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Review

Beta oscillations in the cortico-basal ganglia loop during parkinsonism

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ABSTRACT

In the normal brain beta band oscillatory activity has been associated with retaining of ongoing motor activities. In Parkinson's disease, enhanced beta band oscillatory activity is displayed across the cortico-basal ganglia pathway and is one of the prominent neurophysiological phenomena associated with the disorder. Intraoperative and postoperative recordings of neural activity in patients undergoing stereotactic neurosurgery combined with studies in animal models of parkinsonism have led to the accumulation of complementary data regarding these oscillations. In this review we address some of the key issues facing researchers in the field. These issues encompass existing agreements as well as open debates in modern studies of beta band oscillations, including their defining characteristics, links to clinical symptoms and the functional properties of their formation and effects on behavior. We address these questions by comparing and contrasting the results of neurophysiological observations in human patients, MPTP primate model and 6-OHDA rat model with conceptual and computational models of the normal and parkinsonian basal ganglia. Defining a unifying scheme of beta band oscillations and their relation to neurophysiological, functional and clinical phenomena will enable future targeting of these oscillations for both diagnosis and treatment of Parkinson's disease.

Contents

Introduction

James Parkinson first described the motor deficits associated with the disease which was later named after him almost two centuries ago. The underlying pathology of Parkinson's disease (PD) is complex and involves multi-stage neuronal death throughout different parts of the brain (Braak et al., 2003). However, the primary motor symptoms of the disorder have been associated specifically with death of the

Abbreviations: 6-OHDA, 6-hydroxydopamine; BBO, beta band oscillations; CBG, cortico-basal ganglia; DBS, deep brain stimulation; GPe, globus pallidus externus; GPi, globus pallidus internus; LFP, local field potential; MPTP, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine; NHP, non-human primate; PD, Parkinson's disease; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

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dopaminergic neurons of the substantia nigra pars compacta (SNc). These neurons modulate the activity of the basal ganglia, mostly through their innervation of the striatum. Loss of these dopaminergic innervations leads to abnormal processing of the striatal inputs from the cortex and thalamus and subsequently to changes in neuronal activity of downstream basal ganglia nuclei; i.e., the globus pallidus externus and internus (GPe and GPi respectively), the subthalamic nucleus (STN) and the substantia nigra pars reticulata (SNr). The output of the basal ganglia (efferents of the GPi and SNr) is sent primarily to the thalamus and from there to the frontal cortex, thus forming the partially closed cortico-basal ganglia (CBG) loop (Joel and Weiner, 1994). The anatomical changes in the SNc (Hassler, 1939) and their relation to dopamine levels in the striatum (Hornykiewicz, 1963) were identified over half a century ago. However, studies of the neurophysiological changes underlying the disorder had to wait for the emergence of animal models of the disorder.

Animal models of parkinsonism focused on lesions to the dopaminergic neurons of the nigrostriatal system to mimic the source of the major motor symptoms. The two dominant models used extensively in studies of the parkinsonian neurophysiology are the MPTP primate model and the 6-OHDA rat model. Early studies reported that the neurotoxin 6-hydroxydopamine (6-OHDA) could be injected directly to the nigrostriatal pathway to induce a depletion of dopamine in the ipsilateral side to the injection (Ungerstedt, 1968). This consequently led to abnormal dopamine dependent turning behavior in the injected rats (Ungerstedt and Arbuthnott, 1970). Following the accidental discovery that acute parkinsonism can be induced in human subjects following exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), studies have shown that its systemic injection to non-human primates leads to the formation of all the major parkinsonian motor symptoms (with the possible exception of rest tremor in some species) (Burns et al., 1983; Fox and Brotchie, 2010). Over the years a multitude of variants of these two models have been developed which vary, for example, as regards the site of 6-OHDA injection or the methodology, timing and amount of MPTP injection. While other models of parkinsonism (such as genetically manipulated mice models) are currently used in different research fields, their contribution to neurophysiological studies has been limited so far and will not be discussed in this review.

The emergence of stereotactic surgery as a palliative treatment for PD symptoms and the use of microelectrode recording during surgery have led to an abundance of neurophysiological data recorded in human patients. The most common types of stereotactic surgeries in PD are ablation (primarily targeting the GPi) or deep brain stimulation (DBS) electrode placement (primarily in the STN). Neurophysiological data may be collected either during the procedure itself via the navigation microelectrode used for better localization of the target nucleus (Levy et al., 2002b) or postoperatively using the implanted DBS leads (Kuhn et al., 2009). These recordings constitute a rare opportunity in neuroscience enabling direct comparison of data from patients suffering from the disorder and data from animal models of the same disorder. This makes both the corroboration of the animal data and the expansion of human data possible.

