

Neural Networks and Neurofeedback in Parkinson's Disease

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Abstract

Aberrant neural network synchrony in basal ganglia thalamocortical circuits has been implicated in the pathophysiology of Parkinson's disease. Manipulating these abnormal activation patterns may therefore offer a novel avenue for treating this disabling condition. Evidence suggests that network activity can be normalized with both dopaminergic drug treatment and deep brain stimulation (DBS), and protocols that directly target specific oscillatory patterns ("closed-loop DBS") are under development. Another potential avenue for the modulation of specific neural activation patterns is neurofeedback. This noninvasive technique entails providing a continuous update of one's neural activity so that volitional control of selected brain regions, networks, or rhythms can be learned. This could be accompanied by specific therapeutic changes in behavior and clinical symptomatology in disease, according to the neural circuits that are modulated. Most neurofeedback research has used electroencephalography (EEG) but recently neurovascular signals measured with functional magnetic resonance imaging (fMRI) have been targeted as well. In this paper, we discuss the evidence implicating certain rhythms, particularly the beta (10–35 Hz) oscillation, in Parkinson's disease. We also perform a systematic review evaluating the therapeutic efficacy of neurofeedback in Parkinson's disease and make suggestions for future research.

Keywords: Parkinson's disease; neurofeedback; electroencephalography; real-time functional magnetic resonance imaging; deep-brain stimulation

Introduction

The precise mechanisms in which the brain encodes, stores, and computes information has long been the subject of intense debate in modern neuroscience. A popular theorem, which has received great interest, invokes the role of neuronal network oscillations in information processing. Local field potential (LFP) oscillations and, on a more macroscopic scale, electroencephalography (EEG) and magnetoencephalography (MEG) recordings are the product of synchronous firing of populations of neurons. Such oscillations represent rhythmic fluctuations in membrane potential and extracellular currents, and reflect the complex

interplay between cellular and synaptic mechanisms (Buzsáki, 2006; Logothetis, 2003). Rather than representing mere electrophysiological epiphenomena, network oscillations actively sculpt and coordinate neuronal activity patterns, facilitating transmission, communication and consolidation of information streams (Buzsáki, 2002, 2010; Buzsáki & Draguhn, 2004; Buzsáki & Wang, 2012; Fries, 2005; Wang, 2010).

The level of oscillatory synchronization on a spatial and temporal scale determines the precise frequency and amplitude of these oscillations (Von Stein & Sarnthein, 2000), with different frequency bandwidths correlating with specific behavioral, cognitive, perceptual, and sensorimotor functions (Brown, 2007; Buzsáki, 2006; Crunelli & Hughes, 2010; Laurent, 2002; Steriade, 2003; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Although aberrant network activity spanning most frequency bandwidths has been intertwined with a variety of disease states (Basar, Basar-Eroglu, Guntekin, & Yener, 2013; Bragin, Engel, & Staba, 2010; Traub 2003; Uhlhaas & Singer, 2010), in the context of motor functioning and disorders much research has placed particular focus on the beta (10–35 Hz) rhythm (Brown, 2007; Davis, Tomlinson, & Morgan, 2012; Engel & Fries, 2010; Stein & Bar-Gad, 2013).

In this article, we first discuss the canonical model of the basal ganglia circuitry and its dysfunction in Parkinson's disease (PD), while addressing its limitations. We then discuss the impact of oscillatory network dynamics and its pathological nature in PD with a particular emphasis on the role of beta (10–35 Hz) oscillations. The electrophysiological impact of rhythms within other frequency ranges will also briefly be discussed. Finally, we perform a systematic review highlighting empirical data that has investigated the role of neurofeedback, a novel method for modulating brain activity, in PD, with corresponding suggestions for future research.

Putative Mechanisms Underpinning PD

PD is a chronic neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain. This manifests clinically as a combination of bradykinesia or akinesia, muscle rigidity, postural instability, and a resting pill-rolling tremor (4–6Hz; Jankovic, 2008). The precise neural mechanisms underpinning this clinical phenotype remain unclear, but certain theories have been proposed.

According to the canonical model (Albin, Young, & Penney, 1989; DeLong, 1990), an imbalance in activity between the direct and indirect neural pathways resulting from striatal dopaminergic denervation is responsible for generating bradykinesia and rigidity. SNpc neurons activate the direct, and inhibit the indirect, pathway via excitatory D1 and inhibitory D2-receptors, respectively, on segregated classes of medium spiny neurons (MSN), which form the sole output of the striatum (Surmeier, Ding, Day, Wang, & Shen, 2007). MSNs send inhibitory projections to the globus pallidus pars interna (GPi) and globus pallidus pars externa (GPe). GPi, in combination with substantia nigra pars reticulata (SNpr), which are both functionally equivalent, represent the only output nuclei of the basal ganglia and send tonic inhibitory projections to the thalamus. The thalamus sends excitatory signals to the neocortex, which completes the basal ganglia thalamocortical loop via dense glutamatergic afferent innervation of the striatum.

Activation of the direct pathway results in inhibition of GPi/SNpr by D1-MSN striatal neurons, thereby disinhibiting excitatory thalamic output to the motor areas of the neocortex, which facilitates locomotor behavior. Activation of the indirect pathway, however, leads to D2-MSN

striatal neuron-driven inhibition of GPe, which causes disinhibition of subthalamic nucleus (STN; as GPe sends GABAergic inhibitory output to STN). The disinhibited STN, which also receives corticofugal excitatory afferents via a so-called “hyper-direct pathway,” is subsequently free to excite GPi/SNpr-mediated inhibition of the thalamus, and consequently reduce activity in the neocortex—this putatively leads to a reduction in locomotion. Ultimately, as a consequence of SNpc degeneration in PD, there is reduced activation of the direct pathway and reduced inhibition of the indirect pathway, which collaboratively provides a mechanistic explanation for the difficulty in initiation of novel movements in PD (see Figure 1).

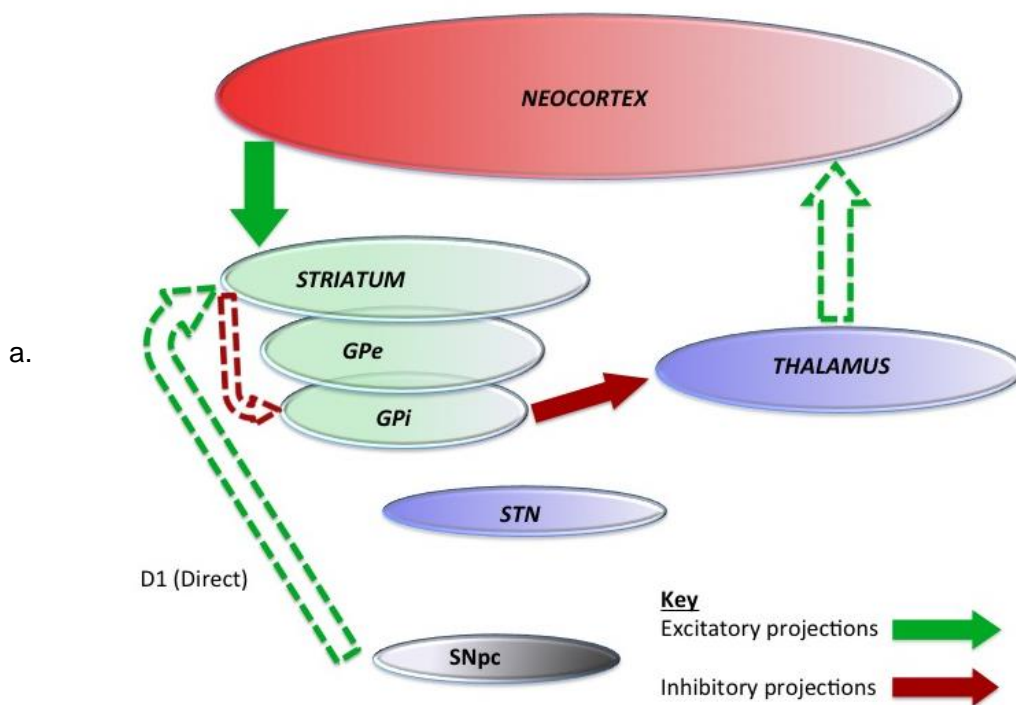


Figure 1. Schematic representations of the canonical basal ganglia circuits in PD. (a) Reduced activation of the striatum in the direct pathway following degeneration of SNpc putatively results in reduced thalamic-driven cortical excitation and subsequent compromised locomotor output.

