Anatomic Review of the Ventral Capsule/Ventral Striatum and the Nucleus Accumbens to Guide Target Selection for Deep Brain Stimulation for Obsessive-Compulsive Disorder

Yong-Sook Park[1], Francesco Sammartino[2], Nicole A. Young[2], John Corrigan[2], Vibhor Krishna[2], Ali R. Rezai[3]

Key words
- Anterior commissure
- Deep brain stimulation
- Internal capsule
- Nucleus accumbens
- Obsessive-compulsive disorder
- Reward circuitry
- Ventral striatum

Abbreviations and Acronyms
AC: Anterior commissure
ALIC: Anterior limb of the internal capsule
BNST: Bed nucleus of the stria terminalis
CB: Calbindin D-28k
DBS: Deep brain stimulation
IC: Internal capsule
MFB: Medial forebrain bundle
NAc: Nucleus accumbens
OCD: Obsessive-compulsive disorder
OFC: Orbitofrontal cortex
PFC: Prefrontal cortex
slMFB: Superolateral branch of the medial forebrain bundle
VC: Ventral capsule
VS: Ventral striatum
VTA: Ventral tegmental area

From the [1]Department of Neurosurgery, Chung-Ang University Hospital, Seoul, Korea; [2]Department of Neurosurgery, The Ohio State University, Columbus, Ohio; and [3]Department of Neurosurgery, West Virginia University Hospital, Morgantown, West Virginia, USA

To whom correspondence should be addressed: Vibhor Krishna, M.D. [E-mail: vibhorkrishna@yahoo.com]

Citation: World Neurosurg. (2019) 126:1-10. https://doi.org/10.1016/j.wneu.2019.01.254

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

BACKGROUND: **Disturbances in the reward network of the brain underlie addiction, depression, and obsessive-compulsive disorder. The ventral capsule/ventral striatum and nucleus accumbens (NAc) region is a clinically approved target for deep brain stimulation for obsessive-compulsive disorder.**

METHODS: **We performed a comprehensive literature review to define clinically relevant anatomy and connectivity of the ventral capsule/ventral striatum and NAc region to guide target selection for deep brain stimulation.**

RESULTS: **Architecturally and functionally, the NAc is divided into the core and the shell, with each area having different connections. The shell primarily receives limbic information, and the core typically receives information from the motor system. In general, afferents from the prefrontal cortex, hippocampus, and amygdala are excitatory. The dopaminergic projections to the NAc from the ventral tegmental area modulate the balance of these excitatory inputs. Several important inputs to the NAc converge at the junction of the internal capsule (IC) and the anterior commissure (AC): the ventral amygdalofugal pathways that run parallel to and underneath the AC, the precommissural fornical fibers that run anterior to the AC, axons from the ventral prefrontal cortex and medial orbitofrontal cortex that occupy the most ventral part of the IC and embedding within the NAc and AC, and the superolateral branch of the medial forebrain bundle located parallel to the anterior thalamic radiation in the IC.**

CONCLUSIONS: **The caudal part of the NAc passing through the IC-AC junction may be an effective target for deep brain stimulation to improve behavioral symptoms associated with obsessive-compulsive disorder.**

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by persistent thoughts and repetitive ritualistic behaviors with a lifetime prevalence of 2.3%.[1] OCD is classified as an anxiety disorder; however, given that compulsions are reward-seeking behaviors performed in an attempt to reduce obsession-induced anxiety, it can also be thought of as addictive behavior associated with defective processing of natural rewards.[2] Treatments for OCD include cognitive behavioral therapy and pharmacotherapy, although approximately 10% of patients remain intractable to medical treatments.[3] Deep brain stimulation (DBS) is a surgical option considered in cases of medically intractable and disabling OCD. The response rate after DBS for OCD with a reduction of symptom severity scale of >35% ranges from 10% to 100%.[4-8] Variable response rates according to targets[9,10] and according to their coordinates[11] have been reviewed by various authors.[12,13] These variable response rates may reflect the variability of targets, stimulation parameters, or patient factors. Several targets for DBS have been attempted, such as the anterior limb of the internal capsule (ALIC),[14-16] ventral capsule (VC)/ventral striatum (VS),[5,6,17,18] nucleus accumbens (NAc),[4,7,19,20] subthalamic nucleus,[21-24] inferior thalamic peduncle,[25] and bed nucleus of the stria terminalis (BNST).[26,27]

DBS of the ALIC for patients with OCD uses a similar target as Gamma Knife capsulotomy and radiofrequency lesioning and yields significant improvement, albeit requiring high stimulation amplitudes.[15,28] Sturm et al.[7] extended the DBS target ventrally to include the NAc and internal capsule (IC) because they determined that the ventrocaudal part of the IC was a critical location for successful clinical outcomes. van den Munckhof et al.[12] noted that selective VC stimulation was effective in 9 of 16 patients with OCD. The active electrodes were placed in the

