Subthalamic burst firing: A pathophysiological target in Parkinson’s disease

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ABSTRACT

Understanding the pathophysiological mechanism of Parkinson’s disease (PD) in the subthalamic nucleus (STN) has become a critical issue since deep brain stimulation (DBS) in this region has been proven as an effective treatment for this disease. The STN possesses a special ability to switch from the spike to the burst firing mode in response to dopamine deficiency in parkinsonism, and this STN burst is considered an electrophysiological signature of the cortico–basal ganglia circuit in the brains of PD patients. This review focuses on the role of STN burst firing in the pathophysiology of PD and during DBS. Here, we review existing literature on how STN bursts originate and the specific factors affecting their formation; how STN burst firing causes motor symptoms in PD and how interventions can rescue these symptoms. Finally, the similarities and differences between the two electrophysiological hallmarks of PD, STN burst firing and beta-oscillation, are discussed. STN burst firing should be considered as a pathophysiological target in PD during treatment with DBS.

1. Introduction

The subthalamic nucleus (STN) plays a pivotal role in the pathophysiology of movement disorders (Bergman et al., 1994; Parent and Hazrati, 1995; Hamani et al., 2004). Early reports demonstrated that STN lesions were closely associated with hyperkinetic movement disorders such as ballism (Whittier and Mettler, 1949; Guridi and Obeso, 2001). In the modern cortico–basal ganglia model, which focuses on electrophysiological changes, increased activity in the STN is considered to cause symptoms of Parkinson’s disease (PD), including akinesia and rigidity (Mitchell et al., 1989; Bergman et al., 1990, 1994). Furthermore, lesions in or pharmacological blockade of the STN were found to significantly improve PD motor symptoms in nonhuman primates (Bergman et al., 1990; Wichmann et al., 1994b). High frequency stimulation (HFS) of the STN was later reported to be highly effective in reversing PD symptoms in a primate model, with an effect similar to causing lesions in or pharmacologically blocking the STN, without damaging the deep brain nuclei (Benazzouz et al., 1993). This nonablative surgical technique provided the foundation for deep brain stimulation (DBS) therapy, in which electrodes implanted in the STN release impulses to treat people with PD (Limousin et al., 1998). Strong short- and long-term evidence shows that STN DBS can successfully treat people with advanced PD, and can negate the need for dopaminergic medication (Benabid et al., 2009; Bove et al., 2021). However, the mechanisms by which the STN contributes to the pathophysiology of PD is not well understood; it has thus become an important issue requiring further study, given its key role in this disease.

Electrophysiology has been an important tool to understand the physiological function of the cortico–basal ganglia circuit (Wichmann, 1994; Ellens and Lewenthal, 2013). Significant firing rate increases were initially noted in the STN after dopamine depletion, indicating STN hyperactivity in primates with parkinsonism (Mitchell et al., 1989; Bergman et al., 1990). Subsequent studies exploring STN changes in Parkinsonism found that neurons in this region switch from irregular spikes to a burst firing pattern with periodic oscillatory activity following dopamine depletion (Bergman et al., 1994; Galvan and Wichmann, 2008). The burst firing pattern in STN neurons was found to be significantly increased immediately after 6-hydroxydopamine (6-OHDA) lesions were made in a rodent model of parkinsonism, which correlated with the degree of dopaminergic depletion (Hollerman and Grace, 1992) (Fig. 1A). In people with PD who were not receiving medication, STN neurons had a marked burst firing pattern during micro-electrode mapping (Hutchison et al., 1998; Benazzouz et al., 2002; Starr et al., 2003), and the burst firing pattern of STN was found to be altered after systemic administration of the dopamine agonist apomorphine in 6-OHDA rodents and in people with PD (Kreiss et al., 1997; Levy et al., 2001). This burst firing became the electrophysiological hallmark for neurophysiologists to locate the STN during surgery (Hutchison et al., 1998; Benazzouz et al., 2002; Starr et al., 2003) (Fig. 1B).

Bursts, which are defined as brief (<25 ms) high frequency action potential trains, are considered of special importance in brain function...
In comparison with irregular spike trains, bursts are reported to transmit neuronal signals more reliably, because in comparison with irregular spike train, neurotransmitter release is facilitated when burst arrives in the axon terminals. (Lisman, 1997; Izhikevich et al., 2003) (Fig. 1A). In addition, bursts with specific resonance frequencies are more likely to cause certain postsynaptic cells to fire according to their natural resonance frequencies, enabling selective communication between neurons, and synaptic depression or facilitation (Izhikevich et al., 2003). Although some bursts occur in the STN under normal conditions, the majority of STN neurons fire in bursts immediately after dopaminergic lesion (Hollerman and Grace, 1992; Bergman et al., 1994). STN burst firing may therefore have pathophysiological significance in the treatment of Parkinsonism (Lobb, 2014).