Early studies of the neurophysiological changes occurring in the cortico-basal ganglia loop during parkinsonism dealt primarily with changes in the mean firing rate within different parts of the pathway (Albin et al., 1989; DeLong, 1990). Later studies shifted to different spatial and temporal properties of neuronal activity. Special attention has been paid to repetitive activity patterns manifested in the temporal domain as oscillations in the activity of single neurons or large neuronal populations and in the spatial domain as coherence between neurons or even nuclei.

Over the last few decades oscillations and coherence were shown to be important features of neural activity in both the normal and abnormal states (Buzsaki and Draguhn, 2004; Engel et al., 2001). Historically, neuronal oscillations are classified according to their frequency into multiple bands that range from low to high frequencies and are known as the delta, theta, alpha, beta and gamma bands respectively. The exact frequency range of each band and their subdivision into sub-bands varies across studies. Multiple studies have reported oscillatory activity in the cortico-basal ganglia pathway in different frequencies ranging from ultra-slow (<0.5 Hz) oscillations (Wichmann et al., 2002) to fast (>100) Hz oscillations (Foffani et al., 2003). However, most studies of basal ganglia oscillatory activity have centered on the 3–50 Hz range which classically includes theta, alpha and beta oscillations that increase in their amplitude considerably during parkinsonism. This range was further subdivided into frequencies classically associated with the parkinsonian rest tremor (3–7 Hz), and higher frequencies (focusing on the 10–35 Hz) were termed beta band oscillations (Gatev et al., 2006).

Beta band oscillations have been associated with both cognitive and motor functions in normal animals and human subjects and have been hypothesized to play a key role in the maintenance of the current behavioral state (Engel and Fries, 2010). The normal levels of beta oscillations and synchronization along the cortico-basal ganglia pathway in the normal state undergo a dramatic increase during parkinsonism. In this review, we will explore these excessive beta band oscillations (BBO) by addressing some of the key questions faced by researchers of the field. The questions are divided into three main categories: characterization of the oscillations in space and time, the relationship of these oscillations to the manifestation of clinical symptoms and the treatment of these symptoms, and finally the potential mechanisms of oscillation formation and their effects on behavior.

Characterization

The term BBO during parkinsonism has been used loosely over the years to describe a wide range of oscillatory phenomena. Assessing the clinical and functional significance of these oscillations requires an initial definition of the properties of these different phenomena enabling their comparison and potential clustering into a single entity. The key issues required for defining BBO as a single unique entity are (1) characterization of the neurophysiological signals displaying BBO, (2) characterization of the spectral, spatial and temporal properties of BBO, (3) characterization of the similarities and differences between species and between individuals, and (4) the relationship of BBO to other oscillations expressed during parkinsonism.

Neurophysiological signals displaying BBO

Oscillatory activity may be detected in different neurophysiological signals. These signals reflect neuronal activities that have different functionalities and spatial scope (Moran and Bar-Gad, 2010). The most local signal is the spiking activity of a single neuron, termed single unit activity. When the recorded extracellular signal contains spikes which cannot be attributed to a single neuron but rather to multiple neighboring neurons, typically in the radius of <200 μm (Lemon, 1984), the spike train is termed multiunit activity. Removal of the large spiking activity from the extracellular signal yields the background unit activity (BUA) which reflects spiking activity within a somewhat larger radius. In contrast to all these signals which reflect the spiking activity of neurons; i.e., neuronal output, slow changes in the extracellular voltage reflect the sum of (primarily) synaptic activity around the electrode (Buzsaki et al., 2012); in other words, the neuronal input to the recorded site at a distance of roughly a millimeter (depending on properties of the brain area and recording electrode). These slow changes are termed local field potential (LFP) when recorded inside the brain. When the same changes are recorded on the cortex they are termed electrocorticogram (ECoG) and electroencephalogram (EEG) when recorded on the scalp. These signals reflect the cumulative neuronal input within an area of ~5 mm^2 (ECoG) to ~10 cm^2 (EEG) (Buzsaki et al., 2012). These slow signals originate from multiple sources, with synaptic potential making the largest contribution and other factors such as fluctuating membrane potentials and even glial cell activity

contributing to the overall signal. Thus, the different recorded neurophysiological signals may reflect either the neuronal input or output in a specified brain area and a spatial resolution ranging from one neuron to a neuronal population occupying few centimeters (Moran and Bar-Gad, 2010). During parkinsonism all of these signals may display BBO, for example: single unit activity (Levy et al., 2002a), multiunit activity (Weinberger et al., 2006), BUA (Moran et al., 2008), LFP (Kuhn et al., 2004), EEG (Silberstein et al., 2005) and ECoG (Crowell et al., 2012; Mallet et al., 2008b). The BBO data recorded using each of these distinct methods, although complementary in nature, can yield different results that represent different neuronal processes affecting the same underlying neuronal tissue (Fig. 1).

