TITLE:

Linking irritability and functional brain networks: a transdiagnostic case for expanding consideration of development and environment in RDoC

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HIGHLIGHTS:

- Functional connectivity and irritability are promising indicators of psychopathology
- Brain networks for emotion, internalization, and cognition vary with irritability
- Advances in characterization may improve detection of atypical brain:behavior
- Consideration of developmental and early life influences on this pathway is vital

ABSTRACT:

The National Institute of Mental Health Research Domain Criteria (RDoC) framework promotes the dimensional and transdiagnostic operationalization of psychopathology, but consideration of the neurodevelopmental foundations of mental health problems requires deeper examination. Irritability, the dispositional tendency to angry emotion that has both mood and behavioral elements, is dimensional, transdiagnostic, and observable early in life—a promising target for the identification of early neural indicators or risk factors for psychopathology. Here, we examine functional brain networks linked to irritability from preschool to adulthood and discuss how development and early experience may influence these neural substrates. Functional connectivity measured with fMRI varies according to irritability and indicates the atypical coordination of several functional networks involved in emotion generation, emotion perception, attention, internalization, and cognitive control. We lay out an agenda to improve our understanding and detection of atypical brain:behavior patterns through advances in the characterization of both functional networks and irritability as well as the consideration and operationalization of developmental and early life environmental influences on this pathway.

KEYWORDS:

Irritability, functional connectivity, transdiagnositic, RDoC, fMRI, functional network, emotion regulation, development, early experience, impairment

MAIN TEXT:

Introduction.

Although neuroimaging tools have been used extensively to study the neural underpinnings of mental health problems, few practical insights into etiology, progression, or treatment have emerged. One potential cause of this problem has been the traditional focus on categorical clinical

diagnoses as discrete entities, which cover a very broad constellation of symptoms and are developmental, making them not ideally suited for linkage to mechanisms (Wakschlag et al., 2010). The Research Domain Criteria (RDoC) framework was introduced to conceptualize psychopathology more mechanistically within a neurodevelopmental context (Cuthbert and Insel, 2013). The RDoC framework recommends using measures relevant to psychiatric disorders that are (1) dimensional along a health-to-disease spectrum; (2) can be measured and linked to neural mechanisms across species; (3) transdiagnostic, to more closely map to cross-cutting elements rather than artificially carving diseases into discrete entities despite high rates of co-morbidity and shared etiology potentially yielding a better chance of revealing real-world applications (Consortium et al., 2018; Kaczkurkin et al., 2020). This framework has the potential to improve our understanding of how brain differences and corollary behavior can explain individual differences in mental disorder and resilience trajectories. As we have noted, deepening the operationalization of the dimensionality and neurodevelopmental context of psychopathology might be necessary to obtain a complete and actionable picture of its neural underpinnings (Mittal and Wakschlag, 2017).

Here, we discuss irritability, a salient and measurable early transdiagnostic marker of later mental health to illustrate how considering clinical patterns early in life via brain and behavioral methods could improve the neurodevelopmental understanding of mental disorders. Irritability, a dispositional tendency to angry emotion that has both mood (also known as “tonic”) and behavioral (also known as “phasic”) elements (Beauchaine and Tackett, 2020; Leibenluft, 2017; Vidal-Ribas et al., 2016; Wakschlag et al., 2017), is a transdiagnostic indicator of mental health risk and aligns well with many of the goals outlined in the RDoC. First, irritability can be measured dimensionally and its normal:abnormal spectrum has been characterized (Wakschlag et al., 2015). Second, frustrative nonreward, which subserves irritable behavior, can be studied in other species beyond humans, making it possible to study irritability across many levels of analysis (Leibenluft, 2017). Third, as previously mentioned, irritability is a common symptom of multiple

