J Neurophysiol 122: 203–231, 2019.
First published May 1, 2019; doi:10.1152/jn.00590.2018.

REVIEW | *Nervous System Pathophysiology*

Oscillations in cortico-basal ganglia circuits: implications for Parkinson's disease and other neurologic and psychiatric conditions

Pär Halje,[1] Ivani Brys,[2] Juan J. Mariman,[3,4,5] Claudio da Cunha,[6] Romulo Fuentes,[7] and Per Petersson[1,8]

[1]*Group for Integrative Neurophysiology and Neurotechnology, Department of Experimental Medical Science, Lund University, Lund, Sweden;* [2]*Federal University of Vale do São Francisco, Petrolina, Brazil;* [3]*Research and Development Direction, Universidad Tecnológica de Chile, Inacap, Santiago, Chile;* [4]*Department of Physical Therapy, Faculty of Medicine, Universidad de Chile, Santiago, Chile;* [5]*Department of Physical Therapy, Faculty of Arts and Physical Education, Universidad Metropolitana de Ciencias de la Educación, Santiago, Chile;* [6]*Laboratório de Fisiologia e Farmacologia do Sistema Nervoso Central, Programas de Pós-Graduação em Farmacologia e Bioquímica, Universidade Federal do Paraná, Curitiba, Brazil;* [7]*Department of Neurocience, Faculty of Medicine, Universidad de Chile, Santiago, Chile; and* [8]*Department of Integrative Medical Biology, Umeå University, Umeå, Sweden*

Submitted 3 September 2018; accepted in final form 25 April 2019

Halje P, Brys I, Mariman JJ, da Cunha C, Fuentes R, Petersson P. Oscillations in cortico-basal ganglia circuits: implications for Parkinson's disease and other neurologic and psychiatric conditions. *J Neurophysiol* 122: 203–231, 2019. First published May 1, 2019; doi:10.1152/jn.00590.2018.—Cortico-basal ganglia circuits are thought to play a crucial role in the selection and control of motor behaviors and have also been implicated in the processing of motivational content and in higher cognitive functions. During the last two decades, electrophysiological recordings in basal ganglia circuits have shown that several disease conditions are associated with specific changes in the temporal patterns of neuronal activity. In particular, synchronized oscillations have been a frequent finding suggesting that excessive synchronization of neuronal activity may be a pathophysiological mechanism involved in a wide range of neurologic and psychiatric conditions. We here review the experimental support for this hypothesis primarily in relation to Parkinson's disease but also in relation to dystonia, essential tremor, epilepsy, and psychosis/schizophrenia.

integrative neurophysiology; synchrony; systems level

INTRODUCTION

Acquisition and expression of adaptive behaviors depend on two critical functions provided by several brain structures, including to a significant degree the basal ganglia (BG): reinforcement learning and action selection (Da Cunha et al. 2009; Frank 2011; Grillner and Robertson 2016; Mink 1996; Nicola 2007; Redgrave et al. 1999). A number of psychiatric and motor symptoms found in disorders such as Tourette syndrome, schizophrenia, obsessive-compulsive disorder, substance abuse disorder, depression, attention deficit/hyperactivity disorder, Parkinson's disease (PD), and Huntington's disease are related to a failure in these functions (DeLong and Wichmann 2007; Dobbs et al. 2017; Tremblay et al. 2015) and, thus, should have a neurophysiological correlate in the BG. The predominant physiological model proposes that changes in the firing rate of the projection neurons of the different BG nuclei constitute the key mechanism of BG functions. Although prominent changes in firing rates have been observed, for example, in association with motor symptoms related to BG impairment, some symptoms also present a strong correlation with rhythmic oscillatory neural activity that occurs in the BG and in functionally connected regions of the thalamus and neocortex [reviewed, e.g., by Hammond et al. (2007) and Richter et al. (2013)]. Before discussing the potential contribution of such oscillations to pathophysiological mechanisms and their association with disease conditions in further detail, it is instructive to briefly review the predominant conceptual model of BG physiology and its underlying anatomical circuitry.

The BG are formed by *1*) an input station [striatum (primate caudate-putamen)], *2*) intermediate nuclei [the external part of the globus pallidus (GPe) and the subthalamic nucleus (STN, which is also an input nucleus)], *3*) output nuclei [the internal

Address for reprint requests and other correspondence: P. Petersson, Dept. of Integrative Medical Biology, Umeå Univ., Linnéus väg 9, 901 87 Umeå, Sweden (e-mail: Per.Petersson@umu.se).

part of the globus pallidus (GPi), the reticulate part of the substantia nigra (SNr), and the ventral pallidum]; and *4*) associated modulatory nuclei [the compact part of the substantia nigra (SNc), the ventral tegmental area (VTA), the pedunculopontine tegmental nucleus (PPTg), and the laterodorsal tegmental nucleus (LDTg; Albin et al. 1989; Alexander et al. 1986; Parent and Hazrati 1995a, 1995b)]. The SNc and VTA and the PPTg and LDTg exert dopaminergic and cholinergic modulatory effects, respectively, on the glutamatergic input synapses of the striatum (Garcia-Rill 1991; Swanson 1982; Wang and Morales 2009). The glutamatergic inputs to the striatum are also modulated by GABAergic and cholinergic striatal interneurons, and the release of neurotransmitters in the striatum is modulated by opioid peptides, endocannabinoids, and adenosine (Di Chiara and Imperato 1988; Ferré et al. 2010; Mulder et al. 1984; Wilson and Kawaguchi 1996). The BG receive inputs from several areas of the sensorimotor, associative, and limbic neocortex and subcortical limbic areas and send indirect projections to the frontal cortex and to motor and limbic areas of the brain stem. BG outputs to the frontal cortex are mediated by thalamic nuclei, which are mostly segregated into motor, associative, and limbic cortico-BG loops. Some thalamic nuclei also send massive projections to the striatum [for anatomic review, see Alexander et al. (1986), Hikosaka et al. (2018), and Parent and Hazrati (1995a, 1995b); Fig. 1].

An influential hypothesis supported by anatomical (Albin et al. 1989; Alexander et al. 1986; Nambu et al. 2002), functional (Alexander and DeLong 1985; Mink 1996; Nambu 2004; Tecuapetla et al. 2016), and computational modeling (Doya 2000; Frank 2011; Gurney et al. 2001; O'Reilly and Frank 2006) evidence proposes that the BG plays a critical role in action selection (Da Cunha et al. 2009; Frank 2011; Grillner and Robertson 2016; Mink 1996; Nicola 2007; Redgrave et al. 1999). According to the firing-rate model of BG function, the actions controlled by the motor areas of the neocortex can be triggered by the glutamatergic projections from neurons of the motor thalamus, which are kept under tonic inhibition by GABAergic neurons of the output stations of the BG, namely, the GPi and the SNr. A specific action can be initiated when a subpopulation of the GPi/SNr neurons is selectively inhibited, thus causing disinhibition of the thalamic neurons that can activate the cortical neurons that control the chosen action. Therefore, action selection depends on selective inhibition of GPi/SNr neurons, which occurs when projection neurons of the main BG input station, the striatum, are selectively activated. Striatal projection neurons are GABAergic, and some of them make selective synaptic connections with the GPi/SNr neurons. This two-neuron circuit is referred to as the "direct pathway" because this subpopulation of striatal neurons makes a direct (monosynaptic) connection with the output station neurons in the GPi/SNr. Another subpopulation of striatal projection neurons makes an indirect projection to the GPi/SNr. These "indirect pathway" striatal neurons are GABAergic neurons that synapse with GABAergic neurons of the GPe, which in turn synapse with GABAergic GPi/SNr neurons. The striatal neurons of the indirect pathway also synapse with the glutamatergic neurons of the STN, which in turn synapse with the GPi/SNr neurons. Either way, activation of the indirect pathway prevents initiation of actions by increasing the tonic inhibition that GPi/SNr neurons exert on thalamic neurons that can activate neurons in motor areas of the neocortex. Thus, proper action selection may depend on simultaneous activation of both the direct and indirect pathways: a subpopulation of the direct pathway neurons is activated to initiate the selected action, and a larger population of indirect pathway neurons is activated to inhibit concurrent nonselected actions (Cui et al. 2013; DeLong 1972; Mink 1996; Nambu 2004).

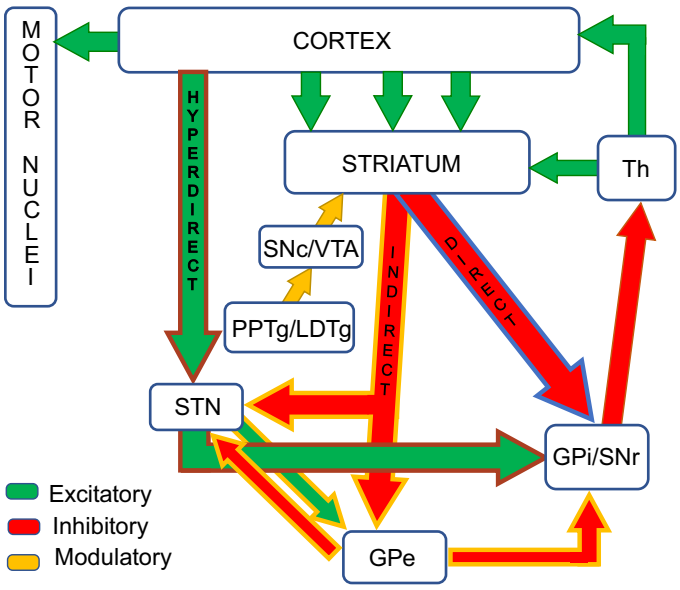

Fig. 1. Schematic representation of a cortico-basal ganglia loop depicting the anatomical connections discussed in this review, highlighting the direct, hyperdirect, and indirect pathways. GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; LDTg, lateral dorsal tegmental nucleus; PPTg, pedunculopontine tegmental nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; Th, thalamus; VTA, ventral tegmental area. [Adapted from Albin et al. (1989), Alexander et al. (1986), and Nambu (2004).]

The striatal neurons of the direct and indirect pathways are named medium spiny neurons (MSNs). In contrast to the pallidal projection neurons, which are tonically active, MSNs are mostly silent, occasionally firing spike bursts (Plenz and Kitai 1998). Computational models of the cortical-BG action selection circuitry propose that the firing pattern of the MSNs of the direct pathway follows a "winner-takes-all" rule: when a few neurons of the direct pathway fire, all the other neurons promoting competing motor programs are silent (Frank 2011). According to the action selection model, it is the activity of the cortical neurons and the strength of the cortical-striatal synapses that determine which MSNs will be activated. Sensorimotor cortex projects to the putamen as part of the BG motor loop, which ends at motor areas of the cortex. This loop is thought to form the basis for stimulus-response habits; that is, facilitating specific motor responses triggered by sensory stimuli (Yin and Knowlton 2006). Prefrontal cortex (PFC) projects mostly to the head of the caudate nucleus, which is part of the BG associative loop, thus affecting goal-directed actions, decision making, and other executive functions (Balleine et al. 2007; Royall et al. 2002). Several limbic structures, including the orbitofrontal and medial cortexes, the anterior part of the cingulate cortex, hippocampus, amygdala, and hypothalamus, project to the ventral part of the striatum [including the nucleus accumbens (NAc)] and to the modulatory nuclei of the BG (e.g., VTA, SNc, PPTg, and LDTg). In this way, rewarding and aversive stimuli can influence expression of motivated behav-

iors (Da Cunha et al. 2012; Ikemoto and Panksepp 1999; Lima et al. 2017; Nicola 2007; Wendler et al. 2014).

Some cortical-BG computational models highlight the importance of the hyperdirect pathway in the action selection processes (Frank 2006; Nambu et al. 2002). They propose that activation of motor cortex neurons subthreshold to triggering a motor action activates STN neurons through direct glutamatergic connections (bypassing the striatum, hence the name "hyperdirect"), thus increasing the inhibitory tone exerted by the GPi/SNr neurons on the motor thalamus. This increases the threshold that the direct pathway neurons must overcome to initiate an action. Consistent with this hypothesis, computational simulations and clinical studies have shown that inhibition of the STN increases impulsive behavior (Frank et al. 2007).

