Anatomy of Targets for Deep Brain Stimulation

2

Ali Jahanshahi, Juergen K. Mai, and Yasin Temel

Abstract

The purpose of Deep Brain Stimulation (DBS) is to modulate the activity of specific anatomical areas in the brain and thereby manage the symptoms of neurological and/or psychiatric disorders. Essential to this surgical management is an understanding of the anatomy and physiology of the target regions. The basal ganglia and the thalamus are the main target areas for DBS. These structures are connected to higher (cortical) and lower (brainstem) areas through both partially parallel and partly integrated projections. These projections are primarily responsible not only for motor control, but also for other functions such as motor learning, associative functions, and emotions. According to the classical basal ganglia model, information flows through the basal ganglia back to the cortex through two pathways, while new models show that parallel circuits subserve the classical functions of the basal ganglia engaging associative and limbic territories. The current targets of DBS for movement disorders are the dorsolateral part of the subthalamic nucleus, the posterior ventrolateral part of the internal globus pallidus, and the ventrolateral nuclei of the thalamus. For psychiatric disorders, relevant targets are the ventral striatum, including the nucleus accumbens, the ventral part of the internal capsule, the ventromedial part of the subthalamic nucleus, the anterior part of the internal globus pallidus, and the medial nuclei of the thalamus. The anterior nucleus of the thalamus is part of the Papez circuit and has been targeted in patients with treatment-resistant epilepsy. The anatomical details of these targets are discussed in this chapter.

A. Jahanshahi (✉) · Y. Temel
Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands

Maastricht University-MHeNS School for Mental Health and Neuroscience,
Maastricht, The Netherlands
e-mail: a.jahanshahi@maastrichtuniversity.nl; y.temel@maastrichtuniversity.nl

J. K. Mai
Institute for Anatomy, Heinrich-Heine-University, Duesseldorf, Germany
e-mail: mai@uni-duesseldorf.de

Introduction

DBS aims to modulate the activity of localized anatomical areas, thereby reducing symptoms of specific neurological and/or psychiatric disorders. DBS has evolved to be an important therapeutic application in patients with specific disorders, including Parkinson's disease (PD) (Deuschl et al. 2006), essential tremor (Benabid

Y. Temel et al. (eds.), *Fundamentals and Clinics of Deep Brain Stimulation*,
https://doi.org/10.1007/978-3-030-36346-8_2

et al. 1993; Hubble et al. 1996), dystonia (Krauss et al. 1999), epilepsy (Fisher et al. 2010), as well as obsessive compulsive disorder (OCD) (Nuttin et al. 1999; Denys et al. 2010). Furthermore, the effects of DBS in managing the clinical symptoms of severe depression, Gilles de la Tourette syndrome (GTS) and various other psychiatric disorders have been explored (Bewernick et al. 2010; Lozano et al. 2012; Ackermans et al. 2011). Although three decades have passed since the introduction of DBS, neurophysiological correlates underlying the therapeutic effects of DBS remain to be clarified (Gradinaru et al. 2009). Knowing how DBS results in therapeutic effects in neurological or psychiatric disorder will be critical to our understanding of not only how DBS works, but also how to make it work better and how to apply it effectively to other neurological disorders. The essence of any mechanistic research, even ones that inherently seeks to unravel the mechanisms behind the therapy or pathophysiology, is one of anatomy. DBS needs to target the regions that have efficient access to anatomic networks involved in disease symptoms. Even though anatomical models relevant to core aspects of psychopathology continue to develop, it is conceivable that anatomic relationships of the basal ganglia, thalamus, and other cortical and subcortical structures are vital for gaining insight into the application of DBS in managing the neurological and psychiatric symptoms. An accurate implantation of the electrodes in DBS operations is therefore essential to obtain the desired effects. In fact, with a clear insight on the anatomy, a large part of therapeutic effects and side effects of DBS can be explained. This chapter aims to elaborate on the anatomy of the most commonly used DBS targets that have been thought to underlie the therapeutic effects of DBS. The focus will be mainly on the basal ganglia and the thalamus anatomy in the context of neurological and to psychiatric disorders. The cortico-basal ganglia-thalamocortical circuits and the individual areas are discussed below.

The Cortico-Basal Ganglia-Thalamocortical Circuits

The basal ganglia consist of the pallidal complex, the striatum, the substantia nigra, and the subthalamic nucleus (STN) (Alexander and Crutcher 1990). The motor loop computes the processes between the motor cortex and basal ganglia by "direct," "indirect," and "hyperdirect" pathways to determine overall thalamic activity. The cortical projections reach the basal ganglia via two major input structures. First is the striatum, which consists of the putamen and caudate nuclei in the dorsal striatum, and the nucleus accumbens (NAc) in the ventral striatum. The second input pathway enters the basal ganglia through the STN.

The striatum has been known as input structure for some time (Albin et al. 1989), but the STN as input structure is a more recent concept (Nambu et al. 2002). This cortico-subthalamic projection is known as the hyperdirect pathway and is glutamatergic, hence excitatory (Fig. 2.1). The cortico-striatal efferents enter the caudate, putamen, and accumbens nuclei to be processed further within the basal ganglia circuit. Cortico-striatal projections arise from the entire ipsilateral and contralateral cortical areas. These pathways are excitatory in nature and use glutamate as neurotransmitter at their synaptic terminals with the spines of striatal neurons, and are topographically organized (Gerfen 1984; Donoghue and Herkenham 1986). Cortico-striatal projections are classified into (1) pyramidal tract neurons, which project through the cortico-pyramidal tract and innervate the striatum ipsilateraly: these pathways mainly innervate the striatal neurons, giving rise to the indirect pathway, and (2) the intra-telencephalic neurons, which provide bilateral input to the striatal neurons in the direct pathway (Lei et al. 2004).

The thalamo-striatal projection is the second major source of innervation to the striatum, which had been largely neglected in the past years. These projections mainly arise from the midline and intralaminar thalamic nuclei (Berendse and Groenewegen 1990) as well as from the ventral thalamic motor nuclei

