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Pediatric OCD in the era of RDoC

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Abstract

The NIMH Research Domain Criteria (RDoC) initiative was established with the goal of developing an alternative research classification to further research efforts in mental health. While RDoC acknowledges that constructs should be considered within a developmental framework, developmental considerations have not yet been well integrated within the existing RDoC matrix. In this paper, we consider RDoC in relation to pediatric OCD, a paradigmatic example of a neuropsychiatric disorder that often has onset in childhood but is also present across the lifespan. We discuss three RDoC subdomains with relevance to OCD as exemplars, providing for each construct a brief review of normative developmental changes, the state of construct-relevant research in pediatric OCD, and challenges and limitations related to developmental considerations within each subdomain. Finally, we conclude with a brief discussion of how RDoC may continue to evolve with regard to developmental considerations in order to further research in pediatric OCD.

Keywords

Obsessive-compulsive Disorder; Research Domain Criteria (RDoC)

INTRODUCTION

Beginning in 2009, the NIMH Research Domain Criteria (RDoC) initiative was established with the goal of developing an alternative research classification to further the study of mental disorders (Cuthbert & Insel, 2013). This classification system was designed to be "based on dimensions of neurobiology and observable behavior," in an attempt (in part) to overcome limitations of existing diagnostic classifications based largely on symptom

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presentation (further discussion of these issues can be found elsewhere; e.g., Cuthbert & Insel, 2013). Designed as "a framework for organizing research/" the RDoC initiative aims to promote progress in understanding of the etiology and pathophysiology of mental illness to ultimately inform development of precision medicine approaches in the domain of mental illness (Cuthbert & Insel, 2013; Insel, 2014).

The general RDoC framework is based on a matrix with units of analysis (e.g., genes, molecules, circuits, behavior) on one axis and constructs on the other, with constructs grouped under five "superordinate domains." The most recent iteration of the RDoC matrix can be found online (https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml). Relatively early in its development, the RDoC framework is not without its challenges. One challenge that has received relatively little attention is the placement of RDoC constructs within a developmental framework. The RDoC initiative has stated the importance of developmental differences to the matrix, noting that developmental trajectories "might be considered as a third dimension in the matrix" (https://www.nimh.nih.gov/research-priorities/rdoc/developmental-and-environmental-aspects.shtml). However, despite acknowledgement of the importance of developmental differences, these factors have not been well integrated within the existing matrix.

Consideration of development within the RDoC framework is important to pediatric OCD research (and more broadly) for several reasons. First, studies of OCD and other psychopathology have demonstrated that results with adults cannot simply be extended downward to youth (Kalra & Swedo, 2009), and this is almost certain to be true in studies of RDoC constructs. Cognitive and behavioral abilities develop throughout childhood, and with them, characterizations of what is "normal" (and, similarly, "abnormal") at a given developmental stage. Thus, the way in which psychopathology presents or manifests itself also differs across developmental stages (Ciccetti & Rogosch, 2002). Similarly, demands placed on children by their environment shift over time, which can reveal deficits that were not previously apparent. Biological changes, including changes in neural development and hormonal changes associated with puberty, add another layer of complexity in considering psychopathology across RDoC units of analysis from a developmental perspective.

In addition to facilitating an accurate understanding of youth psychopathology, a developmental approach to RDoC may uniquely inform the underpinnings and treatment of psychopathology across the lifespan. For example, identifying specific markers of psychopathology that precede onset of significant impairment can inform prevention and early intervention strategies. Embedding knowledge about these early markers into a developmental framework can also identify windows for *optimal* intervention timing, for example, during a sensitive period when associated neural networks are particularly plastic. A developmental approach to RDoC is also likely to contribute to a deeper understanding of the core processes that maintain disorder(s) at all ages. It may become more challenging with age to disentangle the role of each RDoC construct, particularly if increased symptom heterogeneity and/or severity are associated with emergence of new RDoC-related deficits. This may be particularly true for studying OCD, by nature a highly heterogeneous disorder that is likely to develop through a number of potential pathways and which shows a bimodal pattern with regard to age of onset. Studying the onset of RDoC deficits as they emerge

developmentally will contribute to clearer links between constructs and disorder presentation, and across RDoC units of analysis (e.g., neural circuits with behavioral). In sum, there are a number of important advantages to applying a developmental framework to the study of RDoc constructs.

As a first step to considering the interplay between developmental considerations and RDoC constructs as they apply to pediatric OCD, our primary objective is to discuss the state of pediatric OCD research within three relevant RDoC constructs – Potential Threat (Anxiety), Habit, and Response Inhibition/Suppression – as well as briefly discussing associated developmental considerations. For each subdomain, we will provide a general description of the construct of interest, briefly review normative developmental considerations, and discuss the state of pediatric OCD research in this area. These subdomains are discussed as exemplars and are not intended to be comprehensive in nature (i.e., we do not cover all subdomains with potential relevance to pediatric OCD). Additionally, given the breadth and number of units of analyses included as part of RDoC, we have generally limited our discussion to clinically relevant behavior and outcomes, performance on experimental paradigms, and related neuroimaging findings. For similar reasons, we will focus specifically on pediatric OCD, rather than extend our discussion into OC-spectrum disorders. It is our hope that through this discussion, we can highlight important considerations in utilizing the RDoC approach to further research across the lifespan with relevance to the pathophysiology and treatment of pediatric OCD.

DEVELOPMENTAL CONSIDERATIONS IN RDoC DOMAINS

Negative Valence Systems: Potential Threat (Anxiety)

Within the current iteration of the RDoC Matrix (https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml), several threat-related constructs are subsumed under the Negative Valence Systems Domain. Response to potential threat (anxiety) is distinguished from response to acute threat (fear) and response to sustained threat. Where fear represents response to a tangible and realistic threat, typically motivating defensive behaviors (e.g., fight, flight, or freeze), anxiety arises in the face of a perceived potential threat that is likely intangible, ambiguous, and of uncertain probability (https://www.nimh.nih.gov/research-priorities/rdoc/constructs/potential-threat-anxiety.shtml). As with other RDoC domains and subdomains, anxiety exists on a continuum from adaptive (e.g., a few butterflies in one's stomach before an important exam which motivates one to study) to maladaptive (e.g., feeling anxious about whether one has completed every homework assignment perfectly and re-checking each problem numerous times to ensure perfection).

