Subthalamic nucleus and its connections : Anatomic substrate for the network effects of deep brain stimulation

Eduardo E. Benarroch

Neurology 2008;70;1991
DOI 10.1212/01.wnl.0000313022.39329.65

CLINICAL IMPLICATIONS OF NEUROSCIENCE RESEARCH

Section Editor
Eduardo E. Benarroch, MD

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Anatomic substrate for the network effects of deep brain stimulation

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Address correspondence and reprint requests to Dr. Eduardo E. Benarroch, Mayo Clinic, Department of Neurology, 200 First Street SW, West 8A Mayo Bldg., Rochester, MN 55905
benarroch.eduardo@mayo.edu

The subthalamic nucleus (STN) is a nodal component of the basal ganglia circuits. It has been classically considered as a relay of the "indirect" pathway by which the striatum controls the output of the basal ganglia and thus motor function.[1] There is abnormal activity of this pathway as a consequence of dopamine deficiency in Parkinson disease (PD),[1] and this has provided rationale for the use of high frequency stimulation of the STN for treatment of the motor manifestations of this disorder. However, abundant experimental evidence indicates that the STN is a critical component of complex networks controlling not only motor function, but also cognition, emotion, and thalamocortical excitability. This explains the behavioral and cognitive consequences of STN stimulation and provides rationale for the potential application of this procedure to other disorders, including epilepsy and psychiatric disorders. Therefore, updated information on the connectivity and functions of the STN may be helpful to the clinician. These topics have been the subject of extensive reviews[1-7] and some emerging concepts are briefly discussed in this article.

ANATOMY AND PHYSIOLOGY OF THE SUBTHALAMIC NUCLEUS

Organization and connectivity. The basal ganglia influence several aspects of cortical function through parallel corticobasal ganglia-thalamocortical loops or circuits: motor, oculomotor, associative (dorsolateral prefrontal and lateral orbitofrontal), and limbic.[8] Each circuit originates from a specific area of the cerebral cortex, is processed along different components of the striatum, globus pallidus (GP), and substantia nigra pars reticulata (SNr), and, via specific thalamic nuclei, projects back to the cortical input areas. The STN is one of the most important control structures of these circuits[1,7] (figure 1).

The STN, like their other components of the basal circuits, is subdivided into different territories, motor, oculomotor, associative, and limbic, each with different connections and functions[2,4,7] (figure 2). The large dorsolateral portion of the STN corresponds to the motor territory; the ventromedial portion to the associative territory and the medial tip to the limbic territory of the STN. Most STN neurons are glutamatergic projection neurons and provide a powerful excitatory input to the external segment of the GP (GPe) and to the two output structures of the basal ganglia, the internal segment of the GP (GPi), and the SNr. These output nuclei exert a tonic inhibitory influence on thalamic relay neurons and brainstem targets.[2] Via its excitatory influence on the GPi and SNr, the STN has a pivotal role in controlling activity within each corticobasal ganglia-thalamocortical network.[1-7]

The STN receives two main inputs: excitatory glutamatergic projections from the cerebral cortex and inhibitory γ-aminobutyric (GABA)ergic projections from the GPe. The different subterritories of the STN receive functionally organized projections from the cerebral cortex and the GPe and project to different targets (figure 2). The large motor territory of the STN receives somatotopically organized inputs from the primary motor cortex and projects to both the GPe and the GPi. The STN is classically considered a relay of the "indirect" pathway by which the striatum, via GABAergic inputs to the GPe, disinhibits the STN and thus increases activity of the GPi/SNr. This pathway inhibits motor programs that may interfere with the execution of a selected motor program, which is activated via a "direct" striatal

