Title: Four deep brain stimulation targets for obsessive-compulsive disorder: Are they different?

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Running title:

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Running Title: Connections of four deep brain stimulation targets for OCD

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Key Words. Anterior limb of the internal capsule, medial forebrain bundle, subthalamic nucleus, ventral striatum, anatomic tracing, diffusion magnetic resonance imaging, white matter pathways.

Abstract

Deep brain stimulation (DBS) is a promising therapeutic approach for patients with treatment-resistant obsessive compulsive disorder (OCD), a condition linked to abnormalities in cortico-basal ganglia networks. Effective targets are placed in one of four subcortical areas with the goal of capturing prefrontal, anterior cingulate, and basal ganglia connections linked to the limbic system. These include the anterior limb of the internal capsule, the ventral striatum, the subthalamic nucleus, and a midbrain target. The goal of this review is to examine these four targets with respect to the similarities and differences of their connections. Following a review of the connections for each target based on anatomic studies in nonhuman primates (NHPs), we examine the accuracy of diffusion magnetic resonance imaging (dMRI) tractography to replicate those connections in the NHP, before evaluating the connections in the human brain based on dMRI tractography. Results demonstrate that the four targets generally involve similar connections, all of which are part of the internal capsule. Nonetheless, some connections are unique to each site. Delineating the similarities and differences across targets is a critical step for evaluating and comparing the effectiveness of each and how circuits contribute to the therapeutic outcome. It also underscores the importance that the terminology used for each target accurately reflects its position and its anatomic connections, so as to enable comparisons across clinical studies and for basic scientists to probe mechanisms underlying DBS.

Introduction.

Deep brain stimulation (DBS) is a promising therapeutic approach for patients with treatment-resistant obsessive compulsive disorder (OCD)(1-4), a condition linked to abnormalities in the cortico-thalamic-basal ganglia network(5-8). Most commonly the targets are centered on the orbitofrontal (OFC) and anterior cingulate cortical (ACC) circuits. There are four main targets: 1. The ventral anterior limb of the internal capsule (ALIC), to modulate OFC/AC-subcortical connections(2, 3); 2. The ventral striatum (VS), to modulate the reward system(4); 3. The medial subthalamic nucleus (mSTN), to modulate the OFC/ACC hyperdirect pathway and/or the STN-ventral pallidal (VP) loop(1, 9); and 4. A midbrain target, to modulate the ascending ventral tegmental area (VTA) fibers(10, 11). Importantly, at the typical parameters used for stimulation, myelinated fibers are preferentially stimulated over nonmyelinated fibers and axons are stimulated more easily than cells although other neuronal elements can also be involved(12). Thus, electrode targets are typically placed to modulate a particular set of myelinated fibers that carry information from (or to) cortical or basal ganglia areas (supplemental Fig. 1). Critical questions regarding these targets are: 1. What connections are likely involved at each? 2. How similar are these connections across the targets? 3. Can we develop a more precise and common terminology for each target based on their connections? The importance of clarifying these issues cannot be underestimated as it centers on the ability to compare which circuits are modulated at each target across clinical sites. These comparisons form the basis for cross evaluation of therapeutic outcomes and for understanding the underlying mechanisms of those outcomes. Diffusion magnetic resonance imaging (dMRI) tractography is increasingly being used to model or position

electrodes for DBS (9, 13-19) which raises an additional issue regarding the accuracy of diffusion tractography to correctly label connections.

In this paper we examine the connections involved at the four major DBS target sites for OCD based on animal anatomic studies, and animal and human dMRI studies. Individual groups have also explored other targets, the bed nucleus of the stria terminalis (BNST), the globus pallidus (GP), and the inferior thalamic peduncle (17, 20-22). Given their proximity to the ALIC, VS, and STN, these targets will be addressed within those sections (23). We first review the known anatomic connections passing through each target based on tracing experiments in nonhuman primates (NHPs)(24-35). We then review the accuracy of dMRI to replicate those connections by evaluating the ability of dMRI to identify those connections first in NHPs, including experiments in which animals received both tracer injections and a dMRI scan(25). This step is critical for guiding the evaluation of white matter tracts in human dMRI by testing the accuracy of dMRI to demonstrate the correct connections, based on histology. It sets the stage for using dMRI to follow connections in the human brain where tracing experiments are not possible(25, 36, 37). Combining these stringent criteria, we demonstrate that the four targets generally involve similar connections, all of which are part of the internal capsule (IC) (38). Nonetheless, some connections are unique to each site. Delineating the connectional similarities and differences across the different targets will help define accurate and common terminology that reflects the positions and anatomic connections of each target. This enables researchers to make comparisons across clinical studies and discuss how connections might contribute to the therapeutic outcome. It also lays a common platform to probe mechanisms underlying DBS.

