Postmortem Dissections of Common Targets for Lesion and Deep Brain Stimulation Surgeries

Vanessa M. Holanda, MD, PhD [*‡§]
Michael S. Okun, MD [¶]
Erik H. Middlebrooks, MD [‖]
Abuzer Gungor, MD [#]
Margaret E. Barry, MA [*]
John Forder, BA, PhD [**]
Kelly D. Foote, MD [*]

*Fixel Institute for Neurological Diseases, Department of Neurosurgery, University of Florida, Gainesville, Florida; ‡Center of Neurology and Neurosurgery Associates (NeuroCENNA), BP – A Beneficência Portuguesa de São Paulo, São Paulo SP, Brazil; §Department of Neurosurgery, Mayo Clinic College of Medicine, Jacksonville, Florida; ¶Fixel Institute for Neurological Diseases, Department of Neurology, University of Florida, Gainesville, Florida; ‖Department of Radiology, Mayo Clinic College of Medicine, Jacksonville, Florida; #Department of Neurosurgery, Acıbadem Mehmet Ali Aydinlar University, Istanbul, Turkey; **Department of Radiology, University of Florida, Gainesville, Florida

Correspondence:
Vanessa M. Holanda, MD, PhD,
Rua Martiniano de Carvalho, 807, Suite 705,
Bela Vista, São Paulo SP, Brazil 01321-001.
Email: vanessamila@gmail.com

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BACKGROUND: The subthalamic nucleus (STN), globus pallidus internus (GPi), and pedunculopontine nucleus (PPN) are effective targets for deep brain stimulation (DBS) in many pathological conditions. Previous literature has focused on appropriate stimulation targets and their relationships with functional neuroanatomic pathways; however, comprehensive anatomic dissections illustrating these nuclei and their connections are lacking. This information will provide insight into the anatomic basis of stimulation-induced DBS benefits and side effects.

OBJECTIVE: To combine advanced cadaveric dissection techniques and ultrahigh field magnetic resonance imaging (MRI) to explore the anatomy of the STN, GPi, and PPN with their associated fiber pathways.

METHODS: A total of 10 cadaveric human brains and 2 hemispheres of a cadaveric head were examined using fiber dissection techniques. The anatomic dissections were compared with 11.1 Tesla (T) structural MRI and 4.7 T MRI fiber tractography.

RESULTS: The extensive connections of the STN (caudate nucleus, putamen, medial frontal cortex, substantia innominata, substantia nigra, PPN, globus pallidus externus (GPe), GPi, olfactory tubercle, hypothalamus, and mammillary body) were demonstrated. The connections of GPi to the thalamus, substantia nigra, STN, amygdala, putamen, PPN, and GPe were also illustrated. The PPN was shown to connect to the STN and GPi anteriorly, to the cerebellum inferiorly, and to the substantia nigra anteriorly and superiorly.

CONCLUSION: This study demonstrates connections using combined anatomic microdissections, ultrahigh field MRI, and MRI tractography. The anatomic findings are analyzed in relation to various stimulation-induced clinical effects. Precise knowledge of neuroanatomy, anatomic relationships, and fiber connections of the STN, GPi, PPN will likely enable more effective targeting and improved DBS outcomes.

KEY WORDS: Deep brain stimulation, Parkinson disease, Subthalamic nucleus, Globus pallidus internus, Pedunculopontine nucleus

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Over the last 3 decades, deep brain stimulation (DBS) has emerged as the most effective and safe surgical intervention for disorders involving the basal ganglia, specifically Parkinson disease (PD), dystonia, Tourette syndrome (TS), obsessive-compulsive disorder (OCD), and treatment-resistant depression (TRD).[1,2]

DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPi) is a proven therapeutic modality for PD and other movement disorders.[3] Many randomized clinical studies have shown effective suppression of PD motor symptoms when stimulating either target: STN or GPi.[4,5] However, incomplete understanding of the basal ganglia neuroanatomy and the therapeutic mechanisms of DBS impede personalization of this therapy and may contribute to suboptimal outcomes.

ABBREVIATIONS: DBS, deep brain stimulation; **FGATIR,** fast gray matter acquisition T1 inversion recovery; **GPe,** globus pallidus externus; **OCD,** obsessive-compulsive disorder; **GPi,** globus pallidus internus; **PD,** Parkinson disease; **PPN,** pedunculopontine nucleus; **STN,** subthalamic nucleus; **SLF,** superior longitudinal fasciculi; **TS,** Tourette syndrome; **TRD,** treatment-resistant depression; **VC,** ventral caudal; **VIM,** ventral intermediate

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The STN is a topographically organized homogeneous nucleus that has been over the last century functionally divided into inconsistent subdivisions.[6,7] It is possible that precise knowledge of the STN connections may provide the basis for optimal partitioning of the STN based on function.

The GPi is considered the primary output structure of the basal ganglia and is known to have an increase in its neuronal activity before the onset of PD motor symptoms.[8] GPi-DBS has been successfully used to suppress dyskinesias in patients with treatment-resistant hyperkinetic movements.

More recently, some clinical studies have suggested that DBS of the pedunculopontine nucleus (PPN) may be an effective treatment for gait freezing in PD.[9-11] The requirement for accurate surgical targeting demands precise anatomic characterization of the PPN.[12] The PPN is divided into the pars compacta (dorsolateral) and pars dissipata (caudal) by the density of cholinergic neurons. The PPN is considered the major component of the mesencephalic locomotor region, which has been implicated in locomotion.[9,11,13,14] The PPN may act as an integrative interface between the basal ganglia and the cerebellum.[9] Furthermore, it is thought to be involved in the initiation and modulation of gait and stereotyped movements, leading to some recent DBS in vivo and clinical studies supporting the idea that stimulation may reduce aberrant neuronal synchrony involved in freezing of gait.[15,16]

Stimulation-induced side effects as well as cognitive, speech, and walking impairment are frequently the most commonly reported complications related to DBS. Stimulation within specific regions of the STN, GPi, or PPN may have variable effects on mood and cognition depending upon the lead position and the distribution of stimulation due to anatomically linked motor, prefrontal (or associative), and limbic regions.[9,17,18] Identifying which anatomic DBS locations most influence specific behavioral outcomes may facilitate improved prediction of optimal lead placement for motor benefit and side effect reduction.[18] Therefore, a precise understanding of the microanatomic structure of these nuclei and their connections is sine qua non to perform ideal targeting and programming.

This study aims to deconstruct the anatomy and fiber connections of the STN, GPi, and the PPN in order to help clarify the mechanistic microanatomic basis of stimulation-induced side effects, and to elucidate the anatomic structures traversed by the DBS lead en route to the intended target.

METHODS

A total of 10 formalin perfused cadaveric human brains and 2 hemispheres of a cadaveric head were obtained and preserved in a 70% alcohol solution before and between the dissections. The specimens were handled in accordance with the anatomic board and ethics committee regulations. The arachnoid and surface vessels were removed, and all the specimens were frozen at −16°C for at least 2 wk.[19]

A total of 9 specimens were examined using fiber dissection techniques, under ×6 and ×40 magnification. The STN, GPi, and PPN were dissected from inferior, superior, anterior, lateral, and medial aspects to study their anatomy and fiber connections. Details of the preparation of postmortem brain tissue for the targeting magnetic resonance imaging (MRI) in 2 hemispheres of a cadaveric head, and 11.1 T structural MRI, and 4.7 T diffusion tensor imaging (DTI) performed in 1 cadaveric human brain can be found in Methods 1 to 4 in **Supplemental Methods**, **Supplemental Digital Content 1**.

RESULTS

Superior to Inferior White Matter Dissections

In the superior view of the brain, the region corresponding to the hand in the motor homunculus was highlighted (Figure 1A). This region has been used for strip placement in closed-loop DBS.[20,21] The superior white matter of the frontal, parietal, and occipital lobe were resected exposing the lateral ventricles, caudate nucleus, thalamus, and fornices (Figure 1B). Portions of the anterior and posterior limb of the internal capsule and thalamus were removed to expose the GPi, STN, PPN, and their connections (Figure 1C-1F).

Inferior to Superior White Matter Dissections

In the inferior view, the cortex of the frontal, temporal, and occipital lobes, U fibers, inferior portion of the uncinate fasciculus, hippocampus, and optic tract were removed to reveal the anterior commissure and basal ganglia (Figure 2A-2C). After removing the anterior commissure, the basal ganglia were exposed (Figure 2D and 2E). An axial slice from the 11.1 T MRI at the level of the STN and PPN also illustrates the surrounding structures (Figure 2F and 2G). A schematic drawing, based on an axial cut of the Schaltenbrand atlas,[22] shows some of the STN and GPi connections (Figure 2H).