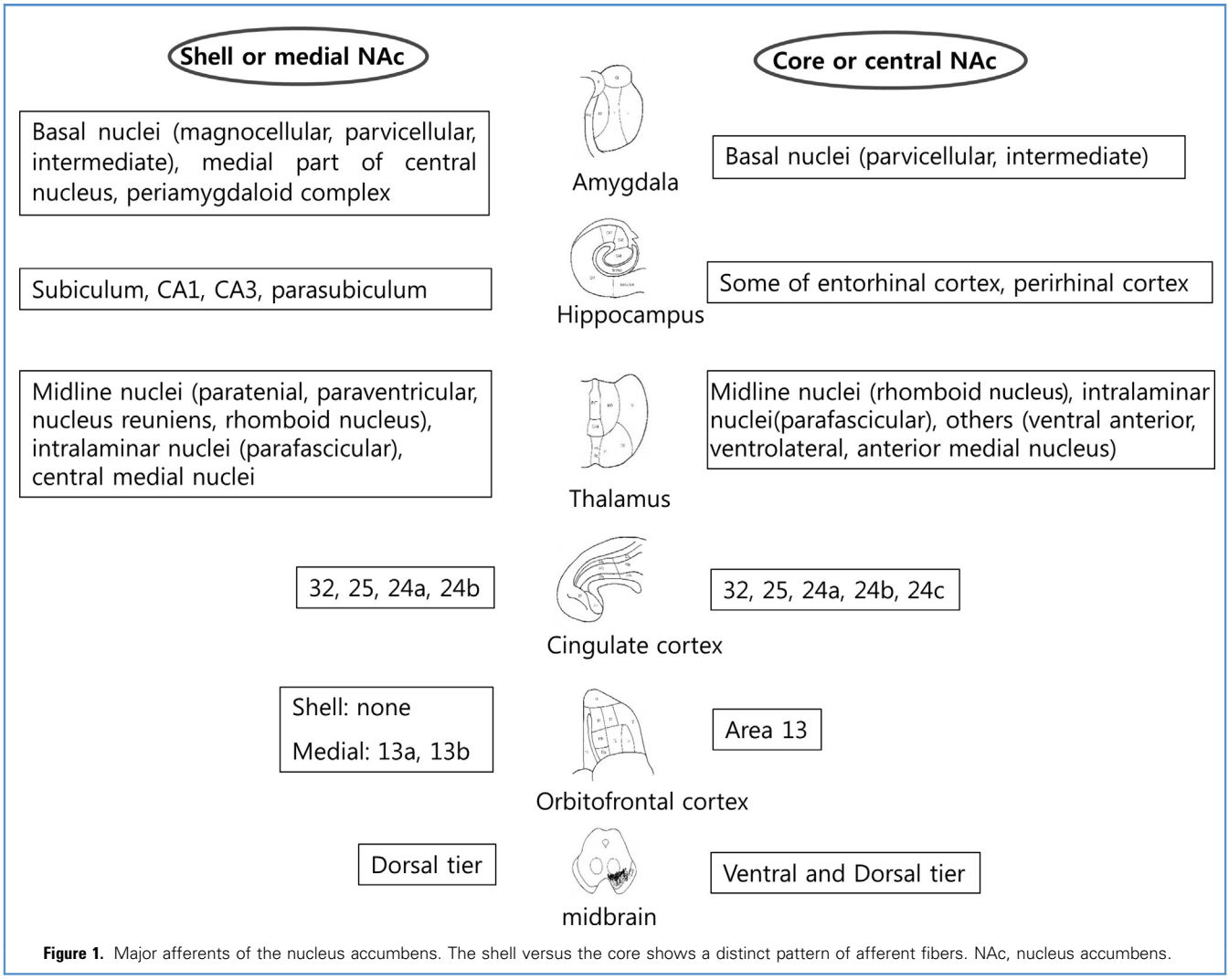

Figure 1. Major afferents of the nucleus accumbens. The shell versus the core shows a distinct pattern of afferent fibers. NAc, nucleus accumbens.

ventral ALIC, although most ventral contacts were located within the NAc. More recently, Greenberg et al.[5] reported multicenter outcomes from VC/VS DBS for OCD. They observed an increase in favorable outcomes as the target migrated toward a more posterior and medial target within 1–2 mm of the posterior border of the AC.[5] Additionally, the posterior location of stimulation electrodes was associated with less battery consumption. It has also been reported that BNST DBS showed comparable or better results than ALIC targets[27] or the NAc.[26] In this review, we aimed to clarify the anatomic structures of the VC/VS and NAc regions, which may be important for DBS as an OCD treatment option. This review contains the following sections: 1) a brief introduction to the reward network; 2) anatomy and histology of the NAc, derived primarily from animal studies; 3) afferent and efferent pathways of the NAc; 4) principal tracts around the NAc and VC/VS; and 5) a critical analysis of our findings as they relate to DBS targeting.

REWARD NETWORK

The reward network drives motivated behavior, and disturbances in this network are associated with addiction,[29-31] depression,[32,33] and OCD.[2,7,34] The reward network includes the NAc as a central node[35] and other interrelated structures, such as the ventral tegmental area (VTA), basolateral amygdala, ventral subiculum of the hippocampus, prefrontal cortex (PFC), ventral pallidum, thalamus, dorsal striatum, anterior cingulate cortex, insular cortex, hypothalamus, subthalamic nucleus, globus pallidus, parabrachial nucleus, and extended amygdala.[35] Within this network, the PFC is involved with executive control and goal-directed behaviors, the ventral subiculum of the hippocampus provides contextual and spatial information, and the basolateral amygdala provides the affective drive.[35-41] Projection fibers from the PFC, amygdala, and hippocampus to the NAc are predominantly excitatory and synapse with the γ-aminobutyric acidergic medium spiny neurons of the NAc.[42] Dopaminergic pathways from the VTA also converge at the NAc and

modulate the balance of excitatory afferents. The NAc is considered to be a key structure within the reward network, mediating motivated behavior via the corticobasal ganglia-thalamic loop.[43-46]

ANATOMY AND HISTOLOGY OF NAc

Anatomy

The VS is the ventral extension of the striatum and includes the NAc, medioventral portion of the caudate and putamen, olfactory tubercle, and anterior perforated substance.[47,48] In rodents, the NAc is divided into 3 subregions, the shell, the core, and the rostral pole,[49-51] whereas in humans and nonhuman primates, it is divided into at least 2 subregions, the shell and the core (**Figure 1**).[52,53] The shell is located in the medial and ventral area that is largely connected to limbic structures and plays a role in motivation and emotional processing. The NAc core is a central and dorsal subunit of this nucleus, which is related to the neostriatum and is involved in motor function. In humans, the subdivisions of the NAc are not easily delineated; however, diffusion tensor imaging and functional magnetic resonance imaging during the task of gambling suggest that the human NAc can be parceled based on structural and functional connectivity and that these subdivisions differentially encode values for reward and aversive experiences.[54]

The NAc is located directly below the ALIC and covers a large area of the basal forebrain. It neighbors medially on the vertical part of the diagonal band of the Broca area, laterally on the claustrum and piriform cortex, and dorsally on the rostral extensions of the globus pallidus and the ALIC. It is not anatomically distinct from the dorsomedially and dorsolaterally located neostriatum. Imaging and anatomic studies show the dimensions of the NAc measuring 7.2–14.5 mm in width, 10.5–15 mm in length, and 7.0–8.1 mm in height.[55,56] Three-dimensional image reconstruction of this nucleus reveals that it progresses from an ellipsoid form, with a biconvex shape, to a dorsolaterally flattened morphology. The medial and ventral borders are slightly convex, but the lateral and dorsal borders have no clear anatomic distinction. Most of the NAc is located subcommissurally. The anterior limits of the human NAc are anatomically indistinguishable from the caudate and the putamen nuclei.[56,57] The posterior part of the NAc is variable in its size and shape[58] and frequently not recognized in stereotactic atlases[59] or on high-resolution magnetic resonance imaging.[60] An assessment of the NAc by Lucas-Neto et al.[61] showed that the area closest to the AC shared similar histologic characteristics with the adjacent BNST.

At the cellular level, NAc neurons showed larger cell bodies, prominent and peripheral nucleoli, and Nissl substance, in addition to medium-sized neurons. These patterns are most evident at the ventromedial border of the posterior part of the NAc, extending supracommissurally to the IC-AC junction.[62] These neurons were different from neurons of the dorsal striatum and the remainder of the precommissural NAc in their morphology and in the distribution of their dopaminergic receptors; they extended into the BNST.[62]

Histologic Characteristics of Core and Shell of NAc

Histologic features and cell densities within the NAc are heterogeneous. The shell and core dichotomy of the NAc was originally based on calbindin D-28k (CB) immunoreactivity. The core of the NAc consists of small, densely packed cells that express intense CB, enkephalin,[63] and γ-aminobutyric acid A receptors[64] and weak substance P immunostaining.[52] The dorsally located caudate nucleus and putamen are also CB-rich and thus are not easily distinguishable from the CB-rich core of the NAc.[53,63] The shell of the NAc is composed of large, loosely arranged cells that express weak levels of CB immunoreactivity but high levels of substance P,[49,65-67] neurotensin,[63] dopamine,[63] calretinin,[57] tyrosine hydroxylase, and serotonin immunoreactivity[68] in mammalian species. The limbic system–associated membrane protein shows heterogeneous immunoreactivity in both the shell and the core.[57] In nonhuman primates, the basal amygdaloid nucleus and the hippocampus are highly immunoreactive for the limbic system–associated membrane protein,[69,70] and thus limbic system–associated membrane protein staining in the shell and core indicates that the NAc receives projections from the amygdaloid nucleus or from the hippocampus.[57] In addition to the shell versus core distinction, within itself the shell shows different histologic characteristics rostrocaudally and mediolaterally.[57,71] The caudal NAc intermingles with the ventral pallidum and the substantia innominate as well as with the cholinergic neurons of the nucleus basalis of Meynert[57] and medially it joins with the lateral part of the BNST and the vertical limb of the diagonal band.[57] In nonhuman primates, the medial ventral striatum sends fibers to the BNST, the nucleus basalis,[72,73] and the lateral hypothalamus.[73] Calretinin immunoreactivity is more intense dorsomedially than laterally.[74] The paraventricular thalamic nucleus is also immunoreactive to calretinin. Prensa et al.[57] interpreted this chemical pattern as fibers from the paraventricular thalamic nucleus that project to the medial part of the NAc. In rodents, norepinephrine is highly expressed in the shell and decreases in expression from medial shell to lateral core,[75] with the most caudal part of the shell receiving dense noradrenergic innervation.[76]

