In: The Basal Ganglia VIII (Editors: Bolam, J.P., Ingham, C.A. and Magill, P.J.) Springer Science and Business Media, New York. Published in 2005.

# OSCILLATIONS IN THE BASAL GANGLIA: The good, the bad, and the unexpected

Thomas Boraud, Peter Brown, Joshua A. Goldberg, Ann M. Graybiel, and Peter J. Magill*

## 1. INTRODUCTION

Oscillations are present at many levels in the basal ganglia (BG), and can describe regular fluctuations in, for example, gene expression, current flow across the plasma membrane, the firing rate of a single neuron, the activity within and between small networks of neurons, and activity at the level of whole nuclei. Many BG neurons, including those of the subthalamic nucleus, globus pallidus (both segments), substantia nigra (both divisions), and some striatal interneurons, are endowed with a battery of intrinsic membrane properties that promote the expression of oscillatory discharge at both 'rest' (or in functional isolation) and in response to organized synaptic input (Richards et al., 1997; Bennett and Wilson, 1999; Bevan et al., 2002). The oscillatory activity of a single cell may or may not be synchronized with the oscillatory activity of another cell or network of cells. Indeed, oscillation and synchronization are distinct properties of neuronal networks. This is well illustrated in the BG; while the firing patterns of pallidal neurons are strongly periodic, the discharges of pairs of these neurons are typically uncorrelated (Bergman et al., 1998; Boraud et al., 2002). Conversely, the activity of BG neurons may be synchronized to within milliseconds but without being strongly periodic. These facts aside, it may be that *synchronized oscillations* offer the BG, and indeed the whole brain, something more than the simple sum of the parts (Steriade, 2000; Engel et al., 2001; Buzsáki and Draguhn, 2004). For example, they may provide the brain with a mechanism to execute tasks that require the combined function of distant and disparate

* Thomas Boraud, Basal Gang., Laboratoire de Neurophysiologie, CNRS UMR 5543, Université Victor Segalen Bordeaux, 33076 Bordeaux, France. Peter Brown, Sobell Dept. of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, WC1N 3BG, UK. Joshua A. Goldberg, Dept. of Biology, University of Texas at San Antonio, San Antonio, TX 78249, USA. Ann M. Graybiel, Dept. of Brain & Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. Peter J. Magill, MRC Anatomical Neuropharmacology Unit, University of Oxford, Oxford, OX1 3TH, UK.

neural networks (Engel et al., 2001). This premise is of great importance in terms of cultivating research on the candidate mechanisms that underlie the elusive 'neural code'.

In this chapter, we will explore the evidence for synchronized network oscillations in the BG. We will focus on those oscillations that are generated by the coordinated and correlated activity of populations of neurons in the BG and their afferent partners *in vivo*. Research on synchronized network oscillations in the BG is still at an early stage. Perhaps as a consequence of this, the intrinsic cellular and circuit mechanisms that must underlie such oscillations remain obscure. Whilst it is conceivable that the intrinsic oscillations of single BG neurons can serve as the basis for collective synchrony and thus, the expression of such network oscillations, we will not venture further than to highlight this interesting possibility. We discuss the hypothetical roles played by synchronized network oscillations that permeate cortico-basal ganglia circuits during motor and cognitive behaviours, and we will re-examine the common view that synchronized network oscillations are primarily a feature of the diseased BG. New data suggest that oscillatory activity within the BG, and particularly the striatum and subthalamic nucleus, is prevalent during, and thus, may be important for, normal behaviour (the "Good"). We also take into account recent studies in humans, specifically patients with Parkinson's disease, that have reinforced the idea that BG population activity synchronized in certain frequency bands may be counter-productive or pathological in the truest sense (the "Bad"). Finally, we synthesise these discussion points in the context of fresh insight into the co-evolution of parkinsonian motor symptoms and BG oscillations (the "Unexpected").

## 2. PREVALENCE OF SYNCHRONIZED OSCILLATIONS IN CORTICO-BASAL GANGLIA CIRCUITS

All oscillations have a frequency associated with them. Oscillatory activities with a wide ranged of frequencies have been reported to occur in the healthy and diseased BG, with examples reported for each constituent nucleus. Thus, oscillations in the subthreshold and suprathreshold activities of single neurons or networks of neurons have been reported to occur at 'ultra-slow' frequencies (0.05-0.5 Hz; Allers et al., 2002; Ruskin et al., 2003) and at frequencies commonly associated with sleep rhythms, such as 'slow-wave activity' (~1 Hz: Stern et al., 1998; Magill et al., 2000, 2001, 2004b; Goto and O'Donnell, 2001a) and 'spindles' (5-12 Hz: Magill et al., 2000, 2004b, 2005; Berke et al., 2004). Some BG oscillations are synchronized within other frequency bands, such as the 'theta' band (4-10 Hz: Brown et al., 2002; Berke et al., 2004; DeCoteau et al., 2004, 2005), the 'alpha' or 'mu' band (8-15 Hz: Raz et al., 2000; Goldberg et al., 2002, 2004), the 'beta' band (15-30 Hz: Levy et al., 2000, 2002b; Brown et al., 2001; Williams et al., 2002; Courtemanche et al., 2003; Magill et al., 2004b; Sharott et al., 2005a), and the 'gamma' band (30-90 Hz: Brown, 2003; Brown et al., 2002; Berke et al., 2004; Masimore et al., 2004). The gamut of synchronized oscillations that occur in the BG extends to 'ultra-fast' frequencies at around 300 Hz (Foffani et al., 2003).

Oscillations in the BG are often defined according to frequency bands that were established decades ago to distinguish between the oscillatory phenomena that are widespread in the neocortex, thalamus and hippocampus (Steriade, 2000; Buzsáki, 2002, Buzsáki and Draguhn, 2004). The functions that may be subserved by synchronized oscillatory activity within and between ensembles of cortical and thalamic neurons have

received much attention over the last twenty years (for reviews, see MacKay, 1997; DeCharms and Zador, 2000; Steriade, 2000; Engel and Singer, 2001; Engel et al., 2001; Buzsáki, 2002; Buzsáki and Draguhn, 2004). It is now well established that neurons in both cortical and subcortical structures can synchronize their discharges to within a few milliseconds, and that such synchrony is often subject to oscillatory modulation. Importantly, synchronized network oscillations are present across systems and species, and the degree and/or frequency of synchronization is often task-dependent or at least dependent on behaviour (see Steriade, 2000; Engel and Singer, 2001). The existence of complex, brain state-dependent synchronizations of neuronal activity in different frequency bands raises the possibility that synchronization itself may be mechanistically important in the functional organization of these circuits. In particular, oscillatory synchronization of activity at frequencies of >20 Hz has been suggested to offer one solution to the so-called 'binding problem' (Engel and Singer, 2001; Engel et al., 2001). That is to say the problem of how to define dynamic functional relations between anatomically-distributed neuronal networks. The functional coupling of circuits through coherent oscillations may facilitate the binding together of distributed neural assemblies during, for example, sensory-motor integration (MacKay, 1997; Roelfsema et al., 1997; Engel and Singer, 2001; Engel et al., 2001). Entrainment of afferents and their targets during synchronous network oscillations could also underlie the cooperativity that is thought to be essential for the long-term modification of synaptic weights (Buzsáki, 2002).

One fundamental issue is whether the BG employ the same strategy for information processing that has been hypothesized to be favoured in the cortex and thalamus, the two structures that together provide the bulk of the extrinsic input to the BG. There is some evidence to suggest that the BG do not encode information in the same way as the cortex, and that the BG might instead perform some sort of active desynchronizing process, as a function of a 'dimensional reduction' of their cortical input (Bar-Gad et al., 2003). The idea that the BG and cortex use distinct mechanisms for information processing seems logical enough in the face of such striking differences in their physiological and anatomical properties. Yet, it would be somewhat surprising if BG networks could not at least distinguish between synchronous oscillatory inputs and a bombardment of uncorrelated and/or arrhythmic inputs. The mechanisms that may underlie the (presumably) meaningful dialogue between the oscillating circuits of the thalamus/cortex and the neuronal networks of the BG are unknown, although the finding of coherent network oscillations in cortico-basal ganglia circuits supports the idea that a dialogue founded on oscillatory activity could take place (Marsden et al., 2001; Williams et al., 2002; Magill et al., 2004b, Sharott et al., 2005b). To determine whether synchronized network oscillations carry information or serve some other computational role, the description of a feasible 'readout' mechanism for the information is required. One hypothetical readout mechanism, as proposed for the hippocampus, is founded on differences in frequency and phase between the subthreshold membrane oscillations of a select few neurons and the synchronized oscillations of the network in which they are embedded (Buzsáki, 2002; Buzsáki and Draguhn, 2004). It is not known whether a readout mechanism exists in the BG or, if it does exist, how it operates. However, with a viable readout mechanism, it is possible that synchronized oscillations in cortico-basal ganglia networks could solve the binding problem by creating a common temporal reference or 'master clock' for the computations carried out in distant regions. The idea

that the BG could encode or transfer information in synchronized oscillations (for better or worse) will be discussed below in more detail.

## 3. RECORDING AND ANALYZING SYNCHRONOUS OSCILLATIONS

Before exploring synchronized oscillations in the BG in more detail, it is important to consider the methods that may be employed to record and analyze oscillatory and synchronized activity. Two distinct, but largely complementary measures, single-/multi-unit activity and local field potentials (LFPs), are most commonly used to determine the prevalence of synchronized and/or oscillatory activity in networks of neurons. The former represents the suprathreshold activity *i.e.,* action potential discharges, of one cell or a small group of neurons. In contrast, LFPs are dominated by synchronized, subthreshold and, to a lesser extent, suprathreshold events in much larger populations of neurons (see section 3.1). In practical terms, single-/multi-unit activity and LFPs may be recorded simultaneously or independently. Single-/multi-unit activity is typically recorded with electrodes of relatively high impedance (*e.g.* 0.5-20 MΩ), whereas LFPs can also be recorded with electrodes of much lower impedance (*e.g.* >0.05 MΩ). The major frequency components of single-/multi-unit activity are at least an order of magnitude faster than those of LFPs and, as such, these signals can be isolated from each other with appropriate high-pass and low-pass filtering.

