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Animal models of OCD-relevant processes: an RDoC perspective

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Abstract

Animal models have been invaluable tools in deciphering pathophysiology in many branches of medicine. Their application in the study of complex neuropsychiatric conditions such as obsessive-compulsive disorder (OCD), however, raises vexing interpretative challenges. The Research Domain Criteria (RDoC) approach of identifying dimensions of function and dysfunction that cut across syndromic diagnoses provides one potential path forward. We review some of the domains in the current RDoC matrix that may inform our understanding of patients with obsessions and compulsions, and how work in animal model systems is helping us to understand them. We focus on three specific RDoC constructs that may be particularly informative for our understanding of OCD: potential threat, habit, and cognitive control. In each case we review selected recent studies in animal models and their potential contribution to our understanding of OCD, and suggest directions for future research, informed by the animal studies. Such mechanistic work in animal models, in parallel with clinical studies refining our understanding of the relationship between these dimensional constructs and the symptomatology of particular groups of patients, may over time help us to generate a more comprehensive understanding of the pathogenesis and complexity of obsessions and compulsions.

INTRODUCTION

Obsessive-compulsive disorder (OCD), like most neuropsychiatric conditions, is a complex and heterogeneous entity. The syndromic diagnosis, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is characterized by the presence of obsessions and compulsions that are substantial enough to cause significant impairment or distress. This straightforward definition, however, masks marked phenomenological variation; two patients with OCD may have few if any specific symptoms in common. Over time, it has become increasingly clear that such syndromic diagnoses are not, in most cases, homogeneous entities. This has impeded pathophysiological research and the development of novel treatment interventions.

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Here, we discuss efforts to use animal models to advance our understanding of OCD (1, 2). Animal models have proven invaluable across many domains of medicine. OCD is 40-50% genetic (3, 4) and involves dysfunction of phylogenetically conserved circuits in the brain (5, 6); this may suggest that OCD derives from disruption of evolutionarily conserved processes, and thus that studies in animals could be informative. However, the nature of the diagnosis impedes such efforts and produces vexing interpretative challenges, for several reasons. First and foremost, OCD, like all DSM diagnoses, is likely to be pathophysiologically heterogeneous. A particular animal model may recapitulate the biological underpinnings of only a subset of patients, or it may capture dimension that cuts across patients with a range of different diagnoses. Such models may prove to be enormously informative, but the fact that they do not map cleanly onto familiar clinical entities complicates both their validation and their interpretation.

Second, some aspects of the phenomenology that defines OCD are difficult or impossible to assess in an animal model, even if pathophysiology could be faithfully recapitulated, because evaluating them depends on verbal report of subjective experiences. It is difficult, for example, to ask an animal whether its repetitive behavior is performed in an effort to neutralize the discomfort engendered by an intrusive irrational thought.

Finally, it may be that aspects of OCD phenomenology simply cannot be reproduced in an animal model, especially in a rodent. While the rodent and the human brain have similar overall structure, they are separated by nearly 100 million years of evolution, and the human brain is over a thousand times larger. Some aspects of the phenomenology and underlying pathophysiology of OCD may not be translatable across this gulf, even in principle.

In the face of these complexities, we must be modest as to what studies in animal models can hope to achieve. It is unrealistic to expect any animal model to convincingly recapitulate all aspects of pathophysiology and symptomatology of any complex neuropsychiatric disorder. OCD is no exception. There are, broadly speaking, three strategies to move forward.

First, one can attempt to capture a cause of disease that can be readily translated to an animal model. An obvious challenge to this approach is that we know so little about the fundamental causes of neuropsychiatric disease. Animal models based on rare genetic mutations of large effect have provided important new insights into other disorders such as autism (7, 8) and Tourette syndrome (9, 10), though no models similarly recapitulating identified genetic causes of OCD have been described to date. Some animal models have used a variation on this approach, seeking to recapitulate circuit abnormalities rather than genetic ones (11, 12). Any model based on a rare cause, genetic or otherwise, must grapple with the question of how generalizable its findings are to individuals whose illness has a different underlying cause or causes. Nevertheless, etiologically grounded models can provide a valuable opportunity to probe pathophysiology.