disorders, particularly the common and modifiable internalizing/externalizing disorders (Beauchaine and Tackett, 2020; Kana et al., 2019; Stringaris et al., 2009). Irritability symptoms were traditionally a primary feature of oppositional defiant disorder (ODD), depression and disorders of anger dysregulation (e.g. intermittent explosive disorder) and in DSM 5 are now also incorporated in an irritability specific disorder, disruptive mood dysregulation disorder (DMDD) (Vidal-Ribas et al., 2016; Wiggins et al., 2020). More recently, it has also been recognized that many other disorders that do not formally include irritability symptoms (e.g., autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)) have irritability as a common presenting feature, which may represent a distinct phenotype in childhood (Hampton et al., 2020; Kana et al., 2019; Musser and Nigg, 2019). In addition, irritability has also been studied using different and/or related constructs. For example, it has been extensively studied as part of negative emotionality in temperamental research (this construct also typically includes other forms of negative emotion i.e., anxiety and sadness) and at times has been considered with adjacent constructs like anger and aggression (Rothbart and Posner, 1985).

In an effort to understand the mechanisms and heterogeneity underlying irritability as well as identify biomarkers that inform early detection or risk factors for mental health problems, several neuroimaging approaches have been used to examine the neural substrates of irritability. Measures of brain structure including subcortical volumes, regional cortical thickness, white matter integrity (Dennis et al., 2019; Jirsaraie et al., 2019), and measures of brain function during implicit emotion processing (Karim and Perlman, 2017), sustained attention (Pagliaccio et al., 2017), frustrating feedback (Deveney et al., 2013) have been associated with both categorical diagnoses (e.g., DMDD) and the dimension of irritability.

One important neural measure for which a role in the expression and progression of irritability has been relatively understudied is functional connectivity MRI, the measurement of coordinated spontaneous fMRI activity across the brain. Here, we first discuss how functional connectivity analyses can provide a unique window into the brain function related to irritability by

matching the multifaceted and stable, yet developmentally plastic nature of the construct (Part 1). Then, we review the extant literature examining the relationship between functional connectivity and irritability and organize these findings according to the functional network architecture of the brain (Part 2). Finally, we discuss opportunities to improve the characterization and measurement of both irritability and functional connectivity and to better consider and operationalize the influences of development and early experience beyond what is currently included in RDoC (Part 3).

Part 1: Rationale for studying irritability and functional networks

Functional connectivity measures the temporal correlation between the fMRI activity from a pair of brain regions, while in a resting state (Biswal et al., 1995), task state (Finn et al., 2017; Gratton et al., 2016), or during natural sleep (Smyser et al., 2011). Even during rest, the activity of brain regions that are commonly recruited together when completing a given task (i.e., functionally related), is highly correlated. Regions comprising a "functional network" are linked by strong, positive correlations at rest (e.g., among regions of the default-mode network). Many types of functional networks have been identified involving the cortex, subcortex, and cerebellum (Greene et al., 2020; Marek et al., 2018; Power et al., 2011; Yeo et al., 2011): sensorimotor networks (e.g., somatosensory (SM), auditory (AUD), visual (VIS)) interface with the external world, top-down control networks (e.g., fronto-parietal (FP), cingulo-opercular (CO), dorsal attention (DAN), ventral attention (VAN), and salience(SAL)) direct cognitive resources and other association networks (e.g., default-mode network (DMN), reward (RW), memory (MEM)) that support internal processes. A rich representation of an individual's whole-brain functional network architecture can be obtained by correlating the intrinsic activity between all pairs of brain regions to yield a region-by-region functional connectivity matrix.

Many types of neuroimaging measures may contribute to our understanding of irritability and prediction of mental health sequelae, but functional connectivity has emerged as an attractive candidate biomarker for several reasons. First, this technique enables the rapid and relatively

easy assessment of many different functional networks from a single, relatively straightforward scan. Second, the putative task-free nature of resting-state fMRI means that issues associated with probing disorder-related differences with experimental tasks (e.g. performance burden, imbalanced task comparisons (Church et al., 2010)) are presumably avoided. This also makes it feasible to collect during natural sleep in very young infants and children, allowing earlier insights and longitudinal measurement of brain-behavior associations. Third, the measured strength of functional connectivity is thought to reflect a history of co-activation across the lifespan (Dosenbach et al., 2010; Harmelech et al., 2013) thus tracking the atypical coordination of different functional networks. Below, we discuss why functional connectivity may be particularly well suited to interrogate the neural substrates underlying irritability.

