

Disorders of the Nervous System

Subthalamic Nucleus Deep Brain Stimulation: Basic Concepts and Novel Perspectives

Clement Hamani,^{1,2,4} Gerson Florence,⁴ Helmut Heinsen,^{3,9} Birgit R. Plantinga,^{5,6}  Yasin Temel,^{6,7} Kamil Uludag,⁸ Eduardo Alho,⁴ Manoel J. Teixeira,⁴  Edson Amaro,³ and Erich T. Fonoff^{4,10}

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¹Division of Neurosurgery Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada, ²Division of Neuroimaging, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, ³Department of Radiology, University of São Paulo Medical School, São Paulo, Brazil, ⁴Division of Neurosurgery, Department of Neurology, University of São Paulo Medical School, São Paulo, Brazil, ⁵Department of Biomedical Image Analysis, Eindhoven University of Technology, Eindhoven, The Netherlands, ⁶Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands, ⁷Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands, ⁸Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands, ⁹Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Clinic of Würzburg, Würzburg, Germany, and ¹⁰Instituto de Ensino e Pesquisa Hospital Sírio-Libanês, São Paulo, Brazil

Abstract

Over the last decades, extensive basic and clinical knowledge has been acquired on the use of subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson's disease (PD). It is now clear that mechanisms involved in the effects of this therapy are far more complex than previously anticipated. At frequencies commonly used in clinical practice, neural elements may be excited or inhibited and novel dynamic states of equilibrium are reached. Electrode contacts used for chronic DBS in PD are placed near the dorsal border of the nucleus, a highly cellular region. DBS may thus exert its effects by modulating these cells, hyperdirect projections from motor cortical areas, afferent and efferent fibers to the motor STN. Advancements in neuroimaging techniques may allow us to identify these structures optimizing surgical targeting. In this review, we provide an update on mechanisms and the neural elements modulated by STN DBS.

Key words: subthalamic nucleus; deep brain stimulation; mechanisms; plasticity; anatomy; physiology; neuroimaging

Significance Statement

Over the last decades, extensive basic and clinical knowledge has been acquired on the use of subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson's disease (PD). It is becoming clear that DBS exerts its effects through several mechanisms and influences various neural structures and circuits. In this article, we discuss electrophysiological findings suggesting that stimulation not only modulates activity of neural elements but also leads to novel dynamic states of equilibrium. We also present anatomic data showing that the STN is not a homogeneous structure and review fiber pathways and regions of the nucleus potentially modulated by DBS. Finally, we discuss novel neuroimaging modalities and how these may be used to optimize technical aspects of the surgery.

Introduction

From its origins to clinical approval, the history of subthalamic nucleus (STN) deep brain stimulation (DBS) for

Parkinson's disease (PD) has been one of extreme success. In the late 1980s, thalamic stimulation was proposed as an alternative to ablative procedures for treating

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patients with tremor (Benabid et al., 1991). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated nonhuman primates, both STN lesions (Bergman et al., 1990) and stimulation (Benazzouz et al., 1993) were shown to improve parkinsonian features. Soon after, a series of PD patients was successfully treated with STN DBS (Limousin et al., 1995). To date, over 120,000 patients worldwide have been implanted with DBS systems. In PD, marked improvements have been reported in motor symptoms and levodopa-induced involuntary movements (Deuschl et al., 2006; Weaver et al., 2009).

Aside from impacting patient care, investigational data from preclinical models and surgical candidates have yielded significant advancements in our understanding of the physiology and pathophysiology of the basal ganglia. Despite this fact and the 30 years of experience with DBS, its mechanisms of action are still not fully understood.

In this review, we provide an update on mechanisms and structures modulated by STN stimulation. We discuss the complexity of DBS and the fact that neural elements may be excited or inhibited, reaching novel dynamic states of equilibrium. We also review neuroanatomical substrates modulated by DBS in the region of the STN. Finally, we examine how advancements in neuroimaging techniques may allow us to identify specific STN regions, so that this therapy may be optimized.

Anatomic aspects of the STN and nearby fiber structures

The STN is a lens-shaped densely populated structure, with extensive membrane apposition between the cell bodies, dendrites, and proximal axonal segments (Chang et al., 1983; Afsharpour, 1985; Hamani et al., 2004). It is predominantly composed of glutamatergic projection neurons with 7.5% of cells in humans being identified as GABAergic interneurons (Hamani et al., 2004; Lévesque and Parent, 2005). In primates, the STN has been subdivided in a tripartite arrangement based on physiologic characteristics and the distribution of efferent/afferent projections (Alexander et al., 1990; Parent and Hazrati, 1993, 1995a,b; Hamani et al., 2004; Krack et al., 2010; Fig. 1). The limbic STN and part of the associative territory lie in medial-rostral portions of the nucleus. The ventral-lateral-rostral portion comprises the remainder of the associative region. The dorsolateral aspects of the rostral STN and the caudal third of the nucleus are associated with motor circuits (Parent and Hazrati, 1995a; Shink et al., 1996; Hamani et al., 2004).

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Correspondence should be addressed to Clement Hamani, Division of Neurosurgery, Sunnybrook Health Sciences Centre, 2075 Bayview av S wing S126, Toronto, ON, M4N 3M5, Canada, E mail: clement.hamani@sunnybrook.ca.

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Fiber systems

One of the characteristics of the STN is that it is enveloped by fibers, including the internal capsule, pallidofugal system, and medial lemniscus.