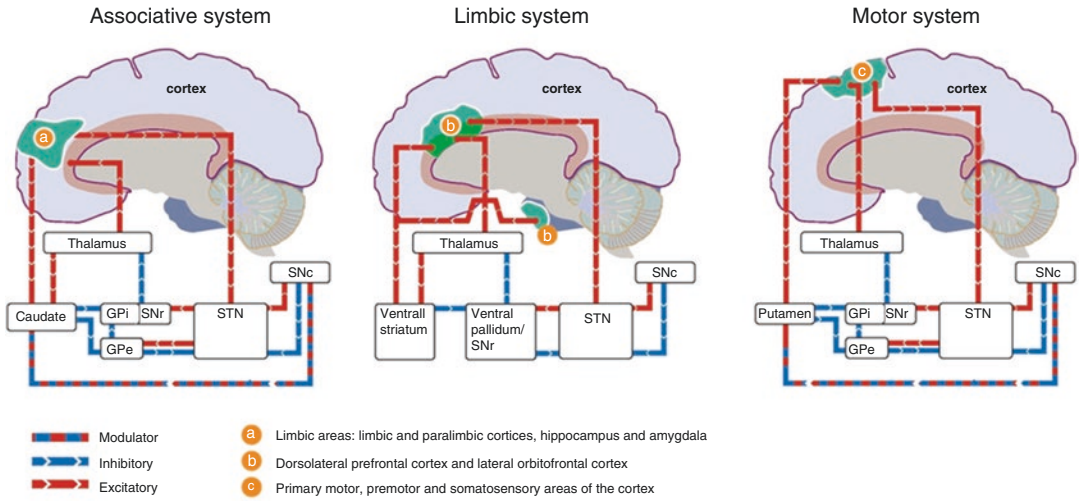

Fig. 2.1 The cortico-basal ganglia-thalamocortical projections can be subdivided into three major functional pathways, namely the motor, associative, and limbic pathways. The connections of the motor pathway are described above. As for associative pathway, the cortico-striatal projections mainly innervate the caudate nucleus. The other connections of this pathway are very similar to those of the motor pathway. The cortical efferents from limbic areas enter the basal ganglia via the STN and the ventral striatum. The output projects through the ventral pallidum to the medial part of the thalamus (Alexander et al. 1990) and from there back to the related cortical areas. *STN* subthalamic nucleus, *GPe* globus pallidus externa, *GPi* globus pallidus interna, *SNc* substantia nigra pars compacta, *SNr* substantia nigra pars reticulata. (Figure reproduced with permission from Temel et al. 2005)

(McFarland and Haber 2001). Thalamo-striatal efferents follow a similar path as the cortico-striatal pathway.

These projections descend on the dorsal striatum to the pallidal complex and feed two major striatal pathways. Via the direct pathway, these projections reach the output structures of the basal ganglia: the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The direct pathway arises from medium spiny neurons (MSNs) that project monosynaptically to the GPi and SNr. These MSNs preferentially express dopamine D1 receptors. The indirect pathway arises from MSNs that express dopamineD2 receptors. Via the indirect pathway, the striatal projections first reach the external globus pallidus (GPe), then the STN, and via the STN, the signals pass on to the output nuclei (GPi and SNr). The indirect pathway involves direct projections from the GPe to the GPi as well. Apart from cortico-striatal and thalamo-striatal projections, the amygdaloid complex also provides glutamatergic input to the striatum (Ragsdale and Graybiel 1988). The GPi and SNr project mainly to the ventrolateral nuclei of the thalamus which, in turn, project back to the cerebral cortex (mainly the frontal lobe). The thalamic projections to the cortex are again excitatory. The efferent GPi and SNr pathways interact with different target structures through axon collaterals (Parent and Hazrati 1995; Parent et al. 2000). All projections within the basal ganglia are inhibitory and use GABA as neurotransmitter, except the STN neurons, which expresses glutamate as a neurotransmitter and is therefore the only excitatory nucleus. From the output nuclei, the projections reach the ventrolateral nuclei of the thalamus, and via the thalamus to the cortex; for more in-depth review, see Lanciego et al. (2012).

The monoaminergic neurotransmitter systems play an important role in modulating the functions of basal ganglia. A normal functioning of the basal ganglia system is highly dependent on intact dopamine release to the input nuclei. The nigro-striatal dopaminergic efferents arise mainly from the A9 group of dopaminergic neurons in the substantia nigra pars compacta (SNc) neurons and to lesser extent from A8 neurons, which are

situated in retrorubral field (Dahlstrom and Fuxe 1964). The SNc projects to the motor and associative parts of the striatum as well as the STN. The mesostriatal and mesolimbic dopaminergic projections arise from the A10 group of dopaminergic cells in the ventral tegmental area (VTA) and project to the ventral striatum (e.g., the NAc) and the ventromedial part of the STN. Perturbed dopamine release is associated with several basal ganglia disorders such as the Parkinsonism, dystonia, chorea, and tics. In addition to dopaminergic projections, the serotonergic cells in the brainstem's raphe nuclei also project to the dorsal and ventral striatum (Anden et al. 1966). However, the exact function of these projections remains unknown, as experimental data are controversial.

Anatomical Structures

The Striatum

The striatum is a heterogeneous structure with a diverse range of neuronal phenotypes and neurotransmitters. Several histochemical and immunohistochemical stains have revealed the presence of two major compartments named striosomes and matrix. The striosomes and matrix are differentiated into discrete territories and are well characterized to differ in their expression of neurochemical markers. For instance, histochemical staining using antibody against acetylcholinesterase enzyme (AChE) (Graybiel and Ragsdale 1978) has revealed the presence of scattered areas showing weak AChE labeling (striosomes) within a more intensely stained background (matrix). Immunocytochemical staining of number of other markers such as substance P, GABA, and neurotensin has also shown a preferential expression of these markers within these two compartments (Pert et al. 1976; Graybiel et al. 1981; Gerfen 1984; Desban et al. 1995). The local axon collaterals and dendritic arborization of MSNs are restricted within the striatal compartment in which they are positioned in either striosome or matrix. For instance, dendrites from striosomal MSNs do not enter the neighboring matrix and vice versa (Penny et al. 1988; Fujiyama et al. 2011). On top of exerting differences in afferent and efferent connectivity, the striosome and matrix compartments have also been suggested to play distinct roles in a range of neurological diseases. MSNs located in the matrix compartment project to the GPe, GPi, and SNr, while striosomal MSNs primarily innervate the SNc. However, these same cells form axon collaterals that reach the GPe, GPi, and SNr (Gerfen 1984; Bolam et al. 1988; Kawaguchi et al. 1989; Gimenez-Amaya and Graybiel 1990; Fujiyama et al. 2011). With regard to the input pathways, glutamatergic projections arising from the cerebral cortex and thalamus as well as dopaminergic fibers originating from the SNc mainly innervate the matrix compartment, while cortical limbic areas and amygdala preferentially project to the striosomes (Graybiel 1984; Donoghue and Herkenham 1986; Ragsdale and Graybiel 1988; Gerfen 1992; Sadikot et al. 1992a, b; Kincaid and Wilson 1996). The exact functional outcomes of striosome-matrix organization remain to be determined (Lanciego et al. 2012).

