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Pathological synchronization in Parkinson's disease: networks, models and treatments

Constance Hammond[1], Hagai Bergman[2] and Peter Brown[3]

[1] Institut de Neurobiologie de la Méditerranée, U29 Inserm, Université Aix-Marseille II and UMR CNRS 5543, Université Bordeaux 2, France
[2] Department of Physiology, The Eric Roland Center for Neurodegenerative Diseases and the Center for Neural Computation, The Hebrew University – Hadassah Medical School, Jerusalem, 91120, Israel
[3] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, WC1N 3BG, UK

Parkinson's disease is a common and disabling disorder of movement owing to dopaminergic denervation of the striatum. However, it is still unclear how this denervation perverts normal functioning to cause slowing of voluntary movements. Recent work using tissue slice preparations, animal models and in humans with Parkinson's disease has demonstrated abnormally synchronized oscillatory activity at multiple levels of the basal ganglia–cortical loop. This excessive synchronization correlates with motor deficit, and its suppression by dopaminergic therapies, ablative surgery or deep-brain stimulation might provide the basic mechanism whereby diverse therapeutic strategies ameliorate motor impairment in patients with Parkinson's disease. This review is part of the INMED/TINS special issue, *Physiogenic and pathogenic oscillations: the beauty and the beast*, based on presentations at the annual INMED/TINS symposium (http://inmednet.com/).

Parkinson's disease and its treatment

Parkinson's disease (PD) is a progressive age-related neurodegenerative disorder, second in frequency only to Alzheimer's disease. It affects tens of millions of people worldwide, and the frequency and associated socioeconomic burden of the condition are set to increase as the elderly population grows. The disease is characterized by poverty of voluntary movements (akinesia), slowness and impaired scaling of voluntary movement (bradykinesia), muscle rigidity and tremor of the limbs at rest. The core, but not exclusive pathology is the degeneration of the dopaminergic neurons in the substantia pars compacta (SNc) of the midbrain that project to the striatum. The latter is the major portal of the basal ganglia, receiving inputs from the cerebral cortex and thalamus, and projecting to the pallidonigral system.

The dopamine prodrug levodopa remains the gold standard for the treatment of PD. However, long-term use of levodopa over five to ten years is associated with the development of motor complications in up to 80% of patients. As a result, the past decade has seen a resurgence of interest in functional neurosurgery. In particular, high-frequency 'deep-brain stimulation' (DBS) of the subthalamic nucleus (STN) with implanted macroelectrodes can be an effective treatment. Surgery is often undertaken as a staged procedure. In the first operation, DBS macroelectrodes are implanted in the STN, with at least part of the procedure undertaken with the patient alert, so as to facilitate the prior functional localization of the target through intra-operative stimulation and microelectrode recordings of the activity of single neurons. Most surgeons then confirm adequate targeting through post-operative imaging, before returning the patient to theatre a day, or more, later for connection and insertion of the subcutaneous stimulator under general anesthesia.

The often dramatic response to functional neurosurgery for PD has renewed interest into how dopaminergic denervation might lead to parkinsonism and spawned the further question of how DBS might reverse motor impairment in this condition. At the same time, this iatrogenic intervention has enabled direct recordings from the human basal ganglia, allowing us to re-assess fundamental observations in animal models of parkinsonism. The latter establish that excessive synchronization of neuronal activity in basal ganglia cortical loops is the hallmark of activity in PD, while studies in patients suggest that exaggerated synchronization might be inextricably linked to motor dysfunction in this disease.

Cellular and network basis for oscillations in the basal ganglia

The operation of the basal ganglia network in health and disease is heavily determined by its dual composition: the striatum on the one hand and, on the other, all the other basal ganglia nuclei, comprising the globus pallidus pars externa (GPe) and interna (GPi), STN and the substantia nigra pars reticulata (SNr) (Figure 1). These two neuronal populations have different membrane properties and different organizational principles. Inside the second network,