Anterior to Posterior White Matter Dissections

The frontal lobe cortex and U fibers were removed to expose the cingulum, insula, and uncinate fasciculus (Figure 3A and 3B). The uncinate fasciculus was removed to expose the nucleus accumbens and substantia innominata (Figure 3C), which together with the diagonal band of Broca, medial septal nuclei, and extended amygdala form the basal forebrain.[23] Removal of the uncinate fasciculus also exposes the subcallosal cingulum, which is a target for depression in some clinical studies.[21] The GPi is located superior to the optic tract, and the STN is inferior, medial, and posterior to the optic tract. The oculomotor nerve is located medially and inferiorly to the STN (Figure 3C-3E). In Figure 3F, the II and III cranial nerves were removed to show the anterior, lateral, and superior position of the STN related to the red nucleus. A coronal cut at the level of the STN shows one view of the basal ganglia typically used for atlas matching and direct targeting (Figure 3G). The 11.1 T MRI coronal cut at the level of the STN and PPN demonstrates the surrounding structures, including the thalamic fasciculus and the lenticular fasciculus (Figure 3H-3I). The thalamic fasciculus (the convergence of lenticular fasciculus and ansa lenticularis, connecting

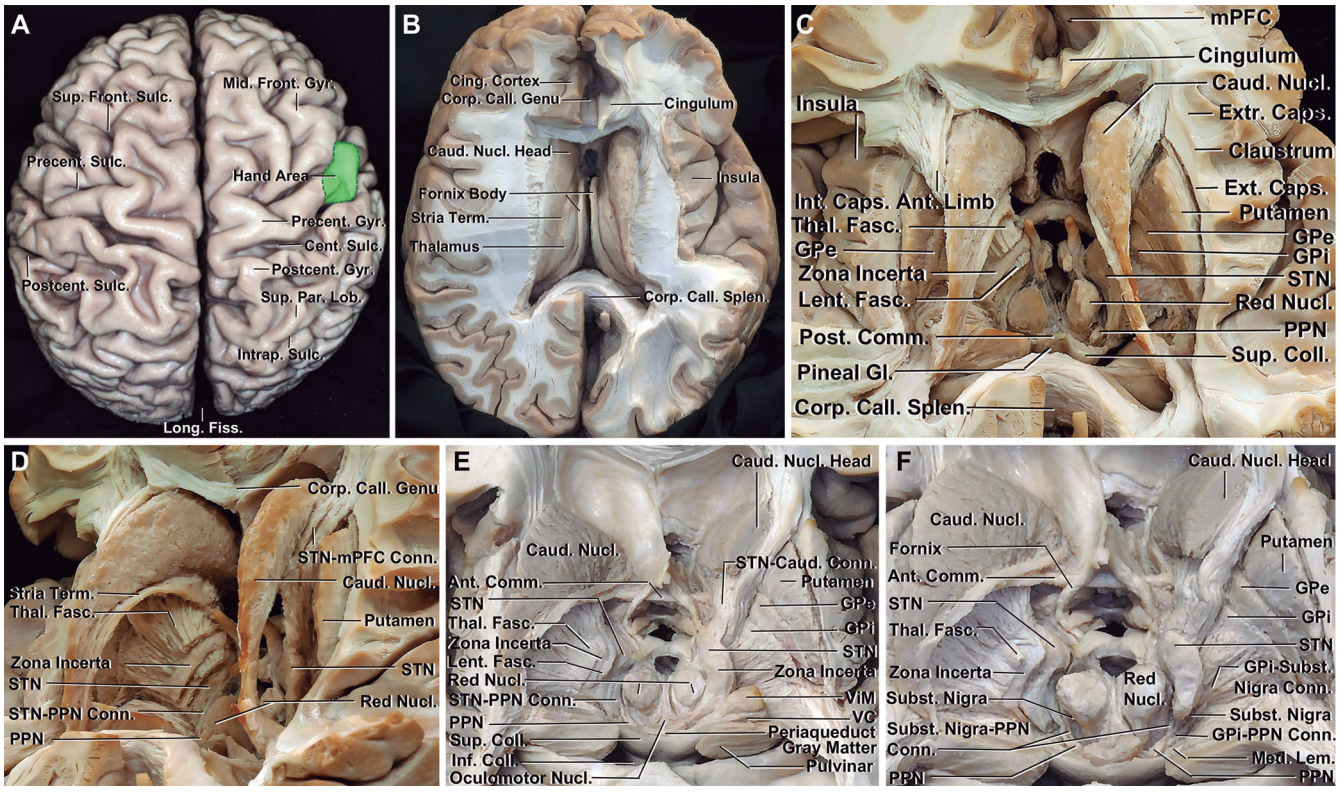


FIGURE 1. *Superior to inferior white matter dissections.* **A**, *Superior view of the brain highlighting the main gyri and sulci and the region corresponding to the hand in the motor homunculus that has been used for electrocorticography strip placement in closed loop studies.* **B**, *Superior white matter dissection exposing the lateral ventricles, caudate nucleus, thalamus, and fornices.* **C**, *Superior white matter dissection of the basal ganglia.* **D**, *Superior oblique view of the STN, GPi, caudate nucleus, and their connections.* **E**, *Superior view of STN, PPN, GPi, zona incerta, and their connections.* **F**, *Superior view of the GPi, STN, PPN, and their connections. Ansa Lent.: ansa lenticularis; Caud. Nucl.: caudate nucleus; Cent. Sulc.: central sulcus; Cing.: cingulum; Claust.: claustrum; Col.: Column; Conn.: connections; Corp. Call.: corpus callosum; Ext. Caps.: External Capsule; Extr. Caps.: Extreme Capsule; Gl.: gland; GPe: Globus Pallidus Externus; GPi: Globus Pallidus Internus; Int. Caps. Ant. Limb: anterior limb of the internal capsule; Intrap. Sulc.: intraparietal sulcus; Lent. Fasc.: lenticular fasciculus; Long. Fiss.: longitudinal fissure; Mamm: mammillary; Mammillothal.: mammillothalamic; Mid. Front. Gyr.: middle frontal gyrus; mPFC: medial prefrontal cortex. N.: nerve; Nucl.: nucleus; Post. Comm.: posterior commissure; Postcent. Gyr.: postcentral gyrus; Postcent. Sulc.: postcentral sulcus; PPN: pedunculopontine nucleus; Precent. Gyr.: precentral gyrus; Precent. Sulc.: precentral sulcus; Sup. Front. Gyr.: superior frontal gyrus; Sup. Front. Sulc.: superior frontal sulcus; Sup. Par. Lob.: superior parietal lobe; Splen.: splenium; STN: subthalamic nucleus; Stria Term.: stria terminalis; Sup. Coll.: superior colliculus; Thal.: Thalamus; Thal. Fasc.: thalamic fasciculus; Tr.: tract.*

GPi to the thalamus) is located between the thalamus and the zona incerta. The lenticular fasciculus is situated between the zona incerta and the STN. A schematic drawing, based on the Schaltenbrand atlas,[22] shows the STN, GPi, and PPN connections (Figure 3J).

Lateral to Medial White Matter Dissections

The frontal, temporal, parietal, and occipital cortex, U fibers, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and the inferior portion of the cingulum fibers were serially removed to demonstrate the positions of the hippocampus, amygdala, putamen, anterior commissure, GPe, and GPi. The hippocampus and superficial and deep transpontine fibers were removed to reveal the medial lemniscus and the corticospinal tract (Figure 4A-4C).

The corticospinal tract, together with the parietal thalamic peduncle and parietopontine fibers, form the posterior limb of the internal capsule. The fibers of the posterior limb of the internal capsule and medial lemniscus were removed to exhibit the relationship between the STN and the substantia nigra (Figure 4D). The medial lemniscus conveys proprioception, vibration sense, and fine and discriminative touch from the dorsal column nuclei to the ventral caudal (VC) and the ventral intermediate (VIM) nuclei of the thalamus (Figure 4E-4G) and demarcates the lateral and the posterior ventral boundaries of the VIM thalamus.[24,25] The sagittal view of the STN region was displayed by 4.7 T DTI tractography to show some of the STN connections

