Disruptive Mood Dysregulation Disorder (DMDD): An RDoC Perspective

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Abstract

In recent years, there has been much debate regarding the most appropriate diagnostic classification of children exhibiting emotion dysregulation in the form of irritability and severe temper outbursts. Most recently, this has resulted in the addition of a new diagnosis, Disruptive Mood Dysregulation Disorder (DMDD) in the DSM 5. The impetus for including this new disorder was to reduce the number of diagnoses that these children would typically receive; however, there is concern that it has only complicated matters rather than simplifying them. For example, a recent epidemiologic study shows that DMDD cannot be differentiated from oppositional defiant disorder (ODD) based on symptoms alone. Thus, these children are an ideal population in which to apply RDoC constructs in order to obtain greater clarity in terms of underlying processes and ultimately, inform nosology and appropriate interventions. The aim of this article is to provide a foundation for future research by examining extant theoretical and empirical evidence for the role of four key RDoC constructs in DMDD.

Keywords

Researchers have become increasingly interested in finding alternative frameworks for understanding mental disorders. This stems from a growing dissatisfaction with the current diagnostic nosology that reduces complex systems of functioning into discrete symptom

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clusters. While the Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition (DSM-5; APA, 2013) has made important revisions, it fails to capture the neurobiological, genetic, behavioral, environmental, and experiential interactions that contribute to the development and maintenance of psychopathology. In response to these deficiencies, the National Institute of Mental Health (NIMH) introduced the Research Domain Criteria (RDoC) initiative. The RDoC initiative provides a dimensional approach to understanding mental disorders by integrating multiple scientific disciplines in a translational manner. The RDoC framework is organized by constructs that represent a particular functional aspect of behavior (Insel & Cuthbert, 2010). Using this approach, researchers can address the heterogeneous mechanisms of dysfunction for each construct.

One disorder that would benefit greatly from an RDoC perspective is Disruptive Mood Dysregulation Disorder (DMDD; APA, 2013). DMDD is a controversial diagnosis characterized by a disturbance in mood (i.e. severe and persistent irritability) and disruptive behaviors (recurrent and severe temper outbursts that are out of proportion to the situational stressor; APA, 2013). This new disorder arose from a concern that pathological irritability and anger in children were not being accurately captured, and thus, treated. More specifically, many of these children were being diagnosed with Bipolar Disorder despite the chronic, versus episodic, nature of their symptoms and evidence for distinct pathophysiology. (Brotman et al., 2010; Wiggins et al., 2016; Adleman et al., 2011; Thomas et al., 2012; Deveney et al., 2012) The challenge is that these symptoms are observed across multiple mood and disruptive behavior disorders (Barlow, 1991); the establishment of DMDD aimed to address this issue. However, researchers have questioned the validity of DMDD as a distinct diagnosis (Stringaris, 2011; Axelson et al., 2012; Roy, Lopes, & Klein, 2014; Lochman et al., 2015). For example, a recent population-based epidemiologic study found that DMDD cannot be differentiated from Oppositional Defiant Disorder (ODD) based on symptomatology alone (Mayes, Waxmonsky, Calhoun, & Bixler, 2016). This suggests that differentiation from other disorders such as ODD will require examination of constructs other than psychopathological symptoms such as those presented in the RDoC initiative.

In this paper, we review RDoC constructs that we propose are most relevant to DMDD. First, we suggest that dysfunction of frustrative non-reward (Negative Valence domain) and reward prediction error (Positive Valence domain) processes may drive symptoms of chronic irritability and severe tantrums. Second, we suggest that the persistence of these symptoms reflect poor emotion regulation, and particularly, impairments in two constructs from the Cognitive domain: attention and language. Several challenges arise when completing such a review. First, few studies have directly examined DMDD and thus, we examine these constructs as they relate to the core symptoms of irritability and severe temper outbursts. Specifically, we primarily focus on disorders that directly informed the development of DMDD due to the prominence of chronic irritability within their symptom presentation, namely oppositional defiant disorder (ODD) and severe mood dysregulation (SMD; a phenotype defined by Leibenluft et al., [2003] that served as the precursor to DMDD). Studies of other disorders (i.e., mood and anxiety disorders) were considered only if they included findings specifically related to symptoms of chronic irritability and temper outbursts. We do not include studies that focus exclusively on pediatric BD since the