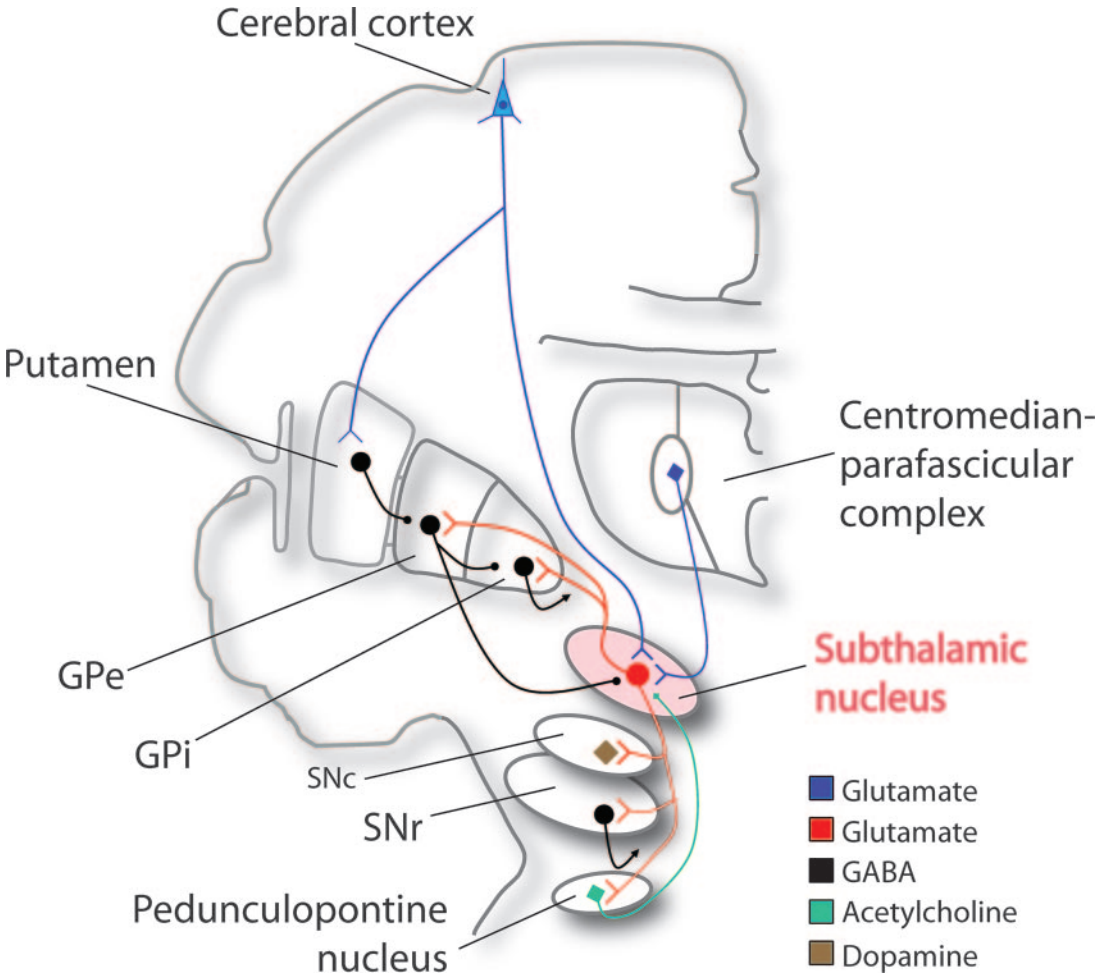
GLOSSARY

GP = globus pallidus; **GPe** = external segment of the globus pallidus; **GPi** = internal segment of the globus pallidus; **PD** = Parkinson disease; **PPT** = pedunculopontine tegmental nucleus; **SNc** = substantia nigra pars compacta; **SNr** = substantia nigra pars reticulata; **STN** = subthalamic nucleus.

From the Department of Neurology, Mayo Clinic, Rochester, MN.

Disclosure: The author reports no disclosures.