1.1 Irritability is multifaceted, potentially relying on multiple functional networks.

One reason that irritability is well-suited to investigation with functional connectivity approaches is that irritability is multifaceted and its neural substrates may be best described by the coordination (or lack of coordination) of many brain regions within a functional network or between multiple functional networks. For example, temper tantrums seem to involve a complex set of processes: a dysregulated emotional response to a frustrating stimulus, an inability to inhibit a negative response, initiation of a complex motor plan, and an inability to divert attention from the upsetting situation. These processes may be supported by distinct functional networks (e.g., inhibitory control - frontoparietal, motor plan - somatomotor, stimulus-driven attention - ventral attention). Task fMRI reveals that the recruitment of a heterogenous set of brain regions varies according to an individual's irritability during inhibitory control and emotion regulation tasks (Liuzzi et al., 2020; Wiggins et al., 2016). Taking a functional network perspective may be useful for understanding irritability as a transdiagnostic indicator of psychiatric disorders. Differing contributions from different functional networks might relate to the overlapping, yet heterogeneous collection of symptoms present across psychiatric disorders. In that vein, an understanding of the neural substrates of psychopathology at the level of functional networks might also facilitate

precision psychiatry approaches aimed at addressing heterogeneity within and across disorders (Sylvester et al., 2012).

1.2 Irritability and functional connectivity vary across similar time scales.

Both functional brain networks and irritability vary to different extents across different time scales, from moment-to-moment, to day-to-day, to year-by-year during development. The utility of functional connectivity as a neural marker of irritability may depend on how the variation measured across these different time scales aligns for these constructs. The coordination of brain regions in a functional network can change rapidly (i.e., moment-to-moment) to flexibly meet cognitive demands, but functional connectivity measured with fMRI is not well-suited to detect these rapid changes (Gratton et al., 2018; Laumann et al., 2017). In adults, the extent of inter-individual differences in functional connectivity dwarfs both the moment-to-moment and day-to-day intra-individual variation in functional networks (Gratton et al., 2018), suggesting that functional connectivity captures "trait-like" rather than "state-like" variation in brain network coordination. A person's ability to regulate their emotions and their response to frustrating events, can also vary from moment-to-moment depending on both internal and external demands (Kobylińska and Kusev, 2019). Moment-to-moment or context-dependent irritability may be better captured via real-time measurement like ecological momentary assessments (EMAs), daily diaries (Leppert et al., 2019), or observation (e.g., the Disruptive Behavior-Direct Observation Schedule (DB-DOS) assessment of irritability (De Los Reyes et al., 2009)), but irritability is most commonly measured via surveys (e.g., Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB) (Kaat et al., 2019), Affective Reactivity Index (ARI) (Stringaris et al., 2012)) which aim to capture stable, "trait-like" variation in a person's ability to regulate their emotions. Variation in irritability assessed by surveys may be the most closely aligned to variation in functional networks. Asking questions about a meaningful developmental epoch of emotion regulation (past 30 days) rather than very brief period which may capture only transient patterns (past week) may improve the intra-individual stability of measurements of irritability (Wakschlag et al., 2012; Wiggins et al., 2020). In

fact, recent work suggests that brain-wide patterns of functional connectivity carry information sufficient to capture trait-like irritability (measured via ARI), but not transient, state-like irritability (measured via self-reported frustration when receiving rigged task feedback (Scheinost et al., 2021).