Anatomic connections.

The ALIC. The ALIC is a heavily myelinated fiber bundle that carries the descending and ascending PFC/ACC fibers to the thalamus and brainstem(26). Importantly, many of the PFC/ACC ALIC fibers are embedded within the VS as small myelinated fascicles and, as such, are considered part of the VS rather than the ALIC. Axons from each cortical area remain clustered as they enter and travel through the ALIC. They are organized into two intertwined bundles, those that exit the capsule to the thalamus and those that continue to the brainstem(24, 39). The ALIC is organized topologically and can be segmented into five regions based on positions of PFC/ACC fibers within it (Fig. 1A)(25). These positions generate a ventrodorsal and mediolateral arrangement within the capsule. Fibers originating in ventral cortical regions travel ventral to those that originate in more dorsal regions. Fibers originating in medial regions travel medial to those that originate in more lateral regions. The ventral-most components carry vACC and OFC fibers. Just dorsal to these axons are fibers from the dorsal ACC (dACC) and ventrolateral PFC, positioned medially and laterally respectively. Dorsal to these components are fibers from the dorsomedial and dorsolateral PFC(24, 25). Thus, electrodes placed in the ventral-most part of the ALIC will involve both thalamic and brainstem fibers connecting the vACC and OFC. Those placed more dorsomedially likely involve axons from the dACC, while those placed laterally will involve vlPFC fibers. The most dorsal electrodes will modulate the dorsomedial or dorsolateral PFC (Fig. 1b)(25). The BNST is located adjacent to the caudal ALIC and contains PFC-thalamic fibers existing ALIC. Electrodes placed here will thus, also modulate these fibers, in addition to BNST connections. Indeed, the distinction between the IC and BNST is noted by the authors(21). Electrodes placed in the inferior thalamic peduncle will more specifically modulate OFC fibers (26).

The striatum. The striatum is the main input structure of the basal ganglia. It receives a massive and topographic input from cerebral cortex, thalamus, and midbrain (28, 40-45). The VS refers to the rostral striatal region that includes the nucleus accumbens, ventromedial caudate nucleus, and the ventromedial putamen. The VS contains myelinated connections of the OFC/ACC, the midline thalamic nuclei, the mediodorsal thalamic nucleus, ventral pallidum, and the unmyelinated fibers from the midbrain. The central striatum is linked with the dorso- and ventrolateral PFC, dorsal ACC, mediodorsal nucleus, ventral anterior nuclei of the thalamus, GP, and central substantia nigra (SN). The dorsolateral striatum is connected to cortical, thalamic, pallidal and brainstem motor control areas. Within this general topography, there is extensive convergence of terminals from multiple cortical areas; ACC and OFC fibers converge in the medial caudate, OFC, dACC, and vLPFC converge in central striatal regions, etc. (Fig. 1c)(29, 46, 47). The VS also has unique connections compared to the dorsal striatum. These include connections to the amygdala, nucleus basalis, preoptic area, bed nucleus of the stria terminalis, hippocampus, and pedunculo pontine tegmentum (Fig. 1d) (48-52). Intermingled with these projections and those of the thalamo-striatal, striato-pallidal, brainstem fibers are the small fascicles that carry ALIC axons that do not terminate in the VS (described above, Fig. 1d, inset). Thus, there is a complex mixture of myelinated fibers that run through the VS. Electrodes placed close to, or within, the small fascicles of the ALIC will involve not only descending and ascending OFC/ACC fibers, but also a complex mixture of additional fibers (thalamic, striato-pallidal, amygdala, brainstem, etc.) (Fig. 3D).