Striatal Neurons

The striatum contains two different types of neurons: projection or striatofugal neurons (90%) and interneurons (10%). Since projection neurons have a small-to-medium cell body (20 μm in diameter), they are also called medium-sized spiny neurons. These neurons are multipolar and their dendritic processes are covered by postsynaptic specializations called dendritic spines. All striatal MSNs are inhibitory neurons and express GABA as neurotransmitter. MSNs are divided further based on their projection pattern, including GPe innervating neurons and those that innervate the GPi and SNr. Striatal MSNs projecting to the GPe express the dopamine D2 receptor (D2R), forming the inhibitory indirect pathway (striato-GPe-STN-GPi/SNr) and thus inhibit the target neurons. In contrast, striatal MSNs, which directly innervate the GPi and SNr, express dopamine subtype 1 receptors (D1R), giving rise to the excitatory direct pathway (striato-pallidal) that stimulates target neurons. Another key difference between the direct and the indirect pathways is

that source neurons in the direct pathway express the neuropeptide substance P, while the indirect pathway neurons contain the neuropeptides enkephalin and dynorphin (Wichmann et al. 2002). The striatum also contains several different types of interneurons, unlike MSNs all of which show smooth dendrites. These interneurons are classified into four groups according to their neurochemical phenotype and morphological features (Kawaguchi et al. 1995). These cell groups are as follows: (1) cholinergic neurons, which express acetylcholine as neurotransmitter and are the largest in size and most abundant among the other groups; according to their electrophysiological fingerprint, these neurons exhibit tonic firing pattern; (2) GABAergic and also contain parvalbumin with fast-spiking activity in electrophysiological recording; (3) GABAergic interneurons containing calretinin; and (4) another type of GABAergic interneurons, known as nitrergic interneurons which express nitric oxide as the neurotransmitter. These interneurons together with MSNs form a complex intra-striatal circuit. For instance, both tonic and fast-spiking GABAergic interneurons are under dopaminergic control, and in turn, modulate the activity of MSNs' neurons; meanwhile, calretinin-expressing and nitrergic interneurons innervate tonic and fast-spiking GABAergic interneurons (for review, see Lanciego et al. 2012).

The Ventral Striatum

The ventral striatum consists of the nucleus accumbens, the ventromedial part of the caudate nucleus and the spined cell part of the olfactory tubercles (Nauta 1979; Parent and Hazrati 1995; Nakano 2000). The most important part of the ventral striatum is the nucleus accumbens (NAc) (Basar et al. 2010). The NAc is located anterior to the posterior border of the anterior commissure (AC) and lies parallel to the midline. It lies ventral and medial of the caudate nucleus and extends dorsolaterally into the putamen (Fig. 2.2). The NAc is more visible in coronal than in sagittal, and more in sagittal than transverse MR images. In T2-weighted MR images, the NAc shows more intense signaling compared with the caudate nucleus and putamen, which leads to easier distinction of the boundaries of the NAc with the caudate and putamen. Unlike the rest of the striatum, the NAc can be divided into a core and a shell, each of which has unique features. The shell surrounds the core medially, ventrally, and laterally. The core and shell are well known to differ in their expression of neurochemical markers and electrophysiological fingerprints. Moreover, they exert differences in afferent and efferent connectivity and have also been suggested to have different involvement in a range of neurological diseases. More than 95% of NAc cells are GABAergic MSN projection neurons.

The NAc is also known as ventral striatum, which has been introduced by Heimer and Wilson (1975) to distinguish it from the dorsal striatum. The NAc is characterized by the strong input from the limbic areas such as the amygdala, hippocampus, and prefrontal areas. For this reason, NAc has been used as a DBS target for psychiatric disorders. The NAc receives direct glutamatergic afferents from the subiculum (which is the most inferior component of the hippocampal formation, lying between the entorhinal cortex and the CA1 subfield of the hippocampus proper), the hippocampus, amygdala, thalamus and prelimbic prefrontal cortex, as well as indirect inputs from the ventral tegmental area (VTA) and substantia nigra via the mesolimbic dopaminergic projections. The main output projections from the NAc arise from the MSNs and terminate in various areas of the mesencephalon and basal ganglia such as the pallidal complex, the stria terminalis, the preoptic region, the nucleus parataenialis, the mediodorsal thalamic nucleus, the lateral habenular nucleus, the substantia nigra-ventral tegmental area, the lateral hypothalamus, cingulum, thalamus, globus pallidus and the subpallidal region, the amygdala and septum (for review, see Salgado and Kaplitt 2015).

In addition to the NAc, the ventral striatum includes the striatal elements of the olfactory system and the ventral, medial, and caudal parts of the caudate and putamen nuclei (Heimer and Wilson 1975; Fudge and Haber 2002). Caudal to the NAc is the bed nucleus of the stria terminalis (BNST). The anatomical boundaries between these two are not always evident. There are indications

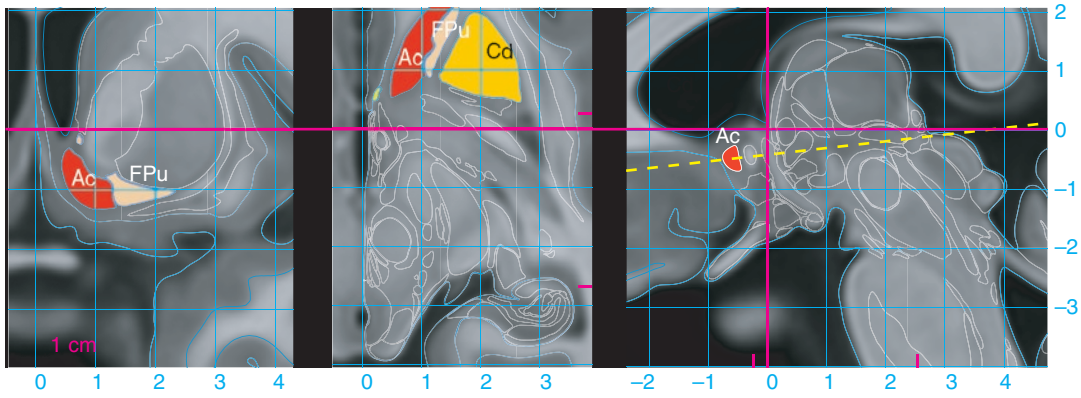

Fig. 2.2 Localization of the nucleus accumbens in MNI space. Arrows indicate the anterior and posterior commissures. *Ac* cucleus accumbens, *FPu* funiculus putaminis, *Cd* caudate nucleus

that the BNST plays an important role in the pathophysiology of OCD and that stimulation of this structure can alleviate the symptoms (Luyten et al. 2016). The BNST has a close relationship with the NAc shell. There are differences in the connectivity of the "core" and "shell." How these two parts in the context of DBS should be seen is not entirely clear. Figure 2.2 shows the localization of the NAc in MNI space.

The Subthalamic Nucleus

The STN, also known as the Corpus Luysi, is a relatively small nucleus with densely packed neurons located in the transition of the diencephalon and the mesencephalon, immediately ventral to the zona incerta and rostral to the substantia nigra (Hameleers et al. 2006). The STN is the main surgical target for electrode implantation for DBS in PD and has gained more attention over the last years, as it also seems to be a potential target for patients with OCD.