Functional connectivity and irritability appear to be stable from day-to-day within individuals, but change occurs over the course of development and in response to behavioral interventions. The strongly correlated brain activity among functionally related regions within a functional network is thought to reflect a history of co-activation during relevant tasks across the lifespan (Dosenbach et al., 2010; Harmelech et al., 2013). Development shapes these functional brain networks, altering the strength of many connections over many years from birth to adulthood (Nielsen et al., 2019; Marek et al., 2015; Smyser et al., 2010). Emotion regulation and the expression of irritability also change over the course of development (Damme et al., 2020) and the trajectory of this change is linked to brain structure (Pagliaccio et al., 2018). Different emotional, attentional, and social regulation strategies build upon one another as infants and toddlers mature (Calkins, 2007). The use of developmentally specified indicators of irritability is critical to capture heterogeneity in the developmental expression of the behaviors, while also maintaining comparable conceptualization across the lifespan (Damme et al., 2020; Wakschlag et al., 2010). Reorganization of functional brain networks can occur in response to atypical behavior that promotes atypically coordinated brain activity. For example, placing a cast on an individual's dominant hand in order to prevent coordinated bimanual movements (atypical behavior) leads to functional disconnection of the sensorimotor circuits responsible for movement of the casted arm within weeks (Newbold et al., 2020). Persistent irritability may involve atypical behavior such as maladaptive or compensatory regulation strategies. Functional connectivity may be well suited to track atypical behavior related to irritability. Functional connectivity provides a window into more expansive and sustained brain functioning than task fMRI and more transiently

modifiable brain organization than structural MRI, potentially well suited to identify the neural underpinnings of irritability.

Though promising, currently there is a dearth of studies linking functional brain networks to irritability. In Part 2, we provide an integrative review of the state of the science in examining the relationship between functional networks and irritability.

Part 2: Current studies linking functional connectivity with irritability.

In this review, a broad net was cast to identify studies with the potential of identifying the functional connectivity and functional networks supporting irritability. Works that assessed any construct related to irritability (e.g., anger, emotional lability, emotion regulation) and any functional connectivity MRI metric (e.g., resting-state or task-state; seed-based or connectome-wide) were included and reviewed. We found that most studies targeted the neural substrates of irritability in childhood/adolescence and in the context of clinically significant disorders including ADHD, bipolar disorder, DMDD, anxiety, and ASD. Details about these works are provided in Table 1. Here, we synthesize these findings to highlight the consistently (or sometimes inconsistently) identified neural circuitry linked to transdiagnostic irritability. Placing these results in a framework of interconnected functional networks provides an integrated picture of the neural circuitry linked to irritability. To better synthesize the review of these works, findings were organized according to how functional connectivity was interrogated: 1) amygdala seed, 2) other *a priori* seeds (e.g., dorsolateral prefrontal cortex), and 3) connectome-wide search.

Table 1. Reviewed works linking irritability with functional connectivity.

				Irritability Measurement		Functional Connectivity		
	N	**Age (yrs)**	**Population**	measure	categorical / dimensional	seed	task / rest	length (min)
Fulwiler et al. 2012	16	20-45	Healthy males	Trait anger (STAXI-2)	D	**amygdala**	rest	5
Posner et al. 2013	42	7-12	ADHD, healthy	Emotional Lability Scale (Conners)	D	dorso-lateral PFC, ventral striatum	rest	10
Hulvershorn et al. 2014	63	6-13	ADHD, healthy	Emotional Lability Scale (Conners)	D	**amygdala**	rest	6.5
Graham et al. 2015	23	0.5-1	Healthy, range of interparental conflict	Negative Emotionality from Infant-Behavior Questionnaire	D	posterior cingulate cortex	natural sleep	6
Stoddard et al. 2015	53	9-18	Bipolar, severe mood dys., healthy	DSM (IV)	C	sub-nuclei of **amygdala**	rest	6
Bennett et al. 2017	58	7-13	ASD males	Emotional Lability Scale (Conners)	D	**amygdala** whole-brain	rest	6
Kann et al. 2017	62	9-12	Community recruitment	Negative Emotionality (Lab-TAB) at 3 yrs old	**D**	**amygdala**-to-fusiform face area	visual matching task	6.2
Stoddard et al. 2017	115	8-17	Anxiety, DMDD, ADHD, healthy	ARI	D	**amygdala**	emotion face process task	21
Dougherty et al. 2018	46	6-10	Oversampled for maternal depression	PAPA	D	**amygdala** ventral striatum	monetary incentive task	14.6
Kircanski et al. 2018	197	8-18	Healthy:clinically significant irritability	ARI	D	**amygdala**	emotional face dot-probe task	14
Roy et al. 2018	56	5-9	Severe temper outbursts, ADHD, healthy	Child Emotion Dysregulation Interview	C	anterior mid-cingulate	rest	6
Davis et al. 2019	44	14-16	Healthy females	Temperament in Middle Childhood Questionnaire	D	**amygdala**-to-prefrontal cortex	emotion labeling task	3
Kryza-Lacombe et al. 2019	120	8-19	ASD, healthy	CBCL	D	**amygdala**	emotion face process task	34
Tseng et al. 2019	195	8-18	DMDD, Anxiety, ADHD, healthy	ARI	D	**amygdala**, IFG	frustrating attention task	32
Weathersby et al. 2019	1003	22-37	Healthy, human connectome project	Anger-Aggression Survey, NIH Toolbox	D	whole-brain	rest	60
Gaffrey et al. 2020	66	4-6	Oversampled for preschool depression	Emotion regulation checklist	D	**amygdala**	rest	9.5