The NAc comprises γ-aminobutyric acidergic medium spiny neurons (approximately 95%), interneurons (1%–2%), and cholinergic large spiny interneurons (1%–2%).[77] Dopaminergic afferents synapse onto γ-aminobutyric acid neurons with medium spiny morphology[78,79] and express both D1 and D2 dopaminergic receptors.[80] The distribution of D_1 and D_2 receptors in the human VS is heterogeneous; although very high D_1 binding is most prevalent in the ventromedial part,[81] their actions at the cellular level can be inhibitory or excitatory depending on receptor subtypes and the state of the receiving neuron's membrane potential.[77] The NAc receives glutamatergic afferents from the hippocampus, PFC, and amygdala, which synapse with all subtypes of NAc neurons.[82] These excitatory inputs are modulated by dopaminergic afferents from the VTA. Rewarding activities or pharmacologic agents increase dopaminergic transmission from the VTA to the NAc.[80] Reward-seeking behavior seems to be regulated by dopamine D_1

signaling of glutamatergic afferents from the amygdala.[50]

STRUCTURAL CONNECTIVITY OF NAc

Afferents to NAc

The NAc is the main input nucleus of the basal ganglia. The NAc receives its input from various structures, importantly from the PFC, ventral hippocampus, basal amygdala, and midline and intralaminar thalamus as well as dopaminergic afferents from the ventral tegmental (A10) and retrorubral (A8) cell groups in rats.[83] In addition, the orbital cortex, posterior agranular insular area, entorhinal cortex, ventral pallidum, serotoninergic median raphe nucleus, noradrenergic (A2) cell groups in the nucleus of the solitary tract, sublenticular substantia innominate, lateral septal nucleus, hypothalamus, and subthalamic nucleus all project afferent fibers toward the NAc in rats.[83-85] Brodmann area 25, anterior commissure, and medial forebrain bundle (MFB) also project afferents to the NAc in minipigs.[86]

Excitatory cortical afferents to innervate the NAc originate from the orbital cortex, insular cortex, cingulate cortex, medial and lateral PFC, and medial temporal lobe.[87] In rhesus monkeys, the medial aspect and shell of the NAc receive input from the rostral part of the anterior cingulate cortex and Brodmann areas 25, 24a, and 24b. The central aspect and the core of the NAc receive fibers from areas 25, 24a, 24b, and the medial part of area BA 24c.[88] The NAc shell region receives projections from both areas 32 and 25, but not from the orbitofrontal cortex (OFC) proper, whereas the medial NAc receives dense innervation from both OFC areas 13a and 13b and areas 25 and 32. The NAc core region receives projections from area 13 in the nonhuman primate.[89]

The amygdala receives processed sensory information from cortical and subcortical structures and is involved in behavioral responses in learning and emotional expression. The amygdala and its efferents to the NAc mediate reward and goal-directed behaviors through dopamine modulation.[50] The basal and accessory basal nuclei of the amygdala are the major source of input to the VS in nonhuman primates.[70,90] The fibers from the magnocellular subdivision of the basal nuclei appear to target the ventral NAc shell. The intermediate subdivision and the parvicellular subdivision project to the shell and core.[90] Friedman et al.[70] showed that magnocellular and intermediate basal nuclei project principally to the medial and the shell of the NAc, with especially dense projections received by the caudal NAc and the BNST in cynomolgus and rhesus monkeys.

In primates, hippocampal excitatory efferents from the subiculum project to the shell of the NAc[70,91] as well as the parasubiculum, the prosubiculum, CA1, and the portion of CA3 attributed to projecting to the NAc.[70] These projections from the hippocampus are carried via the fornix. In contrast, the entorhinal cortex projects to both the NAc and the olfactory tubercle via nonfornical routes. The precommissural fornix carries projections to the NAc, BNST,[92] septal nucleus, and hypothalamus.[70,93] Molecular studies of the rodent hippocampus[20,81] showed that the ventral subiculum, which is roughly analogous to the ventromedial parts of CA1 in primates, projects caudomedially to the NAc shell. The dorsal subiculum, which is roughly analogous to primate dorsomedial CA1, projects to more rostrolateral regions of the NAc, including the core.[84,85,94,95]

The shell and medial NAc are innervated mainly by the midline thalamic nuclei (paratenial nuclei, paraventricular nuclei, rhomboid nucleus, nucleus reuniens) and the intralaminar thalamic nuclei (parafascicular nuclei) and receive the fewest projections from the ventral, anterior, medial, and lateral thalamic nuclei in the primate.[96] The core receives some projections from the midline thalamic nuclei (rhomboid nucleus), intralaminar thalamic nuclei (parafascicular nuclei), and ventral anterior thalamic groups. The paraventricular paratenial nuclei, rhomboid nucleus, and nucleus reuniens are closely interconnected with limbic structures.[96]

Dopamine pathways are traditionally divided into the mesolimbic pathways from the VTA to the NAc and the olfactory tubercle and the nigrostriatal pathways from neurons of the substantia nigra pars compacta to the dorsal striatum. In contrast to this typical classification, 2 tiers of dopaminergic neurons can be identified in the ventral mesencephalon in rats: the dorsal tier, characterized by its loose arrangement of dopaminergic neurons with processes oriented in a mediolateral direction, and the ventral tier, with the pars compacta neurons of the dense cellular zone including the columns of cells penetrating into the pars reticulata.[97,98] Both dorsal and ventral tier neurons innervate the VS; however, neurons projecting to the shell region of the NAc are limited to the dorsal tier.[99]

In brief, limbic cortices, amygdala, hippocampus, midline thalamic nuclei, dorsal tier of dopamine cell group, and the shell of the NAc appear to be included in limbic circuits and are distinct from the core of the NAc. Projections from the PFC, hippocampus, and amygdala to the NAc are glutamatergic, which excites all subtypes of NAc neurons.[82] These excitatory inputs are modulated by dopamine afferents from the VTA. Rewarding drugs or activities increase dopaminergic transmission from the VTA to the NAc,[80] which then modulate glutamatergic projections from the amygdala to the NAc.