Figure 1 Main connections of the subthalamic nucleus



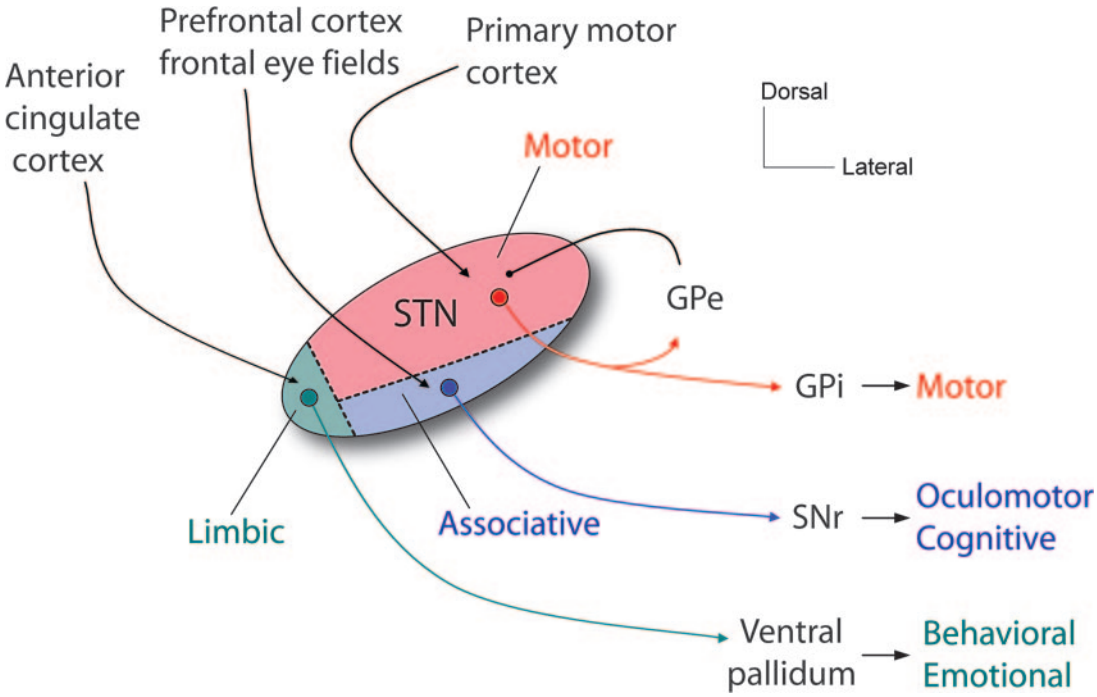
The subthalamic nucleus receives direct excitatory inputs from the cerebral cortex and centromedian-parafascicular nucleus of the thalamus (blue) and sends excitatory projections (red) to the output nuclei of the basal ganglia, the internal (GPi) and external (GPe) segments of the globus pallidus, substantia nigra pars reticulata (SNr) and compacta (SNc), and the pedunculopontine nucleus. The subthalamic nucleus receives reciprocal inhibitory inputs from the GPe, and modulatory inputs from the SNc and pedunculopontine nucleus. The GPi, GPe, and SNr send inhibitory projections (black) to their targets. The pedunculopontine nucleus sends glutamatergic and cholinergic (green) projections to the STN.

projection to the GPi/SNr. However, most inputs from the GPe, as well as those from the motor cortex, target STN neurons that project back to the GPe rather than those projecting to the GPi.[2] This emphasizes the important role of reciprocal STN-GPe connections both in normal motor control and in pathologic basal ganglia activity.

The associative territory of the STN receives inputs from the dorsolateral prefrontal cortex and frontal eye fields and projects to the SNr, which is involved in oculomotor control and cognitive aspects of motor behavior. The limbic territory receives inputs from the medial prefrontal and anterior cingulate cortices and projects to the ventral and medial pallidum, which control motivational and emotional aspects of motor behavior. Thus, the STN is not merely a passive relay station of the indirect pathway but acts as a second, independent input area through which the cerebral cortex controls multiple aspects of motor function and behavior.[2-7]

Despite the segregation of inputs and outputs of the different territories of the STN, there is integration of information by STN neurons, particularly in those located at the boundaries between territories. This has been elegantly shown in a recent mapping study on two patients with PD who underwent selective stimulation of subterritories of the STN with simultaneous assessment of cortical activation using PET.[9] In these patients, stimulation through an electrode contact localized in the anteromedial STN consistently produced a hypomanic state that was associated with changes in activity of both limbic and associative cortical areas; stimulation of this anteromedial contact, as well as the contact im-

Figure 2 Functional subdivisions of the subthalamic nucleus



The subthalamic nucleus (STN) is subdivided into a large dorsolateral motor territory, a ventromedial associative territory, and a medial limbic territory. Each territory receives inputs from different areas of the cerebral cortex and provides output to different target nuclei, including the internal segment (GPi) and external segment (GPe) of the globus pallidus, substantia nigra pars reticulata (SNr), and ventral pallidum. These input-output interactions provide for parallel control of motor, oculomotor, cognitive, and emotional functions independently of "indirect" pathways via the striatum and GPe.

mediately dorsal to it, led to improvement of the motor symptoms.[9]

The STN is also interconnected with other areas that have an important role in control of movement, cognition, emotion, and behavior[10-12] (figure 1). It receives a direct glutamatergic input from the centromedian and parafascicular nuclei of the thalamus, which also project to the striatum and receive topographically segregated outputs from the GPi and SNr. The STN also has important reciprocal connections with the pedunculopontine tegmental nucleus (PPT). The PPT consists of two groups of neurons, glutamatergic and cholinergic, that project to the STN, substantia nigra pars compacta (SNc), thalamus, brainstem, and spinal cord. The PPT is an integral component of the basal ganglia circuits and has an important role in controlling motor pattern generators, including those involved in gait.[10,11] The PPT has also been implicated in behavioral reinforcement, learning, and attention. The STN sends a robust glutamatergic projection to the PPT, which sends reciprocal glutamatergic and cholinergic inputs to the STN.[2] The STN also has reciprocal interactions with the dopaminergic neurons of the SNc. Dopaminergic neurons innervate the STN,[13] and the STN, both directly and via the PPT, conveys excitatory influence from the prefrontal cortex to these dopaminergic neurons, which is critical for their reward-related activity.[14]

