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Neurosurgery for Intractable Obsessive-Compulsive Disorder

A Window into Prefrontal Cortical Function in Humans

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Abstract

Recent advances in functional and diffusion imaging, as well as neuromodulatory devices that can both stimulate and record, have opened up new avenues for advancing hypothesis-driven circuit-based treatments of neuropsychiatric disorders. Neuromodulatory treatments will also expand our understanding of prefrontal cortical function in humans. Across neuropsychiatric illnesses, obsessive-compulsive disorder (OCD) stands out as being a condition where we have an initial understanding of the neural circuitry associated with the illness. Converging evidence has implicated ventrolateral orbital, rostral anterior cingulate, and medio-orbitofrontal and medial frontopolar cortex in OCD psychopathology. Expanded interest of basic scientists in the clinical phenomena of OCD and interdisciplinary collaboration will be essential to further delineate the neurobiologic basis of the illness as well as the mechanism of action of circuit-based treatments.

Introduction

What evidence implicates prefrontal frontostriatal loops in the pathogenesis of obsessive-compulsive disorder (OCD)? How have invasive neurosurgical procedures for OCD contributed to our understanding of prefrontal cortical function in health and disease? In this chapter, I will examine two main bodies of evidence: (a) studies of OCD psychopathology and (b) findings from invasive neurosurgical studies for intractable OCD. Although neurosurgical interventions were designed to develop novel approaches to treatment for patients with intractable neuropsychiatric conditions, they also offer an

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unparalleled opportunity to expand our understanding of prefrontal cortical function in humans.

This chapter focuses on OCD and its symptoms, yet it is important to keep a transdiagnostic perspective in mind. Most OCD patients suffer from comorbid anxiety and depression (Rasmussen and Tsuang 1986). Most depressive episodes are preceded by stress, uncertainty, worry, and anxiety (Barlow and Campbell 2000). The mainstay pharmacologic treatment for all of these conditions are the selective serotonin reuptake inhibitors. A significant percentage of OCD and anxiety disorder patients suffer from behavioral inhibition and separation anxiety during childhood (Rosenbaum et al. 1988). MacLean (1958) pointed to the important role medial prefrontal cortex (PFC) plays in separation anxiety, and as highlighted below, cingulotomy and capsulotomy were used to treat intractable depression as well as intractable OCD. More recently, corticofugal fibers from medial PFC that traverse the anterior limb of the internal capsule have been targeted for deep brain stimulation (DBS) of depression as well as OCD. Haber et al. (2021) have pointed to the connectional similarities and differences in the ventral anterior limb of the internal capsule (vALIC), subthalamic nucleus (STN), subgenual and superolateral branch of the medial forebrain bundle (slMFB) targets for DBS in the treatment of depression and OCD. Future studies will help to clarify the neuroanatomical pathways that are shared as well as unique that correlate with the symptoms of depression, anxiety, and OCD.

Sixty years ago, MacLean put forward the hypothesis that from an evolutionary perspective, the pathogenesis of most neuropsychiatric illnesses were due to abnormalities in the medial PFC and its connections with subcortical regions (Maclean 1958). He posited that these recently developed neocortical regions had not been subject to the process of natural selection, compared to older more highly conserved circuitry. Since then, converging data from studies of brain imaging, cognitive-affective neuroscience, neuromodulation, and animal models suggests that OCD represents a neural network-based disorder (Milad and Rauch 2012; Yuste 2015) involving the dysregulation of cortico-striato-thalamo-cortical (CSTC) loops. The seminal contributions by Alexander et al. (1986) led OCD researchers to examine certain parallel segregated CSTC loops, subserving different motor or cognitive functions, as the neuroanatomical basis for obsessive-compulsive behavior (Baxter, Jr. et al. 1988; Breiter et al. 1996; Saxena and Rauch 2000). Revisions to this model have demonstrated a more complex picture of the organization of CSTC loops (Haber et al. 2020) and show more overlap and functional integration between loops than previously thought. Both positron emission tomography (Schwartz et al. 1996) and functional magnetic resonance imaging (fMRI) studies have shown increased activation in regions of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and portions of the basal ganglia in the symptomatic state compared to healthy controls (Figee et al. 2013). These areas of abnormal activation normalize following successful treatment with either

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pharmacotherapy or behavioral therapy. Successful treatment of OCD with DBS (Figee et al. 2013), surgical ablation (Zuo et al. 2013), and transcranial magnetic stimulation (Dunlop et al. 2016; Nauczyciel et al. 2014) has also been associated with reductions in brain activity in these regions compared to baseline. An important development in circuit-based theories of OCD has been a shift in focus from static regions of interest to investigation of functional networks underpinning different cognitive or behavioral functions related to the symptoms of OCD.