Spectral, temporal and spatial characteristics

The spectral definition of BBO was inspired by the historical classification of oscillations into multiple frequency ranges known as bands or rhythms. The term beta rhythm was first coined by (Berger, 1930) and the range of frequencies which classically belongs to this band has a lower bound of 13 Hz and an upper bound at either 30 or 40 Hz (Niedermeyer, 1999). BBO in parkinsonism are generally defined over an extended range of 8–30 Hz (Brown and Williams, 2005) with the upper bound extending to 40 Hz in some cases (Rossi et al., 2008). This more inclusive definition of the beta band in parkinsonism acknowledges the common properties of the oscillations throughout this larger range which includes most of the band classically defined as the alpha band (Berger, 1929; Niedermeyer, 1999). The exact definition of the BBO frequency band varies to some extent across different studies and especially across different species, such as 8–35 Hz in PD patients (Kuhn et al., 2009), 10–15 Hz for NHP (Moran et al., 2012), and 12–40 Hz in the rat (Avila et al., 2010). The greatest disparity in the definition of BBO spectral properties across different studies pertains to the spectral specificity of the oscillations. While some studies have reported gross changes in the mean power of the whole band (Kuhn et al., 2008) others have observed changes in highly specific frequencies spanning only 1–2 Hz within the whole range (Moran et al., 2008), with additional intermediate cases (Levy et al., 2000). Observations of differences in oscillation properties within the beta band have given rise to a division of the range into sub-ranges with potentially different functional and clinical implications. One gross division splits BBO into a low beta band (~10–20 Hz) and a high beta band (~20–30 Hz) (Avila et al., 2010; Priori et al., 2004), with each sub-band associated with different clinical symptoms (Avila et al., 2010; Priori et al., 2004). This division is supported by different studies which found highly specific (i.e. narrow bandwidth) oscillations of single neurons at either the low end (8–15 Hz) (Moran et al., 2008, 2012) or high end (15–30 Hz) of the band (Levy et al., 2002a).

The temporal properties of BBO tend to be similar across studies. BBO manifest as coherent oscillations with phase locking for prolonged periods of time (Levy et al., 2000, 2002a; Moran et al., 2008). Thus, BBO appear to be related to the overall "tonic" state of parkinsonism rather than to any "phasic" expression of a specific symptom; although

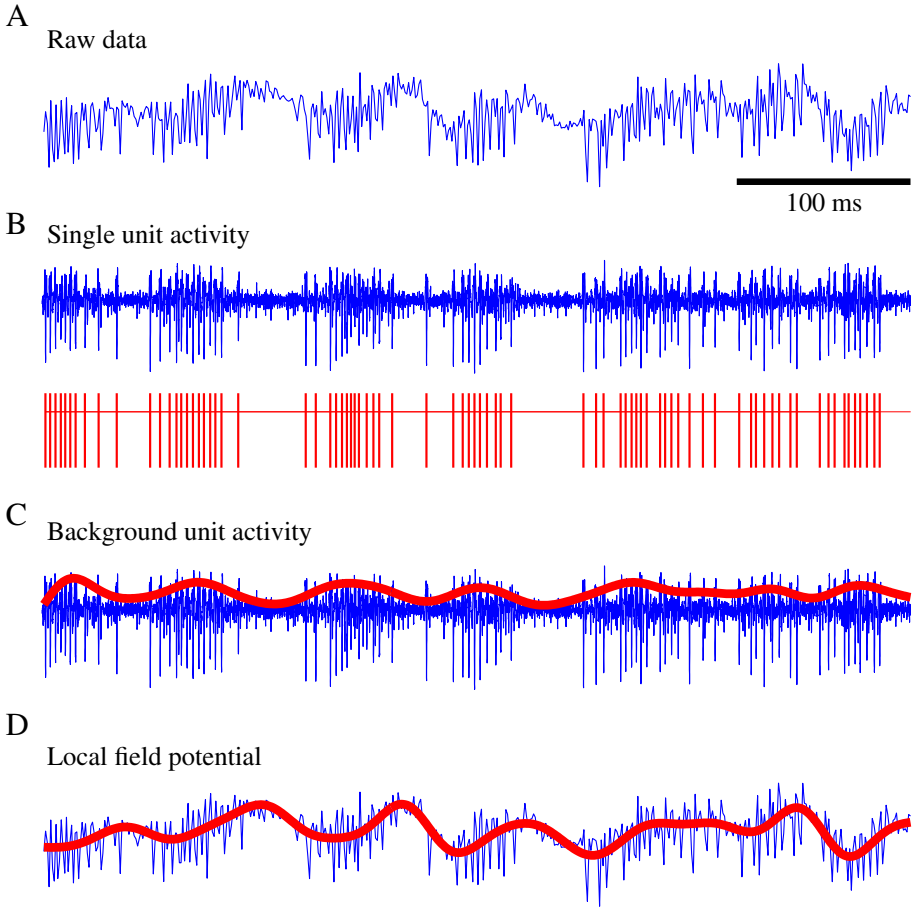

Fig. 1. Extracellular microelectrode recording and the derived signals displaying BBO. (A) Raw data recorded from the GPi of NHP rendered parkinsonian using MPTP. (B–D) Electrophysiological signals extracted from the same raw data recording. (B) Single unit activity extracted from raw data by high pass filtering (blue), followed by marking of the spiking activity of a single unit (red). (C) Background unit activity representing the spiking activity of small localized subpopulations around the electrode tip. The signal is extracted by removal of the unit activity from the high pass filtered raw data (blue) followed by rectification and envelope calculation (red). (D) Local field potential, representing integration of synaptic activity and other processes surrounding the electrode tip, is extracted by low pass filtering (red) the raw data (blue).