Lin et al. 2020	101	7-17	ASD males	CBCL – Dysregulation	D	whole-brain, networks	rest	6
Liuzzi et al. 2020	19	11-15	Community recruitment	ARI	D	**amygdala**	inhibitory control task	8.7
Ross et al. 2021	40	9-21	Bipolar, healthy	ARI	D	**amygdala**, IFG, caudate, putamen, nucleus accumbens	positive & frustrating feedback	32
Scheinost et al. 2021	69	8-22	DMDD, ADHD, Anxiety, healthy	Trait irritability (ARI), state irritability (self-report)	**D**	whole-brain	positive & frustrating feedback	36

State-Trait Anger Expression Inventory (STAXI-2) (Spielberger, 2010)
Connors (Cohen, 1988)
Infant Behavior Questionnaire (Gartstein and Rothbart, 2003)
Laboratory Tempereament Assessment Battery (Lab-TAB) (Gagne et al., 2011)
Affective Reactivity Index (ARI) (Stringaris et al., 2012)
Preschool Age Psychiatric Assessment (PAPA) (Egger et al., 1999)
Temperament in Middle Childhood Questionnaire (Simonds et al., 2007)
Child Behavioral Checklist (CBCL) (Achenbach, 1999)
NIH Toolbox (Gershon et al., 2010)
Emotion Regulation Checklist (Shields and Cicchetti, 1997)

2.1 Amygdala functional connectivity related to irritability

Studies of the neural substrates of irritability, even beyond those using functional connectivity, often focus on the amygdala. Among papers using functional connectivity MRI to investigate the neural underpinnings of irritability, 14 out of 20 specifically tested for the involvement of the amygdala (see Table 1) by including the amygdala as a seed (and often the only seed) to illuminate functional connectivity. Both theoretical and empirical evidence support the hypothesis that amygdala function contributes to an individual's level of irritability. The amygdala has been frequently implicated in human emotional processing and regulation (Zald, 2003). Further, studies of disorders characterized by severe emotion dysregulation, such as DMDD, find reduced amygdala volume and atypical amygdala functional responses during reward and socio-emotional tasks (Wiggins et al., 2016). What remains unclear is which interactions between the amygdala and other functional networks vary according to irritability; the results from extant studies have not been considered in a functional network framework. By looking across these studies, we find that the amygdala functional connectivity that varies with irritability involves functional networks important for internalization, executive control, and sensorimotor processing (Figure 1).

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2.1.1 Amygdala functional connectivity with the default mode network.

In existing literature, the functional connectivity patterns that are most consistently associated with irritability are between the amygdala and the default mode network (DMN). The DMN is comprised of regions including medial prefrontal cortex (mePFC), rostral anterior cingulate (Fulwiler, Stoddard(s), Hulvershorn, Kryza-Lcomb), posterior cingulate cortex/precuneus (Liuzzi, Graham), lateral parietal cortex (Dougherty), and anterior temporal cortex (Hulvershorn, Liuzzi). The DMN plays an interesting role in the brain's functional architecture. Instead of responding during goal-directed tasks, regions in the DMN become activated when directing attention inward, such as during self-focused mentation and mind-wandering (Raichle, 2015). There is typically strong functional connectivity between the amygdala and parts of the DMN, particularly the medial prefrontal cortex, anterior temporal cortex, and posterior cingulate (Pagliaccio et al., 2015; Roy et al., 2009). The functional connectivity that exists between the amygdala and DMN likely represents an important interface for internalized processing of emotions.