pathophysiology is believed to be distinct from that of DMDD as indicated above (Brotman et al., 2010; Adleman et al., 2011; Thomas et al., 2012; Deveney et al., 2012; Wiggins et al., 2016). Second, behavioral and neuroimaging protocols are typically complex and may involve multiple RDoC constructs. We classified studies according to their stated aims but recognize that there is significant overlap. Overall, the aim of this review is to provide guidance for future research on DMDD. Ultimately, future studies leveraging these RDoC constructs will help to empirically parse the significant heterogeneity observed in children with severe temper outbursts and chronic irritability and provide evidence that supports DMDD as a distinct disorder or suggest alternative nosological classification.

Frustration, Reward, and Non-Reward

Irritability has been conceptualized as a "low threshold to experience anger in response to frustration." (p. S32, Krieger, F. V., Leibenluft, E., Stringaris, A., & Polanczyk, 2013). Relatedly, temper outbursts are the behavioral manifestations of these anger responses. Thus, it is logical to consider these symptoms of DMDD within the RDoC domain of Negative Valence Systems, and specifically, in relation to the construct of frustrative non-reward. Frustrative non-reward was originally developed by Abram Amsel (1958) and is defined as an implicit reaction following the absence or delay of a reward that was previously available. When a child anticipates a reward and the reward is omitted, a negative affective state ensues (i.e. "frustration") and typically manifests in the form of aggression (Gatzke-Kopp, Willner, Jetha, Abenavoli, DePuis, & Segalowitz, 2015). The aggressive reaction, such as a temper tantrum, encompasses changes in affective arousal, cognitive control, physiology, and dopaminergic processes (Hubbard et al., 2002; Schoemaker, Mulder, Dekovic, & Matthys, 2013; Deveney et al., 2013; Kreibig, 2010). From a neural perspective, frustration processing has been linked to brain regions involved in error monitoring and cognitive control such as the dorsal anterior cingulate cortex (dACC; Spunt, Lieberman, Cohen, & Eisenberger, 2012; Yu et al., 2014) and those involved in negative affective responses including the anterior insula (Abler, Walter, & Erk, 2005; Rilling et al., 2008; Yu et al., 2014) and amygdala (Rilling 2008; Yu et al., 2014).

The experience of frustration in this context can be normative and may serve as a catalyst for constructive, goal-directed behavior, or it can be pathological and result in maladaptive behavior, such as observed in the severe temper outbursts that are characteristic of DMDD. For example, children with SMD report significantly more arousal in response to frustration than healthy comparisons (Rich et al., 2007). Of note, children with BD exhibited frustration-induced arousal similar to the SMD group suggesting that this response may not be specific to chronic irritability. This is further supported by physiological studies showing that children with conduct (Gatzke-Kopp, Willner et al., 2015; Wang, Guo, You, & Gao, 2007) and other externalizing (Woltering et al., 2016) problems exhibit increased heart rate during frustration, as compared to healthy controls. Thus, children with clinically significant irritability may be particularly vulnerable to feelings of frustration; given the frequency with which frustration is encountered in our daily lives, this would likely lead to increased temper outbursts and significant functional impairment.

Studies of neural responses to frustration within the context of pediatric irritability show altered function of implicated regions. For example, compared to healthy controls, young children (ages 6- 9) with clinically significant symptoms of irritability exhibit decreased activation of the ACC in response to frustration (Perlman et al., 2015). This contrasts an earlier magnetoencephalography (MEG) study with a similar, yet older sample of children (ages 8- 17) with SMD, who showed greater activation of ACC, along with higher ratings of agitation and sadness, in response to negative feedback, as compared to healthy controls (Rich et al., 2011). This latter finding of increased ACC response has also been observed in non-clinical adults with high susceptibility to frustration (Siegrist et al., 2005) suggesting that the direction of the ACC response to frustration may shift with development. Using a similar task in the MRI scanner, Deveney and colleagues (2013) found that chronically irritable SMD children exhibited decreased amygdala and striatal responses during frustration compared to controls. Together, these data provide behavioral and neural support for a role of frustrative non-reward in chronic irritability, and thus DMDD.