the oscillations typically vary over long time scales (Moran et al., 2008; Sen and Dostrovsky, 2007). This contrasts sharply with other oscillations related to parkinsonism, such as tremor frequency oscillations, which appear and disappear in synchrony with muscle tremor (Bergman et al., 1994). Phasic modulation of the power of BBO has been reported to occur during different behaviors. Desynchronization in the BBO was observed prior to voluntary movements in normal subjects (Engel and Fries, 2010; Kilner et al., 1999) as well as in parkinsonian patients (Kuhn et al., 2004; Levy et al., 2002a; Williams et al., 2005). Thus, during parkinsonism BBO typically have higher amplitude than in the normal state but they undergo the same modulation by voluntary movements and behavior.

The spatial distribution of BBO during parkinsonism is non-uniform on multiple scales. On the macro-scale, the power of BBO within different nuclei and regions of the CBG pathway is very different; on an intermediate scale, different regions within each nucleus oscillate to a different extent and on the micro scale, single neurons vary in their expression of BBO. The increase in BBO during parkinsonism is associated with the whole CGB loop, but not all the nuclei along the loop display similar levels of BBO activity. The STN and GPi display the highest BBO activity (Moran et al., 2012), the GPe displays smaller BBO amplitudes (Heimer et al., 2002; Moran et al., 2012), while in the SNr (Wichmann et al., 1999), the thalamus (Guehl et al., 2003; Pessiglione et al., 2005) (but see Xu et al., 2008) and motor cortex (Pasquereau and Turner, 2011) single neuron oscillations are not dominant. Notably, EEG recordings, which reflect the sum of large volumes of cortical neurons, do display BBO in PD patients (Brown, 2000; Silberstein et al., 2005). Spectrally, the oscillations along the CBG loop are similar across the different parts of the loop. This is evident both from the range of oscillations recorded concurrently across different areas (Moran et al., 2012) and the high coherence between nuclei at both the LFP and single neuron level (Kuhn et al., 2004; Levy et al., 2002a; Mallet et al., 2008b; Moran et al., 2012, 2012; Raz et al., 2000; Soares et al., 2004). The magnitude of BBO and the distribution of oscillating neurons within the same nucleus vary: in the STN most oscillatory neurons are located in the dorsal (motor) part of the nucleus (Moran et al., 2008; Weinberger et al., 2006; Zaidel et al., 2010). This spatial–functional distribution is in line with the higher levels of BBO found in the predominantly motor GPi compared to the lesser oscillatory activity in the classically non-motor SNr (Levy et al., 2002b; Wichmann et al., 1999). This may hint at the enhancement of BBO mainly along the motor pathway of the CBG loop.

The extent to which exaggerated BBO are expressed within the same nucleus and functional territory varies greatly according to the type of recorded signal. The probability of detecting oscillating activity is largest in the global signals summing large volumes of neurons (such as the LFP), smaller in the signal summing small populations (multiunit and background unit activity) and smallest in single neurons. For example, STN LFP recordings display BBO oscillations with clear peaks in 90% of the patients (Kuhn et al., 2009), STN background unit activity displays significant oscillatory peaks in half of the recordings (Moran et al., 2008, 2012) and finally only a fifth to a third of single neurons display beta oscillations (Moran et al., 2008, 2012). The GPi and GPe display similar signal-related distributions both in PD patients (Levy et al., 2002b) and MPTP treated NHP (Moran et al., 2012; Tachibana et al., 2011). Spatially, overlapping data across multiple scales implies that BBO in parkinsonism are important phenomena throughout the CBG loop and that its magnitude varies drastically.