A second approach is to identify behaviors in an animal that plausibly recapitulate disease symptomatology (i.e. ‘face validity’), and then to use animal systems to better understand them. In the case of OCD, anxiety-like avoidance (13, 14) and repetitive behaviors such as

elevated grooming (15) have been proposed to have relevance to core symptomatology of OCD (2). A number of animal models of OCD have been proposed based on such putatively symptom-relevant behaviors (16–18). A challenge here is the questionable specificity of such behavioral phenotypes to OCD. Dysregulated grooming, for example, has also been described in models that purport to capture aspects of Tourette syndrome, autism, Rett syndrome, and other conditions (2). Thus, models based on face validity must generally marshal extensive corroborative evidence supporting their relevance to a particular disorder, such as OCD, before they can be accepted. When such corroborative data are available, they can provide fruitful systems for investigations that may provide new insight (1).

A third strategy for using animal models to advance understanding of disease is to parse syndromic diagnoses into more tractable constituents and to study those, rather than attempting to recapitulate more complex disease entities. For example, to advance our understanding of OCD, one can use model systems to study dysregulation of anxiety or disgust, mechanisms of habit learning, regulation of repetitive behaviors and habit, or any of a variety of other constructs with plausible relevance to the human disorder (19). The hope is that such constitutive constructs will prove to be more evolutionarily conserved and analytically tractable in model systems than complex syndromic entities, and that by understanding them individually we may come to better understand our patients. The Research Domain Criteria (RDoC) initiative provides a set of translationally tractable constructs that can be fruitfully investigated in animal models under this third paradigm.

AN RDoC PERSPECTIVE ON OCD

The RDoC initiative, developed and promulgated over the past decade by the National Institute of Mental Health (20, 21), represents an effort to grapple with the complexity of mental illness. The RDoC framework attempts to look beyond syndromic diagnoses to more fundamental dimensions that may better describe the heterogeneity of human mental function and its dysregulation. The application of RDoC constructs to the understanding of OCD is addressed in multiple papers in this Special Issue (cross-reference to other papers as appropriate). There is an inherent intellectual tension in this project, as OCD is a categorical, syndromic diagnosis, and the RDoC framework explicitly rejects the validity of such diagnoses (22). However, decades of work in patients with OCD have identified dysregulation in several of the RDoC domains. Studies in patients and in general population samples may help clarify correlations between variation along these dimensions and different aspects of OCD symptomatology, and the specificity of these associations.

Studies in animal models have great potential to clarify the mechanistic underpinnings of variance along such dimensions (23). The RDoC framework emphasizes the importance of integrating multiple levels of analysis, from genetics to circuits to behavior to self-report of subjective experience. While self-report is not available in animal studies, establishing links between genetics, circuit variation, and behavior is often more tractable than in patients, and causal relationships are more readily established. Over time, convergence of human and animal work is likely to provide new mechanistic insight into the neural and psychological abnormalities that contribute to OCD symptomatology, and may therefore lead to advances in nosology, treatment, and prevention.

Towards this end, it is important to identify specific RDoC domains of greatest relevance to OCD symptomatology. These are reviewed in greater detail elsewhere (22), including in other papers in this special issue. Here, we provide a selective summary of several OCD-relevant RDoC constructs that may be fruitfully studied in animal models, a brief synopsis of key clinical data implicating variance in these domains in the development and/or expression of OCD symptomatology, a selective review of some relevant animal data, and directions for future research. The goal here is not to be comprehensive; that would be a monumental task, as this project can touch on almost every aspect of the cognitive psychology of OCD, and correspondingly vast animal behavioral and neurophysiological literatures. Rather, our purpose is to illustrate how the RDoC perspective can inform and guide animal studies, and how animal data viewed through this framework may contribute to a maturing understanding of the complexity of the nature and pathogenesis of OCD symptomatology. In the course of so doing we highlight a few recent insights from the animal literature that may productively guide human studies in the future.

