Title: Mechanisms of deep brain stimulation

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Abstract

Deep brain stimulation (DBS) is widely used for the treatment of movement disorders including Parkinson’s disease, essential tremor and dystonia, and to a lesser extent certain treatment-resistant neuropsychiatric disorders including obsessive-compulsive disorder. Rather than a single unifying mechanism, DBS likely acts via several, non-exclusive mechanisms including local and network-wide electrical and neurochemical effects of stimulation, modulation of oscillatory activity, synaptic plasticity and, potentially, neuroprotection and neurogenesis. These different mechanisms vary in importance depending on the condition being treated and the target being stimulated. Here we review each of these in turn and illustrate how an understanding of these mechanisms is inspiring next-generation approaches to DBS.

Introduction

Deep brain stimulation (DBS) is the therapeutic use of chronic electrical stimulation of the brain via an implanted electrode. It is most commonly used to treat the motor symptoms of Parkinson’s disease, essential tremor and dystonia, and it is in more limited use or under active investigation to treat a wide variety of neurologic and psychiatric conditions including epilepsy, obsessive-compulsive disorder (OCD) and major depression (Table 1).

The most commonly used DBS system uses a four-contact stimulating electrode stereotactically implanted in the target and connected via a subcutaneous wire to a pacemaker-like unit called an implantable pulse generator (IPG) that is placed on the chest wall underneath the collarbone. Electrodes are typically placed bilaterally although clinical needs sometimes dictate unilateral stimulation. Most targets are deep brain structures (including deep white matter tracts) rather than cortical areas (Table 1). A clinician uses a handheld device to wirelessly
communicate with the IPG to adjust the parameters of stimulation, tuning stimulation to maximize symptom relief and minimize side effects.

Here we review what is known about the effects of deep brain stimulation on local and network neural activity and plasticity, how these effects are thought to result in clinical benefits and side effects, and how our understanding of these mechanisms is driving next-generation approaches to neuromodulation.

**Time course of DBS clinical effects**

In the treatment of movement disorders and psychiatric disease, different symptoms characteristically respond to DBS with different time courses (Figure 1) (Agnesi et al., 2013b).

Ventral intermediate (Vim) thalamus DBS for essential tremor provides relief of tremor over seconds (Flora et al., 2010). Subthalamic nucleus (STN) DBS for Parkinson's disease provides relief of tremor over seconds (Blahak et al., 2009), relief of rigidity and bradykinesia over minutes to hours (Temperli et al., 2003) and relief of axial symptoms that is less profound and often delayed hours or days (Fasano et al., 2015). Similarly, the time course with which symptoms return when STN DBS is stopped mirrors the time course of symptom relief when stimulation is initiated (Temperli et al., 2003). In dystonia, globus pallidus internus (GPI) DBS can induce an early improvement in phasic dystonic movements, while tonic symptoms require months of DBS treatment to become fully realized (Yianni et al., 2003; Krauss et al., 2004). In subgenual cingulate gyrus DBS for the treatment of depression, investigators found that patients experienced immediate intraoperative effects of stimulation such as feelings of sudden calm or lightness, heightened awareness, and changes in positive and negative affect (Mayberg et al., 2005). These immediate effects were followed by subacute effects over days including improvements in interest and activity level, and finally remission of disease with chronic stimulation in some patients.
Mechanisms of deep brain stimulation (Mayberg et al., 2005). However, despite the success in some patients, two larger, randomized clinical trials of DBS targeting the anterior limb of the internal capsule and cingulate area 25 failed to show a lasting clinical benefit (Dougherty et al., 2014). In the case of DBS of the anterior limb of the internal capsule (ALIC) for OCD, investigators reported some immediate effects including improvement in mood and anxiety, although ultimately reduction in OCD symptoms evolved gradually over months (Greenberg et al., 2010; Tierney et al., 2014). In some cases, short-term responses to stimulation may not be predictive of eventual disease remission as has been described in thalamic and GPi DBS for Tourette’s syndrome (Motlagh et al., 2013). Also, symptom onset and return do not always follow the same time course. For example, in Tourette’s syndrome, DBS of the anterior-medial GPi or thalamic centromedian-parafascicular complex-ventral oral complex (CM-Pfc-Voa) results in improvement in tics over months (Servello et al., 2008; Sachdev et al., 2014). However, when thalamic DBS is turned off tics may reappear rapidly (Servello et al., 2008).

That symptoms respond to treatment on dramatically different time scales suggests that DBS is acting via several different mechanisms that have their own intrinsic time courses (Figure 1). Symptoms that respond rapidly are mediated by rapidly-reversible DBS mechanisms such as the immediate neuromodulation of pathologic network activity. Symptoms that respond more slowly are at least in part mediated by longer-term mechanisms such as synaptic plasticity and ultimately anatomical remodeling (Temperli et al., 2003; Agnesi et al., 2013b).

Peri-electrode targets of DBS

Figure 2 illustrates the typical placement of a DBS electrode in the STN, the most commonly used DBS target for Parkinson’s disease. The most effective site of STN stimulation appears to be in the dorsolateral STN or just dorsal to the STN in the zona incerta (ZI) and fields of Forel (Butson...
et al., 2011; but see Richardson et al., 2011). This white matter tract includes efferents from the STN/ZI (Parent and Hazrati, 1995a), afferents from the pallidum (Groenewegen and Berendse, 1990), hyperdirect projections from the cortex (Nambu et al., 1996; 1997; Haynes and Haber, 2013) and fibers of passage including efferents from the pallidum to the thalamus (Severin et al., 1976) and the pedunculopontine nucleus (PPN) (Lee et al., 2000).

The clinician has a limited ability to adjust the shape of the electrical stimulation field by adjusting the number and configuration of anodal (positive) or cathodal (negative) electrode contacts and the voltage or current of the stimulation (Figure 2). In addition, the clinician can alter the duration of each charge-balanced pulse (called the pulse width) as well as the frequency of the pulses. Stimulator settings are chosen empirically to maximize benefit and minimize side effects. For example, whereas stimulation in the region of the dorsal STN and ZI is associated with relief of parkinsonian rigidity, bradykinesia and tremor, stimulation of surrounding structures is thought to give rise to side effects including tonic muscular contractions and slurred speech (internal capsule), declines in executive function (ventral STN and its cortical connections) and mood disorders including mania, anxiety and depression (ventral STN and substantia nigra pars reticulata, or SNr) (Kumar and Johnson, 2011). Although these structure-effect relationships are used as rules of thumb to guide clinical programming, the precise neuroanatomical substrate for the clinical benefits and side effects of DBS remains an area of active investigation.