Normative development.—In typically developing children, fluctuations in anxiety often occur during specific developmental stages (Boyer & Bergstrom, 2011). For example, children between about 8 and 18 months typically develop anxiety around strangers, and separation from caregivers. In early childhood, it is common for children to develop fears of the dark or imagined threats (e.g., monsters hiding in the closet or under the bed). Later in childhood, normative worries tend to become more realistic and specific – such as anxiety

about potential for injury or natural disasters. In the pre-teen and teenage years, the focus of anxiety often shifts to perceived social threat. Such anxieties during childhood and adolescence typically arise at predictable times during development and persist for limited periods (Boyer & Bergstrom, 2011). While potentially distressing for both child and parent, these anxieties are normative and likely do not represent pathology. In applying RDoC to investigate potential threat (anxiety) in pediatric OCD populations, careful attention should be paid to developmental stage to avoid overpathologizing developmentally appropriate anxieties.

Potential Threat in Pediatric OCD.—The specific role of anxiety in OCD has been a topic of some debate in recent years (Bartz & Hollander, 2006; Stein, et al., 2010). Though previously categorized as an anxiety disorder, in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5; APA, 2013) OCD was removed from the Anxiety Disorders umbrella and placed in its own category of "Obsessive-Compulsive and Related Disorders." Of course, anxiety remains central to major theories of the etiology and phenomenology of OCD (e.g., Salkovskis, 1999). In cognitive behavioral models of OCD, intrusive thoughts (obsessions) are believed to give rise to anxiety, with compulsions functioning as an attempt to acutely reduce or neutralize anxiety. However, there is increasing recognition that distressing emotions other than anxiety, such as disgust (Berle & Phillips, 2006) or feelings of incompleteness (Summerfeldt, 2004), likely play a significant role in some OCD presentations. This may be especially relevant in pediatric (vs. adult) OCD, as early onset OCD has often been tied to distressing somatosensory experiences, such as tics or "not just right" feelings (Schubert, Ravid, & Coles, 2016). Moreover, recent work by Rozenman et al. (2017) suggests that different symptom clusters in pediatric OCD may differentially relate to dimensions associated with "fear" and "distress" disorders, highlighting the heterogeneity in pediatric OCD symptomatology beyond anxiety.

Within the Negative Valence RDoC Domain, a significant amount of work has focused on Acute Threat (Fear), rather than on Potential Threat (Anxiety). For example, work utilizing fear conditioning and fear extinction paradigms has suggested that anxious children may not discriminate between "dangerous" conditioned stimuli (CS+) and "safe" conditioned stimuli (Liberman, Lipp, Spence, & March, 2006; Craske, Waters, Bergman, Naliboff, Lipp, Negoro, & Omitz, 2008). Moreover, it appears these children may not sufficiently extinguish conditioned fear over the same period as healthy children (Craske et al., 2008), a phenomenon which has also been reported in children with OCD (Geller et al., 2017). Moreover, within fear extinction, developmental stage appears highly important, as human and rodent research suggests relatively poor fear extinction learning in adolescence (compared to childhood and adulthood; Pattwell et al., 2012), which may be tied to an imbalance between limbic system and frontal cortex development (Casey, Jones, & Hare, 2008).

In contrast to the Acute Threat (Fear) construct, experimental research focusing specifically on the Potential Threat (Anxiety) in pediatric populations has been more sparse, including in OCD. In the current iteration of the RDoC matrix, only one behavioral paradigm (the "NPU Threat Task") has been identified as a metric of anxiety. In contrast to the classic fear potentiated startle task (classified under the Acute Threat (Fear) construct), the NPU threat

task includes both predictable and unpredictable threat conditions, corresponding to fear and anxiety, respectively (Schmitz & Grillon, 2012). While we are not aware of any published studies utilizing the NPU Threat Task in samples of children or adolescents with OCD, past work utilizing this task to examine the relation between anxiety symptoms and potentiated startle in children found unique relationships between mood and anxiety symptoms with predictable vs. unpredictable threat conditions (Nelson & Hajcak, 2017). Thus, this task may be useful in better assessing and experimentally differentiating anxiety from fear in pediatric OCD. Indeed, using paradigms which clearly distinguish between fear and anxiety, (as well as and other types of OCD-related distress) may be particularly important in moving forward understanding of the heterogeneous nature of pediatric OCD.

While, as noted above, we are not aware of any studies in pediatric OCD utilizing behavioral paradigms which are currently categorized under the Potential Threat (Anxiety) construct within the RDoC matrix, we will discuss two additional areas which have been investigated in pediatric OCD which may arguably fall within the sphere of potential threat: cognitive appraisal of potential threat and the elicitation of anxiety via symptom provocation tasks (though it should be noted that these areas may overlap other RDoC domains/constructs, as well). While our focus remains on pediatric OCD, we briefly discuss findings in adult samples, to allow comparisons across these developmental stages.

Potential Threat and Symptom Provocation. Symptom provocation paradigms have been used in OCD to study behavior and brain function during induction of symptomatic states, by using OCD-specific cues to provoke OCD-related symptoms. While many symptom provocation studies have focused more generally on OCD symptoms and distress, (these will not be reviewed here,) a small number have focused specifically on anxiety. In adults, different patterns of neural activity have been found for self-reported OCD symptoms versus anxiety (Rauch et al., 1994). Specifically, while cerebral blood flow (rCBF) in left anterior orbitofrontal cortex (OFC) during provocation correlated with OCD symptom scores, self-reported anxiety during provocation did not correlate with activity in any of the regions of interest (i.e., (OFC, right caudate, and left anterior cingulate). Additionally, work in adults has found relationships between anxiety and neural circuit activation during symptoms provocation may be distinct for different symptom dimensions (Mataix-Cols et al., 2004). In response to checking stimuli, self-reported anxiety correlated directly with left superior and inferior frontal gyrus, globus pallidus, and left thalamus activation, whereas anxiety during presentation of hoarding-relevant stimuli correlated with left precentral/superior frontal gyrus activation. In contrast, during provocation of washing-related symptoms, self-reported anxiety did not correlate with neural activations.

To our knowledge, only one study has used symptom provocation to examine anxiety in pediatric OCD. Gilbert et al. (2009) used symptom provocation within two symptom dimensions (symmetry/ordering and contamination/washing), in addition to a neutral condition, to examine neural correlates of OCD symptoms and the relation between these neural correlates and related clinical variables, including anxiety. With regard to anxiety, results indicated that greater anxiety during contamination/washing symptom provocation corresponded to increased activity in left orbitofrontal cortex (OFC) for OCD participants relative to healthy participants. Additionally, during blocks of neutral pictures interspersed

between blocks of contamination/washing images, anxiety directly correlated with left insular activity in OCD patients, which was not the case for controls. Anxiety was found to be unrelated to neural activity during symmetry/ordering symptom provocation. Comparing these findings to those in adults, it appears there may be different patterns of neural activation connected to washing-related anxiety; however, given the small number of studies, (as well as different symptom foci,) it is difficult to draw any definitive comparisons to the adult literature in this area. However, it is important to note that findings were different for anxiety and OCD symptom severity when examining the relation of these constructs to neural activation, which may reflect the role of other distressing emotions in OCD, beyond anxiety. This highlights the importance of assessing anxiety apart from OCD symptom severity, as well as other distressing emotions in OCD, as these may relate to neural correlates in distinct ways.