Pallidofugal systems

The ansa lenticularis (AL) and fasciulus lenticularis (FL) are largely comprised by globus pallidus internus (GPi)-thalamic projections. In primates, the former was thought to originate largely from the lateral GPi (Kuo and Carpenter, 1973; Kim et al., 1976), sweeping around the internal capsule and curving posteriorly to reach the H field of Forel (Fig. 2). The FL (H2 field of Forel) was believed to arise from the medial GPi (Kuo and Carpenter, 1973; Kim et al., 1976), perforate the internal capsule, and form a bundle ventral to the zona incerta. In contrast to this classical view, however, recent studies suggest that the AL and FL should be considered as ventral and dorsal portions of a morphologic continuum that harbors pallidofugal axons arising from all sectors of the GPi (Parent and Parent, 2004). Independent of the origin of pallidofugal projections, the lenticular fasciculus joins the ansa along with fibers from the superior cerebellar peduncle and brainstem in the H field of Forel, forming the thalamic fasciculus (H1 field of Forel; Hamani et al., 2004; Parent and Parent, 2004). An important aspect to be noticed in nonhuman primates is that a substantial portion of pallidofugal fibers seems to run anterior to the motor STN (Fig. 3).

Afferent and efferent STN projections

STN-basal ganglia

Projections from the basal ganglia to the STN derive largely from the globus pallidus externus (GPe) via the subthalamic fasciculus, a fiber bundle that enters/departs the STN from its inferolateral border and crosses the internal capsule. Efferents from the STN to the basal ganglia comprise glutamatergic projections that innervate the globus pallidus, substantia nigra and striatum. Although most STN-nigral projections innervate the pars reticulata (SNr), fibers to the pars compacta (SNc) have received considerable attention as a substrate capable of regulating dopamine release (Smith et al., 1990; Parent and Hazrati, 1995a; Rodriguez et al., 1998). Overall, STN-basal ganglia projections seem to follow the tripartite distribution (Fig. 1; Parent and Hazrati, 1995a; Shink et al., 1996; Hamani et al., 2004; Krack et al., 2010).

STN-cerebral cortex

The hyperdirect pathway is comprised of motor and premotor cortical fibers that travel through the internal capsule and directly innervate the STN. The former innervates the dorsal STN and arises from the primary motor cortex, supplementary motor area (SMA), pre-SMA, as well as the dorsal and ventral premotor cortices (Nambu et al., 1996; Nambu et al., 1997; Nambu et al., 2000). Ventromedial portions of the nucleus receive afferents from the frontal and supplementary frontal eye fields and are involved in circuits related to eye movements (Matsumura et al., 1992). Prefrontal cortical afferents from

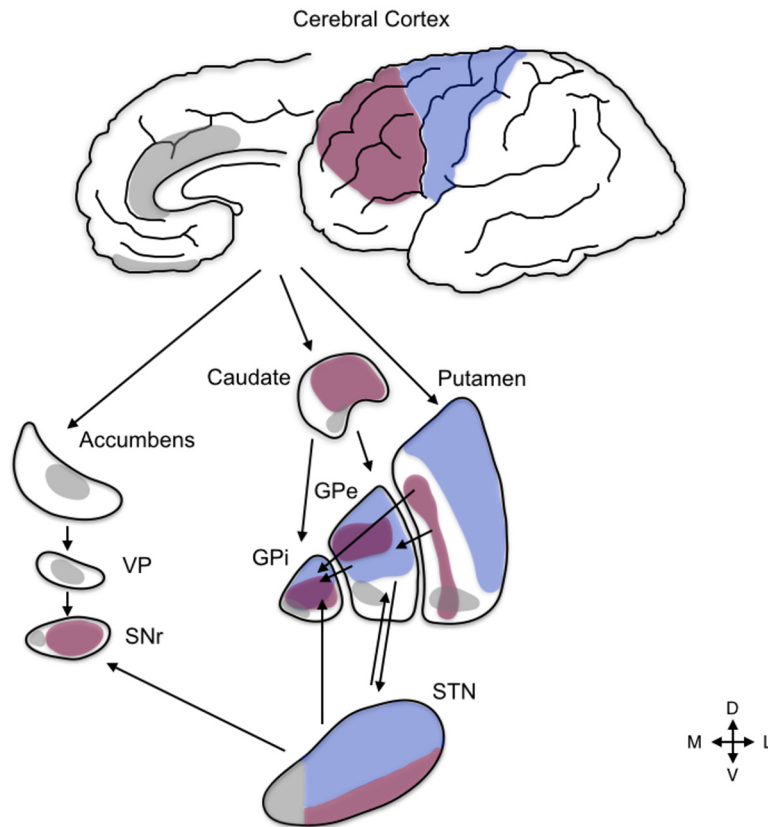


Figure 1. STN and the tripartite model. Intrinsic organization of the STN, basal ganglia structures, and cortical regions according to the tripartite functional subdivision. The motor circuit (blue) includes motor cortical areas (primary motor cortex, supplementary motor cortex, premotor cortex, and portions of the somatosensory dorsal parietal cortex), the dorsolateral portion of the postcommissural putamen, the lateral two-thirds of the globus pallidus (GPe and GPi), and a small portion of the substantia nigra (SNr). In the STN, motor regions comprise dorsal-lateral aspects of the rostrocaudal third of the nucleus (Hamani et al., 2004). Associative circuits (purple) comprise associative cortical regions, most of the caudate nucleus, the putamen rostral to the anterior commissure, the dorsal aspect of the medial third of the globus pallidus (GPe and GPi) and most of the substantia nigra. Associative STN regions may be found in ventral-lateral-rostral portions of the nucleus (Hamani et al., 2004). Limbic circuits (gray) are comprised of limbic cortical areas (e.g., orbitofrontal and the anterior cingulum), the nucleus accumbens and the most rostral portions of the striatum, the subcommissural ventral pallidum (VP), small limbic regions in the ventral portion of the medial third of the globus pallidus (GPe and GPi), the medial tip of the substantia nigra, and the ventral tegmental area. The limbic STN lies in mediorostral portions of the nucleus (Hamani et al., 2004). Arrows represent some of the most important connections between structures. D, dorsal; L, lateral; M, medial; V, ventral. We note that this schematic diagram largely represents structures in two planes with the anteroposterior depiction often lacking. This is the main reason for the superposition of colors representing motor, associative and limbic regions. Parts of this figure were modified and reprinted with permission from Hamani et al. (2004); Krack et al. (2010).

areas the dorsolateral prefrontal cortex and anterior cingulate cortex terminate in ventromedial and medial regions of the STN, respectively (Haynes and Haber, 2013).