The subset of neural elements stimulated is more complicated than the electric field diagram suggests. Many factors influence which neural elements are stimulated (Montgomery, 2010; for review see Brocker and Grill, 2013). Stimulation acts predominantly on axons and dendrites near the electrode, rather than on the soma which have substantially higher stimulation thresholds. The result is that a neuron whose soma is distant from the electrode may be more readily stimulated than one adjacent to the electrode if the former happens to have dendritic or
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Initial hypotheses about the mechanism of DBS were based on the observed similarity between the effects of high-frequency stimulation and the effects of lesions in the same regions, i.e. pallidotomy for the treatment of Parkinson’s disease (PD) (Guridi and Lozano, 1997) or capsulotomy for the treatment of OCD (Jenike, 1998). Because high-frequency stimulation had a therapeutic effect similar to that of ablative surgery, DBS was thought to function as a reversible lesion by inhibiting neurons near the stimulating electrode. Consistent with this idea, chemical inhibition of the STN or GPi reduced parkinsonian motor symptoms in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model (Wichmann et al., 1994; Baron et al., 2002).
The reversible lesion hypothesis also fit well with the prevailing model of basal ganglia function. The cortical-basal ganglia-thalamo-cortical loop had been divided into a direct pathway (cortex-striatum-GPi/SNr-thalamus), which functioned to initiate and facilitate voluntary movement, and an indirect pathway (cortex-striatum-GPe-STN-GPi/SNr-thalamus) which inhibits movement (Penney and Young, 1983; Parent and Hazrati, 1995b; 1995a)(Figure 3). D1-receptor-expressing striatal medium spiny neurons (MSNs) project primarily to the direct pathway and D2-receptor-expressing MSNs project primarily to the indirect pathway (Alexander and Crutcher, 1990). Dopaminergic input from the substantia nigra pars compacta (SNc) to the striatum increases activity in the direct pathway via D1 receptors and decreases activity in the indirect pathway via D2 receptors, facilitating movement (Gerfen et al., 1990). In addition to the motor system, multiple parallel circuits exist that are thought to subserve oculomotor, limbic and associative functions but maintain this same fundamental organization (Alexander et al., 1986; 1990; Middleton and Strick, 2000; Kelly and Strick, 2004; Hoshi et al., 2005; Postuma and Dagher, 2006; Jung et al., 2014).

Over the years, additional, functionally important pathways were recognized. The hyperdirect pathway consists of a direct excitatory input from the cortex to the subthalamic nucleus (Nambu et al., 2000; Tokuno and Nambu, 2000) and is thought to function in conflict-related response inhibition (Frank et al., 2007). The PPN is a part of the mesencephalic locomotor region that has reciprocal connections with the STN, GPe, GPi and the thalamus (Mena-Segovia et al., 2004) and is an experimental target of DBS therapy for Parkinson’s disease with a potential role in the treatment of axial symptoms (Stefani et al., 2007; Pereira et al., 2008; Moro et al., 2010). Other projections, for example the mixed GABAergic and cholinergic inhibitory projection from GPe to frontal cortex (Bolam et al., 1986; Ingham et al., 1988; Sarter and Bruno, 2002; Furuta et al.,
Mechanisms of deep brain stimulation (Saunders et al., 2015), are also likely functionally important, although they have received less attention in pathophysiologic models of movement and psychiatric disease.

In the classical model, movement disorders were conceptualized as hyperkinetic (e.g., hemiballism, dyskinesia, chorea) due to relative direct pathway overactivation or hypokinetic (e.g., Parkinson’s disease) due to relative indirect pathway overactivation (Penney and Young, 1983; Young and Penney, 1989; DeLong, 1990). The core validity of this model were confirmed in recent optogenetic experiments in a rodent model in which striatal direct or indirect pathway medium spiny neurons were selectively activated with resulting alleviation or exacerbation of parkinsonism, respectively (Kravitz et al., 2010). Similarly, a functional lesion induced by high-frequency DBS in either the STN or GPi would be expected to decrease GPi output to thalamus, promoting movement and alleviating parkinsonism.

Early experimental evidence supported the hypothesis that DBS inhibits neuronal activity at the site of stimulation. Intraoperative recordings in the GPi (Dostrovsky et al., 2000) and STN (Filali et al., 2004; Welter et al., 2004) of human subjects showed decreased neuronal spike rates during stimulation. This somatic inhibition may develop via several mechanisms. In vitro, high-frequency stimulation can cause sustained depolarization of neural membranes, inactivating sodium channels (Benazzouz et al., 1995; Beurrier et al., 2001; Magariños-Ascone et al., 2002) and increasing potassium currents (Shin et al., 2007) preventing the initiation or propagation of action potentials (i.e., depolarization block). Additionally, DBS may act through a synaptic mechanism, by activating inhibitory presynaptic terminals on afferents to the cell body. The time course of neuronal inactivation (100 ms after stimulation onset) during GPi stimulation supports the hypothesis that inhibition occurs through the release of the inhibitory neurotransmitter GABA from striatal and GPe afferents to the GPi (Dostrovsky et al., 2000). This would also explain the observation that DBS has been reported to cause local activation rather than inhibition in regions
that have primarily excitatory input such as Vim (Dostrovsky and Lozano, 2002) as well as for some STN neurons (Tai et al., 2003).

In contrast to the observation that soma near the stimulating electrodes are inhibited, evidence accumulated that axons and dendrites in the area of stimulation were activated, leading to an increase in the frequency of action potential output from the region of interest and representing a dissociation between neuronal somatic and axonal activity (Nowak and Bullier, 1998; Dostrovsky et al., 2000; Vitek, 2002; Anderson et al., 2004; McIntyre et al., 2004b).

Computational models suggest that axons and dendrites have lower stimulation thresholds than soma, and so most somatic effects are probably due to propagation of stimulation effects from the membranes of its local arborization rather than on the soma itself (McIntyre et al., 2004a). In the MPTP parkinsonian primate model, neuronal activity in the GPi increased during clinically effective STN DBS, consistent with an increase in excitatory output from the STN (Elder et al., 2003). In humans undergoing STN DBS implantation, microdialysis during clinically effective DBS resulted in increased extracellular cGMP concentration in the putamen, GPi (Stefani et al., 2005; 2006; 2011) and SNr (Galati et al., 2006). Extracellular cGMP is an indirect marker of local glutamatergic synaptic input, consistent with stimulation increasing STN output (Fedele and Raiteri, 1999). In a human subject with dystonia, stimulation in the GPi resulted in net inhibition of Voa thalamus (Montgomery, 2006). There is also evidence that DBS induces action potentials in the passing afferent fibers which are in the region of stimulation (Sato et al., 2000; Anderson et al., 2004; Johnson et al., 2012), and in some cases these tracts are emerging as a principle DBS target. For example, the anterior and ventral internal capsule adjacent to the striatum is a one target used for the treatment of OCD (Machado et al., 2009; Greenberg et al., 2010). Stimulation of the fields of Forel and the ZI dorsal to the STN appears to mediate at least some of the effects of DBS (Plaha et al., 2006; Butson et al., 2011; Blomstedt et al., 2012). DBS also elicits antidromic action potentials.

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to cortex which have been observed using intracellular cortical recordings in rodents (Li et al., 2007) and by short-latency (~1 ms) evoked potentials in human subjects stimulated in the STN or Vim thalamus (Baker et al., 2002; Walker et al., 2012a; 2012b), potentially altering local activity within those regions (Ashby et al., 2001; Baker et al., 2002; MacKinnon et al., 2005; Li et al., 2007). Whereas optogenetic inhibition of excitatory STN neurons in a parkinsonian (6-hydroxydopamine or 6-OHDA lesion) rat model did not have a therapeutic effect, high-frequency selective activation of afferent fibers terminating in the STN resulted in a robust therapeutic effect and a decrease in STN neuronal activity (Gradinaru et al., 2009).

An increase in the action potential output of a target region is not necessarily incompatible with the hypothesis that high-frequency stimulation is acting similarly to a lesion. A change in the mean action potential output of a brain region is only a very coarse representation of an area’s function. Grill and others advanced the concept of an “informational lesion” whereby regularization of neural output from an area by high-frequency stimulation is equivalent to a lesion in that information normally contained in the time-varying neuronal activity cannot pass through the stimulated nucleus (Grill et al., 2004; Dorval et al., 2008). This hypothesis was recently explored in two studies in non-human primates in whom high-frequency stimulation of the GPI partially reduced encoding of joint kinematics in the GP and VLo thalamus (Agnesi et al., 2013a) and completely inhibited GPI responses to electrical stimulation of the motor cortex (Nambu, 2013).