Variance across individuals and species

Comparison of BBO across PD patients has revealed that individual subjects display oscillatory activity which is narrowly concentrated around a single main frequency, while different subjects display various oscillation frequencies which are mainly distributed across the 15–30 Hz beta band (Levy et al., 2000). A similar analysis of MPTP treated NHP (*Macaca fascicularis* (Moran et al., 2012), *Macaca mulatta* (Leblois et al., 2007; Nini et al., 1995; Soares et al., 2004), African green (Bergman et al., 1994) and Vervet (Raz et al., 2001)) displayed BBO activity which was concentrated within a narrow 10–15 Hz frequency band (primarily around 12 Hz) across all subjects and species, in contrast to the relatively large inter-subject variance of PD patients. The NHP beta band (8–15 Hz) is a subset of the whole human beta band (8–30 Hz), occupying only the lower part of the band which is sometimes referred to as "low beta" in human subjects. Some studies of human patients are in line with this limited beta range at least in terms of neuronal output activity (Moran et al., 2008; Zaidel et al., 2010). In contrast to the coherent nature of BBO properties across different species of NHP, there is diversity in the clinical symptoms displayed during parkinsonism. While all species display severe movement disorders, only the African green and vervet NHP display rest tremor (Bergman et al., 1994; Raz et al., 2001) and thus also display tremor frequency oscillations. Full parkinsonism is induced in NHPs either by a single set of intramuscular MPTP injections (Bergman et al., 1994; Moran et al., 2012; Nini et al., 1995; Raz et al., 2001; Soares et al., 2004), or a progressive dopamine depletion process which is achieved by daily injections of small doses of MPTP (Leblois et al., 2007). The different induction methods have not led to differences in the displayed BBO.

In contrast to the consistent characteristics of BBO across MPTP treated NHPs, 6-OHDA treated rats display a wide spectrum of results. STN BBO are observed across the 20–30 Hz frequency band (Mallet et al., 2008b; Sharott et al., 2005). The globus pallidus (GP); which is the rat homologue of the GPe; also displays BBO over the 15-30 Hz frequency band with peaks concentrated around 20 Hz (Mallet et al., 2008a). The entopeduncular (EP) nucleus, which is the rat homologue of GPi, displays oscillatory activity across the lower 4–18 Hz frequency band (Ruskin et al., 2002). Finally, the SNr also exhibits enhanced oscillatory activity across the beta band 12–25 Hz frequency band (Avila et al., 2010) in contrast to observations in PD patients and MPTP treated NHP. It may be possible that the high variability across the different 6-OHDA rat studies is an outcome of the various recording methods; anesthetized (Magill et al., 2001; Mallet et al., 2008b), awake immobilized (Ruskin et al., 2002) and freely moving (Avila et al., 2010; Mallet et al., 2008b). It has already been shown that the neuronal activity patterns in general and the appearance of BBO in particular in 6-OHDA treated rats are dominated by their arousal levels (Mallet et al., 2008a). The spectral characteristics of the BBO; range and magnitude; across the different nuclei along the cortico basal ganglia pathway for the different species are introduced in Table 1.

Relation to other oscillations

The CBG pathway displays oscillatory activity across various frequency bands, in both the normal and parkinsonian states. Spectral analysis of the oscillatory activity across the cortex in the normal state reveals two predominant frequency bands which are associated

Table 1
Characteristics of single neuron β band oscillations.

Brain area	Human PD	MPTP treated NHP	6-OHDA treated rat
Motor cortex	–	–	15–25 Hz
STN	++ 8–30 Hz	++ 8–15 Hz	++ 20 Hz
GPe	+ 15–30 Hz	+ 8–15 Hz	+ 15-30 Hz
GPi	++ 8–30 Hz	++ 8–15 Hz	+ 4–18 Hz
Thalamus	–	–	?
SNr	–	–	?

++: highly oscillatory, +: oscillatory, –: not oscillatory, ?: unknown.
Human: Chan et al. (2011), Levy et al. (2001, 2002a, 2002b), Magnin et al. (2000), Moran et al. (2008), Silberstein et al. (2003), Weinberger et al. (2006).
MPTP: Bergman et al. (1994), Guehl et al. (2003), Leblois et al. (2007), Moran et al. (2012), Nini et al. (1995), Pasquereau and Turner (2011), Raz et al. (2001), Soares et al. (2004), Tachibana et al. (2011), Wichmann et al. (1999).
6-OHDA: Avila et al. (2010), Magill et al. (2001), Mallet et al. (2008a, 2008b), Ruskin et al. (2002).

with movement: the beta band (classically 13–30 Hz (Engel and Fries, 2010)) and the gamma band (classically 35–90 Hz (Niedermeyer, 1999; Engel and Fries, 2010)). The former is associated with maintenance of the current state (i.e. leading to reduced movement) and the latter is associated with initiation of movement (i.e. leading to increased movement) (Brown, 2003; Engel and Fries, 2010). In the normal state it is commonly accepted to denote the BBO as antikinetic oscillations and gamma oscillations as prokinetic oscillations (Brown, 2003). In the normal state beta band desynchronization was observed prior to movement (Crone et al., 1998; Miller et al., 2007). The inverse relation between the beta and gamma bands and their relation to movement are maintained during parkinsonism (Brown, 2003; Crowell et al., 2012; Engel and Fries, 2010).