Thalamus and brainstem

The main projections from the thalamus to the STN originate from the parafascicular and centromedian nuclei (Sadikot et al., 1992; Hamani et al., 2004). Brainstem projections arise from various nuclei and involve multiple neurotransmitter systems. These include dopaminergic fibers from the SNc (Lavoie et al., 1989; François et al., 2000; Hamani et al., 2004), cholinergic and noncholinergic projections from the pedunculopontine nucleus and laterodorsal tegmental nuclei (Carpenter et al., 1981; Mesulam et al., 1992; Lavoie and Parent, 1994), noradrenergic fibers from the locus ceruleus (Carpenter et al., 1981), and

serotonergic fibers likely from the raphe (Parent et al., 2011).

Physiologic properties of the STN and oscillatory activity

STN cells in nonhuman primates fire at 18 ± 25 Hz, mostly in irregular but also regular and bursty patterns (Wichmann et al., 1994a; Hamani et al., 2004). In parkinsonian states, the STN fires more irregularly at higher rates, ultimately disrupting the functioning of downstream basal ganglia structures (Robledo and Féger, 1990; Bergman et al., 1994; Hassani et al., 1996; Hutchison et al., 1998). Also abnormal in PD are cortico-basal ganglia oscillations. STN cells oscillating at frequencies below 10 Hz are sometimes related to parkinsonian tremor (Levy et al., 2000; Magariños-Ascone et al., 2000). Oscillations

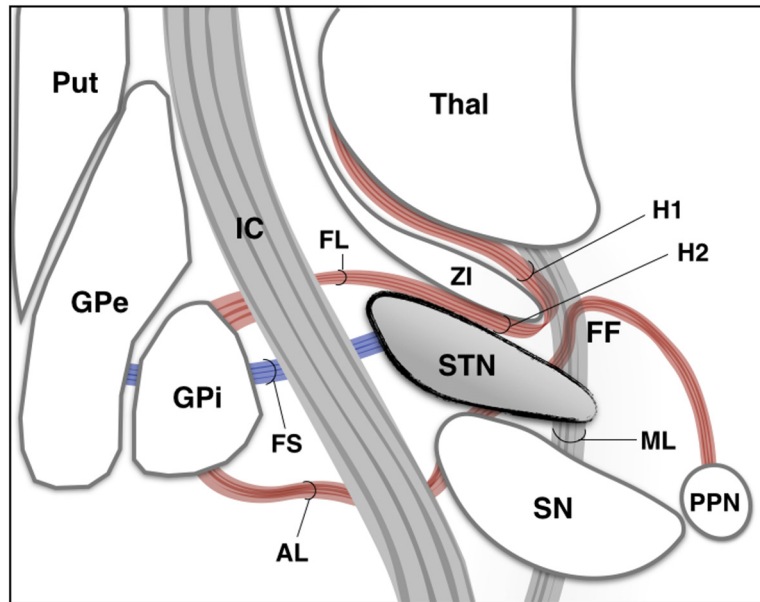


Figure 2. Anatomic aspects of the STN. Principal brain structures surrounding the STN. FF, fields of Forel; FS, subthalamic fascicle; H1, H1 field of Forel (thalamic fasciculus); H2, H2 field of Forel; IC, internal capsule; ML, medial lemniscus; PPN, pedunculopontine nucleus; Put, putamen; SN, substantia nigra; Thal, thalamus; ZI, zona incerta. Part of this figure was modified and reprinted with permission from Hamani et al. (2004).

in the 70- to 85-Hz range occur during movement or treatment with dopaminergic agonists (Magill et al., 2001; Levy et al., 2002; Hamani et al., 2004). Oscillations in the beta range (15–30 Hz) are prominent in sensorimotor regions of the basal ganglia and cortex (Bergman et al., 1994; Brown et al., 2001; Mallet et al., 2008b). These in fact seem to entrain spiking activity in the STN, striatal cholinergic interneurons and basal ganglia downstream structures (Deffains et al., 2016).

In the clinic, while treatment-induced reductions in bradykinesia and rigidity correlate with decreases in beta (Brown et al., 2001; Kühn et al., 2008; Ray et al., 2008; Kühn et al., 2009), STN stimulation at beta frequencies may worsen bradykinesia (Chen et al., 2007; Eusebio et al., 2008). These same results have not been observed in drug-naïve nonhuman primates, which have been shown to develop dystonia and myoclonia but no bradykinesia following STN stimulation (Syed et al., 2012). The