The medial subthalamic nucleus. The mSTN contains myelinated cortical, pallidal, STN and pedunculopontine nucleus fibers (32-34, 53-55). The two best-known pathways are the indirect

pathway (pallido-STN connections) and the hyperdirect pathway (direct cortico-STN connection)(56). The GP connects primarily to the STN via the subthalamic fasciculus, a fiber system that carries both GP-STN axons and STN-GP fibers. The hyperdirect pathway travels through the ALIC, exiting the capsule, lateral to the STN (Fig. 2A)(32). The STN is generally divided into limbic, cognitive, and motor regions(32, 33, 57-59). The OFC/ACC projects to the medial part of the nucleus, extending into the lateral hypothalamus. The dorso- and ventrolateral prefrontal cortical areas project centrally and motor areas terminate in the lateral half of the nucleus (Fig. 2B)(32). However, similar to cortico-striatal connections, there is a high degree of convergence of terminal fields from functionally diverse cortical areas (Fig. 2B, inset)(32). The mSTN(1, 9) targets ACC, OFC and ventral pallidum connections. Its close proximity to the Fields of Forel, zona incerta (ZI), and lateral hypothalamus, and possibly, the ventral inferior thalamic peduncle, suggests the possible involvement of these structures. Importantly, the fields of Forel include, pallidal, cerebellar, tegmental, reticular and corticofugal fibers(60). Taken together, the medial STN target likely modulates the hyperdirect pathway, the ventral pallidal-STN loop, and possibly the fields of Forel and lateral hypothalamus (Fig. 2B). It may also modulate fibers exiting from the IC, including those traveling to (and from) the ZI and several brainstem nuclei.

The midbrain target. The midbrain DBS location was chosen to target the VTA ascending fibers (10, 61). In contrast to the other DBS targets, the VTA contains thinly or unmyelinated fibers (30). Based on dMRI tractography, this target was hypothesized to involve ascending VTA fibers traveling through a newly named pathway, the superior limb of the medial forebrain bundle (slMFB), which runs within the IC(11). However, the ascending VTA dopaminergic axons do not travel in the IC(62). Rather, they exit the VTA, arch laterally over the SN, and cross the IC to

enter the striatum (Fig.2C). To reach the frontal cortex, VTA fibers travel within the classic MFB. The MFB courses rostrally through the ventral forebrain, terminating in the lateral hypothalamus, preoptic area, septum, the bed nucleus of the stria terminalis, amygdala, olfactory tubercle before arching dorsally around the corpus callosum, to enter the frontal cortex(30, 31, 62-65). Tyrosine hydroxylase (TH)-positive-staining is a standard marker for dopamine fibers across species. The classical MFB(66) contains TH-positive staining but, in both NHPs and humans, the IC does not (Fig. 2D) (63, 67, 68). Importantly, frontal cortical fibers connecting the thalamus, the STN, and most brainstem regions travel in the IC, not in the MFB (24-26, 32). The dMRI tractography streamlines labeled as the sLMFB (10, 61) represent fibers of the IC, not the MFB. Nonetheless, this target appears to have clinical efficacy, which raises the question, what pathways are involved? This complex midbrain area contains tightly packed intermixed myelinated bundles. As such, it likely modulates descending and ascending STN, ZI, and VTA/substantia nigra fibers entering and exiting the IC. The area also contains striato-brainstem, pallido-midbrain, cortico-brainstem, and hypothalamo-brainstem fibers (Fig. 2E).

Anatomy and dMRI.

While much of the work on understanding brain connectivity originated in the tract-tracing anatomic literature, human dMRI studies have now taken the lead in this endeavor. This noninvasive approach has the advantage of allowing the study of connections in vivo and is now playing a role in determining DBS electrode placement (9, 13-18, 69). However, tractography does not reconstruct axons but demonstrates so called ‘streamlines’, i.e. paths of least hindrance to diffusion(70). It is an indirect and relatively low-resolution method that has limitations(37, 71-73). The method simply summarizes local orientation information within a relatively low-

resolution voxel to estimate the dominant axonal orientations. Axonal trajectories that give rise to those orientations can be ambiguous, as multiple configurations of axon populations can give rise to similar diffusion profiles. Thus, more dominant directions are emphasized, and smaller bundles with different orientations may be deemphasized or lost. These issues lead to errors in tractography, i.e., false positive and false negative connections(25, 37, 71, 72, 74) or biases in the distributions of cortical terminations(73). Therefore, while tractography is helpful for visualizing known pathways in vivo, it cannot be used on its own to reliably identify ‘new’ pathways in vivo that have not previously been demonstrated using invasive, experimental methods (lesions, animal tracing experiments)(25, 36, 71). Tracing experiments in NHPs are considered the ‘gold standard’ for guiding the interpretation of dMRI connections, by providing the specific origin of axons, their organization within the major fiber bundles, and their terminal fields.