Although dominant, the selection model of the BG cannot fully accommodate all recent and old findings. For example, the cardinal signs of PD—resting tremor, rigidity, and bradykinesia—improve after lesion of the GPi, an output station of the BG, without severely affecting motor control (Obeso et al. 2001). Also, evidence that pallidothalamic coactivation occurs during behavior suggests that a model based only on BG-thalamic disinhibition is not sufficient to fully explain experimental observations (Goldberg et al. 2013).

Perhaps more importantly, the action selection model for BG function can be explained solely by transient changes in firing rate of the projection neurons in each stage of the cortico-BG-thalamic loop. Yet, besides firing-rate changes, the BG display organized temporal patterns of discharge, i.e., regular rhythmic discharges. Although these patterns are discernible at the single-unit level, for example, through autocorrelograms, this rhythmic activity is especially apparent at the population level through the spectral analysis of local field potentials (LFPs). In terms of signal source, the LFP corresponds to the low-frequency component (typically 1–300 Hz) of the electric potential difference recorded with microelectrodes located within nervous tissue. Spectral analyses of LFPs with different methods (Fourier, multitaper, wavelets, irregular-resampling autospectral analysis, etc.) can readily determine the main frequencies of the rhythmic activity, commonly known as oscillations. Notably, however, more transient periods of rhythmic activity are often also referred to as oscillations even though these phenomena may represent other types of processes that differ both phenomenologically and functionally from regular and persistent sinusoidal-like oscillations. LFP oscillations were initially thought to represent the synchronized input signal to an area, as they were proposed to arise from partially temporally coincident postsynaptic potentials in the same area (Eccles 1951). Even though postsynaptic potentials have individually relatively small amplitudes compared with an action potential, they have long durations (up to hundreds of ms) allowing for the temporal summation of synaptic electric activity in the area close to the recording electrodes into a high-amplitude LFP signal. Besides the dendritic source, other proposed additional contributors to the LFP are synchronized changes of somatic membrane potential (Klee et al. 1965) and synchronized afferent and efferent fiber activity (Creutzfeldt et al. 1966). In different pathological conditions, the BG and related structures present abnormally high amplitude oscillatory activity in specific frequency ranges, depending on the disorder. The analyses of oscillatory phenomena and their potential relevance for brain diseases have therefore attracted a growing amount of attention during recent years.

During the International Union of Physiological Sciences symposium at the world congress in Rio de Janeiro, Brazil, in 2017, the experimental support for, and possible implications of, excessive oscillatory activity in cortico-BG circuits were discussed in the context of neurologic and psychiatric disease. These discussions have formed the basis for this review, which surveys oscillatory phenomena thought to be related to PD, dystonia, essential tremor, epilepsy, and psychosis/schizophrenia (for a summary, see Table 1). We also briefly discuss neuromodulatory interventions currently used for symptomatic treatment.

PARKINSON'S DISEASE: OSCILLATIONS RELATED TO HYPOKINESIA AND RESTING TREMOR

PD is the second most common neurodegenerative disorder afflicting ~1–2% of the population above the age of 65 (Tysnes and Storstein 2017). Although subtypes exist, they share the motor signs that lead to diagnosis, i.e., poverty and slowness of movement, resting tremor, muscle rigidity, and impairment of posture and gait. The gradual degeneration of midbrain dopaminergic cells resulting in dopamine depletion in BG circuits is known to be one of the principal causes behind motor impairment, and in accordance, parkinsonian motor symptoms are greatly ameliorated by L-3,4-dihydroxyphenylalanine (L-DOPA), an immediate dopamine precursor that can cross the blood-brain barrier. However, the exact pathophysiological features that ultimately cause the symptoms are still largely unknown. These features may involve multiple components reflected in the timing and rate of neuronal firing in single cells as well as changes in functional connectivity and neuronal synchronization at the neuronal population level. In recent years, several studies have specifically focused on clarifying the role of oscillatory activity. Although oscillations in BG circuits are common in healthy subjects (Bevan et al. 2002; Courtemanche et al. 2003; Leventhal et al. 2012), excessive BG oscillatory activity nevertheless appears to be a hallmark of this disease.

Because resting tremor is one of the cardinal symptoms of PD, the search for pathological oscillatory neural activity related to tremor in PD started early. The "tremor cells," first reported in 1962, refer to neurons from BG, thalamic nuclei, and cortex that fire in bursts in the frequency range of the resting tremor (Guiot et al. 1962). For example, thalamic neurons in patients with PD have been found to discharge bursts at 3–6 Hz, and the occurrence of bursts is highly correlated with limb tremor (Lenz et al. 1988); in patients with PD who have severe tremor at rest this can be the predominant oscillation frequency also in the STN (Alonso-Frech et al. 2006).

Complementary to these slow oscillations, there is also a large body of evidence for parkinsonian oscillatory neural activity in a somewhat higher frequency range, referred to as "beta oscillations." The term "beta" is currently rather broadly used to refer to any neural activity (single units, LFP, etc.) that contains periodic activity patterns, or even transient oscillatory events, with power in a frequency range of ~13–35 Hz. Importantly, the introduction of electrical deep brain stimulation (DBS) for the symptomatic treatment of PD has offered a rare opportunity to obtain human brain recordings from a relatively large number of subjects in conjunction with implan-

Table 1. *Summary of studies cited in this review that relate oscillatory neural activity to specific pathologies or experimental models and manipulations*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
1	Guiot et al. (1962)	Human	Parkinson's disease	Slow rhythmic occurrence of single-cell spike trains	Spikes	Spike trains at 1 and 3	Tremor-related	VPL	Correlated to tremor
2	Lenz et al. (1988)	Human	Parkinsonian unilateral tremor refractory to medical therapy	Slow rhythmic occurrence of single-cell spike trains	Spikes	Spike trains at 3–6	Tremor-related	Ventral thalamic nuclear group	Correlated to tremor
3	Alonso-Frech et al. (2006)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	4–6	Tremor-related	STN	Predominant oscillatory peak correlated with severe tremor at rest
4	Alonso-Frech et al. (2006)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	4–10		STN	Increases during levodopa-induced dyskinesias
5	Alonso-Frech et al. (2006)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	11–30	Beta	STN	Peaks in the "off" medication state reduced by half the "on" state
6	Alonso-Frech et al. (2006)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	60–80	Gamma	STN	Slight increase during "on" state
7	Chen et al. (2006)	Human	Dystonia	Spectral analysis of continuous LFP signal	LFP	[4–10], [11–30], and [65–85]	Low frequency, beta, and gamma	GP	Correlated to sternocleidomastoid activity
8	Sharott et al. (2017)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of continuous LFP signal	ECoG	[20–25] and [15–30]	Beta	Somatosensory motor cortex and DLS	Correlated to 6-OHDA lesion
9	Sharott et al. (2017)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Activity of striatal projection neurons	Spikes	15–30	Beta	DLS	6% in healthy condition and 46% after 6-OHDA lesion (probably most from indirect pathway) entrains to cortical beta
10	Litvak et al. (2011)	Human	Parkinson's disease	Cortical-subthalamic coherence	LFP and MEG	15–35	Beta	Frontal network and STN	Increased coherence during dopaminergic medication
11	Delaville et al. (2014)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of continuous LFP signal	LFP	25–40	High beta/low gamma	Motor cortex, GPe, and SNr	Increased during treadmill walking
12	Kühn et al. (2009)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	8–35	Beta	STN	Suppressed by levodopa
13	Weinberger et al. (2006)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	Spikes and LFP	26	Beta	Dorsal STN	1/4 of the recorded neurons showed oscillatory activity at 26 Hz and were coherent with LFP beta oscillations; positive correlation between the incidence of oscillatory neurons and the clinical output from dopaminergic medications, but not with "off" medication motor deficits

Continued

Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
14	Costa et al. (2006)	Mouse	Acute 100% DA depletion in DAT-KO mice	Spectral analysis of continuous LFP signal	LFP	[1.5–4.0] and [11–30]	Delta and beta	DLS and motor cortex	Increase after DA depletion
15	Costa et al. (2006)	Mouse	Acute 100% DA depletion in DAT-KO mice	Spectral analysis of continuous LFP signal	LFP	[4.5–9] and [30–55]	Theta and gamma	DLS and motor cortex	Decrease after DA depletion
16	Brys et al. (2017)	Rat	Progressive dopaminergic depletion by α-synuclein overexpression	Spectral analysis of continuous LFP signal	LFP	11–30, and >90	Beta and HFO	DLS and motor cortex	Increases when further DA depletion is achieved through DA synthesis depletion
17	Pan et al. (2016)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Single-unit activity	Spikes	Interburst, 1.3; intraburst, 100	Burst	STN	Suppression of bursts rescues bradykinesia
18	Pan et al. (2016)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of continuous LFP signal	LFP	20–50	Beta	STN	Occurrence not related to bradykinesia
19	Ivica et al. (2018)	Rat	D1R/D2R antagonist	Spectral analysis of continuous LFP signal	LFP	12–20	Beta	RFA, forelimb area of M1, DLS/DMS, GP, ventrolateral/ ventroanterior nuclei of the thalamus, STN, and SNr	Power increase precedes akinesia
20	Rodriguez-Oroz et al. (2011)	Human	Parkinson's disease associated with impulse control disorders or with dyskinesias	Spectral analysis of continuous LFP signal	LFP	4–10, peak at 6.7	Theta-alpha	STN	Increased
21	Tamtè et al. (2016)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of continuous LFP signal	LFP	3–9	Theta	STN	Increases during L-DOPA-induced dyskinesia
22	Wang et al. (2019)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of continuous LFP signal	LFP	5–8	Theta	Dorsal striatum and SNr	Increases during L-DOPA-induced dyskinesia; correlated with abnormal involuntary movement scores; oscillatory information flowed from the striatum to the SNr
23	Brown et al. (2001)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	<30	Beta	GPi and STN	Power and GPi-STN coherence predominate while in "off" medication
24	Brown et al. (2001)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	~70	Gamma	GPi and STN	L-DOPA reduces the beta power and results in a new peak at 70 Hz
25	Cassidy et al. (2002)	Human	Parkinson's disease	Spectral analysis of continuous LFP and EEG signal	LFP and EEG	<30	Beta	GPi and STN	STN-power and STN-GPi coherence are dominant during "off" medication condition and are attenuated during movement

Continued

Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
26	Cassidy et al. (2002)	Human	Parkinson's disease	Spectral analysis of continuous LFP and EEG signal	LFP and EEG	70–85	Gamma	GPi and STN	STN-power and STN-GPi coherence are dominant during "on" medication condition and are increased during movement
27	Williams et al. (2002)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	2–10	Theta?	STN, GPi, and cortex	Cortical phase leads STN and GPi
28	Williams et al. (2002)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	10–30	Beta	STN, GPi, and cortex (EEG)	Cortical phase leads STN and GPi
29	Williams et al. (2002)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	70–85	Gamma	STN, GPi, and cortex (EEG)	STN and GPi phases lead cortex
30	Tsang et al. (2010)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	6–10	Theta	PPNR and cortex (EEG)	Strong coherence between PPNR and cortex does not change before or after the movement
31	Tsang et al. (2010)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	14–30	Beta	PPNR and cortex (EEG)	In the "on" but not the "off" state, coherence between the PPNR and the midline prefrontal region is observed during movement preparation and decreases after movement onset
32	Tsiokos et al. (2013)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	200–300, peak at 235		GPi	Increased for the duration of movement
33	Foffani et al. (2003)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	226–412, peak at 319	300-Hz rhythm	GPi	In "off" medication there are variable increases with movement; after L-DOPA and apomorphine these increases are robust
34	Kempf et al. (2009)	Human	Myoclonic dystonia	Spectral analysis of continuous LFP signal	LFP	66–80	Gamma	VIM	Modulated by movement, suppressed during SWS and reemergent during REM, lost in untreated parkinsonian patients, sharply tuned coherence between thalamus and GPi
35	Kempf et al. (2009)	Human	Segmental dystonia	Spectral analysis of continuous LFP signal	LFP	58–90	Gamma	VIM	Modulated by movement, suppressed during SWS and reemergent during REM, lost in untreated parkinsonian patients, sharply tuned coherence between thalamus and GPi
36	Kempf et al. (2009)	Human	Dystonia, generalized dystonia, myoclonic epilepsy, essential tremor, Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	75, 67, 63, 68, and [65–72]	Gamma	VIM and left centromedian parafascicularis (Parkinson's disease)	Modulated by movement, suppressed during SWS and reemergent during REM, lost in untreated parkinsonian patients, sharply tuned coherence between thalamus and GPi
37	Brücke et al. (2013)	Human	Essential tremor	Spectral analysis of continuous LFP signal	LFP	55–80	Gamma	VIM	Gamma power increases on the contralateral side to the movement in a go/no-go task