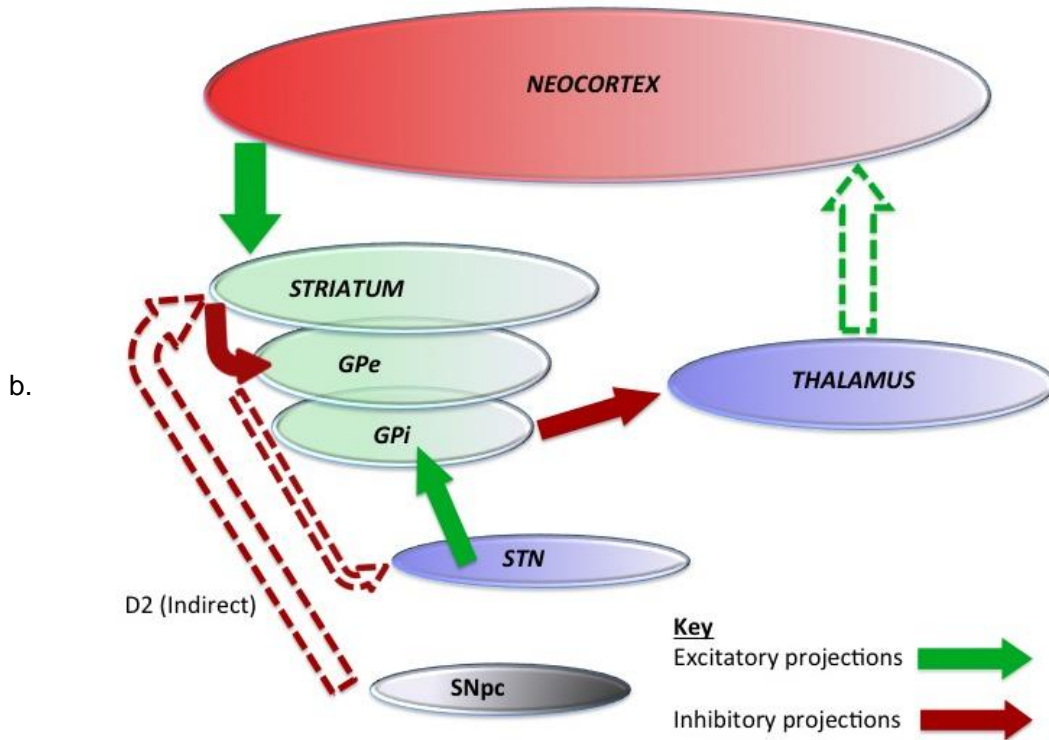


Figure 1. Schematic representations of the canonical basal ganglia circuits in PD. (b) Reduced inhibition of the striatum in the indirect pathway ultimately leads to the same outcome as that of reduced excitation of the direct pathway. Dotted arrows represent reduced activity in the corresponding projections.

The antagonistic functional effects of the direct and indirect pathways have been elegantly illustrated in optogenetic experiments, which have aimed to directly modulate basal ganglia circuits *in vivo* (Gradinaru, Mogri, Thompson, Henderson, & Deisseroth, 2009; Kravitz et al., 2010; Tye & Deisseroth 2012). For example, increasing the activation of the direct pathway in transgenic mouse lines, made to selectively express light-activated ion channels in D1-MSN neurons, has been shown to rescue Parkinsonian symptoms in 6-hydroxydopamine-lesioned mouse models of PD (Kravitz et al., 2010).

However, the canonical model of PD entails an oversimplification. Although it explains the origin of bradykinesia and rigidity in PD, it fails to explain the remaining clinical manifestations, such as resting tremor. It also makes a significant, and possibly unjustified, assumption that firing rate of neurons is the predominant means by which the brain encodes and transfers information from one region to another (Buzsáki, 2006, 2010). Although there has been some empirical support for the firing rate model of PD (Remple et al., 2011; Steigerwald et al., 2008), conflicting findings have emerged from the literature. For example, single unit recordings have revealed that the average firing rate of GPi neurons, in primates rendered Parkinsonian using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), remain largely unchanged, although the canonical model predicts an increase (Tachibana, Iwamuro, Kita, Takada, & Nambu, 2011). During high frequency stimulation of the STN, which is known to improve Parkinsonism (Benazzouz, Gross, Feger, Boraud, & Bioulac, 1993), GPi neurons fail to show the expected decrease in firing rate (Hashimoto, Elder, Okun, Patrick, & Vitek, 2003; Moran, Stein, Tischler, Belevsky, & Bar-Gad, 2011). Furthermore, functional

neuroimaging and noninvasive brain stimulation studies in PD patients have collectively shown that the activation or level of excitability of the motor cortex is not necessarily reduced in PD (Haslinger et al., 2001; Kleine, Praamstra, Stegeman, & Zwarts 2001; Ridding, Inzelberg, & Rothwell, 1995; Sabatini et al., 2000), which again contradicts predictions from the canonical model of PD.

A Physiological Role for Beta Oscillations

Beta oscillations are believed to play a physiological role in coordinating motor function. They are pronounced during steady state, tonic contractions, diminish immediately prior to and during the execution of movements, and rebound after movement (Alegre et al., 2005; Courtemanche, Fujii, & Graybiel, 2003; Hutchison et al., 2004; Kuhn et al., 2004; Williams et al., 2005). Although originally labeled as an “idling rhythm,” increasing evidence has implicated beta in playing a more active role in maintaining the motor set and resisting the enactment and expression of volitional movements (Engel & Fries, 2010). This has been supported by studies, which have shown that stopping or omitting unwanted behaviors was associated with greater synchronization and coherence of oscillations in the beta frequency band (Gilbertson et al., 2005; Swann et al., 2009; Van Wijk, Daffertshofer, Roach, & Praamstra, 2009). Noninvasive brain stimulation techniques have provided further insight into the active role of the beta rhythms in motor control. The use of transcranial alternating current stimulation (tACS) of the motor cortex to entrain beta oscillatory activity has been shown to reduce motor output and the magnitude of force contraction (Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012; Pogosyan, Gaynor, Eusebio, & Brown, 2009). Furthermore, theta burst stimulation (TBS), a particular type of repetitive transcranial magnetic stimulation (rTMS) protocol designed to inhibit neuronal activity, directed onto primary motor cortex of healthy volunteers, has been associated with significantly increased spontaneous beta oscillations. Importantly, this electrophysiological response only occurred in individuals who experienced reduced corticospinal excitability in the relevant M1 region (McAllister et al., 2013).

Insight has also been provided from studies in PD patients undergoing functional neurosurgery for deep brain stimulation (DBS). Within the STN, beta oscillations are largely detected in the dorsolateral region, which is known to topographically represent the motor area (Monakow, Akert, & Kunzle, 1978; Nambu, Takada, Inase, & Tokuno, 1996; Romanelli, Esposito, Schaal, & Heit, 2005). High frequency stimulation of the dorsolateral STN provides the optimal therapeutic outcome in PD patients, providing indirect evidence for the role of beta in motor processing (Herzog et al., 2004; Maks, Butson, Walter, Vitek, & McIntyre, 2009). DBS of STN in PD patients, which drove increased beta power in the frontal cortex, was associated with improved stopping performance in a behavioral stop signal task (Swann et al., 2011). DBS of STN at beta frequencies can also lead to worsening of bradykinesia in PD patients (Eusebio et al., 2008; Fogelson et al., 2005).

