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Cognitive and limbic circuits that are affected by deep brain stimulation

Suzanne N. Haber[1], Justin L. Brucker

[1]Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, New York 14642

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1. ABSTRACT

Several lines of evidence indicate that the neural network that underlies the pathophysiology of obsessive-compulsive disorder and depression centers on the prefronto-basal ganglia system. Particularly involved are anterior cingulate cortex, the orbital prefrontal cortex, the ventral striatum, and parts of the thalamus. Additional integral parts of the network include, the amygdala, the midbrain dopamine cells and the serotonergic neurons. Collectively, these brain regions are involved in various aspects of reward-based learning and good decision-making skills. They are also associated with sadness and depression, pathological risk-taking, addictive behaviors, and obsessive-compulsive disorder. Two of the most successful deep brain stimulation targets for obsessive-compulsive disorder and depression are centered in white matter tracts. These targets were chosen for their central location and ability to capture specific ascending and descending connections, with a particular focus on fibers connecting the subgenual anterior cingulate and orbital cortex with the basal ganglia, thalamus, and amygdala. As more knowledge is obtained concerning the details of these connections, more precise targets may be possible.

2. INTRODUCTION

Deep brain stimulation (DBS) is a proven therapy for intractable movement disorders, such as essential tremor, dystonia, and Parkinson's disease (PD). Although many of these patients experience a dramatic reduction of their motor impairments, the effect of DBS on mood and cognition is also well documented (1-4). DBS is now being investigated for the treatment of severe mental health disorders, including medication-resistant depression and obsessive compulsive disorder (OCD), with encouraging results (5-8). Of the several targets currently under investigation, the two most promising are located within white matter tracts. One site is centered in the ventral part of the anterior limb of the internal capsule (VC), extending into the caudal nucleus accumbens, at the border of the anterior commissure. The second site is located in the subgenual white matter adjacent to area 25 in the ventromedial prefrontal cortex (vmPFC). White matter stimulation sites are in contrast to the subcortical grey matter targets favored in DBS for movement disorders, an example of the latter being the subthalamic nucleus (STN) for PD. However, it should be noted that,

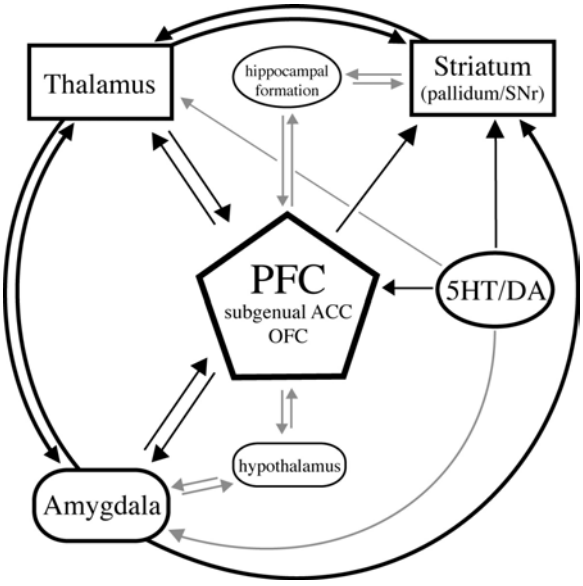

Figure 1. Schematic overview of the cortico-subcortical network involved in obsessive–compulsive disorder and depression: ACC=anterior cingulate cortex; DA=dopamine; prefrontal cortex=PFC; OFC=orbital frontal cortex; SNR=substantia nigra, pars reticulata; 5HT=serotonin. Thick black lines represent the links between key structures involved at DBS sites; thin black lines represent additional important connections.

recently, some groups reported successful results from STN stimulation for OCD, albeit in patients with comorbid PD (9, 10). In addition, other sites are currently being explored at clinical centers throughout the world, including electrodes placed directly into the n. accumbens. Despite the effectiveness of these sites in treating intractable OCD and depression, the mechanism of action for DBS is not well understood and the specific pathways affected by DBS at these sites remain unknown.