Frontostriatal Loops and the Psychopathology of OCD

The limitations of symptom- and diagnosis-based approaches in understanding the cause of anxiety and obsessive-compulsive spectrum disorders strongly suggest the importance of looking beyond symptoms and symptom dimensions toward underlying dimensional endophenotypes. We have identified two core constructs underlying the symptoms of anxiety and obsessive-compulsive spectrum disorders, harm avoidance and incompleteness, that have demonstrated clinical face validity but for which the underlying neural basis is poorly understood. In 1992, we proposed a conceptual model of these two core constructs of OCD that integrated symptom subtypes, temperament, and neurocircuitry to explain the marked comorbidity between OCD, OC spectrum disorders, and anxiety disorders (Rasmussen and Eisen 1992). We defined incompleteness as the need to have a thought or action perfect before moving onto the next motor or cognitive action. In contrast, we defined harm avoidance as the urge to perform an active avoidance behavior so as to prevent something bad from happening to self or others. These two constructs have demonstrated clinical face validity, and we postulated that harm avoidance was differentially associated with avoidance/punishment circuitry (Dalley et al. 2011) and incompleteness with action selection/reward circuitry. While active avoidance has been investigated in numerous studies of anxiety disorders (Kampman et al. 2014), there has been comparatively little recognition of incompleteness in psychopathology or its public health significance. Incompleteness, or the wish to finish something completely or perfectly before moving on to the next task, is familiar to us all. Clinical manifestations of incompleteness can range from procrastination and perfectionism with excessive attention to detail, to marked difficulty with planning and lost productivity, leading to the inability to sustain goal-directed behavior. Harm avoidance and incompleteness share disruptions in goal-directed action control, (Gillan et al. 2011), with harm avoidance minimizing uncertainty and exploratory behavior in favor of security (Hinds et al. 2010; Szechtman and Woody 2004) and incompleteness minimizing speed and productivity in favor of accuracy and precision. The neurocircuitry underlying goal-directed planning, action control, and emotion is complex and widely distributed across multiple large-scale networks (Cocchi et al. 2012; de Wit et

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al. 2009; Everitt and Robbins 2005; Seeley et al. 2007; Valentin et al. 2007). It remains unclear whether abnormalities in the top-down disinhibition of frontostriatal circuits or bottom-up limbic activation of frontostriatal circuits are abnormal in excessive harm avoidance and incompleteness, or if there is a dynamic interaction between the two.

Although frontostriatal circuitry and abnormalities in goal-directed behavior have long been implicated in the pathogenesis of OCD, the relationship of the symptoms and core features of the illness to three key large-scale prefrontal networks remains unclear: the salience network (Seeley 2019; Uddin 2016), the cognitive control network (Badre 2008; Koechlin et al. 2003), and the task execution network (Badre 2020; Badre and D'Esposito 2007; Dosenbach et al. 2006). The representation of value, hierarchical action selection, and action-outcome monitoring that form the basis of goal-directed behavior are made up of highly distributed interacting networks that rely on parallel processing. We define cognitive control as the ability to select mappings between states and actions based on internally maintained representations of context, goals, and anticipated outcomes (Shenhav et al. 2013). Control over action requires maintaining context at different levels of abstraction and over varying time-scales (Holroyd and Yeung 2012). Rostral ACC is at the juncture between cortical structures that represent current and inferred states related to salience and valuation (insula and OFC), structures involved in communicating information about current and past environment and context (temporal lobe), as well as structures that are responsible for task execution (lateral PFC) (see Figure 15.1) (Gläscher et al. 2012; Holroyd and Verguts 2021; Monosov et al. 2020; Shackman et al. 2011; Shenhav et al. 2016).

