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Network effects of deep brain stimulation

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Alhourani A, McDowell MM, Randazzo MJ, Wozny TA, Kondylis ED, Lipski WJ, Beck S, Karp JF, Ghuman AS, Richardson RM. Network effects of deep brain stimulation. *J Neurophysiol* 114: 2105–2117, 2015. First published August 12, 2015; doi:10.1152/jn.00275.2015.—The ability to differentially alter specific brain functions via deep brain stimulation (DBS) represents a monumental advance in clinical neuroscience, as well as within medicine as a whole. Despite the efficacy of DBS in the treatment of movement disorders, for which it is often the gold-standard therapy when medical management becomes inadequate, the mechanisms through which DBS in various brain targets produces therapeutic effects is still not well understood. This limited knowledge is a barrier to improving efficacy and reducing side effects in clinical brain stimulation. A field of study related to assessing the network effects of DBS is gradually emerging that promises to reveal aspects of the underlying pathophysiology of various brain disorders and their response to DBS that will be critical to advancing the field. This review summarizes the nascent literature related to network effects of DBS measured by cerebral blood flow and metabolic imaging, functional imaging, and electrophysiology (scalp and intracranial electroencephalography and magnetoencephalography) in order to establish a framework for future studies.

deep brain stimulation; electrocorticography; magnetoencephalography

DEEP BRAIN STIMULATION (DBS) provides a unique opportunity for further understanding of healthy and aberrant human brain function. DBS is the only paradigm in which specific deep brain regions may be manipulated through focal electrical stimulation while simultaneously recording brain activity. An emerging field of study has begun to elucidate how different DBS targets modulate network activity in connected brain regions.

The field of DBS has experienced substantial growth since its reestablishment in the modern era by Benabid nearly 30 years ago (Benabid et al. 1987). A wealth of clinical evidence has established a role for DBS in the management of movement disorders, including Parkinson's disease (PD) (Limousin et al. 1998b), essential tremor (ET) (Miocinovic et al. 2013), and dystonia (Coubes et al. 2004). More recently, the use of DBS has expanded into the field of neuropsychiatry, with investigators exploring the potential of DBS to produce clinical improvement for patients with major depressive disorder (MDD) (Holtzheimer and Mayberg 2012), obsessive-compulsive disorder (OCD) (Mallet et al. 2008), Tourette syndrome

(Ackermans et al. 2011), neuropathic pain (Pereira and Aziz 2014), and addiction (Alba-Ferrara et al. 2014). Epilepsy also is an important emerging indication for DBS (Bergey et al. 2015; Salanova et al. 2015). In parallel, the technology itself is improving, with closed-loop systems and novel electrode arrays currently under development that are expected to improve the efficacy of DBS (McIntyre et al. 2015).

Despite the fact that DBS has been investigated for over 20 different indications, with targets in nearly 40 distinct brain regions (Hariz et al. 2013), the mechanisms through which DBS modulates brain networks and the effects of focal stimulation on both local and distributed brain functions are not yet clear. Several critical questions remain to be answered in the context of each target and therapeutic application: 1) What are the most therapeutically effective target structures, 2) What are the relevant neurophysiological effects of DBS on those structures, and 3) How do these effects modulate the activation of diffuse functional networks to produce desired or undesired behavioral changes? Brain regions targeted by DBS are variably composed of neuronal somata making up the gray matter in the vicinity of the stimulated electrode contact, axonal projections both through and adjacent to the target, or primarily white matter tracts themselves. The complexity of determining the neurobiological mechanisms of DBS therapy is com-

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pounded by the fact that target structures act as relay nodes in larger networks, which are perturbed by the reverberating effects of stimulation (McIntyre et al. 2004; McIntyre and Hahn 2010; Vitek 2002). An initial explanation for the effects of high-frequency DBS was that stimulation inhibits the targeted structure, thereby producing a functional lesion during (Filali et al. 2004) and after (Beurrier et al. 2001) stimulation. Alternate hypotheses have proposed that activation of the target or induction of long-term synaptic plasticity alters excitability (Kombian et al. 2000). Furthermore, given the oscillatory nature of the train of stimulation pulses employed in DBS, its effects can alter the rhythmic interaction of targeted networks, effectively altering information flow without clearly inhibiting or activating neural tissue (Chiken and Nambu 2014). For instance, axonal and synaptic failures induced by short-term depression following axonal excitation by DBS have been hypothesized to suppress information transfer (Rosenbaum et al. 2014). Finally, DBS may induce a regular rhythm driven by high-frequency stimulation that overrides the pathological rhythm present in the target area (Garcia et al. 2005).

This review describes the cortical effects of DBS primarily in networks linked with the 1) subthalamic nucleus (STN), 2) globus pallidus internus (GPi), 3) thalamus, and 4) nucleus accumbens (NAc) (Fig. 1). We have integrated reports from the functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG), electrocorticography (ECoG), and magnetoencephalography (MEG) literature. Each of these techniques offers different advantages and has unique limitations, which must be appreciated in order to interpret the findings. For instance, functional and metabolic imaging offer spatial resolution superior to scalp EEG, allow for measuring activity in subcortical structures, and are not affected by the electrical artifact of stimulation, but the temporal resolution of network activity is limited and static. MEG and ECoG can demonstrate spectral changes at the cortical level with high temporal and spatial resolution but require that the effect of electrical stimulation is filtered out. These data are reviewed in the context of current hypotheses related to the mechanisms of action of DBS on motor, cognitive, and neuropsychiatric functions.