During parkinsonism low frequency theta oscillations (4–7 Hz); which are not observed in the normal state; are associated with muscular tremor (Bergman et al., 1994; Hutchison et al., 1997), and enhanced BBO (Brown and Williams, 2005) are observed across the CBG pathway. Although the tremor and beta bands do not overlap, the harmonics of the tremor band can reflect as frequencies classified as BBO in some cases (e.g. 6 Hz oscillations may manifest at 12 or even 18 Hz) (Wichmann et al., 1999). These harmonics share both the spatial and temporal properties of the base tremor frequency. Co-analysis of tremor related oscillations and BBO showed that the two are uncorrelated (Levy et al., 2001; Moran et al., 2008) (but see Weinberger et al., 2009) and have very different temporal and spatial properties. In the temporal domain tremor oscillations are more intermittent over time (Hurtado et al., 1999; Moran et al., 2008) whereas BBO are more continuous in nature (Moran et al., 2008). The relation of BBO to additional oscillation bands such as very low (<1 Hz) (Wichmann et al., 2002) or very high (>100 Hz) (Foffani et al., 2003) bands has not been studied yet.

Clinical features

It is commonly accepted that pathological BBO, which are key neurophysiological phenomena in PD, are related to the clinical symptoms of the disease. However, in contrast to tremor band oscillations that are directly related to parkinsonian tremor (Bergman et al., 1994; Hutchison et al., 1997), the relations between BBO and parkinsonian clinical symptoms or states are far more complex. The key issues associating BBO to the manifestation of clinical symptoms are as follows: (1) linking exaggerated BBO and clinical symptoms during parkinsonism, (2) linking changes in BBO and treatments of parkinsonism, and (3) establishing a causal relation between BBO and parkinsonian clinical symptoms.

Relation of BBO to clinical symptoms during parkinsonism

Parkinsonism is characterized by severe motor symptoms including bradykinesia, akinesia, rigidity and tremor (Jankovic, 2008) and by exaggerated BBO compared to the normal state (Kuhn et al., 2008). Surprisingly, although these neurophysiological and clinical characteristics are presumed to be correlated, numerous works have failed to establish a clear relationship between the two during parkinsonism. No significant correlations have been found between patients' overall clinical state, as measured by their Unified Parkinson's Disease Rating Scale (UPDRS) scores, and the percent of oscillating cells (Weinberger et al., 2006), LFP oscillations' main frequency (Kuhn et al., 2009) or LFP power over the 8–35 Hz frequency band (Kuhn et al., 2009). In addition, no significant correlation was found between BBO and specific motor symptoms such as bradykinesia, akinesia and rigidity (Moran et al., 2008). Note that in some cases harmonics of the tremor band oscillations can be misidentified as BBO due to their overlapping frequency range, which can lead to correlations between the activity in the beta band (which is not part of the classic BBO) and parkinsonian tremor (Wichmann et al., 1999).

The failure to correlate baseline beta oscillatory activity with overall clinical state or the manifestation of specific symptoms prompted the analysis of the relationship between the two over shorter time scales, and in particular around the time of voluntary movements. Studies of the relation between BBO during parkinsonism and movement are based on studies in the normal state in which beta activity is associated with maintenance of motor/behavioral in the steady state. These studies demonstrate that beta band power increases while the status quo is maintained, and decreases upon shifting from it (Engel and Fries, 2010; Kilner et al., 1999). These studies have found that the STN BBO desynchronize about 200 ms prior to voluntary movement and resynchronize about 1 s following the end of the movement (Kuhn et al., 2004; Williams et al., 2005), in line with cortical EEG results during normal behavior. Additional evidence in line with these findings is that when no voluntary movements took place, STN single unit activity displayed coherent BBO with phase locking for hundreds of seconds (Levy et al., 2000, 2002a). Taken together, although BBO are a prominent feature of parkinsonism, no correlation has been found between the BBO and the general UPDRS score or any of the parkinsonian motor symptoms in the baseline state.

BBO during treatment of parkinsonism

The standard treatment for PD symptoms consists of dopamine related drugs, such as the dopamine precursor levodopa (L-dopa) (Hornykiewicz, 2010) or dopamine agonists such as apomorphine (Subramony, 2006). Studies have found that suppression of BBO across the BG was observed during elevation of dopamine levels and amelioration of the clinical motor symptoms (Priori et al., 2004). Furthermore, improvement in the clinical motor symptoms with the exception of tremor was found to be correlated with the degree of BBO suppression (Doyle et al., 2005; Kuhn et al., 2006, 2009) and the percent of oscillating cells in the baseline state (Weinberger et al., 2006). However, there are no straightforward relations between the BBO and the clinical state as evidenced from a study in which partial inhibition of the STN led to improvement of the clinical symptoms without a suppression of BBO in the STN (Levy et al., 2001).