Early theories of hierarchical sequential control of the goal-directed behavior involved in task execution focused on cortico-cortical interactions in which rostrolateral PFC affected submodular processing in premotor cortex (Badre and Nee 2018). More recent work has suggested that hierarchical cognitive control may emerge from the interaction of nested frontostriatal loops, where action selection at one cortico-striatal level is constrained or gated by inputs from more anterior levels (Badre and Frank 2012; Frank and Badre 2012). Neuroanatomical evidence has pointed to areas of convergence of these frontostriatal loops at the level of the striatum and thalamus (Haber and Calzavara 2009; Haber et al. 2006). The full range of cognitive control over action is likely to reflect a continuous integrative cascade of processing, from valuation to monitoring, to task specification, and finally to regulation of task execution (Chatham et al. 2014). One can easily see how impairment in these frontostriatal loops could cause problems with action initiation and termination (Heilbronner and Hayden 2016; Hinds et al. 2012; Woody et al. 2005), as well as excessive attention to subgoals and making implicit subgoals explicit versus overall goals leading to the cardinal symptoms associated with OCD. Several lines of evidence point to the idea that these behaviors may result from abnormalities in connectivity between the rostral-most portions of the frontal cortex

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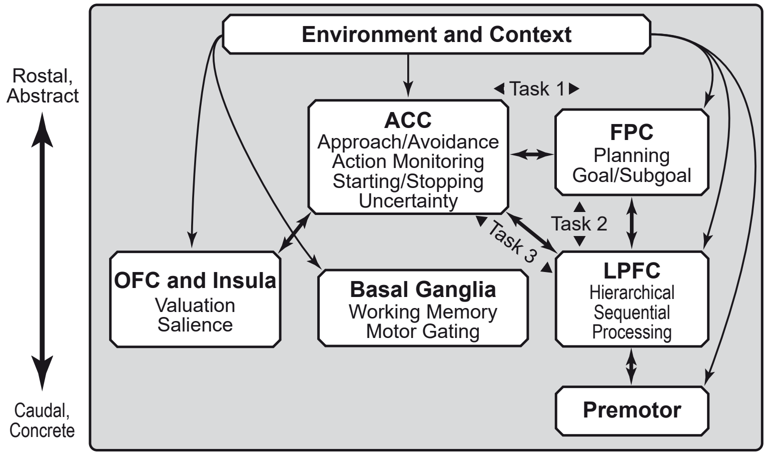

Figure 15.1 Conceptual diagram linking neurocognitive tasks involving goal-directed behavior to the neurocircuitry of incompleteness on three tasks: (1) the Archer task, (2) the sequential control task, and (3) MCIT task.

and its connection with the rostral cingulate and OFC (Braver and Bongiolatti 2002; Burgess et al. 2007; Koechlin et al. 1999; Mansouri et al. 2017; Ramnani and Owen 2004; Rouault et al. 2019). Neuronal ensembles in the frontal pole encode chosen goals during feedback, which suggests that it promotes learning about which kinds of goals and goal-generating processes produce particular costs and benefits. The frontopolar cortex (FPC) selectively mediates the human ability to hold goals in mind while exploring and processing secondary goals. Medial anterior PFC in association with ventral striatum is preferentially engaged when subjects execute tasks in sequences that were expected, whereas FPC was involved preferentially when subjects performed tasks in sequences that were contingent on unpredictable events (Corkin 1979). Taken together, these findings suggest that connections between these regions/networks may underlie deficits in goal-directed behavior associated with OCD.

How Has Invasive Neurosurgery for OCD Contributed to Our Understanding of the PFC?

The extensive literature on the effects of frontal lobotomy on behavior provide a unique source of clinical observations as do the rigorous studies that attempted to correlate neuropathologic examination of the placement and size of the lesions with therapeutic outcomes as well as the correlation of adverse behavioral effects with frontal lobe function. These studies can now be reinterpreted in light of recent findings about PFC function. Freeman et al. (1942) pointed to the role of the highly distributed nature of cortico-cortical connections in

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preserving behavior. He noted that following lobotomy, the frontal cortex is isolated from the thalamus and no longer receives thalamic input except by indirect means. Nonetheless, with the passage of time many patients who had undergone lobotomies were capable of social and working adjustments, thus demonstrating that even with such a profound lesion, the brain was capable of reorganization due to the highly distributed nature of frontal lobe function.