We must defer to statistics to determine whether a given stationary stochastic process, which might be a *point process* (*e.g.* a 'spike train' derived from unit activity) or a *time series* (*e.g.* LFP), is oscillatory. Analyses can be based in either the time domain or frequency domain. In the time domain, *auto-correlograms* can be constructed to test for oscillations in the spike train of a single neuron (Fig.1A; Perkel et al., 1967a; Abeles, 1982; but see Bar-Gad et al., 2001). Similarly, *autocovariance sequences* can be computed in search of periodicities in time series, such as LFPs or the electroencephalogram (EEG). However, spectral analysis in the frequency domain is preferable over time-domain analyses because the estimation of oscillatory activity at each frequency is, in principle, independent of any other. The statistical significance and frequency of rhythmic activity can be assessed in the frequency domain using spectral analysis methods, most commonly based on the discrete or finite Fourier transform (FFT: Brillinger, 1975; Halliday et al., 1995). The *power spectrum* displays the frequency decomposition of the stationary process.

The occurrence of significant peaks in the power spectrum of the LFP is indicative of synchronized network oscillations, because LFPs likely reflect the synchronous activity of many neurons. The principal statistical tool used for determining the relationship between pairs of spike trains in the time domain is the cross-correlation histogram or *cross-correlogram* (Perkel et al., 1967b). The presence of a significant peak and/or trough in these histograms can indicate a firing rate co-variation, or even spike-to-spike synchronization, between the pair of neurons (Fig.1B). The deviation of the centre peak from zero time shows the latency of interaction between the pair. Importantly, cross-correlograms can be used to discriminate between non-oscillatory and oscillatory firing relationships. Indeed, synchronous oscillations are reflected as side peaks or lobes in the histogram (Fig.1C).

Analyses of mixed point process/time series data describing two stochastic processes can also be performed in either the time or frequency domains (Halliday et al., 1995; also

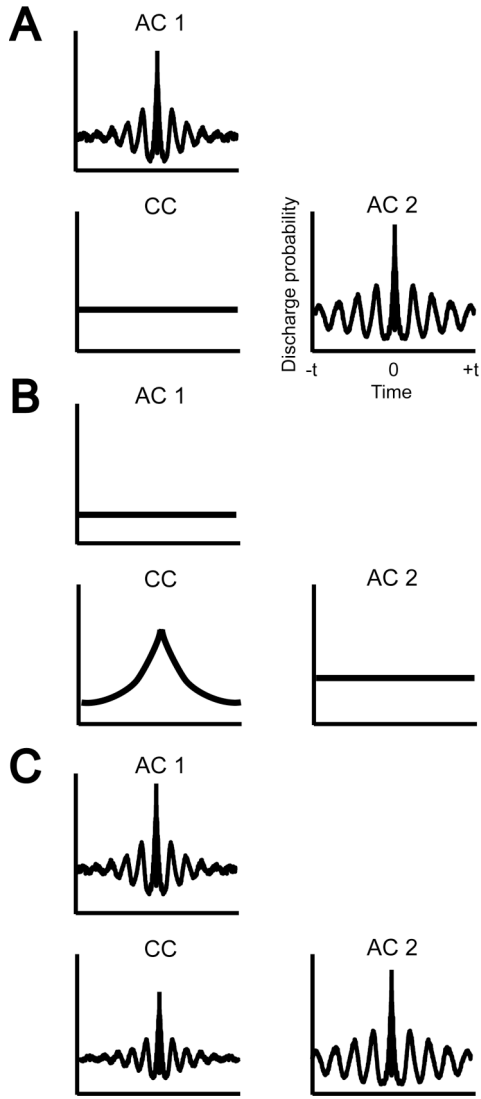


**Figure 1.** Permutations of auto-correlograms and cross-correlograms. *A:* Multiple peaks/troughs in the auto-correlograms of neurons 1 and 2 (AC1 and AC2, respectively) indicate that the firing of each neuron is oscillatory. However, the flat cross-correlogram (CC) suggests that the firing of the pair is not related. *B:* The flat auto-correlograms in this example imply that neither cell is engaged in oscillatory activity. However, the single peak in the CC indicates that there is a non-oscillatory co-variation in the firing of the pair. *C:* In this case, both neurons discharge in an oscillatory manner. The multiple side peaks/troughs in the corresponding CC suggest that there is also an oscillatory firing relationship between this pair of neurons.

see the chapter by Goldberg and Bergman in this volume for a formalism for such mixed processes). Thus, in the time domain, *spike-triggered averages* or *cumulant density estimates* may be calculated to characterise the relationship between the activity of a

single neuron and that of the greater neuronal population, as reflected in the LFP. These measures are particularly useful because they provide information on the relative timing of synchronized oscillatory activity. A useful frequency-domain measure of synchronized oscillations is *coherence* (Halliday et al., 1995). Coherence is a measure of the linear association between two stochastic processes and thus, oscillations must be temporally coupled (phase locked) and their amplitudes must have a constant ratio to be coherent at any given frequency. The relative timing of synchronized (coherent) oscillations can be extrapolated from the related *phase* estimates (Halliday et al., 1995). Unfortunately, paradoxical phase estimates can arise when different coherent activities have overlapping frequency components, which is particularly likely in highly interconnected circuits, such as the cortico-basal ganglia loops. In some cases, difficulties in assessing the effective timing or direction of coherent activity may be overcome with other statistical methods, such as the Directed Transfer Function (Sharott et al., 2005b).

It should be noted that local stationarity of data is a prerequisite for these statistical analyses. Because most contemporary methods require the averaging of data gathered over relatively long periods of time, measures of apparent synchrony, coherence and oscillatory power are often challenged by oscillations that are fleeting, weak or highly dynamic (*e.g.* phase-variable). The successful detection and analysis of synchronized oscillations will be a direct function of the networks examined. Studies in awake and anesthetized animals have shown that high-frequency oscillations can be effete and focal in nature, especially in sensorimotor systems (Murthy and Fetz, 1992, 1996a; Sanes and Donoghue, 1993; MacKay, 1997; Donoghue et al., 1998; Destexhe et al., 1999). Indeed, correlations between single unit and population activities are sometimes elusive, perhaps as a consequence of the rapid recruitment of neurons to, and release from, the population oscillation (Murthy and Fetz, 1992, 1996b; Donoghue et al., 1998).

### 3.1. The Nature of Local Field Potentials Recorded in the Basal Ganglia

The last five years has seen renewed interest in the recording of LFPs in the BG (Brown, 2003). Recordings of single-/multi-unit activity and LFPs are complementary, both in terms of the different scales of synchronized activity that are reflected by these measures and the distinct mechanistic insights that are offered. There is much evidence from studies of laminated structures, such as the neocortex, hippocampus, olfactory bulb, and cerebellum, that LFPs are representative of the aggregate activity of local neuronal populations (Creutzfeldt et al., 1966a,b; Frost, 1968; Hubbard et al., 1969; Mitzdorf, 1985). Currents must be synchronized in time and space in order to significantly influence the field potential. The spatiotemporal summation of currents in a neuronal network is promoted by a regular arrangement of the constituent elements *e.g.* the regimented apical dendrites of principal neurons of the cerebral cortex. Although synchronized action currents or presynaptic currents can be observed in the LFP, as a ‘population spike’ or a ‘fiber volley’, respectively, it is almost certainly the case that LFPs better reflect synchronized, subthreshold currents generated in the somata and dendrites of local neuronal elements (Hubbard et al., 1969; Mitzdorf, 1985).

Although the neural basis of LFPs recorded in layered structures is reasonably well characterized, we currently lack a clear mechanistic understanding of how LFPs are generated in non-layered structures, such as the BG. In fact, it is somewhat surprising that such potentials exist in regions like the BG because their anatomy would be predicted to oppose the generation of strong fields. This of course raises the possibility that LFPs

recorded in the BG are the result of the passive spread of currents generated in other brain areas (so-called 'volume conduction'), rather than the subthreshold and suprathreshold activities of local networks of BG neurons. Nevertheless, there is evidence to support the notion that LFPs recorded in the BG also reflect synchronized aggregate activity. Local field potentials can be registered in the BG using a differential recording configuration, with a near-field reference, which would be predicted to minimize contamination by volume conduction (Brown et al., 2001, 2002; Courtemanche et al., 2003; DeCoteau et al., 2005; Sharott et al., 2005a). Moreover, LFPs recorded across BG nuclei can show a phase shift or polarity reversal, which would not be expected for volume-conducted potentials (Brown et al., 2001). In defining a population oscillation, it is important to demonstrate a relationship between synaptic activity (presumed to be reflected globally in the LFP) and the output of active cells (as reflected in spike trains). Temporal coupling of single-/multi-unit activity to the LFP has been reported for several different oscillations in the BG, thereby substantiating the idea that LFPs can be generated locally by BG neurons (Goto and O'Donnell, 2001a; Levy et al., 2002a; Courtemanche et al., 2003; Berke et al., 2004; Goldberg et al., 2004; Magill et al., 2004a,b; DeCoteau et al., 2005; Kühn et al., 2005). These issues are discussed in more detail by Walters et al. and Berke elsewhere in this volume. This temporal coupling of input and output activities in the BG further suggests that their targets could receive synchronized oscillatory inputs.

