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Obsessive Compulsive Disorder: Beyond Segregated Cortico-striatal Pathways

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Abstract

Obsessive-compulsive disorder (OCD) affects ~2-3% of the population and is characterized by recurrent intrusive thoughts (obsessions) and repetitive behaviors or mental acts (compulsions), typically performed in response to obsessions or related anxiety. In the past few decades, the prevailing models of OCD pathophysiology have focused on cortico-striatal circuitry. More recent neuroimaging evidence, however, points to critical involvement of the lateral and medial orbitofrontal cortices, the dorsal anterior cingulate cortex and amygdalo-cortical circuitry, in addition to cortico-striatal circuitry, in the pathophysiology of the disorder. In this review, we elaborate proposed features of OCD pathophysiology beyond the classic parallel cortico-striatal pathways and argue that this evidence suggests that fear extinction, in addition to behavioral inhibition, may be impaired in OCD.

The current model of OCD

Intrusive thoughts, doubts, or concerns about safety, cleanliness, sex, violence, or symmetry, and urges to count or check “to be sure” are common thoughts, feelings, and behaviors that represent universal human experience to one degree or another. Healthy adaptive human function requires an ability to regulate and inhibit such intrusive thoughts, urges, feelings, and behaviors. People with obsessive compulsive disorder (OCD) are unable to control their thoughts and feelings, and consequently experience obsessions accompanied by anxiety, and typically also engage in associated compulsions -- repetitive, stereotyped or ritualized behaviors apparently designed to neutralize the anxiety associated with their obsessions. Thus, one perspective conceptualizes OCD as a model disorder of self-regulation and behavioral inhibition. Modern cognitive neuroscience has provided experimental tools, including neuroimaging methods, to examine the brain basis of self-regulation and behavioral inhibition.

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A convergence of neuroscience research points to the involvement of cortico-striatal circuits (or loops, see figure 1) in behavioral control functions (1). The anatomy and chemistry of cortico-striato-thalamo-cortical (CSTC) pathways was well established in the latter half of the 20th century (2). Progressive knowledge of this circuitry formed a popular basis for heuristic models of neuropsychiatric diseases, from classic movement disorders involving the basal ganglia to a range of psychiatric conditions (3-5). In principle, the general organizing theme of these circuits is that they project from specific territories in frontal cortex, to corresponding targets within striatum, and then via direct and indirect pathways through the basal ganglia to the thalamus, and finally with recurrent projections back to the original frontal territory where each loop started (2) (see figure 2).

The emergence and evolution of modern brain imaging methods provided an opportunity to establish and refine neurocircuitry models of OCD. Early functional neuroimaging studies of OCD predominantly examined differences in indices of regional brain function between affected subjects and psychiatrically healthy comparison groups, while at rest or during neutral states (for example, see 6, 7, 8). Subsequent research studied subjects with OCD before and after standard courses of treatments, such as with serotonergic reuptake inhibitors or cognitive-behavioral therapy (for example, see 9, 10). Complementary approaches entailed studying subjects with OCD during provocation of their symptoms (e.g., while being exposed to triggers such as a contaminated object or provocative pictures (11-13)). Convergent findings from such studies implicated the CSTC pathways in the pathophysiology of OCD; activity in the nodes of this circuit was elevated at rest, accentuated during symptom provocation, and attenuated toward normal with successful treatment (14, 15).

As the fields of cognitive-affective neuroscience and brain imaging advanced in tandem, more powerful approaches evolved to better examine the substrates of psychiatric diseases. Using such approaches, and building on earlier findings in OCD, investigators next employed cognitive neuroscience methods in combination with functional imaging tools to test the involvement of specific neural networks within the CSTC in the context of specific cognitive-affective paradigms (16-19). This approach enabled better-controlled experiments and also an avenue for bringing together a more granular analysis of pathophysiology with a more sophisticated approach to functional anatomy, delving into sub-territories and specific loci within named brain regions.

In this review, we highlight how the recent advances in cognitive-affective neuroscience may help us formulate an updated conceptualization of OCD. We emphasize: 1) the distinct roles the lateral and medial orbitofrontal cortices may play in reward processing and affect regulation; 2) the role of dorsal anterior cingulate cortex in error processing and its potential role in fear expression; and 3) the role of amygdalo-cortical circuitry in the expression and regulation of fear. We end with a discussion regarding future potential applications of this knowledge to advance treatment for OCD. We note that in this article, we will not conduct a comprehensive review of the OCD literature. We do, however, highlight some of the recent advances and findings related to structural imaging in OCD (text Box 1) and findings related to systems involved in implicit vs. explicit learning and how these findings may relate to the phenomenology of OCD (text Box 2).

Why isn't the CSTC model sufficient?