Reminiscent of the single neurotransmitter theories of schizophrenia in the 1980s, the search has been on for the perfect target for DBS or lesions in OCD and depression. Recognizing the highly distributed nature of, for example, salience or value, most investigators have begun to focus on the effect of stimulation or lesions on networks as opposed to individual white matter tracts or nuclei. Rylander (1948) noted the resilience of the frontal cortex to injury as well as the important effects of lesions on volition and prefrontal control of autonomic function. Patients who underwent lobotomy using local anesthesia revealed no changes after the incisions in the frontal lobe were completed on either side, or after incisions to both upper halves or both lower halves of the two frontal lobes. When a third quadrant was sectioned, there was a notable falloff in the length of the replies and in the display of emotion connected to them as well as no evidence of spontaneous speech. When the fourth quadrant was sectioned, the patient became unresponsive except to urgent questions: his face was expressionless and his orientation was lost, and any preexisting anxiety was no longer present, with corresponding effects on pulse rate and blood pressure.

In a long-term twenty-year follow-up of motor deficits in leucotomized schizophrenic patients, Benson et al. (1981) found no signs of praxis, no elementary motor dysfunction, and no frontal release signs. Patients with schizophrenia with the largest prefrontal damage by structural imaging learned and performed a three-step sequence task better than schizophrenic subjects with less or no bifrontal damage and as well as controls. Most of the subjects with sizeable bifrontal damage could complete go/no-go and alternation of response tests as well as normal controls. Although standardized tests have not uncovered deficits, there is something to be learned from the careful clinical observations made by investigators working with frontal lobotomy patients. This is particularly true in the effects on social awareness of the effects of their actions on others as well as in goal-directed planning. As Robinson (1946) noted:

> They have become not so much social as gregarious, not more interested in the thoughts of others merely less in their own. They have no hint of ulterior motives. Past and future seem telescoped into the present. It is the capacity for deliberateness that they have missing.

A recent paper pointed to the role of the frontal pole in episodic future thinking as well as monitoring action outcomes in the past. Many of our patients are stuck either anticipating the future or regretting the past. Freeman and

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Watts (1950) pointed to the role of the frontal cortex in social interaction and anxiety, delayed discounting as well as its role in projecting the image of the self into the future:

> The frontal lobes are important for insight, for subtlety, for postponing pleasure and for projecting the individual self into the future. They are essential for the elaboration of a vivid picture of the future with all its deviations all its implications all its difficulties and dangers all its triumphs and disasters…the operated patient lives in a perpetual present, his interests in the outside world being much more vivid than his interests and reactions to them.

Rylander (1948) was among the first to report that a slight but fateful intellectual reduction that was difficult to demonstrate with ordinary intelligence tests, but that affected abstract reasoning and the ability to plan was present in long-term follow-up after surgery. Simple planning tasks like the Tower of London failed to show pre-post changes. More complex, real-life planning tasks have yet to be tested (Burgess 2000). Advances in ecological momentary assessment and digital phenotyping should make this possible. The success at completing habitual albeit complex goal-directed behaviors as opposed to the deficits in completing novel goal-directed behaviors suggests we need to look more closely at defining goal-directed versus habitual behavior than the simple dichotomy of model-based versus model-free behavior. It also argues for testing of the cognitive challenges that are found in daily life versus those in a laboratory setting.

Given the size and extent of the lesions of anterior cingulotomy, anterior capsulotomy, and limbic leucotomy, one cannot help but wonder why they do not result in more deficits in executive function and neuropsychological testing. Following cingulotomy, patients exhibited no change in error monitoring. These data are consistent with current neuropsychological studies that show either no deficits or improvements in tests of executive function following DBS or lesions.

Cingulotomy

In 1975, an independent group of psychologists at MIT, experts in neuropsychological function and brain trauma, were enlisted by the U.S. Congress to study cingulotomy patients as part of a white paper on psychosurgery (Valenstein et al. 1977). They followed 18 patients prospectively through a series of in-depth interviews of the patients and their families, as well as an intensive battery of 24 neuropsychological tests administered preoperatively, four months prior to surgery, as well as four months to ten years after surgery. Analysis of the life history data and interview material failed to disclose any major adverse effects from the intervention. There were no lasting effects of the cingulotomy per se on the 24 behavioral tasks. For other indicators of frontal lobe function, there

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was no change in verbal fluency, nonverbal fluency, Porteus maze, or delayed alteration tasks.