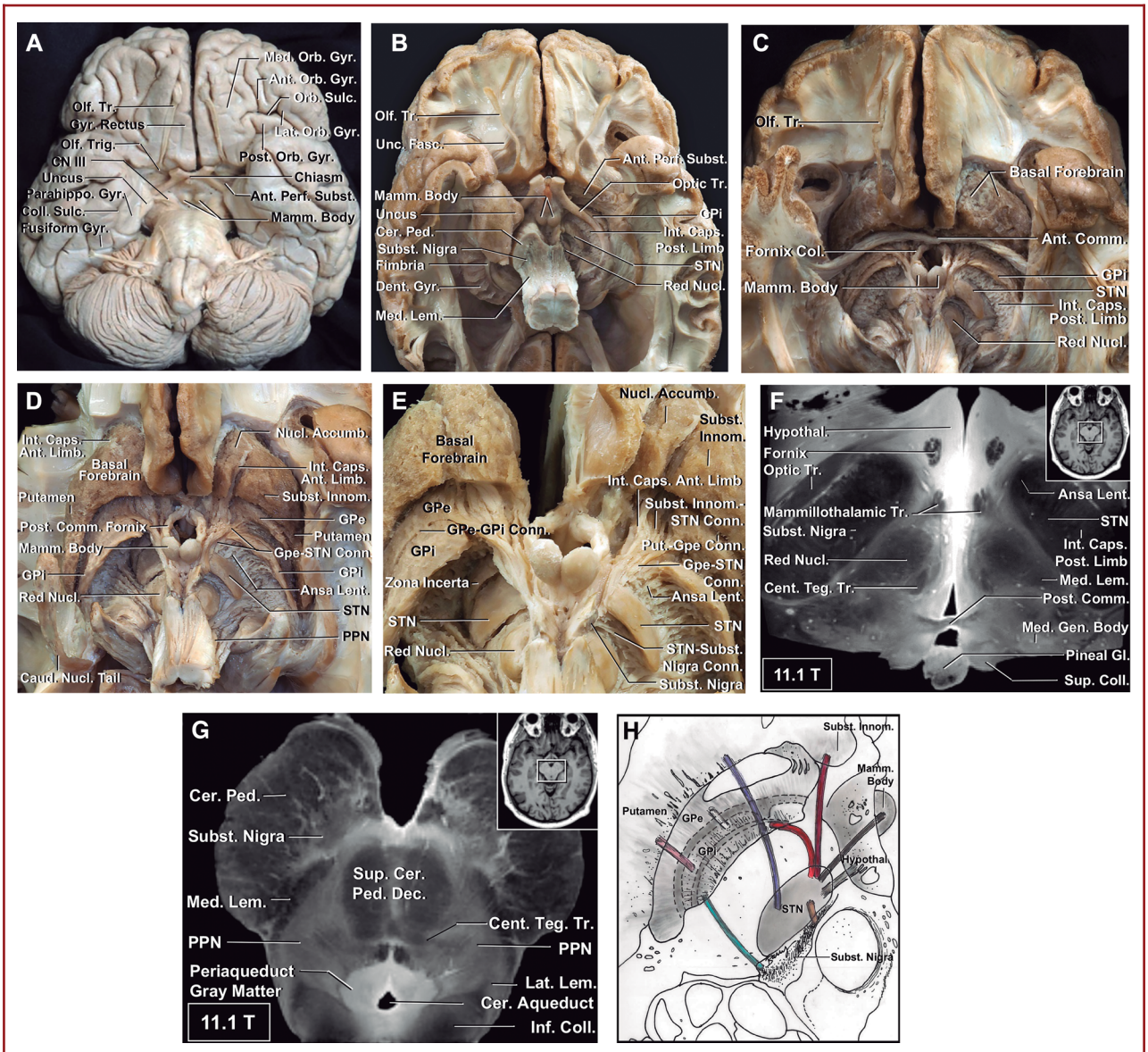
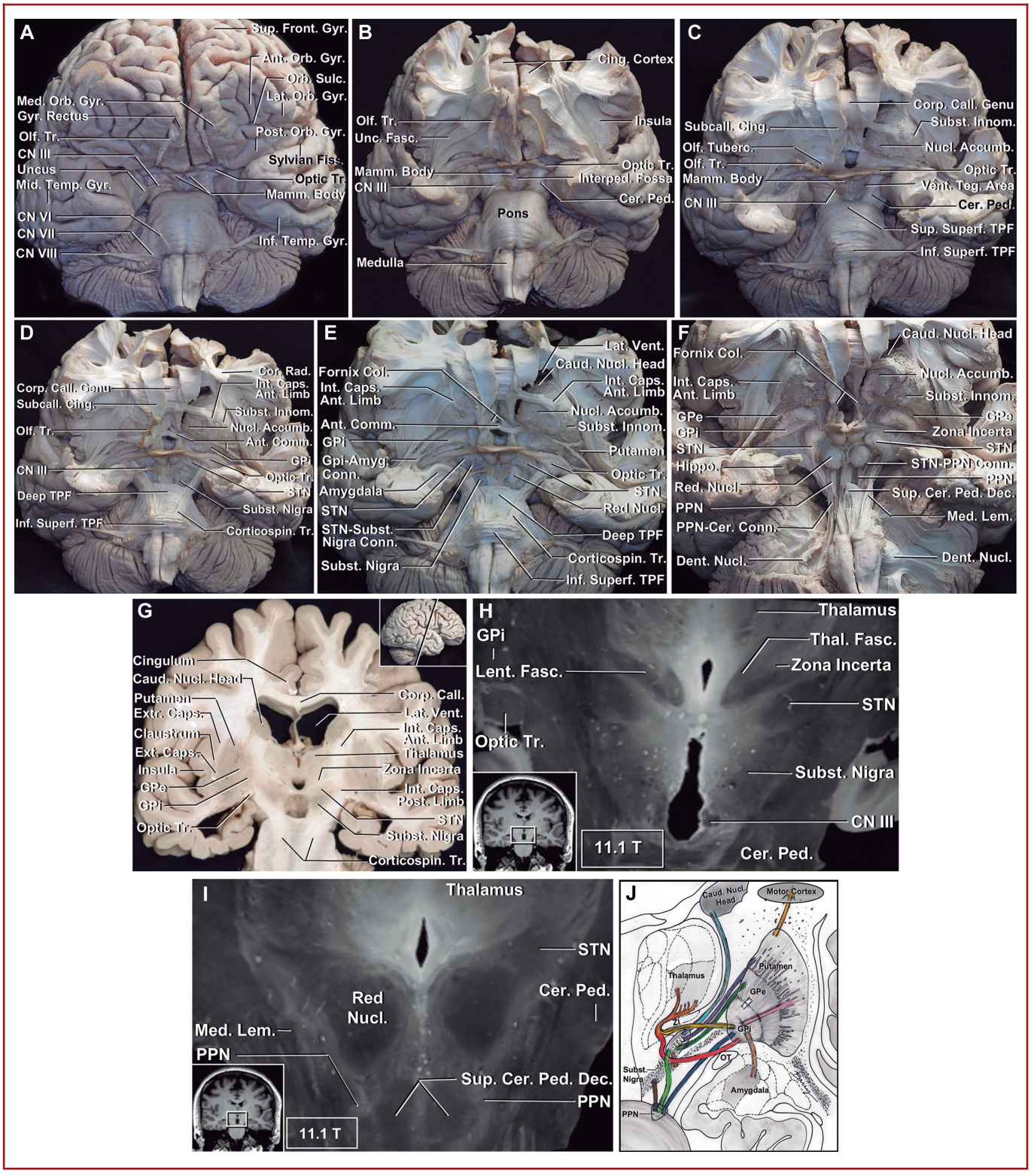


FIGURE 2. *Inferior to superior white matter dissections.* **A**, *Inferior view of the brain.* **B**, *Inferior white matter dissection of the STN and GPI and their relationship with the optic tract.* **C**, *Removal of hippocampus and the optic tract to reveal the anterior commissure and basal ganglia.* **D**, *Removal of the anterior commissure to reveal the basal ganglia and GPe-STN connections.* **E**, *The white matter surrounding the basal forebrain was removed to show the continuity between substantia innominata and putamen. The ansa lenticularis and substantia innominata-STN connections were exhibited.* **F**, *11 T MRI demonstrating an axial cut at the level of the STN.* **G**, *11 T MRI demonstrating an axial cut at the level of the PPN.* **H**, *Schematic drawing of the STN, PPN, and GPi connections, based on the axial cut 2.0 of the Schaltenbrand atlas. Accumb.: accumbens; Ansa Lent.: ansa lenticularis; Ant. Comm.: anterior commissure; Ant. Orb. Gyr.: anterior orbital gyrus; Ant. Perf. Subst.: anterior perforated substance; Caud. Nucl.: caudate nucleus; Cent. Teg. Tr.: central tegmental tract; Cer. Aqueduct: cerebral aqueduct; Cer. Ped.: cerebral peduncle; CN III: cranial nerve III (oculomotor); Conn.: connections; Col.: Column; Coll. Sulc.: collateral sulcus; Dent. Gyr.: dentate gyrus; Gl.: gland; GPe: Globus Pallidus Externus; GPi: Globus Pallidus Internus; Gyr.: gyrus; Hypothal.: hypothalamus; Int. Caps. Ant. Limb: anterior limb of the internal capsule; Int. Caps. Post. Limb: posterior limb of the internal capsule; Intrap. Sulc.: intraparietal sulcus; Lat. Lem.: lateral lemniscus; Lat. Orb. Gyr.: lateral orbital gyrus; Lent. Fasc.: lenticular fasciculus; Long. Fiss.: longitudinal fissure; Mamm: mammillary; Med. Gen. Body: medial geniculate body; Med Lem.: medial lemniscus; Med. Long. Fasc.: medial longitudinal fasciculus; Med. Orb. Gyr.: medial orbital gyrus; N.: nerve; Nucl.: nucleus; Olf. Tr.: olfactory tract; Olf. Trig.: olfactory trigone; Opt. Tr.: optic tract; Orb. Sulc.: orbital sulcus; Parahippo. Gyr.: parahippocampal gyrus; Post. Comm.: posterior commissure; Post. Orb. Gyr.: posterior orbital gyrus; PPN: pedunculopontine nucleus; Precent. Gyr.: precentral gyrus; Precent. Sulc.: precentral sulcus; Put.: putamen; Subst. Innom.: substantia innominata; Subst. Nigra: substantia nigra; STN: subthalamic nucleus; Sup. Cer. Ped. Dec.: superior cerebellar peduncle decussation; Sup. Coll.: superior colliculus; Thal.: Thalamus; Thal. Fasc.: thalamic fasciculus; Tr.: tract; Unc. Fasc.: uncinate fasciculus; Vent.: ventricle.*


