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Review

# Implications of the Research Domain Criteria project for childhood anxiety and its disorders

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## HIGHLIGHTS

- The Research Domain Criteria (RDoC) facilitate advances in the classification and treatment of childhood anxiety disorders.
- Implications of the Systems for Social Processes and the Negative Valence System domains of RDoC are highlighted.
- Behavior, self-report, and brain measures, particularly frontoamygdala circuitry findings are summarized.
- Integrative and translational research provides unique opportunities and challenges for novel treatment development.

## ABSTRACT

Anxiety disorders are among the most prevalent psychiatric disorders in youth; however, progress in treatment for childhood anxiety has stalled over the past decade. The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project represents a shift toward a dimensional and interdisciplinary approach to psychiatric disorders; this shift can reframe developmental psychopathology for childhood anxiety and facilitate novel advances in its classification and treatment. Here we highlight constructs in the Systems for Social Processes and the Negative Valence System domains of RDoC, as they relate to childhood anxiety disorders. Childhood anxiety relates to both RDoC domains. In terms of social processes, through natural reliance on parents to reduce children's fear, attachment represents one particular social process, which plays a central role in anxiety among youth. In terms of negative valence, considerable research links threat conditioning to pediatric anxiety. Finally, fronto-amygdala circuitry relates to all three entities, as it has been shown to underly both attachment processes and threat learning, while it also has been consistently implicated in anxiety disorders across development. Through integrative and translational approaches, RDoC provides unique opportunities and simultaneous challenges for advancing the understanding and treatment of childhood anxiety disorders.

## 1. Introduction

The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project represents a critical shift in conceptualizing psychiatric disorders from a focus on clinician-rated symptoms using a categorical approach to a dimensional approach encompassing domains of human behavior most deeply studied in neuroscience (Insel et al., 2010; Sanislow et al., 2010; Cuthbert & Insel, 2013). RDoC continues to evolve since its inception as new data accumulate, with promise to lead to significant advances in understanding of psychopathology.

Research in anxiety and its disorders is particularly ripe for the changes that are unfolding with RDoC. Although anxiety disorders are prevalent across the lifespan (Costello, Egger, Copeland, Erkanli, & Angold, 2011), the broad range of cross-study prevalence estimates highlights potential inconsistencies in the application of Diagnostic and Statistical Manual (DSM) categories. In addition, as often noted, comorbidity is more often the rule than the exception, particularly in the anxiety disorders (Costello et al., 2011), which suggests that DSM categories fail to "carve nature at its joints". It is not uncommon for children and adolescents to meet criteria for many 'different' anxiety disorders, highlighting the difficulties inherent to the DSM categorical distinctions and the high likelihood of shared underlying pathology. Further, the symptoms needed to meet diagnostic criteria for some disorders often co-occur with those of others, and anxiety symptoms occur in other psychiatric disorders (Curry, March, & Hervey, 2004; Kessler, Chiu, Demler, & Walters, 2005). Moreover, most symptoms that

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characterize the anxiety disorders are clearly excessive or inappropriate manifestations of otherwise adaptive components of human functioning.

The heterogeneous nature of anxiety disorders therefore underscores both the strengths and the challenges of RDoC. Examination of the NIMH RDoC matrix shows that most of the domains identified are pertinent to anxiety disorders: Negative Valence Systems are crucial to the excessive fear and avoidance that are germane to anxiety disorders; Cognitive Systems include allocation of attention, which is biased toward threat in clinically anxious individuals; Systems for Social Processes are also highly relevant to pediatric anxiety as children respond to anxiety with social responses oriented toward attachment figures; and Arousal/Regulatory Systems are disrupted in individuals with anxiety disorders who show difficulty with self-regulation and potent startle reflex.

A comprehensive review of the myriad ways in which anxiety relates to RDoC constructs and domains is beyond this article's scope. We instead focus on two constructs within RDoC that are particularly related to anxiety in children and adolescents, encompassed hereon by the term 'children'. Specifically, within the 'Systems for Social Processes' domain and its associated 'Affiliation and Attachment' construct, we focus on research on attachment in childhood anxiety; within the 'Negative Valence Systems' domain and its associated 'Fear' construct, we focus on research on fear learning in childhood anxiety. Even in this narrower context, an exhaustive review is beyond this article's scope. Rather, we illustrate the relevance of RDoC by showcasing research that most heavily influences therapeutics, and that highlights developmental trajectories of particular pertinence to childhood anxiety disorders.