A series of follow-up papers reported on the long-term follow-up of 64 patients who had anterior cingulotomy for intractable OCD between 1989–2009, with a mean follow-up at 64 months (Baer et al. 1995; Dougherty et al. 2002; Jenike et al. 1991; Sheth et al. 2013). Thirty-six patients had a single pair of lesions and 28 had a triple pair of lesions located along the cingulate bundle, stretching from the genu of the corpus callosum posteriorly. No significant difference in outcome was observed between those who had single- and triple-paired lesions. Using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), 22 patients showed a greater than 35% drop in outcome, with an additional five patients showing a 25% drop. Jung (2006) reported on the one- and two-year follow-up of 17 patients who had anterior cingulotomy for OCD and found that eight patients had a greater than 35% drop in the Y-BOCS at follow-up. Lesions were placed slightly more anterior in the cingulate bundle than in the Massachusetts General Hospital cohort.

Cohen et al. (1994, 1999a, b, 2001) reported on 12 patients who had a single bilateral cingulate lesion, with follow-up at 3 and 12 months post-surgery. Immediately after cingulotomy, mutism, akinesis, blunted affect, lethargy, and apathy were common. These severe symptoms resolved quickly, however, and 3 months post-surgery most patients had returned to baseline with regard to language, visual, motor, memory and intellectual functioning. Despite this preservation of function, many families reported that subtle personality and functional changes remained, particularly continued behavioral passivity. Deficits of executive control and attention also persisted, with spontaneous response production most affected (i.e., spontaneous utterances, object construction, design fluency), a pattern of impairment frequently observed among patients with frontal lobe damage. Patients continued to show performance variability, slowed processing, and vulnerability to interference. Cingulotomy did not affect performance on tasks that placed primary demands on sensory selective attention (e.g., letter cancellation), attention span, and working memory (e.g., digit span). Learning and memory were also intact.

More recently, Banks et al. (2015) reported on 14 OCD patients who had cingulotomy as well as high-resolution structural and diffusion imaging scans. They identified a gray matter cluster just anterior to the lesion in the right anterior cingulate that correlated with poor response using voxel-based morphometry. Using diffusion connectivity measures, they also found increased right-sided connectivity between the lesion site and the caudate that predicted enhanced treatment response.

Intraoperative single or multiunit recordings as well as stimulation prior to making a lesion offers a unique opportunity to extend findings about electrophysiologic studies of the PFC to humans. While most of these studies have been conducted in the context of DBS trials, several electrophysiologic and behavioral studies have been published about cingulate function in humans in

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OCD patients undergoing cingulotomy. The small number of subjects tested limits the conclusions that can be drawn from these results. They are generally in agreement with electrophysiologic studies done in nonhuman primates as well as imaging studies in humans. These studies point to the anterior cingulate's key role in action initiation and monitoring and their relationship to salient events in humans.

Gentil et al. (2009) tested preoperative stimulation at the cingulate and subcaudate target sites and found that stimulation was accompanied by increased autonomic arousal as measured by skin conductance but not heart rate acceleration. Srinivasin et al. (2013) studied the immediate effects of anterior cingulate ablation on action initiation in six OCD patients. Three patients had preoperative and immediate postoperative simple reaction time tests, whereas another three patients completed a pre- and postoperative reward-based decision task. The frequency of false starts following a visual cue increased in the simple reaction task.

Sheth et al. (2012) demonstrated that the modulation of current dorsal ACC activity by previous activity produces a behavioral adaptation that accelerates reactions to cues of similar difficulty to previous ones and retards reactions to cues of different difficulty. This conflict adaptation was abolished after surgically targeted ablation of the dorsal ACC. Sheth et al. concluded that the dorsal ACC provides an updated prediction of expected cognitive demand to optimize future behavioral responses. In situations with stable cognitive demands, this signal promotes efficiency by hastening responses; however, in situations with changing demands, it engenders accuracy by delaying responses.