A
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Olf. Tr.
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CN VIII
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Putamen
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GPi
OT
Subst. Nigra
Amygdala
PPN

FIGURE 3. *Anterior to posterior white matter dissections.* **A**, *Anterior view of the brain.* **B**, *Removal of the frontal lobe cortex and U fibers to expose the cingulum, insula and uncinate fasciculus.* **C**, *Removal of the uncinate fasciculus to expose the nucleus accumbens and substantia innominata that together form the basal forebrain.* **D**, *Exposure of the subcallosal cingulum, which is a target for depression in some clinical studies. The relationship between the optic tract, STN and GPi is shown. The GPi is superior to the optic tract and the STN is inferior, medial and posterior to the optic tract. The oculomotor nerve is located medially and inferiorly to the STN.* **E**, *Removal of the inferior subcallosal cingulum fibers revealing the anterior commissure and the columns of the fornix. The GPi can be seen along with its connections to the amygdala. The STN is located posterior and inferiorly to the optic tract and supero-lateral to the oculomotor nerve. The substantia nigra is located inferiorly to the STN and the STN-substantia nigra connections are shown.* **F**, *The deep transpontine fibers, the medial lemniscus, and the corticospinal tract were removed in the right portion of the brainstem to expose the PPN-cerebellum connections.* **G**, *A coronal cut at the level of the STN demonstrates the basal ganglia used for atlas matching and direct targeting.* **H**, *11.1 T MRI coronal cut at the level of the STN. The thalamic fasciculus and the lenticular fasciculus are shown. The thalamic fasciculus is located between the thalamus and the zona incerta. The lenticular fasciculus is situated between the zona incerta and the STN.* **I**, *11.1 T MRI coronal cut at the level of the PPN.* **J**, *Schematic drawing of the STN, PPN and GPi connections, based on the coronal cut 2.0 of the Schaltenbrand atlas. Yellow: lenticular fasciculus; red: ansa lenticularis; orange: thalamic fasciculus; pink: GPi-Putamen connections; brown: STN-substantia nigra connections; dark brown: substantia nigra-PPN connections; dark blue: GPi-PPN connections; light blue: Caudate nucleus-STN connections; light green: STN-PPN connections; dark green: GPe-STN connections; purple: putamen-STN connections; light orange: GPi-amygdala connections; white: GPe-GPi connections; dark orange: putamen-motor cortex. Accumb.: accumbens; Amyg.: amygdala; Ant. Comm.: anterior commissure; Ant. Orb. Gyr.: anterior orbital gyrus; Ant. Perf. Subst.: anterior perforated substance; Caud.: caudate; Cer. Aqueduct: cerebral aqueduct; Cer. Ped.: cerebral peduncle; CN III: cranial nerve III (oculomotor); CN VI: cranial nerve VI (abducens); CN VII: cranial nerve VII (facial); CN VIII: cranial nerve VIII (vestibulocochlear); Conn.: connections; Col.: Column; Coll. Sulc.: collateral sulcus; Cor. Rad.: corona radiate; Corp. Call.: corpus callosum; Corticospin.: corticospinal; Ext.: external; Extr. Caps.: extreme capsule; Gl.: gland; GPe: Globus Pallidus Externus; GPi: Globus Pallidus Internus; Gyr.: gyrus; Hypothal.: hypothalamus; Inc.: incerta; Inf.: inferior; Int. Caps. Ant. Limb: anterior limb of the internal capsule; Int. Caps. Post. Limb: posterior limb of the internal capsule; Interped.: interpeduncular; Intrap. Sulc.: intraparietal sulcus; Lat.: lateral; Lat. Orb. Gyr.: lateral orbital gyrus; Lent. Fasc.: lenticular fasciculus; Long. Fiss.: longitudinal fissure; Mamm: mammillary; Med. Gen. Body: medial geniculate body; Med Lem.: medial lemniscus; Med. Orb. Gyr.: medial orbital gyrus; Mid. Temp. Gyr.: middle temporal gyrus; N.: nerve; Nucl.: nucleus; Olf. Tr.: olfactory tract; Olf. Tuberc.: olfactory tubercle; Opt. Tr.: optic tract; Orb. Sulc.: orbital sulcus; Post. Orb. Gyr.: posterior orbital gyrus; PPN: pedunculopontine nucleus; Subcall. Cing.: subcallosal cingulate; Subst. Innom.: substantia innominata; Subst. Nigra: substantia nigra; STN: subthalamic nucleus; Superf.: superficial; Sup.: superior; Sup. Cer. Ped. Dec.: superior cerebellar peduncle decussation Sup. Front. Gyr.: superior frontal gyrus; Sylvian Fiss.: Sylvian fissure; Thal. Fasc.: thalamic fasciculus; TPF: transpontine fibers; Tr.: tract; Unc. Fasc.: uncinate fasciculus; Vent.: ventricle; Vent. Teg. Area: ventral tegmental area.*

(Figure 4H). A schematic drawing, based on a sagittal section of the Schaltenbrand atlas,[22] shows the STN, GPi, and PPN connections (Figure 4I).

Medial to Lateral White Matter Dissections

The inferior portion of the thalamus was removed to display the STN and PPN (Figure 5A and 5B). The PPN is located inferior, posterior, and lateral to the red nucleus. The lateral portion of the thalamus was removed, and the GPi was exposed (Figure 5C and 5D). In another brain, the medial view exposes some of the connections highlighted in the 4.7 T MRI tractography: the GPi-PPN, the STN-PPN, and the substantia nigra-PPN connections (Figure 5E and 5F). The 11.1 T MRI reveals the STN, GPi, PPN, and related structures (Figure 5G and 5H). See **Supplemental Results**, **Supplemental Digital Content 2** for complete descriptive results.

DBS Lead Trajectory Dissections From Entry Point to GPi

The GPi was targeted using Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence with the in-house targeting software (Figure 6A-6C). For each hemisphere, a standard 14 mm burr hole was made, and a recess was drilled around it to countersink the DBS cap (Medtronic, Dublin, Ireland; Figure 6D). As previously described, countersinking the DBS cap helps prevent delayed scalp erosion and infection.[26] The entry point was determined by the target and trajectory chosen. The DBS lead (Medtronic) passed through the cortex in the posterior portion of the superior frontal gyrus, the U fibers, superior longitudinal fasciculi (SLF) II and III, the corona radiata, the posterior limb of the internal capsule, the putamen and the globus pallidus externus prior to reaching the posterior GPi (Figure 6D-6J). After stapling the incision, the cap does not protrude, and the scalp surface is smooth (Figure 6K).

DBS Lead Trajectory Dissections from Entry Point to STN

In the left hemisphere, the STN was targeted using the FGATIR sequence with the in-house targeting software (Figure 7A-7D). The selected target and trajectory determined the burr hole placement. The DBS lead entered the posterior portion of the superior frontal gyrus (Figure 7E-7G). The lead passed through the U fibers, SLF II and III, corona radiata, posterior limb of the internal capsule, and the anterior thalamus (Figure 7H-7J) prior to reaching the posterolateral portion of the STN (Figure 7K and 7L). To specifically treat the motor symptoms of PD, the target is intentionally located in the posterior-lateral (somatosensory) portion of STN (Figure 7M and 7N).

