stimulation of the subthalamic nucleus suppresses oscillatory β activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J. Neurosci.*, **28**, 6165–6173.
- Kühn, A.A., Tsui, A., Aziz, T., Ray, N., Brücke, C., Kupsch, A., Schneider, G.-H. & Brown, P. (2009) Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Exp. Neurol.*, **215**, 380–387.
- Little, S., Pogosyan, A., Kuhn, A.A. & Brown, P. (2012) Beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. *Exp. Neurol.*, **236**, 383–388.
- Little, S., Pogosyan, A., Neal, S., Zavala, B., Zrinzo, L., Hariz, M., Foltynie, T., Limousin, P., Ashkan, K., FitzGerald, J., Green, A.L., Aziz, T.Z. & Brown, P. (2013) Adaptive deep brain stimulation in advanced Parkinson's disease. *Ann. Neurol.*, **74**, 449–457.
- Litvak, V., Jha, A., Eusebio, A., Oostenveld, R., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M., Friston, K. & Brown, P. (2011) Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain*, **134**, 359–374.
- Magill, P.J., Bolam, J.P. & Bevan, M.D. (2001) Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. *Neuroscience*, **106**, 313–330.
- Mallet, N., Pogosyan, A., Sharott, A., Csicsvari, J., Bolam, J.P., Brown, P. & Magill, P.J. (2008) Disrupted dopamine transmission and the emergence of pathological beta oscillations in the subthalamic nucleus and cortex. *J. Neurosci.*, **28**, 4795–4806.
- McIntyre, C.C., Grill, W.M., Sherman, D.L. & Thakor, N.V. (2004) Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. *J. Neurophysiol.*, **91**, 1457–1469.
- Moran, A., Stein, E., Tischler, H. & Bar-Gad, I. (2012) Decoupling neuronal oscillations during subthalamic nucleus stimulation in the parkinsonian primate. *Neurobiol. Dis.*, **45**, 583–590.
- Moshel, S., Shamir, R.R., Raz, A., de Noriega, F.R., Eitan, R., Bergman, H. & Israel, Z. (2013) Subthalamic nucleus long-range synchronization—an independent hallmark of human Parkinson's disease. *Front. Syst. Neurosci.*, **7**, 79.
- Murthy, V.N. & Fetz, E.E. (1996) Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. *J. Neurophysiol.*, **76**, 3968–3982.
- Ostrem, J.L., Marks, W.J. Jr., Volz, M.M., Heath, S.L. & Starr, P.A. (2007) Pallidal deep brain stimulation in patients with cranial-cervical dystonia (Meige syndrome). *Movement Disord.*, **22**, 1885–1891.
- Oswal, A., Litvak, V., Sauleau, P. & Brown, P. (2012) Beta reactivity, prospective facilitation of executive processing, and its dependence on dopaminergic therapy in Parkinson's Disease. *J. Neurosci.*, **32**, 9909–9916.
- Ozen, S., Sirota, A., Belluscio, M.A., Anastassiou, C.A., Stark, E., Koch, C. & Buzsaki, G. (2010) Transcranial electric stimulation entrains cortical neuronal populations in rats. *J. Neurosci.*, **30**, 11476–11485.
- Pastötter, B., Hanslmayr, S. & Bäuml, K.H. (2008) Inhibition of return arises from inhibition of response processes: an analysis of oscillatory beta activity. *J. Cognitive Neurosci.*, **20**, 65–75.
- Pfurtscheller, G. (1981) Central beta rhythm during sensorimotor activities in man. *Electroen. Clin. Neuro.*, **51**, 253–264.
- Plenz, D. (2012) Neuronal avalanches and coherence potentials. *Eur. Phys. J.- Spec. Top.*, **205**, 259–301.
- Pogosyan, A., Doyle Gaynor, L., Eusebio, A. & Brown, P. (2009) Boosting cortical activity at beta band frequencies slows movement in humans. *Curr. Biol.*, **19**, 1637–1641.