RDoC is not, as has been noted (Franklin, Jamieson, Glenn, & Nock, 2015), a developmental framework for psychopathology. However, applying the RDoC framework to conceptualizations of childhood disorders provides fresh perspectives on key questions and fruitful avenues for research. RDoC also provides important perspective on two complementary concepts fundamental to developmental psychopathology: equifinality and multifinality (Cicchetti, 1984; Cicchetti & Rogosch, 1996; Sroufe, 1997; Sroufe & Rutter, 1984). Equifinality refers to the ability of multiple causes to lead to the same outcome, while multifinality refers to the variety of outcomes that can follow from the same cause. Taken together equifinality and multifinality describe the variation in causes that contribute to given outcomes, and to the variation in outcomes with shared causes. By modifying the 'outcomes' of interest from DSM diagnoses or symptoms to underlying domains and constructs, RDoC can reframe the questions of equifinality and multifinality as these questions relate to neuroscience. In other words, under RDoC, 'outcomes' can be disrupted functioning as quantified through neuroscience, rather than diagnostic categories. Important new perspectives on equfiniality and multifinality emerge by attending to the problems that arise from overspecification of links between risk factors and outcomes, conceptualized in terms of brain function (Mayes & Spence, 1994). The current review highlights several fertile areas for applying the RDoC framework to the developmental psychopathology of childhood anxiety disorders.

## 2. Social processes

### 2.1. Broad conceptualizations

The RDoC "Systems for Social Processing" domain encompasses functions that shape interpersonal behavior including identifying, interpreting, generating, and reacting to social content. The domain identifies four constructs: (1) Affiliation and Attachment, (2) Social Communication (with subconstructs for Reception and Production of Facial and Non-Facial Communication), (3) Perception and Understanding of Self (with subconstructs for Agency and Self-Knowledge), and (4) Perception and Understanding of Others (with subconstructs for Perception of Animacy and Action, and for Understanding of Mental States). While many of these functions relate to anxiety, Affiliation and Attachment possesses particular relevance for childhood anxiety disorders, as children seek comfort and protection from attachment figures when threatened.

### 2.2. Affiliation and Attachment

Human infants, like most other mammalian infants, are largely altricial and rely on parental caregiving for both sustenance and protection. This forms the basis of the attachment bond (Bowlby, 1978), which shapes core features of mammalian development that impact functioning throughout life (Hazan & Shaver, 1994). Species-specific systems have evolved throughout mammalian life, through which offspring signal their needs and attain protection from caregivers in response to those signals (Feldman, 2015). As a result, systems for threat detection and stress regulation are intricately intertwined with systems for attachment and affiliative behavior, with overlapping behavioral patterns and shared neurochemistry and circuitry (Lebowitz, Leckman, Silverman, & Feldman, 2016; MacDonald & Feifel, 2014; Moriceau & Sullivan, 2006). These systems are relevant to the development, course, and treatment of childhood anxiety disorders. They involve not only the children themselves but also their parents and other attachment figures as partners in an evolved interpersonal, social system related to fear and anxiety. Empirical research, spanning multiple units identified for analysis by the RDoC matrix, implicates the attachment and affiliative systems in childhood anxiety. Key findings are summarized next.

#### 2.2.1. Behavior and self-report

In infants and very young children, seminal research utilizes the Strange Situation paradigm (Ainsworth, Blehar, Waters, & Wall, 1978), which classifies infants as having either secure or insecure attachment based on the infant's response to separation and reunification with the primary caregiver. Meta-analyses demonstrate significant associations between insecure attachment and anxiety in childhood, though findings are inconsistent and effect sizes are small to moderate (Colonnesi et al., 2011; Groh, Roisman, van Ijzendoorn, Bakermans-Kranenburg, & Fearon, 2012; Madigan, Atkinson, Laurin, & Benoit, 2013; van Ijzendoorn, Schuengel, & Bakermans-Kranenburg, 1999). One possible explanation for the inconsistent findings relates to the emphasis on diagnosis as the outcome of interest. It is plausible that insecure attachment would exert larger effects on some domains or constructs relating to anxiety, than on others. For example, excessive clinginess or social avoidance, which relate more directly to attachment and social processing, may be more impacted by insecure attachment than other areas of anxiety. Including data on brain functions associated with these behaviors might generate even larger associations. As such, utilizing an RDoC framework to examine the anxiety-related sequelae of insecure attachment may lead to more consistent findings or larger effect sizes.

Self-report measures have also been developed to assess attachment security in children and provide additional evidence for the link between insecure attachment and anxiety disorders (Muris, Mayer, & Meesters, 2000).

#### 2.2.2. Brain circuitry

Neuroimaging research suggests that brain systems that support attachment are also implicated in childhood anxiety. Frontoamygdala circuitry may malfunction in anxiety disorders, giving rise to diminished prefrontal control, amygdala hyperactivity, and altered connectivity between these regions. The amygdala is a subcortical brain region that responds to affectively salient stimuli in the environment and plays a central role in biologically relevant learning (LeDoux, 2007). Portions of the prefrontal cortex (PFC) can constrain or amplify these amygdalar responses, with differential involvement in emotion processing depending on the given prefrontal region. The ventromedial PFC is involved in inhibition of fear expression during processes such as

fear extinction (Phelps, Delgado, Nearing, & LeDoux, 2004; Sotres-Bayon & Quirk, 2010). Emotion regulation and its effect of reducing amygdala reactivity relies on a more distributed network of prefrontal regions, many of which show a negative coupling with the amygdala (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Kim, Somerville, Johnstone, Alexander, & Whalen, 2003) consistent with regulatory projections from the PFC to the amygdala that have been identified across species (e.g., Ghashghaei, Hilgetag, & Barbas, 2007). The ventrolateral PFC has been implicated in automatic emotion regulation (Lieberman et al., 2007) and attentional control (Phan et al., 2005), whereas the dorsolateral PFC and regions of medial PFC (e.g., dorsomedial) are involved in intentional, more effortful emotion regulation processes such as cognitive reappraisal (Buhle et al., 2014; Ochsner, Bunge, Gross, & Gabrieli, 2002; Phillips, Drevets, Rauch, & Lane, 2003). However, the dorsomedial PFC, along with dorsal anterior cingulate cortex (ACC), has also been implicated in anxious processing and increased positive coupling with the amygdala (Robinson et al., 2014).