Cross-species, cross-modal information (NHP tracing, NHP dMRI in the same animal, and dMRI in humans) is a powerful approach for determining true connectivity patterns in the human brain. Below we review how well the combination of tracer experiments and dMRI tractography in NHP replicates the anatomy for each DBS site. This allows comparing the position of the axons and the position of streamlines produced by dMRI seeds placed at the same site as the tracer injections, demonstrating the correct and incorrect connections identified using dMRI tractography alone.

Anterior limb of the internal capsule. Tractography seeds placed in the same PFC/ACC positions as tracer injections, produce a streamline pattern in the ALIC that is correctly positioned and other streamlines that are not (Fig. 3)(25, 36). Notably, the incorrect streamlines cover a larger region, are more robust, and travel dorsal to the correct ones (Fig. 3A-B). This spurious streamline pattern

is the result of navigating through the complexity of the corona radiata(25). Importantly, a similar pattern is shown with dMRI tractography in the human brain, with one streamline pattern in the position that is expected by the NHP tracing and dMRI and a second, larger one, in a similar position as the false positive in the NHP dMRI (Fig. 3C-D). Without the histological data as a guide, the more robust, but incorrect streamline pattern, would be assumed to be the correct one in both the NHP and human data(25, 36). Using this cross-species, cross-modal information as a guide, the human ALIC can also be segmented based on the positions of axons from different cortical regions within the capsule, showing a similar topology as the NHP (supplemental figure 2). While these studies focus on descending cortical pathways, ascending connections are likely to be organized similarly. In contrast to the fiber positions in the ALIC, those passing through the fascicles of the striatum cannot be followed using dMRI, due to their small size relative to the resolution of the dMRI data, demonstrating a false negative(36).

Striatal and subthalamic targets. The striatal and STN targets are centered in grey matter, which, with the exception of the thalamus, tends to be isotropic in dMRI. The VS target, as indicated above likely involves the small white matter fascicles that pass through the striatum. However, as the resolution of dMRI tractography cannot accurately follow streamlines from the small fascicles that are embedded within the striatum, we must rely on its anatomic organization to predict which fibers are likely to be involved and the conservation of these connections across species. A similar argument applies to the STN. However, dMRI tractography can demonstrate the STN functional subdivisions (14).

Midbrain target. Placing a tractography seed in the NHP dMRI in the same position as a tracer injection into the MFB(75), lateral to the VTA, also produces correct and incorrect streamlines in the NHP (Fig. 4). Streamlines cross the IC to enter the striatum, as in the histological material. However, dMRI also produce erroneous streamlines travelling through the IC (Fig. 4A). At more rostral levels, the dorsal streamlines continue through the ALIC to frontal cortex (Fig. 4B-C). This clear false positive likely results from the seed's location within the heavily compacted and myelinated fibers that flow to and from the IC. Importantly, the same false positive streamlines can be detected following placement of a tractography seed in the human VTA (Fig. 4 A-C). Taken together, the lack of TH-positive staining in both the monkey and human IC, coupled with the anatomic tracing and false positive streamlines in the IC in both monkeys and humans, indicate that VTA dopaminergic fibers do not take this route to reach the frontal cortex(62, 63). The streamlines derived following a tractography seed placed in this midbrain position are, in fact, cortical connections through the IC that connect other brainstem regions with cortex and subcortical areas.

Discussion

The cortico-thalamo-basal ganglia network is comprised of a complex set of recurrent excitatory and inhibitory loop systems (Fig. 5). Thus, modulation at several points within the system may have similar overall effects (38) (9). The ALIC, VS, STN, and midbrain target placements are chosen to affect this network, with a main focus on the connections associated with reward, avoidance, and cognitive control, primarily the OFC/ACC connections. *The electrode position within the ALIC has changed over the years to optimize outcomes (76-78), but is now positioned to primarily modulate OFC/ACC fibers.* Although the precise position of these fibers varies across

