MECHANISMS OF DEEP BRAIN STIMULATION

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Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol 115: 19–38, 2016. First published October 28, 2015; doi:10.1152/jn.00281.2015.—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, nonexclusive 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.

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 (PD), essential tremor, and dystonia, and it is in more limited use or under active investigation to treat a wide variety of neurological 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 DBS 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 (Fig. 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 PD 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 (Krauss et al. 2004; Yianni et al. 2003). 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 ac-
Symptoms that respond rapidly are mediated by rapidly reversible mechanisms that have their own intrinsic time courses (Fig. 1). Tics may reappear rapidly (Servello et al. 2008). However, when thalamic DBS is turned off, tics may reappear rapidly (Servello et al. 2008). However, when thalamic DBS is turned off, tics may reappear rapidly (Servello et al. 2008). However, when thalamic DBS is turned off, tics may reappear rapidly (Servello et al. 2008). However, when thalamic DBS is turned off, tics may reappear rapidly (Servello et al. 2008). However, when thalamic DBS is turned off, tics may reappear rapidly (Servello et al. 2008).

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. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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. Ticks may reappear rapidly (Servello et al. 2008). However, when thalamic DBS is turned off, tics may reappear rapidly (Servello et al. 2008).

Thalamus, CM-PIc-Voa, NAc, STN, GPi, SGZ, ITP, Vim, VPL, VPM, CM, CC, LoC, MB) (Bergey et al. 2015; Fisher et al. 2010). In the case of DBS of the ALIC for OCD, investigators reported some immediate clinical benefit (Dougherty et al. 2015). In the case of DBS of the ALIC for OCD, investigators reported some immediate clinical benefit (Dougherty et al. 2015). In the case of DBS of the ALIC for OCD, investigators reported some immediate clinical benefit (Dougherty et al. 2015). In the case of DBS of the ALIC for OCD, investigators reported some immediate clinical benefit (Dougherty et al. 2015).

Perielectrode Targets of DBS

Figure 2 illustrates the typical placement of a DBS electrode in the STN, the most commonly used DBS target for PD. 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 (Haynes and Haber 2013; Nambu et al. 2003; Zhang et al. 2010), 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 (Fig. 2). In addition, the clinician can alter the activity level and finally remission of disease with chronic stimulation in some patients (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 (ALIC) and cingulate area 25 failed to show a lasting clinical benefit (Dougherty et al. 2015). In the case of DBS of the 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. 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 (Haynes and Haber 2013; Nambu et al. 2003; Zhang et al. 2010), 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).

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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 (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 axonal processes in close proximity to the electrode (Histed et al. 2009). Action potentials in axons propagate both orthodromically (away from the soma) and antidromically (toward the soma). Larger axons and those oriented perpendicularly to the electric field are activated more readily (i.e., at lower voltages and pulse widths) than smaller axons oriented parallel to the electric field (Montgomery 2010; Rattay 1999). In theory, nonsquare stimulation waveforms, conditioning pulses, and other modifications to stimulation parameters could offer greater efficiency and selectivity for specific neural elements (Foutz and McIntyre 2010; Hofmann et al. 2011; Wongsarnpigoon and Grill 2010). However, these remain largely untested in human subjects, as clinically available IPGs deliver only cathodal-leading, charge-balanced, square-wave pulses. Additionally, novel electrodes that allow stimulation fields that are asymmetric around the electrode, sometimes called current steering, may offer further control over the specific neural elements stimulated (Contarino et al. 2014; Martens et al. 2011).

**DBS Acts as a Reversible Lesion**

Initial hypotheses about the mechanism of DBS were based on the observed similarity between the effects of high-fre-
frequency stimulation and the effects of lesions in the same regions, i.e., pallidotomy for the treatment of PD (Guridi and Lozano 1997) or capsulotomy for the treatment of OCD (Je
nike 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, chemo-
figical inhibition of the STN or GPi reduced parkinsonian motor symptoms in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model (Baron et al. 2002; Wichmann et al. 1994).

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-globus pallidus externus (GPe)-STN-GPi/SNr-thalamus] that inhibits movement (Parent and Hazrati 1995a, 1995b; Penney and Young 1983) (Fig. 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; Hoshi et al. 2005; Jung et al. 2014; Kelly and Strick 2004; Middleton and Strick 2000; Postuma and Dagher 2006).

Over the years, additional, functionally important pathways were recognized. The hyperdirect pathway consists of a direct excitatory input from the cortex to the STN (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 thalamus (Mena-Segovia et al. 2004) and is an experimental target of

\[\text{Cortico-basal-ganglia-thalamo-cortical circuitry. The direct, indirect, and hyperdirect pathways are indicated. Red lines denote inhibitory connections, blue lines denote excitatory connections, and green lines denote mixed cholinergic, GABAergic, and glutamatergic connections. Of note, the pedunculo-pontine nucleus (PPN) also exhibits anatomic projections to striatum and cortex (omitted for clarity).}\]
DBS therapy for PD with a potential role in the treatment of axial symptoms (Moro et al. 2010; Pereira et al. 2008; Stefani et al. 2007). Other projections, for example, the mixed GABAergic and cholinergic inhibitory projection from GPe to frontal cortex (Bolam et al. 1986; Furuta et al. 2004; Ingham et al. 1988; Sarter and Bruno 2002; Saunders et al. 2015), are also likely functionally important, although they have received less attention in pathophysiological models of movement and psychiatric disease.

