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## Implications of the Research Domain Criteria Project for Childhood Anxiety and its Disorders

Eli R. Lebowitz, Ph.D.<sup>1</sup>, Dylan G. Gee, Ph.D.<sup>2</sup>, Daniel S. Pine, M.D.<sup>3</sup>, Wendy K. Silverman, Ph.D.<sup>4,\*</sup>

<sup>1</sup>Yale University, Child Study Center, 230 S. Frontage Rd., New Haven, CT 06520, USA.

<sup>2</sup>Yale University, Department of Psychology, 2 Hillhouse Ave, New Haven, CT 06520, USA.

<sup>3</sup>National Institute of Mental Health, Emotion and Development Branch, National Institutes of Health, Bethesda, MD, USA.

<sup>4</sup>Yale University, Child Study Center, 230 S. Frontage Rd., New Haven, CT 06520, USA.

### 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 that may facilitate novel advances in the classification and treatment of childhood anxiety. In this article, we highlight the Systems for Social Processes and the Negative Valence System domains of RDoC as they relate to childhood anxiety disorders. Through natural reliance on parents to reduce children's fear, attachment plays a central role in childhood anxiety. Moreover, frontoamygdala circuitry underlies both attachment processes and fear learning and has been consistently implicated in anxiety disorders across development. Through integrative and translational approaches, RDoC provides unique opportunities and simultaneous challenges for advancing the treatment of childhood anxiety disorders.

### Introduction

The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project represents a critical shift in conceptualizing psychiatric disorders from specific, clinician-rated symptoms using a categorical approach to a dimensional approach that encompasses multiple domains of human behavior and functioning (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,

\*Corresponding Author: wendy.silverman@yale.edu.

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 other disorders. This suggests that disruptions associated with anxiety disorders occur in other psychiatric disorders (Curry, March, & Hervey, 2004; Kessler, Chiu, Demler, & Walters, 2005). Moreover, most symptoms that characterize the anxiety disorders are clearly excessive or inappropriate manifestations of otherwise adaptive components of human functioning.

The heterogeneous nature of anxiety disorders underscores both the strengths and the challenges of RDoC. Examination of the NIMH RDoC matrix shows 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 Processing* are also highly pertinent 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 focus instead on constructs within two RDoC domains 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 summarize research on attachment in childhood anxiety; within the “Negative Valence System” domain and its associated “Fear” construct, we summarize research on fear learning in childhood anxiety. Even with this narrower focus, an exhaustive review is beyond article’s scope. Rather, we discuss these RDoC domains and associated constructs by showcasing research that most heavily influences therapeutics.

## Social Processes

### 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). Although many of these functions relate to anxiety, the functions possess particular relevance for childhood anxiety disorders. When threatened, children seek comfort and protection from

attachment figures, rendering the RDoC construct of Affiliation and Attachment particularly relevant.

### **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 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.

**Behavior and Self-Report.**—Behavioral paradigms and self-report assess attachment and its connections to childhood anxiety disorders. In infants and very young children, particularly important work 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). In older children, 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).

**Brain Circuitry.**—Neuroimaging research suggests that brain systems that support attachment may be relevant to childhood anxiety. Frontal amygdala circuitry may malfunction in anxiety disorders, giving rise to amygdala hyperactivity, diminished prefrontal control, and altered connectivity between these regions. Amygdala engagement enables rapid responses to danger and efficient deployment of appropriate responses (Davis & Whalen, 2001; LeDoux, 2007). Portions of the prefrontal cortex (PFC) can constrain or amplify these initial responses, with portions of medial PFC inhibiting some aspects of the initial response to danger (Sotres-Bayon & Quirk, 2010). Amygdala hyperactivity to emotional stimuli is associated with anxiety during childhood and adolescence (Guyer et al., 2008; McClure et al., 2007; Monk et al., 2008; Thomas et al., 2001), as well as adulthood (Bishop, Duncan, & Lawrence, 2004; Etkin et al., 2004; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Stein, Simmons, Feinstein, & Paulus, 2007). 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.