Efferents from NAc

The NAc principally projects to pallidal, hypothalamic, and mesencephalic areas.[67,100] In cats, fibers from the shell and medial part of the NAc project to the medial part of the ventral pallidum, rostral part of the lateral hypothalamus, lateral septum, BNST, medial preoptic and hypothalamic areas, ventral tegmental area, retrorubral nucleus, central superior nucleus, nucleus tegmentalis pedunculopontinus, and central gray.[67] There are clear distinctions between the projections from the NAc shell and the core: the NAc shell extends projections to the lateral hypothalamus and the extended amygdala, whereas the core does not.[20] Fibers from the core and lateral part of the NAc project to the lateral part of the ventral pallidum, subcommissural part of the globus pallidus, nucleus endopeduncularis, substantia nigra, and retrorubral nucleus.[67]

The ventral pallidum receives projections from the NAc. The ventromedial aspect of the ventral pallidum receives inputs from the NAc shell and projects to the ventral tegmental area. The dorsolateral ventral pallidum receives projections from the NAc core and delivers its fibers to the subthalamic nucleus and the substantia nigra, a major source of dopaminergic innervation of the striatum.[101]

Table 1. Coordinates of Stimulation of Ventral Capsule, Ventral Striatum, Ventral Caudate, Bed Nucleus of Stria Terminalis, and Nucleus Accumbens for Obsessive-Compulsive Disorders

Reference	X (mm)	Y (mm)	Z (mm)	Location
Sturm et al., 2003[7]	6.5	2.5 rostral anterior border of AC	−4.5	NAc
Kuhn et al., 2007[125]	6.5	2.5 anterior to anterior border of AC	−4.5	NAc
Guehl et al., 2008[126]	8 ± 0.7	33.4 ± 2.3 anterior to PC	−2.5 ± 0.5	Ventral caudate
Aouizerate et al., 2009[127]	8.9 (right), 7.6 (left)	36.5, 31.4 anterior to PC	−3, −1.7	Ventral caudate
	8.7 (right), 7.9 (left)	33.5, 35.7 anterior to PC	−2, −2.4	
Denys et al., 2010[128]	7	3 anterior to anterior border of AC	4	NAc
Franzini et al., 2010[8]	3	16 anterior to MCP	−2	NAc
Greenberg et al., 2010[5,*]	6–7	Within 1–2 mm of posterior border of AC (1 to −1)	−3 to 4	VC/VS
Huff et al., 2010[4,†]	7.3	−1.9	−3.6	NAc
Goodman et al., 2010[6]	4.8–12.8	12.2–18.8 anterior to MCP	−3.8 to 4.8	VC/VS
Tsai et al., 2012[17]	6.0–10.2	12.8–18.3 anterior to MCP	−4.9 to 0.6	VC/VS
Roh et al., 2012[18]	8	4 anterior to posterior border of AC	−2	VC/VS
van den Munckhof et al., 2013[12]	10.8	4.4	2.4	NAc
	11.1	3.9	2.0	
Fayad et al., 2016[129]	4.8–13.4	12.2–18.8	−3.8 to 9.4	VC/VS
Doshi, 2016[130]	7, 10	Posterior border of AC	0	BNST
Luyten et al., 2016[27]		0–2 posterior to posterior border of AC		BNST
Winter et al., 2018[131]	2	−2 (probably behind AC)	0	BNST

AC, anterior commissure; NAc, nucleus accumbens; PC, posterior commissure; MCP, midcommissural point; VC, ventral capsule; VS, ventral striatum; BNST, bed nucleus of stria terminalis.
*Mean coordinates of the best result group.
†Best result case, most ventral contact.

PRINCIPAL TRACTS AROUND VC/VS AND NAc

The typical DBS electrode implanted in the NAc traverses the ALIC, VC, and then the NAc proper, in that order. As the therapeutic efficacy of DBS is thought to be mediated by modulation of activity within both the gray and the white matter surrounding the implantation target,[102] it is important to review tracts around the VC/VS and the NAc for prospective DBS treatments.

Anterior Limb of the Internal Capsule

The fibers passing through the ALIC include 3 different tracts: the anterior thalamic radiation, which comprises reciprocal projection fibers between the frontal lobe and the medial and anterior thalamic nuclei; the frontopontine fibers projecting to pontine nuclei; and the corticostriatal fibers projecting to striatum.[103-106] The anterior thalamic radiation lies horizontally within the ALIC and runs in the same direction. The frontopontine fibers occupy 37%–38% of the area of the anterior limb. The superolateral branch of the medial forebrain bundle (slMFB) is thought of as the reciprocal pontofrontal projection of the classical frontopontine tracts, and it projects to the NAc and OFC.[107-110] The MFB connects multiple circuits and represents the central longitudinal pathway between the limbic forebrain and midbrain.[111] The main trunk of the MFB originates from the dentate nucleus of the cerebellum.[110] In the VTA, the MFB divides into 2 branches: an inferomedial branch, which follows the wall of the third ventricle and reaches the lateral hypothalamus, and a superolateral branch (slMFB), which runs laterally, undercuts the thalamus, and ascends into the inferior portion of the ALIC. Within the ALIC, the slMFB runs parallel and lateral to the anterior thalamic radiation.[108] Although the slMFB enters into the ALIC ventrally, it branches into the NAc,[107,108] and then the fibers project out to the OFC and dorsolateral PFC. Activation of the slMFB is thought to activate the entire mesocorticolimbic system by increasing dopaminergic and glutamatergic neuronal activity within the NAc and VTA.[112] The anterior thalamic radiation is thought to be a common surgical target for anterior capsulotomy and ALIC stimulation for patients with OCD,[103] whereas some investigators believe that clinical behavioral improvements with either ALIC or NAc DBS results from activation of the slMFB.[113]

Frontal Radiation

The white matter pathway projecting from the ventral prefrontal and orbital gyrus to the IC has been characterized by tracer studies in nonhuman primates.[35] Fibers from the ventromedial PFC and medial OFC enter the IC ventrally and form