Estimation of Potential Threat. Estimation of potential threat in pediatric OCD has typically been studied by presenting participants with a variety of situations (some standardized, some individually generated) and asking them to evaluate various characteristics of the scenario (e.g., how likely that scenario would be to actually occur, how bad it would be if it did happen, etc.). Barrett & Healy (2003) examined cognitive processes relating to both OCD-specific and more general (i.e., not related to OCD) potential threats in children using an idiographic approach. To define OCD-specific threats, sentence stems were completed by participants with OCD to reflect OCD-relevant fears. Control threat-related sentences were also used. Across samples of children with OCD, anxious controls, and healthy controls, these authors found that children with OCD reported greater estimation of the severity of potential OCD-related threats compared to healthy controls. However, the OCD group did not differ significantly from the anxious control group in their severity ratings (nor did the healthy control group). Interestingly, there was no significant difference between groups on estimated probability of such a threat occurring. Thus, while children with OCD did not estimate potential threats as more likely to occur, they did believe that, should OCD-related threatening events occur, they would be more severe in nature.

In addition to overestimating the severity of OCD-related threats, children with OCD may also be more likely to interpret ambiguous situations in a more threatening light. Farrell and colleagues (2015) presented children with an ambiguous hypothetical situation and found that those with OCD were more likely to interpret the situation as more difficult to manage relative to healthy children. However, it was found that this threat-related interpretation bias in pediatric OCD could be entirely accounted for by self-reported level of anxiety (Farrell, Hourigan, Waters, & Harrington, 2015). Interestingly, while Farrell and colleagues (2015) found differences in children's belief about how they could manage, they did not find biased interpretation of the ambiguous situations in terms of valence of reported thoughts. The authors note that this could be related to age specific cognitive abilities (8-12 years olds), or that biased-threat estimation in OCD may only occur in situations specifically related to OCD symptoms (as prompts used were not targeted to OCD). Thus, overestimation of the severity of potential threat and ability to cope with threat appear relevant, though perhaps not unique, to pediatric OCD.

In comparison, findings regarding overestimation of threat in adult OCD have been somewhat inconsistent, though studies of threat estimation in adults have also been more prevalent. Some studies have supported threat interpretation bias in patients with OCD, relative to clinical control groups (e.g., Steketee, Frost & Cohen, 1998), though others have found no evidence of threat estimation bias (e.g., Tolin, Worhunsky, & Maltby, 2006). Work by Moritz & Jelinek (2009) investigated whether making a distinction between overestimation of "general" versus "personal" threat occurrence may explain such discrepancies. Indeed, they found that while adults with OCD did not tend to overestimate the general likelihood a negative event would occur, relative to healthy controls, they were more likely to believe they were "more vulnerable" to negative events. Moreover, these findings (Moritz & Jelinek, 2009), and others (Woods, Frost & Steketee, 2002), mirror those of Barrett & Healy (2003; see above), suggesting overestimation of the severity of negative events may be a relatively consistent characteristic across pediatric and adult in OCD, even if likelihood of occurrence is not overestimated. However, in contrast with the findings by Farrell et al. (2015; above), work by Jelinek and colleagues (2009; 2014) examining bias in semantic networks in adults with OCD has suggested that, when presented with a variety of cue words and asked to generate associations, adults with OCD tend to make more negative and more OCD-related associations than healthy control participants. Thus, in contrast to children with OCD, it may be that adults show more biased interpretations of otherwise neutral or ambiguous stimuli.

Discussion and limitations.—At the present time, Potential Threat (Anxiety) is one of the least comprehensively explicated constructs in the current RDoC Matrix in terms of specific units of analysis defined within this construct; yet potential threat is decidedly important in studying OCD. That OCD is related to difficulty in appropriately identifying or reacting to potential threat seems intuitive, particularly when viewed within cognitive-behavioral models of OCD. Indeed, abnormalities in estimation and response to potential threat are supported by the work presented here. However, the nature of such difficulties has not been thoroughly interrogated. It is possible that this is due, in part, to the fact that anxiety is frequently, though not always, a predominant symptom of OCD.

Recent research has highlighted a number of other emotions or sensations associated with OCD beyond anxiety, including disgust and feelings of incompleteness (e.g., Berle & Phillips, 2006; Summerfeldt, 2004). In more "classic" OCD presentations, distress associated with symptoms is likely to be largely due to anxiety about a potential threat. For example, in the case of a child who fears becoming severely ill from germs if he touches surfaces at school without using hand sanitizer, it is easy to see how becoming very seriously ill represents a potential threat which most people would feel anxious about if they thought it was likely to happen. On the other hand, in the case of a child who rearranges their belongings until it feels "just right," it is more difficult to determine the potential threat in this situation. Moreover, a child with such symptoms may not endorse feeling anxious, but rather feeling uncomfortable, unsettled, or as though something is unfinished. Incompleteness is more common in youth vs. adults with OCD, and young children are more likely to present without identifiable obsessions. The degree to which potential threat

(anxiety) plays a role in OCD overall, but particularly early in development and in the context of incompleteness symptoms, is unclear.

Transdiagnostic investigations of anxiety may be more fruitful in progressing understanding of potential threat (anxiety) as a dimensional construct, particularly given high rates of comorbidity between OCD and anxiety disorders in children, which may fit well within a dimensional research approach. Better delineation of the relationship between threat-interpretation biases and OCD may specifically be important for informing intervention development, such as cognitive bias modification approaches which have shown preliminary promise in adolescents with OCD (Salemink, Wolters, & de Haan, 2015). Additionally, attempts to more comprehensively assess the relationship between OCD-related discomfort and anxiety and to compare high versus low anxiety patients with OCD may help to clarify the role of anxiety in OCD. Similarly, consideration of symptom subtypes in examining potential threat within pediatric OCD may be fruitful, as anxieties in pediatric OCD often cluster around certain themes (e.g., aggressive, contamination, somatic, etc.)