Closely related to the RDoC negative valence construct of frustrative non-reward is the positive valence construct of reward prediction error (RPE). Reward prediction error is the difference between the reward expected and the reward received (Schultz, 2016). As a result, this signal is essential to learning contingencies: a behavior that results in outcomes better than expected will be repeated, and one that results in outcomes worse than expected will be reduced. The neural basis of RPE lies within midbrain dopaminergic neurons and their projections (see Schultz, 2016 for a comprehensive review). When a reward is received, signaling in these neurons is increased. A similar increase occurs in response to a stimulus that has been shown to predict reward. However, when a reward is expected but not received, signaling that perhaps a change in behavior is needed in order to obtain reward, there is a decrease in this midbrain dopamine signaling (Schultz, 2002). This effect is observed in animals and humans (Davidson et al., 2004; Abler et al., 2005).

It has been suggested that impairments in RPE increase children's risk of becoming frustrated and aggressive because they are expecting a reward when no reward is given (Blair, Colledge, & Mitchell, 2001; Blair, 2010). Evidence suggests that chronically irritable youth do not make use of these error signals as well as healthy children as demonstrated by their weaker performance on reversal learning (Adleman et al., 2011) and set-shifting paradigms (Dickstein et al., 2007), which require the child to switch from one learned response choice to a different response choice when reward contingencies change. These deficits in reversal learning putatively linked to RPE may also reflect disruption in more general reward and punishment processing in irritable youth. For example, compared to healthy children, children with ODD exhibit increased heart rate reactivity to reward and reduced reactivity to penalties during a computerized gambling task (Luman et al., 2010). Greater reductions in the latter were related to an increased preference for larger rewards and higher ODD symptoms. Matthys et al. (2004) showed a similar reduction in response to penalties in children with ODD. They found that compared to healthy boys, boys with ODD responded more quickly to initiate the next trial following a losing trial, suggesting a reduced response to punishment. Further, the boys with ODD exhibited lower skin conductance responses that were positively related to the speed with which they initiated the next trial. These findings contrast others that show no differences in reward or punishment

processing between children with SMD and healthy controls (Rau et al., 2008). This suggests that characterizing RPE-related processes may provide a useful distinction between youth with SMD and those with ODD. However, it is unknown whether children with DMDD would respond more like those with SMD or those with ODD, as no studies have been conducted. One recent study suggests that early symptoms of DMDD are predictive of enhanced reward processing during preadolescence (Kessel et al., 2016). However, this is clearly an area for further investigation.

Neuroimaging findings suggest that disruption of the striatal circuits implicated in RPE may underlie the deficits in reward-based learning observed in chronically irritable children such as those with DMDD. Children with SMD fail to exhibit the differential striatal responses between correct and incorrect trials that are observed in healthy youth (Adleman et al., 2011). Additional support for the role of the striatum and the error prediction signal in irritable children is mixed. Specifically, there is evidence to suggest that compared to healthy comparisons, children with disruptive behavior disorders fail to show the same decrease in striatal activity during non-reward (Gatzke-Kopp et al., 2009) but also that chronically irritable youth show a greater decrease in striatal response when receiving negative feedback (Deveney et al., 2013).

In summary, there is preliminary evidence to suggest that behavioral and neural function across two reward-related domains, frustrative non-reward and reward prediction error, is impaired in children with DMDD. As a result, these youth may be unable to adapt their behavior to changing environmental contingencies increasing their risk for frustration, resulting in more frequent temper outbursts. However, the nature of these disruptions in DMDD is not easily determined from the extant literature as it appears to differ depending on the psychopathology studied. For example, children with irritability in the context of ODD exhibit reduced physiological responding to punishment (Luman et al., 2010; Matthys et al., 2004) that is not observed in studies of children with SMD (Rau et al., 2008). Similarly, children with disruptive behavior disorders including ODD do not show the typical decrease in striatal activity during non- reward (Gatzke-Kopp et al., 2009), while chronically, irritable youth (children with SMD), show an enhanced decrease in striatal activity in response to punishment (Deveney et al., 2013). Thus, further study of these reward-related RDoC constructs in children with DMDD is likely to prove particularly fruitful in informing nosology.