Sklar et al. (2017) tested nine OCD patients undergoing cingulotomy, identifying a population of rostral ACC neurons that respond differentially or in a graded manner to cognitively demanding high- and low-conflict Stroop tasks, including those with emotional valence (Davis et al. 2005). Their data suggested that rostral ACC neurons may be acting as salience detectors when faced with conflictual or emotional stimuli, consistent with neuroimaging results of rostral ACC responses to abrupt novel, task-relevant, or painful stimuli.

Anterior Capsulotomy

Mindus and Myerson reported on the outcome of two capsulotomy cohorts: one with severe intractable anxiety, the other with intractable OCD. Patients were either lesioned with thermocapsulotomy or with a noninvasive radiosurgical instrument called the gamma knife. Twenty-four patients with intractable anxiety were followed at 3, 6, 9, and 12 months after the procedure as well as a long-term follow-up of a mean of 8 years. Nyman and Mindus (1995) administered an extensive neuropsychological battery to 17 of these patients. Tests showed either an improvement or a stable pattern following capsulotomy, with the only exception being the Wisconsin Card Sorting Test, which showed an

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increased number of perseverative errors in five of the 17 patients (Nyman et al. 2001). In a separate study, Mindus et al. (1999) gave the Karolinska Scale of Personality to 24 patients at baseline and one year following thermocapsulotomy. At the one year follow-up, significant decreases (toward normality) were found in eight of the scales. Impulsiveness hostility and aggressiveness were within the normal range.

Zhang et al. (2017) administered the Iowa Gambling Task to 24 OCD patients preoperatively and 3–5 months following bilateral anterior capsulotomy and observed no significant differences in decision making between the preoperative and 3–5 month follow-up groups. At the long-term follow-up, one to three years afterward, decision-making abilities of patients had improved on par with healthy controls. Rück et al. (2003) conducted an independent long-term follow-up (mean of 13.5 years) of 26 bilateral thermocapsulotomy patients with severe anxiety who had no OCD. In their study, seven of 17 patients were rated as having significant adverse effects: the major symptoms were apathy and dysexecutive behavior. Using a simple scale that measured executive function apathy and disinhibition, one of the patients was rated as severe in all three measures, two moderate in executive function and apathy, and one severe in executive function and apathy. These patients also made more perseverative errors on the Wisconsin Card Sorting Test. Though many patients benefited from the procedure, Rück et al. concluded that a minority were left with significant long-term adverse cognitive effects.

In a separate long-term follow-up (mean of 10.9 years) of the OCD cohort, Rück et al. (2008) studied 25 patients with intractable OCD who had had anterior capsulotomy using either thermocapsulotomy or the gamma knife. Twelve out of 25 patients had sustained a greater than 35% drop in the Y-BOCS. Significantly, none of the patients was working at the time of the follow-up. Two patients suffered from severe executive dysfunction, apathy, and disinhibition while six had at least moderate impairment in one of these domains.

In an effort to minimize adverse effects, we began doing ventral gamma capsulotomies located 8–10 mms anterior to the posterior border of the anterior commissure in the coronal plane, and which targeted fibers connecting the orbital and medial frontal cortices with the thalamus and brainstem but left the dorsolateral cortical fibers that ran in the dorsal portion of the capsule intact (Rasmussen et al. 2018). At three year follow-up, we found that 31 of the 55 patients (56%) had an improvement in the primary efficacy measure, the Y-BOCS, that was greater than or equal to 35%. Standard neuropsychological testing found that patients' performance on each of these tests improved at follow-up. Four patients exhibited increased postoperative apathy that improved during the year following the procedure. In addition, three patients experienced the development of cysts around the target site at five years follow-up: two patients were asymptomatic, the third case was associated with radionecrosis. The majority of patients returned to work and/or school and at the 20-year follow-up were leading productive lives as physicians, judges, writers, engineers

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and other professions, all of which required intact executive function. Two additional recent reports of OCD patients with thermal capsulotomies from Eastern Europe have documented capsulotomies efficacy and safety with no impairment seen in frontal function (Csigó et al. 2010; Krámská et al. 2021).