The original RDoC matrix describes five broad domains: positive valence systems, negative valence systems, cognitive systems, social processes, and arousal and regulatory systems (21, 24). Under each of these broad domains are multiple constructs, some of which subsume several subconstructs. For example, the negative valence system domain contains the constructs ‘acute threat’ (i.e. fear), ‘potential threat’ (i.e. anxiety), ‘sustained threat’ (which is related to various forms of chronic stress), ‘loss’, and ‘frustrative nonreward’. Functioning in these domains and constructs varies in the general population and in individuals with neuropsychiatric disease. Importantly, while the RDoC framework lays the domains and constructs out as separate entities out of heuristic necessity, they are likely to interact in many contexts; for example, potential threat may be influenced by cognitive factors, such as threat appraisal and prediction.

The RDoC matrix was always intended to be a living, regularly revised document. In this spirit, a sixth domain, the sensorimotor systems domain, was added to the matrix in 2019 (25). Constructs in this domain, which include Motor Actions (with several subconstructs), Agency and Ownership, Habit – Sensorimotor, and Innate Motor Patterns, are of clear relevance to OCD and related disorders. However, because it is so new, this domain is not further addressed in the current review.

Both the clinical phenomenology and a large number of systematic studies of OCD suggest abnormalities in a number of constructs and subconstructs spread across the negative valence, positive valence, and cognitive systems domains (15). We focus here on three constructs for which data in OCD is robust and animal studies are potentially informative: **potential threat**, **habit**, and **cognitive control**. There are enormous literatures, and some controversy, associated with each of these domains and how they may relate to OCD. We present a brief review of selected topics in each case, to indicate directions in which work in animal models, guided by the conceptual framework of the RDoC matrix, may yield new insights. References to recent reviews are provided to guide readers seeking more comprehensive treatment.

It is worth noting at this juncture that there are aspects of OCD phenomenology that are difficult to place within the RDoC matrix, in its current form. For example, elevated sensitivity to disgust appears to be a primary affective motivator in some cases of OCD (26), and it is not readily situated within the RDoC framework. Similarly, while compulsions, cognitive inflexibility, and avoidance can all readily be associated with RDoC dimensions, obsessions are more difficult to capture (22). It may be that a better mechanistic understanding of obsessions will clarify their relationship to existing RDoC constructs. It is equally likely, however, that the RDoC matrix will need to be expanded in order to fully account for some aspects of OCD symptomatology; as noted above, the matrix has always been intended to be a living document that is expanded and revised in response to new research, as exemplified by the very recent addition of the sensorimotor domain (25).

POTENTIAL THREAT

The RDoC construct of ‘potential threat’ lies within the ‘negative valence systems’ domain. Potential threat is defined as the brain’s response to the perception that harm “may potentially occur but is distant, ambiguous, or low/uncertain in probability.” This corresponds roughly to the more intuitive psychological concept of anxiety (24); it differs from fear (which is captured by the ‘imminent threat’ RDoC construct) in that the threat is vague, distant, or uncertain, not proximate and specific.

Dysregulated anxiety is central to the experience of many who suffer from OCD (though not all). Individuals with OCD exhibit elevated anxiety sensitivity (27) and overestimation of threat (22), and they tend to have high scores on the personality dimension of ‘harm avoidance’ (28). Potential threat is often characterized by uncertainty (this is one of the things that makes it potential, not imminent); and individuals with OCD report an elevated intolerance of uncertainty (29–31).

Interestingly, behavioral studies suggest that clinical anxiety may be more closely associated with avoidance of risk than avoidance of loss (32). (Risk is defined as uncertainty in which the possible outcomes of a choice and their probabilities are known, but the actual outcome is uncertain.) In OCD, on the other hand, behavioral studies have shown aversion both to loss (33) and to ambiguity, defined as a situation in which the probabilities of possible outcomes are themselves uncertain (29, 34, 35). Ambiguity entails a greater degree of uncertainty in the calculation of possible outcomes than does risk.

