Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery

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OBJECTIVE Advances in understanding the neurobiological basis of psychiatric disorders will improve the ability to refine neuromodulatory procedures for treatment-refractory patients. One of the core dysfunctions in obsessive-compulsive disorder (OCD) is a deficit in cognitive control, especially involving the dorsal anterior cingulate cortex (dACC). The authors' aim was to derive a neurobiological understanding of the successful treatment of refractory OCD with psychiatric neurosurgical procedures targeting the dACC.

METHODS First, the authors systematically conducted a review of the literature on the role of the dACC in OCD by using the search terms "obsessive compulsive disorder" and "anterior cingulate." The neuroscience literature on cognitive control mechanisms in the dACC was then combined with the literature on psychiatric neurosurgical procedures targeting the dACC for the treatment of refractory OCD.

RESULTS The authors reviewed 89 studies covering topics that included structural and functional neuroimaging and electrophysiology. The majority of resting-state functional neuroimaging studies demonstrated dACC hyperactivity in patients with OCD relative to that in controls, while task-based studies were more variable. Electrophysiological studies showed altered dACC-related biomarkers of cognitive control, such as error-related negativity in OCD patients. These studies were combined with the cognitive control neurophysiology literature, including the recently elaborated expected value of control theory of dACC function. The authors suggest that a central feature of OCD pathophysiology involves the generation of mis-specified cognitive control signals by the dACC, and they elaborate on this theory and provide suggestions for further study.

CONCLUSIONS Although abnormalities in brain structure and function in OCD are distributed across a wide network, the dACC plays a central role. The authors propose a theory of cognitive control dysfunction in OCD that attempts to explain the therapeutic efficacy of dACC neuromodulation. This theoretical framework should help to guide further research into targeted treatments of OCD and other disorders of cognitive control.

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KEY WORDS dorsal anterior cingulate cortex; cognitive control; obsessive-compulsive disorder; psychiatric neurosurgery; expected value of control; cingulotomy; functional neurosurgery

NEUROMODULATORY procedures are being recognized as increasingly valuable options for patients with treatment-refractory psychiatric disorders. As our understanding and theoretical modeling of the neurocircuitry underlying these disorders improve, we can expect the efficacy and specificity of these therapies to improve in parallel. The process of model refinement and treatment

targeting is often iterative, with advances in one realm driving progress in the other in reciprocal fashion. In this paper, we highlight an example of this process.

We focus on one of the most common psychiatric disorders treated with neuromodulatory approaches, obsessive-compulsive disorder (OCD), which is characterized by both obsessions (persistent, intrusive, often irrational

ABBREVIATIONS ALIC = anterior limb of internal capsule; dACC = dorsal anterior cingulate cortex; CS = conditioned stimulus; CSTC = cortico-striato-thalamo-cortical; DBS = deep brain stimulation; dlPFC = dorsolateral prefrontal cortex; EEG = electroencephalography; ERN = error-related negativity; ERP = exposure-response prevention; EVC = expected value of control; fMRI = functional MRI; IPFC = lateral prefrontal cortex; NIMH = National Institute of Mental Health; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; RCT = randomized controlled trial; RDoC = Research Domain Criteria; US = unconditioned stimulus; VC = ventral ALIC; vmPFC = ventro-mesial prefrontal cortex; VS = ventral striatum; YBOCS = Yale-Brown Obsessive-Compulsive Scale.

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and uncontrollable thoughts, images, or urges) and compulsions (repetitive, often ritualistic behaviors or thoughts performed to reduce anxiety or distress)¹⁰⁷ and has a relatively high lifetime prevalence of 2%–3%.¹³⁸ Almost two-thirds of patients report severe impairment at home and work, as well as in interpersonal relationships and social life.¹³⁸ Both pharmacotherapy (serotonin reuptake inhibitors and other drug classes) and cognitive-behavioral therapy (especially exposure-response prevention [ERP]) have proved efficacious in treating OCD, with approximately 50%–70% of patients demonstrating improvement after completing a treatment course.³⁹ However, patients are frequently left with residual symptoms, and maintaining treatment efficacy remains a significant problem.³⁹ In addition, 10%–15% of severely affected patients remain refractory to long-term standard therapies^{44,150} and therefore may be candidates for neurosurgical procedures, including deep brain stimulation (DBS)^{103,160} and stereotactic lesions.^{19,119}

Several brain regions have been implicated in the pathophysiology of OCD. These include cortical regions such as the orbitofrontal cortex (OFC), ventro-mesial prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC), as well as deep nuclei such as the dorsal and ventral striatum (VS), amygdala, pallidum, and thalamus (for a review^{106,120}). Here, we focus on the role of the dACC given the efficacy of stereotactic lesions in this region (dorsal anterior cingulotomy) in the treatment of refractory OCD.¹⁴⁷

