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REVIEW ARTICLE

Anatomy of the Subthalamic Nucleus

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The subthalamic nucleus (STN) is a densely populated lens-shaped structure that is part of the basal ganglia and is located between the thalamus and midbrain. Deep brain stimulation (DBS) of STN is a proven neurosurgical treatment that can relieve refractory motor symptoms in Idiopathic Parkinson's disease (IPD). The STN has close relationships with other deep brain structures. In order to apply STN-DBS therapy in IPD patients, precise and thorough identification of the 3D anatomy of the STN and related structures is needed to create a more specific understanding of STN for physicians.

KEY WORDS: Subthalamic nucleus · Basal ganglia · Deep brain stimulation · Parkinson's disease.

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a proven neurosurgical treatment that can relieve refractory motor symptoms in Idiopathic Parkinson's disease (IPD). Several series studies have successfully treated IPD with STN-DBS, with marked improvements in motor symptoms and levodopa-induced involuntary movements.[5)10)19)23-25)29)34-37)] Despite extensive use of the STN as a DBS target, understanding the anatomy of the STN is still difficult. The STN has close relationships with other deep brain structures, such as the zona incerta (ZI), medial lemniscus, substantia nigra, red nucleus, and globus palidus. Physicians need a more specific understanding of the STN itself prior to applying STN-DBS in IPD patients. This article reviews the anatomy of the STN in the basal ganglia from various perspectives. The technique of DBS and its neurophysiology will be covered separately in another article.

EMBRYOLOGY OF THE BASAL GANGLIA

The basal ganglia occur within the neural tube. The basis of neural tube development begins when the notochord induces the ectoderm to become neuro-ectoderm. This latter develops into a neural plate. The neural plate has neural grooves that fold and fuse to become a neural tube. The primary vesicle is the forebrain vesicle, which is known as the prosencephalon. The prosencephalon then develops into the telencephalon and diencephalon. The telencephalon eventually gives rise to the striatum (caudate and putamen) of the basal ganglia, and the diencephalon gives rise to the globus pallidus, thalamus, subthalamus, hypothalamus, and STN. On the other hand, the substantia nigra originates from the mesencephalon, and the pons and medulla originate from the rhombencephalon.[16)30)38)]

BLOOD SUPPLY OF THE BASAL GANGLIA

The perforating vessels supply very important regions of the brain stem and basal ganglia. There is a range from 0 to 14 perforating arteries, with the smallest being the diencephalic perforators and the largest being the lenticulostriate arteries. The basal ganglia are primarily supplied with blood by the lenticulostriate arteries, which are branches of the middle cerebral artery. These are prone to bleeding in patients with uncontrolled hypertension, which leads to basal ganglion hemorrhage.[11)33)]

ANATOMY OF THE SUBTHALAMIC NUCLEUS

The STN is a densely populated lens-shaped structure, first described by Jules Bernard Luys in 1865.[26)] The subthalamus is the most ventral part of the diencephalon. It is part of the basal ganglia and is located between the thalamus and midbrain. The basal ganglia include the striatum, globus pallidus, substantia nigra, and STN. The stri-

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atum consists of the putamen and caudate nucleus, while the globus pallidus consists of internal and external segments, and the substantia nigra consists of the pars compacta and pars reticulata.

The subthalamus includes the ZI and the STN. The largest part of the subthalamus is the STN, which is associated with the integration of somatic motor function. The most inferior part of the thalamus is situated below the STN level. More medially, the red nucleus can be defined adjacent to the midline and is medial and posteroinferior to the STN. The substantia nigra spreads along the subthalamic area inferior to the STN and the red nucleus. This is more easily visualized as a 3-dimensional image (Fig. 1), and it appears as in Fig. 2 on MRI.