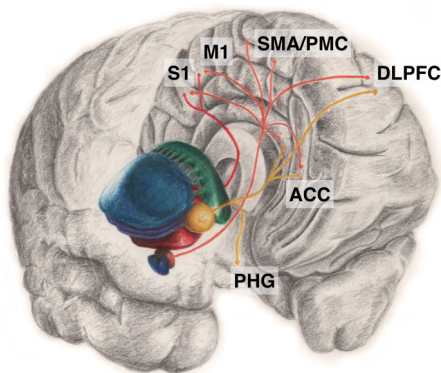


Fig. 1. Schematic of network modulation by deep brain stimulations (DBS) in 3 major targets. Brain regions modulated by DBS of the subthalamic nucleus (STN; orange), thalamus (red), and nucleus accumbens (yellow) are indicated (in the contralateral hemisphere for visual clarity). S1, primary sensory cortex; M1, primary motor cortex; SMA, supplementary motor area; PMC, premotor cortex; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; PHG, parahippocampal gyrus.

Network Effects of Subthalamic Nucleus Stimulation

Although over 100,000 patients have undergone DBS implantation for various indications, the majority of our experience with recording network effects during DBS comes from STN stimulation for the treatment of PD. Unless otherwise stated, the studies reviewed in the STN sections below involve DBS of the sensorimotor territory of the STN for PD. A current hypothesis for the therapeutic effects of STN DBS in PD is that STN stimulation decreases pathological synchronization in the beta frequency band between STN and primary motor cortex (PMC). This pathological synchronization is disrupted by both STN stimulation and dopaminergic therapies and has been correlated with clinical improvement (de Hemptinne et al. 2013; Oswal et al. 2013). However, various associations with disinhibition in cognition and mood have also been documented in patients after surgery (Castrioto et al. 2014). These changes indicate stimulation effects extending beyond local targets in sensorimotor STN. These effects can be explained anatomically given the known involvement of the STN in multiple circuits connecting the basal ganglia to the cortical regions that regulate motor, cognitive, and emotional behavior (Alexander et al. 1986). Furthermore, these diverse effects can be attributed to the systematic and random procedural errors leading to minor location inaccuracies but with substantial neurophysiological effects (Tsai et al. 2007). The mechanisms by which stimulation modulates these brain networks remain controversial and are the subject of active investigation.

STN studies using PET. A substantial amount of work has been accomplished with metabolic imaging using both 18-FDG and [^{15}O]H $_2\text{O}$ PET (Akatsubo and Akabayashi 2009; Asanuma et al. 2006; Ceballos-Baumann et al. 1999; Chul et al. 2007; Devos et al. 2004; Geday et al. 2009; Haegelen et al. 2010; Haslinger et al. 2005; Hilker et al. 2002, 2004; Karimi et al. 2008; Limousin et al. 1997; Mure et al. 2011; Sestini et al. 2002, 2007; Sidtis et al. 2012; Strafella et al. 2003; Trost et al. 2006), the former measuring glucose metabolism and the latter measuring regional changes in cerebral blood flow (rCBF). The main aim of these studies in STN DBS was to assess motor system function in PD and its relation to treatment by examining cortical metabolic changes induced by DBS during both resting state and simple motor tasks. Considering studies with a minimum of 15 subjects, testing patients off medications and without previous surgeries, a general pattern emerges in a motor network including the PMC, lateral premotor cortex, dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), and anterior cingulate cortex (ACC). Compared with off-stimulation, there is decreased activation in this network at rest during STN DBS. In contrast to the effect of DBS at rest, during self-initiated movement STN DBS is associated with increased metabolism in rostral SMA, ACC, and DLPFC. A prospective study in which 40 PD patients and age-matched control subjects were scanned at rest demonstrated that clinical improvement was associated with perfusion decrements in primary motor and premotor cortices. Cerebellar activation increased during stimulation, in conjunction with evidence of modulation of a cerebello-thalamo-cortical loop functionally connected to the cortico-basal ganglia motor loop (Cilia et al. 2009). Thus STN DBS appears to differentially affect the resting-state

network compared with the functional motor network. Part of the discrepancy found among studies recording during movement, however, is also likely attributable to the type of task employed.

Metabolic imaging while subjects perform cognitive tasks has shed some light on the neural bases of cognitive changes reported in DBS. Verbal fluency performance during stimulation has been shown to correlate with activation of the left inferior frontal gyrus, left inferior temporal gyrus, left DLPFC, and ACC (Cilia et al. 2007; Kalbe et al. 2009; Schroeder et al. 2003). STN DBS effects on the DLPFC and ACC have also been investigated in relation to conflict monitoring using the Stroop task (Schroeder et al. 2002), random number generation (Thobois et al. 2007), and working memory and response inhibition (Campbell et al. 2008). In all of these studies, a decrease in regional activity of those regions induced by DBS correlated with the impairments in the corresponding cognitive function being assayed in the former two studies, while the opposite effect was observed in the latter study. Notably, a specific pattern of activation at rest, characterized by metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei, has separately been shown to predict memory performance, visuospatial function, and perceptual motor speed but was not significantly altered by antiparkinsonian medications or DBS (Huang et al. 2007). These findings may suggest a discrepancy between DBS affects during task-related epochs compared with epochs in which a subject is not engaged in a task.

Modulation of key parts of the limbic circuit has been demonstrated in a large series of patients; however, no resultant cognitive improvement was detected on neuropsychological testing except modest improvements in a card-sorting task (Le Jeune et al. 2010). This result is potentially confounded because patients were tested who were still on medication in addition to DBS. In a study of apathy following DBS, positive correlations were observed between apathy scores and increases in glucose metabolism, especially in the right frontal middle gyrus and inferior frontal gyrus (Le Jeune et al. 2009). Finally, DBS-induced deactivation in the fusiform gyrus has been correlated with the impairment of facial expression recognition (Geday et al. 2006).