The National Institute of Mental Health (NIMH) recently proposed a new strategy for classifying disorders of mental health based on neurobiological measures, termed the Research Domain Criteria (RDoC) project.⁶⁶ A phenomenological diagnosis such as OCD would thus be reclassified according to the dysfunction of fundamental constituent aspects of behavior and circuitry. Some of the key aspects of dysfunction in OCD include performance monitoring, response inhibition, and goal selection, all of which are classified under the RDoC construct of “Cognitive Control” (which is contained within the larger domain of “Cognitive Systems”). “Cognitive (or effortful) control” refers to the ability to focus on relevant environmental stimuli while ignoring irrelevant ones, inhibit responses influenced by distracting elements, select appropriate responses, monitor the outcome of those responses, and adjust behavior as needed in the face of changing situations. Several studies have identified deficits in cognitive control in patients with OCD.^{8,11,89,134}

The aim of the present study was to improve our understanding of the neurobiological basis of neurosurgical procedures targeting the dACC for OCD. We begin with a systematic review of studies involving any method of studying dACC function (imaging, electrophysiological, surgical) in adults with OCD. We discuss our current understanding of the role of the dACC in cognitive control, as established by the neuroscientific literature using neuroimaging and electrophysiology in animals and humans. We propose, based on this literature, that an important component of OCD pathology derives from aberrant cognitive control signals generated by the dACC. We then synthesize this proposal, which was derived from the cog-

nitive neuroscience literature, with the literature on psychiatric neurosurgical procedures targeting the dACC for the treatment of refractory OCD. These 2 fields have little mutual interest historically, but their intersection in dACC physiology and pathophysiology provides an opportunity for cross-fertilization. Finally, we discuss the implications of our theory and provide suggestions for future research to explore it further. In doing so, we hope to advance the development of increasingly rationally designed and effective targeted treatments for OCD and other psychiatric disorders.

Methods

To identify the role of the dACC in OCD, we systematically reviewed the English-language literature according to the PRISMA systematic review checklist¹⁰⁸ (Fig. 1). We used the PubMed search terms “obsessive compulsive disorder” and “anterior cingulate” for the period from January 1, 2000, to September 1, 2014, limiting the search to English-language journal articles involving humans. This query resulted in 224 publications. We included only those studies with adults who had a diagnosis of OCD, as the treatment of pediatric or subclinical forms of OCD are outside the scope of this review. We included all publications involving neuroimaging except for the MR spectroscopy studies, as the neurochemical profile of OCD is also outside the scope of this review. While we used reviews to identify issues related to OCD and non-dACC regions, these were not included in the list of publications for review. After excluding the above studies, 85 publications remained in our literature search. Most of these studies involved structural neuroimaging (20), functional neuroimaging (52), or both (3), with or without cognitive testing.

Results

Systematic Literature Review

To examine the scientific evidence underlying our proposed theory, we conducted an evidence-based review of the literature, which ultimately included 85 studies examining the role of the dACC in OCD according to the criteria discussed above (Fig. 1). The bulk of this evidence (72 of 85 studies) consisted of neuroimaging studies, particularly functional neuroimaging (functional MRI [fMRI], PET, SPECT), which provides support for the hypothesis that dACC dysfunction is important in OCD pathophysiology. First, 23 resting-state functional neuroimaging studies were identified in our analysis. These studies have generally demonstrated that the dACC is hyperactive (13 of 23 studies) at rest in OCD,^{6,22,24,27,49,62,63,76,85,87,111,140,142} although some (5 of 23 studies) have shown decreased activity^{9,20,126,128,151} or no difference^{78,84,127,130} (4 of 23 studies) compared with controls.

Task-based studies have shown variable results, depending on the type of task, study design, differences in image analysis, and medication status of the OCD patients, among other factors. In general, however, task-based studies involving dACC function have focused on conflict, response inhibition, symptom provocation, and task or set switching. Twelve studies examining the role of con-

FIG. 1. PRISMA flow diagram of literature review methods; 224 abstracts were obtained by searching the PubMed terms "obsessive compulsive disorder" and "anterior cingulate" over a 14-year period. After excluding 139 studies, 85 were included for review, the majority of which (72) were neuroimaging studies.

flict and/or response inhibition were identified, with some studies demonstrating dACC hyperactivity during high-conflict tasks or response inhibition^{28,41,98,143,158} while others have shown the opposite^{30,76,114,115,136} or no change at all.^{99,156} On the other hand, electrophysiological measures of conflict and error monitoring in OCD patients have generally found an enhancement in error-related negativity (ERN) or event-related potential activity (thought to reflect dACC activity) during task performance.^{2,29,45,82,118} The evidence underlying the role of dACC in symptom provocation and task or set switching is equivocal, with too few studies to make concrete conclusions.^{1,26,51,57,112,132,164}

Finally, the majority of structural neuroimaging studies have shown reduced cortical thickness or gray matter volume (10 of 20 studies) in the dACC^{43,59,62,83,100,149,155,157,162} or reduced white matter volumes (3 of 20 studies) in the cingulum bundle,^{52,90,153} with no studies demonstrating an increase in gray or white matter volume and a few studies showing no change^{7,23,77,133,135} or hemispheric variability.²¹

Thus, these studies represent the evidence base underlying our proposal and can help to inform our hypothesis linking dACC dysfunction and the effectiveness of psychiatric neurosurgical procedures targeting the dACC. Because our proposed theory is centered on dACC function and represents a departure from traditional models underlying OCD pathophysiology, any discussion of

this proposal should begin with the current models of OCD dysfunction to understand how our hypothesis has emerged from these models.