While the pathophysiology of OCD and depression remain incompletely understood, converging lines of evidence point to abnormalities in the anterior cingulate cortex (ACC) and orbital frontal–basal ganglia circuit, as well as the fronto-amygdala network. Indeed, stereotactic neurosurgical lesions in the VC, the anterior cingulate, or the subcaudate white matter, all of which interrupt these circuits, are effective in the treatment of refractory OCD and depression (11, 12). Regardless of the site or disease treated (including movement disorders), the effectiveness of DBS varies between patients. This appears to be, in part, related to specific electrode locations in each individual and emphasizes the importance of understanding more precisely which part (s) of the fronto-basal ganglia and/or amygdalar neural network play a central role in the effectiveness of DBS for OCD and depression (7, 13).

3. NEUROCIRCUITRY AND PATHOPHYSIOLOGY OF OBSESSIVE-COMPULSIVE DISORDER (OCD)

3.1. Neuroanatomical findings in OCD

Neuroimaging studies demonstrate the central role of the frontal-basal ganglia-thalamic circuit (Figure 1) in the pathophysiology of OCD. This is particularly evident in imaging studies that show abnormalities in the orbital frontal cortex (OFC), ACC, striatum and medial thalamus. For example, there are subtle differences in OFC, striatal, and thalamic volumes in subjects with OCD vs. controls (14-18). In addition, decreased gray matter volumes of the medial frontal gyrus and insulo-opercular region have been noted in these patients, while ventral putamen and anterior cerebellar volumes were increased (19). White matter abnormalities, evidenced by diffusion tensor imaging (DTI), are seen adjacent to the ACC in OCD patients (20), suggesting a decreased number of neurons or disrupted axonal microstructure.

3.2. Functional neuroimaging findings in OCD

Functional neuroimaging studies show hyperactivity at rest in this circuit when comparing OCD subjects to controls. This regional hyperactivity is accentuated during provocation of the OCD symptoms versus control states (21, 22), with distinct regional activation patterns shown to correlate with different compulsive behaviors (23). Moreover, there is reduced activity in these regions following successful treatment of OCD. This occurs regardless of the type of treatment, including pharmacological (24, 25), behavioral (21, (26), and neurosurgical (27) therapies. Interestingly, there is also imaging evidence to suggest that at pretreatment, regional activity within OFC predicts subsequent response to treatment with medication or behavioral therapy (25, 28-30). Finally, magnetic resonance spectroscopy (MRS) studies show a reduction in n-acetyl aspartate, a marker of healthy neurons within the striatum and medial thalamus in OCD (31-33). Moreover, elevated glutamatergic transmission from OFC/ACC to striatum has been inferred from MRS measurements of an elevated glutamate index within the striatum that is correlated with OCD symptom severity and returns towards normal with successful treatment (34). Taken together, the available human neuroimaging data suggest that abnormalities in OFC/ACC-basal ganglia-thalamic circuitry are central to the pathophysiology of OCD. Further, there is evidence to suggest that this circuitry mediates OCD symptoms and that established effective treatments for OCD exert their benefits via modulating activity in this circuitry. Moreover, the magnitude of OFC activity is proportional to symptom severity and pretreatment activity within this same region predicts subsequent medication response. The concept that OFC mediates OCD symptoms and represents a substrate for pharmacotherapy also resonates with the results from animal studies; chronic administration of selective serotonergic reuptake inhibitors (SSRIs) in rodents leads to serotonergic receptor changes in OFC over the same time course that anti-obsessional effects are observed in humans (35). Thus, extant human imaging data and the contemporary

neurocircuitry model of OCD are quite consistent with the classic targets for ablative neurosurgical therapies (for review, see Rauch 2003 (36)). In particular, it has been hypothesized that anterior capsulotomy disrupts dysfunctional OFC/ACC-thalamic communication by interrupting reciprocal frontal-thalamic projections (36-38). Similarly, the same pathway and target location have been utilized in DBS for OCD with comorbid depression (39), suggesting overlap of some features of both disorders.