- Pogosyan, A., Yoshida, F., Chen, C.C., Martinez-Torres, I., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M.I. & Brown, P. (2010) Parkinsonian impairment correlates with spatially extensive subthalamic oscillatory synchronization. *Neuroscience*, **171**, 245–257.
- Pollok, B., Krause, V., Martsch, W., Wach, C., Schnitzler, A. & Südmeyer, M. (2012) Motor-cortical oscillations in early stages of Parkinson's disease. *J. Physiol.*, **590**, 3203–3212.
- Ponzi, A. & Wickens, J.R. (2013) Optimal balance of the striatal medium spiny neuron network. *PLoS Comput. Biol.*, **9**, e1002954.
- Ray, N.J., Jenkinson, N., Wang, S., Holland, P., Brittain, J.S., Joint, C., Stein, J.F. & Aziz, T. (2008) Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. *Exp. Neurol.*, **13**, 108–113.
- Ray, N.J., Jenkinson, N., Brittain, J., Holland, P., Joint, C., Nandi, D., Bain, P.G., Yousif, N., Green, A., Stein, J.S. & Aziz, T.Z. (2009) The role of the subthalamic nucleus in response inhibition: evidence from deep brain stimulation for Parkinson's disease. *Neuropsychologia*, **47**, 2828–2834.
- Ray, N.J., Brittain, J.S., Holland, P., Joundi, R.A., Stein, J.F., Aziz, T.Z. & Jenkinson, N. (2012) The role of the subthalamic nucleus in response inhibition: evidence from local field potential recordings in the human subthalamic nucleus. *NeuroImage*, **60**, 271–278.
- Rosa, M., Giannicola, G., Servello, D., Marceglia, S., Pacchetti, C., Porta, M., Sassi, M., Scelzo, E., Barbieri, S. & Priori, A. (2011) Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. *Neurosignals*, **19**, 151–162.
- Rosin, B., Slovik, M., Mitelman, R., Rivlin-Etzion, M., Haber, S.N., Israel, Z., Vaadia, E. & Bergman, H. (2011) Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron*, **72**, 370–384.
- Rubin, J.E. & Terman, D. (2004) High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. *J. Comput. Neurosci.*, **16**, 211–235.
- Sadek, A.R., Magill, P.J. & Bolam, J.P. (2007) A single-cell analysis of intrinsic connectivity in the rat globus pallidus. *J. Neurosci.*, **27**, 6352–6362.
- Schneidman, E., Puchalla, J.L., Segev, R., Harris, R.A., Bialek, W. & Berry, M.J. (2011) Synergy from silence in a combinatorial neural code. *J. Neurosci.*, **31**, 15732–15741.
- Schrader, C., Capelle, H.H., Kinfe, T.M., Blahak, C., Bänzner, H., Lütjens, G., Dressler, D. & Krauss, J.K. (2011) GPi-DBS may induce a hypokinetic gait disorder with freezing of gait in patients with dystonia. *Neurology*, **77**, 483–488.
- Spinks, R.L., Kraskov, A., Brochier, T., Umiltà, M.A. & Lemon, R.N. (2008) Selectivity for grasp in local field potential and single neuron activity recorded simultaneously from M1 and F5 in the awake macaque monkey. *J. Neurosci.*, **28**, 10961–10971.
- Surmeier, D.J., Mercer, J.N. & Chan, C.S. (2005) Autonomous pacemakers in the basal ganglia: who needs excitatory synapses anyway? *Curr. Opin. Neurobiol.*, **15**, 312–318.
- Swann, N., Tandon, N., Canolty, R., Ellmore, T.M., McEvoy, L.K., Dreyer, S., DiSano, M. & Aron, A.R. (2009) Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. *J. Neurosci.*, **29**, 12675–12685.