The classical model of afferent and efferent STN connections consisted of only GABAergic input from the GPe (second relay station of the indirect pathway) and STN efferents targeting basal ganglia output nuclei. This classical model has been challenged by new evidences showing that the STN also receives glutamatergic projections from the cerebral cortex, known as the hyperdirect pathway, which in turn provides a pathway for motor-related cortical areas to access the output nuclei directly, bypassing the input nuclei. These inputs include efferents from the primary motor cortex, the supplementary motor area, premotor cortices, the frontal eye field area and supplementary eye field area, and these inputs are somatotopically organized at the level of the STN (Nambu et al. 1996, 2002). The hyperdirect pathway is characterized by faster transmission than those passed through the basal ganglia via the direct and indirect pathways, and therefore exerts powerful excitation on the output nuclei. Moreover, the STN receives thalamic projections that are topographically organized (Sadikot et al. 1992a). These thalamo-subthalamic projections are bilateral, although with an ipsilateral predominance (Castle et al. 2005). The STN efferents to the basal ganglia nuclei are characterized by highly branched neuronal processes, sending axons that innervate the GPi, GPe, and SNr (Van Der Kooy and Hattori 1980).

Although targeting the STN with DBS effectively relieves severe motor symptoms, it may also produce neuropsychiatric side effects such as apathy, compulsive behavior, hypersexuality, cognitive dysfunction, clinical depression, and suicidal thoughts (Temel et al. 2005). These side effects have been attributed to the unwanted stimulation of supposed nonmotor subregions of the STN. The STN can be divided into three functional subregions based on analogy with the different circuits including a dorsolateral motor

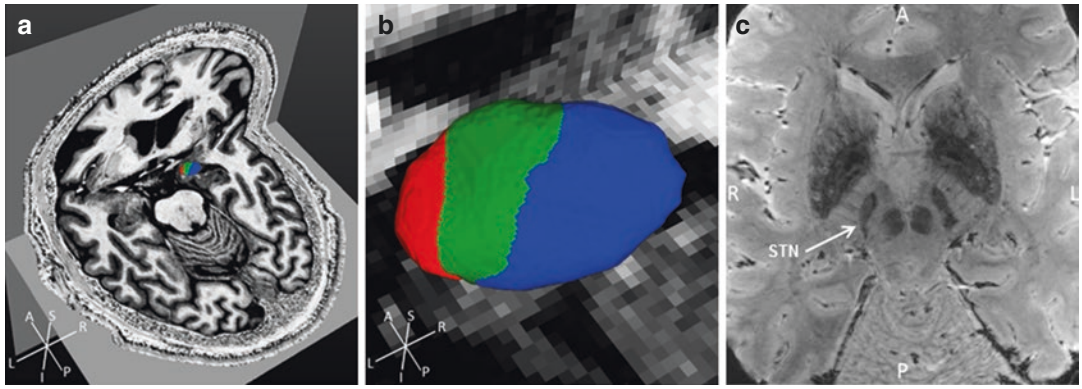

Fig. 2.3 (**a**) Anatomical orientation of the STN. (**b**) The STN can be divided into three functional subregions based on analogy with the different circuits including a dorsolateral motor area (blue), an associative medial section (green), and a ventromedially located limbic tip (red). (**c**) T2 weighted 7 T MR image showing the STN. *A* anterior, *P* posterior, *STN* subthalamic nucleus. (Figure reproduced with permission from Temel et al. 2016)

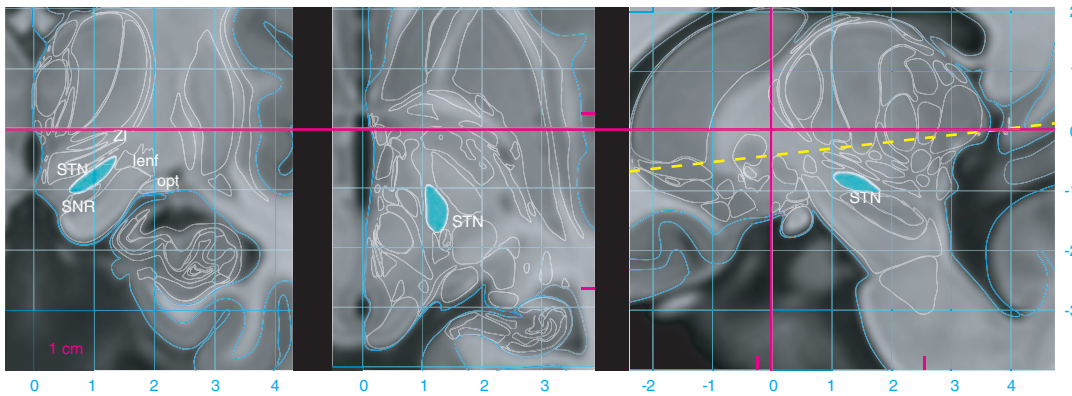

Fig. 2.4 Localization of the subthalamic nucleus in MNI space in synopsis with the Atlas of the Human Brain. In clinical practice, the stimulation electrode in the STN is often implanted in the dorsolateral part. The STN is shown in coronal (left), axial (middle), and sagittal plane (right). The magenta lines provide the horizontal and vertical zero lines of the MNI space. The MNI space is horizontally tilted with respect to the intercommissural plane (yellow dashed line). *STN* subthalamic nucleus, *SNr* substantia nigra pars reticulate, *ZI* zona incerta, *lenf* fasciculus lenticularis, *opt* optic tract

area, an associative medial section, and a ventromedially located limbic tip (Lambert et al. 2012) (Fig. 2.3). Although documented, these functional subdivisions are not yet understood well enough to be specifically targeted for individual patients. However, in clinical practice, the DBS electrode in the STN is usually implanted in the dorsolateral part to modulate only the motor circuit in PD individuals (Fig. 2.4) (Kocabicak and Temel 2013). Stimulation of the ventromedial part affects the limbic circuit and has been performed in individuals with OCD (Mallet et al. 2008). The STN is surrounded by important areas and projections. The superior longitudinal fasciculus or medial forebrain bundle is located mediodorsally to the STN, which is an important monoaminergic projection that is responsible for mood. Stimulation of this area can have an effect on mood-related parameters (Schlaepfer et al. 2013). Mood changes can also be caused by stimulation of the SNr, which is located caudally to the STN (Bejjani et al. 1999). On the other hand, SNr stimulation is used to treat gait disturbances in Parkinson's disease (Weiss et al. 2013). The

anteromedial side of the STN faces the hypothalamic nuclei. Stimulation of these areas can lead to autonomic side effects. The most important side effects are caused by the cerebral peduncle, which is located laterally to the STN. If electrical current spreads to this area of the pyramid tract, the patient might experience tingling, twitching, and dysarthria (Fig. 2.5).

Recent developments in MRI techniques, such as 7-tesla (T) imaging, have significantly improved the ability to visualize the tripartite division of the STN in humans. It is conceivable that this technology might be implemented in clinical setting to guide stereotactic implantation of electrical stimulators in PD and OCD patients, so that specific subparts of the nucleus can be targeted more reliably. These technical developments highlight a need for clear anatomical delineation of the STN's supposed subdivisions to identify surgical targets, which will improve the clinical practice.