4. NEUROCIRCUITRY AND PATHOPHYSIOLOGY OF DEPRESSION

The fronto-basal ganglia circuit also plays an important role in the pathophysiology of depression. This is illustrated in patients with cerebral infarctions disrupting the prefronto-subcortical circuits on the left, who subsequently developed depressive symptoms (40), or by elderly patients with acquired minor depressive symptoms that corresponded with atrophy of the prefrontal and temporal cortices (41). Likewise, post-stroke apathy was associated with reduced regional cerebral blood flow (rCBF) in the left fronto-temporal lobes in some patients, although reductions were also seen in the right dorsolateral frontal cortex (42). This is consistent with reports that mood-induced changes in cerebral blood flow and metabolism occur in the ventral and dorsal prefrontal cortex, albeit in opposite ways (43-46). As in OCD, the neuroimaging studies show abnormalities in several regions of the OFC and ACC, many of which appear to be state-dependent on mood (for review see Drevets (43)). In particular, there are changes in cerebral blood flow and metabolism, with an increase in the pregenual and subgenual ACC and in the OFC. Interestingly, changes in metabolism and blood flow also are increased in the subgenual ACC and OFC during experimentally induced sadness in healthy subjects (47), as well as in the rostral ACC and vmPFC (48). Furthermore, activation of the rostral ACC, with corresponding amygdala deactivation, is seen in normal subjects presented with emotional conflict (49). Similar provocation results in coactivation of the subgenual ACC and amygdala in patients with neuroticism, a risk factor for depression (50). Even among depressed patient populations, specific clinical subtypes possess distinct activation patterns (eg. decreased vmPFC activation in anger subtype) (51). This raises the question, whether clinically depressed patients possess a disregulated, albeit intact prefronto-subcortical circuit (43).

The differences found in mood disorders may, in part, be a result of volumetric changes caused by a reduction of glia number (52, 53) and dendritic arborizations, but not neuronal number. The striatum and amygdala, also show abnormalities in volume, metabolic activity, and signaling (43, 54). MR spectroscopy of the basal ganglia reveals an increased Cho/Cr ratio and phosphodiester (PDE) signal, but low beta-ATP signal in depressed patients (for review, see Kato, 1998 (55)). These findings are suggestive of degenerative changes and abnormal energy metabolism within the basal ganglia. Volume reductions and altered biochemical profiles are seen in the hippocampus, as well. For example, decreased size of the dentate gyrus, with reduced neuronal branching, and diminished expression of brain-derived neurotrophic factor (BDNF), have been reported as a consequence of stress and glucocorticosteroid administration (for review, see Hajszan, 2006 (56)).

5. TARGETS FOR DEEP BRAIN STIMULATION (DBS)

As mentioned above, two of the best DBS targets for OCD and depression are centered in large white matter tracts, the VC, or the rostral subcaudate white matter. The driving hypothesis for these targets is that DBS activates (or deactivates) subcomponents of the ascending and descending ventromedial and ventrolateral frontal circuits. This circuit involves structures that are thought to be central not only to the pathogenesis of OCD and depression, but also to be associated with reward, anxiety, and fear extinction (21, 57, 58). The structures associated with this network are: the ACC and the OFC, the ventral striatum, the thalamus, and the amygdala (Figure 1). In addition, closely connected brainstem regions, including the midbrain dopamine neurons and the serotonergic cells of the raphe nuclei, are also an integral part of the system. The VC and the subcaudate white matter are massive fiber bundles that carry multiple cortical and subcortical fibers. Furthermore, the VC is also embedded in, or adjacent to, the ventral striatum. Thus, electrodes placed at this point will likely cause direct stimulation of the VS and its connections. The VC lies primarily rostral to, or at the level of, the anterior commissure. Its ventral-most region breaks up into relatively small bundles that are imbedded within the VS. These bundles merge rostrally with the underlying subcaudate white matter. The rostral subcaudate white matter lies immediately ventral to the caudate n., rostral to the n. accumbens (Figure 2A). As it extends caudally, circumventing the caudate n., it divides into the external and extreme capsules. Cortico-cortical and descending fibers from the OFC/ventral ACC, along with ascending fibers, enter either the internal capsule, or pass in small bundles through the VS. It is important to note that there is a significant lack of information concerning the specific fibers that run through various parts of these fiber bundles. It may well be that differences in the effectiveness of DBS across patients is related to the specific connections that are stimulated that vary according to electrode placements.