Despite, or perhaps because of, the limitations and uncertainties that are commonly assigned to recordings of LFPs in the BG, it is important to ascertain what LFPs can tell us about the dynamics of neuronal activity in these structures. To refine our understanding of the LFPs, we can study their relationship to another widely-used measure of collective synchrony, the pair-wise cross-correlogram. Elsewhere in this volume, Goldberg and Bergman describe a partial-spectra based method for using the LFP to predict the pairwise cross-correlograms between pairs of neurons. They have recently applied this method to predict cross-correlograms of neurons recorded in the cortex and BG of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated parkinsonian primates (Goldberg et al., 2004). They found that the LFP was a better predictor of the cross-correlograms in the MPTP-treated monkeys than the cross-correlograms in the healthy control animals. This was true regarding neuronal correlations in cortex, among the tonically active neurons (TANs) of the striatum, among pallidal neurons, and between TANs and pallidal neurons. Thus, LFPs may be a useful indicator of the synchronized activity of BG neurons. These findings further suggest that brain dynamics become more 'globalized' in the MPTP-treated parkinsonian condition. In addition, several of the cross-correlograms and spike-triggered averages of the LFPs that were generated following the MPTP treatment showed the presence of oscillatory activity at 10 Hz, indicating a propensity for global, albeit intermittent, oscillations in the diseased condition (see section 5 below).

## 4. THE GOOD: SYNCHRONIZED OSCILLATIONS IN THE HEALTHY BASAL GANGLIA

In contrast to the extensive experimental evidence that oscillatory activity is a prominent feature of the thalamus, neocortex and hippocampus in the normal state, most studies, until very recently, suggested only low levels of oscillatory activity in the BG under normal conditions. This situation has changed, and this change has brought the

challenge of trying to determine the functional significance of such oscillatory activity. The paucity of evidence for oscillatory activity in the BG of behaving animals stands in contrast to growing evidence that oscillatory activity is a property of subthalamo-pallidal circuit neurons, key modulators not only of the output of the BG to the thalamus, but also of other parts of the BG circuitry, including the striatum (Bevan et al., 2002). Yet all studies agree that only small numbers of striatal neurons have oscillatory spike activity in the normal state. As LFP recordings have been re-introduced into the study of BG circuitry, however, it has become evident that there is indeed robust oscillatory activity in the striatum (and subthalamic nucleus) when animals are alert and behaving, and that this activity is modulated as the animals perform behavioral tasks (Brown et al., 2002; Courtemanche et al., 2003; Berke et al., 2004; DeCoteau et al., 2004, 2005; Gervasoni et al., 2004; Masimore et al., 2004; Sharott et al., 2005a). The evidence for striatal network oscillations comes from experiments both in primates and in rodents.

In macaque monkeys, LFP recordings have been made in the caudate nucleus and putamen with chronically-implanted multiple electrodes while monkeys, seated in primate chairs with their heads fixed, are observed under a variety of behavioral conditions (Courtemanche et al., 2003). Low-frequency large-amplitude activity dominates during resting and dozing states. But when the monkeys become alert, and as they perform visuomotor tasks, prominent beta-band activity (ca. 10-25 Hz, average near 15 Hz) appears, along with lower levels of oscillatory activity in other frequency bands (Fig.2A). This oscillatory activity is present with local (near-field) referencing, as well as with distant referencing, indicating that it is not the result of volume conduction (see section 3.1 above).

This 10-25 Hz LFP oscillatory activity in the striatum has several striking features. First, the oscillations are episodic, not continuous. The episodes last for less than a second (average of ~600 msec) and they occur about 20 times a minute, but irregularly, with inter-episode intervals ranging from less than 1 second to about 3 seconds. This suggests that they are related to shifting activity states in the system. The origin of these activity shifts is not known, but it was found that some striatal neurons (classified as either projection neurons, or as TANs) have spiking activity that is in-phase or in anti-phase with the LFP oscillations. In the total population of neurons, there is a discernable tendency for spiking to be related to the LFP oscillations. These findings suggest that the oscillations, in part at least, reflect local neuronal activity in the striatum.

Second, the striatal LFP oscillations are highly synchronous across the caudate nucleus and putamen, with near sites more highly coherent than far sites. For example, in paired two-site recordings, cross-covariance values at zero lag ranged from 0.93 for sites 2 mm apart to 0.63 for sites 10 mm apart, and across all recorded sites in the caudate nucleus and putamen, values ranged with distance from almost 1.0 (sites were relatively near) to ~0.2 (relatively far). This finding suggests that large parts of the striatum can come into synchronous states of beta-band activity episodically, and repeatedly, at irregular intervals averaging half a second or so (Courtemanche et al., 2003).

Third, and perhaps most interestingly, the level of synchrony, as well as the content of these striatal beta-band oscillations, can vary depending on the behavior of the monkey (Fig.2B). In the experiments reported by Courtemanche et al. (2003), macaques were trained to fixate a target light on a screen in front of them and then to perform single saccades in response to visual targets briefly presented at varying locations. Local field potentials were recorded simultaneously from up to five microelectrodes implanted in and near the oculomotor zone of the striatum. Single-unit and multi-unit activity was

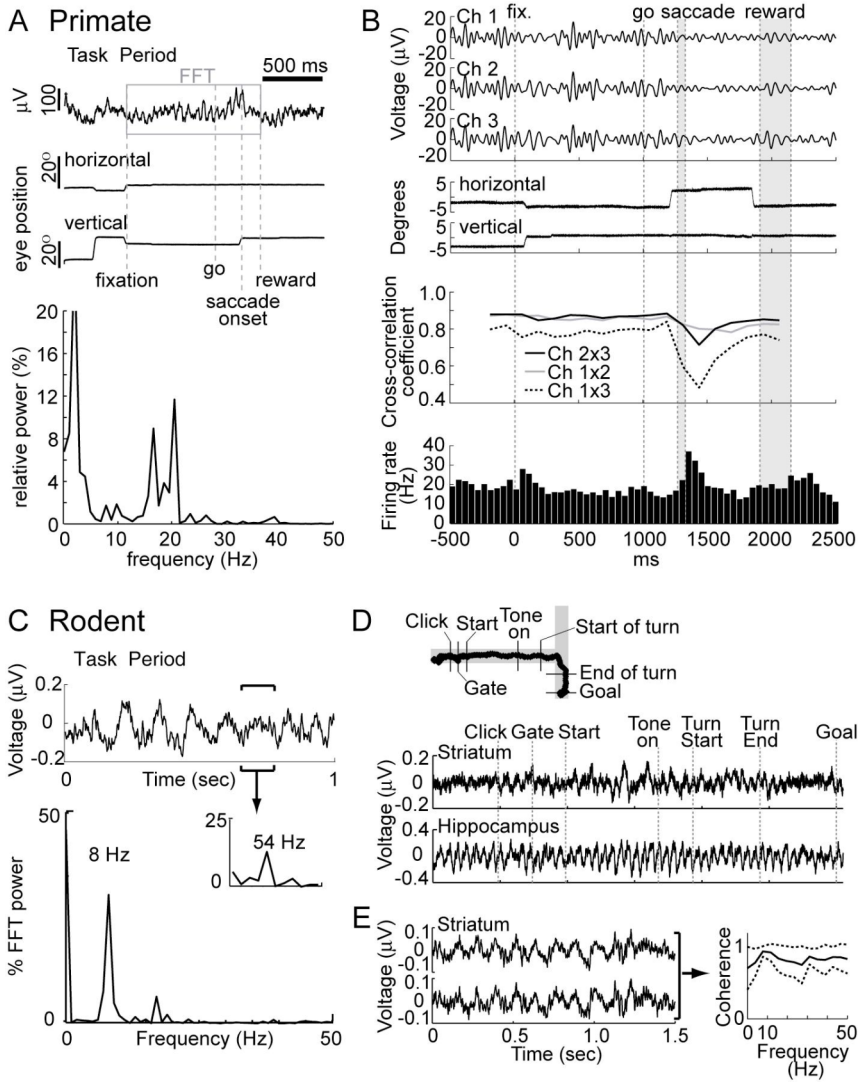


**Figure 2.** Oscillatory activity in the striatum of macaque monkey (A-B) and rat (C-E). *A:* Example of beta-band LFP oscillation in the oculomotor striatum of a macaque monkey performing a single saccade task. Horizontal and vertical eye position is shown below the trace of a raw LFP (*top*). Spectral plot (*bottom*) shows the relative power of oscillatory activity in the 0-50 Hz range. *B:* Raw LFP traces recorded on three electrodes (Ch1, Ch2, Ch3) in the oculomotor striatum during a single saccade task (eye positions shown in degrees under the LFP traces). *Middle* plot shows cross-correlation coefficients calculated for different pairings of the three electrodes. One pair (1 x 3) falls out of the otherwise tight synchrony. There was saccade-related unit activity on electrode 3 (*bottom* plot), in contrast to electrodes 1 and 2. Modified from Courtemanche et al. (2003). *C-E:* LFPs recorded in rats running in a simple T-maze. *C:* illustrates a raw LFP trace recorded as a rat ran down the maze illustrated in D. Power spectra are shown below. *D:* An example of a run trajectory in the T-maze task and, below, the raw LFP traces simultaneously recorded in the striatum and hippocampus during this maze run. Note that striatal and hippocampal theta are not identical. *E:* LFPs recorded from two sites in the lateral striatum as a rat spontaneously moved along the maze (*left*) and the coherogram calculated for these traces, illustrating the high level of cohernce of oscillatory activity in the rat striatum (*right*). Modified from DeCoteau et al. (2005).

recorded from the same electrodes, and LFPs that were recorded at sites with saccade-related unit activity were compared with those simultaneously recorded at sites lacking such saccade-related unit activity (Fig.2B). When the monkeys fixated the fixation point, the level of cross-covariance between pairs of recording sites was consistently high (0.8-0.9). This level remained high for sites at which saccade-related activity was not recorded. But the oscillatory activity at some sites with saccade-related unit activity fell out of such strict synchrony during the peri- and post-saccadic period, only to return afterwards. This finding suggests that the high levels of synchrony in striatal oscillatory LFP activity in the normal monkey can be modulated locally according to the particular activity of units at the sites of recorded LFPs.