One limitation specific to current investigations into potential threat is a relative lack of defined elements within several units of analysis for this RDoC construct; at the time of this writing, only one experimental paradigm is represented in the Matrix (the NPU Threat Task). While the RDoC initiative does not limit investigations to only those constructs or elements listed within the matrix, well defined elements of analysis provide a common set of tools, data from which can be better integrated across levels of the matrix. For example, one challenge in drawing comparisons across symptom provocation and threat estimation tasks is the varying nature of the tasks and stimuli used. Within the symptom provocation studies discussed, all used stimuli selected specifically to provoke OCD-related anxiety, but some used individually tailored stimuli (Rauch et al., 1994), while others used more general sets of OCD-related stimuli (Mataix-Cols et al., 2004; Gilbert et al., 2009). Similarly, within the threat estimation studies, some used OCD-specific probes (Barrett & Healy, 2003) while others used more general prompts (Farrell et al., 2015). Thus, variation in tasks and experimental procedures may contribute to differences in findings, a problem which could be mitigated by defining a more standard set of tasks for investigating constructs of interest. Beyond implementing common sets of experimental procedures, it would be ideal to include behavioral measures and tasks which are applicable across numerous developmental stages. Where paradigms such as potentiated startle and symptom provocation may be more easily applied in children, cognitively based measures of threat estimation, such as those discussed above, present some unique challenges in pediatric populations where awareness, insight into, and possibly occurrence of OCD-related cognitions may be limited.

Positive Valence Systems: Habit

The RDoC construct “habit” (within the Positive Valence Systems domain) has been implicated in OCD and other compulsive behaviors. Habits are repetitive, sequential motor or cognitive behaviors automatically triggered by stimuli that can be completed without constant conscious effort once initiated (https://www.nimh.nih.gov/research-priorities/rdoc/constructs/habit.shtml). Habits are the functional reciprocal of goal-directed behaviors, which are performed intentionally and are sensitive to outcome value (Gillan & Robbins,

2014). Goal-directed control is prominent during initial learning of a stimulus-response-outcome association; with training the behavior becomes habitual. Once habitual, a behavior is insensitive to action-outcome contingency or changes in contingency (Gillan & Robbins, 2014). While habitual behavior is more efficient in familiar situations, it does not allow for flexibility in a changing context (Gruner, Anticevic, Lee, & Pittenger, 2016). Adaptive behavioral control is thought to involve a "fluid and contextually sensitive balance" between habit and goal-directed learning approaches (Decker, Otto, Daw, & Hartley, 2016).

Normative development.—The normative developmental trajectory of habit and goal-directed learning is incompletely understood, but there is general consensus that habit learning predominates earlier in development than goal-directed behavior (Decker et al., 2016). Cross sectional studies suggest that infants and younger children tend to perseverate on previously rewarded behaviors after a change in contingency (Klossek, Russell, & Dickinson, 2008; Piaget, 1954), even if they are able to express explicit knowledge of changes in rules or contingency (Zelazo et al., 1996). Behavioral sensitivity to contingency change and devaluation of outcome emerges at later ages and further increases into adulthood (e.g. Decker et al., 2016; Klossek et al., 2008). These developmental transitions in learning are thought to reflect the maturational trajectory of a prefrontal-hippocampal-striatal circuit that integrates information about states, behaviors, and outcomes to take goal-directed action (Decker et al., 2016). The capacity to take goal-directed action also relies on multiple other component cognitive processes that gradually develop into young adulthood (e.g., working memory, cognitive control; Otto et al., 2015).

Habit learning and OCD.—Habit learning has been proposed to be a core mechanism that underlies development of compulsive behaviors in OCD (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). While the conventional view of OCD is that obsessions drive compulsive behavior, research on the neurobiology of habit learning has led some to propose the opposite (e.g., Gillan et al., 2014; Robbins et al., 2012). In this view, deficits in the goal-directed learning system (prefrontal cortex/dorsomedial striatum) lead to excessive reliance on the habit learning system (dorsolateral striatum), resulting in the development of compulsions. These habitual avoidance behaviors in turn drive the development of obsessions, which are conceptualized to be cognitive interpretations of the compulsive urge arising from cognitive dissonance. In other words, using faulty reverse inference, obsessions form as one concludes that they must have had something to fear if they felt driven to perform a compulsion (Gillan et al., 2014). Repeated performance of compulsions prevents the extinction of these irrational beliefs, because the individual is not exposed to a contingency in which safety follows ritual prevention. Therefore, in this "compulsive-obsessive disorder' model, compulsions are habits that are the critical and central feature of OCD, while obsessions and anxiety are "propagators and consequences of compulsivity" (Gillan & Robbins, 2014). This model highlights the unique role of developmental research for understanding the core pathology of OCD beyond childhood; temporal precedence for an "compulsive-obsessive disorder" model might be established by studying the pattern of habit development over childhood and its emergence relative to other RDoC domains (such as potential threat) and OCD symptoms.

A procedure called outcome devaluation is most commonly used to test for habits (Adams, 1980). In iterations of this task used with human subjects, individuals are trained to make simple instrumental responses to a stimulus to gain outcomes of value (e.g., points) or avoid negative outcomes (e.g., shock). Outcomes are subsequently devalued by explicitly instructing the participant that the trained contingency is no longer in place (e.g., target stimulus is no longer associated with points or shock). Post-devaluation performance is measured in extinction. If the instrumentally trained behavior ceases when the stimulus is presented, it is said to be under goal-directed control, whereas an automatic behavior that continues in spite of devaluation is said to be a habit.

While we are unaware of any research using the outcome devaluation task in a pediatric OCD sample, it has been used to test the role of habit learning in OCD in several adult studies. The first study to do so compared 21 adults with OCD to 30 healthy controls in an appetitive devaluation task (Gillan et al., 2011). Positively reinforced stimulus-response-outcome associations were trained and then subsequently devalued. Groups did not differ in learning the association, but those with OCD showed deficits in their ability to refrain from responding to devalued stimuli. That is, those with OCD kept responding to stimuli that were no longer rewarded. Moreover, those with OCD showed weaker explicit knowledge of the relationship between stimulus-response-outcome associations when asked to describe the contingencies post-task. The authors concluded that OCD may be associated with a significant bias toward habit learning vs. goal-directed learning.