Early characterizations of CSTC loops emphasized their parallel and segregated nature, emanating from various frontal sub-territories and ramifying in specific striatal sub-territories. For instance, one heuristic, dubbed “the striatal topography model of OCD and related disorders” posited that comparable striatal pathology could explain the relationship between OCD and Tourette syndrome (TS); whereby, OCD was due to pathology within the caudate, disrupting OFC/ACC-caudate function, whereas TS was due to pathology within the putamen, disrupting sensorimotor-putamen function (20). Anatomical evidence, however, now indicates that the cortico-striatal loops are in fact much more integrated within the striatum and the thalamus and not fully segregated as initially thought; rather the anatomy is better described as a spiral with information cascading from one loop to the next (21). Moreover, the CSTC model does not take into consideration the role of the amygdala and the hippocampus and their interaction with the frontal cortex in mediating fear and anxiety in OCD patients. Further, imaging findings of the past decade have made clear that such heuristic models of OCD and TS pathophysiology represent a gross oversimplification, that is not born out by the data (22). Finally, while the early CSTC model of OCD placed heavy emphasis on the role of the OFC generically, it is now appreciated that different sub-regions of the OFC play distinct and disparate roles in processing reward, negative affect, and specifically fear and anxiety (23, 24).

The medial and lateral orbitofrontal cortex (OFC)

An extensive meta-analysis of OFC function associates the lateral OFC with processing negative valence and the medial OFC with processing positive valence (24). More specifically, the lateral OFC appears critical in responding to punishment, escape from danger, and may be involved in ritualized behavioral responses (25-27). The medial OFC, on the other hand, appears more involved in emotion regulation and reward processing. Extensive research conducted in rodents and healthy humans now implicates the ventromedial prefrontal cortex (vmPFC), extending to the medial OFC in regulation of fear, especially during the recall of safety memories (28). Lesion studies in rodents (29) and monkeys result in impaired fear extinction, and compulsive-like behavior in bar-pressing for food (30). The medial OFC has also been implicated in olfactory aversive conditioning and reversal of conditioning contingency during classical conditioning (31). The function of the mOFC and adjacent vmPFC correlate with the magnitude of fear extinction memory in healthy humans (32, 33).

In OCD, most of the early PET studies that examined resting metabolic state, employed symptom provocation paradigms, and assessed pre-post treatments have implicated the OFC in the pathophysiology of OCD without explicit distinction between the medial vs. the lateral portions of the OFC (for review, see 14, 34). The distinction between lateral and medial OFC dysfunction in OCD was suggested, however, by an early PET study reporting that OCD symptoms were positively correlated with metabolism in the anterolateral OFC and were negatively correlated with posteromedial OFC regions (11). Subsequent fMRI studies reported positive correlations between hyperactivation of the lateral OFC and OCD symptom severity during the performance of the serial reaction time task (16), and during

symptom provocation (35, 36). Studies of OCD treatment response have shown that lateral OFC hyperactivity prior to therapy predicts subsequent response to serotonergic reuptake inhibitors; the lesser the magnitude of OFC hyperactivity the better response to treatment (37).

In contrast to the lateral OFC, the medial OFC appears hypoactive in OCD. One hypothesis regarding the pathophysiology of OCD is that the disorder is characterized by dysfunctional inhibitory control (38). Indeed, neuroimaging studies report hypoactive medial OFC in OCD and that symptom severity appears to be inversely correlated with mOFC function (16, 23). This is consistent with the idea that the elevated fear and anxiety in OCD may be due to failure to activate the vmPFC/OFC when faced with stimuli that trigger OCD-related fears (39).

A number of studies, however, seem to contradict the hyper-lateral-, hypo-medial OFC model suggested above. For example, some of the earlier PET studies reported enhanced resting metabolism in fairly medial portions of the OFC in OCD patients (for reviews, see 22, 34). Recent functional MRI studies also report significantly increased activation of the vmPFC in OCD patients when engaged in an error-interference task while varying the motivational context of the task related to committing an error (i.e. gaining vs. losing money) (19, 40); a finding replicated in a pediatric OCD cohort (41). Using cognitive and reward reversal tasks and fMRI, some studies reported hypoactivation of the IOFC when OCD subjects were asked to learn that a new object represents the correct answer in the reversal task (42, 43). The reasons for these apparent inconsistencies may be due to a number of factors including differences in the paradigms and tools used, heterogeneity of the disorder, co-morbidities, and the presence or absence of medications while OCD patients are participating in the study. Regardless of the apparent discrepancies, all of the above studies suggest that lateral and medial portions of the OFC are indeed dysfunctional in OCD, and that these regions are playing different roles in the disorder.