The working model prompted by these experiments is that LFP activity in the normal primate striatum is characterized by widespread, coordinated, episodic oscillatory activity, and that local sites in the striatum can 'pop out' of this synchrony when task demands engage the striatal neurons at the pop-out sites. These local sites were estimated to be on the order of a millimeter in diameter, suggesting that they could be related to the compartmental architecture of the striatum. In the oculomotor zone, as elsewhere in the striatum, functionally-related sets of input fibers converge on zones roughly 0.5-1 millimeter wide ("matrisomes") and output neurons in these small regions can in turn project to similar small sites in the pallidum. This model suggests that one function of the oscillatory activity in the primate striatum may be to serve as a thresholding device. If, and only if, activity in a local region exceeds the level of synchronous oscillatory activity would the threshold for exciting spike activity in striatal projection neurons be crossed. These are the neurons responsible for sending outputs to the pallidum and substantia nigra. Thus, the modulatory control over oscillatory activity in the striatum could be part of a dynamic and state-dependent filter mechanism in the striatum, biasing attention and action. If such a filter were set at too high a threshold (as in the exaggerated oscillatory states characteristic of Parkinson's disease), activation of striato-pallidal and striato-nigral outputs could be impaired, contributing to the parkinsonian syndrome.

Oscillatory LFP activity has also been observed in the normal state as rats behave in task paradigms (Berke et al., 2004; DeCoteau et al., 2004; Masimore et al., 2004). Recordings in the striatum (Fig.2C-E) show that the dominant frequency band for these oscillations is in the theta range (4-10 Hz), but activity at lower (<4 Hz; 'delta') and higher (30-50 Hz; 'gamma') ranges is also observed. In the rat, some of this activity has been associated with the activity of (presumed) fast-spiking striatal interneurons, thought to correspond to the parvalbumen-containing GABAergic interneurons of the striatum (Berke et al., 2004). When rats were trained to run mazes, such as simple T-mazes (Fig.2D), robust theta-band oscillatory activity is apparent in striatal recordings made with multiple chronically-implanted tetrodes (DeCoteau et al., 2004, 2005). By contrast, when the rats are grooming or resting, this activity is relatively weak.

Like the beta-band oscillations in the macaque striatum, these theta oscillations in the rodent are highly synchronous across the striatum. In the ventral striatum, theta oscillations are synchronous with those in the hippocampus (Goto and O'Donnell, 2001b; Berke et al., 2004), but the theta oscillations in the dorsal striatum can be uncoupled from those in the hippocampus (Fig.2D), and they occur robustly with local referencing, suggesting their independence from oscillations generated in the hippocampus or other sources (DeCoteau et al., 2004, 2005). As for the beta-band LFP activity in the macaque striatum, local inhomogeneities are found in the theta oscillations in the rat striatum. Furthermore, theta-band activity is modulated during task performance in trained

animals. For example, when rats are trained to run a T-maze in order to receive a reward, theta-band oscillations are highest during the outbound (straight) part of the runs, but they decline before reaching the goal, at which point gamma-band oscillatory activity sharply increases. Interestingly, although the spectral peak of the striatal theta oscillation is near 8 Hz, the highest coherence of unit activity with the LFP oscillations is approximately 4 Hz (DeCoteau et al., 2005).

These and other recent studies raise a number of important questions. If such oscillatory activity is important for normal striatal function, why are the dominant frequencies in rats and monkeys different? What could set up such synchronous network activity? Are these activities actually devices for facilitating network communication with other brain regions? Are they internally generated or predominantly dictated by afferents? Ample evidence suggests that both afferents and local interneuronal networks might be responsible for the activities recorded. What functions do these oscillations serve? As stated at the outset of this chapter, this is a question relevant to all brain regions in which oscillatory activity has been recorded. The perturbations of these oscillations in dopamine-depleted parkinsonian states, however, may offer a special clue to their function in the BG and, at the least, provide a clear indication that when oscillatory activity in the BG is aberrant, then abnormal behavioural states are likely to occur.

## 5. THE BAD: SYNCHRONIZED OSCILLATIONS IN THE PARKINSONIAN BASAL GANGLIA

The chronic loss of dopamine from the forebrain, as occurs in idiopathic Parkinson's disease (PD) and its animal models, is associated with profound changes in the patterning of activity in the BG and their afferent/efferent networks. Much of the early evidence for this was derived from studies of animal models of PD, most often MPTP-lesioned primates and the 6-hydroxydopamine-lesioned rat (Bergman et al., 1998; Bevan et al., 2002; Boraud et al., 2002). Thus, along with the changes in the firing rates of BG neurons that were posited by the now-classic model of BG dysfunction (DeLong, 1990), increases in oscillatory activity and synchronized firing (rate co-variations) have been frequently reported to occur in the BG, most notably in the subthalamic nucleus-pallidum network, and the cortex of parkinsonian animals (Bergman et al., 1994; Nini et al., 1995; Raz et al. 2000, 2001, Magill et al., 2001; Goldberg et al., 2002, 2004; Heimer et al., 2002). In terms of increases in the power and prevalence of oscillations, these studies have emphasized the role of (pathological) activity that is synchronized at frequencies below 15 Hz, including those frequencies associated with parkinsonian tremor, although exaggerated oscillations at higher frequencies have also been reported (Vorobyov et al., 2003; Sharott et al., 2005a). Taken together, data from animal models of PD serve to further highlight the potentially critical roles played by synchronized oscillatory activity in the function and dysfunction of cortico-basal ganglia-thalamocortical circuits.

The recent renaissance in functional neurosurgery has provided an opportunity to record neuronal activity directly from the subthalamic nucleus (STN) and internal pallidum (GPi) in patients with PD. Unit activity, with or without LFPs, can be recorded intra-operatively through microelectrodes, or LFPs (only) may be recorded directly from the deep brain stimulation electrode (DBS-electrode). In the latter case, LFPs may be recorded intra-operatively, or after implantation surgery while the electrode leads are externalized and prior to connection to the subcutaneous stimulator. Such recordings have

demonstrated that oscillatory activity is synchronized in two major frequency bands in PD patients withdrawn from dopaminergic therapy (as is the case intra-operatively). The first band contains activity in the frequency range of parkinsonian rest and action tremor (3-12 Hz). This is seen in microelectrode recordings of pairs of units drawn from the same electrode or electrodes in close proximity to each other (Hurtado et al., 1999; Levy et al., 2000). Paradoxically, however, this form of synchronization is neither a consistent nor strong feature of LFPs recorded in the basal ganglia (but see Liu et al., 2002), perhaps because synchronization between neurons occurs within small local ensembles, thereby mirroring the multiple peripheral oscillators manifest in parkinsonian rest tremor (Hurtado et al., 2000). Moreover, neurons oscillating at tremor frequency tend to vary their phase relationships with one another over time, so that spectral analysis methods that average LFPs over time would tend to underestimate the strength of such synchronized activity when it occurs (Hurtado et al., 1999, 2004; Levy et al., 2000).

The second major band of synchronized oscillatory activity evident in recordings from the STN or GPi of patients with PD is 13-32 Hz, often termed the 'beta' band (Fig.3). It is manifest in single-unit activity and in the cross-correlograms of pairs of neurons (Levy et al., 2002a,b; Amirnovin et al., 2004; Kühn et al., 2005), but is particularly prominent in the LFPs recorded from subthalamic (Brown et al., 2001; Priori et al., 2002; Williams et al., 2002, 2003, 2005; Kühn et al., 2004; Priori et al., 2004) and pallidal (Brown et al., 2001; Priori et al., 2002; Silberstein et al., 2003) DBS-electrodes. Indeed, subthalamic and pallidal LFPs are coherent (*i.e.*, show linear amplitude and phase co-variation) in the beta band (Brown et al., 2001), and, in turn, are coherent with EEG activity recorded over cortical motor areas at the same frequencies (Marsden et al., 2001; Williams et al., 2002). Thus, synchronized beta-band activity, as indexed by the LFP, is a physiological hallmark of cortico-basal ganglia-thalamocortical circuits in PD.

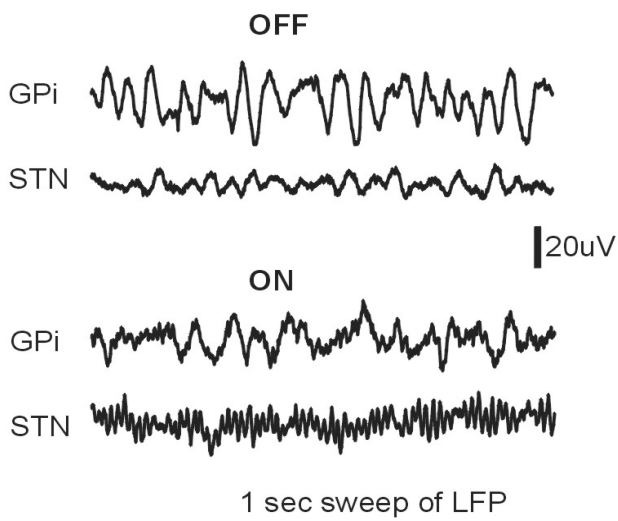


**Figure 3.** Example of LFP activities recorded by DBS-electrodes in the subthalamic nucleus (STN) and globus pallidus interna (GPi) of a patient with PD when withdrawn from antiparkinsonian treatment (OFF levodopa) and following restitution of treatment (ON levodopa). Off medication, there are prominent oscillations at around 20 Hz. These beta-band oscillations are suppressed by treatment with levodopa, which also promotes the expression of higher frequency oscillations at around 70 Hz.