Children with anxiety disorders display alterations in the activation and functional connectivity of many of these regions. Like in adults with anxiety disorders (Bishop, Duncan, & Lawrence, 2004; Etkin et al., 2004; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Stein, Simmons, Feinstein, & Paulus, 2007), one of the most consistent findings among children with anxiety disorders is amygdala hyperactivity to emotional stimuli (Guyer et al., 2008; McClure et al., 2007; Monk et al., 2008; Thomas, Drevets, Dahl, et al., 2001; Thomas, Drevets, Whalen, et al., 2001). Impaired prefrontal control of the amygdala and altered connectivity between the amygdala and PFC have also been observed in both children (Blackford & Pine, 2012; Kujawa et al., 2016; Monk et al., 2006) and adults (Kim et al., 2011; Milad et al., 2009; Phan et al., 2009; Rauch, Shin, & Phelps, 2006; Rauch, Shin, & Wright, 2003; Shin et al., 2005) with anxiety disorders. Though the precise anatomical locations and directions of some findings may be task-specific, children with anxiety disorders specifically show alterations in dorsomedial PFC, ventromedial PFC, and ventrolateral PFC function (e.g., McClure et al., 2007; Monk et al., 2006, 2008).

Child and adolescent development involve dynamic changes in frontoamygdala circuitry, which may contribute to heightened risk for anxiety at specific developmental stages. Cross-species evidence suggests that the amygdala matures earlier than the PFC (Chareyron, Lavenex, Amaral, & Lavenex, 2012; Lenroot & Giedd, 2006; Machado & Bachevalier, 2003; Payne, Machado, Bliwise, & Bachevalier, 2010). Children show robust amygdala reactivity to fearful faces and other emotional stimuli during typical development, with reactivity typically decreasing following childhood (Decety, Michalska, & Kinzler, 2012; Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Silvers, Shu, Hubbard, Weber, & Ochsner, 2015; Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014). This heightened amygdala reactivity may correspond to age-typical, normative expressions of childhood fears, such as separation anxiety, which peaks early in life (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Gullone, King, & Ollendick, 2001).

Reciprocal connections between the amygdala and prefrontal regions including the medial PFC and ACC show protracted development throughout childhood and adolescence both functionally (Decety et al., 2012; Gabard-Durnam et al., 2014, 2016; Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Perlman & Pelphrey, 2011; Vink et al., 2014) and structurally (Gee et al., 2016; Lebel et al., 2012; Swartz et al., 2014). Cross-sectional data suggest that a developmental switch may occur in amygdala-medial PFC connectivity during the transition from childhood to adolescence, which parallels normative changes in anxiety and amygdala reactivity (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Wu et al., 2016). Children show positive functional connectivity when viewing fearful faces, whereas negative functional connectivity emerges around the transition to adolescence. This pattern of negative (inverse) functional connectivity becomes strongest in adulthood, consistent with an increasingly regulatory circuit that has been demonstrated in healthy adults (Hariri et al., 2003; Kim et al., 2003). Importantly, while data are only beginning to emerge, some evidence suggests that this trajectory goes awry in youth with anxiety disorders, who fail to exhibit the expected age-related patterns of amygdala-medial PFC connectivity (Kujawa et al., 2016; Spielberg et al., 2015).

Early in life, attachment figures powerfully reduce fear in their children, leading children to seek such figures when threatened, findings that are reflected in cross-species research (Gunnar & Donzella, 2002; Hofer, 1994; Howell et al., 2013; Moriceau & Sullivan, 2006; Plotsky et al., 2005; Romeo et al., 2003). In rodents and non-human primates, maternal presence maintains low levels of corticosterone and reduces HPA axis reactivity (Levine, Johnson, & Gonzalez, 1985; Moriceau & Sullivan, 2006; Sanchez, 2006), similar to effects of parents in human children (Gunnar & Donzella, 2002; Hostinar, Sullivan, & Gunnar, 2014; Kertes et al., 2009; Seltzer, Prososki, Ziegler, & Pollak, 2012). At the neural level, maternal presence engages the medial PFC (Bock, Riedel, & Braun, 2012; Rilling et al., 2001) and buffers against amygdala reactivity (Moriceau & Sullivan, 2006) in developing animals.