6. CIRCUITRY OF THE VENTRAL PREFRONTAL–BASAL GANGLIA SYSTEM

6.1. Functional overview of prefrontal cortex

A key component to good decision-making is the ability to accurately evaluate elements of outcome including reward value, predictability, and risk. Different prefrontal cortical areas and corresponding striatal regions are involved in various aspects of reward evaluation and incentive-based learning (59-63), and are associated with sadness and depression, pathological risk-taking, addictive

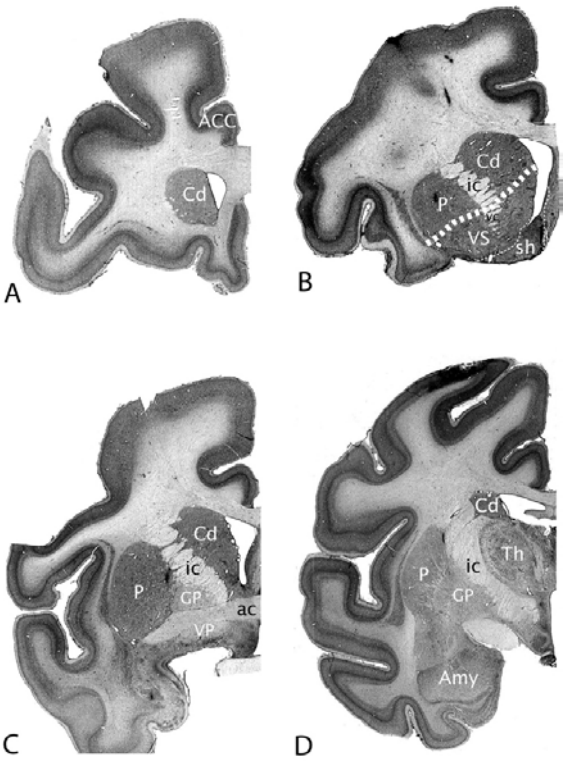

Figure 2. Coronal sections through the forebrain of a non-human primate demonstrating the relevant anatomical structures (see Figure 1) at different rostral-caudal levels. A. At the level of the rostral pole of the striatum; B, at the level of the shell; C, at the level of the anterior commissure; D, at the level of the amygdala. ac=anterior commissure; amy=amygdala; Cd=caudate nucleus; dPFC=dorsal prefrontal cortex; ic=internal capsule; GP=globus pallidus; P=putamen; sh=shell of the n. accumbens; sgACC=subgenual anterior cingulate cortex; Th=thalamus; VC=ventral anterior internal capsule; VS=ventral striatum.

behaviors, and OCD (64-66). The ventral prefrontal areas, the ACC and OFC mediate the different aspects of reward-based behaviors, error prediction and the choice between short and long-term gains. In contrast, the dorsolateral prefrontal cortex (dlPFC) is associated with executive function, and is thought to provide some cognitive control over motivational and emotional behaviors (67-70).