Thus, beta band synchronization is believed to represent an immutability-promoting rhythm, which locks neural circuitry into a low entropy state that maintains the status quo (Brittain & Brown, 2014; Engel & Fries, 2010). Higher oscillatory synchronization in the beta bandwidth engages large neuronal networks, which may span distant brain regions, into stereotyped, predictable spatiotemporal firing patterns. This is hypothesized to lower neural processing capacity, since such ensembles are prevented from operating in relatively more segregated information processing streams resonating at higher frequencies (i.e., gamma), which would otherwise signal more complex, novel behavioral and higher cognitive functions (Bergman et al., 1998; Brittain, Sharott, & Brown, 2014; Nini, Feingold, Slovin, & Bergman, 1995).

Although beta oscillations may display a physiological role in motor processing, and in particular facilitate stopping behaviors (Engel & Fries, 2010; Jenkinson & Brown, 2011), excessive neural network synchrony within this bandwidth has been associated with, and even causally related to, the pathology of PD. Notably, excessive beta synchronization is thought partly to account for symptoms of bradykinesia and rigidity (Zaidel, Arkadir, Israel, & Bergman, 2009), while aberrant oscillations in the theta and gamma range, which we will discuss later, may explain tremor and treatment-related dyskinesia, respectively, although the evidence for the functional role of the latter two rhythms is less robust (Deuschl et al., 2000; Richter, Halje, & Petersson, 2013).

The Putative Pathological Role of Beta Activity in PD

An emerging theory in the PD literature is that striatal dopaminergic denervation leads to excessive beta oscillatory synchronization within the basal ganglia thalamocortical circuits (Hammond, Bergman, & Brown, 2007). Whether this oscillation plays a causal role in driving the pathophysiological manifestations of the disease process, or whether it is merely an epiphenomenon has been the subject of much debate, but increasing evidence is beginning to favor the former scenario. Evidence for the role of beta oscillations in PD have largely stemmed from animal models and from electrophysiological recordings via electrodes in PD patients undergoing functional neurosurgery for DBS.

Nonhuman primates can be rendered Parkinsonian following injection of MPTP as this leads to preferential degeneration of dopaminergic neurons, including the nigro-striatal projections (Piffl, Schingnitz, & Hornykiewicz, 1991; Porras, Li, & Bezard, 2012). Recordings of single-unit activity in STN, GPe, GPi, striatum and motor cortex have revealed significantly increased rhythmic bursting activity following MPTP administration (Boraud, Bezard, Guehl, Bioulac, & Gross, 1998; Goldberg, Rokni, Boraud, Vaadia, & Bergman, 2004; Stein & Bar-Gad 2013). This is accompanied by an increase in correlated, spatiotemporally synchronized neuronal firing in distributed ensembles, which can manifest as an increase in amplitude of beta LFP oscillations within the cortex and basal ganglia (Bergman, Wichmann, Karmon, & DeLong, 1994; Goldberg et al., 2004; Heimer, Bar-Gad, Goldberg, & Bergman 2002; Jaidar et al., 2010; Moran, Stein, Tischler, & Bar-Gad, 2012; Stein & Bar-Gad 2013; Tachibana et al., 2011). Furthermore, recognized treatments for PD, such as STN stimulation and dopamine replacement, have been shown to reduce beta oscillations in the MPTP primate model (Gilmour et al., 2011; Moran et al., 2012).

Rat models of PD, involving selective lesioning of the nigrostriatal pathway following injection of 6-hydroxydopamine (6-OHDA), have provided further support for an association between pathologically elevated beta synchrony and PD. Unilateral hemispheric lesions of the nigrostriatal pathway resulted in increased beta oscillatory activity in SNpr, when compared with the control hemisphere, in combination with contralateral Parkinsonian symptoms (Avila et al., 2010; Delaville et al., 2014). Excessive beta oscillatory synchronization has also been shown to occur in STN-GP networks in 6-ODHA lesioned rat models (Magill, Bolam, & Bevan, 2001; Mallet et al., 2008a, 2008b).

A Dopamine transporter (DAT) knockout mouse has provided a valuable model for studying the neural mechanisms of PD. Costa et al. (2006) simultaneously recorded single-unit activity and LFP oscillations in primary motor cortex and dorsolateral striatum in DAT knockout mice. DAT knockout causes a 5-fold increase in extracellular dopamine levels and results in a hyperkinetic state in novel environments. Administration of the tyrosine hydroxylase inhibitor, alpha-methyl-p-tyrosine (AMPT), which led to rapid depletion of

dopamine levels (within 20 minutes) to < 0.2% of wild-type controls, resulted in significantly increased beta oscillation amplitude in motor cortex and striatum. In the dopamine-depleted state, neurons in these areas were also significantly more likely to be phase-locked to particular phases of the LFP oscillations, resulting in increased coordination of the corticostriatal neuronal ensemble. Importantly, administration of carbidopa/levodopa, which quickly restored dopamine levels back to baseline, reversed the electrophysiological changes and reduced beta oscillatory synchronization of the corticostriatal network. Interestingly, the overall firing rates of the motor cortical and striatal neurons remained unchanged following manipulation of dopamine levels, despite changes in observed behavior from hyperkinetic to bradykinetic states, which again provides evidence against the canonical model of rate-encoding in the basal ganglia circuitry.

Further evidence for the pathogenic role of beta oscillations in PD has emerged from the study of PD patients undergoing functional neurosurgery for DBS. LFP recordings in the STN tend to show prominent oscillatory activity within the beta band (Brown et al., 2001; Levy et al., 2002; Marsden, Limousin-Dowsey, Ashby, Pollak, & Brown, 2001), during which neuronal discharges in the basal ganglia are phase-locked (Kuhn et al., 2005; Weinberger et al., 2006). Importantly, treatment with levodopa, dopamine receptor agonists, or high frequency STN stimulation, attenuates such beta oscillations (Brown et al., 2001; Eusebio et al., 2011; Kuhn et al., 2008; Levy et al., 2002; Priori et al., 2004; Williams et al., 2002). Furthermore, the spatial extent of beta oscillatory activity in the STN has predicted treatment response (Zaidel, Spivak, Grieb, Bergman, & Israel, 2010). The strength of beta oscillatory activity also correlates with the clinical response to levodopa (Weinberger et al., 2006), and reductions in beta LFP activity in STN have been correlated with clinical improvement (Kuhn, Kupsch, Schneider, & Brown, 2006; Kuhn et al., 2008). The level of bradykinesia and rigidity in PD patients has also been positively correlated with the strength of spatially extended beta synchronization within different depths of the STN (Pogosyan et al., 2010), while the proportion of STN units oscillating at beta frequencies has been correlated with levels of limb rigidity (Sharott et al., 2014). Thus, beta oscillations may represent a valuable electrophysiological biomarker for disease activity in PD, particularly bradykinesia and rigidity (Zaidel et al., 2009).

PD is not just associated with increased temporal synchronization of neural firing within basal ganglia circuits, which is facilitated by the increased rhythmicity with which the neurons fire action potentials. There is also an associated enhancement in synchronization in the spatial domain, with neural populations within and between basal ganglia nuclei, and throughout the basal ganglia-thalamocortical loop, firing more coherently as exemplified by animal models of PD (Mallet et al., 2008a, 2008b; Nini et al., 1995; Raz, Vaadia, & Bergman 2000; Raz et al., 2001) and in PD patients undergoing DBS (Alegre et al., 2005; Brown et al., 2001; Marsden et al., 2001; Williams et al., 2002). Raz et al. (2001) simultaneously recorded spiking activity and LFPs in tonically active neurons (TANs) of the striatum and in GPe and GPi in MPTP-treated monkeys. They showed that following MPTP administration, significantly increased coherent oscillatory activity encompassing beta emerged in TAN-GPe and TAN-GPi neuronal pairs, when compared with the normal state prior to MPTP, implying increased striatal-pallidal interregional synchronization in the Parkinsonian state. Another study with MPTP-treated monkeys, demonstrated coherent oscillatory activity in the 10–15 Hz range between STN and GPi neuronal pairs (Moran et al., 2012). High frequency stimulation of the STN, a well-established form of treatment in PD, resulted in a functional decoupling in beta oscillatory synchronization between STN and GPi in these monkeys. Although this implies that decorrelating neural activity patterns in subthalamic-pallidal circuits may be a mechanism explaining the therapeutic efficacy of DBS, the authors did not corroborate this

through an assessment of the corresponding behavioral responses in the MPTP-primates in their study (Moran et al., 2012).