Brain imaging studies extend such cross-species perspectives on neurobiological mechanisms by which attachment figures reduce anxiety early in life. One recent study suggested that the presence of parental stimuli predicts reduced amygdala reactivity in children, as well as phasic induction of more mature patterns of negative amygdala-medial PFC functional connectivity that are associated with lower anxiety (Gee et al., 2014; Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013). Moreover, a subset of children who reported relying particularly heavily on parents when under stress also showed the greatest impact of maternal presence on amygdala-medial PFC functional connectivity. A similar impact of parental presence has been shown in clinically anxious children who requested their mother be present during an fMRI scan (Conner et al., 2012). These findings suggest a potential neural mechanism by which children's reliance on attachment figures reduces anxiety.

Importantly, the effect of parental presence on frontoamygdala circuitry and behavior appears specific to childhood and not to adolescence (Gee et al., 2014; Hostinar, Johnson, & Gunnar, 2015). Given dynamic changes across development, caregiving experiences may interact with developmental stage in ways that allow parents to reduce fear or buffer against stress reactivity in their children in unique ways at particular stages (Gee, 2016; Gee & Casey, 2015). Parents may shape circuitry function in early life, and effective anxiety reduction in later life may reflect the child's evolving capacity to engage this circuitry independently with development (Callaghan & Tottenham, 2016), especially around adolescence and related key developmental transitions. Over time, consistent engagement of frontoamygdala circuitry through attachment figures early in life may contribute to environmental shaping of the more intrinsic function of this circuit in ways that promote independent anxiety reduction as children transition into adolescence and adulthood (Gabard-Durnam et al., 2016). Though caregiver buffering effects appear to be more prominent in childhood than at later ages, social buffering of anxiety and stress reactivity continues with alternative relationships serving buffering roles at distinct developmental stages. For example, evidence suggests that relationships with peers and romantic partners take on similar roles later in life (Adams, Santo, & Bukowski, 2011; Calhoun et al., 2014; Coan, Schaefer, & Davidson, 2006; Ditzen et al., 2007).

Early attachment figures may reduce childhood anxiety through effects on frontoamygdala circuitry. As such, early-life disruptions in caregiving may profoundly impact development of this circuit and its association with anxiety. Substantial variability exists in outcomes following caregiving-related stress, in part due to differences in the timing of the adversity (Gee & Casey, 2015; Sabatini et al., 2007; Schayek & Maroun, 2015). However, forms of early caregiving

adversity such as parental deprivation (i.e., institutionalized care), neglect, and maltreatment are associated with altered function in the HPA axis (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Gunnar & Quevedo, 2007; Koss, Hostinar, Donzella, & Gunnar, 2014; Moriceau, Raineki, Holman, Holman, & Sullivan, 2009; Sanchez, 2006; Tarullo & Gunnar, 2006) and frontolimbic (i.e., prefrontal connectivity with the amygdala and hippocampus) circuitry (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Hanson, Knodt, Brigidi, & Hariri, 2015; Herringa et al., 2013; Howell et al., 2013; Jedd et al., 2015; Ono et al., 2008; Tottenham et al., 2010, 2011). Individuals who experience early caregiving adversity in the form of neglect or trauma are also at increased risk for anxiety (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Goff et al., 2013; Green et al., 2010; Ono et al., 2008; Tottenham et al., 2010; Zeanah et al., 2009), which has been associated with increased amygdala volume (Mehta et al., 2009; Tottenham et al., 2010) and reactivity (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013; Tottenham et al., 2011).

The pathways by which early caregiving adversity increases risk for anxiety disorders may differ depending on the type of adversity experienced. Nevertheless, these distinct pathways may lead to similar appearing symptoms, consistent with the concept of equifinality. At the same time, the same form of adversity can lead to different outcomes and risk for psychopathology. The capacity to trace these unique pathways rests on the degree to which distinct forms of adversity can be quantified. To enhance research in this area, the field increasingly has moved toward a more nuanced approach to understanding the effects of early-life stress, delineating core dimensions such as threat and deprivation (McLaughlin & Sheridan, 2016). Despite increased risk for anxiety following childhood adversity (Green et al., 2010), the specific mechanisms underlying risk may differ across domains such as fear learning (McLaughlin et al., 2016), emotion regulation (Kim & Cicchetti, 2010), and attentional processes (Briggs-Gowan et al., 2015).

As one example of a potential process underlying the association between early caregiving adversity and subsequent anxiety, evidence across species suggests that early parental deprivation may accelerate the development of frontoamygdala circuitry. Cross-sectional data suggest that typically reared individuals manifest a normative, age-related shift from positive to negative amygdala-medial PFC functional connectivity. However, children who experienced parental deprivation during infancy display a pattern of negative amygdala-medial PFC functional connectivity that only manifest among older individuals not exposed to deprivation (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013). These findings in humans are consistent with evidence of accelerated development in non-human animal studies (Bath, Manzano-Nieves, & Goodwill, 2016; Callaghan, Sullivan, Howell, & Tottenham, 2014; Moriceau et al., 2009; Moriceau & Sullivan, 2006; Ono et al., 2008). In both rodents and humans, early frontoamygdala development relates to cortisol levels, suggesting that modifications of the HPA axis may contribute to accelerated development. The precocious maturation of frontoamygdala circuitry may be adaptive for young organisms lacking in parental care. For example, despite overall greater risk for anxiety, within the group of youth who had experienced parental deprivation, those individuals displaying negative connectivity had lower anxiety than their same-aged peers with positive connectivity (Gee, Gabard-Durnam, et al., 2013; Gee, Humphreys, et al., 2013). However, longitudinal studies are necessary to understand the likely consequences of accelerated development.