6.2. Organization of the prefrontal cortex

The ACC is divided into areas 24, 32, and 25. Area 24 is further divided into 24 a, b, and c. 24c is closely linked to premotor areas, 24b is closely linked to the dorsolateral prefrontal cortex, and 24a, 32, and 25 are linked to limbic regions. Area 25 is most closely linked to connections with the amygdala and hypothalamus (71). Recent functional imaging studies support a division of the ACC into dorsal (area 24) and ventral regions (areas 32, 25), with the dorsal region associated with cognitive function and ventral areas associated with reward and mood. The OFC is divided into a medial orbital region and a lateral region. The medial region is closely associated with areas 25 and 32 of the ACC, while the lateral area has tight connections with the lateral prefrontal cortex. Based on cortico-cortical and subcortical connections, the medial OFC provides a bridge between areas associated with emotion and those associated with cognition (72, 73). The dorsal medial (area 9) and dorsal lateral (area 45) are important in self-reference and working memory, respectively. Area 46 is involved in spatial working memory processing and in active selection of the stimuli from memory (74-77). Area 9, especially medial area 9, is associated with social-cognitive processing, involving perception and inference of mental state (78, 79). In summary, taken together, human functional imaging studies have divided the prefrontal cortex into the dorsomedial prefrontal cortex (dmPFC), the vmPFC, OFC, and the dlPFC based on specific roles for mediating different aspects of learning and decision making (59, 68-70).

6.3. Prefrontal cortical-basal ganglia pathways

6.3.1. Organization of the basal ganglia

The basal ganglia are divided into dorsal and ventral systems, associated with motor and cognitive functions (dorsal striatum) and motivational functions (ventral striatum), respectively (Figure 2B). The striatum is the main input structure of the basal ganglia. Its afferent projections are derived from three major sources: 1. It receives a massive and topographic input from cerebral cortex. 2. The second largest input is derived from the thalamus. 3. The third main input is from the brainstem, primarily from the dopaminergic cells of the midbrain. The ventral system includes the ventral striatum (the n. accumbens, and the ventromedial parts of the rostral caudate n. and putamen), the ventral pallidum, the ventral tegmental area (VTA) and the medial region of the STN. The ventral pallidum (VP), the pallidal region specifically connected to the ventral striatum, is located ventral to the anterior commissure and extends rostrally invading the parts of the ventral striatum (Figure 2C). Caudally, it occupies the ventral and medial extremes of the external and internal pallidal segments. The substantia nigra is divided into two parts, the substantia nigra, pars compacta (SNc), and the substantia nigra, pars reticulata (SNr) (Figure 3) (80).

6.3.2. Cortical connections to the basal ganglia

The OFC and ACC project primarily to the rostral and ventral striatum (the medial caudate n., the medial and ventral rostral putamen, and the n. accumbens -- both the shell and the core) (81) (Figure 2B). The shell receives the densest innervation from medial areas 25, 14, and 32, and from the agranular insular cortex; areas involved in monitoring the internal milieu. The entire reward-related striatum, as defined by ACC/OFC inputs, occupies a large rostral region and encompasses approximately 22% of the entire striatum. This region is not limited to the ventral striatum at rostral levels, but extends into a large medial and central area, occupying much of the rostral pole before tapering off caudally. Consistent with this large extent of the reward-related striatum, reward-responsive activation is not limited to the

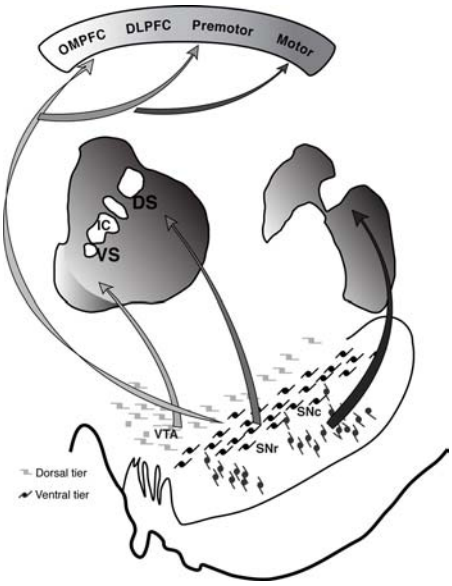

Figure 3. Schematic illustrating the organization of the midbrain dopamine neurons and their projection to striatum and cortex. DLPFC=dorsolateral prefrontal cortex; DS=dorsal striatum; OFC/ACC=orbital frontal cortex/anterior cingulate cortex; SNc=substantia nigra, pars compacta; SNr=substantia nigra, pars reticulata; VS=ventral striatum; VTA=ventral tegmental area.