DISCUSSION

In 1990, Delong et al[27] elucidated the basal ganglia pathways in primates. The authors proposed that the basal ganglia exert excitatory and inhibitory control over the cerebral cortex. The direct pathway, via putaminal inhibitory projections to GPi, decreases pallidothalamic inhibition and facilitates motor cortical activity, while the indirect pathway, with putaminal projections via GPe then STN, sends excitatory projections to GPi, increasing pallidothalamic inhibition and inhibits motor-cortical activity.[1,27]

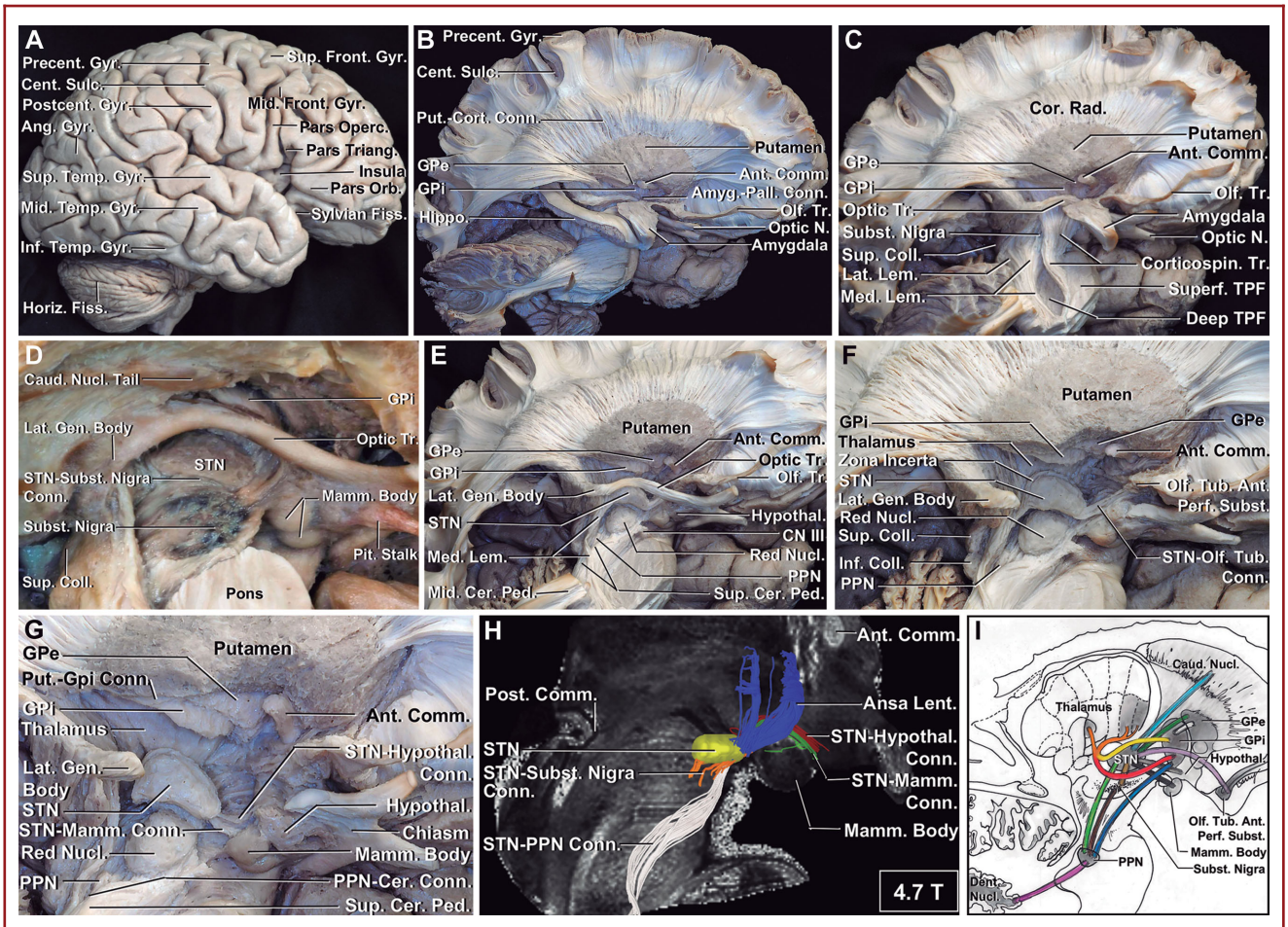


FIGURE 4. *Lateral to medial white matter dissections.* **A**, *Lateral view of the brain.* **B**, *The frontal, temporal, parietal, and occipital cortex, U fibers, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and the inferior portion of the cingulum fibers were removed to demonstrate the position of the hippocampus, amygdala, putamen, anterior commissure, GPe and GPi.* **C**, *The hippocampus, superficial and deep transpontine fibers were removed to reveal the medial lemniscus and the corticospinal tract.* **D**, *Another specimen in which the corticospinal tract and medial lemniscus have been removed to exhibit the relationship between the STN and the substantia nigra.* **E**, *The corticospinal tract was removed to expose the STN and the red nucleus. The optic tract is located inferiorly to the GPi and superior-lateral to the STN.* **F**, *The optic tract was removed to better demonstrate the STN and its connection with the olfactory tubercle of the anterior perforated substance.* **G**, *The STN-olfactory tubercle connections were removed to demonstrate the STN-mammillary body connections and the STN-hypothalamus connections.* **H**, *Sagittal view of the STN region displayed by 4.7 T MRI tractography. Blue: Ansa lenticularis (connection between STN and GPi); Red: STN-hypothalamus connections; Green: STN-mammillary body connections; Orange: STN-substantia nigra connections; White: STN-PPN connections.* **I**, *Schematic drawing of the STN, PPN and GPi connections, based on the coronal cut 2.0 of the Schaltenbrand atlas. Yellow: lenticular fasciculus; red: ansa lenticularis; orange: thalamic fasciculus; pink: GPi-Putamen connections; brown: STN-substantia nigra connections; dark brown: substantia nigra-PPN connections; dark blue: GPi-PPN connections; light blue: Caudate nucleus-STN connections; light green: STN-PPN connections; dark green: GPe-STN connections; purple: putamen-STN connections; white: GPe-GPi connections; black: STN-mammillary body connections; grey: STN-hypothalamus connections; rose: STN-olfactory tubercle connections; purple: PPN-cerebellum connections. Amyg.-Pall.: amygdala-pallidum; Ang. Gyr.: angular gyrus; Ansa Lent.: ansa lenticularis; Ant. Comm.: anterior commissure; Ant. Orb. Gyr.: anterior orbital gyrus; Ant. Perf. Subst.: anterior perforated substance; Caud.: caudate; Cent. Sulc.: central sulcus; Cer. Aqueduct: cerebral aqueduct; Cer. Ped.: cerebral peduncle; CN III: cranial nerve III (oculomotor); Conn.: connections; Cor. Rad.: corona radiate; Corp. Call.: corpus callosum; Corticospin.: corticospinal; Ext.: external; Extr. Caps.: extreme capsule; Gl.: gland; GPe: Globus Pallidus Externus; GPi: Globus Pallidus Internus; Gyr.: gyrus; Hippo.: hippocampus; Hypothal.: hypothalamus; Horiz. Fiss.: horizontal fissure; Inf. Coll.: inferior colliculus; Inf. Temp. Gyr.: inferior temporal gyrus; Int. Caps. Ant. Limb: anterior limb of the internal capsule; Int. Caps. Post. Limb: posterior limb of the internal capsule; Lat. Gen.: lateral geniculate; Lat. Orb. Gyr.: lateral orbital gyrus; Lent. Fasc.: lenticular fasciculus; Long. Fiss.: longitudinal fissure; Mamm: mammillary; Med. Gen. Body: medial geniculate body; Med Lem.: medial lemniscus; Mid. Front. Gyr.: middle frontal gyrus; Mid. Temp. Gyr.: middle temporal gyrus; N.: nerve; Nucl.: nucleus; Olf. Tr.: olfactory tract; Olf. Tuberc.: olfactory tubercle; Opt. Tr.: optic tract; Orb. Sulc.: orbital sulcus; Pars Operc.: pars opercularis; Pars Orb.: pars orbitalis; Pars Triang.: pars triangularis; Pit.: pituitary; Post. Orb. Gyr.: posterior orbital gyrus; Post. Comm.: posterior commissure; PPN: pedunculopontine nucleus; Precent.: precentral; Postcent.: postcentral; Subst. Innom.: substantia innominata; Subst. Nigra: substantia nigra; STN: subthalamic nucleus; Superf.: superficial; Sup.: superior; Sup. Coll.: superior colliculus; Sup. Front. Gyr.: superior frontal gyrus; Sup. Temp. Gyr.: superior temporal gyrus Sylvian Fiss.: Sylvian fissure; Tr.: tract; Vent.: ventricle; Vent. Teg. Area: ventral tegmental area.*