Corresponding author: Brown, P. (p.brown@ion.ucl.ac.uk).
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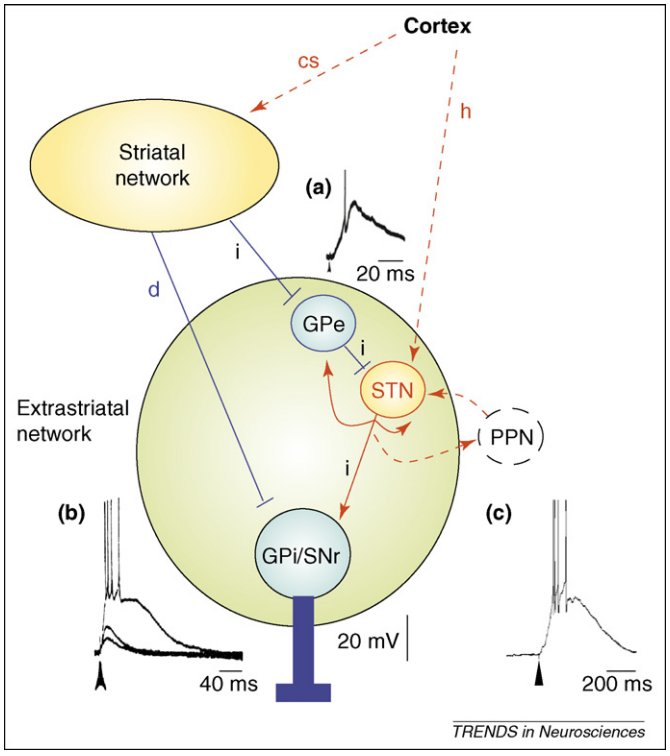

Figure 1. The two main networks inside the basal ganglia, the striatal network (not represented in detail) and the extrastriatal network. The striatum and the STN are both innervated by nigral dopaminergic terminals (yellow) and receive inputs from most cortical areas and frontal areas, respectively. STN neurons, the only glutamatergic neurons of the basal ganglia, send excitatory projections (red) to all nuclei of the extrastriatal network as well as to the pedunculopontine nucleus (PPN). In response to single-shock STN stimulation (black arrowhead on traces), polysynaptic EPSPs are recorded in **(a)** GPe [6], **(b)** GPi [72] and **(c)** SNr (Ammari *et al.* unpublished, see also Ref. [71] for EPSCs) neurons. These intracellular recordings have been obtained in slices *in vitro* during membrane hyperpolarization to suppress spontaneous activity and better see the EPSPs. For two of them [(b) GPi and (c) SNr] a $GABA_A$ antagonist was present in the bath, which might explain the long duration of the evoked EPSPs in comparison with those evoked in (a) GPe. Dotted lines represent pathways outside the basal ganglia.

STN deserves a special mention, given its special place in the surgical treatment of PD.

The striatum is the main input nucleus of the basal ganglia as it receives glutamatergic cortical inputs from all functional subdivisions of the neocortex [1,2]. This information is processed by a striatal network comprising 10% interneurons (GABAergic and cholinergic) and 90% GABAergic projection neurons, the so-called 'medium spiny neurons' (MSNs) that provide the sole striatal output. In physiological conditions, MSNs display up and down states. The down state is determined by the intrinsic inwardly rectifying K^+ current (I_{KIR} activated by hyperpolarization) that clamps the membrane potential at a hyperpolarized level. Up states are entirely triggered and maintained by coincident glutamatergic cortical inputs. Spiking during up states only occurs when excitatory synaptic inputs are of sufficient strength and duration to overcome the plethora of voltage- and synapse-driven inhibitory cellular systems including I_{KIR}, the fast inactivating K^+ currents (I_A and I_D) and the feed-forward and feed-back GABAergic inhibitions generated by local interneurons and axon collaterals, respectively [3–5]. The consequence of this organization is that MSNs seldom fire. Action potential discharge occurs during up states only in response to synchronized activity in many converging cortico-striatal afferents. This has led to the suggestion that MSNs shape their input–output relationship by filtering out uncorrelated synaptic cortical inputs.

The behaviour of striatal neurons contrasts with that of neurons in the GPe, STN, GPi and SNr. Each of these structures comprises a homogenous population of output neurons with intrinsic, spontaneous, tonic activity. STN neurons, for example, have an intrinsic depolarizing Na^+ current I_{NaP} that spontaneously brings the membrane potential to spike threshold. In addition, because of a low threshold Ca^{2+} current (I_T) GP, STN and SNr neurons readily generate rebound spiking following IPSPs [6–8]. Of this complex, STN neurons are the only neurons to be glutamatergic and to receive direct projections from the cortex (hyperdirect pathway from somato-motor cortical areas). They thus provide an important source of excitatory drive onto GPe, GPi and SNr (Figure 1). All these neurons form an extrastriatal network with local inhibitory and excitatory interneurons (GPe and STN) and projection neurons (GPi and SNr), which integrate two types of cortical information, one direct (hyperdirect pathway) and one already processed by the striatal network (direct and indirect pathways).