individuals, their topology is consistent, allowing predictions about the relative positions of fibers from different cortical regions(25, 79). This organization can help guide the positioning of electrodes to optimize capturing the desired OFC/ACC fibers or change the stimulated contacts based on outcome (Fig. 5B). Moreover, the topology can guide electrode adjustments made to optimize the modulation of the best combinations of cortical fiber. For example, recent evidence suggests that the ventro- and dorsolateral prefrontal cortex may play a role in behaviors associated with OCD (80-85) and may thus be a future target. The VS target is also typically positioned to modulate a similar set of OFC/ACC connections as the ALIC target. Additionally, the VS target also includes the thalamo-striatal, striato-pallidal and brainstem connections. Depending on its position, it may also include projections unique to the VS (Fig. 5C). The VS is also topologically organized. This includes not only the cortical projections, but also thalamic and midbrain connections (28, 43, 86, 87). Finally, an electrode placed in the VS will likely modulate the fascicles passing through the VS to join the ALIC.

The mSTN involves several connections, including the hyperdirect pathway, primarily from the OFC/ACC, reciprocal VP-STN and STN-VTA connections. These connections have an immediate secondary effect on the VS and medial thalamus. It also may involve fibers passing through the region, including those entering the ZI (Fig. 5D). The midbrain target is positioned in a region that contains several different myelinated bundles, including those exiting and entering the IC. Thus, streamlines extending into the capsule are captured by placing a seed in this midbrain region. Importantly, these are not part of the MFB. In addition to the general modulation of IC fibers, this target will also involve specific cortical projections to the STN, VTA/SN, and ZI, pallido-STN connections, and several ascending and descending brainstem pathways (Fig. 5E).

While stimulation may modulate VTA fibers, it's main effects will be on myelinated fibers entering and exiting the capsule and those coursing through the region.

Important considerations: To understand the actual fibers involved at each structure, several additional factors should be kept in mind. First, the area within each target that is actually stimulated depends on the electric field. The size of the field depends on a combination of factors specific to each site, including the electrodes used, axon orientation, and diameter, stimulation parameters, etc. This makes it difficult to estimate the actual area stimulated across targets and across studies. Therefore, we focused here only on the electrode placement and its adjacent region. However, when the precise location of the contacts are identified in individual patients and field modeling is applied, care must be taken to consider the entire area that might be included within the electric field. Thus, a primary consideration for what might be necessary and sufficient for a positive outcome should include not only the target itself, but its surrounding structures.

Second, there is individual variation in the position of specific PFC/ACC fibers at each site (16, 25, 88). Moreover, symptoms vary across OCD individuals (16). Thus, the desired targeted structures may also vary and may include, for example, ventro-or dorsolateral cortical circuits. Taken together, understanding the anatomic organization of the brain region both serves as an initial guide for electrode placement and can play a critical role for choosing the contacts to activate based on symptoms and outcomes in individual patients. Third, stimulation is non-directional, and consideration must also be given to possible antidromic stimulation. Thus, the electrodes in the ALIC effect both afferent and efferent cortico-thalamic, and brain stem fibers. Those in the VS involves bidirectional ventro-pallido-VS and brainstem-VS fibers.

Overall, outcome measures across targets demonstrate that approximately 50% of patients show improvement (2, 16, 38, 89). Functional changes in cortex and striatum linked to DBS targets have been reported, some of which are consistent with the expected anatomic connections, others are not (14, 90-94). The effects on relatively large areas (i.e. medial or lateral prefrontal cortex) and/or regions within the stimulated area (i.e. striatum). Before we can link changes to specific connections and assess precisely which connections are necessary and sufficient, we need: 1. To be more precise about electrode locations to assess all fiber, both targets and those passing through that elicit these responses; 2. To be consistent in how we subdivide cortical and subcortical regions. 3. To take into account individual variations.

Summary

1. All four OCD DBS sites likely involve OFC/ACC connections passing through, entering, or leaving the IC, albeit at different brain locations (Fig.8) which might explain similar outcomes(9, 38, 89). The specific cortical region or regions stimulated depend on the specific electrode location. For example, a more ventral ALIC site may involve OFC connections, but a more dorsal and medial ALIC site will involve dACC connections. All sites involve a variety of subcortical pathways including, but not limited to basal ganglia, thalamic and brainstem connections. While all four sites were chosen to involve OFC/ACC connections, each preferentially targets different components of the circuit. *The ALIC targets all ascending and descending connections, and connections in the adjacent VS. The VS target involve VS connections (see Fig.1D) , but also other ascending and descending connections, including, but not limited to, ALIC and amygdala fibers.* Both the STN and the midbrain also target connections of the OFC/ACC along with their basal

ganglia components. Importantly, these sites likely involve a wider range of diencephalic and brainstem connections through passing fibers. The midbrain site targets a combination of the striato-midbrain, pallido-midbrain, cortico-midbrain, cortico-STN, cortico ZI, and a variety of brainstem targets.