Emotion Regulation Capacity

DMDD is typically considered a condition of emotion dysregulation. While irritability has been defined as a negative affective response, the chronicity of this response, which is a core component of DMDD, suggests limited ability to regulate this emotion. Additionally, severe temper outbursts, which also reflect poor regulation of negative affective responses, are also considered to be a hallmark symptom of DMDD, possibly reflecting a more extreme form of irritability (Stringaris, Cohen, Pine, & Leibenluft, 2009; Leibenluft et al., 2003; Leibenluft, 2011). Consistent with this, a study of young children with elevated aggression or disruptive behavior shows an association between greater reactivity to anger and lower teacher-rated emotion regulation skills (Gatzke-Kopp, Greenberg, Bierman, 2015). Further evidence for

deficient regulation comes from studies demonstrating that children with excessive irritability show deficits in cognitive function during emotional arousal. For example, compared to healthy controls, children with disruptive behavior problems, many of whom exhibit frequent temper outbursts, demonstrate worse performance on executive function tasks that elicit, and rely upon, emotional responses (i.e., Iowa Gambling Task), but not on "cool" tasks (i.e., Digit Span; Woltering et al., 2016). Similarly, when frustrated, children with SMD respond more slowly than typical comparisons when completing an affective Posner task (Deveney et al., 2013; Rich et al., 2007). We propose that two RDoC constructs within the Cognitive Systems domain that are essential for emotion regulation are relevant to the study of irritability and temper outbursts associated with DMDD. First, such symptoms may result from deficits in the ability to utilize attention shifting (i.e. distraction) to manage negative affect when faced with frustrating experiences. Second, given evidence that the development of emotion regulation skills typically depends on sufficient and timely language acquisition, we propose a role of language development in DMDD. These are discussed below.

Attention control, such as attentional engagement, disengagement, and shifting, underlies emotional control and self-regulatory behaviors in both children and adults. The allocation of attention helps to reduce distress and improve overall mood by shifting the focus away from the negative emotional stimuli (Bardeen, Tull, Dixon-Gordon, Stevens, & Gratz, 2015; Gross & Thompson, 2007; McRae et al., 2010). The use of attentional control to modify emotions has been observed in infants as young as 6 months of age, who reliably move their gaze away from negative stimuli and towards their mothers as a mechanism of self-regulation (Rothbart, Ziaie, & O'Boyle, 1992). Further, young children self-report the use of attentional distraction techniques when faced with unpleasant situations, such as delayed gratification (Mischel, 1974; Mischel & Ayduk, 2004). Thus, disruption in the development of such techniques may impact a child's ability to regulate negative emotions, resulting in affective symptoms such as those observed in DMDD.

Neurally, attention networks in children begin to develop at or before three months of age (Posner & Dehaene, 1994; Swingler, Perry, & Calkins, 2015). Early attention control is associated primarily with the executive attention networks, including the ACC, lateral frontal and prefrontal cortices, and the basal ganglia (Posner, & Fan., 2008). Specifically, the ACC acts as a switchboard, facilitating reciprocal connections between prefrontal cortices and behavioral control regions, such as the limbic, autonomic, visceromotor, and endocrine systems, in order to regulate behavior and emotions (Beauregard, Lévesque, & Paquette, 2004; Swingler et al., 2015). Studies directly examining the use of attention to regulate negative affect also implicate the dACC as well as other regions such as the dorsolateral prefrontal cortex (DLPFC; Kanske et al., 2011) and superior and inferior parietal cortices (McRae et al., 2010; Kanske et al., 2011), which are typically involved in voluntary attention control, even in the absence of emotional stimuli.

As such, the allocation of attention resources is an important construct for understanding irritable mood and temper outbursts in children. Individual differences in attentional control abilities may impact the efficacy of emotion regulation processing (McRae et al., 2010). This is particularly true during development when the integrity of these pathways is not yet fully

formed. Such attentional deficits are reflected in a recent study showing that youth with SMD have an attentional bias to threatening faces compared to controls, and that this bias to threat is associated with higher levels of irritability and symptoms of depression (Hommer et al., 2014). Researchers have also found that children who were rated temperamentally high in anger proneness by parents and teachers, had difficulty moving attention away from rewarding stimuli (He et al., 2013). In contrast, Rich and colleagues (2010) found that emotional stimuli have less impact on attention in children with SMD than healthy controls or those with BD.