Continued

Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
38	Fogelson et al. (2005)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	5–32	Theta, alpha, and beta	STN	Negatively correlated to 65–85-Hz power
39	Fogelson et al. (2005)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	65–85	Gamma	STN	Negatively correlated to 5–32-Hz power
40	Lalo et al. (2008)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	3–13	Sub-beta	STN (LFP) and cortex (EEG)	Asymmetric bidirectional coupling between STN and cortex
41	Lalo et al. (2008)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	14–35	Beta	STN (LFP) and cortex (EEG)	Asymmetric bidirectional coupling between STN and cortex; drops during movement
42	Lalo et al. (2008)	Human	Parkinson's disease	Coherence between LFP and EEG signal	LFP and EEG	65–90	Gamma	STN (LFP) and cortex (EEG)	Increased symmetrical bidirectional drives between STN and cortex after dopaminergic therapy
43	Litvak et al. (2012)	Human	Parkinson's disease	Power and coherence between MEG and LFP	LFP and MEG	60–90	Gamma	STN (LFP) and M1 (MEG)	Increased power during movement and L-DOPA; coherence between STN and M1 (STN driving)
44	Litvak et al. (2012)	Human	Parkinson's disease	Power and coherence between MEG and LFP	LFP and MEG	300–400	Very fast oscillations	STN (LFP) and M1 (MEG)	Increased power during movement and L-DOPA
45	Muthukumaraswamy (2010)	Human	Healthy	Spectral analysis of MEG signal	MEG	60–90	Gamma	M1	Increases with movement, reaching peak activity 137 ms after EMG onset of movement
46	Huo et al. (2011)	Human	Healthy children 6–17 yr old	Spectral analysis of MEG signal	MEG	65–150	Gamma	M1	Mostly contralateral and some ipsilateral increase of power related to movement
47	Crone et al. (1998)	Human	Epilepsy	Spectral analysis of continuous ECoG signal	ECoG	35–50	Low gamma	Sensorimotor cortex	Increase begins after onset of the movement and is sustained through it
48	Crone et al. (1998)	Human	Epilepsy	Spectral analysis of continuous ECoG signal	ECoG	75–100	High gamma	Sensorimotor cortex	Increase begins during or slightly before the movement and is transient
49	Pfurtscheller et al. (2003)	Human	Epilepsy	Spectral analysis of continuous ECoG signal	ECoG	10–30	Mu and beta	Frontal, parietal, and sensorimotor cortex	Decreases during self-paced movement
50	Pfurtscheller et al. (2003)	Human	Epilepsy	Spectral analysis of continuous ECoG signal	ECoG	60–90	Gamma	Frontal, parietal, and sensorimotor cortex	Increases during self-paced movement
51	Ball et al. (2008)	Human	Healthy, epilepsy	Spectral analysis of ECoG signal	EEG and ECoG	60–90	High gamma	Sensorimotor cortex	Increases around reaching movement onset and becomes most pronounced at movement end
52	Halje et al. (2012)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of LFP signal	LFP	60–90	High gamma	M1	Pronounced increase during L-DOPA-induced dyskinesia

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Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
53	Swann et al. (2016)	Human	Parkinson's disease	Spectral analysis of ECoG and LFP signal	ECoG and LFP	60–90	High gamma	Motor cortex and STN	Pronounced increase during L-DOPA-induced dyskinesia
54	Miocinovic et al. (2018)	Human	Generalized dystonia	Spectral analysis of ECoG and EEG signal	ECoG/EEG	Peaks at ~82 and ~81	High gamma	Sensorimotor cortex	Induced by movement and associated with emergence of dystonia
55	Delaville et al. (2015)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis and coherence of LFP signal	LFP	29–36	Low gamma	STN and motor cortex	Increased power and coherence after dopaminergic lesion
56	Delaville et al. (2015)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis and coherence of LFP signal	LFP	45–55	Low gamma	STN and mPFC	Increased power and coherence during walking before and after dopaminergic lesion
57	Dupre et al. (2016)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of LFP signal	LFP and spikes	70–110	High gamma	Motor cortex	Increased during dyskinesia induced by L-DOPA, D1R, and D2R agonists; phase locking of cortical pyramidal spiking to high-gamma oscillations decreased
58	Belić et al. (2016)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral, causality, and cross-frequency analysis of LFP signal	LFP	80	High gamma	M1 and sensorimotor striatum	Increased during dyskinesia induced by L-DOPA
59	Tamtè et al. (2016)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of LFP signal	LFP	65–100	High gamma	RFA, M1, DMS, DLS, GP, thalamus, STN, and SNr	Increased in M1 during dyskinesia
60	Yang et al. (2014)	Human	Parkinson's disease	Spectral analysis of LFP signal	LFP	200–500	HFO	STN	Increased beta/HFO PAC
61	Connolly et al. (2015)	Rhesus macaque	Dopaminergic lesion by intracarotid and intramuscular injections of MPTP	Spectral analysis of LFP signal	LFP	256–362	HFO	GP	Beta/HFO PAC increases with the severity of dopaminergic lesion
62	Hirschmann et al. (2016)	Human	Parkinson's disease	Spectral analysis of LFP signal	LFP	[200–300] and [300–400]	Slow and fast HFO	STN	Ratio of slow to fast HFO power increases with tremor both in "on" and "off" conditions
63	Wang et al. (2016)	Human	Akinetic-rigid Parkinson's disease	Spectral analysis of LFP signal	LFP	[13–30] and [250–350]	Beta and HFO	STN	26/28 patients had a peak of beta power, and 19/28 had increased beta/HFO PAC
64	Wang et al. (2016)	Human	Dystonia	Spectral analysis of LFP signal	LFP	[13–30] and [250–350]	Beta and HFO	STN	11/12 patients had a peak of beta power, and 6/12 had increased beta/HFO PAC
65	van Wijk et al. (2017)	Human	Parkinson's disease	Spectral analysis of LFP signal	LFP	[13–30] and [150–400]	Beta and HFO	STN	In 50% of the cases, largest beta and HFO power came from the same recording location
66	Brys et al. (2018)	Rat	Unilateral infusion of 6-OHDA into the medial forebrain bundle	Spectral analysis of continuous LFP signal	LFP	~130	HFO	RFA, M1, DMS, DLS, GP, thalamus, STN, and SNr	Increased slow-delta/HFO PAC, L-DOPA increased the power and coupling

Continued

Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
67	Shreve et al. (2017)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	[8–35] and [200–400]	Alpha/beta and HFO	STN	Alpha/beta oscillations and beta/HFO PAC are stronger in the more affected hemisphere
68	López-Azcárate et al. (2010)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	~265	HFO	STN	Strong beta/HFO PAC during "off" state, absent during "on" state
69	de Hemptinne et al. (2013)	Human	Parkinson's disease	Spectral analysis of continuous LFP signal	LFP	[13–30] and [50–200]	Beta and gamma/HFO	M1	Increased beta/HFO PAC, reduced by STN-DBS
70	Schnitzler et al. (2018)	Human	Tremor of different origins: essential, parkinsonian, Holmes, and dystonic	Spectral analysis of continuous LFP signal	LFP	150–300	Slow HFO	VIM	Increased power in all conditions
71	Marsden et al. (2000)	Human	Essential tremor and benign tremulous Parkinson's disease	Spectral analysis and coherence of LFP-EEG signals	LFP, EEG, and EMG	8–27	Beta	VIM (LFP)	Increased coherence between VIM and sensorimotor cortex
72	Pedrosa et al. (2014)	Human	Essential tremor	Spectral analysis and coherence of LFP-EMG signals	LFP and EMG	2–8	Tremor oscillations	Posterior parts of the ventrolateral thalamus	Tremor onset occurs 220 ± 460 (SD) ms before the start of significant thalamomuscular coherence
73	Barow et al. (2014)	Human	Dystonia	Spectral analysis and coherence of EEG-EMG signals	LFP, EEG, and EMG	4–12	Low-frequency oscillations	GP (LFP) and motor cortical areas (EEG)	130-Hz DBS reduces the GP power, the corticopallidal coherence, and the pallidomuscular coherence
74	Neumann et al. (2015)	Human	Dystonia	Coherence and Granger directionality analysis	LFP and whole head MEG	[4–8], [7–13], and [13–30]	Theta, alpha, and beta	GP (LFP)	Theta pallidotemporal and alpha pallidocerebellar coherence with pallidal LFP leading; corticopallidal coherence led by MEG cortical source
75	Bragin et al. (1999)	Human	Mesial temporal lobe epilepsy	Spectral analysis	LFP and spikes	[80–160] and [250–500]	Ripples and FRs	Entorhinal cortex and hippocampus	Ripples appear to be normal, whereas FRs are found in the epileptogenic region
76	Jirsch et al. (2006)	Human	Refractory focal epilepsy	Spectral analysis	LFP	[100–200] and [250–500]	High frequency and very high frequency	Mesial temporal lobe	High frequency appears during the seizure, and very high frequency appears near the seizure onset
77	Weiss et al. (2013)	Human	Refractory focal epilepsy	Spectral analysis	ECoG, LFP, and multiunit spikes	[1–25] and [80–150]	Low-frequency ictal rhythm and high gamma	Cortex	Transient increases in high-gamma power (phase locked to the low-frequency ictal rhythm, correlated with multiunit firing bursts in the area of the seizure) are seen several seconds after seizure onset
78	Ochi et al. (2007)	Human	Children with intractable neocortical epilepsy who underwent cortical resection	Retrospective detection with multiple-band frequency analysis	ECoG	[60–164], ~170, and ~250	HFO	Cortex	Resection of cortical areas with higher HFO results in postsurgical seizure-free outcomes

Continued

Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
79	Wu et al. (2010)	Human	Children with intractable epilepsy who underwent cortical resection	Retrospective detection of FRs	ECoG	250–500	FRs	Cortex	Complete resection of areas with high FR correlates with postoperative seizure freedom
80	Bragin et al. (2002)	Rats	Unilateral infusion of kainic acid in the right posterior hippocampus	Spectral analysis	LFP	[200–400], peak at ~375	FRs	DG and CA1	Areas generating FRs do not exceed 1 mm^3
81	Newson and Thiagarajan (2019)	Human	Schizophrenia	Meta-analysis	EEG	2–30	Delta, theta, alpha, and beta	Cortex	Eyes open: increased theta, alpha, and beta; eyes closed: increased delta and theta but decreased alpha
82	Kwon et al. (1999)	Human	Schizophrenia	ASSR	EEG	30–50	Gamma	Cortex	Patients with schizophrenia show reduced (compared with control) gamma EEG power in response to auditory stimulation
83	Spencer et al. (2008)	Human	Schizophrenia	ASSR	EEG	20–40	Gamma	Cortex	Reduced gamma response to auditory stimuli
84	Krishnan et al. (2009)	Human	Schizophrenia	ASSR	EEG	40	Gamma	Cortex	Reduced gamma response to auditory stimuli
85	Thuné et al. (2016)	Human	Schizophrenia	Meta-analysis	EEG and MEG	40	Gamma		40-Hz ASSR is reduced in schizophrenia
86	Rutter et al. (2009)	Human	Schizophrenia	Synthetic aperture magnetometry frequency bands	MEG	30–80	Gamma	Posterior region of the medial parietal cortex	Gamma activity is reduced in patients with schizophrenia during resting state
87	Andreou et al. (2015)	Human	Schizophrenia	Orthogonalized power envelope correlation	EEG	40	Gamma	Cortex	Increased gamma connectivity in the left inferior frontal/orbitofrontal-lateral medial temporal-inferotemporal network
88	Baradits et al. (2019)	Human	Schizophrenia	Spectral analysis	EEG	30–48	Gamma	Cortex	Spontaneous gamma activity is increased (resting, closed eyes)
89	Spencer (2012)	Human	Schizophrenia	Spectral analysis	EEG	40	Gamma	Cortex	Baseline power before auditory stimulation is higher in patients with schizophrenia (compared with control) at 40 Hz in the left auditory cortex
90	Mitra et al. (2015)	Human	Schizophrenia	Spectral analysis	EEG	70–100	Gamma	Cortex	Spontaneous gamma activity is increased (resting, closed eyes)
91	Tikka et al. (2014)	Human	Schizophrenia	Spectral analysis	EEG	51–70	Gamma	Cortex	Spontaneous gamma activity is increased (resting, closed eyes); correlates with a number of Schneiderian 1st-rank symptoms
92	Senkowski and Gallinat (2015)	Human	Schizophrenia	Meta-analysis	EEG	30–80	Gamma	PFC	Induced gamma activity is decreased over PFC during cognitive tasks in patients with schizophrenia
93	Grent-'t-Jong et al. (2018)	Human	Schizophrenia	Spectral analysis	MEG	30–90	Gamma	Cortex	Decreased prefrontal gamma but increased posterior gamma (resting, open eyes); positive correlation between 64- and 90-Hz power and cognitive deficits/psychotic symptoms