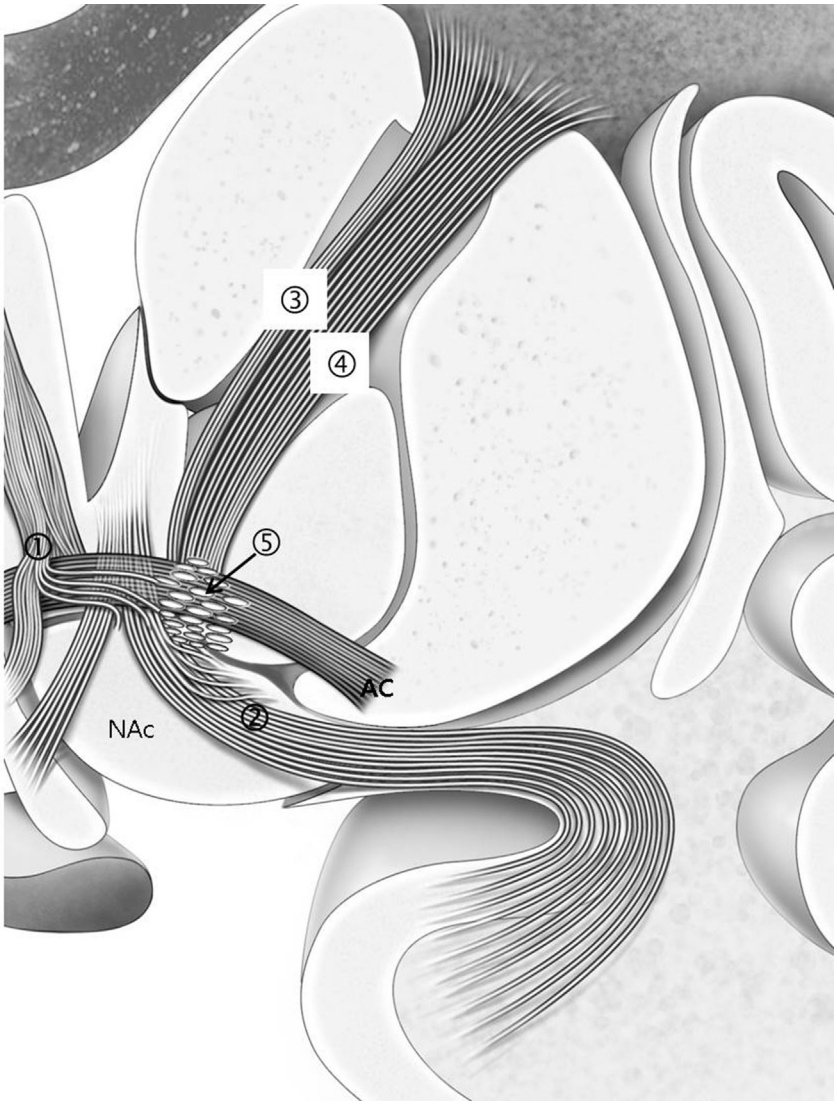

Figure 2. Schematic representation of major afferents to the nucleus accumbens around the junction of the internal capsule (IC) and the anterior commissure (AC) on the coronal sections. Precommissural fibers of the fornix (*1*) extend horizontally parallel and anterior to the AC and innervate the nucleus accumbens.[92,116,119] The ventral amygdalofugal pathway (*2*) is underneath the AC, which splits into the ascending and descending branches. The ascending fibers innervate the nucleus accumbens. The descending branches project to the anterior hypothalamic nuclei.[119] The anterior limb of the IC includes the anterior thalamic radiation medially (*3*) and the superolateral medial forebrain bundle laterally (*4*).[108] Axons from the ventral PFC and medial orbitofrontal cortex (*5*) occupy the most ventral part of the rostral anterior limb of the IC. Some fascicules embed within the nucleus accumbens and run through the AC perpendicularly.[114] NAc, nucleus accumbens; AC, anterior commissure. (*Used with permission from Mai JK, Assheuer J, Paxinos G. Atlas of the human brain, San Diego, CA: Academic Press; 1997, 170*)

fascicles within the VS and the AC. The fibers projecting to the thalamus from the ventromedial PFC and medial OFC pass either through or just dorsal to the AC, whereas fibers to the brainstem pass either through or ventral to the AC. Within the IC, a dorsal group of ventromedial PFC fibers terminate in the midline medial dorsal thalamic nuclei. Axons from the ventral PFC occupy the most ventral part of the rostral anterior limb of the IC. These axons include the small fascicles embedded within the VS and fibers running ventral to and through the AC, perpendicularly.[114]

Ventral Amygdalofugal Fibers

The ventral amygdalofugal pathway and the stria terminalis are the major efferent pathways of the amygdala. The stria terminalis travels along with the fornix and terminates in the BNST. The ventral amygdalofugal pathway originates from the basolateral nucleus and central nucleus of the amygdala and connects to the NAc, basal forebrain, medial dorsal nucleus of the thalamus, and lateral hypothalamus.[115] Fibers in the ventral pathway pass underneath the lenticular nucleus and spread out to the base of the brain, ending in the septal nuclei and the hypothalamus, olfactory regions, anterior perforated substance and piriform cortex, orbital and anterior cingulate cortices, and VS.[116] In a recent study, the spatial locations of the ventral amygdalofugal fibers, stria terminalis, and AC were recently visualized using high-resolution diffusion tensor imaging.[117] The ventral amygdalofugal pathway courses inferior to the lentiform nuclei and runs medially alongside and underneath the AC and IC.[118] This pathway divides into the ascending and descending branches at the most medial aspect. The ascending fibers course through the NAc and continue toward the subgenual anterior cingulate cortex and terminate in the septal nuclei.[117] The amygdalofugal tract takes part in reciprocal connections of the amygdala with the cingulate gyrus and orbitofrontal and basal prefrontal cortices to mediate emotions or conscious perception of emotion.[115]

Fornix

The fornix is a collection of white matter tracts connecting the hippocampus and the hypothalamus. The fornical column splits into precommissural and postcommissural fibers superior to the AC. The precommissural fibers project ventrally to the AC, descend anterior to the lamina terminalis, and terminate in the septal nuclei. Some of the precommissural fibers continue horizontally from the septal nuclei, parallel and anterior to the AC, and course laterally toward the uncus.[119] Precommissural fibers innervate the NAc.[92]

CRITICAL ANALYSIS OF ANATOMY FOR DBS TARGETING

In consideration of our anatomic review, it is important to note that principal tracts of the NAc were localized around the IC-AC junction. This area roughly coincides with the precommissural fibers of the fornix (input from the hippocampus) and the ventral PFC fibers that travel through the NAc and AC toward the IC. The ventral amygdalofugal pathway courses inferior to the lentiform nuclei and runs alongside and underneath the AC and IC. As mentioned earlier, the PFC, hippocampus, and amygdala are 3 major excitatory inputs to the NAc.[82,120] The ALIC, containing the anterior thalamic radiation and slMFB, provides the dopaminergic input from the brainstem.

The slMFB has emerged as a novel DBS target for treatment of refractory depression because of its antianhedonic and motivational effects.[108,121,122] Finally, the major output of the NAc (shell and core) to the ventral pallidum is also located in this area. The AC is not directly connected to the NAc; however, it receives fibers from the temporal lobe, OFC, prepiriform cortex, inferior occipital cortex, some upper part of the hemispheric convexity, and amygdala.[123] It also plays a role in the interhemispheric transfer of visual, auditory, olfactory, and gustative information.[124]

The target coordinates from publications of OCD DBS tend to be close anteroposteriorly to the AC and superoinferiorly around the AC-PC level. As Greenberg et al.[5] mentioned, the VC/VS target around the IC-AC junction toward the NAc could be a critical area. The reported variability in outcomes may also be related to differences in targeting, and given the complex anatomy of this region, these subtle differences in electrode locations (**Table 1**) may have modulated a different set of neural substrates (**Figure 2**).

CONCLUSIONS

The VC/VS and NAc region is a complex structure functionally and anatomically. We believe the VC/VS and NAc region is a promising surgical target for effective DBS electrode placement for OCD based on the results of recent clinical studies of DBS for OCD, the anatomic afferent and efferent patterns of the NAc and histologic characteristics, and the location of the caudal NAc relative to the IC-AC junction. Future research should focus on studying the anatomy of the NAc region in health and disease states and better visualization of the NAc and surrounding structures, including white matter tracts, to improve reliability and consistent targeting and potentially clinical outcomes after DBS. Finally, studies to identify tracts involved in both therapeutic efficacy and generation of stimulation-induced side effects are also needed.

ACKNOWLEDGMENTS

The authors thank Reghan Borer for manuscript editing.