In a follow-up study, (Gillan et al., 2014) tested whether OCD was associated with deficits in avoidance-based habits, which more closely parallels the avoidance function of compulsions. Participants were 25 adults with OCD and 15 controls. During the training phase, participants learned to avoid electric shock by responding on the correct foot pedal associated with warning stimuli. The devaluation phase involved visibly removing the shock electrodes from one wrist (devalued) while leaving the other wrist connected (valued). While groups did not differ in the number of avoidance responses made to the valued stimulus predicting the shock, the OCD group showed greater avoidance of the devalued stimulus that was no longer associated with shock. This behavioral difference occurred despite the groups performing equally on tests of physiological arousal, threat appraisal, and explicit knowledge of contingencies. These results complement those of Gillan et al. (2011), lending further evidence to the notion that those with OCD have a bias toward habit development.

A third study from this research group (Voon et al., 2015) showed that patterns of altered habit learning in OCD may have valence effects. In the context of reward outcomes, adults with OCD showed impaired goal-directed learning and enhanced habit learning. However, with loss outcomes, a pattern similar to healthy controls was observed, showing greater goal-directed and lower habitual learning.

It has been noted that the studies described above (Gillan et al., 2011; Gillan et al., 2014; Voon et al., 2015) stand in contrast to findings from a variety of implicit learning tasks that have much in common with habit learning tasks (e.g., both involve behavior that becomes increasingly automatic with training, implicit learning tasks are also striatum-dependent; Deckersbach et al., 2002; Rauch et al., 2007). While studies using instrumental habit

learning tasks suggest weakness in the goal-directed system and over reliance on habit, implicit learning studies indicate an over-reliance on the goal-directed system (Gruner et al., 2016). These discrepant findings led Gruner et al., (2016) to propose that inflexibility in OCD may result not from deficits in either the goal-directed or habit systems, but from a functional weakness in the mechanism responsible for dynamic, context-appropriate switching between these systems.

The pathophysiology underlying habit process in OCD remains unclear. OCD in both children and adults is characterized by dysfunction within cortico-striato-thalamo-cortical (CSTC) neurocircuitry (Blackford & Pine 2012; Brem et al., 2012). Deficits in nodes within this network, specifically prefrontal cortex/caudate (which controls goal-directed behaviors) and the putamen (which is responsible for habit learning), may lead to a bias toward the habit system. Within OCD, habitual responding has been associated with hyperactivation in the caudate (Gillan et al., 2015). In this study, urge to perform habits was “parametrically associated” with the strength of activity in the caudate. Patients who did not have habitual responding showed positive coupling between the caudate and the right inferior frontal gyrus and the left pallidum during the early acquisition of avoidance. The pattern was reversed for those who had habitual responding, with negative coupling between the caudate and the right inferior frontal gyrus and pallidum and positive coupling with the subgenual anterior cingulate. Excessive habit formation was not related to differences in activation in the putamen (Gillan et al., 2015). Though task-based functional neuroimaging data using this construct in OCD are scarce, early indications support dysfunction in regions implicated in the pathophysiology of OCD. Whether similar activation patterns would be observed in a pediatric sample remains unknown and is important to investigate. While pediatric and adult OCD studies of brain activation during task performance converge in showing abnormal activity in CSTC circuits, the direction of activation differences (e.g., hypo- vs. hyperactive) within particular circuit nodes or node-to-node connections may shift across development (Brem et al., 2012).

Presently, it is not completely clear whether OCD symptoms may arise due to dysfunction within the habit system, goal-directed system, or an “arbitrator system” that is able to switch between rapid habit-like, automatic processes and slower, more flexible evaluative (i.e. goal directed) processes (Gruner et al., 2016). Based on a convergence of neuroimaging findings, the candidate locus of this “arbitrator system” is thought to involve inferior lateral prefrontal, frontopolar, and anterior cingulate cortices. The precise neural substrates of this arbitrator system, and whether it is indeed dysfunctional in OCD and responsible for inflexibility in OCD, remains unknown and awaits direct testing.

Discussion and limitations.—While the convergence of evidence suggests aberrant habit learning in OCD, the reasons for this remain unclear. Possibilities could include a deficiency in mechanisms underlying goal-directed learning, an over-reliance on mechanisms involved in habit learning, globally impaired instrumental extinction, abnormal arbitration between goal-directed and habit control, or some combination of these factors. More work is needed to identify the neural underpinnings of these mechanisms in normative and OCD populations. Comparisons of habit learning behavioral patterns and neural activation across OCD and other psychiatric samples is also needed to understand whether a

specific profile of dysfunction is related to OCD. Also unclear is the role of other factors, such as stress or anxiety in OCD, within this habit-driven framework. It is possible that anxiety is epiphenomenal or independently contributes to excessive habit learning (e.g., biases attention toward aversive stimuli and away from outcomes; Gillan & Robbins, 2014).

The role of development in OCD-related aberrant habit learning is not understood: no research to date has examined if or how the adult OCD findings pertain to pediatric OCD. Habit learning, goal-directed learning, and reward-related processing are driven by neural circuitry that undergoes significant change and maturation across childhood and adolescence (Fareri, Martin, & Delgado, 2008). Furthermore, with age comes exposure to different learning contingencies and contexts that afford new learning opportunities *and* challenges to flexible application of prior learning history. Multimethod research capturing behavioral patterns and neural correlates of habit learning across development is needed to understand the role of habit in the onset and progression of OCD across the lifespan.

Pediatric OCD samples may afford the unique opportunity to directly test the "compulsive-obsessive disorder' model. It is common for young children with OCD to be aware of compulsions but have an inability or great difficulty articulating specific obsessions (Freeman et al., 2012). While this has typically been attributed to less advanced ability to monitor and verbalize cognition, the habit framework suggests an interesting alternative hypothesis: perhaps these young children are in the "compulsive disorder" phase of OCD progression and have not yet developed obsessions at all. It is possible that repeated queries from parents or others about compulsions may actually contribute to the child developing obsessions in an effort to explain behaviors. Longitudinal testing of habit learning in early onset OCD or in youth at high risk for developing OCD alongside clinical interviews assessing obsessional content may help illuminate the developmental unfolding of symptoms across time.

Cognitive Systems: Response selection and inhibition

Response Inhibition (RI), or the ability to suppress irrelevant or interfering responses, is a critical cognitive process for supporting voluntary, planned behavior (i.e. cognitive control; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Bari & Robbins, 2013). RI deficits have been implicated in OCD, which is characterized by a high rate of non-functional behaviors that are driven by avoidance of negative experiences (i.e. compulsivity) rather than by pleasure-seeking (i.e. impulsivity; Leonard et al., 2015, Zor, Szechtman, Hermesh, Fineberg, Eilam, 2011). RI includes several subconstructs that all require top-down modulation of behavior and represent early, middle, and late phases of RI processing (Sebastian et al., 2013). Neurocognitive tasks measuring RI may tap these subconstructs differentially: interference control refers to the ability to limit cognitive interference from irrelevant stimuli in order to make a goal-directed response (e.g., Stroop, Flanker, or Simon tasks); action restraint is the process of inhibiting a response before it has been initiated (e.g., Go/No Go task); action cancellation occurs latest in the process, and involves inhibiting a response after it has been initiated (e.g., Stop Signal Task). Action cancellation is considered by some to be the most cognitively demanding point of inhibition (i.e. carrying the highest inhibitory load; Schachar et al., 2007).