How do the basal ganglia 'read' cortical inputs under physiological conditions? Taking advantage of the cortical slow oscillations induced by urethane anaesthesia, the 'reading' of this cortical activity has been studied in the rat. Although up and down states correlated to those of the cortex are recorded in the MSNs [9], these neurons remain largely silent during up states because of their efficient inhibitory control. By contrast, STN neurons 'read' quite faithfully cortical up states and fire accordingly, although this does not influence most GPe and SNr neurons that discharge in tonic mode [10].

Depriving the basal ganglia of their dopaminergic innervation alters the 'reading' of cortical activity by the striatum [11] and STN. Thus, in 6-hydroxydopamine (6-OHDA)-lesioned rats, MSNs show a higher probability of firing during up states [9]. There is also an increased coupling between cortex and STN activities [12], with the transmission of slow cortical oscillations to the STN probably facilitated by feedback GABAergic inhibitory inputs from the GPe [13]. Many GPe and SNr neurons now display mixed bursting activities, which are all tightly correlated with coincident cortical rhythms and are disrupted by cortical desynchronization or after cortical ablation [12]. A similar behaviour occurs in many STN, GPe, GPi and SNr neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys.

What are the cellular mechanisms underlying this dramatic change in the 'reading' of cortical activity by the dopamine-depleted basal ganglia? This is still largely unknown mainly because cortical up and down states, and cortico-striatal connections together with the hyperdirect cortico-STN pathway are difficult to preserve in slices, the preparation of choice for the study of cellular and ionic mechanisms. The increased firing of MSNs might result from the absence of modulation by dopamine of their intrinsic K^+ currents, afferent glutamatergic EPSPs and local GABAergic IPSPs [14]. Alternatively, the greater impact of cortical oscillations on STN neurons could be

explained by the fact that STN neurons can now be synchronized by both hyperdirect and indirect cortical inputs. A local lesion of the dopaminergic fibres in the STN *in vivo* affects neuronal discharge less than does a lesion of the SNc, reflecting the influence of the indirect striato–GPe–STN pathway on STN aberrant activity [15]. The recent finding, that the isolated subthalamic-globus pallidus network *in vitro* obtained from dopamine-depleted mice is not itself sufficient to generate synchronous oscillatory activity of STN neurones [16], further supports the influence of a wider network in the generation of STN pathological activity [17]. Thereafter, STN neurons, via their abundant excitatory projections (Figure 1), might entrain their target neurons and maintain aberrant firing within the extrastriatal network. This would explain why diverse interventions at the level of the STN and its connections act to reduce synchronization unmasked by dopamine deficiency.

Excessive synchrony in animal models of PD

Monkeys treated with the toxin MPTP show an increase in the fraction of basal ganglia neurons that discharge in bursts. These bursts are either irregular or oscillatory (Figure 2) and have been found in STN, GPe and GPi [18]. In most cases, the bursts follow the frequency of tremor or its higher harmonics. Both STN inactivation [19] and dopamine replacement therapy [20] significantly ameliorate the MPTP tremor and other motor symptoms and reduce 8–20-Hz oscillations in GPi, supporting the crucial role of oscillations in this frequency band in the pathophysiology of PD symptoms.

Physiological studies of simultaneously recorded neurons in the pallidum, as well as among striatal cholinergic tonically active interneurons (TANs) and between TANs and pallidal neurons in MPTP-treated monkeys demonstrate that their oscillatory bursts are often also synchronized after MPTP treatment. In most cases, the maximal power of the synchronous oscillations was found to be at 10–12 Hz, that is, at double the tremor frequency [20]. As in the studies of oscillations in single neurons, the abnormal pallidal oscillatory synchronization between neurons decreases in response to dopamine replacement therapy [20].

Synchronicity in the nervous system is commonly seen among oscillating units and, therefore, might be assumed to share the same pathophysiological mechanisms. Indeed, many experimental and theoretical studies have revealed that increased neuronal coupling can lead to synchronous oscillations. However, mechanisms such as subthreshold cellular resonance phenomena and increased inhibitory coupling might contribute differentially to synchronization and oscillation, and it is of note that non-oscillatory synchronization has been found to coexist with oscillatory synchronization in the basal ganglia of MPTP-treated monkeys [20,21]. Thus, synchronization and oscillation might occur together or separately within the dopamine-depleted basal ganglia, probably reflecting biases in a variety of pathophysiological mechanisms in the parkinsonian state.