In patients undergoing surgery for DBS in PD, LFPs simultaneously recorded in GPi and STN show significant coherence at approximately 20 Hz and a smaller peak at 6 Hz (Brown et al., 2001). Significant coherence in the beta range has also been demonstrated between STN LFPs in sensorimotor and noninvasive scalp EEG activity over the supplementary motor area (SMA) in PD patients (Alegre et al., 2005; Fogelson et al., 2006; Marsden et al., 2001; Williams et al., 2002). A major limitation in invasive studies involving PD patients is the fact that—for obvious reasons—direct comparisons cannot be made with healthy human controls, but patients have to serve as their own controls. Identifying changes in the levels of coherence and oscillatory synchronization between different foci of the basal ganglia-thalamo-cortical loop in response to PD treatments has indeed provided valuable insights into the functional significance of such interregional neural synchrony. For example, high frequency stimulation of the STN adjacent to the recorded area that demonstrates the most coherence in the 15–30 Hz range with SMA produced the most effective relief of Parkinsonian symptoms (Marsden et al., 2001). Furthermore, levodopa treatment has been shown to substantially reduce coherence, at rest and during motor tasks, between GPi and STN, and between STN and SMA, in the beta range (20 Hz), but interestingly increase coherence at 70 Hz (gamma; Brown et al., 2001; Cassidy et al., 2002). The coherence within the beta range between these structures tends to decrease during movement, while gamma coherence tends to increase (Brown et al., 2001; Cassidy et al., 2002). As will be discussed later, oscillations in gamma range may have a prokinetic role.

Recent evidence has supported significant interhemispheric phase-locking within the beta frequency band in PD patients, at the cortical (Silberstein et al., 2005) and subcortical level (Little et al., 2013b). For example, the strength of cortico-cortical coupling in the beta band has been correlated with severity of Parkinsonism and reductions in such coupling strength have been correlated with clinical improvement following L-DOPA and STN stimulation (George et al., 2013; Silberstein et al., 2005). Significant phase-locking at beta frequencies between bilateral subthalamic nuclei in individual PD patients has been demonstrated, and this is selectively attenuated by levodopa (Little et al., 2013b). Thus, excessive beta synchronization on the interhemispheric scale could be another defining electrophysiological characteristic of PD.

However, some contradictory findings have emerged from the literature as well. The role of interregional spatial synchronization, for example, has recently been disputed by Devergnas, Pittard, Bliwise, & Wichmann (2014). The authors made simultaneous recordings of LFPs in GPi and STN, and EEG in M1 cortex using epidural electrodes, and measured signal coherence between each of these structures, in monkeys rendered progressively Parkinsonian with repeated injections of MPTP. The severity of Parkinsonism was correlated with significant increases in spectral power at frequencies below 15.5 Hz (overlapping with the low beta range) and reductions in spectral power at frequencies above 15.6 Hz in M1 and GPi, but with little change in STN. In agreement with the aforementioned studies, these intraregional changes in spectral power were reversed by levodopa treatment. Furthermore, the increasing strength of low-beta coherence between M1 EEG and GPi and STN LFPs were positively correlated with the severity of Parkinsonism. Although this latter finding suggests that increases in spatial synchronization between different nodes of the basal ganglia-thalamocortical loop may underlie Parkinsonian severity, levodopa treatment did not reverse these changes in interregional signal coherence (at < 15.5 Hz). These results may suggest that it is the increased oscillatory synchronization (at least at frequencies below 15.5

Hz in MPTP-treated primates) within the separate nodes of the basal ganglia-thalamocortical loop that plays a more important role in the manifestation of PD symptoms, as opposed to interregional coherence on a more global scale. Alternatively, the failure of dopamine replacement therapy to fully treat Parkinsonism, may suggest a disparate mechanism for its therapeutic efficacy.

In another paper, Leblois et al. (2007) also rendered monkeys progressively Parkinsonian with cumulative MPTP injections. Electrophysiological recordings made in GPi revealed that, despite the emergence of bradykinesia relatively early in the dopamine depletion process, increased oscillations encompassing beta manifested significantly later in the course of Parkinsonism. Although this undermines a causal role for beta oscillatory activity in the pathogenesis of PD, it is important to interpret such data with caution. Recordings were only made in GPi, and therefore the time course for the development of beta oscillations in this brain structure may not necessarily reflect the temporal dynamics in the rest of the basal ganglia-thalamocortical circuit. In addition, the rapid induction of Parkinsonism in the MPTP-primate model does not truly reflect the course of disease progression in PD patients, and so the genesis and mechanisms of the underlying oscillatory dynamics may differ between human disease and corresponding animal models.

Closed-loop DBS Paradigms

Recent studies employing closed-loop DBS paradigms have provided another means of investigating the pathophysiological significance of beta oscillatory dynamics in PD. Rosin et al. (2011) implanted microelectrodes in GPi and M1 of MPTP-treated monkeys in order to enable the recording of spike and oscillatory activity in both regions, while electrically stimulating GPi. The authors examined the effects of several adaptive closed-loop paradigms, which involved the automatic stimulation of GPi neurons, as a single or train of pulses, in response to action potential spikes detected in GPi or M1. They showed that this closed-loop setup was significantly more effective and efficient in ameliorating akinesia of the MPTP-treated monkeys, when compared with the conventional open-loop DBS paradigm that encompassed GPi stimulation regardless of any ongoing neuronal activity. An unexpected but fortuitous finding of this study was that stimulation of GPi (using a train of pulses) triggered by detection of GPi spikes, as part of a closed-loop paradigm, was associated with worsening of the monkeys' akinesia. Importantly, this was accompanied by a reduction in GPi neuronal firing rates—and not the increase that would be predicted by the canonical model—despite a significantly increased oscillatory bursting activity within the low beta range (12.5 Hz). The authors showed that there were no correlations between pallidal firing rate and oscillatory activity, thereby supporting independent mechanisms. Thus, this study is “proof of concept” that beta oscillatory activity, and not firing rate, is responsible for dictating the level of akinesia in PD models.

If beta oscillations causally drive the pathophysiological manifestations of PD, then manipulating it should lead to corresponding changes in behavior. Indeed, Little et al. (2013a) has provided a major line of evidence for this. The authors used a closed-loop adaptive DBS design in PD patients ($n = 8$) undergoing neurosurgery for DBS of the STN. LFP oscillations within the beta frequency bandwidth were detected using microelectrodes in STN. The adaptive DBS device was designed such that once the beta oscillatory amplitude exceeded a prespecified threshold, implanted electrodes would automatically send a high frequency train of impulses to the STN, until the beta oscillations dropped back down to below threshold. The authors revealed that this paradigm led to significantly greater improvements in Parkinsonian symptoms (rigidity, bradykinesia and tremor) when compared

with continuous and random intermittent DBS. Clinical parameters were recorded by observers both blinded and unblinded to experimental condition. Closed-loop adaptive DBS led to significantly greater improvements in motor symptom scores on the Unified Parkinson's Disease Rating Scale (UPDRS) compared with continuous DBS (50% vs. 27% improvement). The adaptive design was also more energy-efficient as it achieved greater improvements in symptoms using a 56% reduction in stimulation time. This study thus provides convincing evidence for the causal role of beta in the pathogenesis of PD. These results will need to be replicated by future studies employing larger sample sizes as part of robust randomized-controlled clinical trials.