The anterior cingulate cortex: error processing and fear expression

The dorsal anterior cingulate cortex (dACC) is involved in numerous cognitive and affective functions and is particularly relevant to OCD psychopathology. This brain region is involved in detecting the presence of cognitive conflict, and error monitoring and detection (44, 45). Common paradigms used to test the function of the dACC use an element of interference such that there are two conditions: congruent vs. incongruent. Response to the congruent condition represents a prepotent or automatic response that is easy to perform. The incongruent condition requires the inhibition of the automatic/prepotent response in favor of the more challenging response; hence represents a conflict to the participant. The function of the dACC has commonly been assessed when subjects are about to respond (assessment of conflict) and during the period after the subject has responded (potential period where subjects would have realized that an error was committed). These tasks include variants of the Stroop, go/no-go, and multisource interference tasks (46-48). There exists an extensive literature using fMRI (for review, see 47) and electrophysiological tools (i.e. measuring event-related potential)(49) on the utilization of these paradigms that shows increased activation of the dACC when contrasting the incongruent vs. the congruent condition thus

supporting its role in the assessment/detection of interference or conflict (50). Failing to suppress the prepotent responses in antisaccade tasks where subjects are instructed to look away from a stimulus presented on a computer screen leads to activation of the dACC (51). In OCD, a number of studies show hyperactivation of the dACC to the incongruent relative to the congruent conditions (19, 41, 52-55). Moreover, task-induced functional connectivity analysis in OCD patients while performing the Stroop task revealed significantly enhanced connectivity between dACC and the dorsolateral prefrontal cortex, supporting the idea of abnormal error processing in OCD patients, and a cortico-cortical interaction that may adversely affect decision making in OCD (55).

In addition to error and conflict monitoring, the dACC may also be critical for the expression of conditioned fear. Fear conditioning studies have previously noted dACC activation (33, 56), but the significance of this response as a predictor of fear was not highlighted. In recent years, neuroimaging studies have specifically focused on the dACC in fear expression. As with the relationship between vmPFC and extinction recall, cortical thickness and activation of the dACC positively correlates with psychophysiological measures of fear learning (Galvanic skin responses) during fear conditioning. Moreover, dACC is activated during presentation of conditioned as well as unconditioned cues, suggesting a role in fear expression (57, 58).

In OCD patients, lesions of the dACC (eg, anterior cingulotomy) have been shown to significantly reduce OCD symptom severity in patients with severe otherwise treatment-refractory illness (59). Moreover, successful treatment of OCD with serotonergic reuptake inhibitors has been found to reduce dACC metabolism (60). These data are significant in implicating the dACC in addition to the OFC-striatal circuits, in the pathophysiology of OCD. Perhaps hyperactivation of the dACC mediates faulty error signals that contribute to the obsessions observed in OCD. An alternative hypothesis is that hyperactivation of the dACC in OCD may mediate the elevated fear and anxiety observed in this disorder. Future studies should examine the role of the dACC in fear conditioning and expression in the OCD population to test this hypothesis.

The amygdala and OCD

While the amygdala responds to novelty, salience and a variety of emotional stimuli, its role in mediating fear and anxiety is the most commonly referenced (61). In fact, the amygdala is often referred to as the hub of fear. A variety of experimental designs have been employed to test the amygdala's role in fear and anxiety; these include the presentation of emotional faces, international affective picture system (IAPS) stimuli, and classical fear conditioning. Such paradigms have consistently shown that presentation of negatively valenced stimuli (implicitly or explicitly) activate the amygdala in healthy individuals (62-64). Moreover, consistent with prevailing hypotheses, exaggerated amygdala responses have often been observed in disorders characterized by excessive or inappropriate fear expression (65, 66).

Across the anxiety disorders, however, aberrant amygdala function does not seem to be present uniformly under all circumstances (65). For example, in posttraumatic stress disorder, hyperactivation of the amygdala is present in response to stimuli with negative

valence, and during fear conditioning as well as symptom provocation (67, 68). In specific phobia, however, while disorder-specific stimuli (eg, phobic stimuli) do yield exaggerated amygdala responses (69, 70), general threat related stimuli (eg, emotional faces) do not (71). Interestingly, OCD appears to exhibit a unique profile in this regard; although OCD-specific stimuli have been associated with exaggerated amygdala responses (12, 36, 72), non-specific emotional stimuli (eg, faces) actually yield lesser amygdala responses than those found in healthy comparison subjects (17). Comparable findings have been reported in a pediatric OCD sample as well (73). However, one recent study using a different paradigm found increased amygdala activation in OCD patients during active responses to emotional faces (74). Another study reported that while amygdala hyperactivation was observed in response to symptom-provoking stimuli, such hyperactivation was also noted in response to negative stimuli unrelated to the OCD symptoms (12). Thus, it is important to note that the role of the amygdala in the pathophysiology of OCD is in need of additional investigation to clarify whether or when amygdala dysfunction in OCD is related to OCD-specific vs. non-specific emotional stimuli.

What is next in OCD research?