Continued

Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
94	Pinault (2008)	Rat	Ketamine or MK-801 injection	Spectral analysis	LFP	30–80	Gamma	Cortex	Dose-dependent increase of gamma with subanesthetic doses
95	Sanacora et al. (2014)	Human	Ketamine or lanicemine	Spectral analysis	EEG	32–48	Gamma	Cortex	Dose-dependent increase of gamma in healthy humans
96	Leishman et al. (2015)	Rat	PCP injection	ASSR	ECoG	20–55	Gamma	Cortex	Increased ASSR for stimulation frequencies below 50 Hz, decreased response at 55 Hz
97	Schuelert et al. (2018)	Mouse	Ketamine or MK-801 injection	ASSR	ECoG	40	Gamma	Cortex	Decreased ASSR for 40-Hz stimulation
98	Sullivan et al. (2015)	Rat	MK-801 injection	ASSR	LFP	20–40	Gamma	A1 and hippocampus	Increased ASSR (intertrial coherence) at 20 and 40 Hz
99	Sivarao et al. (2016)	Rat	Ketamine injection	ASSR	ECoG	40	Gamma	Cortex	Decreased ASSR (phase-locking factor) during early phase, increased during late phase
100	Plourde et al. (1997)	Human	Ketamine injection	ASSR	EEG	40	Gamma	Cortex	Increased ASSR
101	Goda et al. (2013)	Rat	Acute exposure to serotonergic hallucinogens	Spectral analysis	LFP	[40–60], [70–90], and [130–180]	Gamma and HFO	NAc	Serotonergic hallucinogen-induced changes in HFO and gamma are mediated, at least in part, by 5-HT_{2A} receptors
102	Hunt et al. (2006)	Rat	Ketamine or D-amphetamine injection	Spectral analysis	LFP	130–180	HFO	NAc	Ketamine induces rapid increases in HFO that correlate with behavioral hyperactivity; D-amphetamine induces locomotor activity but small increase in HFO
103	Hunt et al. (2011)	Rat	Ketamine injection	Spectral analysis	LFP	[130–180] and 200	HFO and ripples	NAc and hippocampus (CA1)	HFO increases in NAc but not in CA1, where ripples are decreased after ketamine injection
104	Nicolás et al. (2011)	Rat	Ketamine at subanesthetic dosages	Spectral analysis	LFP	~50, ~80, and ~150	Low and high gamma and HFO	Motor cortex, striatum, SNr, and STN	Increased oscillations and coherence in low and high gamma and HFO
105	Kulikova et al. (2012)	Rat	Single systemic injection of ketamine	Spectral analysis	LFP	30–80	Gamma	Somatosensory thalamocortical circuit	Increased gamma, reduced sensory-evoked response, and decreased sensory-evoked gamma power
106	Phillips et al. (2012)	Rat	Ketamine/PCP/MK-801 injections to rats treated with methyl-azoxymethanol acetate on *gestational day 17*	Spectral analysis	EEG	40–80	Gamma	Cortex	Large increase in gamma power
107	Caixeta et al. (2013)	Rat	Ketamine injections	Spectral analysis	LFP	[5–10], [30–100], and [110–160]	Theta, gamma, and HFO	CA1	Increased gamma and HFO; gamma-HFO phase coherence increased, theta-HFO PAC increased
108	Olszewski et al. (2013)	Rat	Systemic administration of NMDAR antagonists plus localized infusion of TTX	Spectral analysis	ECoG	130–180	HFO	NAc, PFC, and caudate	Inactivation of NAc but not PFC or caudate prevents HFO increase induced by NMDAR antagonist
109	Lee et al. (2017)	Rat	Systemic or local infusion of NMDAR antagonists	Spectral analysis	LFP	[30–80] and [130–180]	Gamma and HFO	NAc, PFC, and dorsal hippocampus	Both systemic and local infusion in the 3 areas studied of NMDAR antagonist increases gamma and HFO power

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Table 1. —*Continued*

	Study	Species	Condition or Experimental Manipulation	Analysis Type	Signal Type	Frequency Peak or Band, Hz	Oscillatory Activity Classification	Neural Area or Structure	Results
110	Hunt et al. (2019)	Rat	Ketamine at subanesthetic dosages	Spectral and Granger causality analysis	LFP and unitary activity	130–180	HFO	OB and ventral striatum	Ketamine-induced HFO is of higher magnitude and is phase advanced in the OB relative to ventral striatum; Granger causality suggests OB as the source of HFO; both unilateral local inhibition of the OB and naris blockade attenuate HFO recorded in OB and ventral striatum

Numbers in the first column correspond to the order of the first mention of the study in the text. A1, primary auditory cortex; ASSR, auditory steady-state response; CA1, CA1 region of the hippocampus; D1R and D2R, dopamine type 1 and type 2 receptors, respectively; DA, dopamine; DAT-KO, dopamine transporter knockout; DBS, deep brain stimulation; DG, dentate gyrus; DLS, dorsolateral striatum; DMS, dorsomedial striatum; ECoG: electrocorticography; EEG, electroencephalography; EMG, electromyography; FR, fast ripple; GP, globus pallidus; GPe, external GP; GPi, internal GP; HFO, high-frequency oscillation; 5-HT, 5-hydroxytryptamine; L-DOPA, L-3,4-dihydroxyphenylalanine; LFP, local field potential; M1, primary motor cortex; MEG, magnetoencephalography; mPFC, medial prefrontal cortex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDAR, *N*-methyl-D-aspartate receptor; OB, olfactory bulb; 6-OHDA, 6-hydroxydopamine; PAC, phase-amplitude coupling; PCP, phencyclidine; PFC, prefrontal cortex; PPNR, pedunculopontine nucleus region; REM, rapid eye movement sleep; RFA, rostral forelimb area; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; SWS, slow-wave sleep; TTX, tetrodotoxin; VIM, ventral intermediate nucleus; VPL, ventral posterolateral nucleus.

tation surgeries. In agreement with findings in animal models of the disease, excessive oscillatory activity in beta band frequencies has been reported in recordings from patients with PD (Brown et al. 2001; Hammond et al. 2007). The mechanisms underlying these oscillations have therefore attracted considerable attention. However, identifying the specific cellular components generating oscillatory patterns at a network level is a challenging task. Practically all the structures making up the cortico-BG-thalamic loop are affected by the substantial loss of midbrain dopaminergic innervation in PD, which may result in different alterations of connections strengths and resonance properties both within and between different brain structures (Rommelfanger and Wichmann 2010). Yet, cells in the striatum are known to be strongly influenced by the loss of dopaminergic input in PD (Grillner et al. 2005; Wilson and Kawaguchi 1996), and as a consequence, aberrant beta oscillations are thought to originate intrinsically in the striatum. Evidence supporting this view comes, for example, from experiments in mice, in which chronic dopamine depletion has been found to enhance the connectivity between striatal fast-spiking interneurons and D2 dopamine receptor MSNs belonging to the indirect pathway, increasing the synchrony between MSNs (Gittis et al. 2011). In addition, acute pharmacological manipulation of the cholinergic striatal interneuronal network has also been found to induce striatal beta oscillations (McCarthy et al. 2011).

The finding that cells in the indirect pathway of the BG are particularly easily entrained to oscillatory activity (Sharott et al. 2017) may be of importance in this context because the reciprocal connections between GPe and STN, which have been found to be functionally and structurally potentiated after depletion of dopamine (Cruz et al. 2011; Fan et al. 2012), could help maintain and even amplify such rhythmic network activity (Bevan et al. 2002; Plenz and Kitai 1999). Further evidence for a disturbed network connectivity in PD comes from computer models. For example, dynamic causal modeling of the propagation of low-frequency oscillations have highlighted the STN as a key component that, via cortical patterning of activity, promotes beta synchrony (Marreiros et al. 2013). Indeed, other hypotheses stress that BG oscillations may primarily originate from cortical patterning of striatal and subthalamic activity (Bevan et al. 2006; Brittain and Brown 2014). Support for this idea comes, for example, from optogenetic stimulation of afferents to the STN, which has been shown to immediately relieve parkinsonian motor signs in rodent PD models in a frequency-dependent fashion (Gradinaru et al. 2009). In this study, the optogenetically stimulated STN afference was confirmed to originate in layer 5 of the primary motor cortex. Moreover, both STN and GPe have been shown to fire action potentials coherently with cortical slow oscillations (Magill et al. 2000). This kind of synchrony-driven coupling has also been observed in patients with PD, specifically between parietal-frontal cortexes and the subthalamic region, and is enhanced in the beta band during the resting state (with indications from partial directed coherence analyses that cortex is primarily leading STN; Litvak et al. 2011). Inside the cortico-BG-thalamic loop, the GPe could in this situation enhance STN oscillatory activity by increasing the capability of the descending excitation from the cortex to drive coherent rhythmic activity in the STN (Tseng et al. 2001). According to this line of reasoning, the therapeutic effects of DBS can be partially

explained as antidromic stimulation of the motor cortex that would reduce the beta synchrony at the level of the BG (Arbuthnott and Garcia-Munoz 2017; Gradinaru et al. 2009). Indeed, in animal models of PD it has been reported that stimulation of the STN leads to a short-latency cortical response that correlates with the suppression of activity in the beta band (Li et al. 2007). Finally, in human subjects, STN-DBS is known to induce short-latency (1–2 ms) EEG-evoked potentials, which are considered to arise from synchronized cortical activity (Baker et al. 2002), and it has also been shown that motor-evoked potentials can be modulated by paired pulses delivered by DBS and transcranial magnetic stimulation, respectively, with a short delay, which indicates a modulation of the short-latency excitability induced by the DBS (Kuriakose et al. 2010). Thus, several independent findings appear to suggest that cortical patterning of BG activity is a main driver of aberrant neuronal synchrony in the parkinsonian brain.

An interesting alternative possibility is that beta oscillations do not have a single origin within the cortico-BG-thalamic circuit (Brittain and Brown 2014), which is a notion that has received certain support from recent computational modeling studies (Liu et al. 2017). These studies suggest that abnormal beta band activity in PD could emerge in the lower part of the band (12–20 Hz) because of dysfunctional coupling in the striatum-GPe-STN network and that these oscillations additionally could be driven to higher frequencies (21–35 Hz) via cortical afferents (Liu et al. 2017). From a therapeutic standpoint, it can be noted that different structures could potentially be differentially affected depending on the type of intervention. For example, although dopamine medication modulates the complete range of beta activity, a cortical contribution to the higher beta band could perhaps explain cases in which patients exhibit poorer responses to dopamine replacement therapy (Litvak et al. 2011).

A few cautionary notes are needed with respect to the interpretation of beta oscillations in animal models of PD. Although rodent models have been extremely useful in elucidating mechanisms underlying BG oscillations, it is important to emphasize that species differences exist. For example, although studies in anesthetized rats typically focus on oscillatory activity in the lower beta band (Cruz et al. 2011; Magill et al. 2000; Sharott et al. 2017), the most robust PD-associated oscillation in the awake-behaving rat is normally found in the very high end of the beta band (25–40 Hz; Delaville et al. 2014, 2015). It remains to be clarified whether these two oscillations should both be considered rodent counterparts of the human beta, which in the awake state typically is found in the lower beta range but which varies greatly between individuals (~8–35 Hz ; Kühn et al. 2009).