Physiology of the STN. The pattern and rate of activity of STN neurons are regulated by the interplay among their intrinsic membrane properties and the interaction between inhibitory GABAergic inputs from the GPe and excitatory glutamatergic inputs from the cerebral cortex.[7] Cortical inputs evoke burst firing in STN neurons when these neurons are hyperpolarized by GABAergic inputs from the GPe. This interaction may elicit rhythmic, coherent activity in both the STN and GPe, via the powerful reciprocal connections between these two structures. This rhythmic synchronized activity may then be conveyed via the GPi/SNr to thalamocortical neurons.[15,16] Dopamine, acting via different types of receptors expressed in the STN, exerts a critical modulatory role on this circuit and sets the pattern of activity of STN neurons.[17] For example, activation of presynaptic D_2 receptors reduces the probability of release of GABA or glutamate in the STN whereas activation of both D_1 and D_2 receptors promotes regular, single spike tonic firing and prevents burst firing of STN neurons.[17]

CLINICAL CORRELATIONS **Parkinson disease.** PD is characterized by the emergence of pathologic activity in the STN, GPe, and GPi/SNr.[15,16] This is characterized by a correlated, coherent, and rhythmic activity at both beta (13–30 Hz) and tremor (4–10 Hz) frequencies within and between these structures. High-frequency (>60 Hz) STN stimulation or dopamine receptor activation interrupt this beta-synchrony and improves motor function in these patients.[15,16] However, despite the clinical efficacy of high-frequency STN stimulation on ameliorating the motor manifestations of PD,[18] the precise mechanisms by which this occurs are not fully understood and remain controversial.[19] For example, whereas high frequency STN stimulation generally elicits inhibition of STN neurons,[20] it may result in decreased[21] or increased[22] activity in the SNr. In addition, findings in the monkeys with MPTP-induced parkinsonism indicate that high frequency STN may reduce the degree of dopaminergic cell loss in the SNc.[23]

Recently, the stimulation of the PPT, a nucleus that is intimately interconnected with the STN, has been explored as a therapeutic target to improve gait and posture in PD.[24] A recent report indicates that bilateral PPT stimulation associated with STN stimulation may improve gait in patients with advanced PD who had failed to respond to STN stimulation alone.[25]

Epilepsy. There is experimental evidence that the basal ganglia, via the STN and SNr, contribute to determining susceptibility to seizures.[26] The STN sends an excitatory projection to the SNr, which exerts a tonic GABAergic influence on thalamocortical neurons, which predisposes to rhythmic burst activity of these cells. This may trigger rhythmic cortical activity that manifests with spike and wave discharges characteristic of absence seizures[27] and may propagate to the basal ganglia via cortico-STN-SNr pathways.[28] Stimulation of the STN interrupts different types of seizures in experimental animals.[26] Several reports indicate that STN stimulation may reduce seizure frequency in patients with refractory partial epilepsy[29] or progressive myoclonic epilepsy.[30] The parameters of STN stimulation necessary to control seizures are different from those effective in PD, suggesting involvement of different STN-related networks in these disorders.[31]

Psychiatric disorders. The ventromedial (associative) and the medial (limbic) territories of the STN have connections with pallidal and nigral circuits that influence the functions of the prefrontal, orbitofrontal, and anterior cingulate cortices, which are critical in cognition, emotion, and control of behavior.[5,6] Not surprisingly, STN stimulation, particularly when the contacts are located ventromedially to the intended motor territory, may result in adverse cognitive and neuropsychiatric outcomes.[32,33] These include transient confusion, apathy, and reduced verbal fluency; impaired attention, working memory, and response inhibition; and depression, anxiety, hypomania, hypersexuality, hallucinations, psychosis, and even suicide.[32,33] The observation that after STN stimulation there was improvement of obsessive and compulsive symptoms in few patients with PD[34,35] led to the suggestion that this procedure may be a potential treatment for refractory cases of obsessive-compulsive disorder.

PERSPECTIVE The STN is a pivotal component of parallel networks that regulate motor, cognitive, and affective behavior. Recent therapeutic developments, such as gene therapy with adeno-associated virus borne glutamic acid decarboxylase (the enzyme required for synthesis of GABA) transferred into the STN[36] and the beneficial effect of targeting the STN for treatment of epilepsy and psychiatric disorders, are likely to continue to stimulate basic and clinical research focused on this critical structure.

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