The ZI, a superior continuation of the brainstem reticular formation, is enveloped by efferent fibers from the globus pallidus interna (GPi) that pass to the ventrolateral and ventral anterior nuclei of the thalamus. The STN is located ventral, anteroinferior, and slightly lateral to the ZI. The rostral part of the ZI extends over the dorsal and medial surfaces of the STN, and its caudal part lays posteromedial to the STN. The STN is surrounded by other fibers, including the internal capsule, pallidofugal system, and medial lemniscus. The ansa lenticularis (AL) and fasciculus lenticularis (FL) constitute the majority of the GPi-thalamic projections.[18)22)] The AL, which is composed of pallidofugal fibers, lies between the GPi and STN within the prerubural region. The AL initially travels infero-medially through the posterior limb of the IC toward the STN, passes inferior to the STN, and stays medial to the nucleus during its final ascent.

CONNECTIVITY OF THE STN

The STN is a critical component of complex networks controlling not only motor function, but also cognition, emotion, and thalamocortical excitability. The STN has three subdivisions and is functionally divided into three segments; 1) sensorimotor (dorsolateral), 2) limbic (medial), and 3) cognitive-associative (ventromedial).[13-15)] The dorsolateral sensorimotor region of the STN is the generally accepted target of DBS for motor symptoms such as tremor or bradykinesia in IPD patients.[6-8)20)32)]

Basal ganglia-Thalamocortical Circuit

In order to discuss the motor function of the STN, the basal ganglia-thalamocortical circuit must be described. The basal ganglia can be functionally divided into input zones, output zones, and intermediate zones. The input zone corresponds to the striatum, the output zone corresponds to the GPi and substantia nigra pars reticulata (SNr), and the intermediate zone corresponds to the globus pallidus externa (GPe) and STN.

As the striatum, the input zone, the nerves originating from the cerebral cortex of all regions are mainly innervated. A motor circuit originates in the supplementary motor area, motor cortex, and somatosensory cortex. The striatum is also innervated by dopaminergic neurons from the ventral tegmental area. The output zones, GPi and SNr, are connected to the VA and VL thalamic nuclei. These relay the signal back to the frontal cortex, which is responsible for movement. There is also a route down to the pedunculopontine nucleus (PPN) that originates from the SNr and does not proceed via the thalamus. This connection provides a pathway through which the basal ganglia can connect to the brainstem or spinal cord without passing through the cerebrum.

Corticostriatal projections, STN-GPi/SNr projections, and thalamocortical projections all use glutamate as excitatory, while the nigral-striatal projection secretes do-

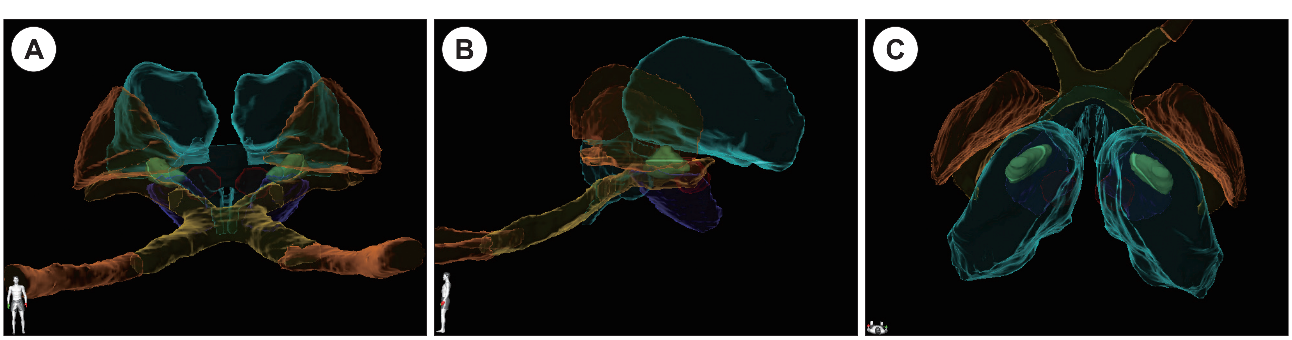

Fig. 1. The subthalamic nucleus and surrounding structures in a 3-dimensional image. A: Anterior view. B: Lateral view. C: Superior view. Solid green mass: subthalamic nucleus; Hollow green mass: Thalamus; Hollow orange mass: Globus pallidus; Hollow red mass: Red nucleus; Hollow blue mass: Substantia nigra; Solid yellow and orange track: Optic nerve and optic chiasm.