In terms of the pathophysiological mechanisms underlying attentional biases in emotionally dysregulated children, researchers have found reduced N1 amplitudes, suggesting deficits in initial attention (Rich et al., 2007). Deveney and colleagues (2013) found decreased activity in posterior cingulate and parietal cortices during frustration in children with chronic irritability, as compared to healthy controls. Evidence suggests that deficits in the ability to utilize reward prediction errors to change behavior in irritable youth, as described earlier, may also reflect attentional disruptions. For example, during a reversal learning task, children with SMD failed to show the increase in inferior frontal gyrus (IFG) activity during incorrect trials that was observed for healthy comparisons (Adleman et al., 2011). The IFG plays a role in attention and works with the caudate to adjust behavior after errors (Budhani, Marsh, Pine, & Blair, 2007). Thus, this lack of activity may indicate deficits in both attention and RPE in these children, which is further supported by their poor performance on this task compared to healthy comparisons. Altogether, these studies suggest disruptions in neural substrates underlying attention in children with chronic irritability and severe temper outbursts, consistent with the DMDD diagnosis. Further work is needed to better integrate neural and behavioral findings to improve understanding of the pathophysiology of this phenotype.

Another construct within the Cognitive Systems domain, language, may also play a role in chronic irritability. Language gives children access to a richer base of self-regulatory strategies, through which they are better able to modify negative emotions, including anger and frustration. Previous work has shown that both expressive and receptive language abilities are related to the development of emotion regulation skills (e.g., Botting & Conti-Ramsden, 2000; Silva, Justin, McGee, & Williams, 1984). Baker and Cantwell (1987) proposed an explanation for this relationship, asserting that delays in language acquisition may underlie a child's emotional dysregulation as the child is increasingly pressured to conform to environmental demands that they are unable to fully understand, resulting in frustration and non-compliance. Consistent with this, delays in expressive (Beadle, 1979), as well as receptive (Beitchman, 1985) language have been associated with tantrums, emotional lability, and negativity in young children (Roben, Cole, & Armstrong, 2013). Studies of clinical populations have found similar associations between language and emotional dysregulation. According to one study of extreme temper outbursts, language difficulty significantly predicted both the occurrence and number of rages in an inpatient hospital setting and was closely linked to a child's number of prior hospitalizations (Carlson, Potegal, Margulies, Gutkovich, & Basile, 2009). Further, half of all children with teacher- reported rage outbursts additionally demonstrated comorbid language or learning problems (Carlson & Dyson, 2012). Due to the severity of the disruption associated with rage outbursts,

language problems typically go unnoticed and undiagnosed in children with behavioral dysregulation, often leading to exacerbation of the aggressive behavior in the absence of language intervention (Ripley & Yuill, 2005).

To date, there are no studies of how language and emotion regulation are linked neurobiologically. However, the development of language skills in children is associated with a shift from involvement of the insula and the anterior cingulate to adult language centers, including the inferior and middle frontal, middle temporal, and angular gyri of the left hemisphere and the lingual and inferior temporal gyri of the right hemisphere (Szaflarski et al., 2006). In adults, emotion regulation and emotional reactivity are typically housed within these early language networks, including the insula and anterior cingulate, which are implicated in the interoceptive valuation and motivational demand of emotional stimuli (Etkin, Buchel, & Gross, 2015). As a result, we can speculate that this shift in the neural basis of language processing may also be necessary for successful maturation of emotion regulation and thus, that these circuits may show some immaturity in children with chronic irritability or temper outbursts; this remains to be empirically tested.

In summary, there is evidence to support a role of deficient emotion regulation in the symptoms of DMDD. Specifically, children with chronic irritability show deficits in attention, particularly in the context of emotional stimuli, and this may limit the use of strategies such as distraction to reduce emotional arousal. From an etiological perspective, evidence supports a link between deficient language development and emotion dysregulation (Cole, Armstrong, & Pemberton, 2010). However, the literature is limited and, to date, no studies have specifically examined language skills in children with SMD, ODD or DMDD so this is a new area to explore.