#### 2.2.3. Molecules

Neurochemical research on attachment has focused in large part on oxytocin. Oxytocin and the closely related molecule arginine vasopressin are nine-amino acid peptides with a long evolutionary history (Donaldson & Young, 2008; Feldman, Monakhov, Pratt, & Ebstein, 2015). Variants of oxytocin are found in a wide range of species across the animal kingdom and are implicated in modulating aspects of species-specific attachment and anxiety regulation behaviors (Feldman et al., 2015). In mammals, oxytocin shapes caregiving and pair bonding behavior in several species (Carter, DeVries, & Getz, 1995; Insel & Young, 2001; Pedersen & Prange, 1979). Studies in animal models have also demonstrated the role of oxytocin in anxiety behavior. Central administration of oxytocin in mice reduces anxiety behavior and increases social behavior (Lukas et al., 2011; Mak, Broussard, Vacy, & Broadbear, 2012; Slattery & Neumann, 2010), while central administration of oxytocin receptor antagonists leads to avoidant behavior (Lukas et al., 2011). The anxiolytic effects of oxytocin administration are less pronounced however, when examining startle response to unpredictable threat cues (Missig, Ayers, Schulkin, & Rosen, 2010).

Research into the roles of oxytocin in attachment and anxiety in humans is constrained by the barriers to direct central measurement or administration of oxytocin and its agonists or antagonists. Research has thus by necessity focused largely on peripheral oxytocin measurement and/or administration. There remain important questions regarding the validity and reliability of the oxytocin immunoassays which have been frequently used in this context, the degree to which peripheral levels may be taken as indicators of central oxytocinergic functioning, the optimal measurement methods and processes (e.g., use of extracted or unextracted samples; enzyme- or radio-immunoassay etc.) and the best fluid in which to measure peripheral oxytocin levels (i.e., saliva, blood, urine, or the more difficult to study cerebrospinal fluid (CSF)) (Carter et al., 2007; Kagerbauer et al., 2013; McCullough, Churchland, & Mendez, 2013; Szeto et al., 2011; Young & Anderson, 2010). Salivary oxytocin in particular has been increasingly used in research because of the ease with which it can be obtained, because saliva tends to yield higher concentration values compared to extracted samples, and because saliva levels tend to correlate moderately with levels measured in plasma (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Grewen, Davenport, & Light, 2010). Despite these important questions, data from numerous studies support behavioral effects of peripherally administered oxytocin and the coordination between central and peripheral oxytocinergic functioning. As such, data on peripheral oxytocin and social behavior are valuable, but must be interpreted with caution, in particular in with regard to establishing absolute oxytocin levels, rather than relative levels within samples.

A single study has examined CSF oxytocin levels in relation to childhood anxiety (Carson et al., 2015). In ten non-clinical youth who were undergoing CSF-related medical procedures, CSF oxytocin levels were negatively correlated with ratings of anxiety symptoms. Two more recent studies reported on plasma oxytocin in clinically anxious children. In one study, salivary oxytocin levels correlated negatively with anxiety symptoms in the clinically anxious children, in particular separation anxiety (Lebowitz et al., 2016). In the other study, a brief positive parent-child interaction was followed by a rise in children's salivary oxytocin levels, and the degree of oxytocin response was positively correlated with levels of separation anxiety (Lebowitz et al., 2017) leading to the hypothesis that children with separation anxiety disorder seek parental proximity to regulate a low functioning oxytocinergic system. Should additional research confirm a particular role for the oxytocinergic system in childhood separation anxiety, this would be one example of an RDoC construct helping to establish the distinction between specific domains of anxiety, at a level of analysis beyond the behavioral or self-report. The scant findings in childhood anxiety and oxytocin levels extend research in adults, showing associations between peripheral oxytocin and measures of anxiety, but results in adults have been inconsistent and meta-analyses are needed (Anderberg & Uvnas-Moberg, 2000; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Light et al., 2000; Scantamburlo et al., 2007; Stuebe, Grewen, & Meltzer-Brody, 2013).