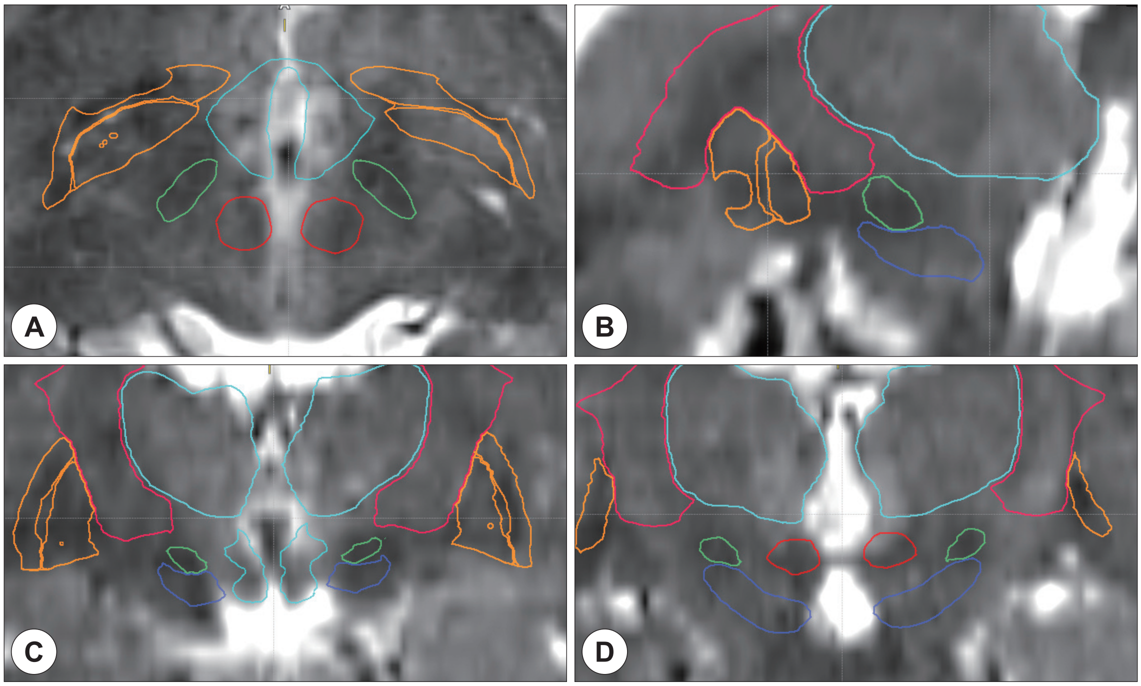

Fig. 2. Brain atlas of basal ganglia overlaid within T2-weighted images. A: Axial image at the level of the STN. B: Sagittal image at the level of the STN. C: Coronal image at the level of the STN. D: Coronal image at the level post-STN. Green: Subthalamic nucleus; Sky-blue: Thalamus; Orange: Globus pallidus interna and externa; Red (circled): Red nucleus; Red (between sky-blue and orange): Internal capsule; Violet: Substantia nigra. STN: As its name suggests, it is located under the thalamus. The red nuclei are medial and the substantia nigra is inferior. The internal capsules pass between the globus pallidus and the thalamus.