The neural circuitry and mechanisms underlying anxiety have been extensively studied in both humans and animal models. Structures implicated in the induction and regulation of fear (the response to imminent threat) and anxiety (the response to potential or uncertain threat) include the amygdala, the bed nucleus of the stria terminalis (BNST), the hypothalamus, the hippocampus, and the frontal cortex (36–38). Uncertainty avoidance has been linked to activity in and cortical connectivity between the amygdala and the nucleus accumbens and anterior insula (39, 40). Neurochemically, potential threat responses are associated with elevated cortisol levels (41) and corticotropin releasing factor (CRF), as well as a number of other neuropeptide transmitters (42).

The distinction between imminent threat (fear) and potential threat (anxiety) in the RDoC matrix is a particularly cogent one. The mechanisms underlying fear learning and experience have been extensively studied in animal models and are increasingly well understood; the amygdala plays a particularly prominent role in this circuitry (38). But OCD is more typically characterized by anxiety: a negative, aroused emotional state state (which may be physiologically similar to fear) in response to a potential or uncertain threat. Work in animals has demonstrated that while the amygdala is central to the regulation of fear, anxiety depends more on the BNST (36, 37). It is therefore striking that, while abnormalities in amygdala function and regulation have been examined in OCD (43), the BNST has received scant attention.

The BNST is a small nucleus in the ventral telencephalon, strategically situated close to the ventral striatum, insula, amygdala, hippocampus, and hypothalamus. Seminal animal studies implicating the BNST in the regulation of anxiety came from Michael Davis and colleagues at Emory University, beginning in the late 1990s (37, 44, 45). Careful studies in rats showed that lesions to the central amygdala disrupt learned fear responses but not the more general anxiety-like responses produced by, for example, an aversive bright light, or the infusion of CRF. Conversely, lesions to the BNST disrupted generalized responses to potential threat, but not the more discrete conditioned fear response (46). Subsequent studies have confirmed and extended this double dissociation, establishing a key role for the BNST in the development of hypervigilance and stress-induced learning (36). Pharmacological studies have also supported the dissociation between imminent and potential threat responses (47). Common anti-anxiety medications, such as benzodiazepines and chronic SSRIs, reduce chronic fear/anxiety behaviors, but not cued/phasic fear responses. In contrast, the 5-HT1A agonist buspirone can reduce phasic but not chronic fear behaviors.

The relationship between imminent and potential threat is complex and dynamic. Imminent threat may become potential threat with the passage of time or the introduction of ambiguity. When an animal trained in fear conditioning undergoes extinction, for example, the memory of the cue-fear association is not erased, but rather is superseded by new safety associations. The original fear association remains as a potential and can return after any of a variety of manipulations, such as spontaneous recovery (after the passage of time) or renewal (when fear associations are tested in a novel context). In a sense, therefore, extinction converts an imminent threat (conditioned fear) into a potential one. The recovery of extinguished fear associations can limit the efficacy of therapy (48), as has been illustrated in an animal model of extinction and OCD therapy (13), which is further described below. Better understanding the functional and mechanistic relationship between imminent and potential threat may lead to new strategies to mitigate this limitation.

In sum, the distinction between fear and anxiety highlighted within the negative valence domain of the RDoC matrix has received little attention in clinical studies of OCD and merits greater scrutiny. Animal studies have provided elegant demonstrations of this dissociation and important insights into the underlying neurocircuitry and neurochemistry. This highlights a powerful way in which mechanistic studies in animals, guided by a dimensional framework, may shed light on important new directions for research into pathophysiological mechanisms.

POSITIVE VALENCE DOMAIN: HABIT.

The positive valence systems domain of the RDoC matrix describes processes "primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning." A number of processes within this domain are implicated in OCD. For example, the relief produced by execution of a compulsion produces negative reinforcement of the behavior, making it stronger (49). Recent data suggest that the representation of rewarding stimuli may be perturbed in OCD (29), and that responses to rewarding stimuli may be blunted (i.e. anhedonia), above and beyond the effects of comorbid depression (50, 51). In this section we focus on a third construct within this domain that has received substantial recent attention: habit learning.