REFERENCES

1. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15:53-63.
2. Figee M, Vink M, de Geus F, et al. Dysfunctional reward circuitry in obsessive-compulsive disorder. *Biol Psychiatry*. 2011;69:867-874.
3. Denys D. Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. *Psychiatr Clin North Am*. 2006;29:553-584.
4. Huff W, Lenartz D, Schormann M, et al. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: outcomes after one year. *Clin Neurol Neurosurg*. 2010;112:137-143.
5. Greenberg BD, Gabriels LA, Malone DA Jr, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Mol Psychiatry*. 2010;15:64-79.
6. Goodman WK, Foote KD, Greenberg BD, et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biol Psychiatry*. 2010;67:535-542.
7. Sturm V, Lenartz D, Koulousakis A, et al. The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat*. 2003;26:293-299.
8. Franzini A, Messina G, Gambini O, et al. Deep-brain stimulation of the nucleus accumbens in obsessive compulsive disorder: clinical, surgical and electrophysiological considerations in two consecutive patients. *Neurol Sci*. 2010;31:353-359.
9. Alonso P, Cuadras D, Gabriels L, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PLoS One*. 2015;10:e0133591.
10. de Koning PP, Figee M, van den Munckhof P, Schuurman PR, Denys D. Current status of deep brain stimulation for obsessive-compulsive disorder: a clinical review of different targets. *Curr Psychiatry Rep*. 2011;13:274-282.
11. Mavridis IN. Nucleus accumbens stereotaxy for deep brain stimulation: anatomical focus. *Acta Neurochir (Wien)*. 2014;156:589-591.
12. van den Munckhof P, Bosch DA, Mantione MH, Figee M, Denys DA, Schuurman PR. Active stimulation site of nucleus accumbens deep brain stimulation in obsessive-compulsive disorder is localized in the ventral internal capsule. *Acta Neurochir Suppl*. 2013;117:53-59.
13. Blomstedt P, Sjoberg RL, Hansson M, Bodlund O, Hariz MI. Deep brain stimulation in the treatment of obsessive-compulsive disorder. *World Neurosurg*. 2013;80:e245-253.
14. Anderson D, Ahmed A. Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. Case report. *J Neurosurg*. 2003;98:1104-1108.
15. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet*. 1999;354:1526.
16. Abelson JL, Curtis GC, Sagher O, et al. Deep brain stimulation for refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2005;57:510-516.
17. Tsai HC, Chang CH, Pan JI, et al. Pilot study of deep brain stimulation in refractory obsessive-compulsive disorder ethnic Chinese patients. *Psychiatry Clin Neurosci*. 2012;66:303-312.
18. Roh D, Chang WS, Chang JW, Kim CH. Long-term follow-up of deep brain stimulation for refractory obsessive-compulsive disorder. *Psychiatry Res*. 2012;200:1067-1070.
19. Kuhn J, Lenartz D, Huff W, et al. Transient manic-like episode following bilateral deep brain stimulation of the nucleus accumbens and the internal capsule in a patient with Tourette syndrome. *Neuromodulation*. 2008;11:128-131.
20. van Kuyck K, Gabriels L, Cosyns P, et al. Behavioural and physiological effects of electrical stimulation in the nucleus accumbens: a review. *Acta Neurochir Suppl*. 2007;97:375-391.
21. Mallet L, Mesnage V, Houeto JL, et al. Compulsions, Parkinson's disease, and stimulation. *Lancet*. 2002;360:1302-1304.
22. Chabardes S, Polosan M, Krack P, et al. Deep brain stimulation for obsessive-compulsive disorder: subthalamic nucleus target. *World Neurosurg*. 2013;80:S31.e31-S31.e38.
23. Fontaine D, Mattei V, Borg M, et al. Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease. *Case report. J Neurosurg*. 2004;100:1084-1086.
24. Mulders AEP, Leentjens AFG, Schruers K, Duits A, Ackermans L, Temel Y. Choreatic side

effects of deep brain stimulation of the anteromedial subthalamic nucleus for treatment-resistant obsessive-compulsive disorder. *World Neurosurg*. 2017;104, 1048.e1049-1048.e1013.

25. Jimenez F, Nicolini H, Lozano AM, Piedimonte F, Salin R, Velasco F. Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. *World Neurosurg*. 2013;80: S30.e17-S30.e25.

26. Islam L, Franzini A, Messina G, Scarone S, Gambini O. Deep brain stimulation of the nucleus accumbens and bed nucleus of stria terminalis for obsessive-compulsive disorder: a case series. *World Neurosurg*. 2015;83:657-663.

27. Luyten L, Hendrickx S, Raymaekers S, Gabriels L, Nuttin B. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. *Mol Psychiatry*. 2016;21:1272-1280.

28. Nuttin BJ, Gabriels LA, Cosyns PR, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*. 2003;52:1263-1272 [discussion: 1272-1274].

29. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci*. 1992;13:177-184.

30. Altman J, Everitt BJ, Glautier S, et al. The biological, social and clinical bases of drug addiction: commentary and debate. *Psychopharmacology (Berl)*. 1996;125:285-345.

31. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*. 2006;29:565-598.

32. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron*. 2002;34:13-25.

33. Salamone JD, Correa M, Mingote SM, Weber SM. Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine. *Curr Opin Pharmacol*. 2005;5:34-41.

34. Munte TF, Heldmann M, Hinrichs H, et al. Nucleus accumbens is involved in human action monitoring: evidence from invasive electrophysiological recordings. *Front Hum Neurosci*. 2007;1: 11.

35. Sesack SR, Grace AA. Cortico-basal ganglia reward network: microcircuitry. *Neuropsychopharmacology*. 2010;35:27-47.

36. Moore H, West AR, Grace AA. The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. *Biol Psychiatry*. 1999;46:40-55.

37. Wolf ME. Addiction: making the connection between behavioral changes and neuronal plasticity in specific pathways. *Mol Interv*. 2002;2: 146-157.

38. Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron*. 2005;45:647-650.

39. Ambroggi F, Ishikawa A, Fields HL, Nicola SM. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. *Neuron*. 2008;59:648-661.

40. Ito R, Robbins TW, Pennartz CM, Everitt BJ. Functional interaction between the hippocampus and nucleus accumbens shell is necessary for the acquisition of appetitive spatial context conditioning. *J Neurosci*. 2008;28:6950-6959.

41. Gruber AJ, Hussain RJ, O'Donnell P. The nucleus accumbens: a switchboard for goal-directed behaviors. *PLoS One*. 2009;4:e5062.

42. O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. *J Neurosci*. 1995;15:3622-3639.

43. Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. *Curr Opin Neurobiol*. 1996;6:228-236.

44. Schultz W, Apicella P, Scarnati E, Ljungberg T. Neuronal activity in monkey ventral striatum related to the expectation of reward. *J Neurosci*. 1992;12:4595-4610.

45. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997; 275:1593-1599.

46. Breiter HC, Rosen BR. Functional magnetic resonance imaging of brain reward circuitry in the human. *Ann N Y Acad Sci*. 1999;877:523-547.

47. Heimer L. The olfactory cortex and the ventral striatum. In: Livingston KE, Hornykiewicz O, eds. *Limbic Mechanisms*. New York, NY: Plenum Press; 1978:95-187.

48. Fudge JL, Haber SN. Defining the caudal ventral striatum in primates: cellular and histochemical features. *J Neurosci*. 2002;22:10078-10082.

49. Zahm DS, Brog JS. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. *Neuroscience*. 1992;50:751-767.

50. Zahm DS, Heimer L. Specificity in the efferent projections of the nucleus accumbens in the rat: comparison of the rostral pole projection patterns with those of the core and shell. *J Comp Neurol*. 1993;327:220-232.