With routine and widespread use of STN DBS in the treatment of PD, an understanding of the pathophysiological role of STN burst firing in this disease is important for clinician as well as neuroscientists to predict disease status and the effect of DBS (Benazzouz and Hamani, 2020). With the development of closed-loop DBS in treatment of PD, there is an urgent need to identify useful biomarkers reflecting disease status in people with parkinsonism (Little and Brown, 2014; Delenclos et al., 2016; Johnson et al., 2016). Potential electrophysiological biomarkers should be easily detectable, reliable over time and have a clear causal relationship with the underlying pathophysiology of PD (Delenclos et al., 2016). Currently, beta-oscillation has been suggested as a biomarker for closed-loop DBS; it would be useful to know whether STN burst firing could be used in a similar capacity (Johnson et al., 2016).

In this review, to highlight and address this gap in understanding, the following issues are discussed: (1) the formation and regulation of STN bursts in PD, including neurotransmitters, network, voluntary and passive movements, and electrical stimulation; (2) the consequence of STN burst firing mode in Parkinsonism.

(A) Schematic diagram of the cortico-basal ganglia model, including the cortico-striato-globus pallidus internus (GPI)/substantia nigra (SNr) ‘direct,’ cortico-striato-globus pallidus externus (GPe)-STN-GPI/SNr ‘indirect’ and cortico-STN-GPI/SNr ‘hyperdirect’ pathways (Modified from Nambu et al. 2002). STN neurons shift from spike to burst firing in states of dopamine deficiency in Parkinsonism, causing abnormal motor signal transmission through both hyperdirect and indirect pathways.

(B) Brain magnetic resonance image (MRI) showing the location of the STN and electrophysiological sweep of STN burst firing, recorded in people with PD using microelectrodes during deep brain stimulation (DBS) surgery.

Fig. 1. Subthalamic nucleus (STN) switch from spike to burst firing mode in Parkinsonism.
bursts in PD, including electrophysiological alterations, motor behavior change, and behavior rescue after electrical stimulation; (3) the possible roles of STN burst firing as a biomarker and a therapeutic target in PD.

2. STN burst formation and regulation

2.1. The origin of STN burst firing

STN burst firing originates from its intrinsic membrane properties: in a study of the electrical properties of STN neurons and the underlying ionic mechanisms under normal physiological conditions in vitro, Beurrier and colleagues (1999) revealed that STN neurons can intrinsically switch from single-spike firing to burst firing mode when the membrane is hyperpolarized. Agonists facilitate this switch through binding to STN metabotropic glutamate receptors. Burst firing in the STN was found to be characterized by the presence of a plateau potential, consisting of a low-threshold Ni$^{2+}$ sensitive spike. The cascade of currents underlying STN burst firing was subsequently studied in detail: the ionic currents forming the plateau potential include the sequential activation of (1) $\text{T-type Ca}^{2+}$, (2) $\text{l-type Ca}^{2+}$, (3) $\text{Ca}^{2+}$-activated inward, and (4) $\text{Ca}^{2+}$-activated $\text{K}^{+}$ currents; the high frequency spikes of the plateau potential result from the activation of resurgent Na$^{+}$ currents (Beurrier et al., 1999) (Fig. 2A). This special intrinsic property enables STN neurons to spontaneously switch between different firing modes according to changes in the baseline membrane potential in vitro (Kass and Mintz, 2006). Recordings in vivo reveal three different firing patterns in the STN: tonic, burst, and slow oscillation. Through spontaneous activation of different sets of ion channels according to the membrane potential status, the STN firing pattern can also be influenced by different neurotransmitters, e.g., dopamine, glutamate, and gamma-Aminobutyric acid (GABA), from STN afferent terminals (Magill et al., 2001; Kass and Mintz, 2006).