STN DBS has also been used as a treatment for OCD, with electrode placement in the limbic territory of the STN. A PET study showed that this therapy resulted in a decrease in metabolism of the left cingulate and medial gyrus of the left frontal lobe. Clinical improvement was correlated with a decrease of metabolic activity in the orbitofrontal cortex (OFC)-ventral medial prefrontal region in ON vs. OFF conditions (Le Jeune et al. 2010).

STN studies using functional magnetic resonance imaging. The application of fMRI to investigation of DBS has been hindered by concerns regarding safety (Finelli et al. 2002; Georgi et al. 2004; Shrivastava et al. 2012) and by significant artifacts in the acquired images, although there is evidence that its use under strict guidelines may be safe (Carmichael et al. 2007). Because of these safety concerns, this imaging modality remains underutilized, with few studies published using fMRI during active stimulation and limited to the use of 1.5-T scanners (Arantes et al. 2006; Hesselmann et al. 2004; Jech et al. 2001; Kahan et al. 2012, 2014; Stefurak et al. 2003) except for Phillips et al. (2006), where a 3-T scanner was used. Each

of these patient cohorts did not exceed five patients, outside of the work by Kahan and colleagues. The reader also is referred to Boertien and colleagues (Boertien et al. 2011) for a recent extensive review of functional imaging in STN DBS.

Nonetheless, initial fMRI studies of DBS effects at rest essentially have corroborated earlier metabolic imaging findings. In addition, Kahan and colleagues studied the effects of DBS on the motor network directly by using dynamic causal modeling in 10 subjects (Kahan et al. 2014). Their findings suggest that the therapeutic effects of DBS arise from strengthening the cortico-striatal, direct, and thalamocortical pathways while disrupting all afferent and efferent inputs to the STN. Disruption or weakening of incoming and outgoing connectivity with STN DBS is beneficial when it involves the overly connected motor network. However, this interference with other networks also may explain side effects related to cognitive functions for which the STN is an important network node. While it offers potential new insight into DBS effects, this model lacks some elements of the actual human network (like the globus pallidus) and still requires validation on a larger data set.

STN studies using EEG and ECoG. During rest, STN DBS has been shown via scalp EEG to induce a broadband decrease in spectral power in frontocentral electrodes (Jech et al. 2006) and a widespread decrease of coherence predominantly in the beta frequency band (Hotton et al. 2005). During movement preparation, STN stimulation was shown to partially restore normal patterns of cortical activation by decreasing abnormal desynchronization prior to movement onset over the bilateral frontocentral regions (Devos et al. 2004), suggesting increased activation of the premotor cortex by DBS.

In addition to motor effects, STN stimulation can have effects on the processing of sensory information. Cortical encoding of sensory stimuli has often been analyzed with event-related potentials (ERPs), which represent time-locked cortical neuronal population activity in response to a certain stimulus. The synchronization of this activity depends on several factors including the intrinsic membrane properties of the neurons and the state of their local and global networks (Pfurtscheller and Lopes da Silva 1999). The downstream effects of stimulation on these factors can be seen in the generation of ERPs and possibly extrapolated to the cognitive processes related to the stimulus used. This paradigm was used in several studies in the PD population listed in Table 1. Cortical sensory ERPs typically were reduced or unchanged by stimulation. Thus stimulation may interfere with neuronal synchronization, potentially disrupting the phase reorganization needed for the generation of an ERP (Sayers et al. 1974), but this effect on sensory processing, when present, appears to be weak. Stimulation generally has not demonstrated an effect on ERP latency. Only one study (Selzler et al. 2013) has reported a slowing in latency to match that of the control group, although task performance did not change. The lack of correlation between task performance and ERP generation suggests that more sophisticated measures are required to assess the effects of DBS, a point directly demonstrated by Swann et al. (2011), where time-frequency plots showed greater sensitivity to the effects of DBS whereas ERPs were insensitive to these effects. This implies that DBS affects oscillatory dynamics not well captured by ERPs. This concern, in addition to the difficulty associated with removing the

Table 1. Studies reporting ERPs measured by scalp EEG after STN stimulation

Study	Sensory Stimulus Used	Cognitive Task Used	ERP Recorded and Stimulation-Induced Amplitude Changes
Pierantozzi (1999)	Somatosensory EPs	None	N20/P25, unchanged N30 increased
Priori et al. (2001)	Somatosensory EPs and visual EPs	None	N20/P100, decreased
Insola et al. (2005)	Somatosensory EPs	None	N9/P14, unchanged N20/N30, increased N70/P100, decreased
Jech et al. (2006)	Visual EPs	None	N20/P25 and P25/N33, decreased
Conte et al. (2010)	Somatosensory EPs	None	P1/N1, unchanged
Gulberti et al. (2014)	Auditory EPs	None	Not reported
Gerschlagner et al. (2001)	None	Auditory oddball	P300/N200, unchanged
Kovacs et al. (2008)	None	Auditory oddball	P300, unchanged
Klostermann et al. (2010)	None	Choice response, oddball	N2/P3, unchanged
Swann et al. (2011)	None	Stop signal	N200, decreased
Selzler et al. (2013)	None	Working memory	

ERP, event-related potential; STN, subthalamic nucleus; EP, evoked potential.

stimulation artifact in EEG, has led some to turn to MEG to study the cortical effects of DBS.