2. Diffusion MRI tractography is error prone and must be evaluated in the context of known connections from anatomic studies(25, 36, 37, 71, 72). One argument used when dMRI tractography in humans differs from NHP anatomic experiments centers on evolution and the expansion of the cortex, suggesting that the full extent of a pathway can only be discovered in the human by dMRI(10). However, the four DBS subcortical targets are highly conserved across mammalian species, particularly primates(26, 62, 66, 95). While these pathways may increase or decrease in size through evolution, they are unlikely to take different routes. Effective use of tractography for surgical planning and interpreting outcomes should be informed by anatomic experiments, particularly for pathways conserved across species. The false-positive labeling of an MFB component in the IC has led to a misleading concept: that the IC is divided into a medial anterior thalamic radiation (ATR) and a lateral sLMFB, component (15, 61). The ALIC is topographically organized and fibers from the medial prefrontal regions, including the ACC and medial dorsal PFC, travel medially to those from lateral prefrontal regions (25) . Based on this topography, the streamlines identified as sLMFB should represent fibers of the lateral PFC, and those of the ATR should represent fibers of medial cortex. However, the streamlines identified as the sLMFB appear to target midline cortical areas.

3. Translational neuroscience depends on developing a common terminology for brain regions across species. DBS is not only an effective clinical treatment, it also provides an important opportunity for researchers to understand the mechanism underlying disease and the effectiveness of treatment. As such, a standard nomenclature is essential for facilitating, not only comparisons across clinical studies, but also mechanistically probe circuits in animals. The ALIC, striatum, STN, and the MFB, are well studied, definable, different, and separable structures and it is important to use the correct nomenclature regarding each. Specifically, the definitions of the MFB and IC are consistent across species and should not be conflated based solely on dMRI for the reasons outlined above. Clear cross-species definitions are critical to move the field forward, not only for developing the best DBS targets and parameters for stimulation for each disease, but also for probing the circuits experimentally so as to better understand the underlying mechanisms, and to eventually develop individualized targeting. Taken together, finding the stimulation ‘sweet spot’ for DBS treatment for psychiatric disorders, including but not limited to OCD, requires a solid understanding of the connections that pass through each target combined with imaging, network analyses and physiological data.

Acknowledgments

This work was supported by the National Institute of Health (Grants Nos. MH106435 and MH045573 to Dr. Haber).

Financial Disclosures.

Drs. Haber, Yendiki, and Jbabdi reported no biomedical financial interests or potential conflicts of interest.

Figure Legends.

Figure 1. Connections through the ALIC(A/B) and VS (C/D) sites. A. Organization of PFC/ACC fibers in the ALIC-coronal view. B. electrode position to capture OFC fibers-sagittal view. C. Schematic showing convergence of frontal terminals fields in the striatum. D. Electrode placement positioned to capture OFC fibers. It also illustrates the additional connections of the VS in the area of the electrode. Inset demonstrates the electrode placement with respect to the small fascicles traveling through the VS. Abbreviations: Amy=amygdala, BNST=bed nucleus of the stria terminalis, Cd=caudate nucleus, Pu=putamen, Hipp=hippocampus, hypo=hypothalamus, MD=mediodorsal nucleus of the thalamus, NB=nucleus basalis, PPT=pedunculopontine nucleus, VP/GP=ventral pallidum/globus pallidus, VS=ventral striatum, VTA/SN= ventral tegmental area/substantia nigra. Color code: Fuchsia=vACC/mOFC, red=OFC, dark orange=dACC, light orange=vlPFC, yellow=dPFC, green=premotor cortex, blue=motor cortex.