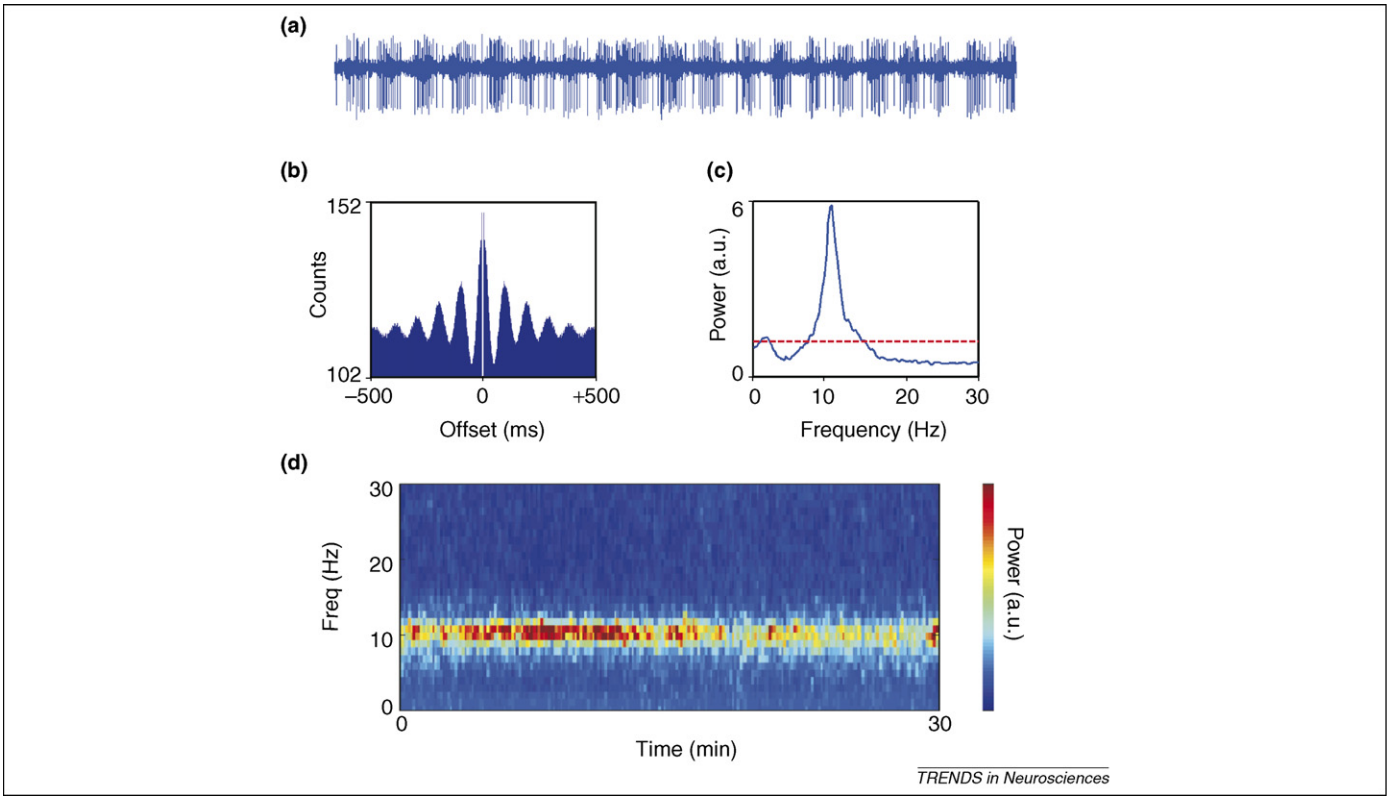

Figure 2. Oscillations (~10 Hz) of a single GPi neuron in the MPTP-treated monkey. The neuron was recorded for 30 min. **(a)** An example of two seconds of the raw analogue signal (amplified by 5000 and 300–6000-Hz band-pass filtered). **(b)** Autocorrelation function of the spike trains of this neuron. **(c)** Power spectrum and **(d)** spectrogram of the full period of the discharge of the cell, confirming that the latter is highly oscillatory, with a frequency centred on ~10 Hz (H. Bergman *et al.*, unpublished). Abbreviation: a.u., arbitrary units.