Gamma Oscillations

High frequency oscillations within the gamma range (35–90 Hz) are believed to be pivotal in neural computational processing (Fries, 2009). It is assumed that they are primarily generated as a consequence of rhythmic inhibitory postsynaptic potentials (IPSPs) reverberating within interneuronal networks, and between inhibitory interneuron and excitatory pyramidal populations, via recurrent feedforward and feedback loops (Buzsáki, 2006; Buzsáki & Draguhn, 2004; Buzsáki & Wang, 2012). The behavioral correlates of gamma oscillations have been extensively investigated and especially linked with higher cognitive functions spanning attention, memory and perceptual binding (Buzsáki & Wang, 2012; Dehaene & Changeux, 2011; Fries, 2009; van der Helm, 2012). In the context of motor programming, less is known about the role of gamma oscillations compared with beta, but the two are thought to play reciprocal roles (Schoffelen, Oostenveld, & Fries 2005). Whereas beta has been inextricably associated with sustaining the motor set in a tonic state, maintaining the status quo and stopping unwanted behaviors, gamma oscillations have been positively correlated with voluntary movements and limb kinematics (Jenkinson, Kuhn, & Brown, 2013).

Gamma represents a broad range of frequencies, and data from human studies have especially implicated the 60–90 Hz frequency range in motor processing (Jenkinson et al., 2013). EEG studies in healthy volunteers, and data from invasive electrocorticographic (ECoG) recordings in patients with epilepsy, have collectively shown that during voluntary arm-reaching movements, there are focal increases in power and synchrony within the gamma band in corresponding regions of sensorimotor cortex and supplementary motor area (Ball et al., 2008; Miller et al., 2007; Ohara et al., 2000; Pfurtscheller, Graimann, Huggins, Levine, & Schuh, 2003). Direct LFP recordings in STN in PD patients provide convergent evidence. For example, performance of a voluntary movement during a stop signal paradigm was associated with an increase in gamma power in the subthalamic nucleus and cortico-subthalamic coherence in the gamma range, whereas successful inhibition of the response had the opposite effect (Alegre et al., 2013).

Treating PD patients with levodopa increases gamma power within the STN and enhances gamma synchrony between STN and GPi (Brown et al., 2001; Cassidy et al., 2002; Kempf et al., 2009), providing support for its beneficial, prokinetic functional role. However, gamma oscillations have also been associated with dyskinesia (Halje et al., 2012; Richter et al., 2013). Indeed, one of the major side effects of levodopa is dyskinesia, and since this medication has been associated with increases in gamma oscillations, such a deleterious clinical correlate of gamma should come as no surprise (Richter et al., 2013). In the hemiparkinsonian, 6-hydroxydopamine lesioned rat model, Halje et al. (2012) showed that periods of dyskinesia following levodopa therapy were strictly associated with gamma oscillations in the cortex and to a lesser extent, the ipsilateral striatum, of the affected

hemisphere, centered at approximately 80 Hz. Furthermore, localized cortical application of a D1-receptor antagonist significantly attenuated the dyskinesia and the corresponding 80 Hz oscillation. Evidence for the pathological role of gamma oscillations in dyskinesia, however, is still in its infancy, and further support for this theory remains to be evaluated in human studies (but see Alonso-Frech et al., 2006).

Although causal evidence for gamma oscillatory synchrony in driving novel motor behavioral patterns is still lacking, the evidence thus far described is supportive of the following theory: Motor processing and the expression of voluntary behavioral movements is determined by the relative balance between oscillatory synchrony in the beta and gamma range, throughout the basal ganglia thalamocortical loops. Neural networks within, and between, the cortex, basal ganglia, and thalamus communicate via oscillatory synchrony in parallel topographic spatial channels, somatotopically corresponding to different body regions. Furthermore, the frequency channels in which these neural loci interact dictate their behavioral representations, thereby creating another dimension to neuronal interplay. Pathological levels of synchrony at different frequency bands lead to corresponding pathological behavioral and clinical patterns. Excessive intra- and interregional beta synchronization, in particular, leads to a loss of segregation of these parallel-processing loops, ultimately creating the akinetic-rigidity phenotype of PD (see Figure 2). Although requiring more empirical support, excessive gamma synchronization may potentially underpin the chaotic kinaesthetic activity that characterizes dyskinesia syndromes.

The role of oscillations outside the beta and gamma range has been less explored. Theta (4–7 Hz) oscillations may also contribute to the development of dyskinesia (Alonso-Frech et al., 2006) and Parkinsonian tremor. Indeed, excessive oscillatory synchronization throughout a loop encompassing the neocortex, basal ganglia, thalamus, and cerebellum in the theta bandwidth, which coincides with the frequency of the Parkinsonian resting tremor, may represent a putative mechanism for such tremor (Schnitzler & Gross, 2005; Timmermann et al., 2003). However, as with beta oscillations, it remains to be determined precisely which component of this loop is responsible for generating the tremor rhythm (Deuschl et al., 2000; Dvzhenok & Rubchinsky, 2012).

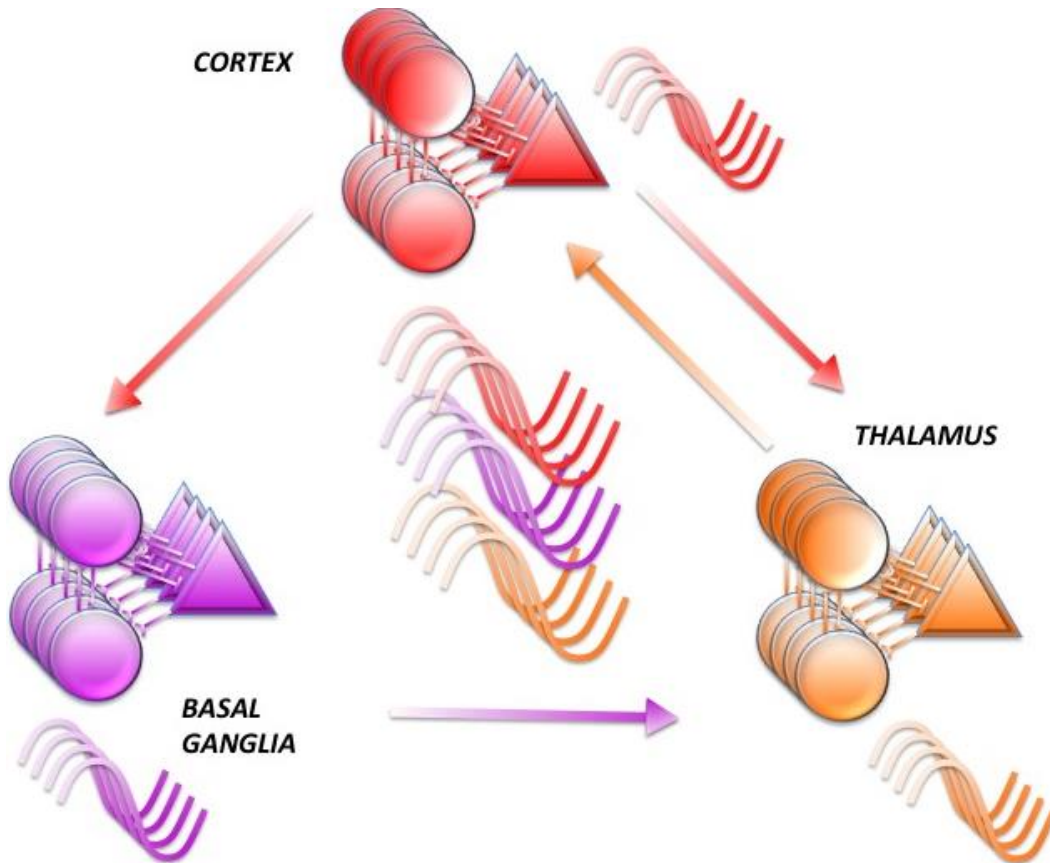


Figure 2. Synchronous interactions between neuronal groups occur at two distinct spatial scales. Oscillatory activity arises at the local neural circuit level within the cortex, basal ganglia, and thalamus. Oscillatory synchronization can also arise on a larger scale, which involves coherent activity across entire basal ganglia-thalamo-cortical networks. Although oscillatory synchronization plays a key physiological role in computational processing, excess synchronous oscillatory activity within local networks, and excess coherence across global networks, putatively contributes to the pathophysiology of PD.