Figure 2. Connections through the STN(A/B) and midbrain (C/D) sites. A. Fiber bundles and connections through the STN. Red arrows=targeted connections, blue arrows=other pathways through the area. B. Organization of cortical terminals in the STN. Color code: Fuchsia=vACC/mOFC, red=OFC, orange=dACC, yellow=dPFC/vlPFC, blue= premotor/motor cortex. C. Dark field illumination demonstrating TH-positive fiber-positive staining (appears gold) as they travel from the VTA laterally, cross the IC to terminate in the globus pallidus and striatum. D. Sagittal section demonstrating the trajectory of TH-positive fibers to frontal cortex. Note, the TH-positive fibers are only found in the striatum, but not in the IC. E. Fibers bundles and connections through the midbrain site. Red arrows=targeted connections, blue arrows=other pathways through the area. Abbreviations: AC=anterior commissure, ALIC=anterior limb of the

internal capsule, Cd=caudate, GP=globus pallidus, H=H fields of Forel, HD=hyperdirect pathway, Hypo=hypothalamus, IC= internal capsule, MT=mammillothalamic tract. PPT=pedunculopontine nucleus, OT=optic tract, R=red nucleus, SN=substantia nigra, STN=subthalamic nucleus, TH=tyrosine hydroxylase, Thal=thalamus, VTA=ventral tegmental area, ZI=ZI, 3n=third nerve. Scale bar=5mm.

Figure 3. Anatomic tracing and dMRI through the ALIC. (A). Histology showing fiber pathways following an injection site in the dACC. Scale bar=5mm. (B). NHP dMRI streamlines generated from a seed at the injection site location from (A). Scale bar=4.9. The coronal levels match those shown in (A). Correct streamlines are indicated with yellow arrows, incorrect streamlines with blue arrows. (C-D). Human dMRI data illustrating streamlines following placement of a seed in a similar area of dACC. Based on the NHP data, yellow arrows show the likely correct streamlines, and blue arrows show the likely incorrect ones. Scale bar=10mm. Abbreviations: AC=anterior commissure, Cd=caudate, CC=corpus callosum, GP=globus pallidus, IC= internal capsule, Pu=putamen. Republished from Safadi et al.

4. Projections from the VTA. Top panels= NHP histology following a tracer injection into the VTA, bottom panels, left=NHP dMRI tractography in NHP, right= human dMRI tractography. Top panel. A. asterisk=tracer injection site, Red=seed placement at the same site as the injection in monkey and human dMRI. Similar to the anatomic tracing, streamlines cross the IC, to the striatum. However, unlike the anatomic tracing experiment, streamlines also enter the IC and continue to travel rostrally, through the ALIC. B-C. Histology demonstrates fibers in the MFB, ventral and medial to the anterior commissure. There are no fibers in the ALIC. In contrast, the dMRI tractography in both the monkey and human show streamlines in the ALIC. Abbreviations: AC=anterior commissure, ALIC= anterior limb of the internal capsule, GP=globus pallidus,

IC=internal capsule, MFB=medial forebrain bundle, OT=optic tract, PO=preoptic area, SN=substantia nigra, VS=ventral striatum. Scale bars: top panel-5mm; bottom panel, NHP-4.9mm; human-10mm.

5. Summary of connections through the four DBS target: A. summary of the PFC-subcortical circuits. Color coding represents the topography of cortico-striatal connections. Arrows indicate the projections through each structure. Color code: Fuchsia=vACC/mOFC, red=OC, dark orange=dACC, light orange=vlPFC, yellow=dPFC, green=premotor cortex, blue=motor cortex.

Abbreviations: dACC= dorsal anterior cingulate cortex, dPFC=dorsal prefrontal cortex, GPe=globus pallidus, external segment, GPi=globus pallidus, internal segment, mOFC=medial orbitofrontal cortex, OFC=orbitofrontal cortex, STN=subthalamic nucleus, Thal=thalamus, vACC=ventral anterior cingulate cortex, vlPFC=ventrolateral prefrontal cortex, SN=substantia nigra. B. Electrode placement demonstrates cortical pathways likely modulated through the ALIC site. C. Electrode placement demonstrates cortical and subcortical pathways likely modulated through the VS site. D. Black asterisk indicates cortical and basal ganglia pathways likely modulated through the STN site. E. Electrode placement demonstrates cortical pathways likely modulated through the midbrain site. Asterisks=electrode contacts. Color code: Fuchsia=vACC/mOFC, red=OC, dark orange=dACC, light orange=vlPFC, yellow=dPFC, green=premotor cortex, blue=motor cortex. Abbreviations: Amy=amygdala, BNST=bed nucleus of the stria terminalis, Cd=caudate nucleus, dACC= dorsal anterior cingulate cortex, dPFC=dorsal prefrontal cortex, GPe=globus pallidus, external segment, GPi=globus pallidus, internal segment, Hipp=hippocampus, hypo=hypothalamus, MD=mediodorsal nucleus of the thalamus, mOFC=medial orbitofrontal cortex, PPT=pedunculopontine nucleus, Pu=putamen, OFC=orbitofrontal cortex, NB=nucleus basalis, STN=subthalamic nucleus, Thal=thalamus,