However, regularization of neuronal activity does not obligatorily decrease information content in the network. For example, in the 6-OHDA rat model of parkinsonism, the induction of parkinsonism increased neuronal entropy while clinically effective DBS decreased entropy (Dorval and Grill, 2014). A measure of directed entropy derived from multiunit recordings suggested that information transfer was decreased in the parkinsonian state (despite increased
entropy) both between and within the GPi and SNr and that information transfer was partially recovered in the DBS ON state (despite decreased entropy). This fits within a computational framework whereby low-entropy (i.e., correlated or regular) activity is important for information transfer (Buehlmann and Deco, 2010).

**Neurochemical effects of stimulation**

In addition to the local electrical effects of DBS, there are a myriad of other neurochemical changes including DBS-induced release of neurotransmitters locally and throughout the stimulated network. DBS of the anterior thalamus for the management of seizures may depend in part on stimulation-induced release of adenosine. In a rodent seizure model, stimulation increased adenosine release in the hippocampus, and adenosine antagonists blocked the antiepileptic effect of DBS (Bekar et al., 2008; Miranda et al., 2014). Local, nonsynaptic generation of adenosine in the thalamus may also account for some of the anti-tremor effects of DBS (Bekar et al., 2008).

DBS in the caudate nucleus results in increased extracellular dopamine as measured *in vivo* via fixed potential amperometry, and stimulation of the dorsal STN or ZI also results in dopamine release in the caudate, presumably by stimulation of the nearby median forebrain bundle (Gale et al., 2013). The relevance of this finding to Parkinson’s disease is uncertain given the relative paucity of intact dopamine fibers, although high-frequency stimulation of the STN or GPi can induce dopamine release detected by microdialysis in human subjects (Zsigmond et al., 2012; Martinez et al., 2013). Clinically, the effect of DBS on Parkinson’s symptoms appears to be additive with the effect of levodopa suggesting that DBS acts via a dopamine-independent mechanism (Piboolnurak et al., 2007). Additionally, symptoms of Parkinson’s disease that worsen or are unresponsive to dopamine replacement in some subjects, such as dyskinesias or tremor, nevertheless can respond to DBS. In contrast, dopaminergic mechanisms may be relevant to the
use of STN DBS for the treatment of cervical dystonia (Ostrem et al., 2011) or OCD (Mallet et al.,
2008a). In a rodent obesity model, DBS of the nucleus accumbens (NAc) shell increased
extracellular dopamine levels as well as D2 receptor gene expression (Zhang et al., 2015). In a
rodent addiction model, NAc DBS led to decreased glutamate and increased GABA concentrations
in the ventral tegmental area, NAc, and ventral pallidum in rats which had been exposed to
morphine (Yan et al., 2013), and increased dopamine, serotonin and noradrenaline concentrations
in the prefrontal cortex (van Dijk et al., 2012) with less consistent effects on monoamines near the
site of stimulation (van Dijk et al., 2011). The DBS-mediated changes in prefrontal monoamine
signaling is a potential mechanism by which NAc DBS might alter symptoms of OCD, depression,
addiction and other neuropsychiatric disorders (Hirschfeld, 2000).

Most preclinical and clinical studies of the neurochemical effects of DBS report only short-
term effects of DBS over seconds or minutes. In contrast, neurochemical changes relevant to the
chronic effects of DBS must last years. Developing technology to chronically assess CNS
neurochemical state, and perhaps using this state as a signal for closed-loop control of DBS, is an
area of active investigation (Grahn et al., 2014).

**Role of pathologic oscillations in Parkinson’s disease**

Oscillations are a ubiquitous finding in normally functioning neural networks, are
remarkably conserved across mammalian evolution (Buzsáki et al., 2013) and are thought to
facilitate dynamic communication and plasticity between spatially disparate populations of
neurons by temporally aligning the collective synaptic activity related to a particular neural
process (Fries, 2009). Rather than being composed of a single circuit with a characteristic
oscillatory frequency, the brain is a complex combination of countless nested oscillators
functioning in parallel and in series, including intrinsic cellular membrane oscillations, oscillations arising in local microcircuits and long-range networks (Montgomery, 2010).

Pathologic oscillatory activity in sensorimotor loops between the cortex, basal ganglia, thalamus and cerebellum is thought to contribute to the motor symptoms of Parkinson’s disease, specifically tremor, bradykinesia and rigidity. Oscillations in the beta frequency band (12-30 Hz) are of particular interest in Parkinson’s disease. In healthy subjects, beta band oscillations are observed throughout the brain but are most prominent in the sensorimotor cortex and associated regions of the thalamus, basal ganglia and cerebellum (Courtemanche and Lamarre, 2005). Beta band oscillations are observed in the local field potential, in the coherence of the local field potential across brain regions, in the synchronization of single neurons with the local field potential and in the synchronization between single neurons (Hammond et al., 2007). In the motor network, beta-band oscillations are greatest in the resting state or during tonic contraction and decrease during movement where they are replaced by higher frequency oscillations in the gamma (30-100 Hz) and higher (100-500 Hz) bands called high-frequency oscillations (HFOs) (Cassidy et al., 2002; Courtemanche et al., 2003; Amirnovin et al., 2004; Labyt et al., 2005; Doyle et al., 2005b; Brown, 2007; Pogosyan et al., 2010; Jenkinson and Brown, 2011; Özkurt et al., 2011).

Computational models suggest that beta oscillations may transiently decrease the computational flexibility of the neural network, promoting maintenance of the status quo over new patterns of activity (Brittain:2014jt).

In the healthy brain, beta oscillations occur in bursts lasting 200-600 ms (Murthy and Fetz, 1996; Courtemanche et al., 2003; Spinks et al., 2008). In Parkinson’s disease there is an increase in the coherence and spread of beta oscillations compared to healthy controls and patients with dystonia (but see Starr et al., 2005; Weinberger et al., 2006; Pollok et al., 2012; Weinberger et al., 2012; Moshel et al., 2013) and these beta oscillations persist during attempted movement (Doyle
et al., 2005a; Little et al., 2012; Oswal et al., 2012). The increase in beta power is most robust in
the sensorimotor basal ganglia (STN and GPi) but is also evident in the motor cortex (Crowell et
al., 2012; de Hemptinne et al., 2013). Similar changes are seen in dopamine-depleted rodent and
non-human primate models of Parkinson’s disease (Bergman et al., 1994; Magill et al., 2001;
Mallet et al., 2008b; McCairn and Turner, 2009).

In addition to the increased prominence of beta oscillations, Parkinson’s disease is
associated with an increase in the entrainment of high-frequency oscillations (phase-amplitude
coupling) and single-neuron action potentials (spike-field coupling) to the local beta rhythm in the
cortex, STN and GPi (Schrock et al., 2009; de Hemptinne et al., 2013; Shimamoto et al., 2013; de
Hemptinne et al., 2015)(Figure 4). Although dynamic phase-amplitude coupling in motor cortex is
a normal feature of motor cortex (Miller et al., 2012), it is exaggerated in Parkinson’s compared to
subjects with dystonia or epilepsy (de Hemptinne et al., 2013). Broadband gamma and high-
frequency oscillations are thought to reflect the organization of local population spiking activity
(Manning et al., 2009; Miller et al., 2009) and to have a central role in cortical computation (Fries,
2009), although recent recordings in human STN showed that spiking activity was not correlated
with changes in local HFO power in that nucleus (Yang et al., 2014). Taken together, these results
suggest that elevated phase-amplitude coupling reflects the enslavement of local cortical
computation to the pathological, sensorimotor-circuit-wide beta oscillations, locking the network
into a computationally ineffective state.