Amygdala-to-DMN functional connectivity has been consistently linked with irritability, but the nature of the identified relationship appears to be complex, such that the valence differs across studies and contexts. For example, amygdala functional connectivity related to medial prefrontal cortex has been repeatedly identified as varying with irritability, but across studies, there is not agreement about whether stronger functional connectivity supports better or poorer emotion regulation. Some have found that stronger functional connectivity between the amygdala and DMN is related to lower levels of trait irritability. In healthy male adults, stronger functional connectivity between the amygdala and ventromedial prefrontal cortex was associated with reduced trait anger and better anger control (Fulwiler et al., 2012). Further, when viewing angry faces, stronger correlations between activity in the amygdala and medial prefrontal cortex were linked to fewer irritability symptoms in children with accompanying elevated anxiety (Stoddard et al., 2017). In preschoolers at risk for depression (which has a significant irritability component),

stronger functional connectivity between the amygdala and medial prefrontal cortex was indicative of better emotion regulation and less negative affect (Gaffrey et al., 2020). Since strong functional connectivity is thought to result from frequent coactivation, a positive relationship between this functional connectivity and emotion regulation might suggest that poor coupling of the neural circuitry relevant for internalization and emotional processing is a cause or a consequence of elevated irritability.

However, other studies have found the opposite pattern, that stronger functional connectivity between the amygdala and medial prefrontal cortex is related to elevated irritability. Stronger functional connectivity between the amygdala and rostral anterior cingulate cortex was observed in children with ADHD with high emotional lability, but not low emotional lability (Hulvershorn et al., 2014) and in both youth with and without high-functioning ASD that experienced more irritability symptoms (Kryza-Lacombe et al., 2020). When explicitly labeling emotions, the positive relationship between the functional connectivity involving the amygdala and mePFC and negative emotionality is modulated by cognitive control such that increased cognitive control reduces the relationship between negative emotionality and this neural circuitry (Davis et al., 2019). A positive relationship between this functional connectivity and irritability might suggest that atypically frequent engagement of neural circuitry relevant for internalization and emotional processing is a cause or consequence of elevated irritability. Determining the true valence of the relationship between irritability and the functional connectivity between the amygdala and mePFC may help reveal the mechanism by which this interface important for the internalization of emotional stimuli can deviate. Potential sources of this inconsistency and potential avenues to disambiguate the relationship between this circuitry and irritability are discussed in Part 3.

2.1.2 Amygdala functional connectivity with executive control networks.

The amygdala also interacts with executive control functional networks across the brain. The cingulo-opercular (CO) and fronto-parietal (FP) networks are two distinct executive control

networks that support sustained task maintenance and adaptive control, respectively (Dosenbach et al., 2007; Power et al., 2011). Elevated irritability may arise from altered top-down, overt control over emotional processes evidenced by atypical coordination of the amygdala with these control networks. When children with elevated irritability completed a task with monetary incentives, the coordination of the amygdala and the insula (part of the CO network), as well as the amygdala and the inferior parietal lobule (part of the FP network), varied by the receipt of a reward (Dougherty et al., 2018). When youth along the autism spectrum completed a task with implicit emotional face processing, coordination of the amygdala and superior frontal gyrus (part of the CO network) also varied with an individual's irritability when viewing sad or angry faces (Kryza-Lacombe et al., 2020). Further, in children with ADHD, reduced functional connectivity between the amygdala and insula was associated with elevated emotional lability (Hulvershorn et al., 2014). The atypical coordination of the amygdala and control networks under different cognitive demands and in the context of poorer attentional capabilities illuminates the mediating role of top-down control on individual differences in irritability.