Normative Development.—Understanding healthy development of response inhibition provides a framework for considering its potential role in the pathophysiology and maintenance of pediatric OCD. In general, available research supports the idea that performance and neural underpinnings of RI emerge developmentally. Performance on RI tasks is generally improved in adults vs. adolescents and in adolescents vs. children (e.g., van de Laar, van den Wildenberg, van Boxtel, & van der Molen, 2014) Moreover, RI may continue to develop even into adulthood (e.g., Casey, Tottenham, Liston, & Durston, 2005).

Studies of healthy neural development associated with RI have focused on prefrontal cortex (PFC) including inferior frontal gyrus (IFG) and premotor regions, with mixed findings regarding developmental differences in circuitry and associated RI performance. Findings have generally been consistent with the general notion of prolonged maturation of the fronto-striatal network (Booth et al., 2003). In developmental studies, PFC regions show increased activation for adults vs. children during a wide variety of RI tasks (e.g., Rubia et al., 2006; Rubia, Smith, Taylor, & Brammer, 2007). However, activation was not always associated with improved performance and some studies found decreases in task-based PFC activation (IFG, medial frontal gyri) in some age groups (Tamm, Menon, & Reiss, 2002; Luna, Padmanabhan, & O'Heam, 2010). For example, in a study linking event related potential measured neural activity to RI, age groups did not differ on RI performance, but children were less efficient and less able to suppress cortical motor outflow compared to adults (van de Laar et al., 2014), and adolescents demonstrated heightened neural responsiveness vs. both children and adults. Thus, changes in RI performance from childhood to adolescence may occur via improved ability to recruit PFC regions (i.e. increased activation), while changes from adolescence to adulthood may occur via improved efficiency (i.e. decreased activation) – explaining discrepant neural findings despite continued improvement in performance. It is also possible that adolescent recruitment of different strategies could modulate developmental trajectories of cognitive control (e.g., Friedman, Nessler, Cycowicz, & Horton, 2009). However, it is unclear whether age-related differences reflect that younger ages use different strategies, with a distinct circuitry vs. adults, or that they utilize a comparable strategy but recruit the same neural circuitry in a suboptimal manner. Additionally, although the available literature supports the hypothesis that there is continued emergence of RI skills from childhood through young adulthood, a majority of studies are cross-sectional, thus limiting our understanding of whether it is a truly developmental phenomenon. Despite this, considering the available cross-sectional RI findings informs a developmental approach, highlights the complexity of interpreting RI performance and underlying neural process across ages, and must be considered alongside RI findings in the pediatric OCD literature.

Response Inhibition in Pediatric OCD.—Although our focus is on a developmental understanding of RI in OCD, briefly reviewing RI deficits in adult OCD provides a useful reference point for understanding potential trajectories of emerging RI deficits in youth. Moreover, the large majority of RI studies in OCD have been completed with adult samples, the results of which are likely to assist with generating hypotheses about this domain in pediatric research. RI deficits have been found in adults with OCD, with a lifetime OCD diagnosis, and in unaffected relatives, leading some to propose that RI deficits are an

important OCD endophenotype (e.g., Chamberlain et al., 2007; deWit et al., 2012). However, findings in adults appear to depend on the specific RI subprocess targeted and/or the cognitive load associated with specific RI tasks. Action cancellation (stop signal task; SST) shows generally consistent differences in OCD vs. healthy controls (e.g., Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006), whereas action restraint (Go/No-go, CPT) has shown mixed results (van Velzen et al., 2014). In a meta-analysis of SST-measured RI deficits across psychiatric disorders, OCD was associated with the largest deficits (g = 0.77), followed by ADHD (0.62) and schizophrenia (g = 0.69), and low or no RI deficits present in other disorders (e.g., anxiety, autism, MDD, ODD/CD; Lipsczyz & Schachar, 2010). This is in contrast to a similar meta-analysis using the go/no-go and continuous performance (CPT) tasks, which found no differences across psychiatric problems, indicating that these tasks are not well-suited to characterize related underlying deficits (Wright et al., 2014). Therefore, action cancellation appears to be consistently impaired in adults with OCD, and this does not appear to be a deficit associated with psychopathology more broadly.

Although literature lags behind that for adults, multiple studies support the presence of RI deficits in pediatric OCD (Rosenberg et al., 1997; Taner, Bakar, & Oner, 2014; Waters & Farrell, 2014; McGuire et al., 2014). However, other studies have failed to find RI performance deficits associated with pediatric OCD. Hybel et al. (2016) found no significant performance differences on the SST and Flanker tasks in youth age 7-17 with OCD vs. healthy controls. A recent meta-analysis of cognitive findings in pediatric OCD showed only a small, nonsignificant mean effect size for RI deficits as compared with healthy youth (Abramovitch et al., 2015). However, this included only six studies of RI, each with small sample sizes (N of 14–23 per study). Importantly, only one of those studies specifically examined action cancellation using the SST (Chang, McCracken, & Piacentini, 2007), which demonstrated the largest effect size in youth (g = −0.49 vs. −0.02 to 0.16). Perhaps most importantly, nearly all studies of RI in pediatric OCD have combined youth across developmental stages. Some have suggested that RI deficits in OCD emerge developmentally – consistent findings in adults but not in children would seem to support this – yet the large majority of studies have grouped ages together and would therefore miss valuable information about the timing of first deficit emergence.

Brain areas responsible for flexible behavior, such as the PFC, mature later in development and have shown dysfunction in patients with OCD (Elliott & Carson, 2000). Broadly, adult OCD is characterized by decreased activation within PFC executive control networks and increased activation in affective processing networks (van den Heuvel et al., 2010). This may present as increased affective response through through hyperactivation of cortico-limbic circuitry, with a lack of top down control from prefrontal networks, which are thought to result in difficulty inhibiting inappropriate thoughts and behaviors. It is possible that developmental immaturity of the fronto-parietal pathways may interact with OCD-related neuropathology in youth to contribute to dysfunctional RI in this population.