ventral striatum, but rather found throughout a large dorsal-ventral region (82-87). The dorsomedial prefrontal cortex projects primarily to the rostral central region of the caudate n. and extends from the rostral pole of the striatum through its caudal extent (81). Consistent with input from this cortical area, cells in the head of the caudate n. fire during the delayed portion of the task, resembling activity observed in the dlPFC (88-90). Furthermore, imaging studies support the idea that the head of the caudate is instrumental in delayed tasks, particularly in specific working memory tasks (91, 92). While there is a clear general topography of cortical inputs to the striatum, resulting in an overall functional distribution of afferent projections, it is now known that there is an equally important mechanism for integration across functional cortico-striatal circuits. This is accomplished through a convergence between cortical afferent projections from different functional regions (81). Thus, within the ventral striatum, innervation from the dlPFC interfaces with inputs from several other cortical areas, including those from both the ACC and OFC.

6.3.3. The ventral striatum

While the ventral striatum is similar to the dorsal striatum in most respects, there are some important and unique features (93). The ventral striatum contains a subterritory called the shell (94), an area that plays a particularly important role in the circuitry underlying goal-directed behaviors, behavioral sensitization, and changes in affective states (95-99). While several transmitter and receptor distribution patterns distinguish the shell, the most consistent marker is the lack of calbindin-positive staining (100). This striatal region, along with immediately adjacent areas of the ventral striatum, unlike the rest of the striatum, has a unique connection to the hypothalamus. In addition, while the basic cortical basal ganglia loop is similar in all basal ganglia circuits, the ventral striatum alone receives additional subcortical input from the amygdala and from the hippocampus. These regions do not project extensively to other parts of the striatum (101, 102). The hippocampus has a relatively confined projection, terminating primarily in the shell of the n. accumbens. In contrast, the amygdala projects more widely throughout the ventral striatum. These two inputs place the ventral striatum in a unique position for modulating emotion and motivation. Finally, the ventral striatum also receives a dense serotonergic input. Although serotonin fibers are found throughout the striatum, its innervation of the ventral striatum is particularly dense.

6.3.4. Subcortical connections to the basal ganglia

The output from the striatum is GABAergic and primarily projects to the globus pallidus and the SNr. From these output structures of the basal ganglia, information is transferred back to cortex via the basal ganglia relay nuclei of the thalamus. For a complete review of basal ganglia circuitry, see Haber, 2004 (80). It is the ventral striatal projection to the VP that is most relevant to the discussion of DBS for OCD and depression. The VP extends ventrally, below the anterior commissure. In addition, cells of the VP continue rostrally to invade the rostral and ventral portions of the ventral striatum, sending finger-like extensions into the anterior perforated space (103). There is a well-characterized glutamatergic input from the STN nucleus to all pallidal components, including the VP. These fibers also run through the ventral forebrain region to reach their forebrain targets. Finally, ascending dopaminergic fibers terminate in the ventral pallidum, as they pass through on their way to the striatum.

7. THE DIRECT CORTICO-THALAMIC PATHWAY

While evidence suggests the involvement of the basal ganglia in the pathophysiology of OCD and depression, the most direct and robust cortical fiber connections through the internal capsule are those that connect directly to the thalamus (104, 105). The general function of thalamic nuclei, including the relay nuclei of the basal ganglia, was thought to simply transfer information from afferent systems to cortex. However, this notion has undergone some important revision in recent years (106). While the thalamo-cortical projection has long been known to be reciprocal (107), it has now been demonstrated that the corticothalamic projection is ten times the density of the thalamocortical projection. This has important implications for cortical control of ascending information that passes through the thalamus. Moreover, there are two components of the corticothalamic projection: a reciprocal one, and a non-reciprocal one (105, 108-111). The non-reciprocal component (cortex projects to a thalamic region that does not receive its input) is considered to be a feed-forward mechanism in which the thalamus can influence higher cortical areas (104-106).