The studies of pairwise correlations between neurons discussed above might tend to underestimate the extent of synchrony present in the neuronal population as a whole. Even weak pairwise correlation can imply a highly synchronized network state [22]. In this regard, studies of local field potential (LFP) activity in the basal ganglia might be more informative. A study of LFP and spiking activity in the cortex and the basal ganglia of monkeys [23] concluded that, in the parkinsonian condition, cortex–basal ganglia networks are more tightly related to global modes of brain dynamics that are echoed by the cortex and basal ganglia LFP. LFP studies also serve to connect observations in the MPTP-treated primate and rodent models of parkinsonism to those in patients, where most observations relate to synchrony indexed by oscillations in the LFP. In the rodent, chronic and acute dopaminergic denervation leads to excessive oscillatory activity in basal ganglia LFPs that can be suppressed by treatment with dopamine agonists or levodopa [24,25]. Interestingly, the frequency of synchronization tends to be higher in the parkinsonian rodent than in the MPTP-treated primate and similar to that seen in patients with PD. Whether this relates to the reduced severity of the parkinsonian syndrome compared with the MPTP-treated primate or to bias introduced by different measures of synchrony remains to be established.

Excessive synchrony in patients with PD

LFPs are more readily recorded from the basal ganglia than the activity of single neurons in patients because the former recordings can also be made in the interval between surgical implantation of the STN or globus pallidus and connection of macroelectrodes to a subcutaneous stimulator a few days later (Figure 3a–c). LFP recordings in patients withdrawn from their antiparkinsonian medication have consistently revealed prominent oscillations between 8 Hz and 30 Hz [26–36], which we term the 'basal ganglia beta frequency band' (although acknowledging that this frequency range is broader than that termed beta in clinical studies of scalp electroencephalographic activity). It has been argued that these basal ganglia LFP oscillations are the product of synchronized subthreshold