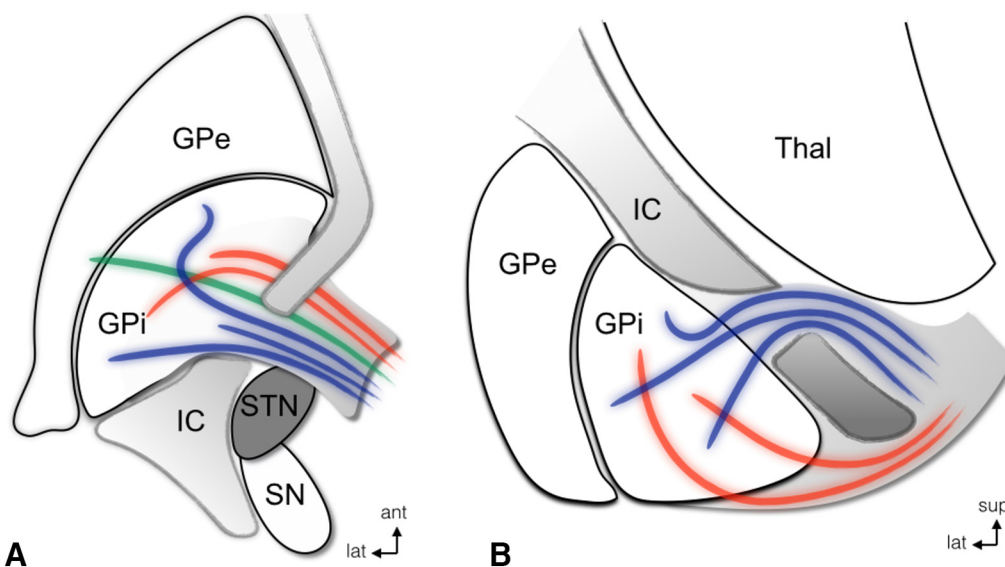


Figure 3. STN and pallidofugal fibers. Axial (A) and coronal (B) schematic representations of the AL (red) and LF (H2; blue), in relationship to the STN, in nonhuman primates. Note that both the tracts travel dorsal to the most anterior aspect of the STN. A, The thalamic fasciculus is represented in green. ant, anterior; lat, lateral; sup, superior. Modified and reprinted with permission from Parent and Parent (2004).

actual role of beta oscillations on mechanisms of bradykinesia remains disputed.

Also characteristic of PD are altered cross-frequency interactions (CFIs; López-Azcárate et al., 2010; Shimamoto et al., 2013; de Hemptinne et al., 2015). These are often appreciated when a more complex analysis of interactions between different frequency bands is conducted (Canolty and Knight, 2010). Similar to beta oscillations, CFIs correlate with motor symptoms and may be reversed by the administration of dopaminergic medications (López-Azcárate et al., 2010).

Behavioral effects of STN stimulation

In rodents, focal injections of GABAergic antagonists into the STN induce postural asymmetry and abnormal movements (Dybdal and Gale, 2000; Périer et al., 2000). Similar to the clinical scenario (Dewey and Jankovic, 1989; Lee and Marsden, 1994), both lesions and the focal inactivation of the STN in nonhuman primates induce ballism, choreic and dyskinetic movements (Hammond et al., 1979; Crossman et al., 1980; Hamada and DeLong, 1992; Beurrier et al., 1997). STN DBS delivered to otherwise naïve nonhuman primates may induce dyskinesias and abnormal movements, particularly when applied at relatively high currents (Beurrier et al., 1997; Hamani et al., 2004). In parkinsonian rodents and primates, STN lesions or high-frequency stimulation (HFS) mitigate motor deficits, bradykinesia, rigidity, and tremor (whenever this is present; Bergman et al., 1990; Aziz et al., 1992; Benazzouz et al., 1993; Wichmann et al., 1994b; Carvalho and Nikkha, 2001; Darbaky et al., 2003; Hamani et al., 2004).

In addition to motor effects, clinical studies suggest that STN DBS may be associated with impulsivity, cognitive and psychiatric adverse events (Rodríguez-Oroz et al., 2005; Frank et al., 2007; Hälbig et al., 2009; Okun et al., 2009; Weaver et al., 2009; Follett et al., 2010; Bronstein et al., 2011; Rothlind et al., 2015). As patients receiving DBS often have PD and are under pharmacological treatment, the physiologic role of the STN in nonmotor behavior may be better appraised in preclinical models (Hamani and Temel, 2012).

In animals, some of the most commonly investigated nonmotor behaviors are impulsivity, compulsivity, and drug and reward consumption (Hamani and Temel, 2012). Impulsivity can be broadly defined as acting or making decisions without appropriate forethought (Winstanley, 2011). Overall, impulsive behavior encompasses multiple facets, from motor disinhibition to maladaptive decision making, involving motor, attention, and nonplanning aspects (Brunner and Hen, 1997; Evenden, 1999; Winstanley, 2011). Frequently used paradigms to study impulsivity in rodents are those in which individuals need to withhold from making a response (e.g., measurements of reaction time) or have to properly select a response to obtain a reward (e.g., five-choice serial reaction time task; Winstanley, 2011). Commonly observed inappropriate responses during such tasks include prematurely responding to the stimuli or making errors of perseveration. In some of these paradigms, STN lesions or the focal administration of GABAergic agonists in otherwise naïve rats induce

impulsive-like behavior (Baunez et al., 1995; Baunez and Robbins, 1997, 1999b). In parkinsonian rodents, STN lesions increase perseverative responses (Baunez and Robbins, 1999a). Compared to lesion studies, the effects of STN DBS are far more controversial. In naïve animals, HFS has been shown not to affect impulse-like behavior (Desbonnet et al., 2004), reduce premature responses (Desbonnet et al., 2004), or even impair performance (e.g., is a visual attention task; Baunez et al., 2007). Similarly, studies in PD animals have shown reversal (Temel et al., 2005; Temel et al., 2006a), no effect (Darbaky et al., 2003), or a transient worsening of associated deficits (Baunez et al., 2007). Reasons for discrepancy across studies remain unclear but may be related to differences in behavioral paradigms, current intensity or the use of unilateral versus bilateral stimulation.

Along with impulsivity, gambling and punting are aspects commonly described as part of the so-called dopamine dysregulation syndrome (DDS; Fenu et al., 2009; O'Sullivan et al., 2009). In the clinic, STN DBS has been used to treat these conditions following the reduction in dopaminergic medication intake (Broen et al., 2011). Preclinical paradigms suited to model some aspects of gambling-type behavior involve the presentation of animals with options associated with variable amounts of reward, from smaller immediate to late but more gratifying compensations (Cocker and Winstanley, 2015). In otherwise naïve rodents, STN-DBS significantly increases the number of premature responses in some of these paradigms (i.e., the selection of immediate disadvantageous rewards; Aleksandrova et al., 2013). In contrast, animals bearing STN lesions have a decrease in impulsive decision making and are able to wait for larger delayed rewards (Winstanley et al., 2005; Uslaner and Robinson, 2006).