Electrical stimulation has a predilection for activating axons in long tracts compared with cell bodies near the source (Nowak and Bullier 1998). This can be captured in subjects as evoked potentials (EPs) time-locked to the stimulation train. The resultant EP demonstrated synchronization of cortical activity with stimulation, where the different parts of the EP were thought to represent different modes of synaptic transmission. Both a short latency (<8 ms) and a long latency (>18 ms) were observed (Ashby et al. 2001; Baker et al. 2002; Eusebio et al. 2009; Kuriakose et al. 2010; Limousin et al. 1998a; MacKinnon et al. 2005; Walker et al. 2012b). The topography of these EPs encompassed frontal and central areas. The timing of the short-latency components is more consistent with antidromic conduction through the corticosubthalamic projections. The longer latency might represent orthodromic polysynaptic conduction through the basothalamocortical circuit. Of note, Walker and colleagues went further to explore the short-latency component by summing two sets of recordings with reversed anode/cathode pairs in order to suppress the stimulation artifact. This uncovered a component at a latency of 1 ms, suggesting that the short-latency components seen in previous studies might represent the tail of the waveform that was obscured by the stimulation artifact. However, a number of these studies only use low-frequency stimulation (5–30 Hz), making interpretation of these results to explain clinical high-frequency stimulation difficult.

Patients with PD often exhibit cognitive dysfunction in addition to classical motor symptoms. An important question is how pathology in brain networks contributes to this dysfunction and how DBS affects these networks. Even in early, untreated PD patients, widespread increases in the amplitude of theta and low alpha rhythms have been observed, with increased alpha power in the centroparietal region associated with abnormal perseveration (Stoffers et al. 2007). Separately, STN DBS has been shown to result in a decrease in spectral power in the alpha band (Jech et al. 2006), but whether this normalization of low-frequency activity contributes to cognitive improvement is unknown.

On the other hand, impulsivity is a consequence of STN stimulation not seen in patients receiving L-DOPA therapy (Frank et al. 2007; Hälbjg et al. 2009). The leading explanation is that stimulation interferes with normal STN inhibition that

withholds actions until a decision threshold is reached, especially during conflict. For instance, during conflict monitoring, DBS has been shown to disrupt the relationship between the level of theta in medial prefrontal cortex and the decision threshold during conflict leading to response speeding (Cavanagh et al. 2011). Swann et al. (2011), however, showed that DBS improved response inhibition and linked this improvement to modulating the beta response seen in the frontal cortex to comparable levels seen in the control group. The difference in DBS effects on response inhibition might be explained by the task employed. For example, improvement was seen with exclusively motor decision making tasks (Mirabella et al. 2012; Swann et al. 2011; van den Wildenberg et al. 2006), while cognitive decision making tasks were associated with a decline in performance (Cavanagh et al. 2011; Frank et al. 2007). These findings suggest that disrupting the STN locally may affect functionally connected cortical regions via differential effects on two different circuits converging in the STN (Wylie et al. 2010). Likewise, a recent study of the effects of STN stimulation on go-only and countermanding tasks also indicated that both inhibitory control and the selection of the most appropriate motor strategy for a given context may be regulated by two different circuits that both include the STN (Mirabella et al. 2013).

The use of ECoG offers better localization and higher signal-to-noise ratio compared with EEG, both of which remain hurdles to the use of EEG during active stimulation. The use of ECoG, by temporarily sliding a strip electrode through the burr hole, during DBS surgery was introduced by Starr's group at the University of California San Francisco. For instance, de Hemptinne and colleagues explored the relationship between the pathological beta rhythm in PD and gamma activity in M1. Intraoperative ECoG recordings from PD, cervical dystonia, and epilepsy patients showed exaggerated phase-amplitude coupling (PAC) between the beta rhythm and broadband gamma activity in PD, with the phase of the beta rhythm in the STN modulating the amplitude of broadband gamma activity in M1 (de Hemptinne et al. 2013). This coupling was decreased in the recording after therapeutic stimulation, suggesting that pathological STN-M1 synchronization is disrupted by DBS. In addition, these authors proposed that broadband cortical gamma activity might maintain this abnormal coupling by feedback via the hyperdirect pathway from cortex to STN. Separately, Whitmer and colleagues

targeted the hyperdirect pathway of the M1 cortex for ECoG, based on diffusion tractography imaging. They compared the effects of DBS on the signal from that region to nonspecific regions. In the two patients that had accurate targeting, they demonstrated a selective decrease in neural synchrony over M1 during stimulation in the frequency band between 5 and 35 Hz (Whitmer et al. 2012). However, the findings of Whitmer and colleagues were not reproducible across a larger patient sample, and in more extensive work de Hemptinne and colleagues showed that DBS reversibly reduced an exaggerated coupling between the phase of the beta rhythm and the amplitude of broadband activity in motor cortex (de Hemptinne et al. 2015). This effect was seen across different stages of movement and regardless of the effect on cortical beta frequency power changes. These findings strongly argue for DBS disrupting abnormal cortical synchronization as a mechanism for its therapeutic effects.

STN studies using MEG. MEG offers superior spatial resolution compared with EEG and superior temporal resolution compared with fMRI. In addition, the relatively large number of sensors used in MEG (most modern MEG systems have 200 or more sensors) greatly improves researchers' ability to remove the stimulation artifact from the signal relative to EEG. Specifically, the introduction of temporal signal space separation (tSSS) (Taulu and Simola 2006) and null beamforming (Mohseni et al. 2012) has been shown to successfully minimize the effects of the stimulator artifacts, facilitating studies examining the acute effects of DBS by comparing cortical activity during the DBS-on state to the DBS-off state. As a validity study, Park et al. (2009) showed increased corticomuscular coherence in the beta band during STN stimulation. Another report supporting MEG feasibility during stimulation comes from the same group that developed the tSSS method for stimulator artifact removal (Airaksinen et al. 2011). In a group of PD patients, these authors showed that the recording of somatosensory ERPs and auditory ERPs was feasible during stimulation.