Habits are learned behaviors that take on an automatic character through extensive repetition. They are defined in the RDoC matrix as "sequential, repetitive, motor or cognitive behaviors elicited by external or internal triggers that, once initiated, can go to completion without constant conscious oversight" (24). Habits are a normal part of the human experience (52) and can be adaptive, in that they increase the reliability of routine behaviors and free up cognitive resources for more flexible and attention-demanding tasks. But excessive reliance on habits, or habits that are situationally inappropriate or lead frequently to undesirable outcomes, can be maladaptive. Parallels between habits and compulsions, and perhaps between cognitive habits and obsessions, have motivated interest in the relationship between habits and OCD symptomatology for nearly two decades (53). A relationship is supported by anatomical data; the cortico-striatal circuitry that has long been implicated in OCD pathophysiology is also associated with habit formation and execution (5, 54).

Operationally, habits are characterized as learned behaviors that persist independently of whether or not they are motivated by current goal seeking (55, 56). Importantly, learned behaviors are not identifiable as habits on the basis of their topography; it is not the specific behavior that defines a habit, but rather the functional role of that behavior and how it relates (or fails to relate) to flexible goals. One way to identify a behavior as a habit is through outcome devaluation – to make the outcome associated with a behavior no longer needed or desired. For example, if pressing a button produces food, but a subject will continue to press it even when not hungry, the button-press may be considered habitual. Such operational definitions are equally applicable in both human and animal studies, which makes them powerful for translational work.

Behavioral studies of habit typically contrast habitual behavior with goal-directed choices (57, 58). A large recent literature has used rigorously designed behavioral tasks in patients, modeled closely on animal literature and grounded in computational models of action control, to examine habit in OCD, and in other conditions characterized by compulsivity (19, 59–62). These studies converge on the conclusion that individuals with OCD, and compulsive disorders more generally, rely on habits more than controls, at least in the execution of simple learned choice behaviors. The cause of this bias – hypertrophied habit circuitry, weak goal-directed circuitry with which it competes, or some dysfunction in the interaction between the two – remains the subject of debate in the literature (6, 55, 63).

Abnormalities in cognitive control, a distinct RDoC construct to which we return below, can lead to an over-reliance on habit.

The circuits and neural processes underlying habit learning have been extensively studied in animal models (54, 64). Imbalance between goal-directed and habitual behavior has been linked to abnormalities in the cortico-basal ganglia circuitry (54). One anatomical principle that has emerged from this large animal literature is that the dorsolateral or sensorimotor striatum in rodents, roughly homologous to the putamen in primates, has a key role in the learning and execution of habits; lesions of this region disrupt the development of habits in both rats and mice (65, 66). Interestingly, the putamen is larger in individuals with OCD than in age-matched controls, in proportion to the duration of symptoms; this has been interpreted as representing hypertrophy due to chronically elevated reliance on habit over years (67). A second anatomical principle is that frontal cortical regions – the infralimbic and prelimibic cortices, in rodents – play a key role in modulating habit behavior. Manipulation of these regions can both enhance and suppress habits (68). Frontal dysfunction may impact cognitive control, reviewed below, and thereby 'release' subcortical circuits that subserve habitual responding.

Habit learning has been explicitly examined in the SAPAP3 knockout mouse, one of the better-studied putative genetic models of OCD (69). Mice with a knockout of the SAPAP3 gene have abnormal synaptic transmission within the basal ganglia circuitry and exhibit anxiety and compulsive grooming, both of which respond to chronic treatment with the SSRI fluoxetine. Graybiel and colleagues paired a tone with a water droplet, which induced grooming; over time, the tone came to produce grooming behavior on its own. This transition to droplet-independent grooming was enhanced in the SAPAP3 knockout model. This habit-like behavior was mitigated by stimulation of cortico-striatal afferents arising in the orbitofrontal cortex (69).