51. Zaborszky L, Alheid GF, Beinfeld MC, Eiden LE, Heimer L, Palkovits M. Cholecystokinin innervation of the ventral striatum: a morphological and radioimmunological study. *Neuroscience*. 1985; 14:427-453.

52. Meredith GE, Pattiselanno A, Groenewegen HJ, Haber SN. Shell and core in monkey and human nucleus accumbens identified with antibodies to calbindin-D28k. *J Comp Neurol*. 1996;365:628-639.

53. Voorn P, Brady LS, Schotte A, Berendse HW, Richfield EK. Evidence for two neurochemical divisions in the human nucleus accumbens. *Eur J Neurosci*. 1994;6:1913-1916.

54. Baliki MN, Mansour A, Baria AT, et al. Parceling human accumbens into putative core and shell dissociates encoding of values for reward and pain. *J Neurosci*. 2013;33:16383-16393.

55. Mavridis I, Boviatsis E, Anagnostopoulou S. Stereotactic anatomy of the human nucleus accumbens: from applied mathematics to microsurgical accuracy. *Surg Radiol Anat*. 2011;33: 583-594.

56. Neto LL, Oliveira E, Correia F, Ferreira AG. The human nucleus accumbens: where is it? A stereotactic, anatomical and magnetic resonance imaging study. *Neuromodulation*. 2008;11:13-22.

57. Prensa L, Richard S, Parent A. Chemical anatomy of the human ventral striatum and adjacent basal forebrain structures. *J Comp Neurol*. 2003;460: 345-367.

58. Lucas-Neto L, Neto D, Oliveira E, et al. Three dimensional anatomy of the human nucleus accumbens. *Acta Neurochir (Wien)*. 2013;155: 2389-2398.

59. Mai JK, Paxinos G, Voss T. *Atlas of the Human Brain in Stereotaxic Coordinates*. 3rd ed. San Diego, CA: Academic Press; 2007.

60. Cho Z-H. *7.0 Tesla MRI Brain White Matter Atlas*. 2nd ed. Heidelberg, Germany: Springer; 2015.

61. Lucas-Neto L, Reimao S, Oliveira E, et al. Advanced MR imaging of the human nucleus accumbens—additional guiding tool for deep brain stimulation. *Neuromodulation*. 2015;18: 341-348.

62. Lucas-Neto L, Mourato B, Neto D, et al. The nucleus accumbens beyond the anterior commissure: implications for psychosurgery. *Stereotact Funct Neurosurg*. 2014;92:291-299.

63. Ikemoto K, Satoh K, Maeda T, Fibiger HC. Neurochemical heterogeneity of the primate nucleus accumbens. *Exp Brain Res*. 1995;104: 177-190.

64. Shirayama Y, Chaki S. Neurochemistry of the nucleus accumbens and its relevance to depression and antidepressant action in rodents. *Curr Neuropharmacol*. 2006;4:277-291.

65. Voorn P, Gerfen CR, Groenewegen HJ. Compartmental organization of the ventral striatum of the rat: immunohistochemical distribution of enkephalin, substance P, dopamine, and calcium-binding protein. *J Comp Neurol*. 1989; 289:189-201.

66. Meredith GE, Blank B, Groenewegen HJ. The distribution and compartmental organization of the cholinergic neurons in nucleus accumbens of the rat. *Neuroscience*. 1989;31:327-345.

67. Groenewegen HJ, Russchen FT. Organization of the efferent projections of the nucleus accumbens to pallidal, hypothalamic, and mesencephalic structures: a tracing and immunohistochemical study in the cat. *J Comp Neurol*. 1984;223:347-367.

68. Deutch AY, Cameron DS. Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell. *Neuroscience*. 1992;46:49-56.

69. Cote PY, Levitt P, Parent A. Limbic system-associated membrane protein (LAMP) in

primate amygdala and hippocampus. *Hippocampus*. 1996;6:483-494.

70. Friedman DP, Aggleton JP, Saunders RC. Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: combined anterograde and retrograde tracing study in the Macaque brain. *J Comp Neurol*. 2002; 450:345-365.

71. Morel A, Loup F, Magnin M, Jeanmonod D. Neurochemical organization of the human basal ganglia: anatomofunctional territories defined by the distributions of calcium-binding proteins and SMI-32. *J Comp Neurol*. 2002;443:86-103.

72. Parent A, Bouchard C, Smith Y. The striatopallidal and striatonigral projections: two distinct fiber systems in primate. *Brain Res*. 1984; 303:385-390.

73. Haber SN, Lynd E, Klein C, Groenewegen HJ. Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study. *J Comp Neurol*. 1990; 293:282-298.

74. Brauer K, Hausser M, Hartig W, Arendt T. The core-shell dichotomy of nucleus accumbens in the rhesus monkey as revealed by double-immunofluorescence and morphology of cholinergic interneurons. *Brain Res*. 2000;858: 151-162.

75. McKittrick CR, Abercrombie ED. Catecholamine mapping within nucleus accumbens: differences in basal and amphetamine-stimulated efflux of norepinephrine and dopamine in shell and core. *J Neurochem*. 2007;100:1247-1256.

76. Berridge CW, Stratford TL, Foote SL, Kelley AE. Distribution of dopamine beta-hydroxylase-like immunoreactive fibers within the shell subregion of the nucleus accumbens. *Synapse*. 1997;27: 230-241.

77. O'Donnell P, Greene J, Pabello N, Lewis BL, Grace AA. Modulation of cell firing in the nucleus accumbens. *Ann N Y Acad Sci*. 1999;877: 157-175.

78. Pickel VM, Towle AC, Joh TH, Chan J. Gamma-aminobutyric acid in the medial rat nucleus accumbens: ultrastructural localization in neurons receiving monosynaptic input from catecholaminergic afferents. *J Comp Neurol*. 1988;272: 1-14.

79. Totterdell S, Smith AD. Convergence of hippocampal and dopaminergic input onto identified neurons in the nucleus accumbens of the rat. *J Chem Neuroanat*. 1989;2:285-298.

80. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci*. 2011;12:623-637.

81. Berendse HW, Richfield EK. Heterogeneous distribution of dopamine D1 and D2 receptors in the human ventral striatum. *Neurosci Lett*. 1993; 150:75-79.

82. Kalivas PW. The glutamate homeostasis hypothesis of addiction. *Nat Rev Neurosci*. 2009;10: 561-572.

83. Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. *Ann N Y Acad Sci*. 1999;877: 49-63.

84. Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. *Neuroscience*. 1987;23:103-120.

85. Brog JS, Salyapongse A, Deutch AY, Zahm DS. The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. *J Comp Neurol*. 1993;338:255-278.

86. Meidahl AC, Orlowski D, Sorensen JC, Bjarkam CR. The retrograde connections and anatomical segregation of the Gottingen minipig nucleus accumbens. *Front Neuroanat*. 2016;10:117.

87. Haber SN. Neuroanatomy of reward: a view from the ventral striatum. In: Gottfried JA, ed. *Neurobiology of Sensation and Rreward*. New York, NY: CRC Press; 2011.

88. Kunishio K, Haber SN. Primate cingulostriatal projection: limbic striatal versus sensorimotor striatal input. *J Comp Neurol*. 1994;350:337-356.

89. Haber SN, Kunishio K, Mizobuchi M, Lynd-Balta E. The orbital and medial prefrontal circuit through the primate basal ganglia. *J Neurosci*. 1995;15:4851-4867.