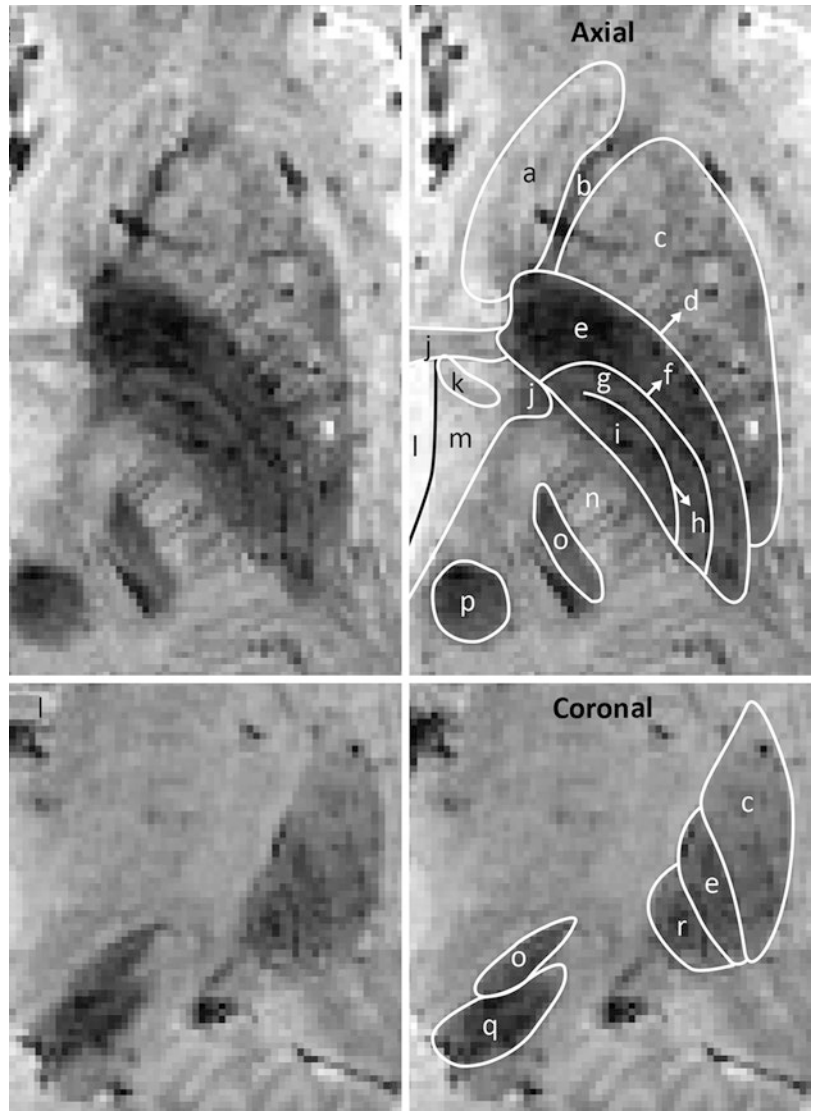

Fig. 2.5 Orientation of anatomical structures in the vicinity of the subthalamic nucleus (STN). (a) caudate nucleus, (b) anterior segment of the internal capsule, (c) putamen, (d) lamina pallidus lateralis, (e) globus pallidus externa, (f) lamina pallidus medialis, (g) lateral segment of the globus pallidus interna, (h) lamina pallidus incomplete, (i) medial segment of the globus pallidus interna, (j) anterior commissure, (k) fornix, (l) third ventricle, (m) hypothalamus, (n) posterior segment of the internal capsule, (o) subthalamic nucleus, (p) red nucleus, (q) substantia nigra, (r) globus pallidus interna. (Figure reproduced with permission from Plantinga et al. 2014)

The Globus Pallidus

The External Globus Pallidus

The GPe (also known as the lateral division of the globus pallidus) is part of the pallidal complex together with GPi and the ventral pallidum (Fig. 2.6). The GPe is surrounded laterally by the putamen. The GPe and GPi exert a number of similarities in several cyto- and chemo-architectural features, as both nuclei are made of sparsely distributed GABAergic neurons with large cell bodies. Another characteristic of GPi and GPe neurons is an enriched expression of the calcium-binding protein parvalbumin. GPe neurons receive two main afferent systems: a GABAergic projection from D2R-containing striatal MSNs, which is an inhibitory input forming the first synaptic relay station of the indirect pathway. In addition, GPe neurons receive striatal projections containing adenosine type 2A receptors (Rosin et al. 1998). Through a reciprocal connection between the GPe and STN, GPe neurons receive strong glutamatergic excitatory projections. This reciprocal connectivity between the two structures suggests a greater role for the GPe in basal ganglia function beyond being a simple relay station between the striatum and the STN (Shink et al. 1996). Moreover, it has long been known that GPe and GPi are also reciprocally interconnected. Another source of glutamatergic inputs to the GPe is projections from the caudal intralaminar nuclei, although considered to be minor (Kawaguchi et al. 1990).

The Internal Globus Pallidus

The GPi also known as the medial division of the globus pallidus located medial to the GPe and lateral to the hind leg of the internal capsule (Fig. 2.7). The lamina pallidi medialis defines the border between the GPi and GPe. The lamina pallidali lateralis is another thin lamina that separates the GPe from the putamen. Sometimes a lamina can also be found in the GPi itself, which is called the lamina pallidali incompleta. These laminae can be recognized as silent zones in electrophysiological microelectrode recordings during DBS surgeries. The side effects of the DBS in the GPi are often related to the medially located internal capsule and may consist of tingling and dysarthria. Notably, the optic tract runs at the caudal part of the GPi and unwanted stimulation of this tract can cause visual side effects.

The GPi and the SNr are often grouped together not only because they functionally serve as basal ganglia output nuclei, but also because they exhibit a number of similarities in cyto-architectural and chemo-architectural characteristics, and to a lesser extent in types of their afferent and efferent projections. The pallidal cells consist of inhibitory GABAergic projection neurons with long axons and high rate of discharge that fire tonically to inhibit their targets. The GPi shows a

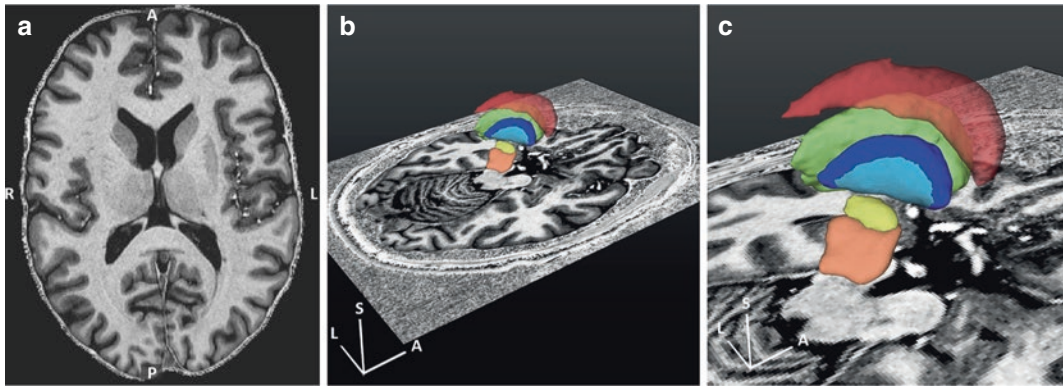

Fig. 2.6 (**a**) An axial view of the basal ganglia; (**b**), representation of the basal ganglia without sorrounding structures; (**c**) magnified "b". Three-dimensional orientation of the caudate nucleus (red), putamen (green), globus pallidus externa (dark blue), globus pallidus interna (light blue), subthalamic nucleus (yellow) and substantia nigra (pink). (Figure reproduced with permission from Temel et al. 2016)