Current Model: CSTC Architecture

The prevailing theory regarding the neurobiology of OCD consists of the cortico-striato-thalamo-cortical (CSTC) loop model.³ In this model, regions of cortex, basal ganglia, and thalamus that subserve related functions are anatomically and functionally interconnected (Fig. 2A). While the specific regions differ, each loop contains 2 pathways—a direct pathway that is net excitatory and an indirect pathway that is net inhibitory. Specifically, 2 distinct loops have been proposed to be dysregulated in OCD.^{141,159} First, a loop involving the OFC and ventromedial caudate has been shown to be hyperactive in OCD patients.^{13,17,130,152} Originally, an imbalance between the direct and indirect pathways resulting in OFC loop hyperactivity was proposed as the main factor underlying pathology seen in OCD.¹⁴¹ This circuit is thought to be involved in the motor response to emotionally salient stimuli. This theory postulates that excess activity in the circuit is responsible for the repetitive, stereotyped behaviors seen in OCD, as excess tone in this pathway lowers the threshold to permit ritualistic, compulsive behaviors.¹⁴¹

Over time, evidence from neuroimaging studies indicated that a second loop consisting of the dorsolateral

FIG. 2. Models of the neurobiology of OCD. **A:** The traditional CSTC model. Regions of the dACC, OFC, and dorsolateral pre-frontal cortex (dlPFC) are connected with the caudate and VS, as well as the ventral anterior and mediodorsal thalamus. **B:** The dACC is ideally situated at the interface between sensory input streams, cognitive and affective processing regions, and structures regulating behavioral output. Copyright Sameer A. Sheth. Published with permission. Figure is available in color online only.

prefrontal cortex (dlPFC) and dorsolateral caudate^{86,141} is hypoactive in patients with OCD. This hypoactivity is thought to underlie the cognitive inflexibility and deficits in executive function seen on neuropsychological assessments in OCD patients. Thus, the prevailing hypothesis asserts that an imbalance between these 2 circuits is the underlying basis for OCD, as a hyperactive OFC generates obsessions and their associated ritualistic compulsions, while a hypoactive executive network prevents the individual from being able to switch to a new behavior.^{141,159}

While the CSTC loop hypothesis has dominated the OCD literature over the last decade, recent efforts have been made to refine it.¹⁰⁶ Anatomical studies have demonstrated that although there is a functional and topographic organization to fronto-striatal projections, the striatal anatomy is actually much more complex and contains more integration between regions than previously thought. Indeed, projections from the vmPFC, OFC, and dACC overlap and converge throughout adjacent regions of the

striatum,⁵³ a finding confirmed in human diffusion tensor imaging studies.³⁸ In fact, striatal GABAergic interneurons receiving convergent input are more responsive to cortical input than the typical striatal medium spiny neuron,^{53,96} underscoring the importance of multidimensional integration. In addition, studies examining reward pathways have also demonstrated the sequential activation of adjacent striatal regions beginning with the VS (including the nucleus accumbens), a region known to have direct projections from reward-related dopamine neurons, and ending with the dorsal caudate, a region with fewer connections to reward circuitry.¹⁴ This evidence has led to the modern proposition that information is carried in “spirals,” rather than isolated “loops,” such that each adjacent region of the striatum integrates information from cortical, nigral, and limbic inputs and then sends that information to adjacent striatal regions and the thalamus.^{53,106}

As the nature of this integrative process has become apparent over time, more attention has been paid to po-

tential “hubs” in the neurocircuitry thought to underlie OCD, with the idea that functional modulation of these hubs could lead to symptom improvement. In particular, the role of the dACC has come into focus, as its connectivity highlights its potential as a hub of cognitive control (Fig. 2B). Originally identified within a separate loop including the VS, ventral pallidum, and mediodorsal thalamus,³ the dACC has also been considered a component of other loops, including the vmPFC affective loop.¹⁰⁶ Regardless of the loop nomenclature, the dACC has been shown to be hyperactive in a number of fMRI,^{1,17,27,50,98,164} PET,^{102,123,130,152} and SPECT studies⁹⁴ of OCD. However, other studies have demonstrated downregulated or unchanged dACC activity.^{52,56,67,78,124}

The dACC has extensive reciprocal cortical connections with lateral prefrontal cortical (IPFC) regions, particularly the dlPFC, which are thought to underlie cognitive flexibility and executive function. Lateral PFC efferents mainly project onto cingulate motor regions, which are somatotopically organized and project to primary, premotor, and supplementary motor cortices.^{121,122} This organization places the dACC in an ideal position to both receive incoming sensory information and act on that information via downstream motor regulators.