Beta-band oscillations appear to emerge and are amplified within the parkinsonian cortico-
basal ganglia circuit. Based on resonant amplification of evoked potentials, this circuit has a
resonance frequency of around 20 Hz in parkinsonian patients (Eusebio et al., 2009).
Pharmacological lesion studies in parkinsonian non-human primates suggests that beta-band
oscillations depend critically on both cortico-STN hyperdirect projections and reciprocal
connections between the STN and GPe as pharmacologic blockade of any of these pathways attenuates beta-band oscillations (Tachibana et al., 2011; Nambu and Tachibana, 2014). In contrast, blockade of striatal projections to GPe and GPi did not attenuate beta-band oscillations (Tachibana et al., 2011), although beta-band oscillations can be induced in a non-dopamine-depleted mouse by intrastriatal cholinergic agonists (McCarthy et al., 2011). M1 gamma activity precedes STN spiking, consistent with a role of M1 HFOs in driving basal ganglia spiking (Shimamoto et al., 2013). The beta-entrainment of this M1-STN coupling appears relatively specific for Parkinson’s disease; while M1 gamma activity also precedes spiking in the STN of patients with dystonia, the gamma band activity and STN spiking were not phase locked to the beta rhythm (Shimamoto et al., 2013).

These oscillations, and the entrainment of high-frequency activity, correlate with the presence of motor symptoms between subjects and within subjects as a function of their medication state. Beta band power in the STN and GPi decreases with levodopa medication, and this decrease correlates with the magnitude of clinical improvement in bradykinesia and rigidity (but not tremor) (Brown et al., 2001; Cassidy et al., 2002; Williams et al., 2002; Weinberger et al., 2006; Kühn et al., 2008; Ray et al., 2008; Kühn et al., 2009). Phase-amplitude coupling in the STN is 100x greater in amplitude in the OFF medication vs. the ON medication state, and HFOs exhibit greater peri-movement phasic modulation in the ON medication state (López-Azcárate et al., 2010). Although changes in cortical beta power after levodopa administration have been somewhat inconsistent (Silberstein et al., 2005; Litvak et al., 2011; Whitmer et al., 2012; Melgari et al., 2014), levodopa robustly decreases phase-amplitude coupling in motor cortex (de Hemptinne et al., 2013; Shimamoto et al., 2013). Lastly, STN HFO power inversely correlates with clinical severity in PD (Wang et al., 2014). In contrast, in a non-human primate progressive dopamine depletion model of Parkinson’s disease, excessive synchronous oscillations in the pallidum...
emerged only after severe bradykinesia was observed, arguing that these pathological oscillations are not required for the expression of parkinsonism after dopamine depletion (Leblois et al., 2007).

**Role of pathologic oscillations in tremor**

Unlike for bradykinesia and rigidity in Parkinson’s disease, beta-band oscillations and phase-amplitude coupling are not robustly linked to tremor in Parkinson’s disease (Silberstein et al., 2003; Amirnovin et al., 2004; Weinberger et al., 2006; Kühn et al., 2008; Ray et al., 2008; Kühn et al., 2009). However, unlike bradykinesia and rigidity which are not inherently oscillatory phenomenon, the existence of tremor demands a neural oscillator. In both Parkinson’s and essential tremor, even tremor in the ipsilateral arm and leg are not coherent (Raethjen et al., 2000), suggesting that multiple, parallel oscillators can occur within the motor circuit in the same hemisphere. Multiple neural structures have been found to oscillate at tremor frequency or its first harmonic (4-8 or 8-16 Hz) including motor cortex (Timmermann et al., 2003; Shimamoto et al., 2013), STN (Rodriguez-Oroz et al., 2001; Reck et al., 2009; Weinberger et al., 2009; Rodriguez-Oroz et al., 2011; Hirschmann et al., 2013; Shimamoto et al., 2013), GPi (Bergman et al., 1998; Hurtado et al., 1999; Magnin et al., 2000) and the cerebellar-receiving thalamus (Vim) (Lenz et al., 1994; Magnin et al., 2000; Hua and Lenz, 2005). In essential tremor, similar oscillations are seen in Vim (Hua and Lenz, 2005). However, for each of these observations the possibility remains that the tremor-synchronized activity is secondary to sensory feedback from the tremulous limb, rather than the tremor generator, *per se.*

The origin of the oscillatory activity remains uncertain, although the most prominent hypotheses center on cerebellothalamic bursting inputs that drive the thalamic tremor-synchronized oscillations, analogous to those recorded in the cat harmaline model of essential
tremor (de Montigny and Lamarre, 1973). In an fMRI study of Parkinson’s tremor, activity in the cerebellar-thalamic circuit correlated closely with tremor amplitude (Helmich et al., 2011). In contrast, the presence of tremor in Parkinson’s disease was most closely associated with pallidal (but not striatal) dopamine depletion, suggesting a model whereby pallidal dopamine depletion allows for tremor-driving oscillations to arise in the cerebellothalamic circuit.

**DBS disrupts pathological oscillations to treat tremor, rigidity and bradykinesia**

Several line of evidence suggest that disruption of beta-band oscillations underlies some of the DBS effect on bradykinesia and rigidity. Placement of the DBS electrode in an area of coherent beta oscillations recorded during DBS electrode implantation is predictive of subsequent clinical response to DBS (Zaidel et al., 2010). High-frequency STN DBS suppresses local beta oscillations in a manner that lingers after DBS cessation, analogous to DBS clinical effects (Wingeier et al., 2006; Kühn et al., 2008; Bronte-Stewart et al., 2009; Giannicola et al., 2010; Eusebio et al., 2011) (Figure 4). High-frequency DBS of the STN also decreases beta-band oscillations and phase-amplitude coupling in the GPi (Brown et al., 2004), motor cortex (Devos et al., 2004; Silberstein et al., 2005; de Hemptinne et al., 2013; 2015) and STN-cortical beta coherence (Kühn et al., 2008) (Figure 4). GPi DBS reduced beta oscillations in the GPi (Bar-Gad et al., 2004; McCairn and Turner, 2009) and motor cortex (McCairn and Turner, 2015). In contrast to high-frequency stimulation, STN stimulation at beta-frequencies, which increases beta-band oscillations (Brown et al., 2004), worsens bradykinesia (Chen et al., 2007; Eusebio et al., 2008).

If abnormal oscillatory activity is at the root of Parkinsonian motor symptoms, then stimulation patterns designed specifically to disrupt this oscillatory activity should be at least as good as, if not superior, to continuous, high-frequency DBS. Little et al. tested this directly in 8 PD patients who had been acutely implanted with externalized DBS electrodes, which allowed for...
application of stimulation in response to real-time measurements of beta-oscillation power.

Delivery of high-frequency STN DBS triggered on an STN beta power threshold set to achieve 50% stimulation on time resulted in a 50% improvement in blinded motor ratings compared to traditional, continuous high-frequency stimulation and was superior to an randomly delivered stimulation with a similar on time (Little et al., 2013)(Figure 5). It remains to be seen if similar closed-loop strategies will perform in ambulatory subjects given the natural beta fluctuations associated with movement (Quinn et al., 2015).