- Tan, H., Pogosyan, A., Anzak, A., Ashkan, K., Bogdanovic, M., Green, A.L., Aziz, T., Foltynie, T., Limousin, P., Zrinzo, L. & Brown, P. (2013) Complementary roles of different oscillatory activities in the subthalamic nucleus in coding motor effort in Parkinsonism. *Exp. Neurol.*, **248**, 187–195.
- Tass, P.A. & Majtanik, M. (2006) Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study. *Biol. Cybern.*, **94**, 58–66.
- Tripoliti, E., Zrinzo, L., Martinez-Torres, I., Pinto, S., Foltynie, T., Holl, E., Petersen, E., Roughton, M., Hariz, M.I. & Limousin, P. (2011) Effects of subthalamic nucleus deep brain stimulation on speech of consecutive patients with Parkinson's disease. *Neurology*, **76**, 80–86.
- Tzagarakis, C., Ince, N.F., Leuthold, A.C. & Pellizzer, G. (2010) Beta-band activity during motor planning reflects response uncertainty. *J. Neurosci.*, **30**, 11270–11277.
- Vaillancourt, D.E., Schonfeld, D., Kwak, Y., Bohnen, N.I. & Seidler, R. (2013) Dopamine overdose hypothesis: evidence and clinical implications. *Movement Disord.*, **28**, 1920–1929.
- Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A. & Pollok, B. (2013) Effects of 10 Hz and 20 Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. *Behav. Brain Res.*, **241**, 1–6.
- Weinberger, M., Mahant, N., Hutchison, W.D., Lozano, A.M., Moro, E., Hodaie, M., Lang, A.E. & Dostrovsky, J.O. (2006) Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. *J. Neurophysiol.*, **96**, 3248–3256.
- Weinberger, M., Hutchison, W.D., Alavi, M., Hodaie, M., Lozano, A.M., Moro, E. & Dostrovsky, J.O. (2012) Oscillatory activity in the globus pal-

- lidus internus: comparison between Parkinson's disease and dystonia. *Clin. Neurophysiol.*, **123**, 358–368.
- Whitmer, D., de Solages, C., Hill, B., Yu, H., Henderson, J.M. & Bronte-Stewart, H. (2012) High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. *Front. Hum. Neurosci.*, **6**, 155.
- van Wijk, B.C., Daffertshofer, A., Roach, N. & Praamstra, P. (2009) A role of beta oscillatory synchrony in biasing response competition? *Cereb. Cortex*, **19**, 1294–1302.
- Williams, D., Kühn, A., Kupsch, A., Tijssen, M., van Bruggen, G., Speelman, H., Hotton, G., Yarrow, K. & Brown, P. (2003) Behavioural cues are associated with modulations of synchronous oscillations in the human subthalamic nucleus. *Brain*, **126**, 1975–1985.
- Williams, D., Kühn, A., Kupsch, A., Tijssen, M., van Bruggen, G., Speelman, H., Hotton, G., Loukas, C. & Brown, P. (2005) The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. *Eur. J. Neurosci.*, **21**, 249–258.
- Wilson, C.J. (2013) Active decorrelation in the basal ganglia. *Neuroscience*, **250**, 467–482.
- Wilson, C.J. & Kawaguchi, Y. (1996) The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J. Neurosci.*, **16**, 2397–2410.
- Wilson, C.J., Beverlin, B. & Netoff, T. (2011) Chaotic desynchronization as the therapeutic mechanism of deep brain stimulation. *Front. Syst. Neurosci.*, **5**, 50.
- Wyart, V., de Gardelle, V., Scholl, J. & Summerfield, C. (2012) Rhythmic fluctuations in evidence accumulation during decision making in the human brain. *Neuron*, **76**, 847–858.
- Zaidel, A., Spivak, A., Grieb, B., Bergman, H. & Israel, Z. (2010) Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. *Brain*, **133**, 2007–2021.
- Zhang, Y., Chen, Y., Bressler, S.L. & Ding, M. (2008) Response preparation and inhibition: the role of the cortical sensorimotor beta rhythm. *Neuroscience*, **156**, 238–246.