The last decade has witnessed expansive growth in neuroimaging and cognitive-behavioral neuroscience. Below we highlight two prospective areas of research that may be ripe for additional advancements in knowledge regarding the neural basis of OCD and in the development of novel therapeutic approaches.

Interrogation of the neural circuitry mediating fear extinction in OCD

The neurobiology of fear extinction is increasingly well delineated and involves the interaction between the vmPFC/mOFC, dACC, and amygdala (75, 76) -- key structures implicated in OCD pathophysiology as noted. Thus the profile of regional brain dysfunction and clinical presentation of OCD prompt the hypothesis that fear extinction may be impaired in OCD patients. Figure 3 represents a meta-analysis of studies reporting significant findings within nodes of the fear extinction network during fear learning, fear extinction and extinction recall (see supplemental material for more details). This figure highlights the overlap between the brain regions implicated in fear learning and its subsequent extinction and a number of the brain regions implicated in the pathophysiology of OCD, including the dACC, vmPFC, thalamus, amygdala, and hippocampus. There are, however, no published studies examining fear extinction and its retention in OCD. Consonant with a growing interest in fear conditioning/extinction in anxiety disorders research (28), we propose that examining fear conditioning and extinction circuits in OCD patients could be beneficial for understanding the pathogenesis, pathophysiology, and treatment of OCD. It could be argued, however, that the fear extinction model may be a better fit for understanding other anxiety disorders, such as posttraumatic stress disorder, and does not necessarily represent or explain the etiology, phenomenology and psychopathology of OCD. Indeed, the impaired fear extinction in OCD that we hypothesize herein is not intended to explain the reasons for why one develops OCD and are not intended to explain the entire complex phenomenology of OCD. Rather, given that 1) the elevated fear and anxiety observed in OCD may be causal in driving or sustaining some of the compulsions, and 2) the neural circuits mediating fear

extinction and those implicated in psychopathology of OCD overlap, we anticipate that understanding the neural circuits mediating fear extinction in OCD patients may be particularly useful for a number of reasons.

First, cognitive behavioral therapy (CBT) is currently among the most effective treatments for OCD. CBT and other forms of exposure therapies rely on extinction mechanisms (77). Thus, such studies would allow for understanding the neural mechanisms underlying one of the most effective treatments for OCD and other anxiety disorders. Second, a key feature of OCD is the inability to inhibit or extinguish fear associated with obsessions (78). Individuals with OCD avoid fear-provoking situations and stimuli and often cope with them by developing avoidance strategies to protect themselves; thus hindering fear extinction from occurring. Hence, while not accounting for the etiology of OCD, fear extinction may be a valid model of the major maintaining factor in OCD. Examining fear extinction in OCD could therefore allow for measuring neural responses involved in the pathogenesis and maintenance of OCD. A third advantage of employing fear extinction paradigms in studying OCD psychopathology is the capacity for conducting animal studies that are complementary to human neuroimaging studies of fear extinction (28). The cross-species validity of the extinction model, therefore allows the use of rodents to address questions that are not possible to answer directly in humans.

It is important to note that translational fear extinction research has led to the development of novel therapeutic approaches that are being examined with promising results such as reconsolidation blockade (79, 80) and adjuncts to CBT such as D-cycloserine (DCS) (81). DCS has in fact been used as an adjunct to CBT in OCD patients with positive clinical outcome in some (82, 83) but not in all studies (likely due to variance in dosage or experimental procedures) (84). Perhaps further research bridging rodents and man could help elucidate why DCS is effective in some experimental conditions but not others, or otherwise help to develop novel or improved therapies for OCD. Thus, learning about the neural circuits of fear extinction in OCD could elucidate how the fear and anxiety induced by obsessions are sustained, reveal new opportunities or targets for therapeutic intervention, and provide a model system for exploring strategies for augmentation or relapse prevention with regard to CBT.

Enhancing Treatment for OCD

One of the primary objectives in examining the neurobiology of OCD is to advance the development of more effective treatments. Behavioral (i.e. CBT) and pharmacological interventions are established as effective for OCD, and have been used for decades (85). Still, a significant proportion of patients are left with substantial residual symptoms. A variety of alternative strategies have been explored for treatment-resistant OCD.

Most pertinent to neurocircuitry models of OCD are surgical and neurostimulation modalities that are reserved for the most severely ill and explicitly represent intervention at the level of regional brain function and/or structure. For instance, modern ablative neurosurgical procedures entail lesions at specifically targeted loci within the brain, such as the dACC in anterior cingulotomy. Furthermore, gamma knife technology has been used to

create lesions for smaller targets, such as in anterior capsulotomy, thereby circumventing the need for craniotomy (86). More recently, deep brain stimulation (DBS), involving the implantation of electrodes, has enabled chronic stimulation of targeted brain areas. In OCD, multiple DBS targets have been studied and are currently utilized in DBS treatment. Those include the anterior limb of the internal capsule, the ventral capsule/ventral striatum (VC/VS) the subthalamic nucleus, and the nucleus accumbens (86, 87). The aim of the stimulation in OCD has been conceptualized in some instances to achieve disruption of the overactive cortico-striatal loops.