Neural findings regarding RI deficits among youth with OCD might be informed by side-by-side consideration of normative RI neural development along with findings from the adult OCD literature. As with studies of RI task performance in adult OCD, neural findings in

adult OCD samples differ by RI subconstruct and/or task. Areas within the cortico-straito-thalamo-cortical (CSTC) circuitry, implicated in OCD, appear to be *hyperactive* during interference control, although these findings are inconsistent (van Velzen, 2014). This is similar to findings for interference control task performance among adults with OCD. Neural findings have been more consistent for restraint and action cancelation, with nodes of CSTC circuits generally showing *hypoactivation* for OCD vs. healthy controls (van Velzen, 2014). Specifically, these tasks appear to be associated with decreased activation of dorsolateral PFC, IFG, striatum, and thalamus, and increased activation of presupplementary motor area (pSMA) in OCD patients (van Velzen, 2014; de Wit et al., 2012). Seemingly discrepant RI findings in OCD-related hyperactivation during interference control and hypoactivation during action restraint and cancellation could be explained by compensation during early, less demanding RI tasks through recruitment of additional neural areas. During more demanding, “late stop” tasks such as the SST, such compensation may fail, resulting in hypoactivation and impaired performance.

As with studies examining behavioral performance detailed above, we are aware of very few studies examining functional imaging on RI tasks in youth with OCD. Available findings suggest that, compared with peers, youth with OCD may also recruit additional strategies and/or circuitry to support RI performance. For example, Woolley and colleagues (2008) described deceased brain activation in the orbitofrontal cortex bilaterally, as well as the right thalamus and basal ganglia on successful versus unsuccessful stop trials. On unsuccessful stop - go trial contrasts, boys with OCD showed decreased activation as compared with controls in the mesial frontal gyrus, extending laterally into left dorsolateral prefrontal cortex and ventrally into anterior cingulate gyrus. On a Simon task, Rubia et al. (2011) found reduced activation in SMA in OCD patients as compared to controls on incongruent-oddball trials. On oddball-congruent trials, OCD participants showed reduced activation in right dorsolateral prefrontal cortex relative to controls. Moreover, BOLD response in the posterior cingulate cluster was positively correlated with the CY-BOCS obsessions score. In general, these findings are largely consistent with the adult literature and provide converging evidence for the relevance of these circuits for RI processing in OCD. However, as noted above, there are very few studies that have investigated neural correlates of RI in pediatric OCD and those that have, have been limited to small, all-male samples. Considering the normative neural development of RI demonstrates the potential importance of neural measures for capturing earliest signs of RI deficits--if compensatory cognitive processes occur, performance would be unaffected and deficits could be masked. Thus, additional research in this area is critical for understanding RI development in OCD.

In summary, findings regarding RI performance in pediatric OCD have been variable. This is in contrast to results for adults with OCD, where performance deficits, particularly on the SST, are generally present. However, neural correlates of RI task performance appear altered in both youth and adults with OCD. It is possible that both youth and adults can maintain RI performance through compensatory hyperactivation or recruiting additional circuitry, but with increased task demands performance suffers and hypoactivation occurs. Although RI and supporting circuitry continue to develop into early adulthood, youth with OCD show distinct patterns of neural activation relative to typically developing peers. It may be that RI circuit abnormalities emerge before impaired task performance among youth with OCD.

Although some have suggested that RI deficits in OCD emerge developmentally, no study to our knowledge has investigated this longitudinally. Importantly, nearly all studies have combined youth across development and would therefore miss important information about first emergence of RI deficits in OCD.

Discussion and Limitations.—Conclusions regarding the role of RI deficits in the pathophysiology of pediatric OCD are precluded by notable sample differences across studies. Sample sizes are generally small (e.g., N of 14-23 reported in Abramovitch et al., 2015) and inclusion/exclusion criteria are highly variable across samples in terms of symptom severity, comorbidity, age, and sex distribution. As a result, studies are difficult to compare and results could be heavily influenced by subgroup differences. For example, ADHD and tics are also characterized by abnormal RI and/or differences in response inhibition neural networks (Lipszyc & Schachar., 2010; Ganos et al., 2014) and more commonly occur with childhood-onset vs. adult OCD (Kalra & Swedo, 2009). Excluding youth with these comorbidities may miss important subgroups of OCD for which RI deficits are most relevant. Pediatric OCD has also been associated with greater male preponderance (Geller et al., 2008); some studies have used a mostly female sample and may not be generalizable to pediatric OCD broadly.

Other clinical differences between youth and adults with OCD are important to consider in relation to the role of RI. Although some have theorized that childhood onset OCD may be considered a distinct subtype (Kalra & Swedo, 2009), there are no differences in RI performance (SST) based on self-reported child vs. adult OCD onset (Lei et al., 2017). OCD symptom subtype may be critically related to RI, as there is evidence that RI deficits differ by subtype among adults (Hashimoto et al., 2011), and youth with symmetry/ordering symptoms show greater deficits in RI vs. other subtypes (Stroop; McGuire et al., 2014). Youth are also more likely to experience compulsions that are not preceded by obsessions, and compulsion-only OCD is common in very young children (Freeman et al., 2012, Kalra & Swedo, 2009). Some have theorized that development of OCD compulsions may precede the onset of RI deficits, and that RI deficits then contribute to OCD symptom maintenance via increased obsessions. Some very early evidence from adult OCD analog studies supports this hypothesis: those with poor RI demonstrate greater uncertainty and memory distrust after repeated checking (Linkovski, Kalanthroff, Henik, & Anholt, 2013) and RI can causally affect behavioral responses to uncertainty (Kalanthroff et al., 2016). However, we note a critical lack of longitudinal studies that examine developmental emergence of RI in OCD, or even those that examine developmental emergence of OCD symptoms themselves. Thus, hypotheses about relative development of these must be initially generated based on what is known from cohort or cross-sectional designs.

Negative valence is of direct relevance to OCD symptom expression, and the role of RI may differ under conditions of threat or nonreward. Among adults with OCD, RI deficits are greater with threat cues vs. neutral cues, and greatest when cues are fear-relevant for contamination OCD (Adams, 2015). Moreover, this effect was specific to response inhibition vs. response activation. This is in contrast to findings with healthy adults, where danger cues were associated with longer overall response times and greater errors during response activation vs. inhibition (Liu, Cao, Chen, & Wang, 2017). Although one study

found that youth with OCD did not demonstrate RI deficits in response to emotional (vs. neutral) stop cues (Waters & Farrell, 2014), the emotional cues (angry and happy faces) were not relevant to OCD content and may not have generated threat conditions. Studies of RI performance and neural underpinnings under conditions of negative valence are likely to be critical for understanding its role in OCD. Given that healthy adolescents show RI impairments and attenuated activity in frontal regions under conditions of increased arousal and emotion (Andres et al., 2007), a developmental approach should be a key component of such studies.