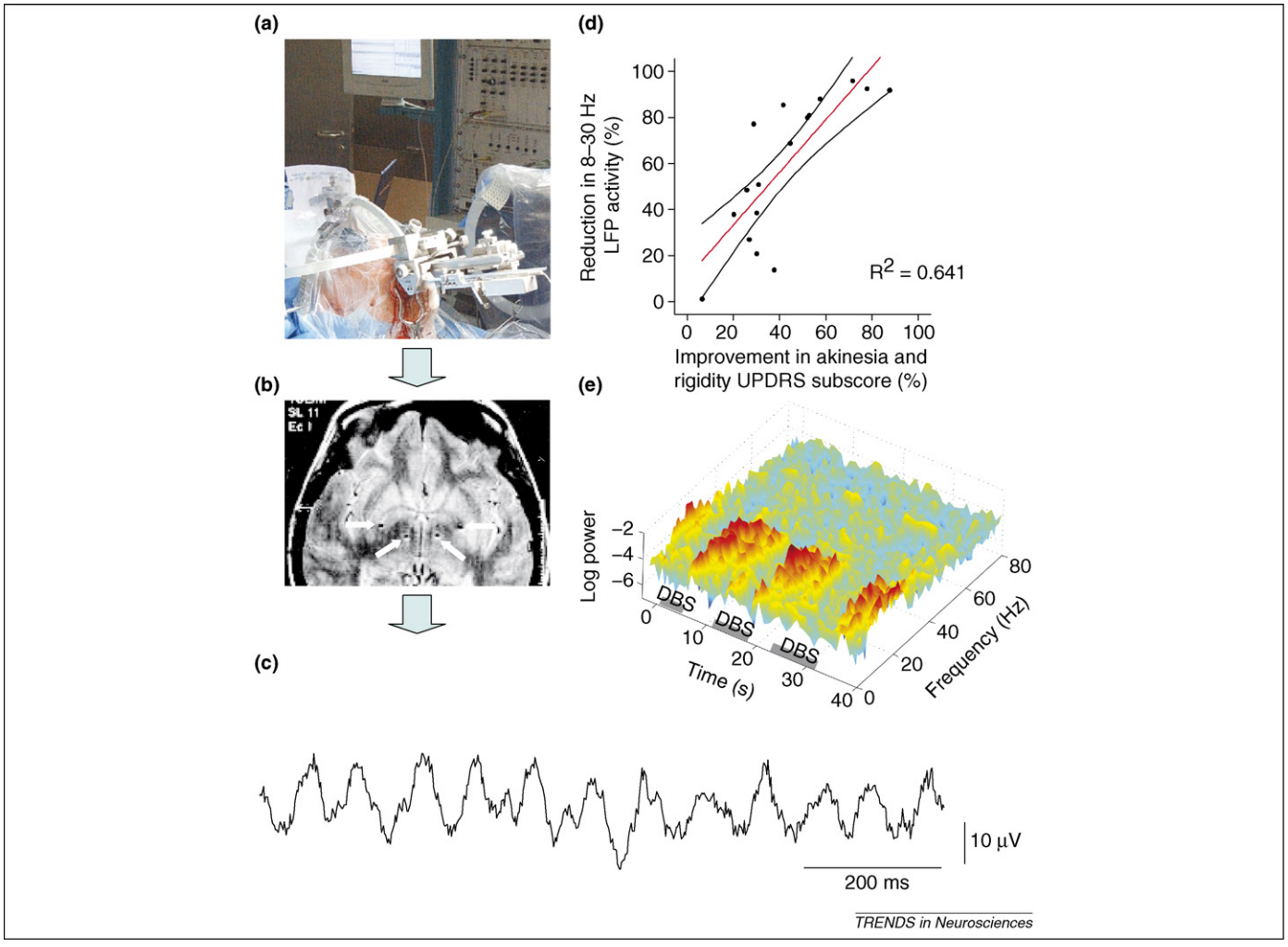

Figure 3. Treatment-related changes in synchronization in human PD. **(a)** DBS electrodes are implanted in the head of a patient with PD following localization of the target with the use of a stereotactic metal head frame and microelectrode recordings. **(b)** Post-operative magnetic resonance image showing artefact from DBS electrodes in globus pallidus (upper pair of arrows) and subthalamic nucleus (lower pair of arrows) bilaterally. **(c)** LFP activity at ~15 Hz recorded post-operatively from a DBS electrode in the STN. **(d)** Correlation ±95% confidence limits between the suppression of 8–30 Hz STN LFP activity induced by dopaminergic therapy and the improvement in bradykinesia (slowness of movement) and rigidity induced by dopaminergic therapy. **(e)** Time-frequency representation of pallidal LFP recorded during and between three periods of high frequency stimulation of the ipsilateral STN. The prominent LFP power over 8–30 Hz was suppressed during DBS (P. Brown *et al.*, unpublished).

activity across large populations of local neuronal elements and, hence, indicate pathological synchronization between neurons. This conclusion has been strongly supported by intra-operative recordings that demonstrate that local neuronal discharges in the STN, in particular, are locked to oscillatory LFP activity in the beta band [30,34]. Nevertheless, although LFP oscillations are locally generated, the excessive synchronization that they index is a feature of the whole basal ganglia–cortical loop, with coupled beta band oscillations identified in STN, globus pallidus and cerebral cortex [26].

Similar to the pathological synchronization in animal models of PD, the oscillatory LFP activity in the beta band in PD patients is suppressed by treatment with dopaminergic drugs in tandem with clinical improvement. This, together with the relative lack of beta LFP activity in the STN and GP in healthy animals, is the basis for presuming that beta activity in untreated patients is pathologically exaggerated. However, this remains to be conclusively established by comparison of STN recordings in patients with untreated PD with those made from this nucleus in patients without parkinsonism, such as patients implanted for the treatment of epilepsy.

The suppression of activity within the beta frequency band by treatment with dopaminergic drugs also suggests that synchronization might be related to motor impairment. Other correlative evidence in patients supports this view. First, beta oscillations in the LFP picked up in the STN and GP are reduced in PD patients before and during self and externally paced voluntary movements [26]. Exceptions to this rule are rare [32], and might relate to differences in electrode location or disease phenotype. Indeed, the mean timing of the drop in beta activity following a cue to move has been found to precede and positively correlate with the mean reaction time across PD patients [35] and even across single trials within individual subjects [36]. However, the major deficit in PD is bradykinesia, rather than prolongation of reaction time. To explain this deficit, beta suppression should be reduced during, as well as before, movement. Here the evidence is less clear, with some studies indicating reduced suppression during movement in untreated compared to treated patients [37,38], but others failing to replicate this finding and even suggesting that it is modulation of frequency in the beta band that is more relevant [32]. Finally, further evidence relating synchronization in the beta band to effective inhibition of motor processing has been sought by considering what happens when a pre-prepared movement requires cancellation, as in the 'Go and No-Go' paradigm. In this situation, and in line with the proposed antikinetic properties of beta synchrony, there is an augmentation of STN LFP activity in the beta band when patients with PD have to suppress a movement [35].

The beta frequency band described above is wide and there is increasing evidence that, within this broad grouping of oscillations, there might be more specific patterns of activity. Of particular relevance here is the division of LFP power into the lower (<20 Hz) and upper (>20 Hz) beta band, highlighted by the work of Priori and colleagues [31]. They stress that it is activity in the lower beta band that is sensitive to dopaminergic therapy and suggest that any drug-induced suppression in the upper beta band is due to harmonic 'contamination' from oscillatory activity in the low beta band [33]. The distinction is attractive, as it suggests that the exaggeration of oscillatory synchronization caused by parkinsonism *per se* occurs over the lower half of the beta band, at frequencies closer to those seen in animal models of parkinsonism. The corollary of this is that oscillatory activity in the upper beta band might be, in part, unrelated to PD and possibly physiological in nature [33]. There is also evidence for different patterns of pharmacological sensitivity [31] and cortico-subthalamic coupling that might support a relative functional division between activities in the beta band [29].