While the results of invasive neurotherapeutic interventions for OCD have been encouraging in some instances, the risks are significant and only a proportion of patients exhibit positive response (59, 88). Therefore, it is appealing to consider that cognitive neuroscience and imaging methods could be used to enhance outcomes in two ways. First, such methods could be used to identify predictors of treatment response as an aid in patient selection (89). Second, such tools could actually be used to guide the therapeutic intervention itself, such as by identifying optimal targets or optimal stimulation parameters in individual cases (86).

Summary and Conclusion

The cortico-striatal circuitry model of OCD pathophysiology emerged in the latter part of the 20th century, and for the past 25 years provided the principal platform for hypothesis-driven research in the field. Advances in neuroscience and progress in neuroimaging methods provided the means for extending and refining the original model. Specifically, 1) cortico-striatal loops are now understood to be interconnected rather than fully segregated, and OCD and related disorders may not exhibit pathology that maps neatly onto gross striatal sub-territories; 2) orbitofrontal cortex (OFC) is known to have meaningful functional subdivisions, such that hyperactivity in lateral OFC may mediate obsessions, and deficient medial OFC function may be associated with limitations in extinction recall; 3) dorsal anterior cingulate cortex (dACC) dysfunction in OCD may play a role in aberrant error monitoring and fear conditioning/expression; and 4) fundamental differences in amygdala responsivity may mediate anxiety in OCD and yet distinguish this condition from other anxiety disorders. We propose that this framework prompts new testable hypotheses about how dysfunction in these brain regions may be related to deficient fear inhibition, severity of symptoms and predictors of treatment response. Moreover, this model suggests new targets for neuromodulatory treatments to enhance vmPFC and mOFC function with the aim of strengthening fear extinction; neutralizing dACC function to reduce error signaling; and attenuating excessive IOFC activity to mitigate unwanted obsessions and worries. Addressing some of these hypotheses and other related questions (see box 3) may be relevant to the evolving model of OCD pathophysiology as it provides a basis for a contemporary research agenda spanning imaging, cognitive-affective and clinical neuroscience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Cognitive Behavioral Therapy (CBT)

CBT is a type of psychotherapy commonly utilized for the treatment of anxiety and mood disorders. The general focus of this therapy is to aid patients in restructuring their thinking patterns, to reduce unhelpful/unrealistic thoughts using cognitive (i.e., reappraisal) approaches; and to modify behavioral responses, such as through graded exposure to fear-provoking stimuli and situations.

Deep Brain Stimulation (DBS)

DBS is an intervention currently used for treatment of severe otherwise treatment-refractory OCD (under a humanitarian device exemption, from the FDA). This modern technology enables the chronic electrical stimulation of deep brain regions via surgical implantation of fine electrodes into the targeted brain region, connected to an implanted power source. DBS has also been approved for Parkinson disease, and is being actively studied for additional neuropsychiatric indications, such as major depression. Various indications for DBS involve stimulation of different regional brain targets.

Error Monitoring

Error monitoring refers to the cognitive process of monitoring and responding to one's own errors during the performance of a task.

Fear Conditioning

Laboratory fear conditioning is an experimental paradigm used to teach animals or humans to form an association between a neutral stimulus (such as a light or a tone) and an aversive unconditioned stimulus (US, such as a mild electric shock). The presentation of the now conditioned stimulus (CS) triggers the organism to exhibit a number of physiological responses. Most commonly measured conditioned responses are freezing and potentiated startle in rodents, and skin conductance and potentiated startle responses in humans.

Fear Extinction

This is a training phase in conditioning studies that occurs after fear conditioning. During fear extinction, the cue (the conditioned stimulus, CS) is repeatedly presented in the absence of the unconditioned stimulus (US). This extinction training (or within-session extinction learning) leads to decrement of the conditioned responses over trials. Subsequent test of the

extinction learning after a delay (i.e. 24 hours) is referred to as extinction recall (or retention) test.

Obsessive Compulsive Disorder (OCD)

OCD is a disorder characterized by intrusive, unwanted thoughts (i.e., obsessions) and ritualized, repetitive behaviors (i.e., compulsions). The obsessions are commonly accompanied by anxiety that drives the compulsions. The compulsions, therefore, are performed to neutralize and attenuate the obsessions and anxiety.