In the classical model, movement disorders were conceptualized as hyperkinetic (e.g., hemiballismus, dyskinesia, chorea) due to relative direct pathway overactivation or hypokinetic (e.g., PD) due to relative indirect pathway overactivation (DeLong 1990; Penney and Young 1983; Young and Penney 1989). The core validity of this model was confirmed in recent optogenetic experiments in a rodent model in which striatal direct or indirect pathway MSNs 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; Magarinos-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 is 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 (Anderson et al. 2004; Dostrovsky et al. 2000; McIntyre et al. 2004b; Nowak and Buhl 1998; Vitek 2002). 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 that are in the region of stimulation (Anderson et al. 2004; Johnson et al. 2012; Sato et al. 2000), and in some cases these tracts are emerging as a principal DBS target. For example, the anterior and ventral internal capsule adjacent to the striatum is one target used for the treatment of OCD (Greenberg et al. 2010; Machado et al. 2009). Stimulation of the fields of Forel and the ZI dorsal to the STN appears to mediate at least some of the effects of DBS (Blomstedt et al. 2012; Butson et al. 2011; Plaha et al. 2006). DBS also elicits antidromic action potentials to cortex that have been observed with intracortical 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; Li et al. 2007; MacKinnon et al. 2005). Whereas optogenetic inhibition of excitatory STN neurons in a parkinsonian [6-hydroxydopamine (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 (Gradinariu 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 (Dorval et al. 2008; Grill et al. 2004). This hypothesis was recently explored in two studies in nonhuman primates in whom high-frequency stimulation of the GPi partially reduced encoding of joint kinematics in the GP and ventralis lateralis pars oralis (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 multunit recordings suggested that information transfer was decreased in the parkinsonian state (despite increased entropy) both between and within the GPI and S-Nr 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 antitremor 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 PD 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 (Martinez et al. 2013; Zsigmond et al. 2012). Clinically, the effect of DBS on PD 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 PD 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 that had been exposed to morphine (Yan et al. 2013) and increased dopamine, serotonin, and norepinephrine 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). DBS-mediated change 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 Pathological 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 dis-
resonant amplification of evoked potentials, this circuit has a
to the patholog-
ity. These oscillations, and the entrainment of high-frequency
kinesia and rigidity (but not tremor) (Brown et al. 2001; Cassidy et al.
motor symptoms be-
stant 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 min) 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 ~1 min after DBS is stopped. Reproduced with permission from de Hemptinne et al. (2013) (A–C) and Künn et al. (2008) (D).

2009), although recent recordings in human STN showed that
vation of low-frequency power.
duction, 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 min 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

Though 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; Künn et al. 2008, 2009; Ray et al. 2008; Weinberger et al. 2006; Williams et al. 2002). Phase-amplitude coupling in the STN is 100 times greater in amplitude in the OFF medication vs. the ON medication state, and HFOs exhibit greater perimovement 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 (Litvak et al. 2011; Melgari et al. 2014; Silberstein et al. 2005; Whitmer et al. 2012), levodopa robustly decreases phase-amplitude coupling in motor cortex (de Hemptinne et al. 2013; Shimamoto et al. 2013). Finally, STN HFO power inversely correlates with clinical severity in PD (Wang et al. 2014). In contrast, in a nonhuman primate progressive dopamine depletion model of PD, 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 Pathological Oscillations in Tremor

Unlike for bradykinesia and rigidity in PD, beta-band oscillations and phase-amplitude coupling are not robustly linked to tremor in PD (Amirnovin et al. 2004; Künn et al. 2008, 2009; Ray et al. 2008; Silberstein et al. 2003; Weinberger et al. 2006). 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 (Shimamoto et al. 2013; Timmermann et al. 2003), STN (Hirschmann et al.
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adaptive or closed-loop stimulation, electrical stimulation (bottom) is delivered only when a control signal, in this case beta-band power (middle), is elevated above a threshold (Little et al. 2013). Other potential control signals in PD include phase-amplitude coupling in motor cortex or the basal ganglia or MI 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 to the GPi triggered on an STN beta power threshold set to achieve 50% stimulation on time resulted in a 50% improvement in blinded motor ratings compared with traditional, continuous high-frequency stimulation and was superior to an randomly delivered stimulation with a similar on time (Little et al. 2013) (Fig. 5). It remains to be seen whether 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 PD, 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.