Beyond CSTC: Fear Extinction

One of the initial findings leading to the CSTC hypothesis was the fact that symptom provocation did not activate subcortical and limbic structures in OCD patients as strongly as in patients with other types of anxiety disorders.^{129,130} Over time, however, we have increasingly recognized that abnormalities in fear learning, conditioning, and expression may contribute to the symptoms seen in OCD. Pavlovian fear conditioning pairs a neutral stimulus such as a sound (conditioned stimulus [CS]) with an inherently aversive stimulus such as a mild electric shock (unconditioned stimulus [US]). As the CS is repeatedly paired with the US over time, the subject associates the CS with fear and will begin to demonstrate the fear response to the CS itself. When the CS/US association is weakened (for example, by providing the sound without the shock), the fear response to the CS decreases as well, a term called “fear extinction.” Although formulated over a century ago, this model is still relevant today.

Fear extinction may be deficient in patients with OCD (for review¹⁰⁶), as they demonstrate electrophysiological signs of reduced fear extinction,¹¹⁶ with increased activation of the vmPFC and decreased activation of the dACC on fMRI when undergoing fear conditioning tasks.¹⁰⁴ Fear extinction is an important part of ERP, an effective form of cognitive-behavioral therapy for OCD in which patients are gradually exposed to their specific obsessions and then trained to prevent ritualistic behaviors.^{31,60} Structural MRI studies of the dACC have shown that its cortical thickness correlates with measures of fear learning, such as galvanic skin response,¹⁰⁵ and have actually shown cortical thickness reductions in the dACC in patients who respond to ERP.⁴³

Thus, while it is likely that vmPFC, amygdala, and other limbic structures are the main contributors to the deficits in fear extinction and aversive learning seen in OCD

patients, the subcortical and limbic connections of the dACC place this structure within this circuit as well (Fig. 2B). For example, the dACC receives direct input from the spinothalamic tract, which relays sensory information on pain from the periphery.¹⁴⁴ In addition, the substantia nigra and VS, mainly implicated in reward-related learning but also activated by a wide range of aversive stimuli, have projections to and from the dACC, respectively.^{18,167} Finally, the lateral basal nucleus of the amygdala, implicated in the avoidance learning of aversive stimuli, projects to both ventral and dorsal ACC.^{12,109}

Interestingly, an example of the convergence of pain, negative affect, motor activity, and cognition in the dACC lies in the control of facial expressions. The monkey homolog of dACC projects directly to neurons in the facial nucleus that control muscles of the upper face,¹¹⁰ and stimulation can produce facial expressions associated with the primate flight or fight response.¹⁴⁴ In humans, these muscles produce characteristic facial expressions demonstrating anger, fear, and pain, some of which (for example, brow furrowing) are also observed during significant cognitive effort.¹⁴⁴

Control Signal Theory of dACC Function

We now discuss dACC function from the cognitive neuroscience viewpoint. This literature has implicated the dACC in several cognitive processes including performance monitoring, action selection, and goal-directed behavior.⁶¹ The dACC appears to be specifically activated in tasks that require significant cognitive effort, as well as negative feedback, pain, and other aversive cues (Fig. 3).¹⁴⁴ As neuroscientists continue to appreciate the connectivity of the dACC and its role in these neurocognitive processes, theories attempting to integrate these roles have begun to emerge.^{61,144,145}

One common point of agreement across these models is the role of the dACC in cognitive control. As discussed above, “cognitive control” refers to the ability to attend to decision-relevant information while ignoring irrelevant information; inhibiting rapid, prepotent, “automatic” responses in favor of slower but better reasoned responses; monitoring outcomes of these responses; and adjusting behavior according to shifting goals or situations. Performing the Stroop test is a classic example of the requirement for cognitive control. When instructed to name the color of the ink in which a word is written, participant response times are longer when the identity of the word and the color of the ink are incongruent (for example, the word “red” written in green ink). In contrast, when participants are given no instruction or are instructed to read the word, response times are significantly faster, indicating that the processes involved in reading the word are automatic, whereas ignoring the word identity and attending to ink color requires suppression of a prepotent response and the engagement of cognitive control. Real-world examples include rapid decision making in the face of a threat (deciding to hit the brake or accelerator when approaching an intersection with a yellow traffic light) or motor adjustments in the face of changing environmental stimuli (adjusting one’s swing to hit an off-speed pitch after 2 fastballs). Behavioral economics applications of

FIG. 3. The dACC is activated in studies involving negative affect, cognitive control, and pain. A coordinate-based meta-analysis of nearly 200 functional neuroimaging studies in humans demonstrates the dACC as the overlapping region activated in all 3 types of studies. ALE = activation likelihood estimate. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience, Shackman AJ et al: *Nat Rev Neurosci* 12:154–167, copyright 2011. <http://www.nature.com>. Figure is available in color online only.

this concept are keenly articulated in Nobel Prize-winning economist Daniel Kahneman's book *Thinking, Fast and Slow*.⁷⁵

A recently elaborated theory of dACC function has attempted to encapsulate the various roles previously attributed to the dACC in cognitive control. According to the expected value of control (EVC) theory, the dACC estimates a quantity known as the EVC, the sum of the anticipated positive and negative outcomes of a “controlled” decision.¹⁴⁵ Benefits of exerting control to correctly execute the task in light of long-term goals (for example, reward of correct performance) are weighed against the cost (effort, time, expense) of exerting control. This information is conveyed in the form of a control signal to downstream motor/behavioral effectors. In the Stroop example, as incoming information (for example, visual processing of ink color

and language processing of word identity) is monitored for relevance to the specified rule (attend to the color, not the identity), the possible outcomes (size of reward if answered correctly vs size of punishment if answered incorrectly) are weighed against the costs associated with the choice to exert cognitive control (time and effort), and the appropriate amount of control is exerted. In the traffic light example, the benefit of exerting control (avoiding a collision or ticket) is weighed against its cost (effort, the need to pause an ongoing conversation), and the dACC control signal allows the appropriate allocation of resources to make the optimal decision.