Another commonly reported side effect of STN DBS is depression (Temel et al., 2006b). Similar to the clinical scenario, rodents treated with STN DBS present depressive-like behavior in different models (Temel et al., 2007; Creed et al., 2013).

In recent years, DBS has been used to treat patients with refractory obsessive-compulsive disorder (OCD; Mallet et al., 2002; Mallet et al., 2008a; Haynes and Mallet, 2010). Preclinical models to mimic this condition are usually characterized by repetitive, excessive and inappropriate behaviors, which may occur either naturally or as a consequence of pharmacological and behavioral manipulations (Joel, 2006; Albelda and Joel, 2012; Hamani and Temel, 2012). A limitation of these paradigms, however, is that they only mimic compulsivity but not obsessions (Albelda and Joel, 2012; Hamani and Temel, 2012). In rodents, STN HFS has been shown to improve perseverative and compulsive-like behaviors (Winter et al., 2008; Klavir et al., 2009). Similarly, nonhuman primates treated with HFS in the limbic portion of the STN had an improvement in compulsive-like features induced by the injections of GABAergic antagonists into basal ganglia structures (Baup et al., 2008).

Another interesting aspect of the STN physiology is its role in mechanisms of reward and addiction. In rodents,

bilateral STN lesions increase motivation to obtain food reward (Baunez et al., 2002; Baunez et al., 2005; Rouaud et al., 2010) while reducing the preference and willingness to work for cocaine (Baunez et al., 2005; Rouaud et al., 2010). When alcohol is considered, STN lesions increase motivation for drug intake in animals considered to be “high drinkers,” inducing an opposite effect “low drinker” rats (Lardeux and Baunez, 2008). These results highlight the complexity of physiologic mechanisms of the STN on reward.

Mechanisms of DBS

Single pulses of cathodic extracellular stimulation depolarize cells, axons, and dendrites. Once action potentials are fired, neurons tend to repolarize, and the normal ionic/neurotransmitter baseline equilibrium is reestablished. These same physiologic responses do not occur when stimulation is delivered at clinical frequencies (i.e., 130–185 Hz). For one, only neural appendages fire action potentials in response to HFS. In addition, the continuous delivery of HFS overloads mechanisms responsible for the extracellular removal of certain ions and transmitters (Florence et al., 2016). Ultimately, stimulated regions reach a new dynamic state, characterized by altered ionic currents, nonsynaptic mechanisms, excessive extracellular levels of neurotransmitters/ions (e.g., potassium), and microenvironmental changes that favor the development of plasticity (Hamani and Temel, 2012; Florence et al., 2016).

From a neuronal perspective, a commonly proposed pattern of response following HFS involves the depolarization of axons and functional inhibition of cell bodies (Lozano et al., 2002; Vitek, 2002; Hamani and Temel, 2012; Florence et al., 2016). Although this is well suited to explain some DBS responses, it is rather simplistic. For example, one of the proposed mechanisms for the effects of HFS is the so-called “depolarization block” (Beurrier et al., 2001; Magariños-Ascone et al., 2002; Kringelbach et al., 2007). This has been largely defined as a state in which cells undergo depolarization with an almost complete abolishment of spontaneous action potentials (Beurrier et al., 2001; Magariños-Ascone et al., 2002). The rationale suggesting that depolarization block and a functional target inactivation may play a role in a HFS response stems from the fact that clinical outcome in some DBS applications (e.g., tremor, PD) resembles that observed with lesions. To date, stimulation-induced depolarization blocks have been largely demonstrated in brain slices. *In vivo* studies conducted in rodents (Tai et al., 2003), nonhuman primates (Meissner et al., 2005), and humans (Filali et al., 2004) have shown striking reductions in the firing of STN cells nearby the electrodes. Yet, the mechanisms responsible for this effect may not only involve a depolarization block but also the excitation of pallidal GABAergic terminals to the STN (Filali et al., 2004).

An aspect not commonly reported, however, is that depolarization blocks are not sustainable events. Over time, cells restore repolarizing mechanisms and become once again capable of firing action potentials until the development of a new depolarization block (Zheng et al.,

2011; Florence et al., 2016). As a result, the same stimulated region may contain cells that are either functionally blocked or firing in tonic or even bursty modes (Kass and Mintz, 2006; Wu and Shuai, 2012). Also, not commonly described is the fact that cells held in a depolarization block are theoretically capable of releasing neurotransmitters. As the membrane potential becomes more positive and the amplitude of action potentials decreases, both intracellular calcium influx and neurotransmitter release are decreased. Depolarized membranes, however, may still release neurotransmitters in smaller nonquantal amounts, even when the cell stops firing. This “synaptic noise” has in fact been shown to modulate postsynaptic currents (Ammari et al., 2011). Depending on the released neurotransmitter, postsynaptic neurons may depolarize or hyperpolarize, becoming more or less responsive to inputs from other presynaptic cells (Fellous et al., 2003; Faisal et al., 2008). Highlighting the importance of this mechanism, STN synaptic noise has been shown to interrupt abnormal oscillatory patterns in parkinsonian animals (Ammari et al., 2011). That said, further evidence is required to confirm the relevance of synaptic noise-associated neurotransmitter release as a mechanism of DBS.