Synchronized oscillatory activity in the STN and GPi of patients with PD may also occur at frequencies in excess of 65 Hz, which, for convenience, we will term the 'gamma' band (Fig.3). In particular, after treatment with dopamine agonists or the dopamine precursor, levodopa, some PD patients develop a new pattern of LFP oscillation at 65-85 Hz (Brown et al., 2001; Cassidy et al., 2002; Williams et al., 2002; Brown, 2003). This high-frequency activity is observed at rest and is increased with movement (Cassidy et al., 2002; Brown et al., 2002) and may therefore have some similarities to the cortical activity of similar frequency that has been implicated in the planning of movement (Crone et al., 1998). There is a single report of a further band of activity at 200 to 350 Hz in the LFP recorded from the STN region that behaves in a similar manner (Foffani et al., 2003). However, activities above 65 Hz are an inconsistent feature of BG LFP recordings in patients with PD, and have not been detected in the cross-correlation of pairs of neurons, or in correlations between unit activity and the LFP. In the absence of direct evidence that such oscillations are coupled to neuronal activity in the BG, we will not consider these activities in any further detail, other than to highlight their potential interest in the future.

### 5.1. Do Synchronized Oscillations in the Parkinsonian Basal Ganglia Contribute to Motor Abnormalities?

Oscillatory synchronization at tremor frequencies might be related to the genesis of tremor, but the same neurons that synchronize at these frequencies also tend to be activated by passive movements, raising the possibility that some of this activity may be afferent rather than efferent in nature. Both oscillations at tremor-related frequencies (Volkmann et al., 1996) and those in the beta band (Brown, 2003) have been implicated in the sparsity and slowness of movements in PD. The evidence is strongest in the case of activity in the beta band, which generally exhibits an inverse relationship with motor function. Thus, a reduction in the power of beta oscillations is often coincident with the improvement of motor symptoms that is seen after levodopa administration (Fig.3) or high-frequency (>70 Hz) stimulation of the STN region (Brown et al., 2004). Furthermore, beta oscillations in the STN are suppressed prior to, and during, self- and externally-paced voluntary movements, and following environmental cues informative of subsequent movement demands (Cassidy et al., 2002; Levy et al., 2002a; Priori et al., 2002; Williams et al., 2003, 2005; Kühn et al., 2004; Doyle et al., 2005). In reaction-time tasks, the timing of the reduction in power of beta activity positively correlates with both the mean reaction time across patients (Kühn et al., 2004; see also Fig.4) and the reaction time across single trials within a single patient (Williams et al., 2005). Similarly, in self-paced movements, the onset of suppression of beta oscillations in STN can be used to predict the timing of voluntary movements on-line (Loukas and Brown, 2004). The critical feature in these paradigms is that oscillatory activity fluctuates with motor-related information processing, rather than any non-specific changes in attention. Thus, in reaction-time tasks, warning cues that allow premovement motor selection are associated with more frequent and prominent suppression of beta-band LFP activity in STN than those warning cues that are uninformative and do not allow premovement motor selection (Williams et al., 2003). Such warning cues do not vary in their attentional demands.

The above indicates a strong relationship between the onset of suppression of beta-band activity in STN and the timing of subsequent voluntary movements. If such a reduction in the power of beta oscillations is linked specifically to the facilitation of

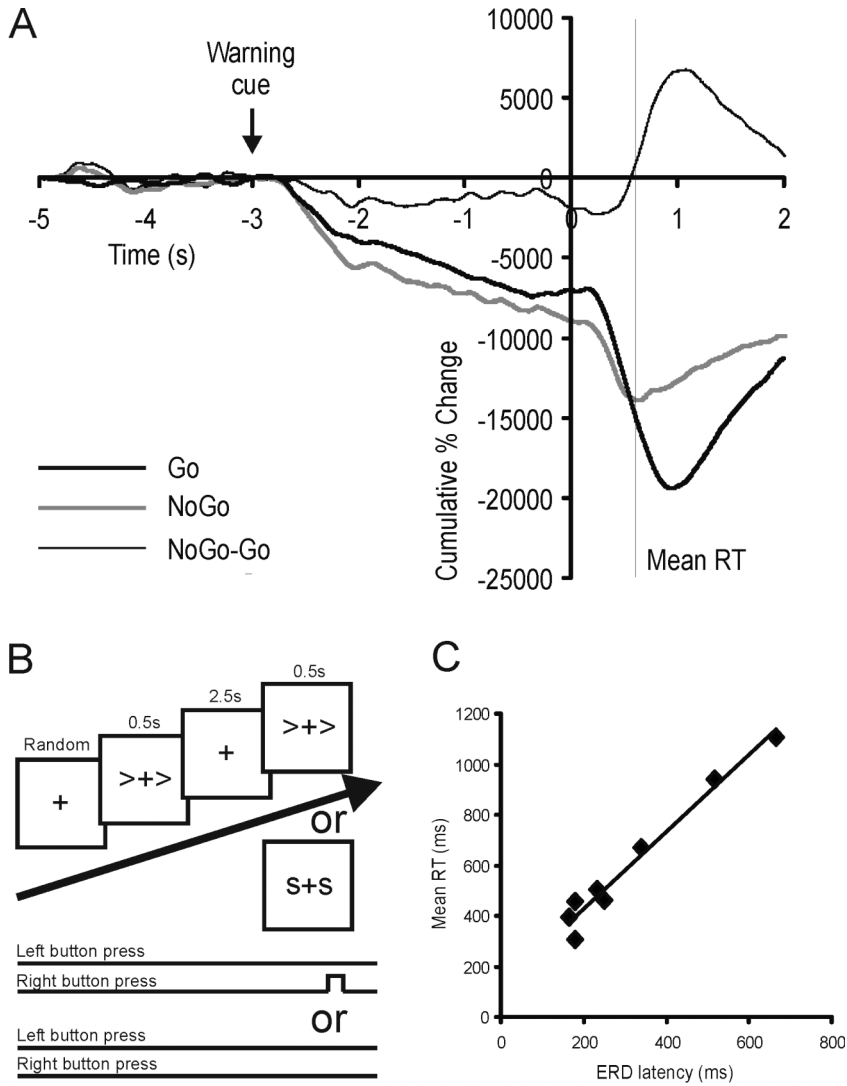


**Figure 4.** Change in the power of beta activity (13-30 Hz) in the STN LFP while PD patients are engaged in a Go No-Go task. *A*: Averaged power changes represented in the form of a cumulative sum (8 patients, 16 STN). In such cumulative sums, periods of zero, negative and positive gradients demonstrate no change, power decreases and power increases, with respect to baseline, respectively. *B*: Paradigm. Patients sat with a button device held in each hand and an imperative 'go' signal on a computer screen instructed patients to press the button with either their left or right hand as fast as possible. Under these circumstances (*thick black* trace in *A*), there is a drop in beta power after the warning signal, and an even more marked drop following the go signal, but preceding the mean reaction time (RT), as indicated by the thin vertical line in *A*. The 'go' cue was preceded by a warning cue that correctly anticipated the form of the 'go' signal. In 20 % of trials, however, the 'go' signal was substituted by a stop signal (S), instructing the subject not to make a movement. In these circumstances, the drop in power after the imperative cue was abbreviated, and followed by an early increase in beta power (*grey trace* in *A*). This is best seen in the trace illustrating the difference between the average 'go' and 'no-go' cusums (*thin black trace* in *A*). *C*: Correlation between latency of onset of 'go' cue (event)-related desynchronization (ERD) of beta activity and mean reaction time (RT) across eight patients. Note the highly significant correlation ($r = 0.986$, $p < 0.001$). Adapted with permission from Kühn et al. (2004).

subsequent movement, an augmentation of power might also be predicted when a pre-prepared movement requires cancellation and, indeed, this also seems to be the case (Kühn et al., 2004).

The inverse relationship between beta-band activity and motor function suggests that the information processing necessary for renewed movement may be actively antagonized by the synchronization of activity in this band. Recent recordings in primates confirm an inverse relationship between oscillatory LFP activity in the beta band and task-related coding of movement by neurons, so that oscillations are preferentially suppressed in the local area of the striatum that contains neurons exhibiting task-related increases in discharge rate (Courtemanche et al., 2003; see section 4 above). Parallel observations have been made in the primate motor cortex, as exemplified by the 'clamping' of single-unit firing rates during periods of 20-40 Hz oscillatory synchrony (Murthy and Fetz, 1996b) and the tendency of firing rate modulation to occur as oscillations decrease in motor cortical LFP (Donoghue et al., 1998).

In summary, activity synchronized in the beta band is prominent in the STN and GPi of parkinsonian patients and inversely correlates with motor-related information processing, or at least motor function. Studies in the striatum of healthy rats (Vorobyov et al., 2003; Berke et al., 2004) and monkeys (Courtemanche et al., 2003), and recordings in the putamen of a patient without PD (Sochurkova & Rektor, 2003), suggest that synchronized beta oscillations, and their task-related suppression, are not a *de novo* feature of parkinsonism. However, the parkinsonian state certainly seems to be associated with an exaggeration of this form of synchronized activity, as demonstrated by comparisons of activity in the cortex and STN of healthy and 6-hydroxydopamine-lesioned rats (Sharott et al., 2005a), and PD patients before and after treatment with levodopa (Brown et al., 2001; Silberstein et al., 2003; Priori et al., 2004). This exaggeration of an activity that is inversely related to motor information processing might contribute to a lack of movement (akinesia) in untreated PD. In addition, the elevated beta-band activity in PD seems less easily suppressed when movements are made after withdrawal of levodopa (Doyle et al., 2005). Restoration of levodopa treatment improves movement-related suppression of beta LFP activity in the STN. Thus, an impaired ability to suppress the synchronization of activity in the beta band might also contribute to the slowness of movement (bradykinesia) in untreated PD.