Neurofeedback

Neurofeedback is a technique of learned self-regulation of neural activity. Participants receive online information about a parameter of neural activity and have to regulate it in a particular direction. Volitional regulation of brain rhythms or circumscribed brain regions (or networks) can be achieved through EEG or real-time functional magnetic resonance imaging (real-time fMRI) (see deCharms, 2008; Esmail & Linden, 2011; Ruiz, Buyukturkoglu, Rana, Birbaumer, & Sitaram, 2014; Sulzer et al., 2013). Such regulation of regional neural activity has been shown to be associated with predictable cognitive and behavioral effects (Ruiz et al., 2014) and has been extended to the treatment of psychopathologies, such as depression (Esmail & Linden, 2011; Linden et al., 2012; Linden, 2014). Having discussed the neural networks and oscillatory dynamics that putatively play a pathological role in PD, we will now perform a systematic review of the literature and discuss relevant studies that have explored the application of neurofeedback to PD.

Methods

We searched the following databases, during April and May 2014 (cut off date 27 May 2014), for clinical trials that investigated the therapeutic efficacy of neurofeedback training in Parkinson's disease: EMBASE 1947 to 2014, Ovid MEDLINE 1946 to 2014, PubMed 1990 to 2014, and SCOPUS 1960 to 2014. Our search terms included Parkinson's disease in combination with the terms: neurofeedback, EEG feedback, and real-time fMRI. Inclusion criteria included articles published in the English language and in peer-reviewed journals.

Results and Discussion of Neurofeedback Trials

We identified a total of six relevant papers investigating neurofeedback training in patients with Parkinson's disease: one case study and five controlled trials (two of which were randomized). An overview of these studies is summarized in Table 1.

Thompson and Thompson (2002) published the first case study, which analyzed the effects of EEG neurofeedback in a patient with Parkinson's disease and dystonia. In the ON medication state, the patient was trained to increase the 12–15 Hz rhythm of sensorimotor cortex, while inhibiting 6–10 Hz and 25–32 Hz cortical activity. Neurofeedback training was combined with biofeedback of respiratory and heart rate, in combination with diaphragmatic breathing exercises. The patient showed subjective improvements in her dystonic symptoms, the ability to overcome “freezing” of movements as part of PD, and improved quality of life.

Erickson-Davis, Anderson, Wielinski, Richter, and Parashos (2012) employed the first randomized, sham-controlled neurofeedback study design in PD. Patients in the ON medication state, and reporting levodopa-induced dyskinesia for at least 20% of the waking day, were randomly assigned to complete 24 thirty-minute sessions of active EEG-feedback training ($n = 5$) or sham feedback ($n = 4$). The active treatment group was trained to enhance 8–15 Hz (alpha and low beta) cortical activity at C3–C4 EEG electrodes, while inhibiting 4–8 Hz (theta) and 23–34 Hz (high beta) activity. Amplitude and coherence measures of the selected frequency bands were translated to audio feedback for participants. Initial efforts at down-regulating 4–8 Hz oscillations were abandoned as patients reported immediate subjective worsening of PD symptoms and reductions in their sense of wellbeing. Patients in the active treatment group were otherwise able to successfully manipulate EEG activity via operant conditioning, in the remaining target EEG frequency bands. Specifically, the active neurofeedback group significantly decreased 23–34 Hz, and increased 8–15 Hz power, in the right and left frontal and posterior regions. Within the coherence parameter, the only significant changes were increases in the 8–15 Hz range, and this was observed in the left frontal-right posterior linked regions. Despite significant changes in EEG measures, patients in the active treatment group showed no significant improvements in primary outcome measures of levodopa-induced dyskinesia, nor in secondary outcome measures of clinical features of PD represented by UPDRS scores, as with sham controls (whom did not receive veridical feedback).

Table 1
Overview of Studies

Study	Design	Training Paradigm	No. of Sessions	Medication State	Outcome
Thompson and Thompson (2002)	Case Study	Increasing 12–15Hz, while inhibiting 6–10 Hz and 25–32 Hz cortical rhythm; combined with biofeedback and diaphragmatic breathing exercise	30; over 6 months	ON	Overall improved quality of life. No standardized outcome measure was used.
Subramanian et al. (2011)	Non-randomized controlled trial; NF (<i>n</i> = 5 PD) vs. MI (<i>n</i> = 5 PD)	Up-regulation of SMA BOLD activity	2; over 2–6 months	ON	Only NF group successfully up-regulated SMA and achieved significant improvements in UPDRS and finger tapping scores.
Erickson-Davis et al. (2012)	Randomized-controlled trial; NF (<i>n</i> = 5 PD) vs. sham (<i>n</i> = 4 PD)	Increasing 8–15 Hz, while inhibiting 4–8Hz and 23–34Hz cortical activity	24; over 12–15 weeks	ON	Neither group showed significant improvements in LID (primary outcome measure) or UPDRS scores (secondary outcome measure).
Buyukturkoglu et al. (2013)	Small controlled study; NF (<i>n</i> = 1 PD) vs. NF (<i>n</i> = 3 healthy controls)	Up-regulation of SMA BOLD activity	Variable, ranged from 2 to 6	Not specified	Up-regulation of SMA slowed movements on a motor sequence task in all participants
Fumuro et al. (2013)	Non-randomized controlled trial; NF (<i>n</i> = 10 PD) vs. NF (<i>n</i> = 11 healthy controls)	Enhancing negative SCP shifts (negativation)	2–4 one-day sessions; at 1–6 day intervals	ON	Good NF performance resulted in increased early BP. Poor NF performance had the opposite effect. Behavioral measures not assessed.
Azarpaikan et al. (2014)	Randomized-controlled trial; NF (<i>n</i> = 8 PD) vs. sham (<i>n</i> = 8 PD)	Increasing 12–15 Hz, while decreasing 4–7Hz cortical activity	8; spanning 2.5 weeks	ON	Significant improvements occurred in static and dynamic balance in the NF group only.

Note: LID = Levodopa-induced dyskinesia; MI = motor imagery; NF = Neurofeedback; PD = Parkinson's disease; SCP = slow cortical potential; SMA = supplementary motor area; UPDRS = Unified Parkinson's Disease Rating Scale.

Although the clinical results have been disappointing, several issues must be borne in mind:

1. The study utilized a small sample size ($n = 9$).
2. Patients in the active neurofeedback group were not matched with those in the sham group (the treatment group were significantly older and had lower baseline dyskinesia).
3. The failure to significantly decrease coherence in the high beta range (23–34 Hz) over sensorimotor cortex may have underestimated the potential therapeutic efficacy of EEG feedback training.
4. Most importantly, the target frequency ranges for neurofeedback training may not have been appropriately selected.

Regarding the last point, we must review the frequency ranges that have been implicated in the pathophysiology of PD. The issue is somewhat complicated by the varying frequency ranges in which excessive oscillatory activity is seen amongst different animal models of PD and in PD patients. In rat models of PD, excessive synchrony is predominantly seen within the 30–35 Hz range (Delaville et al., 2014), while in MPTP-treated primates, excessive oscillations tend to be localized to a lower 8–15 Hz range overlapping alpha (Goldberg et al., 2004; Stein & Bar-Gad, 2013; Tachibana et al., 2011). In PD patients, the frequency range representing the corresponding antikinetic beta bandwidth has been attributed to 8–30 Hz, although this varies according to brain region (Levy et al., 2002; Stein & Bar-Gad, 2013). Indeed, with such a broad range, beta has been divided into low beta (up to 20 Hz) and high beta (20–35 Hz). The functional significance of this dissociation remains unclear, but studies have demonstrated that they may be differentially expressed in certain brain regions and respond to treatment differently. For example, in the STN of PD patients, there is often a higher power of spontaneous low beta, which is more significantly suppressed by dopaminergic treatment, when compared with high beta (Brittain & Brown, 2014; Litvak et al., 2011; Lopez-Azcarate et al., 2010). Thus, in the study by Erickson-Davis et al. (2012), training patients to up-regulate oscillatory activity in the 8–15 Hz range (which falls within the low beta range) and down-regulate activity in the 23–34 Hz (high beta), may have produced conflicting behavioral effects and could therefore account for their null findings. Furthermore, the authors did not target the potentially important frequency that has recently been implicated in levodopa-induced dyskinesia (80 Hz) (Halje et al., 2012), which was their primary outcome measure.