#### 2.2.4. Genes

Recent changes in genetics research emphasize whole-genome approaches, which are not easily applied to RDoC-focused approaches to genetics. Despite their limitations, approaches in RDoC that target

particular forms of genetic variation also inform understandings of attachment. This includes genetics research on the oxytocinergic system in attachment and anxiety disorders (Onodera et al., 2015; Chen, Barth, Johnson, Gotlib, & Johnson, 2011) as well as genetics research on (Notzon et al., 2016) familial, environmental, and neural correlates of anxiety (Chen et al., 2011; Myers et al., 2014; Thompson, Parker, Hallmayer, Waugh, & Gotlib, 2011; Tost et al., 2010; Wang et al., 2014). Research in animals can take advantage of the higher levels of experimental control to overcome limitations in research on humans to precisely map genetic contributions to attachment and other social processes related to threat-responsive behavior (Amico, Mantella, Vollmer, & Li, 2004; Sala et al., 2011; Takayanagi et al., 2005). Overall, preclinical and clinical studies emphasize the role of oxytocin in both stress and social behavior in ways likely to inform studies of childhood anxiety (Feldman et al., 2015).

Research findings that implicate oxytocin and its social effects in other, non-anxiety, phenotypes underscore the importance of the RDoC framework for understanding disruptions in functioning across traditional diagnostic lines. For example, oxytocin administration has been found to produce antidepressant effects, and to augment the effects of antidepressant medication, in animal models of depression (Arletti et al., 1995; Arletti & Bertolini, 1987; Nowakowska, Kus, Bobkiewicz-Kozlowska, & Hertmanowska, 2002; Ring et al., 2010). Its roles in modulating social behavior, including social recognition of conspecifics, also have implications for autism spectrum disorders (Ferguson, Aldag, Insel, & Young, 2001).

## 3. Negative valence systems

### 3.1. Broad conceptualizations

The negative valence systems domain under RDoC encompasses processes engaged in the context of aversive or dangerous situations. The RDoC matrix identifies five constructs in this domain: (1) Fear or Acute Threat, (2) Potential Threat, (3) Sustained Threat, (4) Loss, and (5) Frustrative Nonreward. Demarcating these constructs is challenging, in part because threats that are realistically remote or of low likelihood can be inaccurately perceived as immediate among individuals with anxiety disorders. RDoC describes the Fear construct as the complex 'defensive motivational system to promote behaviors that protect the organism from perceived danger'. This definition distinguishes responses to immediately perceived dangers or threats from responses to more distal, less certain threats. Disruptions in the fear system have clear implications for childhood anxiety disorders and have been studied at multiple levels of the RDoC matrix, and we thus focus on this construct here. By contrast, relatively little research has focused on the other constructs in anxious children.

### 3.2. Fear

Key features of the fear system are highly conserved across species, making translation of research in other species to humans more direct than in many areas (LeDoux, 2000; Phelps & LeDoux, 2005). For example, the neural correlates of threat conditioning and extinction can be assessed using very similar procedures across species, such that neutral and aversive unconditioned stimuli can be paired repeatedly to examine threat learning, or decoupled to examine extinction learning (Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009; Quirk & Mueller, 2008). In humans, the response to these procedures, at the behavioral, molecular, and circuitry levels, parallels those observed in other species (Lissek et al., 2005).

#### 3.2.1. Behavior and self-report

Self-report of subjective anxiety levels has been used in classical conditioning studies to examine fear acquisition and extinction. Meta-analysis demonstrates robust fear acquisition and delayed extinction in patients with anxiety (Lissek et al., 2005). Studies using behavioral outcomes to examine fear acquisition or extinction (i.e., operant conditioning) in humans are less common, despite data showing increased avoidant behavior in children and adults with anxiety disorders (Hayes, 1976; Klein, Becker, & Rinck, 2011; Tsao & McKay, 2004) and given the central role of avoidance for most theoretical models of anxiety disorders. Early studies used shock as the unconditioned stimulus in attempts to recreate conditions used to measure learned avoidance in rodents (Ader & Tatum, 1961, 1963); a small number of studies have used alternative stimuli such as CO2, or unpleasant images or sounds (Dymond, Roche, Forsyth, Whelan, & Rhoden, 2007; Lejuez, O'Donnell, Wirth, Zvolensky, & Eifert, 1998). Behavioral avoidance research has been hampered in part by theoretical challenges (LeDoux, Moscarello, Sears, & Campese, 2017) and challenges in accurately measuring avoidance. Novel approaches to measuring avoidance using sophisticated technological advances hold promise for future research in this direction (Lebowitz, Shic, Campbell, Basile, & Silverman, 2015; Lebowitz, Shic, Campbell, MacLeod, & Silverman, 2015).

#### 3.2.2. Physiology

Threat learning and extinction paradigms have been used to compare anxious and non-anxious individuals during the acquisition and extinction of fear, quantified at multiple levels of analysis. Almost sixty years ago Howe (1958) reported elevated skin conductance response during acquisition of fear in patients with severe anxiety, compared to others. While some studies replicate these findings (Ashcroft, Guimarães, Wang, & Deakin, 1991; Clum, 1969; Fayu, 1961; Hermann, Ziegler, Birbaumer, & Flor, 2002; Orr et al., 2000) (Grillon, Ameli, Goddard, Woods, & Davis, 1994; Grillon & Morgan Iii, 1999; Jovanovic et al., 2014; Morgan Iii, Grillon, Southwick, Davis, & Charney, 1995; Hermann et al., 2002; Peri, Ben-Shakhar, Orr, & Shalev, 1999; Schneider et al., 1999), many others fail to do so. In fact, quantitative meta-analyses do demonstrate some perturbations on these paradigms, but these perturbations do not include enhanced fear acquisition (Lissek et al., 2005). In contrast, for studies of extinction learning, more consistent results arise, with evidence of deficient extinction in anxious individuals (Del-Ben et al., 2001; Peri et al., 1999; Pliszka, Hatch, Borcherding, & Rogeness, 1993; Schneider et al., 1999).