Another commonly proposed mechanism underlying the effects of HFS is the excitation of fiber pathways (afferent and efferent projections from targeted regions as well as en passant fibers; Kringelbach et al., 2007). This is of importance, as the anterograde and retrograde propagation of action potentials may influence the physiology of brain regions at a distance from the original stimulation site (Windels et al., 2000; Hashimoto et al., 2003; Kringelbach et al., 2007; Temel et al., 2007). Fibers modulated by HFS may be those arriving, departing or passing through (en passant) the target zone. Neurotransmitters released may dictate the effects of DBS at a distance. For example, with a predominance of glutamatergic projection cells DBS in the STN has been shown to increase cell firing in structures innervated by the nucleus (Hashimoto et al., 2003). Microdialysis studies corroborate this assertion, showing glutamate release in output basal ganglia structures (Windels et al., 2000). However, with a complex interplay of modulated afferent and efferent projections, the net effects of DBS are not always predictable. As an example, STN DBS has been shown to significantly reduce neuronal firing in the nigra, particularly when applied at lower amplitudes (Maurice et al., 2003; Tai et al., 2003). This may occur due to an increased release of GABA via the modulation of pallidal activity (Windels et al., 2005). Also contributing to a functional inhibition of circuits, cells at a distance from the DBS target may not recognize stimulation-driven high-frequency rhythms that replace physiologic firing patterns (i.e., “jamming”; Benabid et al., 2002). Finally, we note that, though the main consequence of DBS at 130–185 Hz is to drive axonal projections, frequencies closer to 200 Hz may potentially lead to a state of intermittent excitation or even partial blockage of axonal firing (Kilgore and Bhadra, 2004; Florence et al., 2016).

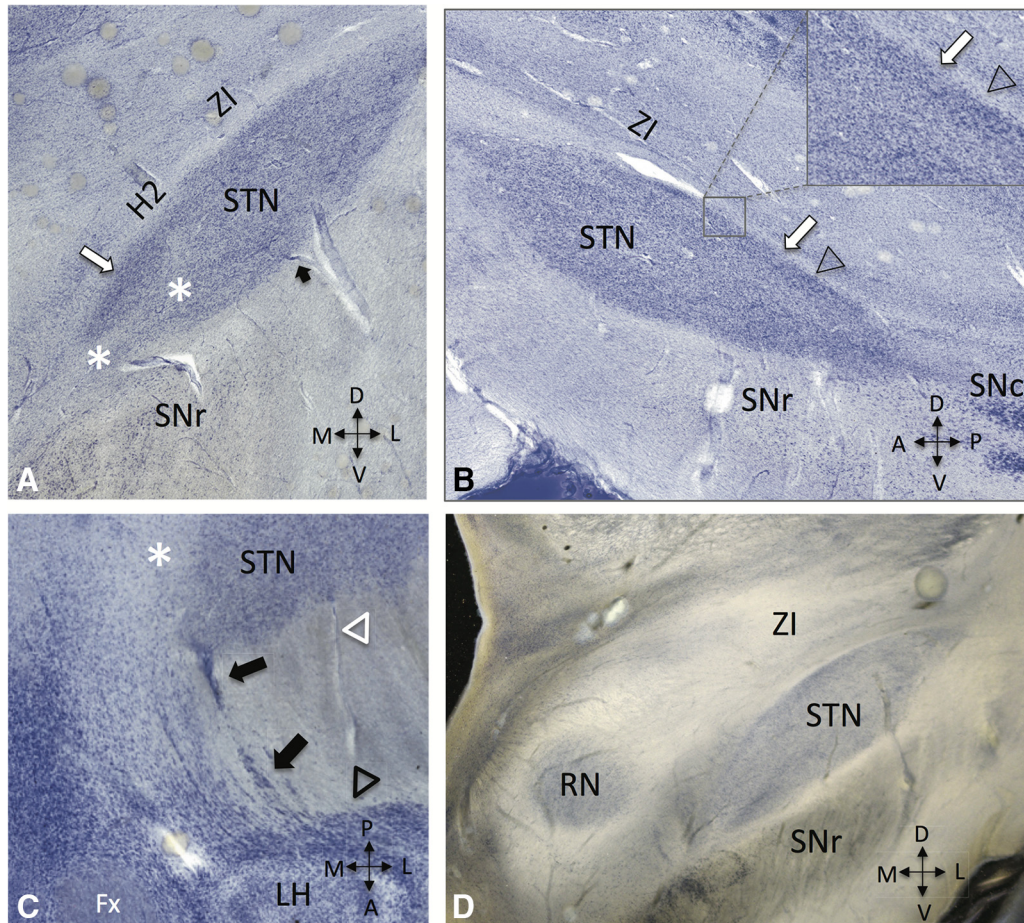


Figure 4. Histologic sections of the subthalamic nucleus (STN) region in individuals with no neurologic disorders stained for gallocyanin. **A**, Note the presence of high-density cellular regions near the borders of the nucleus (white arrow) and fibers inside its core (*). The dark arrow points to a vessel branching in the vicinity of the STN. **B**, Sagittal section (400- μm thickness) showing high-density neuronal clusters (white arrow) and a region largely comprised by capsular fibers (arrowhead) near the dorsal border of the STN. Magnified view is presented in the square above. **C**, Axial (horizontal) section (440- μm thickness) showing the anteromedial aspect of the STN in relation to the lateral hypothalamus (LH) and fornix (Fx). Black arrows denote subthalamic cell strands piercing the internal capsule and forming dissipated accessory cell groups (black open triangle) near the lateral hypothalamus. White open triangles represent the irregular boundary between STN cell clusters and capsular fibers. **D**, Coronal section (440- μm thickness) showing the STN region under dark-field illumination (RN, red nucleus). SNr, substantia nigra reticulata; SNc, substantia nigra compacta; ZI, zona incerta.

Also described following HFS are changes in glial activity, synaptic transmission and the development of various forms of plasticity (Hamani et al., 2012; Cooperrider et al., 2014). In some clinical applications (e.g., dystonia, epilepsy) the effects of DBS are often protracted or build up with time. Although an immediate clinical benefit is often appreciated in PD, when batteries expire patients may not present the same preoperative symptoms or medication requirements, suggesting that plastic events may have reorganized the system.