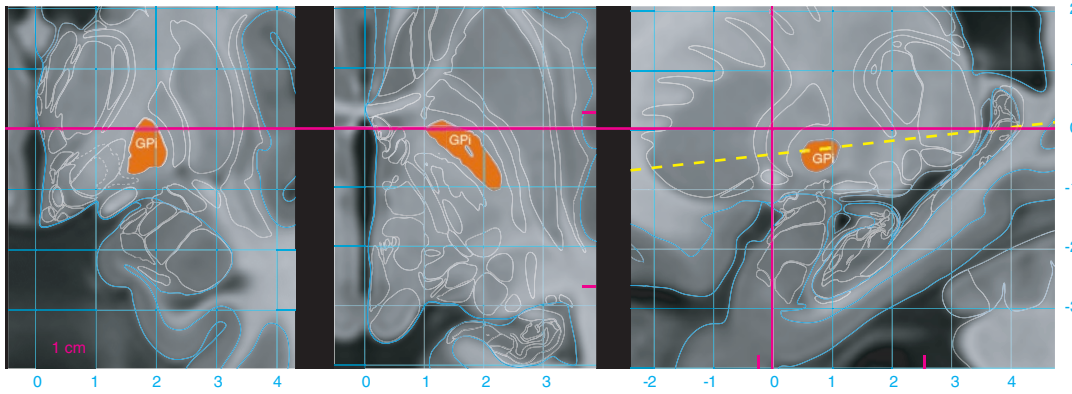

Fig. 2.7 Localization of the globus pallidus interna in MNI space. Upper arrow in axial plane and left arrow in sagittal plane indicate the anterior commissure. The posterior commissure is indicated by the other arrow. *GPi* globus pallidus interna

lesser cell density compared to the striatum. Besides, it hosts a considerable amount of crossing myelinated striatofugal fibers, which provide the GPi with a distinct appearance in T2 weighted MR images when compared with the striatum. The main inputs to the GPi consist of direct and indirect projections of the dorsal striatum and the STN. The direct pathway containing the D1R-expressing striatal MSNs is a major source of inhibition to the GPi. As part of the indirect pathway, the STN provides an excitatory glutamatergic projection to the GPi. In addition, collateralized glutamatergic subthalamo-pallidal and subthalamo-nigral projections provide excitatory input to the GPi. Both excitatory and inhibitory projections converge onto GPi (and SNr) neurons, which, in turn, innervate thalamic and brainstem regions.

The three major output projections from the GPi are: (1) the ansa lenticularis (ansa lentiformis in older texts), which originate from neurons located in lateral GPi regions and runs ventromedially and rostrally along the internal capsule, eventually entering the so-called field H of Forel (also known as the prerubral field), (2) the lenticular fasciculus (Forel's field H2), which is located between the STN and the zona incerta, and contains axons from more medially located GPi neurons, and passes through the internal capsule. The ansa lenticularis and lenticular fasciculus merge together at the level of field H of Forel and enter the thalamic fasciculus (H1 of Forel) and finally end in ventral and intralaminar thalamic nuclei, forming the pallidothalamic projection. (3) The third bundle is the pallidotegmental projections, which, innervates the brainstem regions, such as the superior colliculus and the pedunculopontine tegmental nucleus (PPN) (Haber et al. 2011). The pallido-thalamic projections innervate the densicellular and parvicellular regions of the ventral anterior motor thalamus (VAdc and VApc, respectively). The GPi, one of the two output structures of the basal ganglia, has been used as a target for functional neurosurgery. Lars Leksell was probably one of the first who performed lesions of the GPi (pallidotomy) in patients with PD, and this treatment was further developed by Laitinen (Laitinen et al. 1992). The part that was lesioned was the sensorimotor part, which is located in dorsolateral territory of the GPi. In 1994, DBS of the GPi was shown to be a clinically relevant approach in patients with PD (Siegfried and Lippitz 1994). Today, the sensorimotor part of the GPi is primarily a target for patients with primary or secondary dystonia (Vidailhet et al. 2013) (Fig. 2.7). In selected cases, patients with PD can also be treated with this approach. The anterior part of the GPi has been used as a DBS target for some years in patients with Tourette syndrome (Smeets et al. 2016).

The Thalamus

The thalamus is more or less localized in the center of the brain under the lateral ventricles (Ohye 1990). It consists of two parts that are connected to each other via interthalamic adhesion (also known as the massa intermedia or middle commissure). The thalamus is responsible for providing motor, sensory, limbic, and associative information to and from the cortex (Kandel 2000). The thalamus receives and processes sensory and motor input signals and has reciprocal connections with the cerebral cortex. It transmits the sensory information to the cortex and is involved in motor function, arousal, and mood functions. Classically, the thalamus is subdivided into nuclei based on the cyto-architecture and myleo-architecture as well as the anatomical localization. The main core groups are anterior, medial, midline, intralaminar, lateral, posterior, dorsal, and ventral nuclei (Ohye 1990). Despite being heterogeneous, these nuclei form a well-organized assembly. The thalamic neurons mainly use glutamate as a neurotransmitter.

With regard to DBS, two core groups of thalamic nuclei are important. The first group includes the ventrolateral nuclei, of which the nucleus ventralis intermedius (VIM) is the most relevant (Fig. 2.8). VIM has been targeted in functional neurosurgery for tremor management. The other relevant nucleus is the anterior nucleus (AN) of the thalamus, which has been targeted during stereotactic surgeries for treatment-resistant epilepsy (Fig. 2.9). The VIM gets its

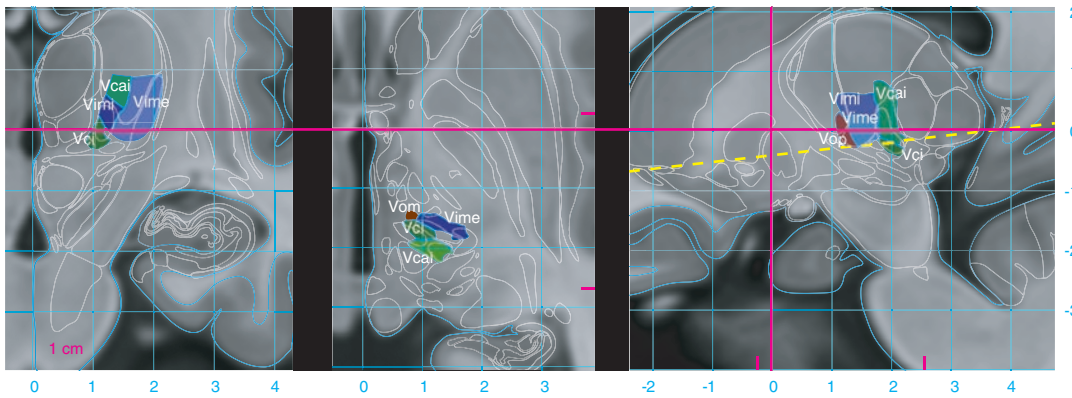

Fig. 2.8 Localization of the ventrointermedius nucleus of the thalamus in MNI space. Arrows indicate the anterior and posterior commissures. *vimi* ventrointermedius nucleus internus, *vime* ventrointermedius nucleus externus, *vci* ventrocaudalis internus, *vcai* ventrocaudalis anterior internus