In an MPTP primate model of Parkinson’s disease, short, ~50 ms bursts of 130 Hz stimulation were delivered to the Gpi triggered on single-neuron action potentials in motor cortex (Rosin et al., 2011). Using measures of movement speed and tremor, this cortex-triggered DBS was superior to continuous, high-frequency stimulation of the Gpi. Importantly, this effect critically depended on the latency between the cortical action potential and the Gpi stimulation. Latencies of 10, 20 or 40 ms were ineffective, whereas a latency of 80 ms was highly effective. Stimulation at 80-ms latency uniquely reduced oscillatory power in the 9-15 Hz frequency range in both cortex and Gpi, and reduced firing rates in the Gpi. This result offers compelling evidence that the precise timing of stimulation relative to the underlying oscillations was critical to the clinical effect, and indirectly supports the importance of cortical input in driving pathological low-frequency oscillations. However, as triggering on other nodes in the cortico-thalamic-basal ganglia loop was not studied, it is not known whether this efficacy was unique to triggering on motor cortex.

An alternative approach is the asynchronous delivery of stimulation at spatially separated electrode contacts, termed coordinated reset neuromodulation, that is designed to desynchronize local neuronal populations with respect to the dominant slow (theta or beta) oscillation (Figure 5). The concept, backed by computational modeling, is that by forcing local populations out of pathologic synchrony, the network will settle back into a desynchronized state and that over time...
the network can in effect be trained out of its abnormal synchrony (Popovych and Tass, 2012). A test of this approach in an MPTP primate showed sustained relief of bradykinesia lasting several days after cessation of coordinated reset stimulation, as opposed to effects lasting less than 30 minutes after standard high-frequency DBS (Tass et al., 2012). A preliminary test of this approach in six patients with Parkinson’s disease and STN DBS leads was recently conducted with further promising results (Adamchic et al., 2014). Coordinated reset neuromodulation was applied intermittently in two sessions per day, each less than two hours long, over a period of three days. The authors observed a cumulative decrease in beta band power and a correlated improvement of motor performance. These effects were also long-lasting, persisting overnight despite the lack of overnight stimulation.

Despite the converging lines of modeling and experimental evidence that the clinical effects of DBS are in part mediated by disruption of pathological oscillations, the evidence linking the two remains correlational. One could imagine an experimental intervention that alters neuronal synchrony but leaves other properties of the network activity, such as average firing rate, patterns of time-varying firing rates, entropy, etc., unchanged. Notwithstanding the inherent challenge of experimentally separating these fundamentally interrelated features, this highlights the need for improved tools to record and manipulate neural activity at fine temporal and spatial scales.

**Why high frequency?**

For most applications, DBS has been found empirically to be most effective at high frequency (> 130 Hz). In essential tremor, stimulation between 5-50 Hz worsened tremor or was ineffective, while stimulation > 100 Hz is effective (Grill et al., 2004; Kuncel et al., 2006; Ushe et al., 2006; Pedrosa et al., 2013). In PD, DBS at 5-10 Hz worsens bradykinesia, stimulation at 30-100 Hz is generally ineffective and stimulation at 130-200 Hz is effective (Moro et al., 2002; Timmermann
et al., 2004). In contrast, there is more limited evidence that 60-70 Hz stimulation can be effective in focal and generalized dystonia (Alterman et al., 2007; Kim et al., 2012; Velez-Lago et al., 2012) and Parkinson’s disease (Khoo et al., 2014). In MPTP primate models, burst stimulation of the GPi at 80 Hz has been reported to be effective (Baker and Vitek, 2011). In particular, dystonia and dyskinesia may respond more effectively to lower frequencies than rigidity and tremor (Merola et al., 2013). In Parkinson’s disease there may be specific low frequencies that are effective for individual patients which can only be discovered through extensive empirical testing that is not routinely performed in clinical practice (Huang et al., 2014). Other targets, like the PPN for Parkinson’s disease are typically stimulated at lower frequencies (~25 Hz) (Hamani et al., 2011).

There is presently no unifying hypothesis as to why different individuals and targets require different frequencies (for review see Birdno and Grill, 2008). Based on the hypothesis that DBS in PD is effective by increasing the gamma/beta power ratio that is decreased in PD, Tsang et al. customized the stimulation frequency to each patient’s intrinsic gamma frequency and found it was no more effective than standard high-frequency stimulation at 130 Hz (Tsang et al., 2012). Computational modeling of coordinated reset stimulation suggested that optimal desynchronization of the theta and beta oscillations occurs when coordinated reset cycles are aligned with the dominant LFP rhythm so as to maximally distribute the phases of the spiking neuronal subpopulations relative to that dominant rhythm. Whereas high-frequency stimulation may attenuate a range of low-frequency rhythms, lower frequency stimulation may allow pathologic oscillations to pass in the interpulse intervals unless stimulation is precisely aligned with the pathologic oscillation.

Alternatively, high-frequency stimulation may shift the intrinsic resonant frequency of the circuit. Garcia et al. proposed that antidromic action potentials in cortico-subthalamic projections induced by high-frequency STN DBS would preferentially disrupt slow cortico-subthalamic
projections over fast ones, because slow fibers are more susceptible to antidromic action potential collisions due to the slower velocity and thus longer duration of the antidromic action potential (Garcia et al., 2013). By functionally removing the slowest cortical projections, the latency of the cortico-basal-ganglia-thalamo-cortical loop shortens and the resonant frequency elevates out of the range that supports tremor. This model awaits empiric testing.

How critical is the regularity of high-frequency stimulation? Although current DBS IPGs can only deliver regular pulse trains, investigators have used custom pulse generators connected to externalized DBS leads to test temporally irregular pulse sequences. For a given mean stimulation frequency, irregular stimulation trains were shown to be less effective than regular stimulation trains to treat tremor in essential tremor (Birdno and Grill, 2008) and bradykinesia in Parkinson’s (Dorval et al., 2010). In subsequent experiments the decreased efficacy of irregular trains was shown to be related to the long pauses in the irregular trains used rather than the irregularity, per se. Irregular stimulus trains that avoided long pauses were in fact superior to regular high-frequency stimulation for the treatment of finger-tapping bradykinesia in Parkinson’s disease (Brocker et al., 2013) (Figure 5C). The degree to which these spike trains disrupted beta oscillations in a simple computational model of the basal ganglia correlated with their effect on finger-tapping bradykinesia in PD patients. To our knowledge, the effect of these irregular trains on beta-oscillations in a parkinsonian patient or PD model system has not yet been tested.

In essential tremor, temporally irregular trains were still not as effective as regular trains, but the efficacy inversely correlated with the degree of pausing, further suggesting that the presence of pauses were the primary factor in reducing DBS efficacy (Birdno et al., 2012). A computational model suggested that the efficacy of DBS was in its suppressing burst-driver input to the thalamus from the cerebellum, and that pauses in DBS trains allowed for burst-driver inputs to pass. This is consistent with the observation that the most effective DBS location for essential tremor.
tremor is near the cerebello-thalamic afferents (Struppler et al., 1978; Jiménez et al., 2000; Kitagawa et al., 2005; Hamel et al., 2007; Herzog et al., 2007; Coenen et al., 2011).

Pathological synchrony in other disorders as targets for DBS

Although abnormal neuronal oscillations have been most rigorously implicated in the pathology of Parkinson’s disease and essential tremor, many neurologic and psychiatric disorders exhibit abnormal neuronal oscillations. If disruption of pathological oscillations is a general principle by which DBS operates, pathological oscillations themselves may represent new pathophysiological targets for DBS. In tic disorders, for example, suppression of tics was associated with increased, frontal cortical alpha-band coherence (Serrien et al., 2005) and broad premotor cortical spectral changes were reported during the premonitory phase before a tic (Almeida et al., 2015). These signals are being actively pursued as potential closed-loop stimulation control signals (Almeida et al., 2015).