Box 1**Structural imaging in OCD**

Structural imaging studies continue to evolve and employ novel methodological tools to assess the structural integrity of brain regions implicated in the pathophysiology of OCD. Some of those studies focus on gray matter volume or thickness, while others focus on the white matter and fiber tracks connecting the different components of the striatum and the prefrontal cortex in OCD patients. Furthermore, some use a whole-brain analysis approach while others use region of interest analysis based on the CSTC model. A number of recent excellent reviews and meta-analyses focusing on structural imaging of OCD have recently been published (22, 90). Below we highlight some of the most consistent as well as the inconsistent findings in this domain.

Given the major emphasis on the OFC in the pathophysiology of OCD, a number of studies have primarily focused on examining anatomical differences in this brain region between healthy controls and OCD patients. The early studies that focused on region of interest analysis approach consistently reported reduced OFC volume in OCD patients (reviewed in 22). A recent meta analysis found no evidence of significant structural alterations in the OFC in OCD patients, (90) and another study suggested that potential structural changes in the OFC within the OCD may be compensatory (91). As for the striatum in OCD, a number of studies reported increased gray matter volume (for example see (92)), while other studies, using a region-of-interest approach reported significant volumetric reductions in the caudate (22). Unlike the striatum and the OFC, however, findings with regards to structural abnormalities in the dACC appear to be the most consistent regardless of the methods utilized. The consistent finding is that dACC gray matter volume is significantly reduced in OCD patients (see for example (90)). With respect to white matter abnormalities, a few studies using diffusion tensor imaging (DTI) reported abnormalities in OCD involving a variety of white matter tracts, such as the cingulum bundle, the anterior limb of the internal capsule, (93, 94) and corpus callosum (94, 95). However, the nature of these abnormal DTI findings has not been consistent.

Box 2**Is OCD psychopathology associated with multiple memory system dysfunction?**

One key function of the cortico-striatal circuit is the mediation of implicit (or procedural/habit) learning. Cortico-temporal lobe circuits, on the other hand, mediate more explicit (i.e., conscious) types of learning. Given the dysfunction of CSTC circuits in OCD, a number of studies have been conducted to compare and contrast implicit vs. explicit forms of learning in OCD patients. In the serial reaction time (SRT) paradigm, commonly used to assess implicit learning, a visual cue appears on a computer screen in one of 4 positions. The participant is instructed to press a button corresponding to the location of the cue as fast as possible. Two types of trial blocks are usually presented: a random block (in which the cue appears at random locations) and an implicit sequence block (during which a pattern of locations repeats). Though participants are not consciously aware of the sequence, their reaction time in the implicit sequence block improves over trials, indicative of facilitated implicit procedural learning. The performance of this task reliably activates cortico-striatal networks in healthy individuals (96). In OCD patients, deficient performance in this task has been reported, though the presence or absence of the deficiency at the behavioral level appears to depend on memory load of the participant (16, 46, 97). At the functional level, however, the pattern of activation induced by this and similar tasks shifts from cortico-striatal to cortico-hippocampal in OCD patients (16, 98). These studies inspired the formulation of a model to suggest that the CSTC system that mediates non-conscious information processing is deficient in OCD, and that the observed hippocampal (in the case of the SRT) activity may represent a compensatory mechanism, leveraging (fronto-hippocampal) circuitry that is normally responsible for conscious information processing. It is therefore proposed that this could explain why in OCD information normally processed outside of consciousness intrudes into the conscious domain (i.e., obsessions), as a consequence of the core CSTC deficit together with fronto-hippocampal compensation (96).

There is another emerging cognitive model for OCD that is also based on a multiple memory system heuristic (99). Briefly, activity of a goal-directed system normally drives individuals to maintain actions in order to obtain a preferred outcome. The repetition of this goal-directed behavior normally results in a shift to a second habit-mediating system, thereby allowing for greater efficiency by optimizing uncommitted functional capacity in the cognitive/goal-directed system. It has recently been proposed that OCD may result from dysfunction in the goal-directed response system, thus necessarily increasing the reliance on the habitual responding system, manifest as compulsive behavior (100).

Box 3**Questions for Future Research**

1. Would fear extinction deficiency be present in all different subtypes of OCD or would it be present in some but not others?
2. Could fear extinction capacity serve as predictor of treatment response to CBT in OCD?
3. Could the well-documented dysfunction in the different components of the striatum interfere with or interact with fear extinction capacity in OCD?
4. If fear extinction is in fact deficient in OCD patients, will the underlying neural mechanisms of this deficiency be the same or different to that reported in other anxiety or psychiatric disorders (i.e. PTSD or Schizophrenia)?
5. Could neuromodulation of vmPFC/mOFC fortify extinction capacity and hence CBT response in OCD?