pamine. All other pathways are inhibitory and are mediated by GABA. The signal entering the striatum is connected to GPi and SNr, through the direct and indirect pathway. The direct pathway is the GABA pathway of the striatum, which is directly connected to the output zone. Substance P and dynorphin co-exist in the GABA neurons involved here. The indirect pathway reaches the output zone via GABAergic neurons, the GPe, and the STN of the striatum, where enkephalin exists. The STN is the only excitatory nucleus in the basal ganglia and may be a driver of basal ganglia output.[4] The connection from the STN to the output zone is an excitatory pathway that uses glutamate. These direct and indirect pathways have the opposite effect on the output zone neurons. The direct pathway is excitatory and is in charge for the initial part of the movements, while the indirect pathway is inhibitory and it prevents the unnecessary movements. In the cortex, the direct pathway provides positive feedback, and the indirect pathway provides negative feedback. The balance between direct and indirect pathways is regulated by the differential actions of dopamine from neurons in the SNc on striatal neurons. The release of dopamine in the striatum increases activity along the direct pathway and reduces activity along the indirect pathway. Together these actions result in a net reduction in GPi and SNr activity.[1][3][9][17] Meanwhile, hyperdirect pathway is a monosynaptic axonal connection from cerebral cortex to the STN. It bypasses the striatum and thus functions in parallel with the direct and indirect pathways.[28] This pathway has increased its importance, as it is positioned to provide a rapid global inhibition that may shape temporal dynamics of action selection and cancellation (Fig. 3).[12][21]

Associative and limbic function

The STN is interconnected with other areas that have an important role in the control of not only movement, but also cognition, emotion, and behavior. The associative area receives inputs from the dorsolateral prefrontal cortex and frontal eye fields and projects to the SNr, which is involved in oculomotor control and the cognitive aspects of motor behavior.[2][31] The limbic area receives input 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.[2][31] PPN has also been implicated in behavioral reinforcement, learning, and attention. The STN sends a glu-

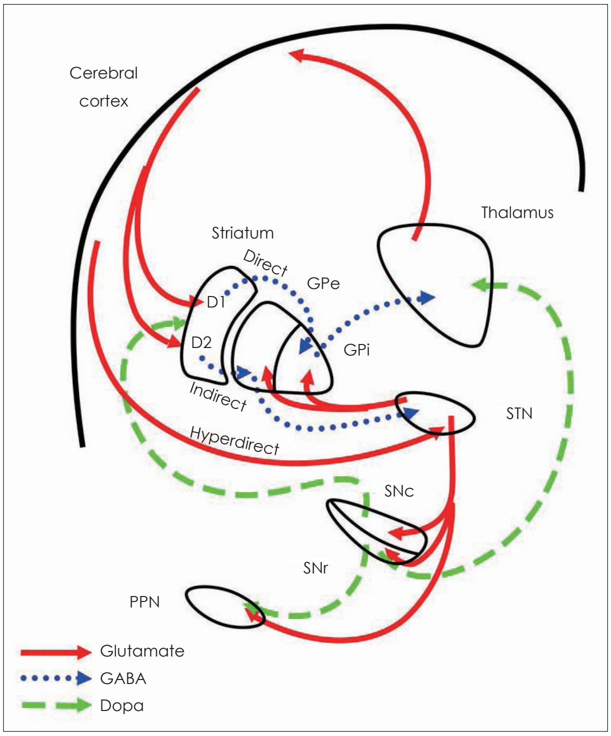

Fig. 3. Basal ganglia-Thalamocortical Circuit. In the cortex, the direct pathway provides positive feedback, and the indirect pathway provides negative feedback. The balance between direct and indirect pathways is regulated by the differential actions of dopamine from neurons in the SNc on striatal neurons. A hyperdirect pathway is a connection from cortex to the STN, bypasses the striatum.

tamatergic projection to the PPN, and it sends reciprocal glutamatergic and cholinergic inputs to the STN.[27)]

CONCLUSION

The STN is a pivotal component of the circuits that control motor, cognitive, and affective behavior. Precise and thorough identification of the 3D anatomy of the STN and related structures is essential. Various computer graphic programs for pre-operative planning have recently been developed, and these can help surgeons to easily and clearly understand the anatomy of the STN. Moreover, we expect that the treatment of the correct areas will increase surgical accuracy and lower the complication rate to maximize patient satisfaction.

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The figures included in this article were processed with the prior informed consent from the subject. The MRI obtained from the patient underwent object segmentation using the "automatic anatomical mapping" feature from BrainLab Pre Planning SW.

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