90. Fudge JL, Kunishio K, Walsh P, Richard C, Haber SN. Amygdaloid projections to ventromedial striatal subterritories in the primate. *Neuroscience*. 2002;110:257-275.

91. Kelley AE, Domesick VB. The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: an anterograde- and retrograde-horseradish peroxidase study. *Neuroscience*. 1982;7:2321-2335.

92. Swanson LW, Cowan WM. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *J Comp Neurol*. 1977;172:49-84.

93. Aggleton JP. EPS Mid-Career Award 2006. Understanding anterograde amnesia: disconnections and hidden lesions. *Q J Exp Psychol (Hove)*. 2008;61:1441-1471.

94. Dong HW, Swanson LW, Chen L, Fanselow MS, Toga AW. Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1. *Proc Natl Acad Sci U S A*. 2009;106: 11794-11799.

95. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*. 2010;65:7-19.

96. Gimenez-Amaya JM, McFarland NR, de las Heras S, Haber SN. Organization of thalamic projections to the ventral striatum in the primate. *J Comp Neurol*. 1995;354:127-149.

97. Gerfen CR, Herkenham M, Thibault J. The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *J Neurosci*. 1987;7: 3915-3934.

98. Gerfen CR, Baimbridge KG, Thibault J. The neostriatal mosaic: III. Biochemical and developmental dissociation of patch-matrix mesostriatal systems. *J Neurosci*. 1987;7:3935-3944.

99. Lynd-Balta E, Haber SN. The organization of midbrain projections to the ventral striatum in the primate. *Neuroscience*. 1994;59:609-623.

100. Nauta WJ, Smith GP, Faull RL, Domesick VB. Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. *Neuroscience*. 1978;3:385-401.

101. Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience*. 1991;41:89-125.

102. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry*. 2008;64:461-467.

103. Axer H, Lippitz BE, von Keyserlingk DG. Morphological asymmetry in anterior limb of human internal capsule revealed by confocal laser and polarized light microscopy. *Psychiatry Res*. 1999;91:141-154.

104. Strominger NL, Demarest RJ, Laemle LB. *Thalamus. Noback's Human Nervous System*. 7th ed. New York, NY: Humana Press; 2012:397-409.

105. Axer H, Niemann K. Terminology of the thalamus and its representation in a part-whole relation. *Methods Inf Med*. 1994;33:488-495.

106. Hassler R. Architectonic organization of the thalamic nuclei. In: Schaltenbrand G, Walker AE, eds. *Stereotaxy of the Human Brain*. New York, NY: Thieme; 1982:140-180.

107. Coenen VA, Honey CR, Hurwitz T, et al. Medial forebrain bundle stimulation as a pathophysiological mechanism for hypomania in subthalamic nucleus deep brain stimulation for Parkinson's disease. *Neurosurgery*. 2009;64:1106-1114 [discussion: 1114-1115].

108. Coenen VA, Panksepp J, Hurwitz TA, Urbach H, Madler B. Human medial forebrain bundle (MFB) and anterior thalamic radiation (ATR): imaging of two major subcortical pathways and the dynamic balance of opposite affects in understanding depression. *J Neuropsychiatry Clin Neurosci*. 2012;24:223-236.

109. Hurwitz TA, Mandat T, Forster B, Honey C. Tract identification by novel MRI signal changes following stereotactic anterior capsulotomy. *Stereotact Funct Neurosurg*. 2006;84:228-235.

110. Engelhardt E, Madeira Moreira D, Laks J. Cerebrocerebellar system and Arnold's bundle, a tractographic study: preliminary results. *Dement Neuropsychol*. 2010;4:293-299.

111. Nieuwenhuys R, Geeraedts LM, Veening JG. The medial forebrain bundle of the rat. I. General introduction. *J Comp Neurol*. 1982;206:49-81.

112. Sesack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. *J Comp Neurol*. 1992; 320:145-160.

113. Coenen VA, Allert N, Madler B. A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. *Acta Neurochir (Wien)*. 2011;153: 1579-1585 [discussion: 1585].

114. Lehman JF, Greenberg BD, McIntyre CC, Rasmussen SA, Haber SN. Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. *J Neurosci*. 2011;31:10392-10402.

115. Strominger NL, Demarest RJ, Laemle LB. *The reticular formation and the limbic system*. *Noback's Human Nervous system*. 7th ed. New York, NY: Humana Press; 2012:380-394.

116. Vanderah TW, Gould DJ. *Drives and emotions*. *Nolte's the Human Brain: An Introduction to Its Functional Anatomy*. Philadelphia: Elsevier; 2016: 579-604.

117. Kamali A, Sair HI, Blitz AM, et al. Revealing the ventral amygdalofugal pathway of the human limbic system using high spatial resolution diffusion tensor tractography. *Brain Struct Funct*. 2016;221:3561-3569.

118. Klingler J, Gloor P. The connections of the amygdala and of the anterior temporal cortex in the human brain. *J Comp Neurol*. 1960;115:333-369.

119. Kamali A, Yousem DM, Lin DD, et al. Mapping the trajectory of the stria terminalis of the human limbic system using high spatial resolution diffusion tensor tractography. *Neurosci Lett*. 2015; 608:45-50.

120. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*. 2005;162:1403-1413.

121. Galvez JF, Keser Z, Mwangi B, et al. The medial forebrain bundle as a deep brain stimulation target for treatment resistant depression: a review of published data. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015;58:59-70.

122. Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol Psychiatry*. 2013;73:1204-1212.

123. Di Virgilio G, Clarke S, Pizzolato G, Schaffner T. Cortical regions contributing to the anterior commissure in man. *Exp Brain Res*. 1999;124:1-7.

124. Peltier J, Verclytte S, Delmaire C, Pruvo JP, Havet E, Le Gars D. Microsurgical anatomy of the anterior commissure: correlations with diffusion tensor imaging fiber tracking and clinical relevance. *Neurosurgery*. 2011;69:ons241-246 [discussion: ons246-247].

125. Kuhn J, Lenartz D, Mai JK, et al. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. *J Neurol*. 2007;254:963-965.

126. Guehl D, Benazzouz A, Aouizerate B, et al. Neuronal correlates of obsessions in the caudate nucleus. *Biol Psychiatry*. 2008;63:557-562.

127. Aouizerate B, Cuny E, Bardinet E, et al. Distinct striatal targets in treating obsessive-compulsive disorder and major depression. *J Neurosurg*. 2009;111:775-779.

128. 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;67:1061-1068.

129. Fayad SM, Guzick AG, Reid AM, et al. Six-nine year follow-up of deep brain stimulation for obsessive-compulsive disorder. *PLoS One*. 2016; 11:e0167875.

130. Doshi PK. Mania induced by stimulation following DBS of the bed nucleus of stria terminalis for obsessive-compulsive disorder. *Stereotact Funct Neurosurg*. 2016;94:326.

131. Winter L, Heitland I, Saryyeva A, et al. Acute effects of electrical stimulation of the bed nucleus of the stria terminalis/internal capsule in obsessive-compulsive disorder. *World Neurosurg*. 2018;111:e471-e477.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 22 June 2018; accepted 24 January 2019

Citation: World Neurosurg. (2019) 126:1-10.
https://doi.org/10.1016/j.wneu.2019.01.254

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***

1878-8750/$ - see front matter