In an effort to study DBS-induced modulation of cortical activity, Airaksinen et al. (2012) demonstrated that stimulation decreased the amplitude of the alpha peak, corroborating the findings of Jech et al. (2006) from EEG. They also showed correlation between the amplitudes of pericentral alpha and low beta to the Unified Parkinson Disease Rating Scale (UPDRS) rigidity scores with stimulation turned on. A similar study by Cao et al. (2015) described DBS effects detectable by MEG emerging 1 yr after stimulation rather than after 1 wk. These phenomena consisted of acceleration in the average cortical frequency in multiple regions, a widespread decrease in theta power, and an increase in low beta (14–18 Hz) power. Finally, they reproduced (Airaksinen et al. 2012) results describing correlations with UPDRS scores and cortical activity. The work related to beta oscillatory reduction is important since excessive beta synchronization of the cortico-basal ganglia loop is considered a pathological hallmark of PD. This excessive synchronization impairs the ability of the basal ganglion system to receive and process new information, thus hindering the initiation of new actions (Brittain et al. 2014). Nevertheless, the importance of changes in other oscillatory frequencies remains to be defined.

Conclusions regarding STN stimulation. STN stimulation effects across measurement modalities fall into a number of

different categories. During movement, PMC activation appears to be enhanced with increased involvement of frontal regions during movement execution. A global effect of stimulation appears to be disruption of neuronal synchronization, particularly in the alpha and low beta frequency ranges. While this is shown to improve the motor symptoms of PD, cognitive function may be negatively affected in some cases after DBS, particularly if DLPFC and ACC activity are significantly affected (Pinto et al. 2014).

Network Effects of Globus Pallidus Internus Stimulation

The GPi is the convergence point of the classically described indirect, direct, and hyperdirect basal ganglion pathways. This structure provides the most important inhibitory outflow from the basal ganglia to the thalamus and is hypothesized to play a role in action selection, among other functions (Mink 1996). Stimulation of the GPi provides therapeutic suppression of both primary and secondary dystonia (Katsakiori et al. 2009; Kupsch et al. 2006; Vercueil et al. 2001). In patients with PD, stimulation of the GPi is an attractive alternative to STN stimulation (Follett et al. 2010), especially when dopaminergic therapies are complicated by dystonia (Vitek 2002). Stimulation of the GPi has been studied with metabolic imaging and EEG. These studies have largely demonstrated that GPi stimulation aids in reducing overactivity in cortical areas associated with dystonia and in desynchronizing oscillatory activity in downstream sensorimotor cortices.

GPi studies using PET. An early FDG-PET study found that high-frequency GPi stimulation increased glucose metabolism in ipsilateral premotor cortex and bilateral cerebellum that correlated with improvement in UPDRS scores (Fukuda et al. 2001). A subsequent H₂¹⁵O PET study found that DBS of GPi in six patients with severe primary generalized dystonia decreased abnormal overactivity in the DLPFC, gyrus frontalis medialis, superior frontal gyrus, fronto-orbital cortex, and thalamus that is characteristic of dystonia; this effect accompanied significant improvement in dystonic symptoms during a motor task (Detante et al. 2004). These studies suggest that patients with dystonia have characteristic overactivity in numerous cortical regions notably including premotor cortex. Furthermore, this overactivity can be suppressed by pallidal stimulation, and suppression is associated with improved motor symptoms.

GPi studies using EEG. An early study using EEG during a movement task in patients with PD similarly found that GPi stimulation aided desynchronization over premotor cortex during movement planning and movement-related desynchronization over PMC (Devos et al. 2002). A study of EEG during low-frequency (10 Hz) GPi stimulation in subjects with dystonia (Tisch et al. 2008) found EPs that were maximal in the central contacts but absent on a patient-side with previous thalamotomy. The timing was consistent with pallidothalamo-cortical pathway activation of sensorimotor cortex that has also been documented after STN stimulation (MacKinnon et al. 2005).

Conclusions regarding GPi stimulation. Although sparse data exist related to stimulation of GPi, EEG findings are supported by observations from functional imaging studies that the downstream effects of pallidal stimulation are expressed in premotor cortex. Furthermore, EEG studies suggest that motor

improvement from GPi DBS may be at least partially due to stimulation-aided desynchronization of low-frequency oscillations (μ rhythms) in premotor cortex that have been associated with movement suppression.

Effects of Thalamic Stimulation

The thalamus is a complex structure composed of many nuclei, segregated by motor and associative functions, that offer both accepted and proposed DBS targets for various disease states affecting thalamocortical networks. The heterogeneity of patient populations and specific thalamic targets has generated compelling yet somewhat contradictory results related to network effects of thalamic DBS.

Thalamic studies using PET. A $H_2^{15}O$ PET study in ET patients (Ceballos-Baumann et al. 2001) described increases in rCBF of the ipsilateral PMC with DBS of the ventral intermediate nucleus (Vim). Later, they went on to show linear and nonlinear relationships between cortical activity and increases in stimulation frequency and amplitude suggesting that DBS recruits different parts of a larger circuit gradually with varying stimulation parameters (Haslinger et al. 2003). Perlmutter and colleagues (using PET; Perlmutter et al. 2002) and Rezai and colleagues (using 1.5-T fMRI; Rezai et al. 1999) both failed to reproduce these findings, instead showing SMA and primary somatosensory activation, respectively. These heterogeneous effects might be attributed to the small number of subjects enrolled in each of the studies ($n = 2-10$), or to the statistical stringency each group employed. Importantly, all these studies were performed in the resting state, and none examined treatment effects on the action tremor of ET.