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 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 et al., 2013; Gullone, King, & Ollendick, 2001). Reciprocal connections between the amygdala and medial PFC appear to support effective emotion regulation and fear extinction in healthy adults (Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Phelps, Delgado, Nearing, & LeDoux, 2004). These connections may show protracted development throughout childhood and adolescence both functionally (Decety et al., 2012; Gabard-Durnam et al., 2014; Gabard-Durnam et al., 2016; Gee 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 frontoamygdala connectivity during the transition from childhood to adolescence, which parallels normative changes in anxiety and amygdala reactivity (Gee 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, Mattay, Tessitore, Fera, & Weinberger, 2003; Kim et al., 2003). Importantly, although data are only beginning to emerge, they suggest that this trajectory goes awry in children with anxiety disorders who fail to exhibit the expected age-related patterns of frontoamygdala 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, Prosocki, 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. Recent work suggests that the presence of maternal 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 et al., 2013). Moreover, a subset of children who reported particular heavy reliance on their parents when under stress showed the greatest impact of maternal presence on frontoamygdala circuitry. A similar pattern of maternal presence impact 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 maternal 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 children'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, 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 are associated with altered function in the HPA axis (Gee et al., 2013; Gunnar & Quevedo, 2007; Koss, Hostinar, Donzella, & Gunnar, 2014; Moriceau, Raineki, Holman, Holman, & Sullivan, 2009; Sanchez, 2006) and frontoamygdala circuitry (Gee et al., 2013; Hanson, Knodt, Brigidi, & Hariri, 2015; Howell et al., 2013; Ono et al., 2008; Tottenham et al., 2011; Tottenham et al., 2010). Individuals who experience early caregiving adversity are also at increased risk for anxiety (Gee 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 et al., 2013; Tottenham et al., 2011).

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 frontoamygdala functional connectivity. However, children who experienced parental deprivation during infancy display a pattern of negative frontoamygdala functional connectivity that manifests only in older individuals not exposed to deprivation (Gee et al., 2013). These findings in humans are consistent with evidence of accelerated development 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 barriers to direct central measurement or administration of oxytocin and its agonists or antagonists. Cerebrospinal fluid oxytocin levels in ten non-clinical youth who were undergoing CSF-related medical procedures were negatively correlated with anxiety ratings (Carson et al., 2015). Two recent studies more directly relate oxytocinergic functioning to childhood anxiety disorders. In one study, salivary oxytocin levels in a sample of clinically anxious youth correlated negatively with anxiety symptoms, particularly 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, which positively correlated with levels of separation anxiety (Lebowitz et al., 2017). Plasma oxytocin levels may also be associated with measures of anxiety in adult samples but results are 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).

**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 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 youths who had experienced parental deprivation, those individuals who displayed negative connectivity had lower anxiety than their same-aged peers with positive connectivity (Gee et al., 2013). These are intriguing findings and longitudinal studies are necessary to understand the likely consequences of accelerated development.

**Molecules.**—Neurochemical research on attachment has focused in large part on oxytocin. Oxytocin and the closely related molecule arginine vasopressin are 9 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 and are implicated in modulating aspects of species-specific attachment and anxiety regulation behaviors (Feldman et al., 2015). In several mammal species, oxytocin shapes caregiving and pair-bonding behavior in (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, 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-Kozłowska, & Hertmanowska, 2002; Ring et al., 2010). Its roles in modulating social behavior, including social recognition, also have implications for autism spectrum disorders (Ferguson, Aldag, Insel, & Young, 2001).