The generator of this control signal requires access to information regarding long-term goals and incoming contextual information, as well as efferent connections to control allocation centers that can influence behavior. The dACC is an excellent candidate region for estimating EVC given the range of afferent inputs (cortical, limbic, nigral, spinothalamic) and efferent projections (lateral prefrontal, motor) detailed above. The control signal is thought to be passed on to “regulatory centers” (probably the dlPFC) that use the signal to exert top-down control over downstream effectors (motor, cognitive, emotional) of the chosen behavioral plan. A number of human and monkey electrophysiological and imaging studies support the EVC conceptualization of dACC function.^{4,5,16,25,34,36,55,69,81,101,139,146,165,168}

Critical to the EVC theory, and to our argument below, are the 2 defining components of this signal: identity and intensity. The control signal must specify both which control-requiring task (of potentially several) to pursue and how intently to pursue it. Details regarding this conceptualization can be found in the original paper,¹⁴⁵ but this requirement does accord with intuition. The identity of the chosen task must be specified to allow regulatory regions to mobilize the appropriate machinery to accomplish it, and the intensity of engagement will certainly impact both the cost of control and the likelihood of success. An error in identity specification will lead to the pursuit of tasks misaligned with long-term goals. An error in intensity specification will lead to too little control (and subsequent failure in the task) or too much control (and inappropriate persistence in a task that should have been abandoned).

In the following proposal, we apply EVC concepts to suggest how dACC dysfunction can contribute to the symptomatology observed in OCD.

Proposal: the dACC Aberrant Control Signal Hypothesis

Given the evidence presented above, we advance the hypothesis that dACC dysfunction and resultant aberrant cognitive control signal specification contributes to the pathophysiology underlying OCD symptoms and behaviors (Fig. 4). Specifically, we propose that the observed behaviors arise from errors in specification of the identity and/or intensity of cognitive control signals.

The mis-specification of control signal identity drives the pursuit of tasks that do not accord with long-term goals. The performance of such tasks would produce negative feedback, including delays in attaining the overall goal, omission of expected rewards, discomfort or pain, errors, or other negatively valenced outcomes. In the healthy scenario, these indicators of suboptimal behavior would

FIG. 4. Proposed control signal theory of dACC dysfunction in OCD. **A:** The subject is exposed to an aversive stimulus, for example, a contaminant in the environment. Regions such as the amygdala and VS produce feelings of displeasure and aversion, and cortical areas including the OFC, vmPFC, and dlPFC coordinate an avoidance response based on established goals. Connectivity to the dACC results in its activation, as it detects the anxiety and negative affect of the current state (contamination). It, therefore, generates an appropriate control signal to downstream effector regions, including the dlPFC, pre-supplementary motor area (SMA), and SMA, which in turn promote behaviors to remove the threat (washing). **B:** In a healthy subject, removing the threat leads to baseline restoration of dACC activity, extinguishing of the dACC control signal, and cessation of the behavior. **C:** In a patient with OCD, however, the dACC remains pathologically active despite removal of the threat, potentially because of persistent activity in other regions, such as the OFC or striatum (not shown). Unable to silence the alarm, the dACC continues to generate a mis-specified control signal (see *Proposal: the dACC Aberrant Control Signal Hypothesis* for mis-specification scenarios). Persistence of the control signal results in a continuation of the now maladaptive behaviors. The emotional distress related to the persistence of control signals and the continued behaviors fruitlessly attempting to assuage these feelings may represent an important neurobiological component of obsessions and compulsions, respectively. Copyright Sameer A. Sheth. Published with permission. Figure is available in color online only.

trigger the dACC to adjust its control signal and identify a different behavior. In the dysfunctional scenario, these indicators do not readily extinguish the previous behavior to produce an adaptive change in strategy.