Because beta activity is so often found in patients with PD, it has been hypothesized that these oscillations are the mechanistic link between the loss of dopamine and parkinsonian motor impairments (Brown 2003). However, other lines of evidence do not fully support this notion. First, the severity of PD symptoms in patients does not seem to be directly related to the power of beta oscillations in the STN, and for parkinsonian tremor in specific there appears to be no clear association to beta at all (Kühn et al. 2009; Weinberger et al. 2006); for further discussion, see, e.g., Eusebio and Brown (2009). Second, in rodent PD models, pronounced beta oscillations are discernible only during severe dopaminergic depletion (Costa et al. 2006), but not during milder or moderate depletion (Brys et al. 2017; Quiroga-Varela et al. 2013). Also, in these models of PD, akinesia/bradykinesia can be induced without simultaneously increased beta oscillations (see, e.g., Ivica et al. 2018; Pan et al. 2016), suggesting that parkinsonian beta oscillations are at least not causally linked to motor impairment.

PARKINSON'S DISEASE: OSCILLATIONS RELATED TO HYPERKINESIA/DYSKINESIA

L-DOPA pharmacotherapy is the first treatment choice for the vast majority of patients with PD, and in most cases, it provides an efficient amelioration of PD symptoms. Unfortunately, however, chronic L-DOPA treatment often causes complications on average after 5 yr of treatment (Fahn 2003), at which point almost half of the treated patients develop L-DOPA-induced dyskinesia (LID): abnormal involuntary movements that are often debilitating. Furthermore, L-DOPA can also induce nonmotor complications, such as poor impulse control or psychosis (with components of, e.g., hallucinations, delusion, and excitement), a complication particularly common in older patients with PD and often associated with cognitive deterioration (Fénelon and Alves 2010). The pathophysiological mechanisms leading to side effects of L-DOPA pharmacotherapy are therefore a highly important area of research in themselves. In this context, a potential role of slow BG oscillations (in the wide theta range, 4–10 Hz; Alonso-Frech et al. 2006) has been suggested. Interestingly, recordings in patients with PD displaying impulse control deficiency have shown excessive theta oscillation in the ventral, more limbic part of the STN, as opposed to patients with dyskinesia, where oscillations were found in the more dorsal motor part of the STN. This shows that similar pathophysiological activity patterns can be found in BG structures processing different kind of information (motor vs. cognitive/limbic), hinting at a common mechanism behind these very different types of side effects (Rodriguez-Oroz et al. 2011). Later studies in animal models of LID have confirmed the presence of BG theta oscillations (e.g., Tamtè et al. 2016; Wang et al. 2019). It should be cautioned, however, that the relative increase in theta power could be partly related to the general increase in motor activity rather than to dyskinetic motor signs, per se [for a discussion, see Tamtè et al. (2016)].

As mentioned in PARKINSON'S DISEASE: OSCILLATIONS RELATED TO HYPOKINESIA AND RESTING TREMOR, electrophysiological recordings obtained during the early postoperative period in patients treated with DBS have provided a unique opportunity to characterize activity patterns in deep structures of the human brain. Under these conditions, a number of studies involving different patient groups have characterized neuronal activity, for example, in the GPi (Brown et al. 2001; Cassidy et al. 2002; Tsiokos et al. 2013; Williams et al. 2002), STN (Alegre et al. 2012; Alonso-Frech et al. 2006; Brown et al. 2001; Cassidy et al. 2002; Foffani et al. 2003; Trottenberg et al. 2006; Williams et al. 2002), pedunculopontine nucleus (Tsang et al. 2010), and thalamus (Brücke et al. 2013; Kempf et al. 2009). In addition to beta oscillations, synchronized oscillatory activity of much higher frequencies, reaching into the high-gamma band, has been a frequent finding (typically in a frequency band at ~60–90 Hz; Jenkinson et al. 2013). This type of oscillations,

arising in deep BG structures, was first reported by Brown et al. (2001) in the form of a clear peak at ~70 Hz in the STN and GPi of patients with PD after levodopa treatment and was subsequently further characterized in follow-up studies (see, e.g., Alonso-Frech et al. 2006; Fogelson et al. 2005; Williams et al. 2002). In a few instances, recordings from deep structures have been combined with cortical EEG/magnetoencephalography (MEG), indicating that cortical oscillations in the same frequency range sometimes also emerge after L-DOPA treatment. Interestingly, these oscillations appeared to be functionally coupled to the oscillations recorded in deeper structures because the LFP signals were to some extent coherent and displayed relatively constant phase differences (Cassidy et al. 2002; Lalo et al. 2008; Litvak et al. 2012; Williams et al. 2002).

However, from the recordings in patients it has been difficult to establish whether the presence of 60–90-Hz oscillations is associated with the beneficial prokinetic effect of L-DOPA therapy or whether they instead indicate the transition to a pathological hyperkinetic brain state, eventually leading to dyskinetic manifestations (Fogelson et al. 2005). Overall, the data seem to support the notion that a relative increase in high-gamma power (at least in the deep BG nuclei) is primarily associated with increased motor activity and/or a state of arousal that may enable motor activity [reviewed by Jenkinson et al. (2013)].

However, the tentative physiological role of high-gamma oscillations in deep BG structures may not be shared by motor cortex. Investigations using noninvasive recording technologies such as EEG and MEG (Cheyne and Ferrari 2013; Huo et al. 2011; Muthukumaraswamy 2010) or intracranial electrocorticography (ECoG) recordings in patients with epilepsy (Ball et al. 2008; Crone et al. 1998; Pfurtscheller et al. 2003) have shown that high-frequency oscillations (HFOs) in the 60–90-Hz frequency band can indeed be found in the motor cortex in association with movements. However, these findings relate only to brief episodes of movement-related increases in gamma power rather than sustained oscillatory activity. Hence, in nonparkinsonian individuals, activity in this band does not seem to be characterized by clear rhythms with a well-defined frequency, but rather by a relatively broad gamma band power increase that occurs during movement onset. On the basis of experiments using microwire recordings from motor cortex and dorsal striatum in unilaterally 6-hydroxydopamine (6-OHDA)-lesioned rats, a pathological role of 60–90-Hz oscillations in the motor cortex was proposed (Halje et al. 2012). These authors found distinct 80-Hz oscillations that were only present in the lesioned hemisphere during LID (Halje et al. 2012). They also found that the topical application of a dopamine type 1 receptor (D1R) antagonist onto the cortical surface was sufficient to break the oscillation and concomitantly suppress dyskinesia. Hence, in the rat model, persistent high-gamma oscillations in cortical structures are tightly linked to dyskinesia.

This finding was more recently confirmed in patients with PD, as a result of the first long-term recordings performed in patients with dyskinesia using a combined DBS-ECoG device (Swann et al. 2016). Notably, chronically implantable bidirectional electrodes help circumvent experimental caveats associated with the early postoperative phase following DBS electrode implantation. This phase is not ideally suited for brain recordings, as symptoms are often significantly reduced following electrode implantation (i.e., even when no current is passed through the stimulation electrode), suggesting that the symptomatic relief in this situation is primarily related to the lesion inflicted by the electrode (Groiss et al. 2009). By recording neuronal activity over motor cortical areas and in the STN for 12 mo, Swann et al. showed that dyskinesia in patients with PD is linked to the same type of motor cortical oscillations as observed in the rat model of LID. Furthermore, a more detailed analysis of the high-gamma oscillations in the STN revealed that this narrowband activity is principally pathological rather than prokinetic. That is, the oscillations were found to be minimally affected by voluntary movements, whereas their presence proved to be a reliable biomarker of dyskinesia. These findings are therefore somewhat inconsistent with previous studies that have associated gamma oscillations with the beneficial prokinetic effect of the levodopa therapy (Alonso-Frech et al. 2006; Fogelson et al. 2005). Similarly, as mentioned above, brief increases in oscillation amplitude have been found to occur in the STN and in other parts of the cortico-BG loop in direct association with motor actions also in non-PD subjects (Jenkinson et al. 2013; see also Miocinovic et al. 2018). However, even if the two phenomena have similar spectral contents, these movement-modulated oscillations are probably not functionally equivalent to the excessive and long-lasting oscillations observed in dyskinetic states.

Since the original finding by Halje et al. (2012), the role of narrowband gamma oscillations in LID has been further explored in rodents (Belić et al. 2016; Delaville et al. 2015; Dupre et al. 2016; Tamtè et al. 2016). The study by Dupre et al. (2016) showed how the oscillations develop together with dyskinetic symptoms with daily levodopa administration during a 1-wk priming period. Concomitantly, LID becomes gradually more severe. These authors also showed that the oscillation can be induced in L-DOPA-primed rats by independently activating either D1Rs or D2Rs (Dupre et al. 2016). At the level of LFPs, the narrowband gamma oscillations are particularly strong in corticostriatal circuits and are also observed in both the globus pallidus (corresponding to the external pallidal segment in primates) and in motor nuclei of the thalamus but are typically less pronounced in the STN compared with patients (Brys et al. 2018; Swann et al. 2016; Tamtè et al. 2016). Given the tight link to different disease states, LFP oscillatory activity including narrowband gamma oscillations could be utilized as a robust electrophysiological biomarker to classify parkinsonian and dyskinetic states. To this end, Tamtè et al. quantitatively compared the spectral components in eight different brain structures in parallel, to clarify which components most reliably predict brain states associated with untreated parkinsonism or dyskinesia (Cenci et al. 2018). Classification performance was found to improve steadily with inclusion of a broader spectral content and/or addition of brain structures. In particular, oscillations of ~80 Hz in the rostral forelimb area (a premotor/supplementary motor area in rodents) were found to be a very useful physiological marker of LID (Tamtè et al. 2016), which also agrees well with the findings of Swann et al. in patients with PD (Swann et al. 2016). Thus, it stands clear that a strong body of evidence points to an association between fast cortical oscillations and LID, but it remains to be explored whether these aberrant

activity patterns are directly causing dyskinesia [for an in-depth review, see Petersson et al. (2019)].

PARKINSON'S DISEASE: OTHER OSCILLATORY PHENOMENA

Oscillations at even higher frequencies (100–500 Hz) have been observed in the BG of patients with PD and in animal models of PD; in the literature these are often referred to as HFOs (Connolly et al. 2015; Foffani et al. 2003; Hirschmann et al. 2016; van Wijk et al. 2017; Wang et al. 2016; Yang et al. 2014). Whereas beta oscillations in the cortico-BG circuit have been associated with akinesia and theta and narrowband 80-Hz activity has been associated with LID, HFOs have been more diffusely linked to motor signs in PD and appear to be modulated by behavioral state. However, HFOs have also, outside the context of PD, been linked to cognitive and limbic processes (Tort et al. 2013). Surprisingly, even though several studies have reported HFOs in recordings from patients with PD, so far, these oscillations have not been systematically investigated in animal models of the disease. Observations of HFOs in rodent models of PD have, however, been reported in a few studies at frequencies above 100 Hz. Brys et al. (2017) found that following acute and severe systemic dopamine depletion via pharmacological inhibition of tyrosine hydroxylase synthesis with α-methyl-DL-tyrosine methyl ester hydrochloride (AMPT) in rats, very fast gamma oscillations emerged in motor cortex and dorsolateral striatum. This pharmacologically induced dopamine depletion had a slow onset and lasted for several hours. Drug-treated animals displayed severely reduced motor activity and excessive oscillatory activity with a peak at 120 Hz that was most prominent a couple of hours after AMPT administration and with a peak at 90 Hz 24 h after the administration (Brys et al. 2017). In another study, very fast gamma oscillations with a peak at ~130 Hz that were coupled to slow delta waves (2–3 Hz) were observed in cortico-BG-thalamic circuits of 6-OHDA-lesioned rats (Brys et al. 2018). Levodopa treatment, resulting in LID, lowered the oscillation peak frequency while increasing the power and cross-frequency coupling to slow oscillations.