In dystonia, simultaneous pallidal LFP and magnetoencephalography has identified dissociable cortical-pallidal networks coherent in distinct frequency bands: pallido-temporal (theta, 4-8 Hz), pallido-cerebellar (alpha, 7-13 Hz) and sensorimotor-cortex-pallidal (beta, 13-30 Hz) (Neumann et al., 2015). In that study, pallido-cerebellar alpha band power was negatively correlated with dystonia severity. In patients with generalized dystonia, there is a reduced beta desynchronization during movement similar to Parkinson’s disease (Crowell et al., 2012). In the GPe and GPi of patients with cervical dystonia, there is enhanced theta band oscillations in the LFP and neural spiking, and coupling of gamma power to theta phase (Silberstein et al., 2005; Moll et al., 2014). Dystonic spasms are associated with increases in broad low-frequency (3-18 Hz) power in the GPi (Liu et al., 2008).
In OCD, intraoperative LFP recordings from two patients undergoing STN DBS showed a significant increase in low-frequency (1-12 Hz) anterior STN oscillatory activity during acute OCD symptoms, although the specificity of this finding is uncertain (Bastin et al., 2014). Compared to PD patients, STN neurons in OCD patients displayed more theta (4-11 Hz) activity (Welter et al., 2011). OCD symptom severity also correlated with higher intraburst frequency and increased oscillations in low frequency bands in STN neurons (Welter et al., 2011). Lastly, DBS of the nucleus accumbens reduced excessive prefrontal-striatal resting state functional connectivity and reduced prefrontal low-frequency (2-5 Hz) oscillations associated with symptom-provoking stimuli (Fige et al., 2013).

Pursuing novel neurophysiologic signatures as targets for DBS will require continued, basic research to better understand the role of neuronal synchrony in both normal brain function and in illness, as well as a refined ability to use stimulation to target pathological synchrony while preserving normal neural dynamics.

**Synaptic plasticity and network reorganization**

DBS effects that emerge over minutes to days likely result at least in part from synaptic plasticity-related changes in the stimulated neural network; such network changes are occur over similar time scales in natural behaviors such as learning (Caroni et al., 2014). High-frequency stimulation of STN in rat brain slices induced varied forms of synaptic plasticity in different subpopulations of STN neurons including short-term potentiation (STP), long-term potentiation (LTP) and long-term depression (LTD) (Shen et al., 2003). In dopamine depleted rats, high-frequency stimulation induced short-term depressions (STD) and LTD, an effect which was abolished by treatment of the slice with a dopamine agonist (apomorphine) suggesting that stimulation-related synaptic plasticity is sensitive to dopaminergic state (Yamawaki et al., 2012).
In contrast, in human subjects with Parkinson’s disease, a study of STN-stimulation evoked potentials in SNr showed that LTP-like potentiation of evoked potentials was obtained when patients were treated with levodopa, but not when their levodopa was withheld (Prescott et al., 2009). Although these results highlight the potential for DBS-like stimulation to induce synaptic plasticity, to date there is scant direct evidence that any of these synaptic changes underlie the clinical effects of DBS. However, a recent study in a rodent addiction model used low-frequency stimulation of the nucleus accumbens paired with a dopamine receptor D1 antagonist to selectively depotentiate excitatory inputs on D1-expressing medium spiny neurons, with a resulting reversal of cocaine-evoked plasticity (Creed et al., 2015). This approach represents a novel use of combined pharmacology and DBS to specifically shape neural plasticity, and a potential model for plasticity-targeted DBS for other disorders.

Imaging studies using functional MRI (fMRI), positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have also provided a window into the global and long-term changes in network activity due to DBS (Tang and Eidelberg, 2013) (Figure 6). In non-human primates, STN DBS increases fMRI BOLD activation in a broad sensorimotor network including sensorimotor, supplementary motor and cingulate cortex, insula, caudate nucleus, pedunculopontine nucleus and cerebellum (Min et al., 2014). Patients with Parkinson’s disease exhibit a particular spatial covariance pattern of glucose metabolism on fluoro-D-glucose (FDG)-PET imaging, called the PD-related metabolic pattern (PDRP), which includes hypermetabolism in the pons, globus pallidus and thalamus, and hypometabolism in the premotor cortex, supplementary motor area, and parietal association areas (Ma et al., 2007; Wu et al., 2013). The expression of PDRP can be quantified and has been shown to correlate with clinical disease severity (Eidelberg, 2009). Both GPi (Fukuda et al., 2001) and STN DBS (Asanuma et al., 2006; Trost et al., 2006) have been reported to decrease PDRP expression, suggesting that both
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Treatments may normalize network activity in a similar way. Tremor-predominant Parkinson’s patients with Vim thalamic DBS exhibit a different change in the spatial covariance pattern between DBS on and off, termed PD tremor-related metabolic pattern (PDTP), that correlates with tremor severity and is distinct from PDRP (Mure et al., 2011). PDTP is characterized by increased activity in the cerebellar dentate nucleus, primary motor cortex, and to a smaller degree, the striatum (Mure et al., 2011). Whereas Vim DBS modulated PDTP expression but not PDRP expression, STN DBS reduced the activity of both PDTP and PDRP (Mure et al., 2011), consistent with the observation that Vim DBS treats tremor only, whereas STN DBS treats tremor, bradykinesia and rigidity. Similarly, multiple SPECT studies have provided evidence that STN and GPI DBS both lead to the normalization of abnormal regional cerebral blood flow (rCBF) patterns associated with Parkinson’s disease (Antonini et al., 2003; Cilia et al., 2009; Tang and Eidelberg, 2013). Others have argued that these patterns of metabolic changes in PD are nonspecific and an artifact of global mean normalization, in which regional tracer uptake is normalized to the global mean of all grey matter voxels (Borghammer et al., 2009; but see Dhawan et al., 2012). By using alternative methods of normalization (including normalization to the mean of all white matter voxels), they instead report widespread cortical hypometabolism in untreated, newly diagnosed PD patients (Berti et al., 2012), early stage PD patients (Borghammer et al., 2010) and later stage PD patients (Moeller et al., 1999). This remains an area of unsettled debate.

The above results demonstrate that, perhaps unsurprisingly, continuous DBS results in network-level changes in activity. However, these could reflect acute stimulation-related effects alone rather than network plasticity. In a recent single-subject study, a patient underwent diffusion tensor imaging and resting-state fMRI both pre-DBS and after five months of DBS at which time the system was explanted due to emotional lability and motor side effects (van Hartevelt et al., 2014). Using a graph theoretic measure of nodal efficiency, the authors argue that
the structural connectivity of the subject’s brain post-DBS had shifted towards values more typical of healthy controls. Future studies will be required to assess whether these changes are reproducible, or whether they emerge from appropriately therapeutic DBS lead placement.

Numerous PET imaging studies have also demonstrated long-term changes in metabolic activity after DBS including DBS of the anterior limb of the internal capsule for OCD (Rauch et al., 2006; Suetens et al., 2014), GPi DBS for dystonia (Kumar et al., 1999; Yianni et al., 2005), PPN DBS for PD (Strafella et al., 2008), and subgenual cingulate DBS for depression (Mayberg et al., 2005; Lozano et al., 2008). Successful subgenual cingulate DBS was shown to reverse some abnormalities seen in depressed patients at baseline (elevated subgenual cingulate blood flow, and decreased prefrontal blood flow) (Mayberg et al., 2005) similar to the changes seen in patients responsive to antidepressant medication (Mayberg et al., 2000). Subgenual cingulate DBS-induced changes in metabolic activity include decreases in orbital, medial frontal and insular cortex, and increases in lateral prefrontal, parietal, anterior mid-cingulate, and posterior cingulate areas (Lozano et al., 2008).