Kim et al. (2018) reported on the use of high-intensity focused ultrasound to make ventral capsulotomy lesions in 11 OCD patients. At 12 months, six (54.5%) patients were responders and three (27.3%) patients were partial responders. At 24 months, six patients were responders, two (18.1%) were partial responders, and one had achieved full remission. The mean Memory Quotient score improved significantly across the24-month follow-up period: $F3, 6.5 = 236.3$, $p < 0.001$. In addition, no significant changes were observed in K-WAIS, COWAT, Stroop, or Digit Span scores. Davidson et al. (2020a) created a single 7 mm lesion using high-intensity focused ultrasound to study the cognitive effects of a single lesion in the anterior capsule in ten patients with refractory OCD or depression. They followed patients at 6 and 12 months, utilizing tests of executive function, memory, and processing speed. Patients endorsed fewer symptoms of apathy at 6 and 12 months and fewer overall frontal symptoms at 12 months. Kim et al. also used high-intensity focused ultrasound to make lesions placed in the same location as the gamma knife lesions in the Rasmussen et al. study: seven (58%) of the 12 patients showed a greater than 35% drop in the Y-BOCS, no adverse cognitive effects were noted at 6- and 12-month follow-up with improvement in the Memory Quotient Scale and no change in frontal measures.

Following the gamma knife lesion studies that targeted the ventral half of the anterior limb of the internal capsule (vALIC), DBS that targeted the same white matter tract was found to be beneficial in three of four cases of intractable OCD (Nuttin et al. 1999). Since then, DBS of the ALIC (Abelson et al. 2005) or neighboring targets (i.e., the ventral striatum or nucleus accumbens, a subregion of the ventral striatum) have shown response rates in the range of 40–70% (Goodman and Alterman 2012; Goodman et al. 2010; Greenberg et al. 2010). In 2010, the FDA approved a Humanitarian Device Exemption for vALIC DBS in intractable OCD. Recently, progress has been made in trying to define more precisely the anatomy of exactly where these fibers run in the capsule in macaques. High-resolution diffusion tensor imaging was combined with anterograde and retrograde tracers in the same animal and then used to extrapolate to high-resolution diffusion tensor imaging in humans (Haber et al. 2020; Jbabdi et al. 2013).

The optimal "target" for the DBS electrode or lesion has been a matter of debate. Some studies have focused on deep gray matter structures (e.g., the ventral striatum, nucleus accumbens, or bed nucleus of the stria terminalis) as critical mediators of response (Luyten et al. 2016). Others have suggested that these nuclei are useful guideposts, but that the white matter fibers connecting PFC and thalamus, which course through the vALIC superjacent to these nuclei, are critical as they convey the influence of neuromodulation to the wider

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symptomatic network (Figee et al. 2013). The fact that DBS targeting similar white matter pathways in disparate brain regions (e.g., ventral capsule/ventral striata, subthalamic nucleus) achieves comparable results provides support for the white matter hypothesis. Li et al. (2020a) analyzed data from four cohorts of patients (N = 50) who underwent DBS targeting at either the ALIC, nucleus accumbens, or subthalamic nucleus and identified a specific white fiber tract that was associated with optimal clinical outcome. This bundle connects frontal regions directly to the subthalamic nucleus and may represent a unified connectomic target for successful clinical response to DBS in OCD. However, as noted by Robbins et al. (2019), while DBS in the vALIC led to improved mood, DBS in the subthalamic nucleus site significantly improved cognitive flexibility.

Converging evidence suggests the ventral internal capsule white matter tracts connecting the rostral cingulate and ventrolateral PFC to thalamus and brainstem are the optimal target for clinical efficacy across multiple DBS targets for OCD. Recently, Cui et al. (2023) examined which prefrontal regions and underlying cognitive processes might be implicated in the effects of capsulotomy by using both task fMRI and neuropsychological tests to assess OCD-relevant cognitive mechanisms known to map across prefrontal regions connected to the tracts targeted in capsulotomy. Post-capsulotomy OCD subjects showed improved OCD symptoms, disability and quality of life, and no differences in cognitive task performance on a battery of executive, inhibition, memory, and learning tasks. Task fMRI revealed post-capsulotomy decreases in the nucleus accumbens during negative anticipation, as well as in the left rostral cingulate and left inferior frontal cortex during negative feedback. In spite of these lesions, there were remarkably few changes in cognitive function, particularly given the overall therapeutic impact on OC symptoms. These data suggest that we may be looking in the wrong place for deficits. The prefrontal network that underlies the social brain, that involves the discrimination of social context, language, and action, is one place to focus. There have been almost no studies of the effect of capsulotomy or DBS on complex context-related social decision making, real-world planning, or probabilistic approach avoidance paradigms. Some of the astute clinical observations made of behavioral changes following prefrontal lobotomy may provide additional clues.