Overall, task-based RI deficits are implicated in adult OCD, with emerging evidence in pediatric OCD. However, debate continues regarding the clinical significance and role of RI in pathophysiology, development, and maintenance of OCD (Abramovitch et al., 2015). Studying development of RI in youth with OCD can contribute uniquely to understanding core disease processes and critical periods for intervention. Future work to develop and refine theories integrating pathological and developmental processes will help reconcile seemingly discrepant findings and progress the field in a principled way.

CONCLUSION

In this discussion, we have presented three RDoC constructs with relevance to pediatric OCD and discussed the state of the literature and developmental considerations in investigating these constructs. Within each construct, some findings appear to hold more consistently across developmental stages. On RI tasks probing action cancellation, both adults and children with OCD appear to show neural abnormalities compared to psychiatrically healthy counterparts, though findings regarding RI performance are inconsistent in children. However, a limited number of studies have examined action cancellation in pediatric OCD, dampening the strength of conclusions that can be drawn from such comparisons. Similarly, in studies of threat estimation, results suggest that while OCD patients may not overestimate the likelihood of a potential threat actually occurring, both children and adults may tend to overestimate the severity of threats, were they to occur. Unfortunately, use of different paradigms to capture threat estimation in adult vs. pediatric samples prohibits direct comparison. Ultimately, development of more standardized paradigms, adapted in a consistent manner for use across the lifespan, may better allow for comparisons across developmental stages, and understanding of change in these constructs overtime.

While some behavioral findings exhibit relative consistency between adult and pediatric samples, other findings appear contradictory. This is particularly apparent in comparing neuroimaging outcomes between children and adults with OCD. Understanding “normal” developmental trajectories for constructs of interest and associated neural correlates will be especially important in defining the continuum from “normal” to “abnormal” and in understanding specific pathological developmental trajectories that may lead to OCD. Moreover, as stated above, use of consistent methodologies and paradigms across developmental stages could enable better understanding as to whether seemingly contradictory results are accurate reflections of developmental shifts in disease progression or inaccurate conclusions due to methodological mismatch.

One concern highlighted by this review is the general neglect of pediatric populations in research studying many of these domains in OCD. While some domains appear more consistently researched across both pediatric and adult samples (e.g., RI), other domains show a relative dearth of pediatric research. Within the habit subdomain, specifically, we are not aware of any pediatric research using devaluation paradigms, despite the popularity of this paradigm to examine habit in adults and the use of these data to drive theory about OCD development. As we know, children are not just little adults. Findings in adults cannot necessarily be extended downward to pediatric populations, nor can developmental processes be inferred from cross-sectional data gathered in adult-only samples. This is also true across developmental stages within childhood, and recognition of developmental differences may be differentially important across RDoC domains. Despite this, many studies combine pediatric samples from multiple stages of development, which may ultimately cloud key developmental differences. Precise understanding of the developmental unfolding of aberrant functioning in these RDoC domains may prove important in treatment research focused on prevention or personalized tailoring of intervention strategies.

While consideration of developmental stage is, in and of itself, important, a number of other concerns will need to be addressed in the RDoC framework in order for this classification system to develop in a way that moves toward better understanding of mental illness across the lifespan and generation of developmentally appropriate precision medicine interventions. In its current form, RDoC does not effectively integrate biology-environment interactions. It is known that life experiences are capable of shaping biology in a lasting way (e.g., Romens, McDonald, Svaren, & Pollak, 2015), and youth are actively embedded in contexts that involve significant new learning experiences. Specific to OCD, family, school, and social contexts can play key roles in perpetuating or attenuating OCD symptoms. Research that effectively measures the role of environmental/contextual factors with social, cognitive, and physical development will be particularly important for understanding the continuum between normal and abnormal behavior in children and perhaps illuminate novel targets for intervention.

Similarly, interaction between domains or constructs is likely, if not assured, particularly in a complex disorder such as OCD. For example, positive (e.g., reward learning) or negative valence constructs (e.g., fear, anxiety) may moderate cognitive system functioning (e.g., attention) or social processes (e.g., affiliation and attachment). The nature of such interactions between constructs may also vary over time as cognitive and social processes develop, along with changes in neural development.

Beyond linking constructs across dimensions, building evidence of links within constructs will also be important. There is a particularly critical need for studies that link neural and task data to ecologically valid and clinically relevant behavioral correlates. Without such evidence, behavioral and clinical implications of neural and task-based findings should be considered with caution. Longitudinal designs and use of representative, diagnostically mixed samples are needed in order to draw conclusions about emergence of abnormal functioning within a given construct of interest.

Finally, while the focus on this manuscript has been on pediatric OCD, we acknowledge that the intention of the RDoC initiative was to move beyond existing diagnostic categories, rather than to serve as an attempt to explain one classification system with another (Cuthbert & Insel, 2013). Diagnostic classifications based primarily on clusters of symptom presentations understandably result in a large amount of heterogeneity within a single diagnostic group. Perhaps one subgroup of children with DSM-5 defined OCD may show high anxiety and poor response inhibition, but habitual behavior within normal limits, whereas another group may show lower anxiety, but a strong bias toward habitual responding. Considering how RDoC domains may apply to specific presentations or subgroups of OCD patients may also ultimately better explain comorbidity, which is common in both children and adults with OCD. Applying RDoC constructs to the study of pediatric psychopathology clearly presents a number of challenges, which are recognized at this early stage:

> "These domains and levels of analysis are not the entire universe of psychopathology -- they are a starting point. They do not yet incorporate the critical role of development, environmental exposures, or the evolution of psychopathology over time. The domains and the levels of analysis will evolve as tools improve and the clinical database expands." (Insel, 2014, pg. 396)

As RDoC continues to evolve, attention to developmental considerations will be necessary to encourage creation and modification of methodologies appropriate for use across the lifespan. This may ultimately speed the translation of knowledge about dimensions of psychopathology across developmental stages, informing both prevention and treatment development efforts.

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Highlights:

- In its current iteration, the RDoC matrix is limited in terms of its integration of developmental considerations.
- Many RDoC constructs with relevance to OCD show normative behavioral and/or neural changes across development.
- In order to further our understanding of RDoC constructs with relevance to OCD, it is important to study these constructs across developmental stages.