In patients with PD, subthalamic HFOs have been associated with dopaminergic medication (levodopa and apomorphine) and voluntary movement but also linked to the occurrence of rest tremor with a modulation within the tremor cycle (Hirschmann et al. 2016). A recent study recorded intraoperative LFPs from the STN from a large cohort of patients with PD and found that HFOs (200–400 Hz) were present in 87% of cases (41 of 47 recorded STNs). Beta HFO phase-amplitude coupling was detected in >98% of cases and was stronger in the more affected hemisphere (Shreve et al. 2017). HFOs (300 Hz) have also been observed in the STN of patients with PD in both the "off" and "on" levodopa motor states. In the "on" state, the high-frequency activity is modulated by movement, and in the "off" state, beta (12–30-Hz) phase is coupled to the amplitude of HFO (López-Azcárate et al. 2010). Although not an HFO phenomenon, it deserves to be mentioned that an exaggerated coupling between beta phase (13–30 Hz) and the amplitude of nonoscillatory broadband activity (50–200 Hz) has also been observed in the motor cortex of parkinsonian patients (de Hemptinne et al. 2013, 2015).

In a related context, more detailed subthalamic HFO topography and its relation to beta oscillatory activity location in PD have been investigated to improve DBS targeting and treatment. Intraoperatively recorded LFPs from STNs showed that HFOs (150–400 Hz) seem to arise from spatially close, but slightly more superior, neural populations than beta oscillations (13–30 Hz; van Wijk et al. 2017).

It should be cautioned, however, that although a growing body of evidence shows the occurrence of very high frequency oscillations in the BG of patients with PD and in rodent models of PD, the fact that this oscillatory activity is also present in the control hemisphere of unilateral animal models of PD (Brys et al. 2017, 2018) and comparisons with similar oscillatory activity recorded in patients suffering from other tremor syndromes (Schnitzler et al. 2018) suggest that this phenomenon may not be restricted to the BG or to PD. In these latter studies, HFOs have been found in LFPs recorded from the ventral intermediate nucleus (VIM) from patients with essential tremor, parkinsonian tremor, Holmes tremor, and dystonic tremor (Schnitzler et al. 2018). Moreover, similar subthalamic HFOs (250–350 Hz) have been observed in patients suffering from PD and isolated dystonia, with the same type of coupling of beta phase to HFO amplitude (Wang et al. 2016). Thus, it remains controversial whether thalamic and subthalamic HFOs and beta HFO phase-amplitude coupling are potential biomarkers of PD, and the possible link between patient HFOs and animal experiments clearly needs further verification.

ESSENTIAL TREMOR

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part and is classified according to clinical characteristics as well as etiology. When bilateral upper limb action tremor is present in the absence of other neurological signs, the condition is commonly classified as essential tremor (Bhatia et al. 2018). Accumulating evidence points to a central origin of essential tremor, and thalamotomy or DBS of the VIM of the thalamus results in effective symptomatic treatment (Huss et al. 2015; Pedrosa et al. 2014; Vaillancourt et al. 2003). Similarly to motor symptoms in PD, it has been hypothesized that rhythms in brain networks generate tremor in these conditions and that central oscillation frequencies correspond to those observed in the muscles (which are typically 4–8 Hz; Bhatia et al. 2018). The central tremor networks have been suggested to include both cortical and subcortical brain structures since scalp (EEG/MEG) recordings show coherence between neuronal population activity in cortex/thalamus and the concomitantly recorded electromyogram (EMG) activity in trembling muscles (Marsden et al. 2000; Schnitzler et al. 2009). However, even though the peripheral and central oscillation frequencies have been found to overlap and to display significant coherence, direct evidence for a causal role of central rhythms in the generation of muscle tremor has so far not been presented. Indeed, LFP oscillations in this frequency band are also present during resting conditions in the total absence of tremulous activity (Pedrosa et al. 2014). Furthermore, more detailed investigations of the temporal emergence of LFP-EMG coherence in relation to tremor onset have shown that tremor onset precedes thalamomuscular coherence (Pedrosa et al. 2014). This finding is suggestive of a role of sensory feedback in the functional coupling of central and peripheral rhythms. It should be cautioned, however, that analyses in the frequency domain, such as the analysis of

coherence, ought to be based on signals containing true oscillatory activity and that coherence estimates based on more transient phenomena, where the relative power of different frequency components are fluctuating over time, are less robust. Taken together, even though some experimental data support the role of central oscillations in essential tremor, it is at present too early to conclude that rhythmic activity in central circuits is the direct cause of muscle tremor.

DYSTONIA

Dystonia has diverse clinical manifestations and causes. According to widely accepted definitions (Jinnah and Albanese 2014), dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements or postures. The movements displayed are typically patterned and twisting and may be tremulous. Moreover, as recognized already in the original description by H. Oppenheim in 1911, dystonia is often initiated or worsened by voluntary actions and associated with an overflow of muscle activation (Klein and Fahn 2013). According to recent guidelines, dystonias should be classified on the basis of both clinical features, which may facilitate diagnosis and treatment, and etiologies, which may provide more information on underlying mechanisms and a better understanding of the pathogenesis (Jinnah and Albanese 2014). A preferred target for DBS treatment in patients with medication-refractory idiopathic dystonia is the GPi (Volkmann et al. 2012). Importantly, just as for PD, recordings obtained in conjunction with DBS surgery have given valuable insights into a possible physiological disease mechanism.

Recordings of LFPs in these patients with electrode placement in GPi, in combination with cortical EEG/MEG and EMG, have revealed excessive corticopallidal low-frequency oscillations (4–12 Hz; Barow et al. 2014; Chen et al. 2006). As in patients with PD, these low-frequency oscillations are often coherent between brain structures, suggestive of a high degree of functional coupling. However, the preferred oscillation frequency for different interconnected structures may differ, as indicated by the finding that shared oscillations in the pallidum and cerebellum versus in different parts of the cerebral cortex appear in somewhat segregated frequency intervals (including frequencies reaching up into the high end of the beta band; Neumann et al. 2015).

Recently, intracranial recordings from two patients with generalized dystonia revealed pathological narrowband 80-Hz oscillations in the sensorimotor cortex (Miocinovic et al. 2018). These oscillations were strikingly similar to the oscillations found in patients and rodents with LID (Halje et al. 2012; Swann et al. 2016), suggesting common features in the network disturbances that underlie these diseases.

In addition to patient data, symptomatic animal models have also significantly contributed to our understanding of the pathophysiology (Wilson and Hess 2013). In particular, the potential role of the cerebellum has been highlighted by the generation of animal models of cerebellar dysfunction in both rodents and nonhuman primates, which have proven to recapitulate several important clinical manifestations (Wilson and Hess 2013). It should be noted, however, that species differences may exist, and it remains to be investigated to what extent cerebellar dysfunction is a cause of dystonia in patients (Shakkottai et al. 2017). Finally, it is highly likely that different types of dystonia involve partly different neuronal networks that may ultimately result in different types of dysfunctions (Quartarone and Ruge 2018).

EPILEPSY

The classical absence seizure is characterized by a paroxysmal outburst of rhythmic, high-voltage EEG fluctuations that often manifests behaviorally as a static (tonic) or rhythmic (clonic) contraction of muscles and often is accompanied with a partial or complete loss of consciousness. Despite a diverse etiology that spans structural, genetic, infectious, metabolic, and autoimmune causes (Scheffer et al. 2017), the electrophysiological correlate of epilepsy is fairly specific for the majority of epilepsy syndromes: the typical ictal EEG pattern is a rhythmic pattern consisting of a short spikelike deflection followed by a longer and smoother wavelike shape. This spike-wave complex is repeated at ~3–7 Hz in a fully developed seizure, but the dominant frequency can go up to ~20 Hz, especially in the beginning of the ictal phase (Alarcon et al. 1995). Between seizures, the EEG often shows sporadic, transient potential shifts, so-called interictal spikes. These sporadic events are believed to be related to the sudden depolarization of neurons for a few hundred milliseconds, a so-called paroxysmal depolarization shift, that causes the individual neuron to fire in bursts (McCormick and Contreras 2001).

The convergence of the epileptic symptomatology from diverse underlying causes is usually explained by the inherently unstable nature of a system with excitatory feedback. In a healthy brain, a catastrophic chain reaction of excitatory events is actively prevented by adaptive inhibitory feedback, typically from GABAergic interneurons, and disturbances in this delicate balance between excitation and inhibition will lead to increased depolarization of individual neurons and rhythmic hypersynchronization of neural populations. The tendency of feedback systems to enter stable oscillatory states is a well-studied phenomenon in dynamical systems theory, and models based on dynamical systems theory elegantly explain ictal phenomena (Lopes da Silva et al. 2003; Stefanescu et al. 2012). The viewpoint that epilepsy should be regarded as a dynamical disease, rather than a purely excitatory one, is further supported by experiments showing that excessive hyperpolarization can, in fact, induce similar oscillations and hypersynchronous states (Huguenard and McCormick 2007).

During the last two decades it has become increasingly clear that excessive fast oscillatory activity is linked to epileptogenesis. HFOs were first reported in patients with epilepsy by Bragin et al. (1999). Since then, their clinical significance has been established by several studies showing that HFOs are more frequent in the seizure onset zone (Jirsch et al. 2006; Weiss et al. 2013) and that tissue resection based on HFO occurrence correlates with a favorable surgical outcome [Ochi et al. 2007; for a review, see Jacobs et al. (2012)]. Epileptiform HFOs are most frequently reported in entorhinal and hippocampal structure but are also present in the neocortex (Wu et al. 2010). They are usually divided into two varieties: ripples (150–250 Hz) and fast ripples (250–600 Hz), and it is primarily the fast ripples that have been associated with epilepsy, since they do not overlap with physiological ripples (Zijlmans et al. 2012). Fast ripples are believed to be generated by burst

firing in two distinct ways: either by precise in-phase firing, where individual cells fire in bursts at the same frequency as the ripple, or by loose firing, where the ripple emerges from a synchronization of a local population of cells, where each cell does not necessarily fire on every cycle (Jefferys et al. 2012). The temporal precision required to maintain a fast ripple is believed to limit ripple-related synchronous firing to a volume smaller than 1 mm^3 (Bragin et al. 2002). However, it might serve as kindling for transitions into synchronous states at lower frequencies and on a larger scale.

In the context of the present review, it deserves to be mentioned that although epilepsy to date mainly has been studied at the cortical level, it is highly likely that BG circuits are directly affected by the aberrant cortical activity and may in turn contribute to cortical state changes via different feedback loops. In particular, the ventral pallidum, a main output nucleus of the limbic/cognitive cortico-BG loop, is thought to provide feedback potentially regulating excitability and neuronal dynamics of the cerebral cortex (Mahoney et al. 2018; Nair et al. 2018).

PSYCHOSIS AND SCHIZOPHRENIA

Clinically, psychosis is characterized by hallucinations, delusions, and disorganized thinking. Recurrent psychotic episodes are a hallmark of schizophrenia, but psychosis can also be triggered by a wide range of other circumstances, such as severe sleep deprivation or corticosteroid therapy. However, the shared symptomatology between psychoses triggered by different causes suggests that the underlying neurophysiological states also share important characteristics.

Genetically, strong risk factors for developing psychosis have been identified in patients with schizophrenia (Gottesman 1991; Sullivan et al. 2003), but they are complex and scattered across the genome: in a recent genome-wide association study, >100 independent loci were found to be associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Other studies have identified genes that implicate all major neural receptor types on most neural cell types (Harrison and Weinberger 2005), making the search for pathophysiological mechanisms via genetics very difficult. The only common denominator seems to be that these genes are involved in synaptic signaling and plasticity in one way or another.