Neurocognitive studies provide several examples of this phenomenon in patients with OCD. First, OCD patients typically describe their symptoms as difficulty in stopping their behavior.^{64,131} Indeed, behavioral studies have shown

that OCD patients tend to have few, extended episodes of compulsive behavior rather than frequent episodes of short duration.⁶⁴ For example, patients with hand-washing compulsions demonstrate extended episodes of hand washing even if their initial sensitivity to the threat of germs is similar to that in control subjects.⁵⁸ In addition, individuals with OCD change their behavior more slowly after making a mistake while completing a task,¹⁶¹ indicating difficulty

reassigning the identity of a new behavior despite evidence that the current behavior is maladaptive. This cognitive inflexibility has been associated with altered fMRI activation of the dACC and other cortical areas.^{51,161}

Mis-specification of control signal intensity (hyperintense signal in this example) places inappropriately elevated importance on a particular (internal or external) stimulus despite evidence that the stimulus does not warrant such attention. A hyperintense dACC control signal would allocate substantial cognitive resources toward generating behaviors to address the perceived threat, repulsion, or conflict represented by the stimulus. In the healthy scenario, realization of the benign nature of the stimulus would rapidly drive down the intensity of the control signal and extinguish those behaviors. In the dysfunctional scenario, maneuvers to address the perceived offending stimulus are unable to reduce the intensity of the control signal. Thus the anxiety remains, and the futile, unnecessary, or unprofitable behaviors persist. This dysfunction in control signal intensity can therefore manifest as threat overestimation. Moreover, the inability to eliminate the threat despite the “need” to do so can produce an over-inflated sense of personal responsibility. Both threat overestimation and an exaggerated sense of responsibility are often observed in OCD.^{71,113,154}

Together, these mis-specified control signals produce a phenotype in which there is a persistent anxiety-producing sense of threat or unease generated by otherwise innocuous stimuli that cannot be extinguished. Repetitive behaviors to reduce this distress signal are ineffective, but the individual persists with these maladaptive behaviors, unable to abandon them and switch to more useful strategies (Fig. 4). The contamination and cleansing dimension of OCD serves as an example. Overestimating the threat of germs and exaggerating the importance of the act of cleansing lead to contamination obsessions and washing compulsions. Unable to quench the feeling of threat from the contaminant, the individual continues to perform the exaggerated cleansing rituals.

As another example, the persistence of a signal indicating that a task is still “unfinished” can produce the obsession of incompleteness, and the inability to switch to a different behavior produces the associated perseverative checking compulsions. Whereas a fleeting thought about whether one has actually locked the door may induce momentary concern in an unaffected individual, mis-specified control signals in OCD can allow that concern to persist despite repeated attempts to extinguish it. Similarly, obsessions of disorder and compulsions for ordering and symmetry can be thought of as control signals for orderliness that are never assuaged and cannot be changed.

This framework may also be useful for understanding the impaired fear extinction seen in OCD patients.¹⁰⁴ In the classical conditioning example described above, fear extinction requires realizing that a CS (for example, sound) is no longer associated with an US (for example, electric shock). In the case of a dysfunctional dACC mis-specifying control signals, the CS’s label of “threat” is carried for longer than usual, and the individual has a difficult time abandoning the fear associated with the perceived threat. The dACC is activated during threat assessment,⁴⁰ and

threat overestimation has been linked with the generalization of fear in OCD patients.⁷⁴ Thus dACC dysfunction may also contribute to the impaired fear extinction seen in OCD patients.

Of course while a dysfunctional dACC is central to our proposed model, it is not the sole component of the affected network. As discussed above, the dACC is part of a cognitive/affective network including the OFC, vmPFC, dlPFC, and associated subcortical and limbic structures. All of these structures perform in a coordinated fashion; thus there may be nuances to the produced behaviors in OCD resulting from various contributions of other network components. In fact, the degree and nature of their involvement may influence the dimension of symptoms (contamination/cleaning, symmetry/ordering, forbidden thoughts/checking, and so forth) in these patients. Nonetheless, we propose that the dACC aberrant control signal hypothesis is a useful prism through which to conceptualize OCD symptoms and behaviors.

Therapeutic Effect of dACC Lesions in OCD

If dACC dysfunction is a key factor underlying the pathology seen in OCD, it is reasonable to pursue the hypothesis that modulating dACC function will improve the symptoms of OCD. The effect of dACC modulation for the treatment of OCD was noticed as early as the 1950s when a group in Oxford performed bilateral ACC resections in patients with a variety of psychiatric diagnoses on the basis of monkey studies and postmortem examination of patients who had undergone frontal lobotomy.¹⁶⁶ While cingulectomy had minimal effect on patients with schizophrenia, remarkable improvement was noted in patients with primarily obsessive or anxiety-related symptoms.¹⁶⁶

Stereotactic cingulotomy was developed by Ballantine in the 1960s, partly inspired by the English experience.¹⁰ Early results in the MRI era demonstrated a significant response in at least 25%–30% of patients.⁶⁸ Updated results using the Yale-Brown Obsessive-Compulsive Scale (YBOCS) demonstrated at least partial response ($\geq 25\%$ improvement on YBOCS) in 45% (20) of 44 patients treated with bilateral cingulotomy.³⁷ More modern surgical series have demonstrated similar results, although the preponderance of clinical evidence remains Class II or III (Table 1).^{32,33,35,46,47,65,70,72,73,88,91,95,117,137,147,172,173} One study with a 5-year mean follow-up in 64 patients recently showed that 69% obtained at least a partial response, and 47% attained a full response ($\geq 35\%$ YBOCS improvement).¹⁴⁷ Another group demonstrated similar results, with a 47% full response rate (using similar criteria) to bilateral cingulotomy in 17 patients with a 2-year follow-up.⁷³ Given the fact that years and often decades of conventional pharmacological and cognitive-behavioral therapy had failed in all of these patients, this degree of improvement is substantial.