2.1.3 Amygdala functional connectivity with sensorimotor networks.

Other work finds that the interaction between the amygdala and sensorimotor networks may also be related to irritability. Both the lateral somatomotor (SM) network, devoted to facial representations and facial expressions, and the inferior temporal portion of the visual (VIS) network, involved in face perception, exhibit functional connectivity with the amygdala that varies according to irritability. Stronger functional connectivity between the amygdala and the lateral SM network has been associated with lower emotional lability in children with ADHD (Hulvershorn et al., 2014) and fewer irritability symptoms in children along the autism spectrum (Kryza-Lacombe et al., 2020). In contrast, stronger functional connectivity between the amygdala and the fusiform gyrus (part of the VIS network) was found to be linked to poorer emotion regulation in preschoolers at risk for depression (Gaffrey et al., 2020) and among pre-adolescents with a history of negative emotionality during early childhood (Kann et al., 2017). Even during an inhibitory control task

without explicit or implicit face processing, amygdala functional connectivity involving the lateral SM network and VIS network is related to irritability (Liuzzi et al., 2020). This might suggest that the neural circuitry supporting emotional responses and the perception and production of facial expressions is atypically coupled in individuals with emotion dysregulation.

It is also important to note that a number of studies that specifically tested whether amygdala functional connectivity varied with irritability did not find a significant association. When comparing typically developing children and children with two related types of irritability syndromes (bipolar disorder, and severe mood dysregulation disorder), functional connectivity between the amygdala and medial prefrontal cortex was not atypical in severe mood dysregulation (Stoddard et al., 2015). In children with ASD, functional connectivity involving the amygdala and sensorimotor networks did not vary with emotional lability (Bennett et al., 2017). Amygdala connectivity to the cingulate (part of the DMN) and precentral gyrus (part of the lateral SM network) was associated with higher anxiety but did not vary according to irritability in children spanning multiple diagnostic categories (Kircanski et al., 2018). When feedback during cognitive tasks was manipulated to be either positive or frustrating (i.e., rigged), amygdala functional connectivity varied by the type of feedback but did not vary according to individual differences in irritability in children and adolescences with DMDD, anxiety, ADHD, and bipolar disorder (Ross et al., 2021; Tseng et al., 2019). There are several potential reasons for this inconsistency, which are discussed in Part 3.

2.2 Other *a priori* seeds for functional connectivity related to irritability

Even though, to date, most studies have examined functional connectivity linked to irritability involving the amygdala, a limited number of studies have examined functional connectivity linked to other *a priori* brain areas hypothesized to be important for different components of irritability.

2.2.1 Default-mode network seed regions

The default-mode network (DMN) has been most consistently linked with atypical amygdala functional connectivity, but only a few studies have specifically targeted the relationship between

functional connectivity involving regions in the DMN and irritability. Because the DMN is important for internally directed attention and cognition, it is possible that atypical circuits within the DMN or between other networks important for emotion regulation might contribute to differences in internalized vs. externalized expression of emotion related to irritability. In infants, stronger functional connectivity between the posterior cingulate cortex and the rest of the DMN is related to greater negative emotionality (Graham et al., 2015b), suggesting that components of irritability are reflected in the integration of the network of regions important for internalization even very early in the lifespan.

2.2.2 Executive control network seed regions

Because of the potential role of cognitive control in managing frustration, some hypothesize that the functional connectivity involving regions in cognitive control networks, such as the cingulo-opercular (CO) and fronto-parietal (FP) network, may be linked with irritability. In particular, the cingulo-opercular (CO) network includes the inferior frontal gyrus, anterior insula, and dorsal anterior cingulate and produces control signals including information about errors and ambiguity which may be relevant to experience frustration (Dubis et al., 2016; Neta et al., 2014). Functional connectivity related to feedback processing has been shown to vary according to irritability—the functional connectivity involving the inferior frontal gyrus (part of the CO) differed when doing a task and receiving positive vs. frustrating feedback and this difference varied according to irritability transdiagnostically (Tseng et al. 2019). Reduced functional connectivity between the mid anterior cingulate and the rest of the CO network has also been observed in children with the combination of ADHD and severe temper outbursts (Roy et al., 2018). Taken together, these findings suggest that aberrant executive control, potentially even separate from emotional processing, also relates to an individual's irritability.