An alternative therapeutic intervention in PD is stereotactic surgery that involves either ablation (primarily targeting the GPi) or implantation of DBS electrodes (primarily targeting the STN). This intervention takes place when the dopaminergic treatment is no longer effective or induces severe side effects such as dyskinesias (Alonso-Frech et al., 2006). The mechanism underlying the ameliorating effects of high frequency DBS is still largely unknown (Kuhn et al., 2008). The analysis of the changes that BBO undergo during DBS is complex due to the large artifact of the stimulating currents and the interacting effects of the specific stimulating electrode type and configuration (Carlson et al., 2010; Erez et al., 2010; Kuhn et al., 2008). Conflicting results have been reported in different studies examining the level of BBO in the STN during DBS. On one hand it was reported that the power of BBO does not change significantly despite the ameliorating effects of DBS (Rossi et al., 2008). On the other hand, another study reported suppression of beta band power during DBS which returned to its baseline level following the end of stimulation (Kuhn et al., 2008). Another study on MPTP treated NHPs reported that during STN DBS the oscillations underwent relatively mild reduction, but a major decrease in coherence between neurons displaying BBO across the BG was observed (Moran et al., 2012).

Are the oscillations causal to the symptom?

The relation between BBO and motor symptoms which was historically based solely on correlative evidence gave rise to the hypothesis of a causal link between the two. The validation or rebuttal of such a link has a crucial role in emerging treatment methodologies of the clinical motor symptoms in PD (Tass, 2001). The basis for the assumption of a causal relation between BBO and clinical symptoms relies extensively on a set of studies which imposed exaggerated beta band coherent oscillations in the BG and the cortex. Induction of 10 Hz (Timmermann et al.,

2004) and 20 Hz (Chen et al., 2007; Eusebio et al., 2008) oscillations in the STN of PD patients through electrical stimulation led to a significant but subtle worsening of the clinical motor symptoms, mainly akinesia. In addition, boosting 20 Hz cortical oscillations in healthy subjects using transcranial alternating-current stimulation (tACS) slowed voluntary movement (Pogosyan et al., 2009). On the other hand, a study of the progression of BBO and clinical symptoms during the progressive formation of parkinsonism in NHP using low doses of MPTP found that the manifestation of the clinical motor impairments is not dependent on BBO. This study found that the clinical symptoms appeared several days prior to the formation of BBO (Leblois et al., 2007). These findings were corroborated by a computational model suggesting that moderate dopamine depletion is sufficient to induce clinical motor symptoms whereas BBO emerge in addition to these clinical symptoms only following high levels of dopamine depletion (Leblois et al., 2006). A study in PD patients showed that the percent of beta band oscillating cells is uncorrelated to the clinical state of the patient, but is correlated to the degree of symptom amelioration upon application of levodopa; hence pointing on a dissociation between the oscillatory beta band activity and the clinical symptoms (Weinberger et al., 2006). An additional study in PD patients following STN DBS; reported on reduced rigidity without a significant change in the power spectrum across the beta, gamma and 300 Hz frequency bands; hence, pointing on a dissociation between the BBO activity and the clinical state (Foffani et al., 2006). Finally, partial inhibition of the STN in PD patients led to an improvement of the clinical symptoms without a suppression of BBO (Levy et al., 2001). Thus, there are currently seemingly conflicting findings regarding the existence of a causal relation between BBO and clinical motor symptoms in PD. Due to the major implications of this key issue on PD research and treatment, further physiological, theoretical and clinical research is needed to identify a unifying mechanism consistent with all these findings.

Functionality

Comparative anatomy of the basal ganglia demonstrates that these nuclei are well preserved across vertebrate species (Reiner, 2009). However, despite accumulating pharmacological, physiological and anatomical data, their role in the normal state and their effect in different BG-related pathologies are still unclear. Currently the leading BG model is still the classical rate based model introduced more than 20 years ago (Albin et al., 1989; DeLong, 1990), which fails to address temporal changes in the neuronal activity such as oscillations and coherence. In order to shed light on the functionality aspects of the findings presented in the previous sections, two key issues should be addressed: (1) the mechanism underlying the formation of BBO and (2) the mechanism by which BBO may result in abnormal behavior during parkinsonism.

Mechanism of BBO formation

The underlying mechanism of BBO formation during parkinsonism is still unclear. The nature of BBO requires their definition in a dynamic, time varying nature, which contrasts with the current static modulatory perception of the 'box and arrow' model of the CBG loop. Multiple hypotheses have been put forward over the years which were supported primarily by theoretical models and computational studies. The common denominator underlying all these models is that the presumed source of BBO formation is within the basal ganglia nuclei and from this source they propagate downstream to the thalamus and consequently to the cortex. This is consistent with the experimental findings of increased BBO within the BG during parkinsonism relative to the rest of the CBG pathway, across multiple neuronal signal types. Moreover, the existence of BBO in EEG recordings but not in single units may hint to their nature as input signals to the cortex rather than output of the cortical system. The leading theory of oscillation formation is based on the massive reciprocal and opposing connectivity between the STN and GPe; namely, STN inhibition by GABAergic GPe projections and GPe excitation by glutamatergic STN projections (Bevan et al., 2002). Theoretical studies of such feedback loops have shown that this structure is prone to oscillatory unstable activity. In-vitro studies of brain cultures demonstrated the formation of pace making activity using the feedback between the STN and GPe (Plenz and Kital, 1999) which may be achieved in isolation from other synaptic inputs. The involvement of these two major components of the BG indirect pathway in oscillation formation was also demonstrated computationally (Terman et al., 2002). The formation of oscillations within the STN–GPe network has been associated with multiple potential factors: increased coupling of the GPe–STN (Magill et al., 2001), increased coupling within the STN (Gillies et al., 2002), a short time constant of neuronal reaction (Holgado et al., 2010), and an increase of synaptic input from the striatum to the GPe (Kumar et al., 2011). Notably another model implicated different parts of the cortico-basal ganglia pathway: Leblois et al. (2006) demonstrated computationally that the dopamine induced imbalance between the competing direct and hyperdirect pathways is potentially capable of forming oscillatory activity. In this model the indirect pathway and consequently the GPe–STN interaction do not play a primary role in oscillation formation.