## Negative Valence Systems

### 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 under the negative valence systems domain: (1) Fear or Acute Threat, (2) Potential Threat, (3) Sustained Threat, (4) Loss, and (5) Frustrative Nonreward. Under RDoC, Fear refers to the complex ‘defensive motivational system to promote behaviors that protect the organism from perceived danger’. The RDoC definition further distinguishes responses to immediately perceived dangers or threats from responses to more distal, less certain threats, labeled with the terms “Potential Threat or Anxiety”. Demarcation of these responses can be challenging however because threats that are realistically remote or of low likelihood may be inaccurately perceived as immediate in individuals with anxiety disorders especially children. As with many aspects of RDoC, it is also not possible to fully disentangle the fear system from other domains of functioning necessary for survival. That is, an individual recognizes and responds to threats with fear; these processes engage multiple interacting systems for attention, perception, and associated processes. Nevertheless, disruptions in the

fear system have clear and major implications for anxiety disorders and have been studied at multiple levels of the RDoC matrix.

## 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 highly 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, 2005).

**Behavior and self-report.**—Self-report of subjective fear 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. Studies that have used 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 the anxiety disorders. Early studies used shock as the unconditioned stimulus, in efforts 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 carbon dioxide, unpleasant images, or unpleasant 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) involved 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).

**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. More than half a century ago, Howe (1958) reported elevated skin conductance response during fear acquisition in patients with severe anxiety, compared with others. Although these findings have been replicated by some, many others have failed to replicate (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). Further, meta-analyses do demonstrate some perturbations on these paradigms, but the perturbations do not include enhanced fear acquisition; for studies of extinction learning, in contrast more consistent results arise, with



the data showing deficient extinction in anxious individuals (Del-Ben et al., 2001; Peri et al., 1999; Pliszka, Hatch, Borcharding, & Rogeness, 1993; Schneider et al., 1999).

**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, 2003; LeDoux, 2007; LeDoux, 2000; Medina, Christopher Repa, Mauk, & LeDoux, 2002; Phelps, 2006; Phelps et al., 2004; Phelps & LeDoux, 2005). Animal studies indicate 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. 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 et al., 2007; Thomas et al., 2001). By contrast, the PFC (particularly ventromedial PFC) and hippocampus play a central role in fear extinction (Milad et al., 2007; Phelps et al., 2004). Specifically, the ventromedial PFC inhibits the central nucleus of the amygdala through the intercalated cells. Poorer extinction memory in patients with anxiety has been associated with weaker activation of the ventromedial PFC and hippocampus (Milad et al., 2009).

## Implications and Future Directions for Research and Clinical Practice

RDoC provides challenges and opportunities for advancing knowledge and 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 (Silverman, Pina, & Viswesvaran, 2008). Despite clear progress, advances in therapeutics have recently stalled, and a mechanistic understanding of childhood anxiety has not emerged, as is the goal for the RDoC levels of analysis. 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 opportunities 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, Pina, & Viswesvaran, 2008); Silverman, Kurtines, Pina, & Jaccard, 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 (Flessner et al., 2011; Lebowitz, Panza, & Bloch, 2016; Lebowitz, Scharfstein, & Jones, 2015; Lebowitz, Scharfstein, & Jones, 2014; Lebowitz et al., 2013; 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 et al., 2016). These findings have led to the increased targeting of family accommodation in child anxiety treatment. The SPACE Program (Supportive Parenting for Anxious Childhood Emotions), for example, is a fully parent-based treatment 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, 2013, 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. Such interventions show the power of multi-dimensional approaches such as RDoC to inform therapeutics.

Work on 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 research driving translational innovations, in the Negative Valence Systems Domain. 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 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, Lovibond, Dadds, Mitchell, & Richardson, 2007; Guastella et al., 2008; Hofmann et al., 2006; Otto et al., 2010; Ressler et al., 2004; Storch et al., 2010). Importantly, 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. Work on DCS provides a useful model of research at multiple levels of analysis being translated into potentially novel intervention strategies.

## Conclusion

Recent research has advanced understanding of childhood anxiety disorders. Applying the RDoC model can exponentially increase these advances by integrating 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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