A different picture is seen in Vim stimulation for PD compared with Vim stimulation in ET patients. Multiple PET studies have shown results of decreased activation in the primary sensorimotor areas, SMA, and contralateral cerebellum (Deiber et al. 1993; Fukuda et al. 2004; Wielepp et al. 2001). This is contrary to what is seen in ET and probably relates to the nature of the resting tremor of PD, compared with the action tremor of ET. Mure and colleagues (Mure et al. 2011) later used the data set from Fukuda et al. (2004) to delineate a tremor-related metabolic network in PD, referred to as a PD tremor pattern (PDTP), comprised of the cerebellum, PMC, and to a lesser extent the striatum. This pattern was validated on a different subset of patients and correlated with tremor amplitude. Previous work characterized a network responsible for the akinesia and rigidity in PD, a PD-related pattern (PDRP), shown as a relative decrease in metabolic activity of the premotor, SMA, and parietal association regions (Eidelberg 2009). While STN stimulation modulated the PDRP network and improved rigidity, it had little effect on the PDTP network (Mure et al. 2011). This justifies the clinical use of Vim stimulation for tremor management (Rehncrona et al. 2003) while STN stimulation is used for rigidity management (Katz et al. 2015).

Although stimulation of the somatosensory thalamus also has been used for more than two decades to treat chronic pain, the mechanisms mediating stimulation-produced therapeutic analgesia are not understood. A PET study of rCBF in five patients who received successful long-term relief of chronic pain with somatosensory thalamic stimulation demonstrated activation of the insular cortex ipsilateral to the thalamic

electrodes (Duncan et al. 1998). A subsequent case report demonstrated that blood flow significantly increased in the amygdala and anterior insular cortex during successful stimulation in a patient with chronic facial pain (Kupers et al. 2000). Thus activation of the ipsilateral insula may be important for relief of chronic pain treated by thalamic DBS.

Thalamic studies using EEG. The technique of using ECoG to record intraoperatively was also applied by Starr and colleagues in ET patients (Air et al. 2012). They showed that Vim stimulation resulted in desynchronization of the alpha activity in primary motor and theta in primary somatosensory cortical areas. The relation to pathology remains unclear. In another arm of the same study, the authors found that thalamotomy had the opposite effect on these oscillations, despite the same level of observed tremor control. Although the relationship between Vim stimulation and M1 activation prior to movement execution was not elaborated upon in that study, it is possible that Vim stimulation activates M1 in preparation for movement execution. Clearly more work is needed to understand these findings.

Walker et al. (2012a) demonstrated short-latency cortical effects of Vim DBS recorded with scalp EEG that were a part of a complex EP. Effective Vim thalamic stimulation appeared to activate the cortex at ~ 1 ms after the stimulus pulse, leading the authors to suggest that DBS may improve tremor by synchronizing the precise timing of discharges through the thalamocortical network to the stimulation frequency or one of its subharmonics.

A small case series using scalp EEG and low-resolution electromagnetic tomography (LORETA) investigated effects of anterior nucleus of the thalamus (ANT) stimulation on cortical synchronization in epilepsy (Zumsteg et al. 2006b). Similar evoked cortical potentials following low-frequency stimulation were observed in the frontal and temporal contacts on EEG for stimulation of the anterior and dorsomedial nuclei. With LORETA, the underlying sequential activation of the different ipsilateral cortical areas responsible for these responses was demonstrated. Despite the fact that the low number of subjects studied precludes drawing definitive conclusions about the functional relationship between the sources of cortical responses and these thalamic nuclei, this study also was valuable in demonstrating the need to overcome the limitations of standard EEG analyses. These authors subsequently reported that stimulation caused EEG synchronization (Zumsteg et al. 2006a), indicating downstream activation of thalamocortical pathways, but synchronization was not demonstrated with objective metrics. In a separate case report, evoked responses were recorded from bilateral hippocampal depth electrodes, simultaneous with scalp EEG, in response to acute ANT stimulation (Kim et al. 2014). The authors used this technique during repositioning of the DBS electrode in the ANT to confirm electrode placement in a patient with refractory bilateral temporal epilepsy, suggesting that recording synchronous cortical and mesial temporal network activity may be useful in guiding DBS placement for this indication.

Conclusions regarding thalamic stimulation. The literature on thalamic stimulation is diffuse because of the wide number of disease states treated and the number of nuclei targeted within the thalamus itself. More work is needed to define network effects from stimulation of individual thalamic nuclei. However, evidence collected regarding Vim stimulation sug-

gests it is involved in a network that is separate from the network related to akinesia in PD.

Network Effects of Nucleus Accumbens Stimulation

Several studies have shown that stimulation of the NAc holds promise for treating neuropsychiatric diseases, including OCD (Denys et al. 2010; Greenberg et al. 2006), major depression (Malone et al. 2009), Tourette syndrome (Neuner et al. 2009), and addiction (Kuhn et al. 2007). Overall success rates have been low in these experimental therapies, however, including the recent report of a failed pivotal trial for treatment-resistant depression (Denys et al. 2010). It is possible that NAc DBS may have different mechanisms of therapeutic action within different patient populations, and that the modest symptom control achieved in these studies is not a result of normalizing the fundamental etiology of the respective disorders. However, the NAc is a basal ganglion structure whose function has been heavily implicated in goal-directed behavior, reward processing, and addiction. Importantly, this nucleus receives major inputs from the prefrontal cortex and amygdala and dopaminergic innervation from the ventral tegmental area, and it projects to the ventral pallidum as part of the limbic basal ganglion circuit (Kopell and Greenberg 2008). Furthermore, the NAc is situated immediately adjacent to the anterior limb of the internal capsule of the basal ganglia, whose white matter tracts connect limbic and orbitofrontal structures (Tass et al. 2003). Thus, in addition to altering local activity, NAc stimulation can modulate the function of a number of distal targets that are implicated in psychiatric disorders. Indeed, both imaging and electrophysiological studies support a broad network mechanism for the effects of NAc DBS.