Mechanisms of BBO effect on behavior

The actual mechanism by which BBO in the basal ganglia during parkinsonism affect behavior has been addressed using two major modeling approaches: conceptual modeling of the BBO effect based on an analogy to their apparent effect in normal behavior and computational modeling of the BBO effect based on the modulation exerted by the BG on neuronal activity downstream. Recently, BBO have been associated with the role of maintaining the status quo; i.e., maintenance of the current state (Engel and Fries, 2010). According to this conceptual model, high BBO levels signal that the current state should be maintained while low BBO levels signal that a change of state is about to occur. This notion is supported by linking enhanced cortical beta oscillations to posture maintenance and to the absence of movement (Gilbertson et al., 2005). In this context the enhanced BBO observed during parkinsonism constantly signal to the rest of the brain to maintain the current state and reduce shifts to different behaviors, resulting in akinesia and bradykinesia. Other disorders have been associated with abnormal neuronal activity along the CBG pathway. Enhanced BBO is a feature of some of these pathologies. In dystonia, BBO are observed across the basal ganglia, in both LFP and single unit activity (Schrock et al., 2009; Weinberger et al., 2012) and typically occupy a lower frequency band (8–20 Hz) (Weinberger et al., 2012). PD patients display a significantly higher level of single unit oscillatory activity (Schrock et al., 2009; Weinberger et al., 2012) and coherence between single unit and LFP activity (Weinberger et al., 2012) than dystonia patients. In contrast, studies in Tourette syndrome patients (Marceglia et al., 2010) and in the NHP model of the disorder (McCairn et al., 2009) have not observed BBO. Thus, although BBO may be more broadly associated with movement abnormalities, their manifestation during PD appears to be the most pronounced.

The mechanism by which such oscillations in sub-cortical areas affect behavior, presumably through the thalamus and cortex, is still unclear and is studied primarily using computational models of the CBG pathway. These models rely on the accumulated anatomical and physiological data demonstrating that the output of the basal ganglia controls thalamo-cortical transmission using a disinhibition mechanism (Deniau and Chevalier, 1985). Oscillations in the output neurons of the basal ganglia lead to reduced fidelity of information transmission by thalamo-cortical neurons (Rubin and Terman, 2004). The correlated oscillatory activity in the GPi may in turn increase the thalamic correlations, thereby decreasing the information transmission (Reitsma et al., 2011). The reduced fidelity of thalamo-cortical information transmission combined with the reduced information capacity of the basal

ganglia during parkinsonism (Bar-Gad et al., 2003) may prevent the required information for making a behavioral choice from reaching the frontal cortex.

Summary

The abundance of data relating to BBO in recent years from recordings in both human PD patients and animal models of the disorder has greatly increased our understanding of these oscillations. These complementary data collected by using multiple methods and species have led to a widespread consensus concerning some BBO properties, provided insufficient data on others and have left some issues under intense debate. There is a general agreement that BBO form a single group of phenomena which share a common basis. These oscillations, which are manifested in a differential way throughout the CBG loop, are correlated with the overall parkinsonian state but do not directly reflect the severity of any of the symptoms or their combination. The oscillations decrease drastically during different treatments of parkinsonism such as dopaminergic medication or high frequency DBS. Unlike these well-established agreements, other issues are still lacking conclusive evidence: both the mechanism of the formation of BBO and the mechanism of their effect are currently addressed primarily by conceptual and computational models but there is little experimental data to support any theory. Other properties of BBO have been the subject of implicit or explicit debate over the last few years such as conflicting data on the frequency range of BBO and their subdivision into different sub-bands has received conflicting evidence. Most importantly, the causal relationship between BBO and clinical symptoms remains elusive with some studies demonstrating that imposing oscillations leads directly to some parkinsonian symptoms while others note the formation of such symptoms without noticeable BBO. This key question will ultimately decide the fate of BBO as either a key pathology of Parkinson's disease or an epiphenomenon of the disease.

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