2.2. Regulation of STN burst formation

Situated at the convergence between the indirect and hyperdirect pathways of the cortico-basal ganglia circuit, the STN receives major afferent neurons from the globus pallidus externus (GPe) and motor cortex, which secrete the neurotransmitters GABA and glutamate, respectively (Parent and Hazrati, 1995; Nambu et al., 1996; Hamani et al., 2004; Nambu, 2005). The STN also receives nerve fibers from the substantia nigra pars compacta (SNc), which secretes the neurotransmitter dopamine (Parent et al., 2000; Cragg et al., 2004). A previous study showed that dopamine can directly depolarize STN neuronal membranes and increase neuron firing frequency in this region (Gajendiran et al., 2005). Dopamine deficiency may therefore result in relative membrane hyperpolarization and subsequently induce STN burst firing (Filion et al., 1991; Gajendiran et al., 2005; Ammari et al., 2011), as observed during the dopamine deficiency state of Parkinsonism. GPe fibers are the major GABAergic afferent neurons terminating in the STN. GABA agonists decrease while GABA-A antagonists increase the overall firing rate and burst firing in the STN (Wichmann, 1994; Urbain et al., 2002). In addition, the STN and GPe are reciprocally connected; this STN–GPe complex has been shown to spontaneously produce oscillating bursts during dopamine deficiency in an in vitro study. Lesions in the GPe were shown to abolish STN burst firing, and this special STN–GPe connection is considered as a generator of bursts and oscillations in the basal ganglia (Plenz and Kita, 1999). Further studies have demonstrated that burst firing in the STN–GPe complex during chronic dopamine deficiency can be greatly affected by the cortico-subthalamic pathway and cerebral cortex activation (Magill et al., 2000; Nambu et al., 2000; Magill et al., 2001; Urbain et al., 2002; Loucif et al., 2005). Creating lesions in the motor cortex or in cortico-subthalamic pathway has been shown to effectively abolish burst firing and oscillatory activity in STN (Magill et al., 2001; Kita and Kita, 2011). Activating group I metabotropic glutamate receptors...
(mGluRs) can readily increase the firing rate and induce burst firing in the STN in vitro (Beurrier et al., 1999; Awad et al., 2000) (Fig. 2B). Furthermore, blocking N-methyl-D-aspartate (NMDA) receptors interfering transmission of cortico-subthalamic pathway can also decrease abnormal burst firing in the STN in animal parkinsonism models. (Pan et al., 2014, 2016; Bhattacharya et al., 2018). A summary of the factors that promote or inhibit burst formation is shown in Table 1.

2.3. Movement-induced STN spike train changes

Movement can induce STN spike train changes through afferent signal transmission via hyperdirect pathways (Nambu, 2005). Voluntary and passive movements induce brisk changes in STN firing frequency and pattern under experimental conditions in primates (DeLong et al., 1985; Wichmann, 1994) and in humans with PD (Hutchison et al., 1998; Magariños-Ascone et al., 2000; Rodríguez-Oroz et al., 2001; Benazzouz et al., 2002; Starr et al., 2003). In a study of people with PD, visually guided joystick movement increased the STN firing rate exactly when the movement took place (Amirnovin et al., 2004). During micro-electrode recordings of DBS surgery in people with PD, 32% of neurons in the STN were activated by both passive and active movement; most of these neurons were located in the dorsolateral STN (Magariños-Ascone et al., 2000). Movement-related STN neurons have been used as a marker of electrode location in the dorsolateral sensory-motor region of the STN (Hutchison et al., 1998; Magariños-Ascone et al., 2000; Benazzouz et al., 2002; Starr et al., 2003). In an experimental cortical micro-stimulation study in primates, there is homunculus distribution of STN neurons related to movement of contralateral body parts, and these neurons were shown to be directly connected with similar homunculus distribution of primary motor cortex (Nambu et al., 1996). Within STN doors-lateral region, neurons are organized in a somatotopic distribution with those corresponding to the face, arms, and legs arranged from lateral to medial positions in primate and human studies. (DeLong et al., 1985; Wichmann, 1994; Magariños-Ascone et al., 2000; Rodríguez-Oroz et al., 2001; Starr et al., 2003). Taken together, these studies show that STN burst firing and associated changes in spike activity in PD is precisely correlated with movement; they also provide support for STN burst firing as a potential biomarker for PD and in closed-loop DBS (Table 1).

2.4. Electrical current alters STN burst firing

Electrical stimulation is another important way in which STN burst formation can be altered, in addition to physiological (movement) and biochemical (dopamine, GABA, glutamate) stimulation as previously described. In an early study of the mechanisms of DBS, the effect of high frequency stimulation (HFS, frequency > 100 Hz) of STN neurons was assessed both in vitro and in vivo in rodents with parkinsonism (Benazzouz et al., 1993, 1995). In vitro, HFS was shown to suppress spontaneous activity in the STN and also generate bursts with spikes that were time-locked to a stimulus pulse (Garcia et al., 2003). In vivo, a template subtraction model was used to cancel stimulation artifacts showed that the majority of STN neuronal activity was partially (61%) or completely (16%) inhibited by HFS in animals with parkinsonism (Tai et al., 2003). In people with PD, a comparison of STN neuronal activity before and immediately after HFS showed inhibitory responses to this type of stimulation in STN neurons (Filali et al., 2004; Welter et al., 2004). Furthermore, patch-clamp recordings of rodent brain slices showed that HFS could suppress STN burst firing in neurons via transient depolarization of the neuronal membrane. This effect was independent of synaptic activity and was mediated by blockade of voltage-gated currents, especially T- and α-type Ca2+ currents and Ca2+-activated inward currents. In brief, the HFS-induced STN burst suppression is closely related to changes of discharge modes by injection of current depolarizing the STN neurons. (Beurrier et al., 2001).