How might excessive synchrony impair motor processing?

Information theoretic studies reveal that the information encoded by the simultaneous activity of neurons can be independent, redundant or synergistic [39,40]. These activity modes are strongly, but not simply, related to the level of pairwise correlations between the neuronal elements of the network [41]. Usually, one can assume that a correlated network is redundant, offering stability against the possible results of the extinction of one or several neurons in the network. In that case, the information encoded by the neuronal population will be smaller than the sum of information encoded by its single elements because of the mutual information shared between neurons. At least in the cortex, however, correlation has also been suggested as a means of increasing information flow [42]. Here, the loss of information across the population brought about by correlation is more than offset by the preferential processing and decoding of synchronized inputs by downstream neurons and networks. The combination of signal correlation (correlation between the average responses of two neurons to events, indicating their tendency to respond similarly), and noise correlation (the correlation between intertrial fluctuations of the neuronal responses) can, for example, create this synergetic information coding [40]. Nevertheless, systems must reach a point at which the mutual information shared between neurons through correlation within a network has a greater functional impact than any potential advantage conferred upon the transmission of network output downstream. In epilepsy, for example, extreme synchronization paralyses local functioning, despite the superlative nature of downstream transmission. In effect, prominent synchronization limits the space available for information coding through spatial selectivity and/or temporal patterning.

Neuronal networks are built of millions of weakly coupled elements (neurons), with a rich plethora of reciprocal, feedforward and feedback connections. Any physical system with such architecture faces a huge tendency to synchronize (for examples and highly readable theoretical analysis see Ref. [43]). It is therefore not surprising that synchrony of neural networks characterizes many disease states [42], including epilepsy and PD [44]. Indeed, some theoretical models have suggested that the computational goal of the basal ganglia networks is to maximize the representation of the cortical information by using decorrelation mechanisms controlled by dopamine reinforcement signals [45].

Normally, what synchronization there is in the basal ganglia is suppressed before and during movement [46], but in PD, baseline levels of synchrony can be elevated and relatively resistant to suppression, so that the selection and compression of cortical information can be impaired. As in many physical systems [43], the neuronal synchronization phenomenon can be the result of phase transition (bifurcation). Accordingly, the amount of synchronization in the network might not be a linear function of the striatal dopamine level, rather, at some critical point, the number of synchronous neurons in the basal ganglia network can increase exponentially.

Do therapies for PD suppress excessive synchrony?

PD is treated today mainly by dopaminergic drugs, particularly levodopa, deep-brain stimulation or lesioning of the basal ganglia. The latter suppresses spontaneous beta synchrony at the operation target, but what of the other therapeutic approaches? As already stated, treatment with dopaminergic drugs suppresses beta synchrony, particularly that at lower frequencies within this band. This relationship is a graded one, with the amount of drug-induced suppression in the STN [27] and cerebral cortex [47] linearly correlating with the level of improvement in bradykinesia and rigidity (Figure 3d). There is also increasing evidence that high-frequency deep-brain stimulation suppresses pathologically synchronized activity at both basal ganglia (Figure 3e) ([48–50], but see Ref. [51]) and cortical levels [47]. Again, at least at the cortical level, the relationship between DBS-induced beta suppression and improvement in bradykinesia and rigidity is approximately linear. In all these studies, the relationship is between treatment-induced beta suppression and motor improvement. A relationship between beta activity *per se* and motor impairment in untreated patients is less consistent [30,47], perhaps because patients undergoing DBS have fairly advanced PD, where some of the baseline motor deficits, such as tremor, and gait and balance dysfunction are not simply dictated by the level of dopaminergic loss and related synchronization.

In these clinical studies, it is conspicuous that treatment-induced suppression of synchrony does not correlate with the degree of improvement in rest tremor, and an early report of an association between beta band activity in the basal ganglia and tremor was not replicated in a larger study from the same group [30]. This is somewhat paradoxical given that parkinsonian rest tremor involves excessive synchronization in the brain, albeit at lower frequencies [52,53]. Nevertheless, a dichotomy between bradykinesia, rigidity and parkinsonian rest tremor is well recognized clinically and finds expression in the differential sensitivity of these parkinsonian signs to treatment with dopaminergic agents and DBS of the cerebellar projection nucleus in the thalamus. The implication is that beta synchrony can contribute to bradykinesia and rigidity, but not to parkinsonian rest tremor, which probably has an independent pathophysiological substrate, a view supported by a recent re-appraisal of findings in MPTP treated primates [54].