Interestingly, this stimulation appeared to normalize striatal activity and reduce habitual grooming behaviors by mitigating deficits in the activity of intrinsic striatal interneurons – specifically, the parvalbumin-expressing fast spiking interneurons (FSIs) (69). This central role for striatal interneurons parallels other lines of animal work that are increasing our appreciation of the importance of these cells in striatal dysregulation and habit-like repetitive behavioral pathology. FSIs are reduced in number in *post mortem* tissue from individuals with Tourette syndrome, which is often comorbid with OCD (70, 71). Experimental depletion of these cells in mice leads to dysregulated repetitive behaviors, suggesting that the deficit seen *post mortem* is causal (72, 73). Neither tics nor the repetitive behaviors seen in animal models are exactly the same as habits, but they may reflect similar underlying mechanistic abnormalities. Regulation of FSIs in the dorsomedial striatum by corticostriatal afferents is disrupted by stress (74). This may represent a mechanism for the well-established observation that stress can potentiate habit learning and lead to maladaptive reliance on habits (75, 76). Interestingly, stress can also potentiate symptoms of OCD (77).

These mechanistic insights from animal studies may inform our thinking about how variation in the RDoC construct of habit learning can contribute to OCD, and related disorders. In particular, the literature reviewed above suggests that corticostriatal projections

are critical regulators of habit learning, able both to promote it and to disrupt it. Dysregulation of this circuitry may be a mechanism for excessive reliance on habit in OCD; exercising or harnessing in the course of cognitive-behavioral therapy, as frontal cortical circuits gain more control over dysregulated limbic responsivity, may be a mechanism of symptom improvement. The important role played by striatal interneurons, identified *post mortem* but mechanistically developed in animal model studies, has yet to be explored in OCD; this is a potentially fruitful area for future investigations.

COGNITIVE CONTROL AND COGNITIVE INFLEXIBILITY

Cognitive control is a complex construct within the RDoC Cognitive Systems domain (24) that maybe of particular relevance in OCD (78). The RDoC Cognitive Systems workshop defined cognitive control as “a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context.” As is underscored by this definition, cognitive control functions primarily by regulation of other systems in the brain, and thus the constructs in this domain interact with other RDoC constructs in most contexts and paradigms. A primary failure or weakness in cognitive control may contribute to a range of psychopathology by dysregulating other emotional or automatic processes (23).

Cognitive control is invoked ‘in the service of goal-directed action’, as is emphasized in the RDoC definition. A growing body of research indicates that there is a weakness in the ability to use goal-directed strategies to control action in OCD (19, 59–62). These studies have already been summarized above, in our discussion of increased reliance on habit in OCD, but they are also relevant here: a deficit in cognitive control strategies, and in the capacity to overcome prepotent tendencies in the service of goal-directed action, is one explanation for an over-reliance on habit.

Within the RDoC framework, cognitive control is broken down into five subconstructs: goal selection; updating, representation, and maintenance; response selection; inhibition/suppression; and performance monitoring (24). The precise nature of cognitive control deficits in OCD, and how they may map onto RDoC subconstructs, remains unclear and is a topic of ongoing study. Invesitgations in animal model systems may be useful here, as they allow us to probe the interactions between the frontal cortical substrates of cognitive control and the circuitries that mediate habit learning, emotional expression, and other ‘lower-order’ capacities that cognitive control systems regulate, with a degree of specificity and causal specification that is difficult or impossible to achieve in clinical work. Higher-order cognitive systems are challenging to probe in animals (though there is a rich literature) (79). The frontal cortices, and corresponding cognitive sophistication, are enormously expanded in humans relative to other animals (especially rodents), and there may be important capacities that are central to OCD (and to neuropsychiatric disease more generally) that are difficult or impossible to model in other species. We focus initially on recent work in nonhuman primates, which may better capture aspects of complex cognitive capacities than rodent models.