## 6. THE UNEXPECTED: WHICH DATA CHALLENGE OUR VIEWS ON THE ROLES SUBSERVED BY OSCILLATIONS IN THE BASAL GANGLIA?

A key question remains as to the functional significance of synchronized oscillations in the human BG. One possibility is that they are a passive characteristic of BG and cortical neuronal networks when they are not engaged in active information processing. In this formulation, the oscillatory activity is viewed as a characteristic of the resting or idling state, as proposed for cortical alpha-band activity (Pfurtscheller et al., 1996), rather than a phenomenon that may actively impede novel processing. Although this possibility has not been completely refuted, several observations would argue against it. First, there is the rebound synchronization of beta activity above resting levels following movement, and there is a premature synchronization of this activity when movement is to be voluntarily suppressed (Cassidy et al., 2002; Kühn et al., 2004). Although there may be degrees of active suppression of dynamic movement-related processing, it seems unlikely

that the BG and cortex would enter into a deeper idling state than that present at rest when movement has to be actively inhibited or terminated (Fig.4). Second, direct stimulation of the BG at tremor and beta frequencies may exacerbate parkinsonism. The worsening of bradykinesia in PD patients has been reported following 5 Hz (Moro et al., 2002), 10 Hz (Timmermann et al., 2004) and 20 Hz (Fogelson et al., 2005) stimulation in the region of the STN. Similarly, stimulation of the putamen in healthy cats at 30 Hz leads to akinesia (Hassler and Dieckmann, 1967). It is important to note, however, that these stimulation experiments were conducted with square-wave current pulses of short duration (<100 μs). Such artificial trains of oscillatory stimuli can differ dramatically from the oscillations in unit activity and LFPs that can be recorded in the parkinsonian BG and thus, the two may engage different mechanisms in producing their effects.

If pathological synchronized oscillations do indeed underlie motor abnormalities in PD, then we can expect that the two will co-evolve during disease progression. In a recent study (Leblois et al., submitted) designed to characterize the evolution of spontaneous and movement-related neuronal activity in the GPi of rhesus monkeys during a slow dopamine depletion induced by daily injections of small doses of MPTP, abnormal synchronized oscillatory activity (10-20 Hz) at rest appeared significantly later in the depletion process than did the first parkinsonian symptoms (Fig.5). Moreover, the appearance of these oscillations was preceded by a drastic change in the movement-related neuronal activity; pallidal neurons responded less specifically to active movement during a motor task, while reaction and movement times increased significantly. In these experiments, the monkeys displayed a pure akinetic-rigid form of the parkinsonian syndrome, without tremor, which is the rule for this species.

The above study determined the level of synchronization through cross-correlation analysis of the discharges of pairs of pallidal neurons. It may be that LFPs provide a more sensitive measure of synchronized activity at the network level. Nevertheless, the data as they stand argue against a strong causative influence of synchronized oscillations upon the bradykinetic symptoms of PD. Instead, the primate data suggest a more complex model in which dopamine depletion leads to the loss of some specific function of the BG yet to be determined, whether related to pure motor control (Mink, 1996) or information processing (Bar-Gad et al., 2003). Moreover, the appearance of oscillations synchronized at mu/beta frequencies in the BG may be related to the progression (worsening), rather than establishment, of the parkinsonian syndrome.

## 7. FUTURE DIRECTIONS

A number of fundamental issues concerning synchronized network oscillations in the BG remain unresolved. Perhaps most importantly, the complex cellular and network mechanisms underlying these oscillations must be further elucidated. With the proven utility of LFP recordings in the BG coming to the fore, there also remains a pressing need for further studies of their neural basis.

Many of the synchronized network oscillations described here are not found (or at least have not been reported to occur) *in vitro*. One possible explanation for this is that the necessary levels of connectivity between the BG and their afferent/efferent partners are not maintained *ex vivo*. This would in turn suggest that some or all of the circuit elements of the intact cortico-basal ganglia-thalamocortical loops are required for the generation and/or maintenance of these synchronized oscillations in the BG. A critical

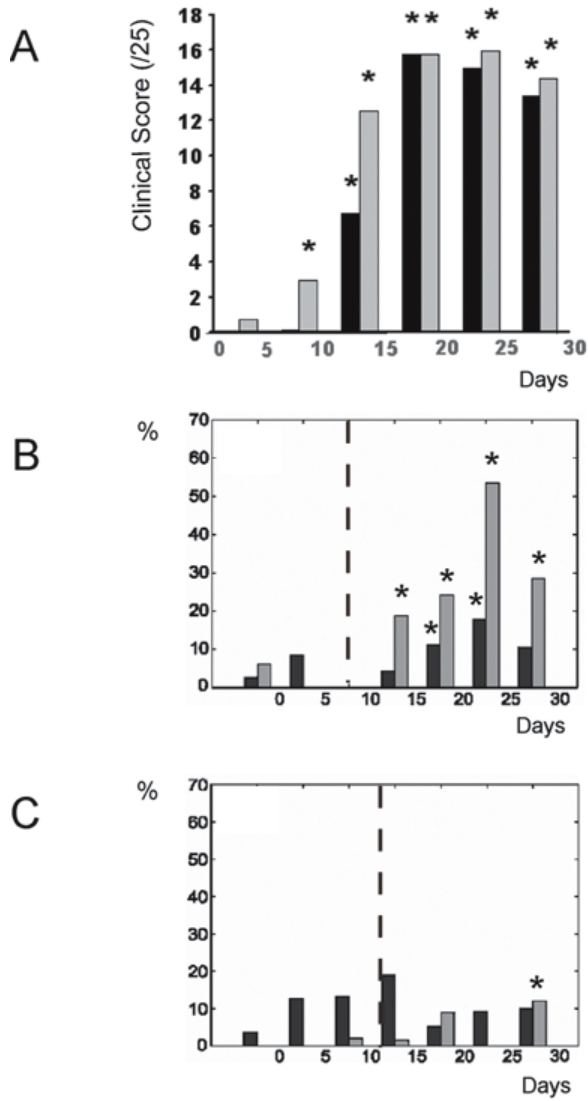


**Figure 5.** Comparison of the evolution of the clinical scores (*A*) and synchronized oscillations in the pallidum (*B* and *C*) during the slow development of a parkinsonian syndrome in 2 monkeys. *A:* Clinical scores of monkey J (*grey*) and M (*black*). *B:* Evolution of the percentage of auto-correlograms (*black*) and cross-correlograms (*grey*) containing significant oscillations with a frequency of between 10 and 20 Hz for monkey J. The dashed line indicates the appearance of significant parkinsonian feature in the animal. *C:* The same for monkey M. *, $p<0.05$, as compared to control situation before MPTP treatment.

question arises as to which circuit element(s) lie at the heart of the oscillations. The network formed by the reciprocally-connected neurons of the STN and external pallidum is one candidate pacemaker, although a mechanism that might generate oscillations at >5

Hz is currently lacking (Bevan et al., 2002; also see Stanford et al. elsewhere in this volume). It has also been proposed that oscillations arise from competition between two feedback loops, namely the cortex-STN-GPi-thalamocortical loop and the cortex-striatal-GPi-thalamocortical loop (Leblois et al., 2005). The cerebral cortex itself may drive much of the synchronous oscillatory activity in the BG (Magill et al., 2000, 2001; Brown, 2003), yet there are clear contradictions (Courtemanche et al., 2003; Goldberg et al., 2004). The thalamus is implicated in several brain rhythms, and most prominently those related to states of vigilance (Steriade, 2000). The ventral nuclei of the dorsal thalamus provide the final connection in the loop circuit, whereas the intralaminar thalamic nuclei provide direct inputs to the BG, notably the striatum (Smith et al., 1998). The physiological and anatomical properties of the thalamic neuronal networks place them in an ideal position to play a lead role in modulating synchronized oscillatory activity in the BG, yet little is known about how and when they might do this. One possibility is that oscillatory activity in the striatum is strongly influenced by the conjoint effects of thalamic and cortical inputs to striatal interneurons; thalamic input to the (cholinergic) TANs and cortical input to the (GABAergic) fast-spiking interneurons (Courtemanche et al., 2003). The contribution of such thalamic and cortical inputs to the physiological and pathophysiological rhythms in the BG is arguably one of the most important scientific issues that face us. The roles played by other structures that are interconnected with the BG, such as the pedunculopontine tegmental nucleus (Mena-Segovia et al., 2004), should also be considered.

Electrophysiological investigations in PD patients have focused on the synchronization of oscillatory activity in the beta band, and the frequencies associated with resting tremor. Synchronized oscillations at >60 Hz have received far less attention. These fast oscillations are an inconsistent finding in recordings of LFPs from the STN of patients with PD (Brown, 2003; Foffani et al., 2003) and thus, their nature remains obscure. Further investigation is warranted as to how they may relate to specific coding of movement-related parameters and how they might contribute to dyskinesias. Beta-band oscillations at 20-30 Hz are a predominant activity pattern in patients with idiopathic PD and thus, it is perhaps surprising that, with only one published exception (Sharott et al., 2005a), similar activity patterns are not widespread in experimental PD. The reasons for this inconsistency are unknown but it calls for a careful re-examination of the pathophysiology of animal models of PD.