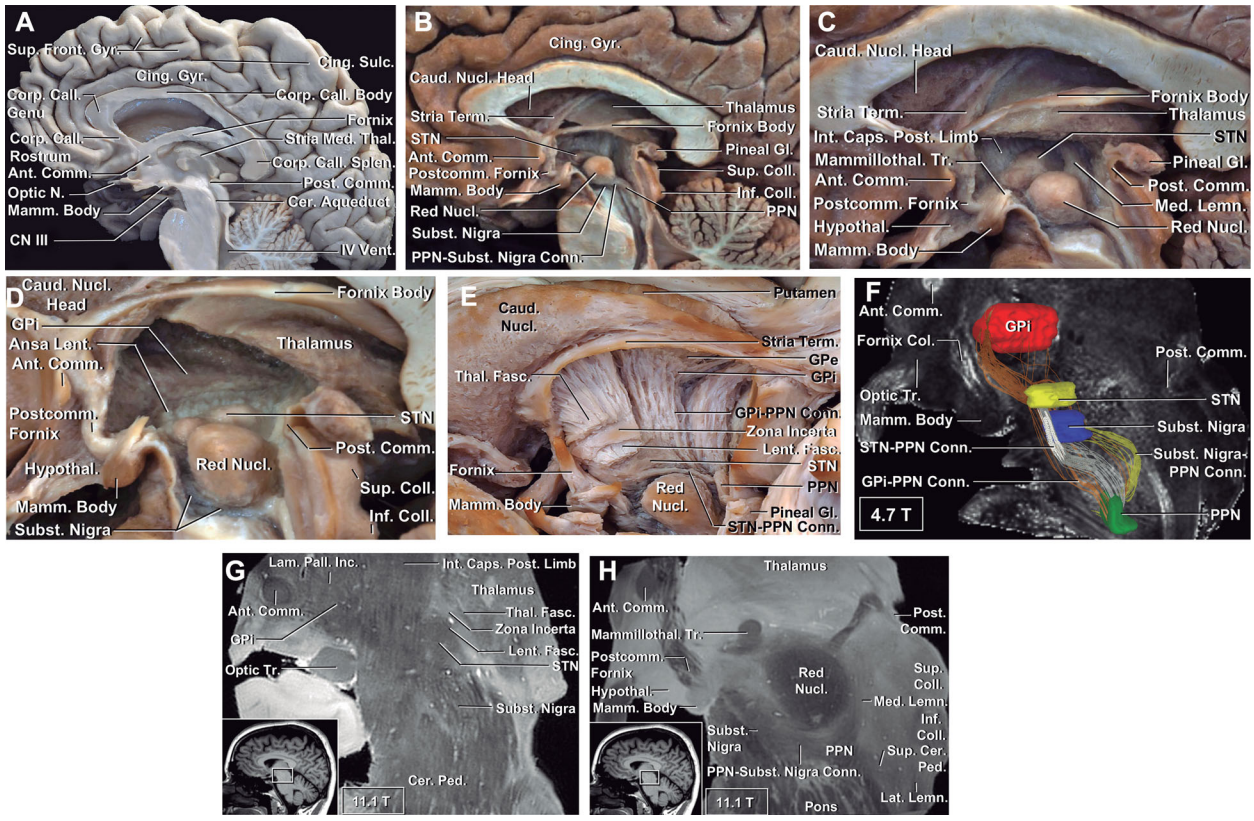


FIGURE 5. *Medial to lateral white matter dissections.* **A**, *Medial view of the right hemisphere.* **B**, *The inferior portion of the thalamus was removed to exhibit the STN. The PPN is located inferior, posterior and lateral to the red nucleus.* **C**, *In a magnified view, the anterior, lateral and superior position of the STN related to the red nucleus is seen.* **D**, *Removing the lateral nuclei group of the thalamus, the GPi is exposed and the ansa lenticularis connecting STN and GPi is demonstrated.* **E**, *Another specimen in a medial-superior view showing the STN-PPN connections.* **F**, *4.7 T MRI tractrography demonstrating the GPi-PPN connections in orange, the STN-PPN connections in white and the Substantia nigra-PPN connections in yellow.* **G**, *11.1 T MRI, sagittal view of the portion of the brain marked with a rectangle in the small 3T MRI to exhibit the STN, GPi and related structures.* **H**, *11.1 T MRI, sagittal view of the portion of the brain marked with a rectangle in the small 3 T MRI to exhibit the PPN and related structures. Ansa Lent.: ansa lenticularis; Ant. Comm.: anterior commissure; Caud.: caudate; Cer. Aqueduct: cerebral aqueduct; Cer. Ped.: cerebral peduncle; CN III: cranial nerve III (oculomotor); Cing.: cingulate; Col.: column; Conn.: connections; Corp. Call.: corpus callosum; Fasc. Retrofl.: fasciculus retroflexus; Gl.: gland; GPi: Globus Pallidus Internus; Gyr.: gyrus; Hypothal.: hypothalamus; Inf. Coll.: inferior colliculus; Inf. Temp. Gyr.: inferior temporal gyrus; Int. Caps.: internal capsule; Int. Caps. Post. Limb: posterior limb of the internal capsule; Lam. Pall. Inc.: lamina pallidi incompleta; Lat. Gen.: lateral geniculate; Lat. Lemn.: lateral lemniscus; Lat. Orb. Gyr.: lateral orbital gyrus; Lent. Fasc.: lenticular fasciculus; Long. Fiss.: longitudinal fissure; Mamm: mammillary; Mammillothal.: mammillothalamic; Med. Gen. Body: medial geniculate body; Med Lem.: medial lemniscus; Mid. Front. Gyr.: middle frontal gyrus; Mid. Temp. Gyr.: middle temporal gyrus; N.: nerve; Nucl.: nucleus; Olf. Tr.: olfactory tract; Olf. Tuberc.: olfactory tubercle; Opt. Tr.: optic tract; Orb. Sulc.: orbital sulcus; Post. Orb. Gyr.: posterior orbital gyrus; Post. Comm.: posterior commissure; PPN: pedunculopontine nucleus; Precent.: precentral; Postcent.: postcentral; Postcomm.: postcommisural; Splen.: splenium; STN: subthalamic nucleus; Stria Med. Thal.: stria medialis thalami; Stria Term.: stria terminalis; Subst. Nigra: substantia nigra; Sulc.: sulcus; Sup.: superior; Sup. Coll.: superior colliculus; Sup. Front. Gyr.: superior frontal gyrus; Thal. Fasc.: thalamic fasciculus; Tr.: tract; Vent.: ventricle.*

Direct and indirect cortical-basal ganglia interactions have been described in some detail in Parkinson's disease, but not validated in cadaveric human dissections as presented in the results of this paper. The depleted dopamine supply from the substantia nigra to the motor striatum in PD results in excessive inhibitory outflow from the basal ganglia to the motor thalamus, diminishing thalamic excitatory input to the motor cortex and producing the hypokinetic Parkinsonian state. More recent studies have shown that excessive synchronization of beta-band oscillations in these basal ganglia-thalamocortical circuits correlates with Parkinsonian bradykinesia and rigidity.[28] Moreover, effective treatment with either extrinsic dopamine or therapeutic DBS diminishes this pathological beta-band synchronization and relieves Parkinsonian bradykinesia and rigidity.[29]

To the best of our knowledge, this is the first microanatomic dissection study demonstrating the precise anatomic relationships