The symptoms of OCD involve a complex interaction at the interface between emotion, cognition, and action. Freeman commented on that intersection, OCD, and the frontal lobe. (McLardy 1950):

> We have compared emotion to the fixing agent that prevents a photographic image from fading back into obscurity. Remove the emotion and the image gradually fades. In the obsessive state, prefrontal lobotomy reduces or abolishes the feeling tone attached to the obsessional ideas. The ideas continue and the compulsions often last a long time but the anxiety or tension associated with them is no longer present. One patient said it is as though the painful idea which used to be in the center of the circle of my attention has receded to the periphery.

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There is an interesting parallel between the subjective experiences of patients who underwent cingulotomy for pain and those who had a similar procedure for OCD. Both report that the awareness of pain or obsessional anxiety continued to be present but that it somehow did not bother them as much; it was easier to divert the obsessional thought or pain into the periphery of their attention. Interestingly, obsessional patients who respond to serotonin reuptake inhibitors also reported that they do not seem to feel as strong of an urge to complete the compulsion and that the obsessional cue does not carry the affective weight that it did prior to treatment. Similarly, patients treated with serotonin reuptake inhibitors or surgery often notice they are much less likely to cry or feel strong negative or positive emotions.

De Haan et al. (2015, 2017) have made a careful qualitative assessment of the long-term effects of vALIC DBS on the lived experience and personality of 18 patients with intractable OCD. Many of their observations are eerily reminiscent of earlier lesion studies: some patients reported less concern about the social consequences of self-motivated behaviors and even changes in interest in music and reading. For the most part, patients and their significant others describe these changes as beneficial and allowing them to grow into their "true selves." Continued qualitative observation of these patients, in combination with more defined task-based approaches to changes in frontal lobe function, are needed to understand how DBS and lesions effect both symptoms as well as an understanding of self.

NIH-funded studies are underway using next generation DBS devices that can record local field potentials as well as deliver neurostimulation (NCT03457675, NCT03244852). The feasibility of recording local field potentials in OCD patients chronically implanted with a DBS device that can both stimulate and sense was recently demonstrated (Sheth and Mayberg 2023). These types of studies may yield insights into the neural signatures of behavioral states associated with changes in OCD symptom severity. Implantation of stereotactic electrodes designed to find the network associated with compulsive urges or the anxiety accompanying obsessive thoughts are currently in progress. Such future studies will surely advance our understanding of frontal lobe function in humans as well as contribute to our growing understanding of the neural network underlying OCD, anxiety, and depression. The ability to record neural data from patients in their natural environment, time locked with behavior and physiology, offers a unique research opportunity to test hypotheses about the neurocircuitry of OCD, prefrontal brain networks, and the resulting remarkable resilience of the human brain to injury. This hodologic model of frontal function emphasizes the redundancy of cortical function and the importance of white matter cortical subcortical connections, and has been validated with electrical stimulation studies of patients undergoing frontal resections for low-grade gliomas (Duffau 2012).

In summary, advances in imaging, device engineering as well as increased understanding of the anatomy, electrophysiology, and behavior associated with

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PFC and its connections are likely to lead to innovative approaches to the treatment of neuropsychiatric conditions like OCD, depression, and anxiety disorders. The relative homogeneity of OCD as well as an emerging consensus about the neural network underlying its symptoms make it a logical place to focus our translational research efforts. Emerging evidence of rostral to caudal continuums, from the abstract to concrete in lateral PFC, cingulo-opercular, and OFC, have implications for our understanding of the abnormalities of goal-directed behavior seen in OCD. The relationship of prospective expected value to overvalued ideation in obsessions, schizophrenia, and delusional disorders merits further investigation. Expanding our understanding of how the prospective expected value associated with future consequences relates to action-outcome monitoring and getting compulsively stuck on motor rituals will be key to developing a working model of the distributed neural network that underlies OCD. These findings should lead to novel hypothesis-driven approaches to treatment. Continued collaborative interaction between basic scientists interested in disease and clinicians interested in basic science is needed to advance the field in this most promising area for future investigation.

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