Finally, it must not be forgotten that much of the evidence linking synchronized network oscillations and function in the BG is correlative in nature and there remains the need for a direct demonstration of a causal relationship. One experimental approach (yet to be attempted) would be to induce, in a physiologically relevant manner, oscillations in the networks of BG and subsequently correlate neuronal activity patterns with behavioral performance.

## 8. ACKNOWLEDGEMENTS

This work was supported by CNRS CTI01_01, CTI02_14 and ACI-NIC0013 (T.B.), Medical Research Council UK (P.B. and P.J.M.), and NIH EY12848, NIH NS25529 and NIH MH60379 (A.M.G.).

## 9. REFERENCES


Abeles, M., 1982, Quantification, smoothing and confidence limits for single-units' histograms. *J. Neurosci. Methods* **5**:317.

Allers, K.A., Ruskin, D.N., Bergstrom, D.A., Freeman, L.E., Ghazi, L.J., Tierney, P.L., and Walters, J.R., 2002, Multisecond periodicities in basal ganglia firing rates correlate with theta bursts in transcortical and hippocampal EEG. *J. Neurophysiol.* **87**:1118.

Amirnovin, R., Williams, Z.M., Cosgrove, G.R., and Eskandar, E.N., 2004, Visually guided movements suppress subthalamic oscillations in Parkinson's disease patients. *J. Neurosci.* **24**:11302.

Bar-Gad, I., Ritov, Y., and Bergman, H., 2001, The neuronal refractory period causes a short-term peak in the autocorrelation function. *J. Neurosci. Methods* **104**:155.

Bar-Gad, I., Morris, G., and Bergman, H., 2003, Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. *Prog. Neurobiol.* **71**:439.

Bennett, B.D., and Wilson, C.J., 1999, Spontaneous activity of neostriatal cholinergic interneurons *in vitro*. *J. Neurosci.* **19**:5586.

Bergman, H., Wichmann, T., Karmon, B., and DeLong, M.R., 1994, The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.* **72**:507.

Bergman, H., Feingold, A., Nini, A., Raz, A., Slovin, H., Abeles, M., and Vaadia, E., 1998, Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. *Trends Neurosci.* **21**:32.

Berke, J.D., Okatan, M., Skurski, J., and Eichenbaum, H.B., 2004, Oscillatory entrainment of striatal neurons in freely moving rats. *Neuron* **43**:883.

Bevan, M.D., Magill, P.J., Terman, D., Bolam, J.P., and Wilson, C.J., 2002, Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. *Trends Neurosci.* **25**:525.

Boraud, T., Bezard, E., Bioulac, B., and Gross, C.E., 2002, From single extracellular unit recording in experimental and human Parkinsonism to the development of a functional concept of the role played by the basal ganglia in motor control. *Prog. Neurobiol.* **66**:265.

Brillinger, D.R., 1975, Statistical inference for stationary point processes, in: *Stochastic Processes and Related Topics*, *Vol.1*, M.I. Puri, ed., Academic Press, New York, pp55–79.

Brown, P., 2003, The oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov. Disord.* **18**:357.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., and Di Lazzaro, V., 2001, Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.* **21**:1033.

Brown, P., Mazzone, P., Oliviero, A., Altibrandi, M.G., Pilato, F., Tonali, P.A., and Di Lazzaro, V., 2004, Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. *Exp. Neurol.* **188**:480.

Buzsáki, G., 2002, Theta oscillations in the hippocampus. *Neuron* **33**:325.

Buzsáki, G., and Draguhn, A., 2004, Neuronal oscillations in cortical networks. *Science* **304**:1926.

Cassidy, M., Mazzone, P., Oliviero, A., Insola, A., Tonali, P., Di Lazzaro, V., and Brown, P., 2002, Movement-related changes in synchronization in the human basal ganglia. *Brain* **125**:1235.

Courtemanche, R., Fujii, N., and 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.

Creutzfeld, O.D., Watanabe, S., and Lux, H.D., 1966a, Relations between EEG phenomena and potentials of single cortical cells. I. Evoked responses after thalamic and epicortical stimulation. *Electroencephalogr. Clin. Neurophysiol.* **20**:1.

Creutzfeld, O.D., Watanabe, S., and Lux, H.D., 1966b, Relations between EEG phenomena and potentials of single cortical cells. II. Spontaneous and convulsoid activity. *Electroencephalogr. Clin. Neurophysiol.* **20**:19.

Crone, N.E., Migloiretti, D.L., Gordon, B., and Lesser, R.P., 1998, Functional mapping of human sensorimotor cortex with electroencephalographic analysis. 2. Event related synchronisation in the gamma band. *Brain* **121**:2301.

DeCharms, R.C., and Zador, A., 2000, Neural representation and the cortical code. *Annu. Rev. Neurosci.* **23**:613.

DeCoteau, W.E., Mao, J., Gibson, D.J., Courtemanche, R., Kubota, Y., and Graybiel, A.M., 2004, Striatal theta-gamma local field potential oscillations coordinate with hippocampus rhythms in behaviorally selective patterns. *Soc. Neurosci. Abstr.* Program No. 70.4.

DeCoteau, W.E., Mao, J., Gibson, D.J., Courtemanche, R., Kubota, Y., and Graybiel, A.M, 2005, Theta-gamma oscillations in local field potentials are prominent in the rat striatum and are coordinated with hippocampal rhythms in behaviorally selective patterns. Submitted.

DeLong, M.R., 1990, Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13**:281.

Destexhe, A., Contreras, D., and Steriade, M., 1999, Spatiotemporal analysis of local field potentials and unit discharges in cat cerebral cortex during natural wake and sleep states. *J. Neurosci.* **19**:4595.

Donoghue, J.P., Sanes, J.N., Hastopoulos, N.G., and Gaál, G., 1998, Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. *J. Neurophysiol.* **79**:159.

Doyle, L.M.F., Kühn A.A., Hariz, M., Kupsch, A., Schneider, G-H., and Brown, P., 2005, Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. *Eur. J. Neurosci.* **21**:1403.

Engel, A.K., Fries, P., and Singer, W., 2001, Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* **10**:704.

Engel, A.K., and Singer, W., 2001, Temporal binding and the neural correlates of sensory awareness. *Trends Cog. Sci.* **5**:16-25.

Foffani, G., Priori, A., Egidi, M., Rampini, P., Tamma, F., Caputo, E., Moxon, K.A., Cerutti, S., and Barbieri, S., 2003, 300-Hz subthalamic oscillations in Parkinson's disease. *Brain* **126**:2153.

Fogelson, N., Kühn, A.A., Silberstein, P., Dowsey Limousin, P., Hariz, M., Trottenberg, T., Kupsch, A., and Brown, P., 2005, Frequency dependent effects of subthalamic nucleus stimulation in Parkinson's disease. *Neurosci. Lett.*, in press.

Frost, J.D., 1968, EEG-intracellular potential relationships in isolated cerebral cortex. *Electroencephalogr. Clin. Neurophysiol.* **24**:434.

Gervasoni, D., Lin, S.C., Ribeiro, S., Soares, E.S., Pantoja, J., and Nicolelis, M.A., 2004, Global forebrain dynamics predict rat behavioral states and their transitions. *J. Neurosci.* **24**:11137.

Goldberg, J.A., Boraud, T., Maraton, S., Haber, S.N., Vaadia, E., and Bergman, H., 2002, Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. *J. Neurosci.* **22**:4639.

Goldberg, J.A., Rokni, U., Boraud, T., Vaadia, E., and Bergman, H., 2004, Spike synchronization in the cortex-basal ganglia networks of parkinsonian primates reflects global dynamics of the local field potentials. *J. Neurosci.* **24**:6003.

Goto, Y., and O'Donnell, P., 2001a, Network synchrony in the nucleus accumbens *in vivo*. *J. Neurosci.* **21**:4498.

Goto, Y., and O'Donnell, P., 2001b, Synchronous activity in the hippocampus and nucleus accumbens *in vivo*. *J. Neurosci.* **21**:RC131.

Halliday, D.M., Rosenberg, J.R., Amjad, A.M., Breeze, P., Conway, B.A., and Farmer, S.F., 1995, A framework for the analysis of mixed time series/point process data - theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog. Biophys. Mol. Biol.* **64**:237.

Hassler, R., and Dieckmann, G., 1967, Arrest reaction, delayed inhibition and unusual gaze behaviour resulting from stimulation of the putamen in awake unrestrained cats. *Brain Res.* **5**:504.

Heimer, G., Bar-Gad, I., Goldberg, J.A., and Bergman, H., 2002, Dopamine replacement therapy reverses abnormal synchronization of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of parkinsonism. *J. Neurosci.* **22**:7850.

Hubbard, J.I., Llinás, R., and Quastel, D.M.J., 1969, Extracellular field potentials in the central nervous system, in: *Electrophysiological Analysis of Synaptic Transmission*, Edward Arnold (Publishers) Ltd., London, pp. 265-293.

Hurtado, J.M., Gray, C.M., Tamas, L.B., and Sigvardt, K.A., 1999, Dynamics of tremor-related oscillations in the human globus pallidus: a single study. *Proc. Natl. Acad. Sci. USA.* **96**:1674.

Hurtado, J.M., Lachaux, J.P., Beckley, D.J., Gray, C.M., and Sigvardt, K.A., 2000, Inter- and intralimb oscillator coupling in Parkinsonian tremor. *Mov. Disord.* **15**:683.

Hurtado, J.M., Rubchinsky, L.L., and Sigvardt, K.A., 2004, Statistical method for detection of phase-locking episodes in neural oscillations. *J. Neurophysiol.* **91**:1883.