Based on these findings, it follows that stimulation at any frequency with sufficient current density to depolarize the STN neuronal membrane should be able to modulate the switch of STN spike trains from burst mode to another discharge mode (e.g., spike mode). An in vivo study also showed that STN burst firing can be reduced by injecting a depolarizing current with low frequency but prolonged pulse width (e.g., 90% interstimulus interval time, compared with the 1% used in DBS), or even by administration of a depolarizing constant current without a frequency (Tai et al., 2011, 2012). A similar effect is observed in vitro in which depolarizing constant currents (without pulse) have been shown to suppress STN bursts in dopamine-deficient states (Tai et al., 2012). In contrast, administration of reversed polarity hyper-polarizing currents in the STN can result in increased STN burst firing both in vitro and in vivo by hyper-polarization of STN membrane potential (Tai et al., 2012, 2020). Taken together, these findings indicate that DBS is a highly effective modulator of STN neuronal activity through directly influencing STN membrane potentials (Tai et al., 2012) (Table 1).

3. Consequences of STN burst firing

3.1. STN burst firing as a cause of parkinsonism motor symptoms

A major physiological role of the STN is to generate ‘stop’ signals to pause motor behavior through activating basal ganglia inhibitory outputs (Zavala et al., 2015; Aron et al., 2016). Experimental evidence has shown that abnormally increased STN burst firing during dopamine deficiency is directly associated with motor symptoms in parkinsonism (Bergman et al., 1994; Leibo following, 2007; Tai et al., 2011; Pan et al., 2014; Sharott et al., 2014) (Fig. 3A). According to the cortico–basal ganglia circuit model, hyperactivity in the STN causes increased basal ganglia outputs, which in turn inhibit thalamo–cortical projection, preventing complete activation of the motor cortex, resulting in the hypokinetic symptoms of parkinsonism (Albin et al., 1989; Delong, 1990). Given the glutamatergic projections from the STN to the globus pallidus internus (GPI) and substantia nigra (SNr), aberrant STN burst formation in a state of dopamine deficiency readily increases basal ganglia output activities, resulting in motor behavior deficits both in 6-OHDA-induced parkinsonism in rodents, and MPTP-induced parkinsonism in primates (Bergman et al., 1994; Parent and Hazrati, 1995; Shink et al., 1996; Murer et al., 1997). There has been evidences showing the link between STN burst firing and the clinical parkinsonism symptoms, such as gait freezing, in human studies during intra-operative recordings (Georgiades et al., 2019) The freezing symptoms could be alleviated by stimulating STN and ameliorating its burst firing. (Andreae et al., 2020; Conway et al., 2021) Furthermore, several time course studies have shown that the initiation and progression of STN burst firing is highly correlated with the onset and development of motor symptoms in parkinsonism (Vila et al., 2000; Ni et al., 2001; Leibo following, 2007).

Table 1

| Factors regulating subthalamic nucleus (STN) burst formation. | State required to promote increased burst | State required to inhibit decreased burst |
|---------------------------------------------------------------|------------------------------------------|-----------------------------------------|
| T-type Ca2+ channel   | Activated   | Blocked   |
| Membrane potential Hyperpolarized | Depolarized |
| Dopamine Deficient | Abundant   |
| Dopamine receptor Activated   | Blocked   |
| GABA receptor Activated   | Blocked   |
| Glutamate receptor Activated   | Blocked   |
| Current stimulation Hyperpolarized current polariy | Depolarized current |

GABA, gamma-aminobutyric acid.
3.2. Modulating effects of optogenetic excitation or inhibition of the STN on motor symptoms

Recent advances in optogenetic studies provide further evidence that aberrant STN activity can induce motor symptoms associated with Parkinsonism (Gradinaru et al., 2009; Kravitz et al., 2010). These studies use solid-state optics to drive or inhibit distinct brain circuit elements in rodents or mice, and have thus become an important tool enabling pathophysiological studies in basal ganglia research. In animal models of Parkinsonism, selective stimulation or inhibition can be given directly to each element in a circuit, such as afferent axons projecting to the STN, or the STN itself (Gradinaru et al., 2009; Kravitz et al., 2010). Optogenetic inhibition of the STN glutamatergic neurons has been shown to improve the symptoms of Parkinsonism effectively in a rodent model (Yoon et al., 2014); in another study, selective optogenetic inhibition of STN enhanced locomotion in freely-moving mice, while excitation of STN neurons increased self-grooming, disturbed gait and jumping/escaping behaviors with reduced overall locomotion. These findings provided further evidence that STN neuronal activity plays a regulatory role in animal motor control (Guillaumin et al., 2020, 2021).