Conclusions & Future Directions

Since its introduction into psychiatric nosology in 2013, DMDD has posed a challenge to researchers and clinicians in terms of the reliability and validity of its symptoms as well as selection of appropriate treatments. Rigorous investigations of DMDD are needed and as we suggest here, several of the NIMH RDoC constructs can provide a solid starting point for this work. First, children with chronic irritability and emotional lability typically exhibit low frustration tolerance, supporting the role of frustrative non-reward processes from the Negative Valence domain. This is supported by behavioral and neuroimaging studies, the latter which show converging evidence of dysfunction in the anterior cingulate cortex (ACC). Closely related to this, the Positive Valence construct of reward prediction error can be informative as it may explain increased behavioral and physiological responses to both reward and frustration in children with DMDD. In fact, when findings across studies are compared, there appears to be preliminary evidence that reward and punishment processing may differ between children with ODD and those with SMD. Thus, this is a particularly important area to study in children with DMDD as it is likely to answer key questions regarding the differentiation of this disorder from ODD.

Constructs from the RDoC Cognitive domain are also implicated, namely attention and language. Evidence supports deficits in attention, particularly in the context of emotional

stimuli, suggesting that children with chronic irritability are less able to access attention-related regulatory strategies (i.e., distraction) during emotional arousal. Neuroimaging studies demonstrating altered function of parietal cortex and inferior frontal gyrus in irritable youth support the putative role of attention in DMDD. Finally, language development is not typically discussed as a central factor in child emotion regulation, despite clear evidence of a relationship between poor language skills and emotion regulation deficits, including severe temper outbursts, and thus, further work in this area is needed.

Overall, while there is growing support for neurobehavioral factors contributing to DMDD, there are also several limitations in the literature that require mention. First, there is significant variability in how essential symptoms such as "irritability" are defined. It is a construct that is often difficult to capture, particularly based on reports of parents and children. While some important advances have been made in the cross-diagnostic assessment of irritability (i.e. the Affective Reactivity Index [ARI]; Stringaris et al., 2012), greater consensus regarding the definition of irritability is fundamental to advancing research in this area. Second, given the recent emergence of DMDD, there are few published studies that specifically examine this diagnosis. Many studies are based on children with severe mood dysregulation (SMD) which is a clinical phenotype described by Leibenluft et al. (2003) that provided the basis for DMDD, but is not identical. For example, SMD requires symptoms of hyperarousal that are not part of the DMDD diagnosis. Related to this, most if not all of the studies on SMD come from the same laboratory. Replication across labs using independent samples is needed to support the external validity of these results. Finally, another challenge to developing comprehensive pathophysiological models of child irritability is the lack of animal models. Some key RDoC constructs such as reward prediction error, were initially established through animal work. However, as there is not yet a convincing animal model of irritability or severe outbursts, translational studies of these constructs are limited and their role in disorders such as DMDD can only be conducted with human populations.

In summary, DMDD is currently a "work in progress." While several RDoC constructs have received empirical support for their roles in chronic irritability and emotional dysregulation in children, further rigorous investigation is clearly needed to replicate and extend such findings. Ultimately, the goal of this work is to clarify the phenotypic presentation of DMDD and, in the process, determine whether it represents a unique disorder or a subtype of a similar disorder such as ODD. As indicated earlier, relying on symptomatology alone is not sufficient to differentiate these two conditions (Mayes et al., 2016). We hope that the present review has provided a starting point for clinical researchers to move the field forward through diagnostic and dimensional evaluation of these relevant RDoC constructs in children with DMDD, with the ultimate goals of informing etiological models and establishing targeted treatments of these impairing symptoms.

Acknowledgments

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Highlights

- Disruptive mood dysregulation disorder requires further careful examination

- Reward-related RDoC constructs may be altered in children with chronic irritability

- RDoC Cognitive domain constructs may explain deficits in emotion regulation in DMDD

- Further research is needed to improve diagnostic clarity and inform interventions