#### 3.2.3. Brain circuitry

Neuroimaging research in humans and other animals implicates the amygdala in the fear response (Davis & Whalen, 2001; Kapp, Whalen, Supple, & Pascoe, 1992; Lau et al., 2011; LeDoux, 2000, 2003, 2007; Medina, Christopher Repa, Mauk, & LeDoux, 2002; Phelps, 2006; Phelps et al., 2004; Phelps & LeDoux, 2005), with the amygdala enabling rapid responses to danger and efficient deployment of appropriate responses. Animal studies indicate that sensory information is received in the lateral nucleus of the amygdala from the thalamus and the sensory cortex, and transmitted to the central nucleus of the amygdala, which triggers changes in autonomic nervous system, endocrine, and motor functioning (LeDoux, 2007). Storage of synaptic changes in this circuitry enables fear acquisition. Human neuroimaging studies show increased amygdala reactivity after fear acquisition (Blackford & Pine, 2012; Büchel & Dolan, 2000; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Phelps et al., 2004), and increased amygdala reactivity in anxious children relative to healthy children (Blackford & Pine, 2012; Blair et al., 2011; Guyer et al., 2008; McClure, Adler, et al., 2007; McClure, Monk, et al., 2007; Thomas, Drevets, Dahl, et al., 2001; Thomas, Drevets, Whalen, et al., 2001). By contrast, the ventromedial PFC and hippocampus play a central role in fear extinction learning and recall (Milad et al., 2007; Phelps et al., 2004). The ventromedial PFC inhibits the central nucleus of the amygdala through the intercalated cells, thus attenuating the fear response (LeDoux, 2007), and is thought to be particularly important for extinction recall (Delgado, Nearing, LeDoux, & Phelps, 2008; Kalisch et al., 2006; Milad et al., 2007) {Phelps et al., 2004 #3401}. The hippocampus is involved in encoding

associations with context and confers context dependence on processing in the vmPFC (Kalisch et al., 2006). Among patients with anxiety disorders, poorer extinction memory has been associated with weaker activation of the ventromedial PFC and hippocampus (Milad et al., 2009). In addition to these regions, research in developmental samples with anxiety suggests altered responding of the subgenual ACC during fear learning {Britton et al., 2013 #3905}. The bed nucleus of the stria terminalis and its role in sustained anxiety and threat remain an area for future research in childhood anxiety.

## 4. Implications and future directions for research and clinical practice

Taken together, research into the roles of Affiliation and Attachment and of Fear exemplifies how an RDoC perspective informs thinking about equifinality and multifinality in the developmental psychopathology of anxiety and its disorders. As Freud (1920, pp. 167-168) famously wrote, “So long as we trace the development from its final outcome backwards, the chain of events appears continuous, and we feel we have gained an insight which is completely satisfactory or even exhaustive. But if we proceed the reverse way, if we start from the premises inferred from the analysis and try to follow these up to the final result, then we no longer get the impression of an inevitable sequence of events which could not have been otherwise determined…In other words, from a knowledge of the premises we could not have foretold the nature of the result.”

Research on multiple levels of analysis of RDoC constructs delineates the promise of such research for understandings of development. This includes research on the role of disrupted early caregiving for attachment security, on the role of frontoamygdala circuitry function in anxiety, on the genetics of the oxytocinergic system and the neural correlates of anxiety. However, work in this area remains in very early stages, and there is a need for an organizational framework. As outlined in the current paper, the perspectives of multifinality and equifinality in anxiety provide a useful approach. These perspectives emphasize the many ways that different risk factors can perturb a core set of behaviors, possibly through final-common pathways, as well as how a core risk factor can perturb many brain functions and associated outcomes, observed within each of these systems.

RDoC also provides challenges and opportunities for advancing the treatment of childhood anxiety disorders. Research at the neurocircuitry, molecular, and genetic levels has had limited impact on clinical practice in general or for childhood anxiety disorders in particular. Treatment development and evaluation research for childhood anxiety disorders progressed rapidly in the final decades of the previous century, particularly research relating to selective serotonin reuptake inhibitors and cognitive-behavioral therapy, respectively (see Silverman, Pina, & Viswesvaran, 2008). Despite clear progress, advances in therapeutics have recently stalled, and a mechanistic understanding of childhood anxiety has not emerged. The same is true with respect to assessment approaches, which also were greatly enhanced during this period through the introduction of reliable diagnostic classification tools (Silverman & Ollendick, 2005), but were rooted in the DSM categorical approach of psychopathology, rather than on domains of functioning as in RDoC.