Cognitive inflexibility and impaired cognitive control are particularly associated with dysfunction in the orbitofrontal cortex (OFC); abnormalities in the OFC are the best replicated finding in functional imaging studies of OCD (5). Studies in humans, rats, and nonhuman primates suggest that OFC plays a key role in the determination of how desirable something in the environment is, which is necessary for the comparison of the value of two different available options during choice (80, 81).

The value associated with particular stimuli or actions can change in response to feedback. During reversal learning, a learned assocation (e.g. that a particular cue indicates the availability of a reward) suddenly changes; a subject must recognize on the basis of feedback that things have changed, and adjust behavior accordingly. Lesions of the lateral OFC (lOFC) have long been known to disrupt reversal learning: monkeys (and rats) with lOFC lesions have difficulty inhibiting a previously learned behavior when environmental contingencies change (82, 83). In OCD, tests of reversal learning have used heterogeneous paradigms and have not demonstrated consistent behavioral deficits (78). A recent study showed deficits in both late acquisition and late reversal, which were attributed to deficient safety signaling in OCD (84). Neuroimaging during reversal has produced more consistent findings, with impaired recruitment of the OFC, suggesting a deficit in this system (85, 86).

More recent studies have refined our picture of lOFC function. For instance, recent work has examined learning in macaques with bilateral lesions of the lOFC, using a three-option variable reward contingency task that is more complicated than the two-option tasks used in simple reversal paradigms (87). In this task (and more recent iterations used in both patients and nonhuman primates), the probability of reward of the three options changes cointinuously, following a pre-determined pattern. Animals with selective lOFC lesions are able to follow fluctuating contingencies early in the task – that is, they chose the most-often rewarded options with greater frequency, and they adapt their behavior in response to feedback. But after a dramatic change in contingencies halfway through the task, in which the previously optimal choice becomes the worst and a previously unrewarded option becomes the best, they are slow to adapt (87). Trial-by-trial analysis of choice behavior revealed that the animals were not perseverative or unresponsive to new information, but rather had difficulty precisely assigning credit for individual rewards to the specific choices that produced them. Rather than being precisely attributed to the most recent choice, credit for a reward was distributed across several recent choices, a process known as ‘spread of effect’; this impeded the learning of new contingencies after a dramatic change. While spread of effect has long been known to be an aspect of learning in intact animals (88), it is typically overshadowed by more specific contingency learning; lOFC dysfunction appears to make it more prominent (89). More recent work has replicated this finding in macaques (90) and has demonstrated similar phenomena in humans with OFC lesions (91).

This work in nonhuman primates has not been guided specifically by the RDoC framework, but it is part of the same general project of using studies across experimental systems and levels of analysis to probe dimensions of normal and abnormal brain function that may contribute to disease. Variation in the specific assignment of credit for outcomes to individual choices may correspond best to the cognitive control subconstruct of ‘updating, representation, and maintenance’ (24).

Studies in rodents suggest a similar role for lOFC in perseverative behavior in the context of a behavioral OCD model. Quirk and colleagues have developed a behavioral model in rats that recapitulates the core characteristics of cognitive behavioral therapy (CBT) for OCD (13, 14). The central CBT strategy for OCD is symptom evocation and response prevention, or ERP. In ERP, symptoms are triggered by the therapist (e.g. by engineering imaginal or real exposure to a contamination stimulus), and the patient's typical compulsive responses (e.g. hand-washing) are prevented. Over time, this leads to reduced urges to perform the compulsive responses and greater control over them. In rats, this has been modeled through the phenomenon of active avoidance (13, 14). An incipient shock is signaled by a cue, and rats learn that they can avoid being shocked by stepping onto a platform. After this association is well learned, rats undergo 'extinction with response prevention', or Ex-RP: They are presented with the tone (thus evoking fear of the shock), but their learned active avoidance response is prevented (i.e. they are prevented from stepping onto the escape platform). No shock is given. Over time, most rats extinguish their active avoidance behavior – they will not seek to step onto the platform in response to the tone, even when they can. But a minority persist in active avoidance, when permitted, even after extinction. This behavior can be considered compulsive. Compulsive avoidance in these rats depends on lOFC: inactivation of the lOFC through local infusion of a GABA agonist eliminates the compulsive avoidance responses (14).