Understanding the effect of DBS at the cellular and network level has proven challenging because of the small delay between the artefact of stimulation and the neuronal response. This explains the discrepancies of results obtained with extracellular and intracellular recordings, the latter allowing a better signal:noise ratio. In fact, monopolar, cathodic, high-frequency, long-lasting stimulation of the STN *in vitro* suppresses all spontaneous STN spikes and replaces them by spikes entirely driven by the stimulation [55]. The stimulation-driven STN activity consists of spikes locked to one out of two or three stimuli. Similar results have been reported in MPTP-treated monkeys, either in the form of resetting of STN activity during STN–DBS [50] or in the complex locking of pallidal activity during GP–DBS [56]. In tissue slice preparations, the suppression of spontaneous activity outlasts the stimulation for several seconds or minutes and is seen as a silence upon termination of the stimulation, paralleling the after-effect of DBS seen in some patients with PD [57]. It is notable that DBS must be given at a frequency above 50 Hz to be therapeutic [58] and only stimulation above 50 Hz reliably suppresses the spontaneous activity and imposes a new pattern to local STN neurons in slice preparations [59].

However, the possibility that STN–DBS acts not only by cutting down aberrant STN activity, but also by projecting a new activity to GPi and SNr, the output structures of the basal ganglia, should not be forgotten. In other words, is DBS different from or equivalent to a lesion? *In vivo* studies in conditioned MPTP monkeys [60], control [61] or neuroleptic-treated rats [62] suggest that the high-frequency stimulation-driven activity of STN neurons is transmitted to GPi, GPe and SNr. Moreover, the recent observations that stimulation of inputs to the STN, including the motor cortex (at high frequency) and pedunculopontine nucleus (at low frequency), also partly alleviate the motor symptoms of MPTP-treated monkeys [63,64] cannot readily be reconciled with the silence or lesion hypothesis. Stimulation of excitatory pathways afferent to the STN is unlikely to cause a silence of the STN but probably reshape the temporal structure of STN activity, as shown in the GP of MPTP-treated monkeys [60]. This suggests that some of the therapeutic action of DBS is due to driven activity that mimics the synchronization in the gamma band [25,26] or at even higher frequencies [65] reported in basal ganglia circuits following dopaminergic therapy. In essence, the new output driven by the stimulation might be more palatable to basal ganglia–cortical loops and their targets than to the suppressed synchronization at lower frequency.

Conclusion and future research

There are increasing amounts of data linking excessive synchrony at low beta frequencies in basal ganglia-cortical loops to impaired motor processing in PD. Nevertheless, this evidence remains correlative in nature and is notably challenged by a recent model of basal ganglia function that suggests that action selection is impaired before the appearance of oscillations [66], although interpretation of this model in the context of PD assumes that failure of action selection leads to bradykinesia. Accordingly, there is a need for studies that establish whether excessive synchronization causes bradykinesia.

One approach would be to demonstrate a significant impairment of motor function during extrinsic synchronization of BG activity through direct stimulation at frequencies within the beta band. Although the worsening of bradykinesia has been reported following 10 Hz [67] and 20 Hz [68,69] stimulation in the region of the STN in patients with PD, these effects were relatively small, perhaps because they were limited by ceiling effects in the untreated drug state or because extrinsic stimulation with trains of single pulses is a poor mimic of spontaneous beta synchrony, which can involve multiple discharges with each cycle [34].

Another issue that requires further clarification is why the synchronization occurs at lower frequencies in the MPTP-treated monkey. One possibility, already alluded to, is the greater severity of the parkinsonism in this model. If so, then one might expect the peak frequency of synchronization to fall progressively in monkeys exposed to more chronic MPTP poisoning. This is an intriguing idea, as it implies that the nature of synchronization evolves as dopaminergic denervation progresses. If so, then this evolution might plausibly explain some of the phenotypic progression in PD, particularly if different basal ganglia-cortical loops have partially independent resonance frequencies so that their relative involvement in pathological synchronization changes over time [29].

Finally, whether synchronization is an epiphenomenon or truly pathogenic in PD, it provides a clear biological marker for the disease process. This could form the basis for drug screening studies in the 6-OHDA midbrain-lesioned rodent, as well as the basis for smart stimulation regimes [70] for human PD patients, which sense beta LFP activity as a measure of concurrent motor impairment and deliver stimulation accordingly.

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