Future studies, recruiting larger patient numbers, should aim to identify the clinical effects of purely down-regulating beta oscillatory activity in sensorimotor cortical regions in PD patients. This could be corroborated by attempting to manipulate, via EEG neurofeedback, spectral power within a set of different, narrow, sub-frequency ranges encompassed by beta in a set of parallel experiments. Indeed, this may lend the opportunity to identify the optimal frequency range (within the broad possibilities of beta) that is most closely related to bradykinesia in PD, which may therefore produce the greatest clinical benefits following down-regulation. Although EEG neurofeedback offers little in the way of direct modulation of beta oscillations in the basal ganglia, modulating cortical beta could have an indirect impact on rhythmic subcortical activity. Studies in PD patients have shown excessive coherence of beta oscillatory activity between neocortex and basal ganglia (Fogelson et al., 2006; Marsden et al., 2001; Williams et al., 2002). Assuming that the pathophysiological basis of PD is underpinned by excessive beta synchronization in large-scale cortical-subcortical networks, the maximal possible efficacy of EEG-based neurofeedback would be limited by the top-down influence of cortical beta and its ability to entrain subcortical networks. The benefits of EEG neurofeedback would therefore be governed by direct down-regulation of

cortical beta, and subsequent indirect entrainment of subcortical beta, so that global oscillatory synchronization can be reset to a physiological level.

Cortico-cortical coherence in pairwise EEG comparisons in the beta range is prominent in the OFF state in PD patients, positively correlates with clinical severity and is reduced following dopaminergic medication and high frequency STN stimulation (George et al., 2013; Silberstein et al., 2005). Future neurofeedback experiments could therefore specifically focus on down-regulating cortico-cortical beta coherence, and then see if this is associated with clinical improvements. Not only would this identify another therapeutic avenue for PD, but it would also causally implicate the role of excessive cortico-cortical beta coherence in driving a major clinical impairment, namely bradykinesia, in PD.

In a more recent randomized-controlled trial (RCT), Azarpaikan, Torbati, and Sohrabi (2014) investigated the effects of EEG neurofeedback training in a group of patients, with mild PD in the ON state, on static and dynamic balance. Patients completed eight sessions of active neurofeedback ($n = 8$) or control sham feedback ($n = 8$) over a period of 2.5 weeks. In the active neurofeedback groups, participants were trained to enhance 12–15 Hz (low beta) oscillatory activity, while suppressing 4–7 Hz (theta), using EEG signals recorded from occipital brain regions (O1–O2). This was achieved by immersing the participants in a video game, which was stopped if oscillatory power increased or decreased, outside a prespecified range, in the wrong frequency band. Sham controls were presented with random feedback, using the same video games, which was not contingent on brainwave activity patterns. Only the experimental group receiving active neurofeedback training successfully enhanced low beta, and suppressed theta, to a level that reached statistical significance. This was accompanied by significant improvements in both static and dynamic balance in the active neurofeedback group only. Unfortunately, the authors did not assess the behavioral effects of this neurofeedback paradigm on other Parkinsonian measures, namely bradykinesia, tremor or global symptom scores (e.g., UPDRS). This therefore limits our interpretation of the full range of behavioral effects that can be derived following manipulation of low beta and theta oscillations in the context of neurofeedback. Indeed, down-regulating theta activity could conceivably improve symptoms of tremor (Deuschl et al., 2000; Dovzhenok & Rubchinsky, 2012). Although this initially produced subjective deleterious effects in a small study (Erickson-Davis et al., 2012), it would need to be further evaluated in larger trials incorporating a broader selection of PD patients spanning different clinical states (e.g., including patients in the OFF state). To our knowledge, no other studies have suggested an association of beta or theta oscillations with balance in PD, so this is an area that will also require further future investigation.

In a different neurofeedback paradigm, Fumuro et al. (2013) investigated the possibility of manipulating the Bereitschaftspotential (BP), otherwise known as the readiness potential, in PD patients. BP represents the negative slow cortical potential (SCP) activation, which precedes, by up to 2 seconds, voluntary, self-paced movements (Shibasaki & Hallet, 2006). This negative shift in SCP reflects the widespread depolarization and increased excitability of the superficial layer of apical dendrites from cortical pyramidal neurons (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). Positive shifts in SCP, by contrast, reflect decreases in cortical excitability. BP is divided into an early and late component. Early BP predominantly reflects widespread bilateral increases in neuronal activity, initially in the pre-supplementary motor area (pre-SMA), followed by somatotopically coordinated activation in SMA and lateral premotor areas (Ikeda, Luders, Burgess, & Shibasaki, 1992; Ikeda et al., 1995; Yazawa et al., 2000) bilaterally. Late BP is somatotopically even more specific for the site of movement, and mainly arises from generator current sources in the contralateral primary motor cortex

(Shibasaki & Hallet, 2006). Dick et al. (1989) showed that the early BP component was significantly smaller in patients with PD in their OFF state, compared with healthy controls. Additionally, early BP displays an increase in amplitude following dopaminergic therapy in PD patients (Dick et al., 1987), suggesting that it may represent an attractive electrophysiological target potentially amenable to modulation via neurofeedback training.

This putative electrophysiological biomarker has recently been targeted by Fumuro et al. (2013). They performed a controlled EEG neurofeedback trial comparing 10 PD patients in the ON medication state with 11 age-matched healthy controls, all of whom were right-handed. EEG data (using the international 10-10 system) encompassing the BP shifts were recorded before and after neurofeedback training. During measurement of BP, all participants were instructed to perform self-paced, brisk button presses every 10 seconds with their right thumb while looking at a blank screen, over approximately 100 trials. The first BP recording session was followed, after a 5-minute break by neurofeedback training. During neurofeedback, subjects were instructed to produce negative SCP shifts (negativation) guided by their own mental strategies, but were provided with appropriate suggestions of mental introspection by the examiners, if required. Neural activity was transformed into a visual representation, and provided the means of feedback that guided participants' mental strategies so that they could learn to manipulate their SCP. BP was subsequently measured post-neurofeedback training in a similar manner as pre-neurofeedback, while participants simultaneously mustered introspective efforts to produce negative SCP shifts. This study showed that PD patients were capable of successfully manipulating early BP, as good neurofeedback performance was associated with a statistically significant increase in early BP amplitude. Unfortunately, the authors did not assess any symptomatic or clinical measures of PD, so the behavioral effects, or functional significance, of such manipulation of early BP could not be determined.

Volitional control of neural activity can also be achieved using real-time fMRI-based feedback, whereby data processing and analysis closely follow data acquisition. This enables fMRI results and images to be produced as the experiment unfolds in real-time (deCharms, 2007). The BOLD signals from a selected brain region can then be fed back to the participant, usually in the form of some dynamic visual representation, in order to permit learned up- or down-regulation of brain activity. The efficacy of real-time fMRI feedback has been extensively investigated in recent years, and it has been demonstrated that learned regulation of regionally circumscribed brain regions is frequently associated with predictable behavioral effects (Ruiz et al., 2014).