NAc studies using PET. One of the consistent metabolic correlates of OCD is hyperactivity in the striatum and OFC at rest (Baxter et al. 1988; Swedo et al. 1989) and after symptom provocation (Breiter et al. 1996; McGuire et al. 1994; Rauch et al. 1994). Importantly, successful pharmacological and behavioral interventions, as well as basal ganglion capsulotomy have been shown to normalize this activity, particularly in the OFC. These findings suggest that the abnormal hyperactivation the OFC-NAc pathway underlies the pathophysiology of this disorder and implicates the OFC as a potential distal functional target of NAc DBS for OCD. Indeed, PET studies using stimulation of the NAc and the internal capsule have shown that symptom control correlates with metabolic decreases in prefrontal areas (Abelson et al. 2005; Van Laere et al. 2006; Nuttin et al. 2003).

An FDG PET imaging study in a series of four patients with anorexia nervosa (AN) found that DBS modulated the activity of frontal and hippocampal regions that were discovered as abnormal compared with the control group (Zhang et al. 2013). This was hypothesized by the authors to reflect interference of the abnormal limbic circuit and the impaired reward network. Another case series involving three patients receiving acute NAc stimulation for major depression (Schlaepfer et al. 2008) showed modulation of the prefrontal cortex, cingulate, amygdala, and parts of the basal ganglia with FDG-PET. The authors argued that the changes seen in the reward circuit are related to the reversal of anhedonia and increased pleasure response.

NAc studies using EEG. One group studying NAc stimulation for OCD (Figeet et al. 2013) showed that stimulation in the region of the NAc modulated abnormal prefrontal connectivity and decreased the low-frequency oscillation response seen for symptom-provoking stimuli, which correlated with clinical improvement. Low-frequency oscillations in the range of 2–5 Hz over the prefrontal cortex were linked to the severity of symptoms in OCD (Pogarell et al. 2006). Although the role of frontal low-frequency oscillations in the pathophysiology of OCD is not clear, frontal theta is hypothesized to correlate with the cognitive control and working memory load (Cavanagh and Frank 2014; Meltzer et al. 2008). Interpretation of the study by Pogarell and colleagues is limited, however, because of the small number of patients, the presence of comorbidities, and most importantly the use of psychoactive medications by a subset of subjects. In this setting, synaptic plastic changes induced by chronic stimulation (Fenoy et al. 2014) might be interrupted by the use of medication. Therefore, the true extent of the network modulated in this setting might not have been fully defined. In a follow-up report Smolders et al. (2013) showed that DBS reduced phase stability of the theta oscillations recorded from frontal regions. This finding may explain how high-frequency DBS decreases the power of low-frequency oscillations by interfering with their synchronization.

Conclusions regarding NAc stimulation. Cross-modality evidence implicates the frontal cortex and particularly the prefrontal cortex as the main area of effect for NAc stimulation. Possible electrophysiological markers have been demonstrated for clinical effects, but they await validation in future studies.

Other Brain Targets

The network effects of various other brain regions investigated as targets for DBS have been sporadically assessed.

Targets for pain. A few studies have examined the cortical effects of hypothalamic stimulation used to treat cluster headaches. Results from PET imaging have demonstrated modulation of somatosensory cortex, precuneus, middle temporal gyrus, inferior temporal gyrus, insula, and anterior and posterior cingulate (May et al. 2006); however, proper washout between scans was not employed. Therefore, these findings might represent plasticity induced from chronic stimulation instead of modulation of the circuitry from DBS. Additionally, corresponding MEG studies have shown cortical activation in the mid-anterior OFC, but only in one case study (Ray et al. 2007).

In single case reports regarding chronic pain, MEG has been used to demonstrate correlations between pain relief and target activity following stimulation in periventricular gray (Ray et al. 2009) and ACC (Mohseni et al. 2012). These studies were important for beginning to demonstrate the feasibility of performing MEG recordings with implanted DBS electrodes, but further assessment of the effects of DBS in these regions will require the study of greater numbers of subjects.

Pedunculopontine nucleus. Pedunculopontine nucleus (PPN) stimulation for the treatment of movement disorders initially showed promise for improvement of gait disturbances in PD (Strafella et al. 2008). However, subsequent studies suggest greater utility as a compassionate option in patients with PD, as it may improve sleep, memory, and executive function (Alessandro et al. 2010). PPN stimulation increased glucose uptake in multiple

prefrontal cortices and left ventral striatum (Alessandro et al. 2010; Ceravolo et al. 2011; Stefani et al. 2010) and caused increased blood flow to multiple structures in the cerebello-thalamo-cortical circuit (Ballanger et al. 2009). What these results mean in the context of mixed clinical results with PPN stimulation for PD is not clear.