**Neuroprotection and neurogenesis**

It has been hypothesized that DBS could be neuroprotective in Parkinson’s disease by slowing the degeneration of dopaminergic neurons in the substantia nigra (Charles et al., 2008). However, several observations suggest that DBS does not arrest or reverse Parkinson’s disease. Clinically, Parkinson’s disease symptoms continue to progress despite effective DBS therapy (Krack et al., 2003; Hilker et al., 2005; Fasano et al., 2010; Merola et al., 2011; Lilleeng et al., 2014), and dopamine terminal loss continues to accrue at a rate similar to non-DBS-treated Parkinson’s patients as assessed using $^{18}$F-fluorodopa (F-dopa)-PET (Hilker et al., 2005). One study compared 106 PD patients who underwent DBS implantation to 41 PD patients who chose to have medical
management only (Ngoga et al., 2014) and showed that DBS-treated patients had a significantly longer survival. However, the non-randomized design was sensitive to selection bias. Furthermore, DBS may improve survival by minimizing Parkinson’s motor disability allowing for maintenance of a healthier lifestyle. There is evidence from a postmortem study of Parkinson’s patients that DBS leads to increased neuronal precursor cell proliferation in the subventricular zone of the lateral ventricles, the third ventricle lining and the tissue surrounding the DBS leads in these patients as compared to age-matched normal controls and Parkinson’s patients who did not undergo DBS implantation (Vedam-Mai et al., 2014). The clinical significance of these neural precursors is uncertain.

Stronger evidence for a neuroprotective effect of DBS comes from animal models. Intermittent STN DBS (1 hour of high-frequency stimulation daily for 3 months) improves the survival of SNc neurons in a parkinsonian rat model (6-OHDA lesion) (Temel et al., 2006). In these experiments, bilateral STN DBS electrodes were implanted in rats during the same surgical session as bilateral striatal 6-ODHA injections were performed (Temel et al., 2006). Similar results have been described in another STN DBS study and for STN lesions (Benazzouz and Benabid, 1996; Satoshi Maesawa et al., 2009). This protective effect was also seen when the STN DBS was initiated 2 weeks after ipsilateral striatal 6-OHDA injection, a period of time in which neuronal degeneration is expected to continue in this parkinsonian model. Although SNc neurons were greater in number with DBS, dopaminergic neurite density in the striatum was unchanged (Spieles-Engemann et al., 2010). In an MPTP primate Parkinsonian model, investigators demonstrated that both STN lesioning (kainic acid lesion) and high-frequency STN DBS results in increased survival of dopaminergic cells in the SNc compared to controls, whether the animals were treated before or after MPTP lesioning (Wallace et al., 2007). They postulated that this protective effect was due to a reduction in glutamate excitotoxicity from STN hyperactivity in the
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Alternatively, STN DBS has been shown to induce the neuroprotective growth factor, brain-derived neurotrophic factor (BDNF), in the substantia nigra, Gpi, and M1 cortex (Spieles-Engemann et al., 2011) and Gpi DBS has been reported to alter splice isoforms of glial derived growth factor (GDNF) expression in the basal ganglia in a non-parkinsonian rat model (Ho et al., 2014). The potential neuroprotective effects of DBS remain an area of active investigation; a pilot clinical trial of STN DBS for early Parkinson’s disease has been conducted (Kahn et al., 2012) and a larger definitive trial is planned.

In an analogous fashion, stimulation of the anterior nucleus of the thalamus induces hippocampal neurogenesis in rodent models (Toda et al., 2008), and a phase 1 trial suggested that chronic, high-frequency stimulation of the fornix can reverse some of the temporoparietal hypometabolism seen Alzheimer’s and might improve cognitive function (Laxton et al., 2010). A larger follow-up trial of forniceal DBS for Alzheimer’s dementia is underway.

The future of neuromodulation

The fundamental approach to DBS—continuous, temporally regular stimulation to a single (often bilateral) target—has remained largely unchanged since the late 1980s, and was derived primarily from empiric observation rather than mechanistic understanding. This is poised to change. The clinical benefits of DBS emerge via multiple, non-exclusive mechanisms of action including the shaping of peri-electrode electrical activity via electrical and neurochemical mechanisms, modulation of neural network activity and plasticity, and possibly by influencing neurogenesis and neurodegeneration directly. In recent years our understanding has advanced in all of these areas. Translating this knowledge into improved therapeutics will require investment in well-controlled, translational and interdisciplinary preclinical and clinical studies.
The next generation of DBS systems promises to be more flexible in stimulation parameters and patterns, to allow greater steering of stimulation current and to be able to respond to ongoing neural activity. In addition, other techniques such as optogenetic neuromodulation and DREADDS (Designer Receptors Exclusively Activated by Designer Drugs), hold promise for manipulating neural network activity in ways that are distinct from electrical stimulation, but will ultimately target the same pathological neural circuits. Together these innovations hold enormous promise to improve the efficacy and side effect profile of neuromodulation for the treatment of neurologic and psychiatric disease, and to open up a range of new neuropsychiatric conditions to neuromodulation therapy.

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<th>Indication</th>
<th>Target(s)</th>
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Table 1. A partial list of indications and targets for deep brain stimulation therapy, divided by approved and experimental indications. Within the approved indications, less well validated targets are included in parentheses. Many of the experimental indications have been explored only in small series without randomization. Seminal clinical trials are referenced and for investigational targets, relevant reviews that summarize the clinical motivation and pilot clinical series are cited. ALIC, anterior limb of the internal capsule; ATN, anterior thalamic nucleus; CC, corpus callosum; CG25, cingulate area 25 or subgenual cingulate; CM, centromedian nucleus of the
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thalamus; CN, caudate nucleus; CT, central thalamic; GPi, globus pallidus internus; ITP, inferior thalamic peduncle; LC, locus of caudate; LH, lateral hypothalamus; LoC, locus coeruleus; MB, mammillary bodies; NAc, nucleus accumbens; NBM, nucleus basalis of Meynert; PAG, periaqueductal grey; PH, posterior hypothalamus; PPN, pedunculopontine nucleus; STN, subthalamic nucleus; VC/VS, ventral capsule / ventral striatum; Vim, ventral intermediate nucleus of the thalamus; VMH, ventromedial hypothalamus; VPL, ventral posterolateral thalamus; VPM, ventral posteromedial thalamus; VTA, ventral tegmental area.