To date, several studies in PD patients and animal models have shown that STN HFS reduces beta oscillations, coherence between motor cortex and STN activity, and phase amplitude coupling (Wingeier et al., 2006; Eusebio et al., 2008; Kühn et al., 2008; Bronte-Stewart et al., 2009; Giannicola et al., 2010; Tass et al., 2012; de Hemptinne et al., 2015). Some of these signals have been recently proposed to feed closed-loop stimulation sys-

tems. Studies in nonhuman primates (Rosin et al., 2011; Johnson et al., 2016) and PD patients (Little et al., 2013) have shown that, compared to regular or intermittent HFS, stimulation delivered following the detection of beta oscillatory bursts or according to the pattern of neuronal firing induce a similar or slightly more pronounced clinical improvement. In a recent report, closed-loop STN stimulation delivered to PD primates did not improve bradykinesia during a reaching task (Johnson et al., 2016). This result has been attributed to the fact that beta amplitude declines during motion and suggests that additional work is still needed before closed-loop stimulation may be implemented in the clinic.

Cytoarchitectonic features and elements modulated by DBS

As most human studies addressing cytoarchitectonic features were conducted with classical staining tech-

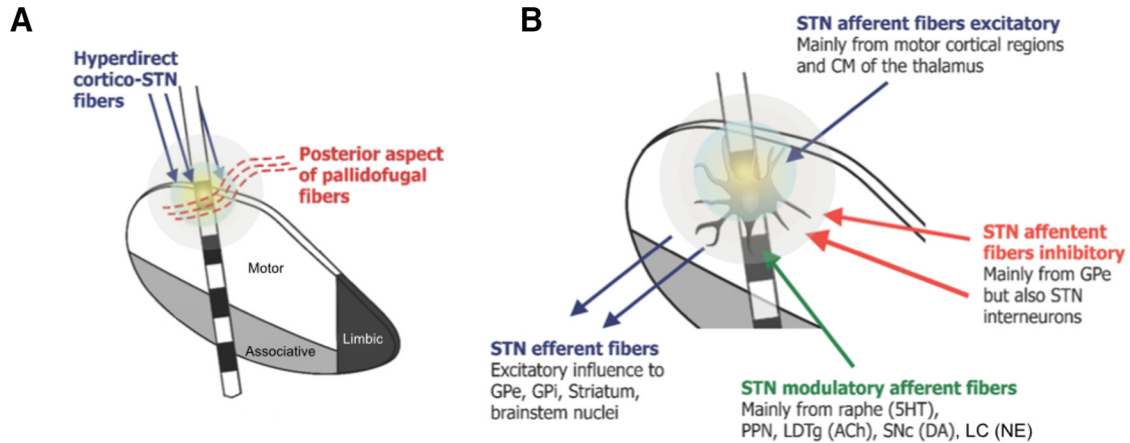


Figure 5. Neural elements modulated by DBS delivered to the dorsal region of the motor subthalamic nucleus (STN) territory. **A**, Schematic representation of the STN showing potential fiber pathways modulated by DBS. Hyperdirect STN projections from motor cortical regions are depicted in blue. Pallidofugal fibers are depicted in red. **B**, Schematic representation of an STN neuron modulated by DBS. STN axons driven by stimulation would excite connected structures. Stimulation of STN afferents would potentially excite these projections, inducing complex effects. STN cells would be excited by stimulation of cortical and thalamic-STN projections (blue) and inhibited by stimulation of globus pallidus projections and appendages from local interneurons (red). Stimulation of brainstem-STN projections would modulate STN neuronal activity via different neurotransmitter systems (green). 5HT, serotonin; ACh, acetylcholine; CM, centromedian nucleus of the thalamus; DA, dopamine; GPe, globus pallidus externus; GPI, globus pallidus internus; LC, locus ceruleus; LDTg, laterodorsal tegmental area; NE, norepinephrine; PPN, pedunculopontine nucleus; SNc, substantia nigra compacta. Part of the figure was reprinted with permission from Hamani et al. (2004).

niques, a few caveats need to be taken into account. First, the STN has an intimate relationship and is partly enwrapped by fibers. Second, its axes are not arranged in parallel to the main axes of the hemispheres. Third, depending on the plane of section, shape and individual orientation, different profiles and grazing artifacts may be observed in Nissl or Golgi-stained sections. Finally, cytoarchitectonic delineations are subject to interindividual variability. When thick gallocyanin stained slices and dark-field illumination sections are examined (Heinsen et al., 2000), a few aspects not previously reported in classical postmortem human studies can be appreciated. (1) Rather than a homogeneous structure, the STN has a looser cellular core and densely packed peripheral regions (Fig. 4). (2) Fiber bundles may be identified near the STN borders as well as in central parts of the nucleus. (3) The medial STN has a fairly irregular outline, with rostro-medial strands of cells almost reaching the hypothalamus (Fig. 4).

Electrode contacts used for chronic DBS in PD are often located near the dorsal border of the nucleus (Herzog et al., 2004; Pollo et al., 2007). In addition to being part of the motor territory, this region is characterized by the presence of high-density cellular clusters in postmortem studies. The main fiber pathways entering the motor STN are hyperdirect projections from motor cortical areas, which in fact may be a major substrate modulated by STN DBS (Fig. 5). In agreement with this statement, optogenetic studies have shown that stimulation of hyperdirect pathways may rescue behavioral deficits in parkinsonian rodents (Gradinaru et al., 2009). To date, the modulation of fibers in the fields of Forel, particularly pallidothalamic projections, have been proposed as a potential mechanism for the effects of DBS. Although not many studies have reported anatomic details of these

systems in humans, data from nonhuman primates suggest that most of the AL and FL lie slightly anterior to the region where electrodes are often implanted. Other substrates that could be potentially modulated by DBS are axons within the motor STN territory. These may comprise afferents/efferents to and from the motor STN. Stimulation of the former would theoretically excite or inhibit the target zone, depending on the neurotransmitter released (e.g., glutamate from cortical/thalamic afferents, GABA from pallidal afferents, serotonin/dopamine/acetylcholine from brainstem afferents). The excitation of STN glutamatergic efferents would drive activity in structures receiving its projections.