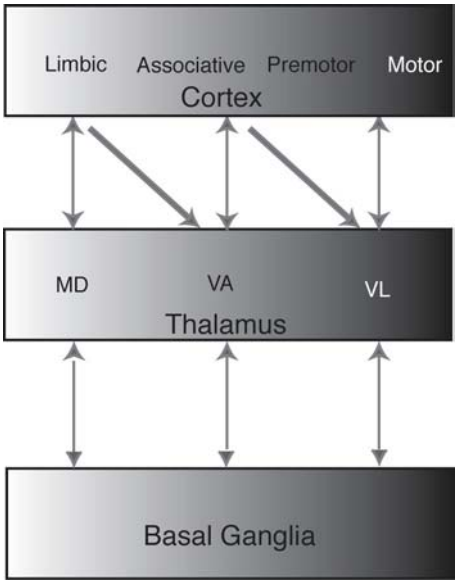

Figure 4. Illustration of information transfer from one functional area of the cortex to another via a non-reciprocal connection to the thalamic relay nuclei. MD=medial dorsal nucleus; VA=ventral anterior nucleus; VL=ventral lateral nucleus.

The basal ganglia relay nuclei (ventral anterior, ventral lateral, and medial dorsal nuclei) appear to mediate information flow from motivational and higher cortical "association" areas of the prefrontal cortex, to rostral motor areas involved in "cognitive" or integrative aspects of motor control, to primary motor areas that direct movement execution (Figure 4). Thus, the thalamus processes complex cortical inputs from multiple areas. This information is conveyed directly back to cortex and to the striatum. The thalamus is therefore in a central position to directly modify information in both cortex and the striatum (105).

8. ADDITIONAL PATHWAYS CENTRAL TO OCD AND DEPRESSION: DOPAMINERGIC AND SEROTONERGIC FIBERS

There are several additional pathways to consider within the framework of DBS. Two important brainstem systems that are involved in both the pathophysiology and/or therapy of these diseases are the ascending dopaminergic and serotonergic fibers. These fibers terminate in several forebrain structures, including both the striatum and cortex. In addition, ascending fibers from both transmitter systems project to a number of brain regions known to modulate emotion, including the amygdala and hypothalamus. The midbrain dopamine neurons are divided into the SNc, and the VTA. The SNc is further divided into a dorsal group and a ventral group (112) (Figure 3). The dorsal group of neurons merges with the immediately adjacent dopamine neurons of the VTA and form a continuous mediodorsal band of cells that are morphologically and chemically similar. Both the dorsal and ventral cell groups project to the striatum. The dorsal group of cells primarily innervates the ventral striatum, while the ventral group terminates in the dorsal striatum. Moreover, in contrast to the ventral group, the dorsal group also projects widely throughout cortex. The dorsal raphe nuclei (DRN), including the dorsal, medial and central raphe nuclei, provide the primary serotonergic input to the striatum and cortex. In a recent study, stimulation within the DRN of rats resulted in focused inhibition of serotonergic neurons, which correlated with depressive behaviors, underscoring the relevance of these pathways to DBS and mood (113).