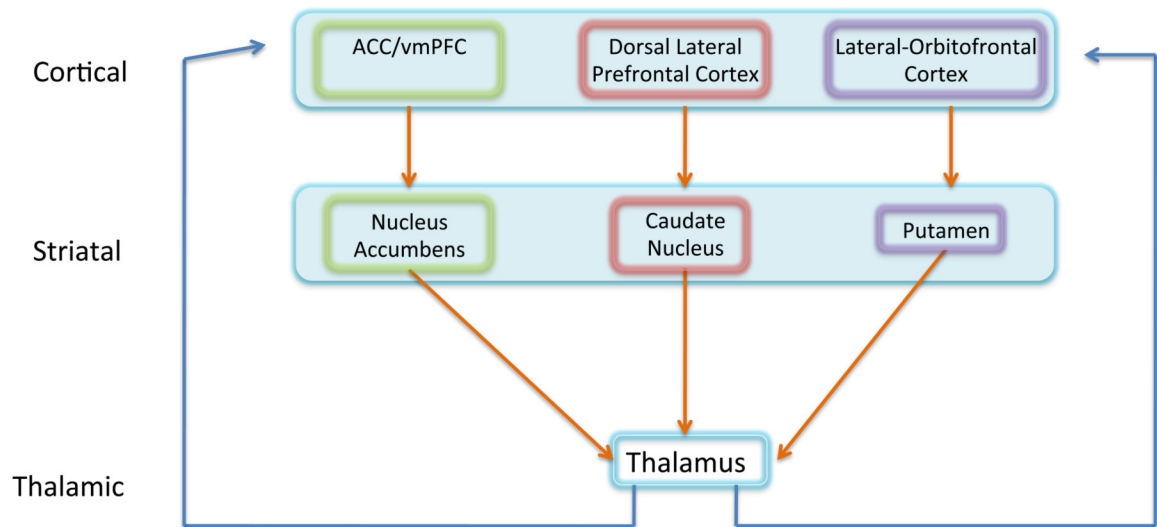


Figure 1. Schematic illustration of the different components of the cortico-striatal-thalamo-cortical (CSTC) pathways commonly implicated in the psychopathology of obsessive-compulsive disorder (OCD). ACC: anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex.

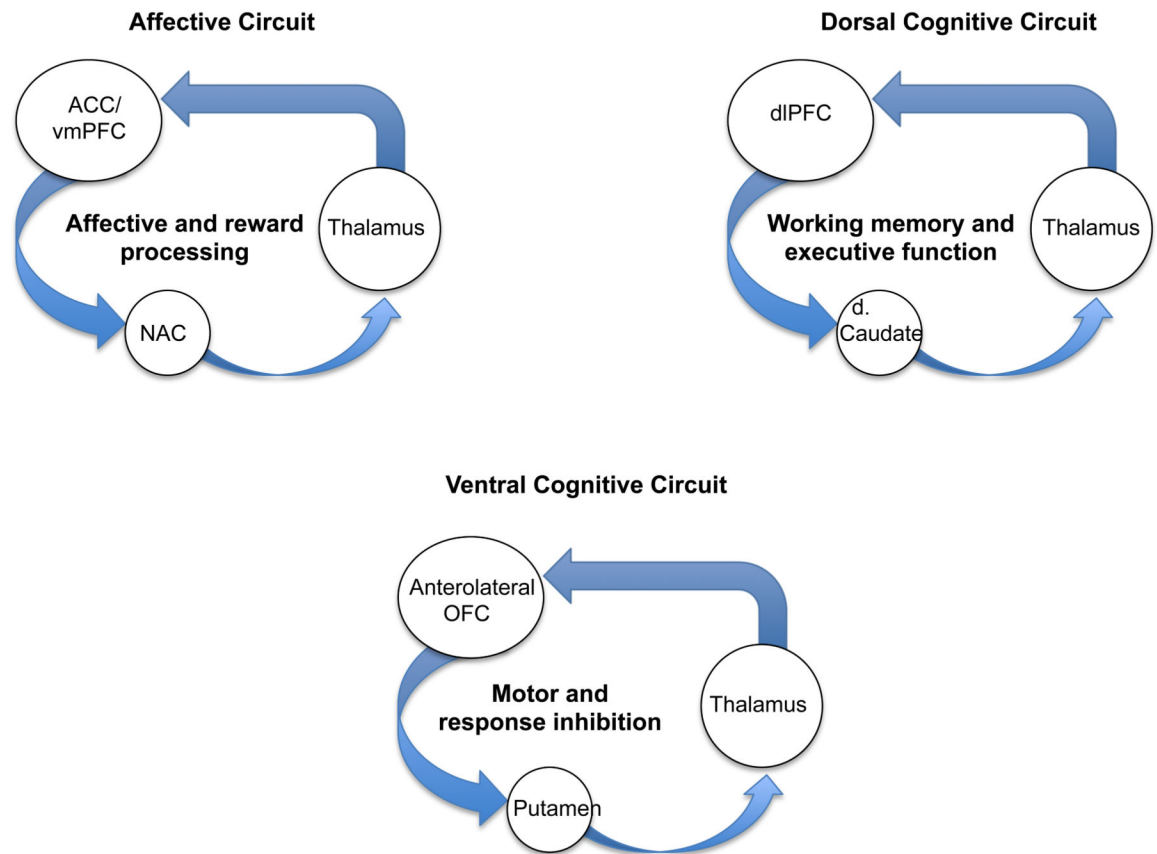


Figure 2. Schematic diagram illustrating the so-called cortico-striatal loops as commonly defined. dlPFC: dorsolateral prefrontal cortex, NAC: nucleus accumbance, OFC: orbitofrontal cortex