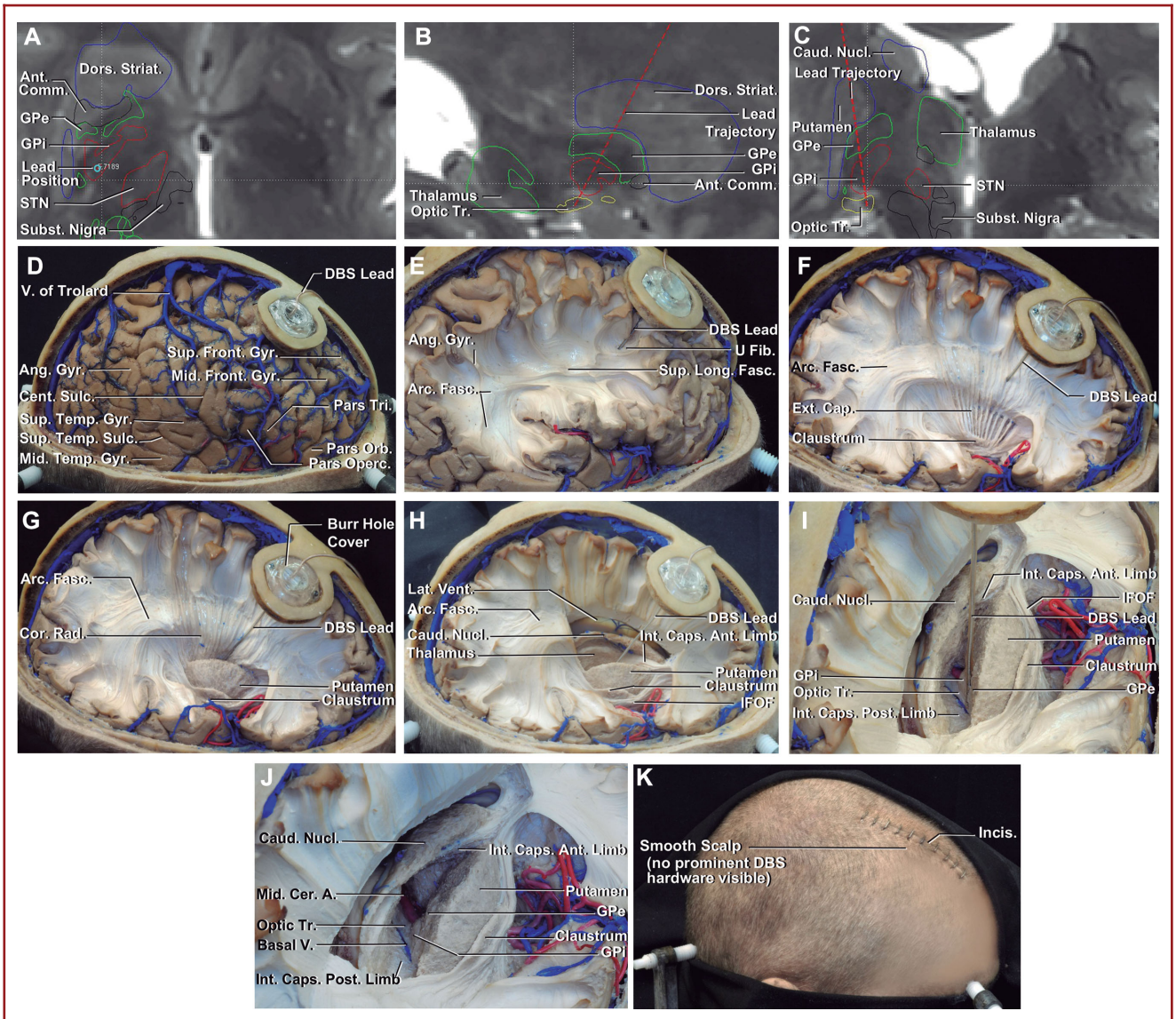
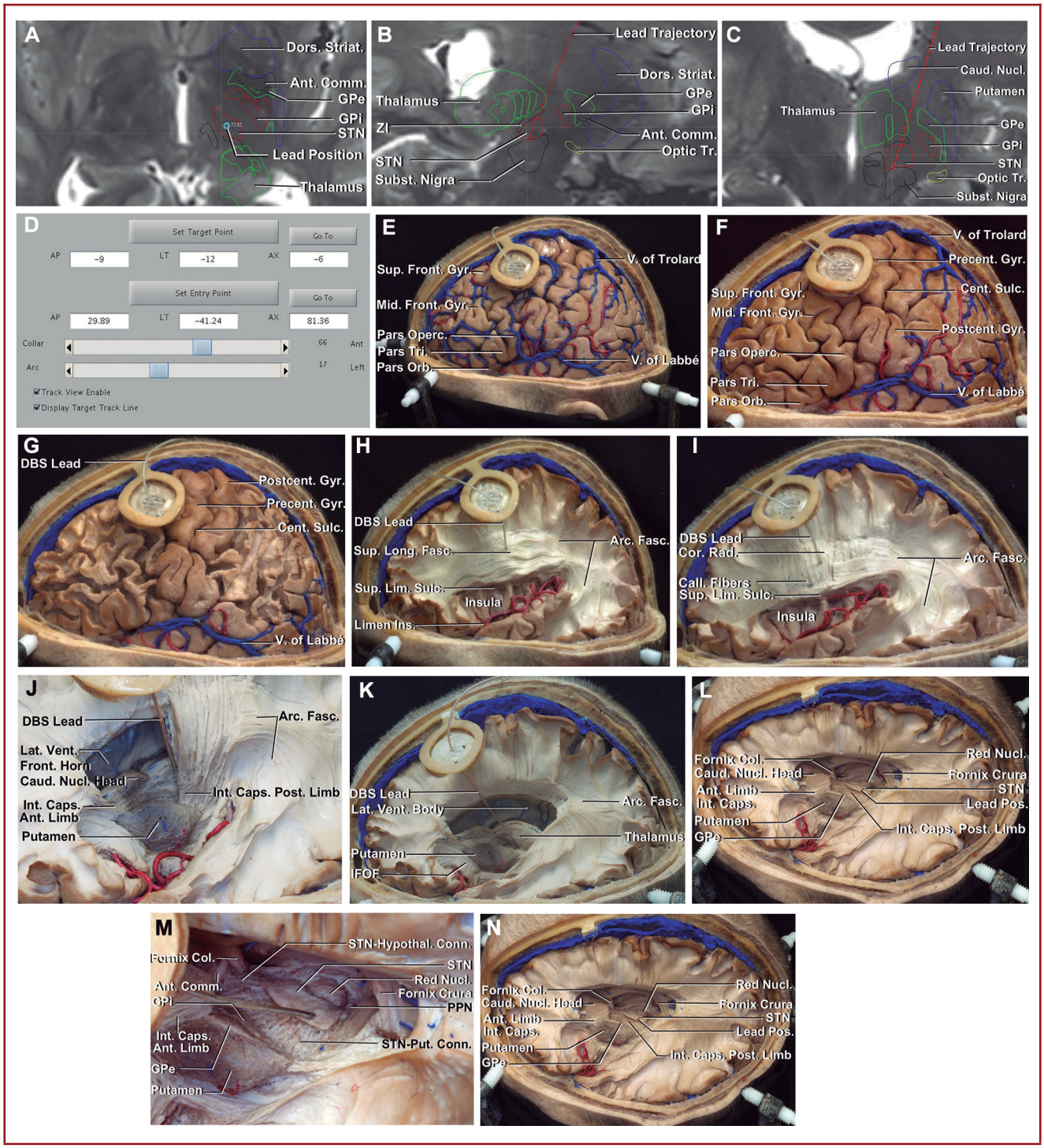


FIGURE 6. *DBS lead trajectory dissections from entry point to GPi.* **A**, *GPi lead position demonstrated in a ventral pallidal axial plane of the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) MRI sequence using UF in-house targeting software.* **B**, *GPi lead trajectory demonstrated in the sagittal plane of the FGATIR sequence.* **C**, *GPi lead trajectory demonstrated in the coronal plane of the FGATIR sequence.* **D**, *A hemicraniectomy was performed, leaving the region around the DBS burr hole cover in place. The dura mater was removed to expose the veins that should be avoided during DBS targeting. The lead penetrated the posterior portion of the superior frontal gyrus.* **E**, *Portions of the cortex of the frontal, parietal, and temporal lobes and U fibers were removed, exposing the superior longitudinal fasciculus reached by the DBS lead.* **F**, *The anterior portion of the superior longitudinal fasciculus, the extreme capsule and the dorsal portion of the claustrum were removed to expose the external capsule.* **G**, *The external capsule was removed and the putamen was exposed. The trajectory of the DBS lead is shown passing through the fibers of the corona radiata.* **H**, *The lateral portion of the corpus callosum and the posterior limb of the internal capsule were removed to expose the caudate nucleus and thalamus.* **I**, *A magnified superior view of the previous figure demonstrating the lead reaching the posterior portion of the GPi.* **J**, *The lead was removed to show the putamen, GPe and GPi with its relationship to the optic tract, the basal vein of Rosenthal and the first portion of the middle cerebral artery (M1).* **K**, *Final view of the incision after stapling. Prominence of the DBS hardware is avoided by countersinking to prevent delayed skin erosion and infection. Ang. Gyr.: angular gyrus; Ant. Comm.: anterior commissure; Arc. Fasc.: arcuate fasciculus; Caud.: caudate; Cent. Semi.: centrum semiovale; Cent. Sulc.: central sulcus; Cor. Rad.: corona radiate; DBS.: deep brain stimulation; Dors. Striat.: dorsal striatum; Ext, Caps.: external capsule; Fib.: fibers; GPe: Globus Pallidus Externus; GPi: Globus Pallidus Internus; Gyr.: gyrus; IFOF: inferior fronto-occipital fasciculus; Incis.: incision; Int. Caps. Ant. Limb: anterior limb of the internal capsule; Int. Caps. Post. Limb: posterior limb of the internal capsule; Lat. Vent.: lateral ventricle; Mid. Cer. A.: middle cerebral artery; Mid. Temp.: middle temporal; Nucl.: nucleus; Pars Operc.: pars opercularis; Pars Orb.: pars orbitalis; Pars Triang.: pars triangularis; Precent.: precentral; Postcent.: postcentral; Sup. Front.: superior frontal; Sup. Long. Fasc.: superior longitudinal fasciculus; Sup. Temp.: superior temporal; Stereo.: stereotactic; STN: subthalamic nucleus; Subst. Nigra: substantia nigra; Tr.: Tract; V.: vein.*


A
Dors. Striat.
Ant. Comm.
GPe
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STN
Lead Position
Thalamus
B
Lead Trajectory
Dors. Striat.
GPe
GPi
Thalamus
ZI
Ant. Comm.
Optic Tr.
STN
Subst. Nigra
C
Lead Trajectory
Caud. Nucl.
Putamen
Thalamus
GPe
GPi
STN
Optic Tr.
Subst. Nigra
D
Set Target Point
Go To
AP -9 LT -12 AX -6
Set Entry Point
Go To
AP 29.89 LT -41.24 AX 81.36
Collar 66 Ant
Arc 17 Left
Track View Enable
Display Target Track Line
E
V. of Trolard
Sup. Front. Gyr.
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Pars Operc.
Pars Tri.
Pars Orb.
V. of Labbé
F
V. of Trolard
Precent. Gyr.
Sup. Front. Gyr.
Cent. Sulc.
Mid. Front. Gyr.
Postcent. Gyr.
Pars Operc.
Pars Tri.
Pars Orb.
V. of Labbé
G
DBS Lead
Postcent. Gyr.
Precent. Gyr.
Cent. Sulc.
V. of Labbé
H
DBS Lead
Arc. Fasc.
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Sup. Lim. Sulc.
Insula
Limen Ins.
I
DBS Lead
Cor. Rad.
Arc. Fasc.
Call. Fibers
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K
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Fornix Col.
Red Nucl.
Caud. Nucl. Head
Fornix Crura
Ant. Limb
STN
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Lead Pos.
Putamen
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GPe
M
STN-Hypothal. Conn.
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STN
Red Nucl.
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Fornix Crura
GPi
PPN
Int. Caps.
Ant. Limb
STN-Put. Conn.
GPe
Putamen
N
Red Nucl.
Fornix Col.
Caud. Nucl. Head
Fornix Crura
Ant. Limb
STN
Int. Caps.
Lead Pos.
Putamen
Int. Caps. Post. Limb
GPe