Neurophysiologically, there are currently no established hallmarks of the acute psychotic state, but aberrant neural oscillations have been implicated in both the psychotic state and the state-independent predisposition of a schizophrenic brain to enter a psychotic state. A recent review (Newson and Thiagarajan 2019) has summarized the resting-state data from the delta, theta, alpha, and beta bands from 37 studies. The authors conclude that patients with schizophrenia who rest with open eyes have significantly increased theta, alpha, and beta power compared with controls. With eyes closed, delta and theta power are significantly increased, whereas alpha power is significantly lower than in controls. However, more specific deviations in brain dynamics have been found when studying induced oscillations caused by rhythmic auditory stimuli. If the stimulus rhythm is sufficiently fast, the neural networks of the auditory system are pushed to a steady state of constant activation, and the amplitude of the evoked potential in this activated steady state can be measured [the auditory steady-state response (ASSR)]. The ASSR depends on the stimulus frequency and is strongest at ~40 Hz (Picton et al. 2003), which interestingly is in the middle of the frequency range where perception of rhythm transitions to perception of musical pitch (19–60 Hz; Guttman and Pruzansky 1962). Kwon et al. (1999) showed for the first time that patients with schizophrenia have an attenuated response in this frequency band, and this finding has since been replicated extensively (e.g., see Krishnan et al. 2009; Spencer et al. 2008; Thuné et al. 2016). Interestingly, this frequency also coincides with the characteristic frequency of the physiological cortical gamma oscillation, which was first discovered in 1942 in the olfactory cortex (Adrian 1942) and subsequently during the 1980s and 1990s in many parts of the neocortex (Gray et al. 1989; Murthy and Fetz 1996). Proper 40-Hz gamma oscillations (not to be confused with broadband gamma activity that does not have a well-defined rhythm) are thought to play an important role in communications between neural networks on the mesoscale and macroscale, because phase locking of gamma oscillations in different brain regions will increase the probability of synchronous spiking of neurons in those regions (Singer 1999). This suggests that an inability to generate gamma oscillations with sufficient strength and accuracy could lead to dysfunctions in normal information processing, which could in turn lead to schizophrenia-type symptoms (Uhlhaas and Singer 2011). This hypothesis predicts that patients with schizophrenia have weaker spontaneous gamma activity and weaker induced gamma activity during cognitive tasks. However, EEG/MEG data are inconclusive on this point: Rutter et al. (2009) found decreased spontaneous gamma activity, whereas several other studies have reported increases (Andreou et al. 2015; Baradits et al. 2019; Mitra et al. 2015; Spencer 2012; Tikka et al. 2014). On the other hand, a review by Senkowski and Gallinat (2015) focusing on induced gamma activity over PFC during cognitive tasks mainly emphasizes reductions in gamma activity. In addition, Grent-'t-Jong et al. (2018) reported that patients with schizophrenia have decreased prefrontal gamma activity but increased posterior gamma activity. They also found a positive correlation between power in a higher part of the gamma band (64–90 Hz) and cognitive deficits/psychotic symptoms. A complicating issue that perhaps contributes to the inconclusiveness of the reports is the difficulty in distinguishing between rhythmic and arrhythmic sources when signal-to-noise ratios are as low as they are in extracranial recordings of the gamma band. Another possibility is that patients with schizophrenia simultaneously suffer from both too little and too much gamma synchrony: perhaps the ability of sensory "bottom-up" processes to create synchrony might be deficient, whereas synchrony driven by cognitive "top-down" processes is abnormally high, resulting in distorted perceptions and delusions.

Acute pharmacological models of psychosis have also drawn attention to the gamma band. Dissociative hallucinogens such as phencyclidine (PCP), ketamine, and MK-801 act as noncompetitive antagonists on the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor (Anis et al. 1983) and are frequently used to induce a temporary psychotomimetic state in humans and experimental animals (Coyle 2012; Vollenweider and Geyer 2001). When given at a subanesthetic dose, these NMDA antagonists profoundly increase neural oscillations in the gamma band at ~40–50 Hz in both rodents (Pinault 2008)

and humans (Sanacora et al. 2014). Their effect on the ASSR is partly consistent with the effect seen in patients with schizophrenia: the amplitude is reduced in the 40-Hz range at least during the early phase of the drug's action (Schuelert et al. 2018; Sivarao et al. 2016). However, there are also reports of increased ASSR (Leishman et al. 2015; Sullivan et al. 2015). To our knowledge, there is only one human study reporting the effect of NMDA antagonists on the ASSR (Plourde et al. 1997). The authors report an increased ASSR with a relatively large dose of ketamine (the majority of the participants were unresponsive during some point of the recording).

The NMDA antagonists also dramatically increase HFOs at 150 Hz in rodents [see Hunt and Kasicki (2013) for a comprehensive review]. Interestingly, they share this effect with another popular class of psychotomimetic drugs, the 5-HT_{2A} receptor agonists (Goda et al. 2013; Hunt and Kasicki 2013). The 5-HT_{2A} agonists do not increase power in the normal gamma band at ~40 Hz in rodents or humans (Muthukumaraswamy et al. 2013), and similar increased 150-Hz HFOs have, to our knowledge, not been reported in conjunction with any nonpsychotomimetic drug. Taken together, this points to 150-Hz HFOs as being a possible neurophysiological marker of the psychotic state that could become very valuable for the development of new therapies. However, convincing evidence of a similar HFO increase in humans has not yet been presented.

The mechanism by which NMDA antagonists and 5-HT_{2A} agonists induce 150-Hz HFOs and a psychotomimetic state is not known. Experimental evidence has been presented that points to the dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) pathway as an important common downstream pathway (Svenningsson et al. 2003), but it is not clear how activation of this pathway would increase HFOs. Others argue that the psychotomimetic action of the NMDA antagonists actually depends on direct interactions with the D2R (Seeman et al. 2005). Moreover, it has been shown that activation of 5-HT_{2A} receptors by psychotomimetic drugs can in itself lead to inhibition of NMDA receptor-mediated transmission (Arvanov et al. 1999). It is, however, also possible that all of the above is true, but the explanatory mechanism principally lies at the level of electrophysiological neuronal interactions, since it has been shown that local networks in many brain regions have a surprising tendency to synchronize at this high frequency. Drug-induced HFOs were first reported in the NAc (Hunt et al. 2006) but are also found in other BG structures: the dorsal striatum, SNr, and STN (Nicolás et al. 2011). They have also been found in the olfactory bulb, the thalamus, the hippocampus, and several regions of the neocortex (prefrontal, motor, somatosensory, parietal, and visual; Caixeta et al. 2013; Hunt et al. 2011, 2019; Kulikova et al. 2012; Nicolás et al. 2011; Olszewski et al. 2013; Phillips et al. 2012). To investigate how the HFOs are generated and spread, Hunt and colleagues injected MK-801 locally in the NAc, which was sufficient to induce HFOs in this structure (Hunt et al. 2010). Also, local infusion of tetrodotoxin in the NAc reduced the spreading of HFOs to other structures, whereas tetrodotoxin infusion in the medial PFC and the caudate did not (Olszewski et al. 2013). This suggests that NAc is an important HFO generator. However, in another experiment, local infusions of MK-801 in the PFC, hippocampus, or NAc all induced HFOs in PFC and NAc in a way that was indistinguishable from a systemic injection (Lee et al. 2017). Together with data on phase coherence between different structures (Nicolás et al. 2011), this suggests that HFOs can be generated locally in several structures and spread to distant brain regions. This is surprising given the temporal precision that is required to transmit oscillations of such high frequencies, which in turn points to the possibility that local networks in many brain regions have an intrinsic resonance at this frequency. If this is true, it suggests that the brain is vulnerable to excessive synchronization at this particular frequency.

Although it is at present too early to draw any definitive conclusions regarding the validity of HFOs (or any other oscillations) as a neurophysiological biomarker for psychosis, this intriguing phenomenon clearly deserves further investigation and could potentially provide novel information that will help guide the development of new treatment approaches.

ELECTRICAL STIMULATION OF THALAMUS, DEEP BASAL GANGLIA STRUCTURES, AND AFFERENT PATHWAYS

Neuromodulatory approaches based on electrical stimulation of neuronal structures aimed at treating central nervous system disease constitute a rapidly expanding field with direct implications for our understanding of the pathophysiology of cortico-BG circuits. Below, we will go through some major aspects of neuromodulatory approaches in tremor, dystonia, schizophrenia, and PD.

For patients with tremor, VIM has been the preferred target for DBS. Although the mechanism of action remains unknown, it is possible that rhythmic activity in central circuits is a key aspect of the pathophysiology causing muscle tremor and that these oscillations perhaps are further amplified by sensorimotor feedback. According to this notion, the therapeutic effect of DBS would essentially be due to a direct disruption of these low-frequency oscillations. However, it should be acknowledged that VIM-DBS loses therapeutic efficacy over the long term, suggesting the involvement of a more complex pathophysiology (Paschen et al. 2019). Nevertheless, at present, the favored conceptual model suggests desynchronization of slow oscillations as the main therapeutic mechanism for VIM-DBS.

In patients with dystonia, it has been suggested that DBS should be designed to specifically interfere with low-frequency oscillations in deep BG structures, assuming that these oscillations are key contributors to the pathology (Piña-Fuentes et al. 2019). However, it remains to be investigated whether this approach is superior to standard GPi/STN-DBS. As discussed above, oscillatory phenomena of higher frequencies have also been implicated in dystonia (Miocinovic et al. 2018). In any case, similarly to essential tremor, desynchronization of pathological activity is regarded by several researchers as a plausible therapeutic mechanism of DBS.

For patients with schizophrenia, striatal DBS is emerging as a novel treatment option (Gault et al. 2018). The rationale behind this is the converging evidence that schizophrenia is a cortex-BG-thalamus circuit disorder similar to PD, but with the ventral striatum, PFC, and hippocampus as important hubs. There are currently a couple of ongoing clinical trials targeting NAc, medial PFC, and SNr involving a handful of patients. It

is still too early to say whether this treatment will be effective, but initial reports are positive (Corripio et al. 2016).

To date, the most widely used neuromodulatory intervention for treatment of BG disease is DBS for the symptomatic treatment of PD. In patients with PD, symptoms can be effectively ameliorated via electrical stimulation of subcortical structures such as parts of the thalamus, the STN, or the GPi (Moro and Lang 2006). The use of high-frequency stimulation of these deep structures was initially intended to achieve a reversible functional inactivation mimicking the targeted lesions that had been shown to alleviate symptoms in animal models of PD and in patients with late-stage PD (Aziz et al. 1991; Benabid et al. 1987, 1989; Bergman et al. 1990). However, subsequent investigation of the neuronal mechanisms responsible for the alleviation of symptoms has made it apparent that the functional effect of high-frequency DBS is much more complex. In particular, the effective activation of axons in the vicinity of the electrode has been shown to cause concurrent anterograde/retrograde activation or inactivation of neurons in several more-distant targets and to induce both long- and short-term effects on synaptic transmission (Deniau et al. 2010). It has therefore been argued that the main mechanism of action of DBS in PD may not be principally related to induced changes in firing rates but instead to a desynchronization of oscillatory activity patterns in the BG and connected networks (Kühn et al. 2008). In specific, DBS could potentially interfere with excessive and strongly coherent low-frequency oscillations that may have a pathogenic role in PD (Brown 2003; Fuentes et al. 2010; Hammond et al. 2007; Marceglia et al. 2006). According to this hypothesis, neuronal circuits become locked in a state prompting immobility through excessive synchronization, thereby preventing the physiological transition required for initiation of voluntary movements.

As an alternative to DBS, researchers have also been evaluating less invasive methods to obtain desynchronization. Because sensory stimulation of somatosensory afferent pathways has long been known to interfere with rhythmic cortical activity (Adrian and Matthews 1934; Chatrian et al. 1959), extracranial stimulation of afferent pathways has been evaluated as a means of interfering with excessive synchronized oscillatory activity. This method has been shown to, for example, block epileptic seizures in both animal models and a few clinical trials of epilepsy (DeGiorgio et al. 2003, 2006; Fanselow et al. 2000). In PD, a similar approach using spinal cord stimulation has been evaluated for the purpose of interfering with synchronized low-frequency oscillations associated with the parkinsonian state. Promising results were first obtained in rodent and primate models of PD (Fuentes et al. 2009), and in subsequent studies, clinically validated treatment effects have also been reported by multiple independent groups (Agari and Date 2012; Akiyama et al. 2017; Fénelon et al. 2012; Hassan et al. 2013; Kobayashi et al. 2018; Landi et al. 2013; Nishioka and Nakajima 2015; Pinto de Souza et al. 2017; Samotus et al. 2018). Thus, it is possible that spinal cord stimulation, being significantly less invasive than DBS, could in the near future become an important therapeutic complement for a large number of patients with PD [for reviews on the use of spinal cord stimulation in PD we refer the reader to Fuentes et al. (2010) and Yadav and Nicolelis (2017)].