Fig. 5. Novel approaches to DBS. A: adaptive or closed-loop stimulation. Top: simulated STN LFP data showing beta-band power fluctuating over time. In adaptive or closed-loop stimulation, electrical stimulation (bottom) is delivered only when a control signal, in this case beta-band power (middle), is elevated above a threshold (Little et al. 2013). Other potential control signals in PD include phase-amplitude coupling in motor cortex or the basal ganglia or MI 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 to the GPi triggered on an STN beta power threshold set to achieve 50% stimulation on time resulted in a 50% improvement in blinded motor ratings compared with traditional, continuous high-frequency stimulation and was superior to an randomly delivered stimulation with a similar on time (Little et al. 2013) (Fig. 5). It remains to be seen whether 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 PD, 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). By 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 (Fig. 5). The concept, backed by computational modeling, is that by forcing local populations out of pathological 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 <30 min after standard high-frequency DBS (Tass et al. 2012). A preliminary test of this approach in six patients with PD 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 <2 h long, over a period of 3 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 and 50 Hz worsened tremor or was ineffective, while stimulation > 100 Hz is effective (Grill et al. 2004; Kuncel et al. 2006; Pedrosa et al. 2013; Ushe et al. 2006). 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- to 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 PD (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 PD there may be specific low frequencies that are effective for individual patients that 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 PD, 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 pathological oscillations to pass in the interpulse intervals unless stimulation is precisely aligned with the pathological 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 because of 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-ganglial-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 PD (Brocker et al. 2013) (Fig. 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 was 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 is near the cerebello-thamic afferents (Coenen et al. 2011; Hamel et al. 2007; Herzog et al. 2007; Jiménez et al. 2000; Kitagawa et al. 2005; Struppler et al. 1978).

Pathological Synchrony in Other Disorders as Targets for DBS

Although abnormal neuronal oscillations have been most rigorously implicated in the pathology of PD and essential tremor, many neurological 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 PD (Crowell et al. 2012). In the GPe and GPi of patients with cervical dystonia, there are enhanced theta-band oscillations in the LFP and neural spiking and coupling of gamma power to theta phase (Moll et al. 2014; Silberstein et al. 2005). 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 with 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). Finally, DBS of the NAc 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 neurophysiological signatures as targets for DBS will require continued, basic research to better understand the role of neuronal synchrony both in 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 occur over similar timescales 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 depression (STD) and LTD, an effect that 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 PD, 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 NAc paired with a dopamine receptor D1 antagonist to selective depotentiate excitatory inputs on D1-expressing MSNs, 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) (Fig. 6). In nonhuman primates, STN DBS increases fMRI BOLD activation in a broad sensorimotor network including sensorimotor, supplementary motor and cingulate cortex, insula, caudate nucleus, PPN, and cerebellum (Min et al. 2014). Patients with PD 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 (Asanuma et al. 2006; Trost et al. 2006) DBS have been reported to decrease PDRP expression, suggesting that both treatments may normalize network activity in a similar way. Tremor-predominant PD 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 (PDRP), that correlates with tremor severity and is distinct from PDRP (Mure et al. 2011). PDRP is characterized by increased 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 from Mure et al. (2011) (copyright Elsevier 2011).

Fig. 6. Fluoro-D-glucose (FDG)-PET identifies candidate neural networks underlying bradykinesia, rigidity, and tremor in PD. 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 from Mure et al. (2011) (copyright Elsevier 2011).

Neuroprotection and Neurogenesis

It has been hypothesized that DBS could be neuroprotective in PD 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 PD. Clinically, PD symptoms continue to progress despite effective DBS therapy (Fasano et al. 2010; Hilker et al. 2005; Krack et al. 2003; Lilleeng et al. 2014; Merola et al. 2011), and dopamine terminal loss continues to accrue at a rate similar to non-DBS-treated PD patients as assessed by 18F-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 nonrandomized design was sensitive to selection bias. Furthermore, DBS may improve survival by minimizing PD motor disability, allowing for maintenance of a healthier lifestyle. There is evidence from a postmortem study of PD 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 compared with age-matched normal control subjects and PD 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 h of
high-frequency stimulation daily for 3 mo) 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-OHDA injections (Temel et al. 2006). Similar results have been described in another STN DBS study and for STN lesions (Benazzouz and Benabid 1996; Maesaawa et al. 2004). This protective effect was also seen when the STN DBS was initiated 2 wk 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 result in increased survival of dopaminergic cells in the SNc compared with 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 dopamine-deficient state (Benazzouz et al. 2000; Rodriguez et al. 1998; Wallace et al. 2007). 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 nonparkinsonian 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 PD 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 I trial suggested that chronic, high-frequency stimulation of the fornix can reverse some of the tempo-motor hypometabolism seen in Alzheimer’s and might improve cognitive function (Laxton et al. 2010). A larger follow-up trial of fornical 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, nonexclusive mechanisms of action including the shaping of perielectrode 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 neurological and psychiatric disease, and to open up a range of new neuropsychiatric conditions to neuromodulation therapy.

REFERENCES


Flohmann L, Ebert M, Taas PA, Hauptmann C. Modified pulse shapes for effective neural stimulation. Front Neuroeng 4: 9, 2011.


Kühn AA, Kempf F, Brücke C, Gaynor Doyle L, Martinez-Torres I, Pogosyan A, Tottenberg T, Kupisch A, Schneider GH, Hariz M,


Effects of low-frequency functional anatomy of the basal ganglia. I. The Parent A, Hazrati LN.

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