vACC=ventral anterior cingulate cortex, vlPFC=ventrolateral prefrontal cortex, SN=substantia nigra, VP/GP=ventral pallidum/globus pallidus, VS=ventral striatum, VTA/SN= ventral tegmental area/substantia nigra.

Figure S1. The four main DBS sites. Top panel: A. anterior limb of the internal capsule (2), B. ventral striatum (96), C. subthalamic nucleus (1), D. midbrain (18). Lower panel: electrodes superimposed on atlases depicting myelinated fibers, demonstrating the complex relationship between the specific targets and the surrounding myelinated tracts; A & B. myelin-stained sections (66), inset in B demonstrates the electrode in relationship to the fascicles embedded in the VS. C & D. myelin drawings (95).

Figure S2. Segmentation of the ALIC in the human brain. The five segments carry fibers from different areas of cortex (coronal view): vmPFC/OFC=red, dACC=yellow, dmPFC=green, vlPFC=teal, dlPFC=blue. Republished from Safadi et al.

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Figure 1

Figure 2

Figure 3

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Figure 5

Supplement

Figure S1. The four main DBS sites. Top panel: A. anterior limb of the internal capsule ([2](#)), B. ventral striatum ([93](#)), C. subthalamic nucleus ([1](#)), D. midbrain ([18](#)). Lower panel: electrodes superimposed on atlases depicting myelinated fibers, demonstrating the complex relationship between the specific targets and the surrounding myelinated tracts; A & B. myelin-stained sections ([66](#)), inset in B demonstrates the electrode in relationship to the fascicles embedded in the VS. C & D. myelin drawings ([92](#)).

Figure S2. Segmentation of the ALIC in the human brain. The five segments carry fibers from different areas of cortex (coronal view): vmPFC/OFC=red, dACC=yellow, dmPFC=green, vIPFC=teal, dIPFC=blue. Republished from Safadi et al.

The goal of this paper is to identify and compare the specific anatomic connections at each of the four subcortical deep brain stimulation (DBS) sites used for OCD. Importantly, these sites (ventral striatum, anterior limb of the internal capsule, subthalamic nucleus, and medial forebrain bundle) are also DBS targets for other illnesses (depression, addiction, etc.). DBS is not only an important therapy, but also provides a unique opportunity to probe circuit dysfunction in mental health illnesses. The field is rapidly moving forward with new technologies that combine stimulation with electrical recording and imaging methods, to further examine the networks involved at each site. However, to compare therapeutic outcomes across clinical groups and to develop translational programs that probe the circuits, precise anatomic delineation of the connections captured at each site is required. This review combines information from anatomic tracing experiments in nonhuman primate studies, coupled with diffusion MRI tractography studies in nonhuman primates to first determine the accuracy of dMRI tractography in demonstrating the correct connections. Using this data as a guide, it then delineates the connections likely involved at each target in humans, which vary based on the precise electrode position. Importantly, the review helps develop a clear and consistent nomenclature for each target that represents their connections.

To my knowledge, no review is available that details and compares the underlying connections involved at these targets, using the unique combination of methods described above. Previous reviews on DBS are primarily focused on clinical outcomes, mechanisms of DBS, and/or support of a particular circuit dysfunction hypothesis. As such, while many of them include an overview of the general pathways involved, our approach is purely written from an anatomic perspective, linking animal anatomic experiments with diffusion tractography in order to identify connections at each site. It is not influenced by any specific circuit dysfunction hypothesis. While useful, such hypotheses often ignore pathways that pass through the site which are potentially important, but perhaps less known or not relevant to the hypothesis.