Further studies on optogenetic stimulation of cortico–basal ganglion pathways also showed the importance of the STN in the pathophysiology of Parkinsonism. Optogenetic excitation of the motor cortex (MC)-striatum(STR)-GPi-STN-GPi indirect pathway can elicit symptoms such as freezing, bradykinesia, and decreased locomotion in mice. In contrast, optogenetic activation of the MC-STR-GPi direct pathway can improve symptoms (Kravitz et al., 2010). Optogenetic stimulation of the MC-STN hyperdirect pathway at high frequency can improve locomotor symptoms in a mouse model of Parkinsonism (Sanders and Jaeger, 2016). Interestingly, in health mice, optogenetic over-activation of the hyperdirect pathway can instantaneously induce Parkinsonism-like locomotor dysfunction, also indicating the influence of the cortico–subthalamic pathway on STN neuronal activity and motor control (Pan et al., 2014).

3.3. Rescue of motor symptoms in Parkinsonism through amelioration of STN burst firing

In primates with Parkinsonism, local injection of ibotenic acid into the STN to induce lesions immediately reversed abnormal firing in the GPi/SNr, with concomitant improvement in motor symptoms ((Wichmann et al., 1994); Guridi et al., 1996) (Fig. 3B). Similarly, systemic administration of the dopamine agonist apomorphine in a 6–OHDA-induced model of Parkinsonism resulted in a marked decrease in STN burst firing and improved symptoms (Kreiss et al., 1997). To document the direct effect of dopamine on the STN, microinjection of apomorphine into the STN was shown to effectively ameliorate motor deficits associated with Parkinsonism, without changing the dopamine balance in the striatum, or inducing any turning behavior in a rodent model of this condition (Pan et al., 2014). STN burst firing can also be reduced by microinjection of GABA agonist muscimol into the STN, with immediate reductions in tremors, rigidity, bradykinesia, even with emergence of dyskinesia, in primates with MPTP-induced Parkinsonism ((Wichmann et al., 1994)). Furthermore, microinjection of selective NMDA receptor antagonist AP5 into the STN can also effectively reduce STN burst firing and ameliorate motor symptoms in experimental rodent Parkinsonism models (Pan et al., 2014, 2016). Amantadine has been proven effective as an oral adjunctive treatment for motor symptoms in PD patients, and this clinical effect may be closely related to its capacity to block NMDA receptors, altering the subsequent firing rate and pattern in the STN (Danywycz et al., 1994; Allers et al., 2005; Danywycz et al., 2021) (Fig. 3C).

Recent studies targeting STN intrinsic membrane properties to reduce STN burst firing also revealed promising results. Microinjection of a nickel solution, which blocks T-type Ca2+ channels and inhibits STN burst formation, has been shown to rescue locomotor deficits in a rodent model of Parkinsonism (Tai et al., 2011; Pan et al., 2016). Zonisamide, a clinical T-type Ca2+ blocker developed for the treatment of seizures, also had a promising effect, decreasing burst firing when locally injected into the STN, and improving locomotor deficit in rodents with Parkinsonism (Yang et al., 2014). In a clinical setting, Zonisamide effectively reduced the motor symptoms in people with PD in a randomized, double-blind study (Murata et al., 2007; Fox, 2013). Another study showed that an ether-a-go-go-related gene K+ channel (ERG-K+) inhibitor, used experimentally as an anti-arrhythmia drug, can reduce STN burst firing and improve Parkinsonism motor deficits in rodents (Huang et al., 2017). These experimental data demonstrate that, by
targeting the mechanisms of STN burst formation, or abolishing STN burst firing by direct lesion, channel blockade, or neurotransmitter modulation, can improve motor deficits in animal models of Parkinsonism (Fig. 3C).