9. GENERAL CIRCUITRY THROUGH THE VENTRAL-ANTERIOR INTERNAL CAPSULAR (VC) AND SUBGENUAL DBS SITES

The VC is surrounded by the VS (Figure 2B). As mentioned above, the VS receives afferent fibers from the amygdala, specific thalamic regions, and brainstem (101, 102, 114, 115). Ascending fibers from these areas, along with descending fibers from the vmPFC and OFC, travel through the VC and through the fiber bundles located ventral to the VC, within the VS. In addition to the typical striatal cell groups, the VS contains cells belonging to other structures, including the ventral pallidum and the n. basalis (116-118), that contribute substantially to the complexity of the neural network likely to be involved in DBS at this location. Cortical pathways that travel through the VC are likely to preferentially connect directly to specific regions of the thalamus, including the anterior, dorsomedial, and ventral anterior nuclei. Furthermore, a subset of fibers passing through these ventral forebrain bundles will terminate in the hypothalamus. Axons from the ventro-amygdalofugal pathways may also be captured by the electrode stimulation sites in the ventral capsule. In contrast, fibers from the fornix, carrying hippocampal inputs, enter the ventral striatum dorsally and are less likely to be directly stimulated by electrodes placed in the VC. Finally, axons from the midbrain dopamine cells form an ascending bundle that travels through the ventromedial part of the forebrain to innervate the hypothalamus, ventral striatum, bed n. of the stria terminalis, and ventral pallidum. This bundle of fibers is embedded within, and ventral to, the anterior commissure and is therefore likely to be effected by stimulation sites at more caudal placement of the electrodes in the VC. However, at rostral levels, dopaminergic fibers course rostrally to innervate the OFC and subgenual cortical areas by traveling within the white matter bundles embedded ventral to the striatum, and then merging with the subcaudate white matter. Therefore, electrode placement at these more rostral sites will likely involve dopaminergic fibers when positioned more ventrally. Ascending serotonergic fibers follow a similar course as the dopaminergic fibers. However, these two groups of ascending projections do not completely overlap.

While stimulation of both the VC and subcaudate white matter will affect many of the same sets of fibers, fewer targets are likely to be affected at the subcaudate site. For example, the VC site will likely contact ascending and descending fibers from both the vmPFC and the lateral OFC, while the subcaudate site will primarily involve

connections of the subgenual grey matter. However, while stimulation at the VC site will capture more cortico-thalamic fibers, (depending on the specific VC site), fibers traveling to and from the hypothalamus may be better captured with the subcaudate target. Likewise, the involvement of the amygdala will depend entirely on precise electrode localization within the ventral forebrain, as its connections mainly travel ventral to the capsule.

10. SUMMARY

While much has been learned about OCD and depression pathophysiology and treatment, there are critical issues that need to be addressed regarding the mechanism of action by which therapies exert their beneficial effects. Human imaging experiments in patients with OCD and depression can provide unique and powerful data regarding regional brain activity (or activation) *in vivo*. However, these methods lack the spatial resolution necessary to conduct fine mapping of the pathways involved. While advances in neurosurgical treatment have been limited by the relatively static and irreversible nature of ablative procedures, the advent of DBS provides a new panorama of opportunity for a better understanding of frontal-basal ganglia circuits. These methods, combined with more refined neuroimaging in humans, will help develop increasingly precise DBS targets and stimulation parameters for OCD and depression.

11. ACKNOWLEDGEMENT

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Abbreviations: ACC: anterior cingulate cortex, ACTH: adrenocorticotropic hormone, BDNF: brain-derived neurotrophic factor, Cho: choline, Cr: creatinine, DA: dopamine, DBS: deep brain stimulation, dlPFC: dorsolateral prefrontal cortex, dmPFC: dorsomedial prefrontal cortex, DRN: dorsal raphe nuclei, GABA: gamma-aminobutyric acid, GP: globus pallidus, MRS: magnetic resonance spectroscopy, OCD: obsessive-compulsive disorder, OFC: orbitofrontal cortex, P: putamen, PD: Parkinson's disease;, PDE: phosphodiester, rCBF: regional cerebral blood flow, SNc: substantia nigra pars compacta, SNr: substantia nigra pars reticulata, STN: subthalamic nucleus, Th: thalamus, VC: ventral anterior internal capsule, vmPFC: ventromedial prefrontal cortex, VS: ventral striatum, VTA: ventral tegmental area, 5HT: serotonin.

Key Words: Dorsolateral Prefrontal Cortex, Executive Function, Ventral Striatum, Anterior Cingulated Cortex, Orbital Prefrontal Cortex, Deep Brain Stimulation, Limbic Circuit, Cognitive Circuit, Review

Send correspondence to: Suzanne N. Haber, Department of Pharmacology and Physiology, University of Rochester School of Medicine, 601 Elmwood Avenue, Rochester, NY 14642, U.S.A., Tel: 585-275-4538, Fax: 585-273-2652, E-mail: suzanne_haber@urmc.rochester.edu

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