Kühn, A.A., Williams, D., Kupsch, A., Limousin, P., Hariz, M., Schneider, G-H., Yarrow, K., and Brown, P., 2004, Event-related beta synchronization in human subthalamic nucleus correlates with motor performance. *Brain* **127**:735.

Kühn, A.A., Trottenberg, T., Kivi, A., Kupsch, A., Schneider, G-H., and Brown, P., 2005, The relationship between local field potential and neuronal discharge in the subthalamic nucleus of patients with Parkinson's disease. *Exp. Neurol.*, in press.

Leblois, A., Meissner, W., Bezard, E., Bioulac, B., Gross, C., and Boraud, T., Evolution of the activity of GPi neurons during a slow dopamine depletion process. Submitted.

Leblois, A., Boraud, T., Bergman, H., and Hansel, D., 2005, Basal ganglia physiology is built on competition between feedback loops, in: *Recent Breakthroughs in Basal Ganglia Research*, E. Bezard, ed., Nova Science Publishers, New York, in press.

Levy, R., Hutchison, W.D., Lozano, A.M., and Dostrovsky, J.O., 2000, High-frequency synchronisation of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J. Neurosci.* **20**:7766.

Levy, R., Ashby, P., Hutchinson, W.D., Lang, A.E., Lozano, A.M., and Dostrovsky, J.O., 2002a, Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. *Brain* **125**:1196.

Levy, R., Hutchison, W.D., Lozano, A.M., and Dostrovsky, J.O., 2002b, Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. *J. Neurosci.* **22**:2855.

Liu, X., Ford-Dunn, H.L., Hayward, G.N., Nandi, D., Miall, R.C., Aziz, T.Z., and Stein, J.F., 2002, The oscillatory activity in the parkinsonian subthalamic nucleus investigated using the macro-electrodes for deep brain stimulation. *Clin. Neurophysiol.* **113**:1667.

Loukas, C., and Brown, P., 2004, Online prediction of self-paced hand movements from subthalamic activity using neural networks in Parkinson's disease. *J. Neurosci. Methods.* **137**:193.

MacKay, W.A., 1997, Synchronised neuronal oscillations and their role in motor processes. *Trends Cog. Sci.* **1**:176.

Magill, P.J., Bolam, J.P., and Bevan, M.D., 2000, Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. *J. Neurosci.* **20**:820.

Magill, P.J., Bolam, J.P., and Bevan, M.D., 2001, Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. *Neuroscience* **106**:313.

Magill, P.J., Sharott, A., Bevan, M.D., Brown, P., and Bolam, J.P., 2004a, Synchronous unit activity and local field potentials evoked in the subthalamic nucleus by cortical stimulation. *J. Neurophysiol.* **92**:700.

Magill, P.J., Sharott, A., Bolam, J.P., and Brown, P., 2004b, Brain state-dependency of coherent oscillatory activity in the cerebral cortex and basal ganglia of the rat. *J. Neurophysiol.* **92**:2122.

Magill, P.J., Sharott, A., Harnack, D., Kupsch, A., Meissner, W., and Brown, P., 2005, Coherent spike-wave oscillations in the cortex and subthalamic nucleus of the freely moving rat. *Neuroscience* **132**:659.

Masimore, B., Kakalios, J., and Redish, A.D., 2004, Measuring fundamental frequencies in local field potentials. *J. Neurosci. Methods* **138**:97.

Marsden, J.F., Limousin-Dowsey, P., Ashby, P., Pollak, P., and Brown, P., 2001, Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson's disease. *Brain* **124**:378.

Mena-Segovia J., Bolam, J.P., and Magill, P.J., 2004, Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci.* **27**:585.

Mink, J.W., 1996, The basal ganglia: focused selection and inhibition of competing motor programs. *Prog. Neurobiol.* **50**:381.

Mitzdorf, U., 1985, Current-source density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiol. Rev.* **65**:37.

Moro, E., Esselink, R.J.A., Xie, J., Hommel, M., Benabid, A.L., and Pollak, P., 2002, The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology* **59**:706.

Murthy, V.N., and Fetz, E.E., 1992, Coherent 25- and 35- Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc. Natl. Acad. Sci. USA.* **89**:5670.

Murthy, V.N., and Fetz, E.E, 1996a, Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. *J. Neurophysiol.* **76**:3949.

Murthy, V.N., and Fetz, E.E., 1996b, Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. *J. Neurophysiol.* **76**: 3968.

Nini, A., Feingold, A., Slovin, H., and Bergman, H., 1995, Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. *J. Neurophysiol.* **74**:1800.

Perkel, D.H., Gerstein, G.L., and Moore, G.P., 1967a, Neuronal spike trains and stochastic point processes. I. The single spike train. *Biophys. J.* **7**:391.

Perkel, D.H., Gerstein, G.L., and Moore, G.P., 1967b, Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains. *Biophys. J.* **7**:419.

Pfurtscheller, G., Stancak, A., and Neuper, C., 1996, Post-movement beta synchronization. A correlate of an idling motor area? *Electroencephalogr. Clin. Neurophysiol.* **98**:281.

Priori, A., Foffani, G., Pesenti, A., Bianchi, A., Chiesa, V., Baselli, G., Caputo, E., Tamma, F., Rampini, P., Egidi, M., Locatelli, M., Barbieri, S., and Scarlato, G., 2002, Movement-related modulation of neural activity in human basal ganglia and its L-DOPA dependency: recordings from deep brain stimulation electrodes in patients with Parkinson's disease. *Neurol. Sci.* **23**:S101.

Priori, A., Foffani, G., Pesenti, A., Tamma, F., Bianchi, A.M., Pellegrini, M., Locatelli, M., Moxon, K.A., and Villani, R.M., 2004, Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp. Neurol.* **189**:369.

Raz, A., Vaadia, E., and Bergman, H., 2000, Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. *J. Neurosci.* **20**:8559.

Raz, A., Frechter-Mazar, V., Feingold, A., Abeles, M., Vaadia, E., and Bergman, H., 2001, Activity of pallidal and striatal tonically active neurons is correlated in MPTP-treated monkeys but not in normal monkeys. *J. Neurosci.* **21**:RC128.

Richards, C.D., Shiroyama, T., and Kitai, S.T., 1997, Electrophysiological and immunocytochemical characterization of GABA and dopamine neurons in the substantia nigra of the rat. *Neuroscience* **80**:557.

Roelfsema, P.R., Engel, A.K., König, P., and Singer, W., 1997, Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature* **385**:157.

Ruskin, D.N., Bergstrom, D.A., Tierney, P.L., and Walters, J.R., 2003, Correlated multisecond oscillations in firing rate in the basal ganglia: modulation by dopamine and the subthalamic nucleus. *Neuroscience* **117**:427.

Sanes, J.N., and Donoghue, J.P., 1993, Oscillations in local field potentials of the primate motor cortex during voluntary movement. *Proc. Natl. Acad. Sci. USA.* **90**:4470.

Sharott, A., Magill, P.J., Harnack, D., Kupsch, A., Meissner, W., and Brown, P., 2005a, Dopamine depletion increases the power and coherence of β-oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. *Eur. J. Neurosci.* **21**:1413.

Sharott, A., Magill, P.J., Bolam, J.P., and Brown, P., 2005b, Directional analysis of coherent oscillatory field potentials in the cerebral cortex and basal ganglia of the rat. *J. Physiol.* **562**:951.

Silberstein, P., Kühn, A.A., Kupsch, A., Trottenberg, T., Krauss, J., Wöhrle, J.C., Mazzone, P., Insola, A., Di Lazzaro, V., Oliviero, A., Aziz, T., and Brown, P., 2003, Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. *Brain* **126**:2597.

Sochurkova, D., and Rektor, I., 2003, Event-related desynchronization/synchronization in the putamen. An SEEG case study. *Exp. Brain. Res.* **149**:401.

Smith, Y., Bevan, M.D., Shink, E., and Bolam, J.P., 1998, Microcircuitry of the direct and indirect pathways of the basal ganglia. *Neuroscience* **86**:353.

Steriade, M., 2000, Corticothalamic resonance, states of vigilance and mentation. *Neuroscience* **101**:243.

Stern, E.A., Jaeger, D., and Wilson, C.J., 1998, Membrane potential synchrony of simultaneously recorded striatal spiny neurons *in vivo*. *Nature* **394**:475.

Timmermann, L., Wojtecki, L., Gross, J., Lehrke, R., Voges, J., Maarouf, M., Treuer, H., Sturm, V., and Schnitzler, A., 2004, Ten-Hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. *Mov. Disord.* **19**:1328.

Volkmann, J., Joliot, M., Mogilner, A., Ioannides, A.A., Lado, F., Fazzini, E., Ribary, U., and Llinás, R., 1996, Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. *Neurology* **46**:1359.

Vorobyov, V.V., Schibaev, N.V., Morelli, M., and Carta, A.R., 2003, EEG modifications in the cortex and striatum after dopaminergic priming in the 6-hydroxydopamine rat model of Parkinson's disease. *Brain Res.* **972**:177.

Williams, D., Tijssen, M., van Bruggen, G., Bosch, A., Insola, A., Di Lazzaro, V., Mazzone, P., Oliviero, A., Quartarone, A., Speelman, H., and Brown, P., 2002, Dopamine dependent changes in the functional connectivity between basal ganglia and cerebral cortex in the human. *Brain* **125**:1558.

Williams, D., Kühn, A., Kupsch, A., Tijssen, M., van Bruggen, G., Speelman, H., Hotton, G., Yarrow, K., and Brown, P., 2003, Behavioural cues are associated with modulations of synchronous oscillations in the human subthalamic nucleus. *Brain* **126**:1975.

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.