3.4. Motor symptom improvements associated with decreased STN burst firing in DBS

DBS is an important clinical tool for the modulation of STN neuronal activities and improvement of motor symptoms in Parkinsonism. STN DBS, which is similar to STN lesioning, can reverse dopamine lesion-mediated electrophysiological changes in the GPe, GPI and SNr, and antagonize gene expression in these output structures, thus improving motor symptoms in rodents with Parkinsonism (Benazzouz et al., 1995; Salin et al., 2002; Tai et al., 2003; Benazzouz et al., 2004). Other in vivo studies using constant current stimulation showed that electrical stimulation with a depolarizing constant current can readily decrease STN burst firing, with concomitant improvements in Parkinsonism behavior in rodents (Tai et al., 2012) (Fig. 3D). Furthermore, reversal of the stimulation current polarity with a hyperpolarizing current can cause excessive burst formation in the STN, which can result in symptoms of Parkinsonism in healthy rodents (Tai et al., 2012; Pan et al., 2016; Tai et al., 2020). Interestingly, current evidence also shows that STN HFS can change cerebral cortex spike activity via antidromic stimulation of the cortico-subthalamic tract (Nambu, 2005; Pan et al., 2010; Degos et al., 2013; Vassal et al., 2020; Benazzouz, 2019); these changes include decreased firing rate and reduced burst firing pattern in pyramidal cells in the primary motor cortex (Degos et al., 2013). STN HFS has also been shown to significantly change cortical excitability, likely via the hyperdirect pathway, in several transcranial magnetic stimulation studies (Cunic et al., 2002; Fraix et al., 2008). These findings suggest that the remedial effects of STN DBS may be at least partly due to cortico-subthalamic antidromic stimulation (Garcia et al., 2003; Benazzouz, 2019; Benazzouz and Hamami, 2020).

However, STN burst firing still has a primary role in the downstream formation of motor symptoms, given that lesion or stimulation of the STN is still the most effective mode of treatment for PD (Bergman et al., 1996; Benazzouz et al., 1993; Limousin et al., 1998).

4. STN burst firing and beta-oscillation

4.1. Co-occurrence of STN burst firing and beta-oscillation in the hyperdirect pathway

STN burst firing and underlying oscillatory activity appear together in Parkinsonism (Bergman et al., 1994; Brown et al., 2001; Levy et al., 2002). Oscillatory activity in the STN can be recorded using the local field potential (LFP) technique, in which the electric potential in the extracellular space is recorded (Brown et al., 2001; Levy et al., 2002). Studies of LFP activity spike-triggered average revealed that oscillations in the LFP are locked to STN neuronal discharges. Thus, this oscillatory activity at a beta frequency range (13–30 Hz) likely represents synchronous activity in neuronal populations within the STN (Levy et al., 2002; Kuhn et al., 2005b). This beta-oscillation has been correlated with Parkinsonism in many studies (Brown et al., 2001; Levy et al., 2002; Sharott et al., 2005, 2005; Kühn et al., 2005f; Foffani et al., 2005; Gatev et al., 2006). In studies of people with PD, beta-oscillation has been detected during off-medication periods, and found to be abolished following administration of dopaminergic medication (Brown et al., 2001; Levy et al., 2002; Sharott et al., 2005; Hammond et al., 2007). In addition, the extent of beta-oscillation is correlated with the severity of some PD symptoms, such as rigidity and akinesia, in human patients (Kühn et al., 2008, 2009; Zaidel et al., 2009; Jenkins and Brown, 2011), and it has also been shown to be stable and detectable over time (Little et al., 2012; Stein and Bar-Gad, 2013). When the amplitude of beta-oscillation is higher than 75 % of average amplitude and the duration of this above-threshold beta-oscillation lasts above 100 ms (usually 100–1000 ms), this activity is marked as “beta burst”, which has been shown to be positively correlated with motor impairment in PD patients. (Feingold et al., 2015; Tinkhauser et al., 2017) In contrast to STN burst firing indicating neuronal action potential pattern, the definition and representations of “beta burst” and “burst firing” of STN is very different in meaning and should be considered separately.

Beta-oscillation can also be recorded concomitantly in the motor cortex and the STN in dopamine-deficient animal Parkinsonism models and in humans with PD (Levy et al., 2002; Williams et al., 2002; Mallet et al., 2008; Galati et al., 2009). Interestingly, similar to STN burst, the formation of beta-oscillation is determined by the hyperdirect pathway connecting the STN and motor cortex (Mallet et al., 2008; Tachibana et al., 2011). Damaging the motor cortex or disrupting the cortico–subthalamic tract can prevent the formation of both beta-oscillation and STN burst firing in animals with Parkinsonism (Magill et al., 2000, 2001; Urbain et al., 2002; Gaynor et al., 2008; Pan et al., 2014). Blocking the cortico–subthalamic pathway using a glutamate antagonist also reduces both forms of activity concurrently in experimental animal models of Parkinsonism (Tachibana et al., 2011; Pan et al., 2014; Chu et al., 2015). These results indicate that the formation of beta-oscillation and STN burst firing are not completely the same but may share some common underlying mechanism or pathway; a comparison of the properties of these two forms of activity are shown in Table 2.