ELECTRICAL TRANSCRANIAL STIMULATION WITH DIRECT AND ALTERNATING CURRENTS

Currently, noninvasive brain stimulation devices are being designed to deliver electromagnetic energy to neuronal circuits externally through the skull in ways that are increasingly refined. In particular, two electrical stimulation techniques, transcranial direct current stimulation (tDCS) and transcranial alternating-current stimulation (tACS), have been tested in both healthy subjects and in patients under different pathological conditions. tDCS delivers energy through electrodes with a constant polarity, unlike tACS, which alternates electrode polarity at a specific frequency. Whereas tDCS modifies the threshold of the transmembrane potential of cells in the stimulated region, bringing it closer to the threshold of action potential generation (anodal tDCS) or moving it away from the threshold (cathodal tDCS; Stagg and Nitsche 2011), tACS has demonstrated the potential to entrain the neuronal discharge to the stimulation frequency (Kanai et al. 2008). In this way, it can induce or favor the endogenous oscillatory activity in a state-dependent manner (Silvanto et al. 2008). That is, the effect of the stimulation protocol depends on the current oscillatory state of the neural population at the moment of stimulation (e.g., the effect of tACS in alpha range depends on whether subjects keep their eyes open or closed; Neuling et al. 2013; Nguyen et al. 2018).

Conditions such as PD, which are characterized by excessive synchronization in specific frequency ranges, could potentially benefit from the use of techniques of noninvasive brain stimulation. The first reports on the use of tDCS in PD date from the last decade and were focused mainly on the relief of motor symptoms. In a succession of reports, anodal tDCS has been shown to improve motor function, as reflected by a decrease in the Unified Parkinson's Disease Rating Scale (UPDRS) score (Ferrucci et al. 2016; Fregni et al. 2006; Ishikuro et al. 2018; Málly et al. 2018) as well as in kinematic variables of gait after stimulation *1*) exclusively with tDCS (Benninger et al. 2010; Valentino et al. 2014; von Papen et al. 2014) or *2*) in combination with repetitive transcranial magnetic stimulation (von Papen et al. 2014), physical training (Kaski et al. 2014; Yotnuengnit et al. 2018), treadmill walking (Fernández-Lago et al. 2017), or visual cues (Costa-Ribeiro et al. 2016, but see also Costa-Ribeiro et al. 2017). Improvements in global motor function are associated with alleviation of specific symptoms, such as bradykinesia of the upper extremity (Benninger et al. 2010; Grüner et al. 2010; Salimpour et al. 2015; Schabrun et al. 2016), deficits of balance (Kaski et al. 2014; Lattari et al. 2017), freezing of gait (Dagan et al. 2018; Valentino et al. 2014), and upper extremity motor control during writing (Broeder et al. In press), as well as dyskinesia (Ferrucci et al. 2016). Along with positive motor effects, an improvement in cognitive performance associated with tDCS has been reported in tasks that demand working memory (Boggio et al. 2006), verbal fluency (Manenti et al. 2016, 2018; Pereira et al. 2013), and executive functioning (Doruk et al. 2014; Ishikuro et al. 2018). In general, these behavioral effects have been associated not only with changes in the neuronal excitability of the stimulated cortical region but also with a direct neurochemical effect related to the release of dopamine (Li et al. 2011, 2015; Tanaka et al. 2013) and brain-derived neurotrophic factor (Hadoush et al. 2018) and a reduction in oxidative stress (Lu et al. 2015).

Another recently published beneficial effect of transcranial stimulation is an improved reinnervation of the surrounding tissue following transplantation of dopaminergic cells in an animal model of PD, which was shown to be favored by anodal tDCS (Winkler et al. 2017).

Although PD is characterized by a gradual and progressive deterioration of motor and cognitive functioning, the described treatment effects have been mostly explored during the period immediately after the stimulation. However, the use of tDCS as a long-term therapeutic alternative has been tested in a smaller number of studies using an experimental design adapted to examine the effects in a time range from 1 wk to 3 mo. Positive effects of tDCS on cognitive functions (executive function, attention, working memory, memory, and language) were described when the target of the stimulation was the PFC (Chang et al. 2017; Doruk et al. 2014; Lawrence et al. 2018; Manenti et al. 2016, 2018), whereas no effects were reported when the cerebellum or the primary motor cortex were targeted (Ferrucci et al. 2016). Regarding the motor aspects of PD, studies have shown variable effects. Effects on bradykinesia have shown improvements that lasted up to 3 mo (Benninger et al. 2010), which, however, contrasts with a subsequent study that showed no difference between anodal tDCS and sham groups (Schabrun et al. 2016). This discrepancy can perhaps be explained by the fact that the latter study employed a combined protocol of physical training plus tDCS, which could lead to changes in the sham group.

tDCS effects have also been variable with respect to improvements in gait, with positive changes reported lasting up to 1 mo only for the group with active stimulation (Costa-Ribeiro et al. 2016; Valentino et al. 2014), which contrasts with the changes reported by a series of other studies (Manenti et al. 2016; Schabrun et al. 2016; Yotnuengnit et al. 2018), which report a higher performance in walking test under both active and sham conditions. This last group of studies used combined protocols of physical training plus tDCS, which again could explain the positive effects in the sham groups. Thus, these results may be taken to suggest that physical interventions can explain the observed improvement in motor performance of patients with PD, which tDCS is not capable of further enhancing, perhaps reflecting a "ceiling effect," which has also been found in motor learning paradigms (Schmidt and Lee 2011). Finally, evaluation of general motor function by UPDRS Part III shows that tDCS does not modify performance in the long term or, if it does, this effect is not different between active and sham tDCS conditions (Chang et al. 2017; Grimaldi et al. 2014; Manenti et al. 2016; Schabrun et al. 2016; Yotnuengnit et al. 2018). Only one study has shown a specific effect of tDCS on the UPDRS score that lasted for 2 of the 6 wk of follow-up (Valentino et al. 2014).

A multiplicity of factors that include the frequency and duration of stimulation, the intensity of the current, and especially the location of the electrodes can explain the variability in the long-term effects described here. Such factors have been previously discussed for the application of tDCS in clinical studies (Antal et al. 2017) and constitute a topic of ongoing discussions. Particularly in the case of PD, most of the studies mentioned above were conducted with patients in the "on" stage of medication (only a couple of studies have explored the effects of tDCS depending on the medication status of the patients; Benninger et al. 2010; Costa-Ribeiro et al. 2016). However, although dopamine level-dependent effects of tDCS in patients with PD are poorly studied, such a relationship has been explored in healthy subjects or under neuropsychiatric conditions (Agarwal et al. 2016; Dennison et al. 2019; Kuo et al. 2008; Nitsche et al. 2006).

Taken together, anodal tDCS appears to produce an enhancement of motor and cognitive functions in patients with PD. Are these effects due to a direct modulation of cortical oscillatory activity beyond the well-established excitability and neural plasticity mechanisms of tDCS? Several studies have reported a modulation of oscillatory cortical activity by tDCS in animals and humans (Antal et al. 2004; Heinrichs-Graham et al. 2017; Jang et al. 2016; Vöröslakos et al. 2018) through a direct interaction with processes at the cellular to network level (Das et al. 2016; Sherman et al. 2016). Even so, until now there have been no reports that directly link tDCS with a modulation of the characteristic oscillations of PD. Hence, some researchers have instead explored the effects of tACS on the oscillatory profile and the relief of motor symptoms in PD.

The first study, by Shill et al. (2011), used a commercially available alternating stimulation device to evaluate its impact on UPDRS scores, as well as on the state of depression, anxiety, and sleep. Although this study did not demonstrate positive effects of the stimulation in the midterm and long term (from 3 days to 14 wk), immediate effects were reported for certain motor parameters, such as velocity, reaction time, and motor learning (Cappon et al. 2016; Pogosyan et al. 2009; Pollok et al. 2015; Wach et al. 2013). Unfortunately, no information on the oscillatory state of the brain was obtained, precluding evaluation of the impact of tACS on cortico-BG oscillations in PD.

Subsequently, Brittain et al. (2013) implemented a closed-loop type of tACS protocol for the relief of tremor in patients with PD. These authors demonstrated a significant reduction in tremor amplitude when the phase of the tACS was individually aligned to the temporal tremor profile for each patient, thus confirming the possibility of modulating the motor symptoms in PD through an individualized tACS protocol. More importantly, although the report does not include the recording of neuronal oscillatory activity, it does suggest the possibility of noninvasive interference with pathologically altered oscillatory states in this group of patients. Finally, Krause et al. (2014) corroborated this conclusion in a study applying tACS at 20 Hz to the primary motor cortex to modify the corticomuscular coherence characteristics in different motor states (including sustained contraction and finger tapping). The stimulation protocol led to a reduction of corticomuscular coherence following the stimulation period, together with a decrease in the variability of the movement amplitude of the tapping finger. Both effects were specific for the PD group compared with the control group. In this way, tACS at 20 Hz seems to modify the oscillatory state in a time window that extends beyond the stimulation period. This effect may possibly involve plasticity phenomena (Herrmann et al. 2013; Vossen et al. 2015), entrainment of neuronal discharge to tACS stimulation frequency (Neuling et al. 2013; Zaehle et al. 2010), or excitability changes of the affected area (Kanai et al. 2010; Wach et al. 2013). Thus, tACS could potentially offer unique opportunities for noninvasive intervention in subjects with PD by controlling their oscillatory pathophysiological status. Further investigations in this field are necessary, for example, to determine the

effect of tACS on the ongoing neuronal activity depending on the phase relation to the pathological oscillatory activity. Until these important questions have been addressed, any predictions relating to the future therapeutic value of transcranial stimulation are most likely premature.

SUMMARY

We have here reviewed how synchronized network oscillations in cortico-BG structures have been implicated in various disease conditions. These aberrant activity patterns, and the potential disruptions they may cause in the normal information processing of neuronal circuits, should be viewed in the wider context of the proposed physiological role of the BG in action selection and motor control, which was thoroughly presented in INTRODUCTION. Moreover, although cortico-BG circuits have been the focus of our discussion, it should be noted that similar oscillatory phenomena involving other central nervous system structures may also be contributing to pathophysiological phenomena in these and other disease conditions.

Although a growing body of evidence points to a mechanistic link between the oscillations discussed and disease pathology, it is important to keep in mind that the co-occurrence of synchronous oscillatory activity with symptoms of disease does not necessarily implicate a causal pathophysiological role. In fact, both low-frequency oscillations in cortico-BG structures and high-frequency cortical oscillations are considered to have important physiological functions in healthy subjects (Baker et al. 2003; Courtemanche et al. 2003; Womelsdorf and Fries 2007). Hence, to clarify the potential role of neuronal oscillations in the healthy brain and to identify the mechanisms that cause excessively synchronized network states in disease conditions will be essential. Diseases affecting the brain can potentially cause profound cellular changes, in particular during chronic disease conditions. These changes may make different brain structures prone to produce oscillations at a network level and lead to the emergence of the characteristic neurophysiological phenomena found in both patients and animal models of disease. However, because oscillations can emerge in practically all types of highly interconnected networks, it remains to be explored which cellular components are predominantly responsible for the tuning of network oscillatory properties and to what extent synchronized rhythmic activity is an important part of network function/dysfunction or merely constitutes an epiphenomenon. In any case, accumulating evidence indicates that oscillations in certain frequency bands involving specific brain structures can be used as reliable biomarkers to identify particular brain states associated with brain disease. We therefore anticipate that physiological characterizations of brain states will become an invaluable tool in the future development of new therapies (Tamtè et al. 2016).

ACKNOWLEDGMENTS

We greatly thank Dr. Saleem Nicola for thoughtful comments on earlier versions of the manuscript.

GRANTS

This work was supported by Magnus Bergvall, Crafoordska stiftelsen (Crafoord Foundation), Kockska stiftelsen, Parkinsonfonden, Sven-Olof Janssons livsverk, Kungliga Fysiografiska sällskapet, Kempestiftelsen, and Vetenskapsrådet (Swedish Research Council) grants to P. Petersson.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.H., I.B., J.J.M., C.d.C., R.F., and P.P. drafted manuscript; P.H., I.B., J.J.M., C.d.C., R.F., and P.P. edited and revised manuscript; P.H., I.B., J.J.M., C.d.C., R.F., and P.P. approved final version of manuscript.

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