Neuromodulation of other nodes in the network is also effective in treating OCD. Lesions in the anterior limb of the internal capsule (ALIC), using either radiofrequency ablation or stereotactic radiosurgery, have shown efficacy for decades.¹¹⁹ Recently, high-frequency MR-guided ultrasonography has been developed as a noninvasive technique to create lesions and has been effectively used to create capsulotomies in patients with pharmacoresistant

TABLE 1. Surgical studies on the treatment of OCD in the modern era

Authors & Year	Study Type	No. of Patients	Target	Type of Surgery	Ablative Technique	Initial→Final YBOCS Score (mean FU period)	Class of Evidence	Outcome
Ablation therapy								
Oliver et al., 2003	Open label	15	ALIC	Bilat capsulotomy	RF	29.7→18.2 (2 yrs)	III	53%/29%/17% patients (33%/50%/66% reduction in YBOCS score)
Jung et al., 2006	Open label	17	dACC	Bilat cingulotomy	RF	35.0→18.2 (2 yrs)	III	47% full responders
Liu et al., 2008	Open label	35	ALIC	Bilat capsulotomy	RF	21.2→4.4 (3 yrs)	III	57%/29%/14% patients (symptom free, significant improvement, no improvement)
Rück et al., 2008	Open label	25	ALIC	Unilat & bilat capsulotomy	RF/GKRS	34→18.2 (10.9 yrs)	III	48% full responders
Csigo et al., 2010	Case control	10 (5 surgical, 5 continued medical therapy)	ALIC	Bilat capsulotomy	RF	Surgical: 38.2→18.2, medical therapy: 36.2→29.4 (2 yrs)	II	Mean YBOCS: 53% vs 19% decrease at 2 yrs
D'Astous et al., 2013	Open label	19	ALIC	Bilat capsulotomy	Mechanical	34.9→23 (7 yrs)	III	37%/10% patients (full/partial responders)
Sheth et al., 2013	Open label	64	dACC	Bilat cingulotomy	RF	31.3→19.6 (5.3 yrs)	III	47%/22% patients (full/partial responders)
Zhang et al., 2013	Open label	7	dACC/ALIC	Bilat capsulotomy & cingulotomy	RF	32.9→20.6 (2 yrs)	III	5/7 full responders (1 yr FU)
Lopes et al., 2014	RCT	16 (8 active, 8 sham)	ALIC	Bilat capsulotomy	GKRS	Active: 33.3→20.9 vs sham: 34.8→31.9 (1 yr)	I	3/8 full responders (1 yr blinded); 7/12 full responders (54-mo open label extension)*
Zhan et al., 2014	Open label	53	ALIC	Bilat capsulotomy	RF	24.7→6.5 (5 yrs)	III	38%/25%/15%/23% patients (full responder/significantly improved/improved/no improvement)
Jung et al., 2015	Open label	6	ALIC	Bilat capsulotomy	FUS	NA	NA	NA
Modulation therapy								
Mallet et al., 2008	Double-blind sham crossover	8	STN	DBS		30→19 (on)→30 (off); 3 mos blinded stimulation	I	32% reduction in YBOCS score, active vs sham; 6/8 responders at 3 mos (responder = 25% reduction in YBOCS score)
Denys et al., 2010	Open label + double-blind crossover	16	Nacc	DBS		33.7→15.7 (8 mos); 8.3-pt reduction, active vs sham, in double-blind crossover portion	II	8.3-pt reduction, active vs sham; 56% full responders (8 mos FU)
Huff et al., 2010	Double-blind sham controlled	10	Nacc	DBS		32.2→25.4 (1 yr); no diff btwn active & sham	II	No diff btwn active & sham; YBOCS: 31 vs 28 (active/sham); 1/10 full responder; 5/10 partial responders (1 yr FU)

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TABLE 1. Surgical studies on the treatment of OCD in the modern era

Authors & Year	Study Type	No. of Patients	Target	Type of Surgery	Ablative Technique	Initial→Final YBOCS Score (mean FU period)	Class of Evidence	Outcome
<i>Modulation therapy (continued)</i>								
Greenberg et al., 2006	Staggered onset	26	VC/VS	DBS		34.0→20.9 (3 yrs)	III	62% full responders, 27% partial responders
Goodman et al., 2010	Staggered onset	6	VC/VS	DBS		33.7→18 (1 yr)	III	4/6 full responders
Jimenez et al., 2013	Open label	6	ITP	DBS		35.8→17.5 (1 yr) median	III	6/6 full responders
Luyten et al., 2015	Double-blind sham controlled cross-over RCT	24	ALIC/ BST	DBS		35→20 (on)→32 (off); 9 mos blinded stimulation	I	37% YBOCS decrease (9 mos blinded); 45% decrease (72 mos open)