4.2. Separate blockade of STN burst firing and beta-oscillation using different NMDA receptor subtypes

Despite the establishment of both beta-oscillation and STN burst firing as factors affecting motor symptoms in Parkinsonism during dopamine deficient states, there are some key differences between these two electrophysiological markers, as shown in Table 2 (Bergman et al., 1994; Leblois et al., 2007; Tai et al., 2011; Pan et al., 2014; Sharott et al., 2005, 2005; Kühn et al., 2005a). STN burst activity appears within the first few hours after dopamine depletion in experimental animal models of Parkinsonism, along with the appearance of motor deficits; in

Table 2

| Burst firing | Beta-oscillation |
|--------------|------------------|
| Primary origin | Dopamine deficiency; STN membrane intrinsic properties; cortico-subthalamic pathway |
| Appearance | Immediately after dopamine depletion |
| Enhanced by | Dopamine depletion; glutamate transmission; hyperpolarizing currents |
| Suppressed by | Dopamine supplementation; glutamate blockade; depolarizing currents GluN2B |
| Associated receptor | GluN2A |
| Correlation with | Correlated |
| Correlation with rigidity and bradykinesia | Correlated |
| Correlation with resting tremor | Changes magnitude during movement |
| Association with movement | Dopamine supplementation, Glutamate blockade; depolarizing currents GluNZ2A |
| Detectability | Difficult to detect |
| (as a biomarker for DBS) | Easy to detect |

DBS, deep brain stimulation.
contrast, beta-oscillation only appears 1–2 weeks after the onset of symptoms, which may indicate that beta-oscillation is a delayed consequence of chronic dopamine depletion (Leblois et al., 2007; Mallet et al., 2008) While some STN neurons exhibiting burst firing have been shown to oscillate at the same frequency as the tremors associated with parkinsonism (Hutchison et al., 1998; Benazzouz et al., 2002), the frequency of beta-oscillation failed to correlate with tremors in people with PD (Levy et al., 2002; Kühn et al., 2008, 2009; Weinberger et al., 2009; Zaidel et al., 2009; Jenkins and Brown, 2011). In addition, beta-oscillation was shown to increase during the movement preparation period, but dampen after movement initiation (Levy et al., 2002; Kühn et al., 2004; Brown and Williams, 2005); in contrast, STN burst firing changes with movement timing and magnitude following movement initiation (Bergman et al., 1994; Hutchison et al., 1998; Benazzouz et al., 2002; Sharott et al., 2014). This evidence reveals major differences between STN burst firing and beta-oscillation in the motor pathophysiology of parkinsonism, as shown in Table 2 (Stein and Bar-Gad, 2013).

As both STN burst and beta-oscillation can be abolished by blocking glutamate transmission in the hyperdirect pathway (Pan et al., 2014, 2016), STN burst firing and beta-oscillation can also be individually blocked through microinjection of NMDA receptor antagonists in the STN. Selectively blocking the GluN2A receptor in the STN, for example, can suppress beta-oscillation formation without affecting STN burst firing, under which conditions locomotor deficits in rodent models of parkinsonism persist (Pan et al., 2016). In contrast, selectively blocking the GluN2B receptor in the STN significantly decreases aberrant STN burst formation with persistent beta-oscillation, which can concomitantly rescue motor deficits in animal models of parkinsonism. These findings show that STN burst firing seems to be more directly connected with Parkinsonism motor deficits than beta-oscillation (Pan et al., 2016). However, administration of a hyperpolarizing constant current in the STN can cause excessive burst formation in the neurons, with no concurrent beta oscillation (Tai et al., 2012; Pan et al., 2016); this can directly produce Parkinson-like locomotor deficits in healthy rodents (Tai et al., 2012; Pan et al., 2016; Tai et al., 2020). In brief, although both STN burst firing and beta oscillations are separate electrophysiological hallmarks of PD, STN burst firing is more directly related to the underlying pathophysiological mechanism, resulting in motor symptoms (Tai et al., 2011, 2012; Lobb, 2014; Pan et al., 2014; Nambu et al., 2015; Pan et al., 2016).