DBS electrodes used to treat OCD are placed in anteromedial regions of the STN (Mallet et al., 2008a). Under these circumstances, cell bodies modulated by stimulation would be those innervating limbic/associative STN territories and nearby hypothalamic regions. Hyperdirect components would be fibers from the dorsolateral prefrontal cortex, orbitofrontal cortex and cingulate gyrus. Stimulated afferents/efferents to and from the STN would be those innervating limbic/associative regions of the basal ganglia, thalamus and brainstem. As PD patients who develop DBS-induced psychiatric side effects often have electrodes implanted medially, the same neural elements could be theoretically involved in mechanisms of these adverse events.

Neuroimaging

Adequate visualization of the STN greatly depends on MRI protocols. On T2, T2*, and susceptibility weighted images, the nucleus appears as a dark structure. At 1.5T and less so at 3T, MRI identification of the STN may be hindered by limited imaging contrast and the poor identification of the STN/SN border (Fig. 6). Ultrahigh field (7T

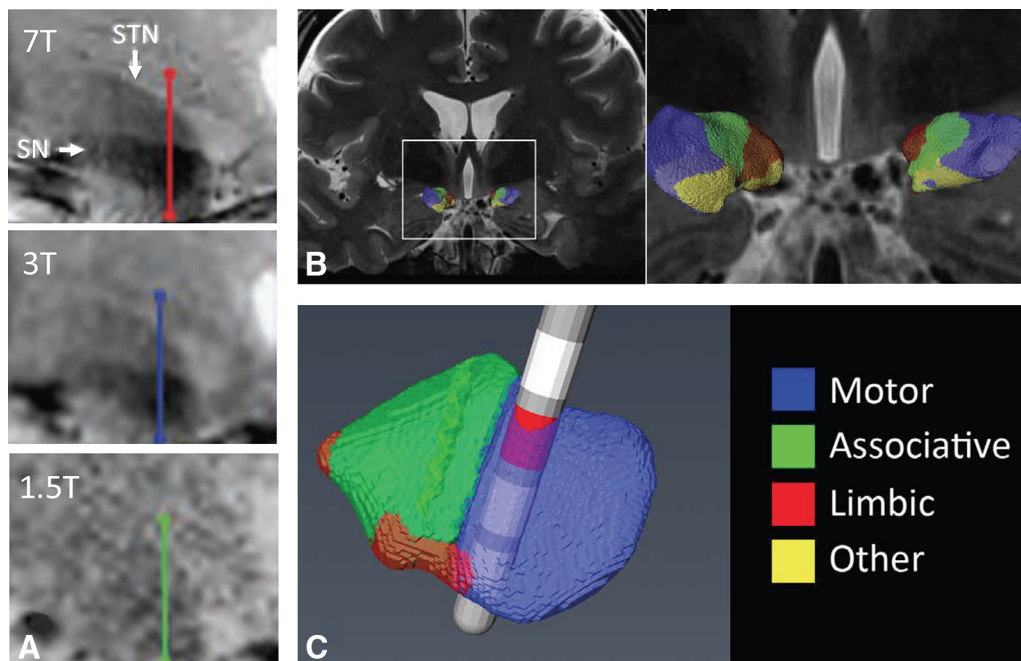


Figure 6. Tractography based subdivision of the STN. **A**, Coronal T2*-weighted images obtained at 7.0T, 3.0T, and 1.5T. **B**, Coronal images showing STN connectivity with limbic (red), associative (green), motor (blue), and remaining (yellow) cortical areas. **C**, Oblique view of the STN with a superposed DBS electrode and an active contact implanted in the motor territory. Reprinted with permission from Cho et al. (2010); Plantinga et al. (2014); Plantinga et al. (2016).

and higher) MRI has the potential to overcome some of these limitations and promises to facilitate patient-specific direct targeting (Plantinga et al., 2014).

As described above, the STN may be subdivided in different subterritories based anatomic connections and physiologic characteristics. The use of diffusion weighted imaging based tractography has been proposed as a potential strategy for classifying deep brain structures into subregions (Behrens et al., 2003). The simplest of these models is diffusion tensor, which can be created with relatively short scan times but fails when there are multiple fiber orientations within one voxel. More advanced models seem to be able to cope with crossing fibers when combined with probabilistic tracking algorithms (Behrens et al., 2007; Tournier et al., 2007). On a group level, these models have been used to subdivide the STN into functional regions in 3T scanners (Lambert et al., 2012). At 7T, the motor region could be successfully discriminated based on structural connectivity (Plantinga et al., 2016; Fig. 6). Although this technique is not without limitations (e.g., false positives and negatives), these results highlight the potential future application of neuroimaging strategies to refine surgical targeting.

Conclusions

In summary, the mechanisms involved in the effects of DBS seem to be far more complex than previously anticipated. Instead of a simple excitation of fibers and inhibition of cells, neural elements influenced by DBS reach novel dynamic states over time. From an anatomic perspective, human pathologic specimens suggest that the STN has dense cellular aggregates near its borders and a less compact central core, which is infiltrated by fibers.

Discriminating the nature of these fibers and those crossing the dorsal STN border (i.e., where active contacts are implanted) will be crucial for a better appraisal of mechanisms responsible for this therapy.

One of the ultimate goals to be achieved with DBS is to maximize efficacy while minimizing side effects. The former has been attempted by mimicking brain rhythms so that some forms of beta band activity and other pathologic rhythms may be reduced. To date, similar strategies have been effective in preclinical models but still need to be perfected for clinical use. With proven efficacy, a key factor to minimize DBS-induced side effects is to avoid stimulating structures and brain regions involved in adverse events. A major advance toward this objective is the use of directional leads, which may deviate and steer current away from these structures. Also important have been recent advancements in neuroimaging modalities. The use of higher magnetic fields and diffusion/connectivity approaches to identify subregions of the nucleus and specific fiber bundles may advance the way we do surgery by improving targeting precision.

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