RDoC provides the potential to elucidate the mechanisms underlying childhood anxiety through a refocusing of priorities. One example from the Systems for Social Processes domain involves innovative parent-based treatments for childhood anxiety disorders. Attempts to reduce childhood anxiety through parent-based treatments initially simply adapted approaches used in child-focused cognitive behavioral therapy. That is, parents were instructed in the theoretical foundation and practical implementation of cognitive behavioral therapy and were encouraged to implement these tools with their anxious child. Despite early promise (Barrett, Dadds, & Rapee, 1996), ultimately numerous clinical trials indicated that this approach does not enhance child outcomes relative to providing only child-focused cognitive-behavioral therapy (Barmish & Kendall, 2005; Breinholst, Esbjorn, Reinholdt-Dunne, & Stallard, 2012; Nauta, Scholing, Emmelkamp, & Minderaa, 2001; Nauta, Scholing, Emmelkamp, & Minderaa, 2003; Silverman et al., 2008; Silverman, Kurtines, Jaccard, & Pina, 2009).

Recent, alternative approaches emphasize Affiliation and Attachment in childhood anxiety disorders, highlighting children’s social response to anxiety and relevance for novel parent-based therapeutic interventions. Specifically, recent research delineates the ways in which parents alter their own behavior to help their children avoid or alleviate distress related to the anxiety, termed family accommodation (Flessner et al., 2011; Lebowitz et al., 2013; Lebowitz, Panza, & Bloch, 2016; Lebowitz, Scharfstein, & Jones, 2014; Lebowitz, Scharfstein, & Jones, 2015; Norman, Silverman, & Lebowitz, 2015; Storch et al., 2015; Thompson-Hollands, Kerns, Pincus, & Comer, 2014). Biological research has also linked the oxytocin molecule to family accommodation of childhood anxiety, with preliminary results indicating that children’s oxytocinergic functioning significantly predicts the levels of reported family accommodation (Lebowitz, Leckman, Feldman, et al., 2016). These findings have led to the increased targeting of family accommodation in child anxiety treatment. For example, the SPACE Program (Supportive Parenting for Anxious Childhood Emotions) is a completely parent-based intervention for child anxiety and related disorders that focuses on reducing parental accommodation of child symptoms and shows promise as an alternative or complementary treatment to child-focused cognitive behavioral therapy (Lebowitz, 2013; Lebowitz, 2015; Lebowitz, 2016; Lebowitz & Omer, 2013; Lebowitz, Omer, Hermes, & Scahill, 2014). Unique features of parent-based interventions such as SPACE relate to their focus on social domains of functioning implicated in childhood anxiety, highlighting the power of multi-dimensional approaches such as RDoC to inform therapeutics. Given the shift from primary focus on parents during childhood to other relationships such as peers and romantic partners during adolescence and into adulthood, applying the principles of attachment has further potential to enhance treatments by building on distinct sources of social support and buffering in later developmental stages.

In the Negative Valence Systems domain, the potential of the compound d-cycloserine (DCS) to enhance the efficacy of exposure-based behavioral therapy for childhood anxiety is another example of RDoC-informed research driving translational innovations. Molecular research in rodents implicated N-methyl-D-aspartate (NMDA) receptor activity in the amygdala in fear extinction (Baker & Azorlosa, 1996; Davis, 2002; Royer & Paré, 2002). NMDA receptor activity can be chemically manipulated through stimulation of the glycine binding site on the NMDA glutamate receptor. DCS acts as a partial agonist of this site, suggesting that it may enhance the efficacy of exposure therapy by modulating NMDA receptor activity, thus increasing plasticity in the relevant circuitry or reducing the likelihood of fear memory reconsolidation. Promising results in animal models of fear extinction supported this possibility (Ledgerwood, Richardson, & Cranney, 2003, 2005; Walker, Ressler, Lu, & Davis, 2002). Subsequent human studies have provided evidence for the ability of DCS, administered during exposure sessions, to enhance fear extinction in exposure therapy in anxiety patients (Guastella et al., 2008; Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007; Hofmann et al., 2006; Otto et al., 2010; Ressler et al., 2004; Storch et al., 2010). Importantly, however, results have not been entirely consistent, and more research is required before DCS can be considered to reliably enhance treatment effects or be routinely prescribed. Research on DCS provides a useful model of research at multiple levels of analysis being translated into potentially novel intervention strategies.

## 5. Conclusion

A rapidly growing literature across species has advanced understanding of both the etiology and treatment of childhood anxiety

disorders. Applying the RDoC model has the potential to greatly build upon these advances through integration across previously siloed research areas. Multidisciplinary research into the roles of Affiliation and Attachment and of Fear in childhood anxiety exemplify the potential of RDoC to facilitate this kind of integrative and translational research, and to ultimately contribute to the development of a novel system for the identification and classification of psychopathology.

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## Contributors

Authors Lebowitz and Dylan conducted the initial search of the literature, extracted the relevant information needed to summarize each study, and composed the first draft of the manuscript. Authors Pine and Silverman provided comments and edits and all authors have approved the final version.

## Conflict of interest

The authors declare no conflict of interest.

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