4.3. Beta-oscillation is superior to STN burst firing as a biomarker in DBS

Since beta-oscillation is correlated with rigidity and bradykinesia and is readily detected through a DBS electrode in people with PD (Kühn et al., 2009), it has been recognized as a clinically useful biomarker for parkinsonism (Jenkinson and Brown, 2011; Johnson et al., 2016). Given its close relationship to STN burst, the power of beta-oscillation (also called beta-power) is correlated with the degree of dopamine deficiency and the appearance of rigidity and bradykinesia (Brown et al., 2001; Levy et al., 2002; Sharott et al., 2005; Giannicola et al., 2010). Beta-power is also diminished with dopaminergic supplementation, and during STN DBS (Giannicola et al., 2010; Eusebio et al., 2011; Whitmer et al., 2012). Although it may not be directly associated with pathophysiology, beta-power can still be an effective biomarker for real-time, closed-loop control of DBS (CL-DBS) (Little and Brown, 2012; Priori et al., 2013), and can be used as a guide for modulation of the duration and/or intensity of stimulation (Little et al., 2013; Priori et al., 2013; Rosa et al., 2015; Little et al., 2016). In recent studies, beta-power driven CL-DBS was shown to be more effective than traditional DBS at improving rigidity and bradykinesia while operating at a reduced stimulation duty cycle (Rosa et al., 2015; Little et al., 2016). However, whether beta-oscillation is the most suitable biomarker for CL-DBS therapy and whether it could be a useful pathophysiological target in PD remains unknown (Johnson et al., 2016).

STN burst firing could also be considered as a biomarker in CL-DBS. However, in comparison to beta-oscillation, which can be readily recorded using DBS electrodes in PD patients, STN spike trains (or so-called “single-units”) require more sophisticated recording techniques, and crucially cannot be recorded using currently available DBS electrodes (Little and Brown, 2012; Sharott et al., 2014). In addition, LFP can record a greater multitude of neuronal activities in the STN, representing a larger population, while current single-unit recording techniques detect only a limited number of STN neuronal activities, near the microelectrode (Jen et al., 2011). Therefore, until single-unit recording can be improved or developed into a more accessible technique, or another new biomarker representing STN burst firing is established, beta-oscillation is still the most useful known biomarker for CL-DBS in PD at present (Fig. 4).

4.4. STN burst firing as a common pathophysiological target for DBS in PD

Although they share similar mechanism in formation, the direct consequences of STN burst firing and beta-oscillation are different. Therefore, it is important to recognize that the STN spike train dynamic ultimately governs how a motor behavior develops. STN burst firing is closely associated with motor deficits in parkinsonism, so the therapeutic goal should aim at reducing STN burst formation. As beta-oscillation remains a useful biomarker for CL-DBS, it is important to take into account that STN burst is more directly associated with PD pathophysiology. And reduction of STN burst should be considered as the major target during DBS programming. Specifically, as STN burst firing is formed mainly through its intrinsic properties and enhanced by cortico–subthalamic transmission, the major strategy of STN DBS directing toward this pathophysiological target should be: (1) modulating STN membrane potentials using depolarizing currents, thus decreasing the ability to burst firing, and (2) antidromic stimulation of the cortico–subthalamic afferent fibers, thus disrupting glutamatergic transmission directly from the motor cortex to block its burst enhancing effect. Therefore, electrical stimulation combining a depolarizing current (for modulating STN membrane potential) and high frequency/short pulse width stimulation (for stimulating afferent cortico–subthalamic axons) is likely a good approach to treat the symptoms and pathophysiology of parkinsonism (Kang and Lowery, 2014) (Fig. 4).

It is important to consider STN burst as a pathophysiological target in PD treatment. Given the current knowledge on STN burst formation, there are several clinical strategies that could reduce STN burst firing, which include: (1) increasing dopaminergic transmission using agents such as levodopa or dopamine agonists; (2) Reducing glutamatergic transmission, using agents such as amantadine, a partial glutamatergic antagonist; (3) Blocking certain channels to alter intrinsic membrane properties with agents such as zonisamide, a T-type Ca$^{2+}$ channel blocker that reduces STN burst formation; and (4) electrical stimulation with a high-frequency pulse and depolarizing current, as in current DBS. All these strategies have been shown to reduce STN burst firing in experiments, and have also been shown to be beneficial in the reduction of clinical PD motor symptoms.

5. Conclusion

In the new era of CL-DBS, effective electrophysiological biomarkers and efficient therapeutic targets are crucial to the development of next-generation DBS for PD. While beta-oscillation works well as a biomarker for symptoms of Parkinsonism, STN burst firing provides the most accurate reflection of PD pathophysiology, and should be investigated as a therapeutic target in the treatment of this disease.

Data availability

No data was used for the research described in the article. Data will be made available on request.
The data that has been used is confidential.

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Declaration of Competing Interest

The author reports no declarations of interest.

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