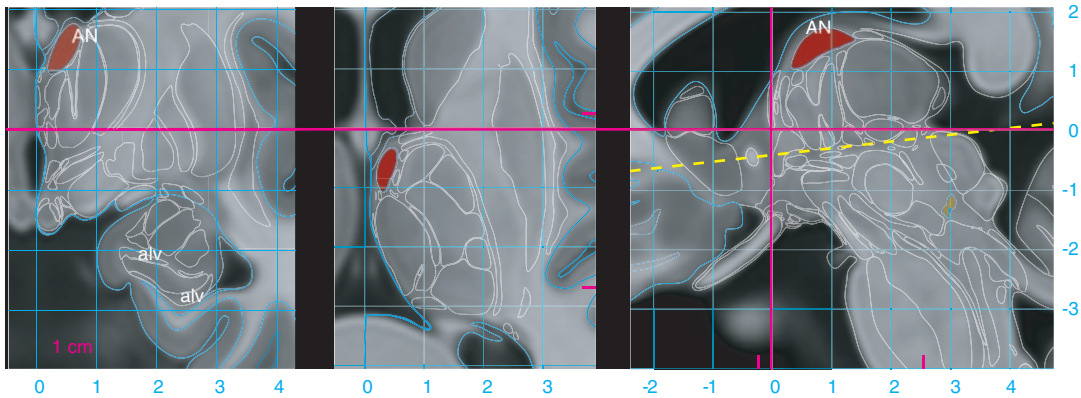

Fig. 2.9 Localization of the anterior nucleus of the thalamus in MNI space. Arrows indicate the anterior and posterior commissures. *AN* anterior nucleus

input mainly from the output nuclei of the basal nuclei and sends projections to the motor areas in the cortex. Furthermore, it receives important input from the cerebellum (Moers-Hornikx et al. 2009). The AN is part of the Papez circuit, an important circuit within the limbic system and involved in the control of emotions and memory (Hescham et al. 2013). The AN projects mainly to the temporal limbic structures and the cingulate gyrus. The mammillothalamic tract, which connects the corpora mamillaria to the AN, is an important structure for the anatomical planning of the electrode trajectory.

Conclusion

Understanding the anatomy and physiology of basal ganglia disorders is a growing field of modern medicine. Neurosurgical management of these disorders is by definition an anatomy-based approach. The main targets for the current neurological and psychiatric indications of DBS are located in the basal ganglia and thalamus. These targets all play a strategic role in the cortico-basal ganglia-thalamocortical motor, associative, and limbic circuits. The anterior nucleus of the thalamus is slightly outside of this system and used for DBS in epilepsy. A better understanding of the essence and extent of network alterations in local and remote neural elements following the application of electrical current will clarify the main components driving the therapeutic benefit, and the facilitating mechanisms that work at cross-purposes in patients.

References

Ackermans L, Duits A, van der Linden C, et al. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. Brain. 2011;134:32–844.

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989;12:366–75.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 1990;13:266–71.

Alexander GE, Grutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res. 1990;85:119–46.

Anden NE, Dahlstrom A, Fuxe K, et al. Ascending noradrenaline neurons from the pons and the medulla oblongata. Experientia. 1966;22:44–5.

Basar K, Sesia T, Groenewegen H, et al. Nucleus accumbens and impulsivity. Prog Neurobiol. 2010;92:533–57.

Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med. 1999;340:1476–80.

Benabid AL, Pollak P, Seigneuret E, et al. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl. 1993;58:39–44.

Berendse HW, Groenewegen HJ. Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J Comp Neurol. 1990;299:187–228.

Bewernick BH, Hurlemann R, Matusch A, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry. 2010;67:110–6.

Bolam JP, Izzo PN, Graybiel AM. Cellular substrate of the histochemically defined striosome/matrix system of the caudate nucleus: a combined Golgi and immunocytochemical study in cat and ferret. Neuroscience. 1988;24:853–75.

Castle M, Aymerich MS, Sanchez-Escobar C, et al. Thalamic innervation of the direct and indirect basal ganglia pathways in the rat: ipsi- and contralateral projections. J Comp Neurol. 2005;483:143–53.

Dahlstrom A, Fuxe K. Localization of monoamines in the lower brain stem. Experientia. 1964;20:398–9.

Denys D, Mantione M, Figee M, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 2010;6:1061–8.

Desban M, Gauchy C, Glowinsk J, Kemel ML. Heterogeneous topographical distribution of the striatonigral and striatopallidal neurons in the matrix compartment of the cat caudate nucleus. J Comp Neurol. 1995;352:117–33.

Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006;355:896–908.

Donoghue JP, Herkenham M. Neostriatal projections from individual cortical fields conform to histochemically distinct striatal compartments in the rat. Brain Res. 1986;365:397–403.

Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51:899–908.

Fudge JL, Haber SN. Defining the caudal ventral striatum in primates: cellular and histochemical features. J Neurosci. 2002;22:10078–82.

Fujiyama F, Sohn J, Nakano T, et al. Exclusive and common targets of neostriatofugal projections of rat striosome neurons: a single neuron-tracing study using a viral vector. Eur J Neurosci. 2011;33:668–77.

Gerfen CR. The neostriatal mosaic: compartmentalization of corticostriatal input and striatonigral output systems. Nature. 1984;311:461–4.

Gerfen CR. The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci. 1992;15:133–9.

Gimenez-Amaya JM, Graybiel AM. Compartmental origins of the striatopallidal projection in the primate. Neuroscience. 1990;34:111–26.

Gradinaru V, Mogri M, Thompson KR, et al. Optical deconstruction of parkinsonian neural circuitry. Science. 2009;324:354–9.

Graybiel AM. Correspondence between the dopamine islands and striosomes of the mammalian striatum. Neuroscience. 1984;13:1157–87.

Graybiel AM, Ragsdale CW Jr. Histochemically distinct compartments in the striatum of human, monkeys, and cat demonstrated by acetylthiocholinesterase staining. Proc Natl Acad Sci U S A. 1978;75:5723–6.

Graybiel AM, Ragsdale CWJ, Yoneoka ES, Elde RP. An immunohistochemical study of enkephalins and other neuropeptides in the striatum of the cat with evidence that the opiate peptides are arranged to form mosaic patterns in register with the striosomal compartments visible by acetylcholinesterase staining. Neuroscience. 1981;6:377–97.