*Neuropace RNS detects and stimulates at the seizure focus, customized to each patient

References: 1Fisher et al., 2010; 2Bergey et al., 2015; 3Benabid et al., 1996; 4Koller et al., 1997; 5Limousin et al., 1999; 6Sydow et al., 2003; 7Pahwa et al., 2006; 8Blomstedt et al., 2010; 9Zhang et al., 2010; 10Mallet et al., 2008a; 11Denys et al., 2010; 12Greenberg et al., 2010; 13Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001; 14Deuschl et al., 2006; 15Schüpbach et al., 2007; 16Weaver et al., 2009; 17Follett et al., 2010; 18Williams et al., 2010; 19Okun et al., 2012; 20Deuschl and Agid, 2013; 21Odekerken et al., 2013; 22Schuepbach et al., 2013; 23Kupsch et al., 2006; 24Kiss et al., 2007; 25Vidailhet et al., 2009; 26Ostrem et al., 2011; 27Kuhn et al. 2013; 28Laxton et al., 2010; 29Lipsman et al., 2013; 30Starr, 2013; 31Pereira et al., 2013; 32Pedersen et al., 2013; 33Mayberg et al., 2005; 34Schlaepfer et al., 2008; 35Malone et al., 2009; 36Kennedy et al., 2011; 37Bewernick et al., 2012; 38Lozano et al., 2012; 39Dougherty et al., 2014; 40Schiff et al., 2007; 41Halpern et al., 2008; 42Whiting et al., 2013; 43Mikell et al., 2009; 44Cheung and Larson, 2010; 45Viswanathan et al., 2012.
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FIGURE LEGENDS

Figure 1: Various disease symptoms exhibit different latencies in response to DBS treatment, supporting the theory that different mechanisms of DBS are responsible, including immediate neuromodulation effects, synaptic plasticity, and long-term effects that may involve anatomical reorganization. *DBS exerts a therapeutic effect on tremor within seconds, in both Parkinson's disease and in essential tremor. In the case of depression, it has been reported that stimulation induced immediate positive subjective experiences that varied in individual patients including feelings of calm, lightness, heightened awareness, etc. (Mayberg et al., 2005). Patients had improved interest, energy and psychomotor speed within days of stimulation, but maximal improvements in mood, anxiety, sleep and somatic symptoms were achieved after months of stimulation (Mayberg et al., 2005; Lozano et al., 2008).

Figure 2. A, Typical placement of a DBS electrode (Medtronic model 3387) in the subthalamic nucleus and zona incerta (green) near the thalamus (blue), substantia nigra (orange and yellow), and striatum/pallidum (red); adapted with permission from (Mai et al., 2008). B, The electric field produced when in a “monopolar” configuration, in which a single electrode contact is the cathode and the IPG case, located distantly in the chest, is the anode. The field is roughly spherical in shape. C, Electric field in a “bipolar” configuration in which the anode and cathode are both on electrode contacts. The bipolar configuration generates a more focused electric field concentrated between the anode and cathode. Using varied combinations of anodes and cathodes, the field of stimulation can be molded. Abbreviations: Amg, amygdala; APr, anteroprincipal n.; Cl, claustrum; ec, external capsule; ex, extreme capsule; fx, fornix; GPe, globus pallidus externus; GPi, globus pallidus internus; H1/2, fields of Forel; LV, lateral ventricle; MD, medial dorsal n.; opt, optic tract; PuV, ventral putamen; Rt, reticular n.; SNC, substantia nigra pars compacta; SNr, substantia nigra pars
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Figure 3. Cortico-basal-ganglia-thalamo-cortical circuitry. The direct, indirect, and hyperdirect pathways are indicated. Red lines denote inhibitory connections, blue lines denote excitatory connections, green lines denote mixed cholinergic, GABAergic and glutamatergic connections. Of note, the PPN also exhibits anatomic projections to striatum and cortex (omitted for clarity).

Abbreviations: GPe, globus pallidus externus; GPi, globus pallidus internus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; PPN, pedunculopontine nucleus; STN, subthalamic nucleus.

Figure 4. High-frequency STN DBS reduces phase-amplitude coupling in the cortex and beta power in the STN in humans with Parkinson's disease. A, Motor cortex LFPs before, during and after STN DBS and log power spectral densities. DBS reduces the peak beta power along with a broadband decrease in low-frequency power. B, Single-subject reduction in phase-amplitude coupling in motor cortex during DBS, which partially recovers within 4 minutes of DBS cessation. Phase-amplitude plots show how fluctuations in power as a function of frequency (y-axis) are entrained to background LFP phase, and demonstrate that gamma-band power (100-200 Hz) is entrained to beta (15-30 Hz) phase. C, Single-subject example showing prolonged (> 4 minutes) suppression of phase-amplitude coupling after cessation of DBS. D, Time-frequency plot of STN LFP beginning at cessation of high-frequency DBS. Beta oscillations are suppressed during DBS, and reemerge over ~1 minute after DBS is stopped. Reproduced with permission, A-C (de Hemptinne et al., 2013); D, (Kühn et al., 2008).
Figure 5. Novel approaches to DBS. A, Adaptive or closed-loop stimulation. Simulated STN LFP data (upper panel) showing beta-band power fluctuating over time. In adaptive or closed-loop stimulation, electrical stimulation (bottom panel) is delivered only when a control signal, in this case beta-band power (middle panel), is elevated above a threshold (Little et al., 2013). Other potential control signals in Parkinson’s disease include phase-amplitude coupling in motor cortex or the basal ganglia or M1 spiking (Little and Brown, 2012). B, Coordinated reset neuromodulation (Adamchic et al., 2014). Short bursts of 3-5 stimulation pulses at 130 Hz are delivered in a staggered fashion to three adjacent contacts of the STN DBS electrode (labeled 0, 1 and 2), with stimulation times staggered to three different phases of the dominant low-frequency rhythm (in this case, 10 Hz). Contacts are stimulated in a random order such that each contact is stimulated in an aperiodic fashion. Cycles of stimulation on and off are cycled in a 3:2 ratio that computational studies suggest is optimal for facilitating desynchronization of the population, which evolves during the off periods (Lysyansky et al., 2011). C, Temporally irregular stimulation (here, a log-uniform distribution of instantaneous spike rates between 90-380 Hz) is superior to temporally regular stimulation in one study of bradykinesia in Parkinson’s disease (Brocker et al., 2013), but inferior for the suppression of tremor (see text for discussion) (Birdno et al., 2012).

Figure 6: FDG-PET identifies candidate neural networks underlying bradykinesia, rigidity and tremor in Parkinson’s disease. Comparison between PD-related metabolic pattern (PDRP, in green) and PD tremor-related pattern (PDTP, in red), which are spatial covariance patterns derived from FDG-PET imaging studies of PD patients and tremor-predominant PD patients, respectively (Mure et al., 2011). Areas of overlap are denoted in yellow. PDTP is characterized by increased metabolic activity in the anterior cerebellum, dentate nucleus, primary motor cortex,
and to a lesser extent, caudate and putamen. PDRP is characterized by relative hypermetabolism in the globus pallidus, putamen, thalamus, pons, cerebellum, and sensorimotor cortex, with metabolic decreases in the lateral premotor cortex and parieto-occipital association regions. Reproduced with permission (Mure et al., 2011).
Figure 1
Figure 4

A Prestimulation

B DBS ON

C Post stimulation

D MI (z-score)

E Log power

F Frequency for phase (Hz)

G Frequency for amplitude (Hz)

H MI (z-score)

I Time (sec)

J Frequency (Hz)

K 100 ms

L 100 µV

M DBS ON

N Prestimulation

O Immediately

P 2 minutes

Q 4 min

R 17 min

S 30s

T 30s

U 30s

V 30s

W 30s

X 30s

Y 30s

Z 30s
Figure 5

A
STN LFP
β power
Stimulation

B
Coordinated reset neuromodulation
β LFP

C
Temporally irregular stimulation

Adaptive stimulation
2 seconds
100 ms
100 ms
β power
STN LFP
A
Adaptive stimulation
Stimulation

Coordinated reset neuromodulation

100 ms

100 ms
Figure 6

Overlay of PDTP and PDRP Voxel Weights

z=43

y=-8

x=-2

PDTP  PDRP