FIGURE 7. *DBS lead trajectory dissections from entry point to STN.* **A**, *STN lead trajectory demonstrated in the axial plane of the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequence in the in-house targeting software.* **B**, *STN lead trajectory demonstrated in the sagittal plane of the FGATIR sequence in the in-house targeting software.* **C**, *STN lead trajectory demonstrated in the coronal plane of the FGATIR sequence.* **D**, *Coordinates used for STN direct targeting in the in-house targeting software.* **E**, *Burr hole and lead position at the level of the superior frontal gyrus.* **F**, *DBS lead traversing the posterior portion of the superior frontal gyrus.* **G**, *DBS lead trajectory and relationship to the pre central gyrus.* **H**, *DBS lead traversing the superior longitudinal fasciculus.* **I**, *DBS lead passed through the corona radiata and callosum fibers.* **J**, *DBS lead traversed the posterior limb of the internal capsule.* **K**, *DBS lead reaching the thalamus.* **L**, *DBS lead reaching the posterolateral portion of the STN.* **M**, *Magnified and more superior view of* **L**, *demonstrating the lead position at the STN and its relationship with the internal capsule and STN-hypothalamus connections.* **N**, *Detailed anatomy after DBS lead removal, demonstrating the posterolateral position of the STN DBS lead. Ant. Comm.: anterior commissure; Arc. Fasc.: arcuate fasciculus; Call.: callosum; Caud.: caudate; Cent. Semi.: centrum semiovale; Cent. Sulc.: central sulcus; Conn.: connections; Cor. Rad.: corona radiate; DBS.: deep brain stimulation; Dors. Striat.: dorsal striatum; Ext, Caps.: external capsule; Fib.: fibers; GPe: Globus Pallidus Externus; GPi: Globus Pallidus Internus; Gyr.: gyrus; Hypothal.: hypothalamus; IFOF: inferior fronto-occipital fasciculus; Ins.: insula; Int. Caps. Ant. Limb: anterior limb of the internal capsule; Int. Caps. Post. Limb: posterior limb of the internal capsule; Lat. Vent.: lateral ventricle; Mid. Cer. A.: middle cerebral artery; Mid. Front.: middle frontal; Mid. Temp.: middle temporal; Nucl.: nucleus; Pars Operc.: pars opercularis; Pars Orb.: pars orbitalis; Pars Triang.: pars triangularis; Precent.: precentral; Pos.: position; Postcent.: postcentral; Sup. Front.: superior frontal; Sup. Lim. Sulc.: superior limiting sulcus; Sup. Long. Fasc.: superior longitudinal fasciculus; Sup. Temp.: superior temporal; Stereo.: stereotactic; STN: subthalamic nucleus; Subst. Nigra: substantia nigra; Tr.: tract; V.: vein; ZI: zona incerta.*

of DBS targets for PD (STN, GPi, and PPN) with their essential connections displayed using meticulous fiber tract dissections. The detailed microanatomic dissections have been coupled with 11.1 T structural MRI, 4.7 T DTI tractography, and schematic drawings to enhance clarity and understanding. It is imperative to mention that there were some limitations of this study, mainly the afferent or efferent projections are not possibly identified in these dissections, the sample size of 10 brains and 2 hemispheres and the lack of previous anatomic research studies on the STN, GPi and PPN connections. These limitations suggest the need for further development in this area of study.

While Delong et al[27] characterized the functional neurocircuitry of the basal ganglia involved in PD 27 yr ago, detailed microanatomic cadaveric dissections of this circuitry have never been published. A correlation of the important structure-function relationships involved in successful DBS therapy has also not been presented in the context of a precisely detailed neuroanatomic demonstration.

Targeting methods for functional neurosurgical interventions have improved substantially with the exploitation of recent technological advances. *Indirect targeting*—whereby the position of a neuroanatomic target relative to the midcommissural point in a stereotactic brain atlas is used to predict its location in the brain of a given patient—while useful as a starting point for DBS targeting, should now be considered obsolete as a stand-alone targeting technique. Various strategies to improve upon indirect atlas targeting have been developed by stereotactic surgeons over the years in an effort to account for the error attributable to neuroanatomic variability from patient to patient, as revealed in Figures 6A-6C and 7A-7D. Modern imaging modalities (T2 MRI,[30] FGATIR MRI,[31] DTI tractography.[32,33]) can provide more direct visualization of neuroanatomic structures of interest than ever before, enabling *direct targeting*, which provides more precise identification of intended brain targets in a given individual. Direct targeting is also enhanced by the use of advanced targeting software that provides 3-dimensional image reconstruction and incorporates neuroanatomic atlas overlays that can be deformed to precisely conform to a given patient's visible anatomy. A high quality *deformable digital brain atlas* enables the modern stereotactic surgeon to more accurately infer the position of important neuroanatomic structures or boundaries that may be imperfectly visualized even with the best available imaging (Figures 6A-6C and 7A-7D).[31] We therefore argue that a solid understanding of the neuroanatomic relationships of the STN, GPi, and PPN and their surrounding structures, as presented in this study, is prerequisite to optimal DBS targeting.

DBS for PD, while typically producing robust symptomatic relief, may also result in significant adverse effects, including the induction of paresthesias, involuntary movements, worsening of gait or speech, gaze deviation, or paralysis, as well as cognitive and mood side effects. Cognitive side effects,[4,34] postoperative depression, mania, anxiety, and apathy have been reported during STN stimulation,[35,36] and all of these effects may be attributable to current spread into the inferomedial limbic STN-substantia innominata connections. Stimulation at the superior border of the STN can produce enhanced suppression of both Parkinsonian tremor and medication-induced dyskinesia by spreading current into the lenticular fasciculus and zona incerta. STN-DBS may disrupt pathological synchronization of β oscillations in the motor network (thereby facilitating movement) by altering the timing of motor cortex firing through orthodromic stimulation of somatosensory afferents to the STN that are most concentrated in the dorsolateral STN.[37] An improved understanding of the various effects of STN DBS can be obtained through study of STN microanatomy and the connections between the STN, GPi, GPe, putamen, and precentral gyrus, as demonstrated in the dissections presented here (Figure 4B-7G).

Because its volume is substantially larger than that of the STN, the functional circuitry of the GPi is less densely packed, and surrounding functional circuits are further away and less likely to be affected by spreading current from therapeutic DBS. One predictable advantage of GPi DBS over STN DBS is, therefore, that fewer unintended stimulation-induced side effects are observed with GPi stimulation. Overall, both STN and GPi have proven to be very effective DBS targets for Parkinson's

disease.[4,38,39] The safety profile of GPi DBS is superior to that of STN, but more energy is required in the GPi to produce optimal therapeutic results. Both targets also have other advantages and disadvantages that should be considered when choosing a DBS target that is optimal for a given patient.[40]

PPN DBS has shown some promise for the treatment of Parkinsonian gait disorder. There are some difficulties inherent to the targeting of the PPN, however. The target is small and situated in the densely packed midbrain-pontine tegmentum, where disruption or stimulation of surrounding structures is poorly tolerated. The topography of the human PPN has to be further clarified, and extrapolation from animal to human studies must be made with caution.[41] Recent data have shown that rostral and caudal PPN may subserve different functions.[42,43] Because the STN and GPi connections are observed at the dorsal, lateral PPN, we hypothesize that the dorsal-lateral PPN may be a reasonable target for therapeutic stimulation.

CONCLUSION

Despite 30 yr of modern DBS experience and research, our understanding of the mechanisms of action of DBS for PD and other neurocircuitry disorders remains incomplete, and absolute consensus has not been reached regarding the optimal neuroanatomic targets for various DBS applications. More accurate and precise anatomic localization of therapeutically active DBS contacts, correlated with carefully measured beneficial and adverse effects of stimulation at these neuroanatomic sites, will refine our understanding of the effects of stimulation of various structures and enable us to optimize DBS targeting for improved global outcomes. We hope that this in-depth neuroanatomic presentation of the STN, GPI, and PPN, with surrounding structures and various fiber connections will serve as a powerful educational tool for DBS practitioners and that it will contribute to more effective DBS targeting with the ultimate goal of improved therapeutic outcomes with fewer adverse effects.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplement Digital Content 2. Supplemental Results. The Supplemental Digital Content expands on the Results provided. Results 1. Location and relationships of STN. Results 2. Connections of the STN. Results 3. Location and relationships of GPi. Results 4. Connections of the GPi. Results 5. Location and relationships of PPN. Results 6. Connections of the PPN.

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