Haber SN, Adler A, Bergman H. Basal ganglia. Cambridge: Academic Press; 2011.

Hameleers R, Temel Y, Visser-Vandewalle V. History of the corpus Luysii: 1865-1995. Arch Neurol. 2006;63:1340–2.

Heimer L, Wilson R. The subcortical projections of the allocortex: similarities in the neural associations of the hippocampus, the piriform cortex, and the neocortex. In: Santini M, editor. Persepectives in neurobiology, Golgi centennial symposium. New York: Raven Press; 1975. p. 177–93.

Hescham S, Lim LW, Jahanshahi A, et al. Deep brain stimulation in dementia-related disorders. Neurosci Biobehav Rev. 2013;37:2666–75.

Hubble JP, Busenbark KL, Wilkinson S, et al. Deep brain stimulation for essential tremor. Neurology. 1996;46:1150–3.

Kandel ER. The neurobiology of behavior. In: Kandel ER, Schwartz JH, Jessel TM, editors. Principles of neural science. New York: McGraw-Hill; 2000. p. 1–36.

Kawaguchi Y, Wilson CJ, Emson PC. Intracellular recording of identified neostriatal patch and matrix spiny cells in a slice preparation preserving cortical inputs. J Neurophysiol. 1989;62:1052–68.

Kawaguchi Y, Wilson CJ, Emson PC. Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin. J Neurosci. 1990;10:3421–38.

Kawaguchi Y, Wilson CJ, Augood SJ, Emson PC. Striatal interneurones: chemical, physiological and morphological characterization. Trends Neurosci. 1995;18:527–35.

Kincaid AE, Wilson CJ. Corticostriatal innervation of the patch and matrix in the rat neostriatum. J Comp Neurol. 1996;374:578–92.

Kocabicak E, Temel Y. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: surgical technique, tips, tricks and complications. Clin Neurol Neurosurg. 2013;115:2318–23.

Krauss JK, Pohle T, Weber S, et al. Bilateral stimulation of globus pallidus internus for treatment of cervical dystonia. Lancet. 1999;354:837–8.

Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg. 1992;76:53–61.

Lambert C, Zrinzo L, Nagy Z, et al. Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. Neuroimage. 2012;60:83–94.

Lanciego JL, Luquin N, Obeso JA. Functional neuroanatomy of the basal ganglia. Cold Spring Harb Perspect Med. 2012;2:a009621.

Lei W, Jiao Y, Del Mar N, Reiner A. Evidence for differential cortical input to direct pathway versus indirect pathway striatal projection neurons in rats. J Neurosci. 2004;24:8289–99.

Lozano AM, Giacobbe P, Hamani C, et al. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. J Neurosurg. 2012;116:315–22.

Luyten L, Hendrickx S, Raymaekers S, et al. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry. 2016;21:1272–80.

Mallet L, Polosan M, Jaafari N, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008;359:2121–34.

McFarland NR, Haber SN. Organization of thalamostriatal terminals from the ventral motor nuclei in the macaque. J Comp Neurol. 2001;429:321–36.

Moers-Hornikx VM, Sesia T, Basar K, et al. Cerebellar nuclei are involved in impulsive behaviour. Behav Brain Res. 2009;203:256–63.

Nakano K. Neural circuits and topographic organization of the basal ganglia and related regions. Brain Dev. 2000;22(Suppl 1):S5–16.

Nambu A, Takada M, Inase M, Tokuno H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J Neurosci. 1996;16:2671–83.

Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci Res. 2002;43:111–7.

Nauta HJ. A proposed conceptual reorganization of the basal ganglia and telencephalon. Neuroscience. 1979;4:1875–81.

Nuttin B, Cosyns P, Demeulemeester H, et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet. 1999;354:1526.

Ohye C. Thalamus. In: Paxinos G, editor. The human nervous system. San Diego: Academic Press; 1990. p. 439–82.

Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev. 1995;20:91–127.

Parent A, Sato F, Wu Y, et al. Organization of the basal ganglia: the importance of axonal collateralization. Trends Neurosci. 2000;23:S20–7.

Penny GR, Wilson CJ, Kitai ST. Relationship of the axonal and dendritic geometry of spiny projection neurons to the compartmental organization of the neostriatum. J Comp Neurol. 1988;269:275–89.

Pert CB, Kuhar MJ, Snyder SH. Opiate receptor: autoradiographic localization in rat brain. Proc Natl Acad Sci U S A. 1976;73:3729–33.

Plantinga BR, Temel Y, Roebroeck A, et al. Ultra-high field magnetic resonance imaging of the basal ganglia and related structures. Front Hum Neurosci. 2014;8:876.

Ragsdale CW Jr, Graybiel AM. Fibers from the basolateral nucleus of the amygdala selectively innervate striosomes in the caudate nucleus of the cat. J Comp Neurol. 1988;269:506–22.

Rosin DL, Robeva A, Woodard RL, et al. Immunohistochemical localization of adenosine A2A receptors in the rat central nervous system. J Comp Neurol. 1998;401:163–86.

Sadikot AF, Parent A, Francois C. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. J Comp Neurol. 1992a;315:137–59.

Sadikot AF, Parent A, Smith Y, Bolam JP. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. J Comp Neurol. 1992b;320:228–42.

Salgado S, Kaplitt MG. The nucleus accumbens: a comprehensive review. Stereotact Funct Neurosurg. 2015;93:75–93.

Schlaepfer TE, Bewernick BH, Kayser S, et al. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013;73:1204–12.

Shink E, Bevan MD, Bolam JP, Smith Y. The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey. Neuroscience. 1996;73:335–57.

Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery. 1994;35:1126–9.

Smeets AJM, Duits AA, Plantinga BR, et al. Deep brain stimulation of the internal globus pallidus in refractory Tourette syndrome. Clin Neurol Neurosurg. 2016;142:54–9.

Temel Y, Blokland A, Steinbusch HW, Visser-Vandewalle V. The functional role of the subthalamic nucleus in cognitive and limbic circuits. Prog Neurobiol. 2005;76:393–413.

Temel Y, PLantinga B, Kuijf ML. Anatomie van de gebruikte targets bij diepe hersenstimulatie. In: Temel Y, Leentjens AFG, de Bie RMA, editors. Handboek diepe hersenstimulatie bij neurologische en psyciatrische aandoeningen. Houten: Bohn Stafleu van Loghum; 2016. p. 11–7.

Van Der Kooy D, Hattori T. Single subthalamic nucleus neurons project to both the globus pallidus and substantia nigra in rat. J Comp Neurol. 1980;192:751–68.

Vidailhet M, Jutras MF, Grabli D, Roze E. Deep brain stimulation for dystonia. J Neurol Neurosurg Psychiatry. 2013;84:1029–42.

Weiss D, Walach M, Meisner C, et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. Brain. 2013;136:2098–108.

Wichmann T, Kliem MA, Soares J. Slow oscillatory discharge in the primate basal ganglia. J Neurophysiol. 2002;87:1145–8.