Active = active intervention; diff = difference; FU = follow-up; FUS = focused ultrasound; full responder = > 35% reduction in YBOCS score unless otherwise noted; GKRS = Gamma Knife radiosurgery; ITP = inferior thalamic peduncle; NA = not applicable; Nacc = nucleus accumbens; partial responder = > 25% and < 35% reduction in YBOCS score unless otherwise noted; pt = point; RF = radiofrequency; STN = subthalamic nucleus.
 * These authors recently published an editorial amending their results, noting that in fact 2/8, rather than 3/8, patients receiving active treatment during the 12-month blinded period were full responders (Lopes et al., 2015).¹⁷⁴

OCD.⁷² The first double-blind randomized controlled trial (RCT) of capsulotomy lesions showed promising results, further supporting the role of therapies in this target.^{91,174}

Furthermore, DBS of several involved nodes has proven to be effective in severe, refractory OCD.⁵⁴ A number of evidence Class II and III studies in the ventral ALIC/VS (VC/VS target),^{46–48} the nucleus accumbens (a subregion of the VS),^{35,65} and the inferior thalamic peduncle⁷⁰ have shown promising results. A Class I, double-blind, cross-over RCT of DBS in the subthalamic nucleus has also demonstrated benefit.⁹⁵ Most recently, a double-blind, randomized, crossover study of DBS targeting the junction of the ALIC and bed nucleus of the stria terminalis has provided further Class I evidence for the benefit of DBS.⁹³ Affective/limbic cortical regions including the dACC, OFC, and vmPFC are connected to the VS and other regions of the basal ganglia and thalamus via the ALIC. Because modulation of a node, with either targeted lesions or electrical stimulation, is not merely a local event but propagates through the network, it is not surprising that several targets are effective. Future investigation will reveal whether certain forms or targets of modulation are more effective for certain patients or symptom dimensions than others.

Applicability to Other Diseases

Our proposed theory also explains the effectiveness of dACC neuromodulation for other disorders such as chronic neuropathic pain and depression. As previously discussed, the dACC appears to be significantly involved in fear expression, negative affect, and pain. A recent meta-analysis of nearly 200 fMRI studies showed that pain, negative affect, and cognitive control all activate an overlapping region of the dACC (Fig. 3), arguing that the dACC acts as a hub that processes negative emotional and reinforcing information and then uses that information to direct motivated behavior.¹⁴⁴ It is therefore likely that disease processes that include negative affect, such as depression or chronic neuropathic pain, can be treated with dACC modulation. While we have focused on cognitive control in this review because of its relationship to OCD, cingulotomy has indeed been effective in patients with chronic, intractable neuropathic pain.^{42,80,125,163,169–171} Recently, the first case series of dACC DBS for chronic pain was reported with similar results.¹⁵ In addition, cingulotomy,¹⁴⁸ subgenual cingulate DBS,^{79,92} and VC/VS DBS⁹⁷ have all been shown to be effective in treating refractory depression.

Conclusions and Predictions

In this proposal we sought to establish a neurobiological basis for the efficacy of neuromodulatory procedures targeting the dACC for the treatment of refractory OCD. In doing so, we synthesized the neuroscientific literature on cognitive control and the psychiatric neurosurgical literature on targeted treatments for OCD. We propose that the mis-specification of cognitive control signals by the dACC is a key element in generating the obsessive thoughts and compulsive behaviors in OCD. We have focused on deficiencies in cognitive control as a central feature of this symptomatology. This emphasis is supported by our litera-

ture review and concords with the NIMH RDoC classification matrix. It should be noted that while the diagnosis of OCD probably has components within other RDoC domains, potentially including “Negative Valence Systems” (constructs of “Fear,” “Anxiety”) and “Positive Valence Systems” (construct of “Approach Motivation”), the largest projection probably lies in the Cognitive Control construct.

Our proposal makes predictions that can be readily tested. There are a number of ways to measure cognitive control, including behavioral tasks (Stroop, Simon, Eriksen flanker, multisource interference, go/no-go, stop signal, set switching, and so forth), functional imaging (task-based fMRI), and electrophysiology (temporal and spectral domain electroencephalography [EEG]). Whereas a number of studies have investigated differences in these measures between patients with OCD and healthy controls, very few have done so longitudinally in patients before and after targeted treatments. Our theory would predict that measures of cognitive control would change in parallel with therapeutic efficacy. Moreover, we would predict that imaging or electrophysiological measures of dACC function would return toward normal (for example, normalizing fMRI activation, normalizing ERN amplitude and spectral measures on EEG), also in parallel with clinical response. This pattern would be particularly interesting to study in the context of procedures that do not target the dACC. For example, how would these measures change following capsulotomy or DBS in the VC/VS or subthalamic nucleus? It is unlikely that benefit following cingulotomy would, from a mechanistic standpoint, differ substantially from benefit following other targeted procedures. We would predict that downstream effects of those procedures would still result in normalization of dACC function in parallel with clinical response.

Future work in this field will, we hope, further dissect the role of the dACC and other cortical and subcortical regions in the pathogenesis of OCD and other disorders of cognitive control. As we improve our understanding of the normal physiology and function of these networks, we will be better equipped to successfully treat disorders arising from their dysfunction.

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Disclosures

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Author Contributions

Conception and design: both authors. Acquisition of data: McGovern. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Sheth. Administrative/technical/material support: Sheth. Study supervision: Sheth.

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