How might this work contribute to our understanding of OCD? As noted above, lOFC dysregulation is consistently seen in functional neuroimaging studies (5), and OFC is inefficiently recruited during reversal learning in individuals with OCD (85). An impairment in specific credit assignment during learning, and an increased reliance on the less precise learning strategy of spread of effect, may lead to the abnormalties in goal-directed action documented in patients. The use of precise behavioral probes to investigate the component cognitive processes that underlie goal-directed action, guided by RDoC or by other theoretical frameworks, is an important area of ongoing research. Careful and increasingly precise studies of cognitive control and its neural substrates in animals have great potential to expand our understanding of these processes and to provide us with conceptual and behavioral tools to clarify their contribution to the phenomenology of OCD.

CONCLUSION

Work in animals is increasingly shedding light on a range of neural processes of potential relevance to obsessive-compulsive disorder. While it is unlikely that an animal model will ever be able to recapitulate all aspects of OCD phenomenology, or that we would be able to confirm and quantify all relevant characteristics even if such a comprehensive model were available, conservation of genetic architecture and the basics of brain organization across evolution suggest that animal studies may shed light on relevant core processes.

The RDoC framework (20, 24) provides a useful set of organizing principles to guide such studies. It identifies dimensional constructs in which variation exists in the general population, and may contribute to disease. By focusing attention on these constructs, rather than complex disease syndromes, this framework facilitates translational studies. While studying obsessions or compulsions in animals requires us to make potentially

anthropomorphic assumptions, studying a more fundamental construct such as anxiety or value representation can be done more objectively.

Here, we have focused on three examples of RDoC constructs in which recent data from animal models may inform our evolving understanding of OCD. These are presented merely as examples. We suggest that insights from animal models that we have summarized, and which are discussed in more detail in the references provided, may represent informative directions for ongoing studies of OCD symptomatology.

In the negative valence RDoC domain, we have focused on the 'sustained threat' construct. The RDoC matrix emphasizes the important distinction between imminent threat (i.e. fear) and potential threat, in which a potential negative outcome is distant, imagined, or uncertain (i.e. anxiety) (24). Studies in animals have validated this distinction, and shown that fear and anxiety depend on dissociable circuits in the brain. In particular, anxiety/potential threat responses depend critically on the bed nucleus of the stria terminalis (BNST); lesions of the BNST dissociate fear from anxiety in rodent models (37). Given the centrality of potential threat/anxiety to most cases of OCD, it is striking that few if any studies of humans with obsessions and compulsions have examined it, at either the structural or the functional level. This represents an area where the concepts crystalized in the RDoC matrix may fruitfully guide future research.

In the positive valence domain we have focused on habit learning, and in the cognitive domain we have focused on goal updating. Substantial clinical literature has characterized abnormalities in OCD in both constructs. Work in animals is rapidly advancing in both domains and has great potential to cross-fertilize with clinical findings to produce new insight into OCD. It is notable that either excessive reliance on habit learning or impaired goal selection may lead to behavioral and cognitive inflexibility. This highlights how different RDoC constructs might contribute to similar clinical phenomenology, even if the underlying mechanisms are quite distinct.

The RDoC matrix is conceptualized as provisional and is meant to evolve. Certain aspects of OCD phenomenology – specifically, obsessions – are difficult to capture within the existing matrix (22). It is possible that a better conceptual parsing of obsessions and how they arise will make clear a relationship with one or more existing RDoC constructs; but it is also possible that additional constructs will need to be developed to fully capture these aspects of OCD. A better understanding of how obsessions relate to RDoC dimensional constructs, either within the existing matrix or in an expanded one, will facilitate the use of animal studies to probe their underlying mechanisms.

Using studies in animals to provide new insight into a complex neuropsychiatric syndrome such as OCD raises difficult conceptual challenges (2). Examination of translationally tractable dimensional constructs such as those outlined by the RDoC framework provides one path forward in the face of these complexities.

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