Subramanian et al. (2011) have evaluated the use of real-time fMRI neurofeedback in patients with PD as part of a non-randomized controlled clinical trial. Patients in the ON state, were allocated to an experimental neurofeedback group (NF, $n = 5$) or a control group (CG, $n = 5$), matched for clinical severity and medication. The target brain region selected for up-regulation in the NF group was SMA, owing to its extensive connections with the basal ganglia thalamocortical circuit implicated in PD. During neurofeedback training, NF patients received a visual display, consisting of a thermometer, which provided a representation of the level of neural activity within the SMA, translated from BOLD signal data in real-time. NF patients were trained to up-regulate SMA in two separate sessions, each consisting of two neurofeedback runs (6.5 minutes each). They were instructed that they may use motor imagery to achieve SMA up-regulation, but were not prescribed any specific strategies. CG patients, however, were also instructed to use motor imagery while undergoing fMRI scanning, but importantly did not receive veridical feedback on SMA neural activity. In the 2–6 months between the two neurofeedback or motor imagery sessions, patients were

instructed to use the same mental strategies at home on a daily basis, but to refrain from practicing overt hand movements. The authors showed that only NF patients were able to significantly up-regulate SMA BOLD activity to a level that was comparable to the activation that was achieved while performing overt hand movements during the initial localizer runs. In contrast, CG patients displayed significantly less BOLD activation in SMA during motor imagery, compared with localizer runs, and neural activity failed to increase during subsequent motor imagery runs. Successful SMA up-regulation following neurofeedback, was accompanied by significant improvements on UPDRS symptom scores (37% improvement in motor function) and on a finger-tapping task. The CG did not show any such clinical or behavioral improvements. This proof-of-concept study of fMRI neurofeedback in PD was limited by the small sample size and unblinded assessments.

A more recent pilot study, employing a similar real-time fMRI neurofeedback paradigm, undertaken by Buyukturkoglu et al. (2013) yielded conflicting results. The authors recruited one patient with PD and three healthy volunteers. Participants undertook pre- and posttest runs separated by a block of neurofeedback training trials. During neurofeedback training, all participants learned to up-regulate activation in bilateral SMA, while using their own cognitive strategies, guided by a visual display representing SMA BOLD signal changes in real-time. Up-regulation of SMA in all participants, including the PD patient, resulted in slower responses on a sequenced motor task. However, the authors did not assess the impact of this task on clinical symptomatology in the PD patient. Although our interpretation of these results is limited, given the small sample sizes, they highlight two important issues:

- 1) The potential variability in pathological activation levels in different PD patients.
- 2) The possible pleiotropic effects of real-time fMRI feedback.

Concerning the former, the evidence from the literature is inconsistent regarding the direction of pathological activation of SMA in PD. Some studies have reported hypoactivation of SMA (Jenkins et al., 1992; Wu, Wang, Hallett, Li, & Chan, 2010; Yu, Sternad, Corcos, & Vaillancourt, 2007), whereas others have reported hyperactivation (Catalan, Ishii, Honda, Samii, & Hallett, 1999; Rowe et al., 2002). This is complicated by the fact that regional differences in activation have also been observed within the SMA itself (Sabatini et al., 2000). Thus, attempting a simple method of grossly increasing or decreasing activation of regional brain activation, through region of interest (ROI)-based univariate analyses, may not necessarily achieve the desired therapeutic effects. In order to more accurately model the aberrant neural network connectivity patterns, spanning the basal ganglia thalamo-cortical loop, which characterizes PD, more sophisticated real-time fMRI algorithms would be required. One such example invokes the use of multi-voxel pattern analysis (MVPA). MVPA centers on training pattern classifier algorithms to decode the mental representation of a behavioral, cognitive, or emotional state based on discriminating between the underlying neural activation signatures. These trained pattern classifiers can then predict subsequent manifest cognitive states by reading the evoked neural activation patterns (represented by a spatially distributed set of activated voxels in the context of fMRI), based on the experience gained during training (for review, see Haynes & Rees, 2006). Pattern classifiers have been applied in real-time fMRI paradigms (Hollmann et al., 2011; LaConte, Peltier, & Hu, 2007; Sitaram et al., 2011) and have been shown to improve performance in perceptual discrimination tasks through neurofeedback training (Shibata, Watanabe, Sasaki, & Kawato, 2011). MVPA could potentially be utilized to overcome the limitations of univariate real-time fMRI methods in the context of PD, by avoiding an *a priori* approach and by closely modeling the complex network dynamics that underpin this pathology. For example, pattern classifiers could conceivably be trained to distinguish distributed neural activation patterns and functional connectivity states between PD patients and healthy volunteers (or between the

ON and OFF medication state in PD patients). This would be predicated on the principle that hypersynchronized network dynamics across basal ganglia thalamocortical loops underscores the pathophysiology of PD. The precise neurofeedback that PD patients would receive therefore, in this MVPA real-time fMRI paradigm, would be a measure of how closely correlated the patient's neural activation pattern is in comparison to the "healthy" state, or the ON medication state, for example. Thus, PD patients could be trained to replicate the spatially distributed activation patterns that are representative of the healthy or ON state, by breaking down inter-neuronal hypersynchrony, and correspondingly derive the associated behavioral and symptomatic benefits. This hypothesis remains to be tested, but the limitations of this potentially powerful tool grounds down to the very signals that fMRI measures, which brings us to the possible pleiotropic effects of real-time fMRI feedback.

BOLD signal dynamics reflect a combination of changes in blood flow, volume and oxygenation, within a brain region, in response to a perceptual, cognitive or motor demand (Logothetis, 2003, 2008). A major limitation to interpreting increases in BOLD signals, therefore, is that it can arise as a consequence of overall increases in excitation, inhibition or a combination of both (Buzsáki, Kaila, & Raichle, 2007; Logothetis 2008). The corollary of this is that modulating BOLD activity through real-time fMRI feedback could produce differential effects, as the participant is given no control over whether, and in what proportion, excitatory or inhibitory networks are activated. Consequently, up- or down-regulating BOLD signals in brain regions, in different times or in different people, may not necessarily yield consistent results, and so may partially explain the conflict in findings between the aforementioned real-time fMRI feedback paradigms (Buyukturkoglu et al., 2013; Subramanian et al., 2011). The other major limitation of real-time fMRI is the poor temporal resolution owing to the unavoidable haemodynamic lag between neural activation and the onset of BOLD signal changes (ca. 3–6 seconds; Logothetis, 2008). This ultimately prevents any real-time fMRI feedback paradigm from probing into the millisecond-range temporal dynamics that is pivotal in determining neuronal oscillatory synchrony. However, it has been suggested that BOLD signals closely correlate with changes in LFP oscillations, particularly in the gamma band (Magri, Schridde, Murayama, Panzeri, & Logothetis, 2012), which could prove useful for attempts at manipulating oscillatory synchrony in PD through neurofeedback.

Conclusions

Although neurofeedback offers a promising, noninvasive means of modulating regional brain activity, or enhancing compensatory networks, the evidence supporting its potential therapeutic efficacy in disease states remains in its infancy. In the context of PD, there is insufficient evidence at present to support the application of neurofeedback in routine clinical practice. Extant studies have suffered from small sample sizes and/or methodological limitations. The EEG feedback studies have trained participants to manipulate oscillations within targeted frequency ranges in a manner that is inconsistent with the mechanisms that have been suggested to contribute to the pathophysiology of PD, which may explain certain null findings (Erickson-Davies et al., 2012). In the EEG study that has yielded positive results of neurofeedback in PD (Azarpaikan et al., 2014), the precise mechanism for this is unclear as the role of cortical oscillatory dynamics in balance in PD patients has not before been explored. Modulating the BP could potentially offer another promising avenue for treating PD (Fumuro et al., 2013), but the behavioral and clinical effects of such modulation will need to be investigated.

Real time fMRI neurofeedback offers a promising prospect for modulating regional brain activity. Initial evidence on the effects of SMA modulation has been promising, but this would need to be verified in larger, controlled clinical trials. By providing brain-wide access with a high spatial resolution on the order of a few millimeters, real time fMRI could enable activity of subcortical basal ganglia structures to be controlled, which cannot be easily accessed using EEG-based paradigms. The effects of modulating activity in various basal ganglia nuclei, or their combinations, on behavior and PD symptomatology will need to be evaluated if this field is to make progress.

Finally, future well-designed robust studies, recruiting larger sample sizes, and applying methodological principles predicated on the existing evidence base for the neural mechanisms implicated in PD are required before neurofeedback could be recommended in clinical practice.

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