Subcallosal cingulate. Stimulation of the subcallosal cingulate white matter (SCCWM) has shown positive results for the treatment of MDD (Holtzheimer et al. 2012). Metabolic imaging with PET showed a decrease in metabolism of subgenual cingulate, OFC, and medial frontal and insular cortex and increases in DLPFC and dorsal cingulate (Mayberg et al. 2005). These results were corroborated by Lozano and colleagues, who additionally showed a metabolic increase in the posterior and anterior midcingulate gyri (Lozano et al. 2008). Acute stimulation also decreased activation in the cingulate gyrus (Martín-Blanco et al. 2015). Further studies investigated potential biomarkers of long-term antidepressant DBS response (Broadway et al. 2012). Theta cordance is an EEG measure thought to correlate with regional blood perfusion. Frontal theta cordance decreases were previously shown to correlate with antidepressant medication effects. Increasing frontal theta cordance over the course of DBS (24 mo), however, was found to predict greater decreases in depression severity scores in patients undergoing SCCWM stimulation (Broadway et al. 2012). These opposite results between pharmacological and DBS effects on theta cordance may reflect technical differences in EEG measurements but nonetheless indicate the need for multiple studies in which more than one recording modality and a larger cohort of patients are used to fully develop a feasible pathologic-therapeutic network model. Although a tractography study has suggested that simultaneous electrical activation of a volume of tissue containing fibers connected to medial frontal cortex, rostral and dorsal cingulate cortex, and subcortical nuclei is necessary for antidepressant effects in SCCWM DBS, neurophysiological data supporting modulation of these connected regions have not been reported.

Discussion

In this state-of-the-science review, we have attempted to summarize the network effects of DBS on cortical activity in the human brain. These studies suggest that DBS modulates network activity through a combination of effects. Direct cortical activation evidenced by stimulation-induced responses with variable timing suggests that multiple transmission pathways may be involved. Most importantly, DBS seems to prevent abnormal synchronization in distant cortical regions by disrupting afferent or efferent communication with the stimulation target. This effect was observed across modalities. In EEG studies this was seen in the widespread amplitude decrease of ERPs, decreased coherence across the cortical regions, and disruption of frontal theta. ECoG has been used to demonstrate that therapeutic STN DBS in PD normalizes PAC within the cortical motor system (de Hemptinne et al. 2015). Functional imaging models suggest that differential and specific modulation of a target's connections best predicts therapeutic response, in line with results from optogenetic studies in parkinsonian rodents that demonstrate that direct selective stimulation of afferent axons projecting to the STN is responsible for therapeutic effects (Gradinaru et al. 2009). This

antidromic activation has been demonstrated across multiple studies as EPs and associated with facilitation of motor responses (Kuriakose et al. 2010). This antidromic activation was hypothesized to disrupt the timing of orthodromic discharges (Walker et al. 2012b).

Neuronal oscillations, rhythmic changes in neuronal excitability that result from the activity of synchronized groups of neurons and are thought to promote multineuronal task coordination, are now commonly recorded in a variety of clinical scenarios. The result has been an increased focus on elucidating their potential role in the regulation of local stimulus processing and long-range information transfer in the human brain. One mechanism for synchronizing neuronal activity is PAC, the involvement of which has been implicated in multiple aspects of cognition (Canolty and Knight 2010). The combined results of Smolders et al. related to DBS effects on phase stability and de Hemptinne et al. showing a DBS-related decrease in PAC at rest and during movement (de Hemptinne et al. 2015) suggest that modulation of PAC is a possible mechanism causing network desynchronization. Network desynchronization by disruption of phase relationships with coordinated reset stimulation is a concept that has been pioneered by Tass and colleagues, who showed remarkable efficacy of this approach in a study of three parkinsonian monkeys (Tass et al. 2012). How this desynchronization leads to clinical improvement is still not clear, and the details are likely different across disorders and DBS targets. In PD, one hypothesis is that DBS normalizes aberrant network synchrony by disrupting the prevalent pathological beta frequency activity arising in the basal ganglia (Oswal et al. 2013). Another possibility is that DBS enhances compensatory networks at the expense of disruptions in baseline pathological network activity. This possibility is suggested by findings from functional imaging studies showing typically inactive areas coming online only during DBS, while areas typically active during performance in the absence of DBS are suppressed.

Common confounders were present in a number of studies, some of which are unavoidable because of the nature of the disease process being studied. First, the subjects being studied have underlying pathologies that have altered the normal brain circuitry and have possibly led to the emergence of new compensatory alterations in communication pathways through surviving connections (Mikell et al. 2015). Second, the inherent variance in the surgical placement of electrodes leads to minor differences in the substructure being stimulated within a given target, evidenced by the typical variability of responses between and within subjects to standard stimulation parameters. Third, a large portion of these studies were performed retrospectively, leading to wide ranges in disease duration and time from surgery to assessment. It is difficult to account for the progressive nature of many DBS indications, as well as the different levels of network plasticity that may be induced by stimulation over different time periods in the setting of variable levels of integrity of remaining network connections. Also, chronic changes induced by the medications patients receive, even with a decrease in dosage after some surgeries, cannot be excluded. In some of the reported studies, acute drug effects cannot be excluded either, because medications were not withdrawn or otherwise standardized. Fourth, the decrease in signal-to-noise ratio caused by stimulation artifact likely leads to missing subtle changes induced by modulation when perform-

ing electrophysiological recording. Finally, most of these studies were performed in a small number of subjects during a resting state. Therefore, inferring the impact of the modulation found in different cortical regions becomes difficult without assaying a particular function through a specific task or neuropsychological test.

In conclusion, understanding how DBS affects multiple cortical regions downstream of each specific target should allow important fundamental advances in the use of this therapeutic modality. Greater knowledge of the network effects of DBS will permit the tailoring of treatment based on biomarkers related to these effects in order to increase therapeutic efficacy and avoid undesirable side effects. Further advancement in the field is anticipated from the development of closed-loop stimulation systems that allow stimulation parameters to be adjusted based on recorded activity. Reaching this goal, however, will require more neurophysiology studies in DBS patients that go beyond simple enumeration of activation changes and that are designed to test specific hypotheses regarding motor or cognitive functions, while controlling for as many experimental confounders as possible.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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