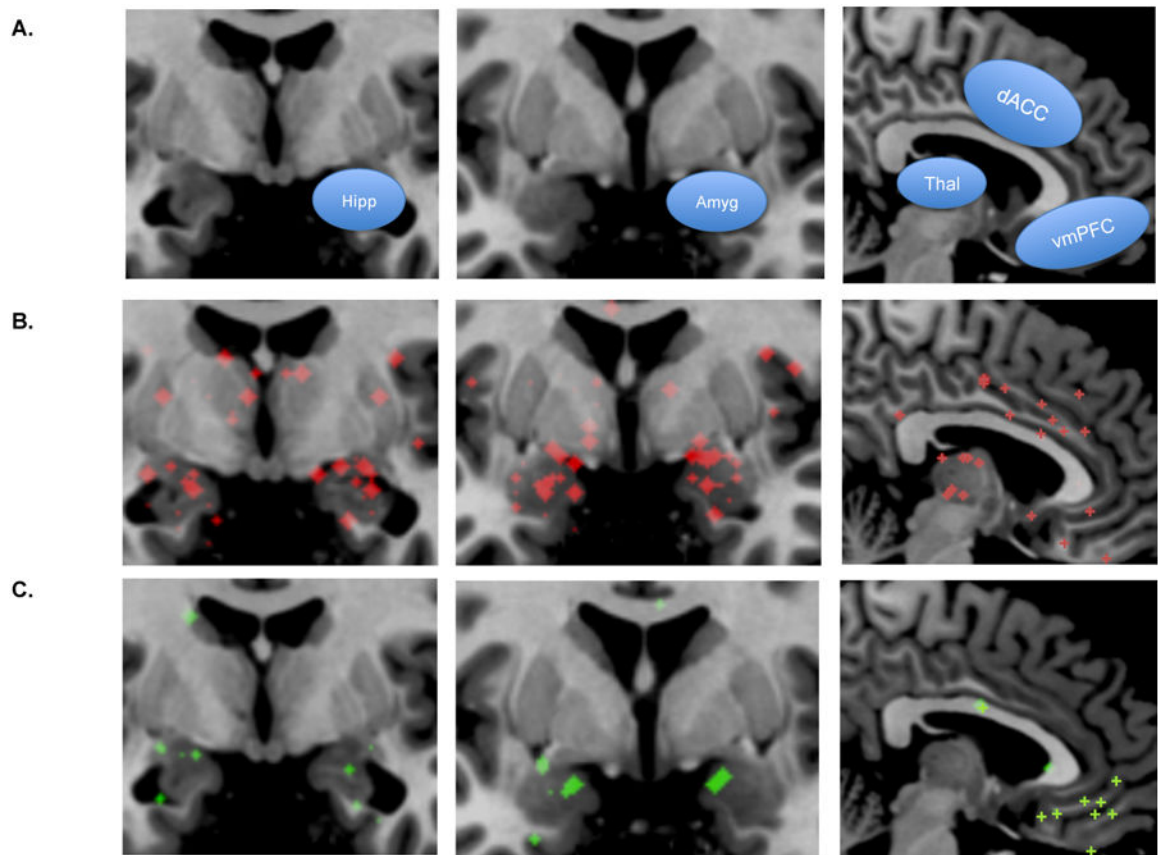


Figure 3.

Brain regions involved in fear conditioning, extinction learning, and recall appear to overlap with brain regions implicated in the psychopathology of OCD. **A.** Anatomical illustration of brain regions commonly implicated in OCD. Hipp: hippocampus, Amyg: amygdala, Thal: thalamus, dACC: dorsal anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex. Striatal regions are not illustrated in blue shapes for simplicity, but are clearly visible. Panels in **B** and **C** represent results from a meta-analysis focusing on functional neuroimaging studies of fear conditioning (**B**), extinction learning and recall (**C**). Crosses displayed on the anatomical images represent change in functional activation during fear conditioning (red) and extinction (green) regardless of the direction of activation (increased or decreased) and includes studies that examined patients with disorders. Structural imaging studies were not included in this meta-analysis. For additional details, see supplemental materials.