2.2.3 Ventral striatum and other subcortical seed regions.

Due to the role of reward processing in experiencing frustration, some have tested whether the functional connectivity involving other subcortical structures, such as the ventral striatum, are

linked with irritability. Neurons in the ventral striatum respond positively to the anticipation and receipt of reward and negatively when expectations and reality do not match (i.e., negative prediction error) (Pagnoni et al., 2002; Schultz et al., 1992), signals that are highly relevant to the expression of frustration and may be irregular in individuals with elevated irritability (Leibenluft, 2017). The ventral striatum also has connections to both the amygdala and various functional networks (Fudge et al., 2002; Greene et al., 2020). Functional connectivity between the ventral striatum and precuneus (part of the DMN) is modulated by the presence or absence of a reward in children with high irritability; when children with high irritability committed errors and did not receive a reward, functional connectivity between the ventral striatum and the precuneus became stronger, but this was not the case when children with low irritability committed errors (Dougherty et al., 2018). Functional connectivity between the putamen and insula (part of the CO) when undergoing a task and receiving positive or frustrating (i.e., rigged) feedback appeared to be atypical in bipolar disorder such that greater connectivity was positively related to irritability (Ross et al. 2021). In children with ADHD, stronger functional connectivity between the ventral striatum and orbitofrontal cortex (part of the DMN) at rest was associated with lower emotional lability (Posner et al., 2013). This might suggest that the neural circuitry linking reward processing, internalization, and error-related control signals varies according to an individual's ability to cope with frustration.

Taken together, the works identifying functional connectivity that varies with irritability with a seed-based approach (either amygdala, or other regions) implicate multiple functional networks. Thus, it is possible that a connectome-wide approach may be able to illuminate the interactions within and between these functional networks that factor into an individual's irritability.

2.3 Connectome-wide functional connectivity related to irritability

Whole-brain or connectome-wide investigations of the functional connectivity are becoming more common, but have been used infrequently when studying irritability (4 out of 20 studies). However, these studies have revealed several findings that, while consistent with prior work using seed-

based approaches, expand upon our previous understanding of the brain networks linked to irritability.

2.3.1 Within the default-mode network.

Stronger functional connectivity within the DMN has been related to increased emotional lability in children with autism (Bennett et al., 2017). As mentioned previously, the DMN contains regions that are more activated by internally- than externally-driven behavior (Fox et al., 2005; Raichle, 2015; Raichle et al., 2001) and thus, atypical enhanced connectivity with the DMN might be indicative of frequent internalization across the lifespan in individuals with elevated irritability. Proper integration of regions within the DMN, a functional network important for internalization, could factor into an individual's ability to regulate their emotion.

2.3.2 Between the default-mode and cingulo-opercular networks.

Several studies have identified functional connectivity between the CO and DMN networks that relates to individual differences in irritability, but this relationship appears to be complex. Stronger functional connectivity between the CO and DMN networks was associated with severe temper outbursts in children with ADHD (Roy et al., 2018) and elevated anger and aggression in healthy adults (Weathersby et al., 2019). In autism, this relationship may be reversed; in one study, reduced functional connectivity between the posterior insula (part of the CO) and the precuneus, middle frontal gyrus, and anterior cingulate cortex (parts of the DMN) was related to increased emotional lability (Bennett et al., 2017). In contrast, the nature of the relationship between the functional connectivity between the fronto-parietal and default mode networks and individual differences in irritability appears to be shared across typically developing individuals and individuals with autism; stronger functional connectivity between the dorsal anterior cingulate cortex (part of the DMN) and the lateral prefrontal cortex (part of the FP) was indicative of increased dysregulation in both typically developing and ASD individuals (Lin et al., 2020). These differing patterns in typical development and in autism may also arise if overall network organization (i.e., delineation of the DMN, FP, or CO) differs in autism. Though complex, these

findings suggest that emotional regulation relies on the coordination of the neural circuitry responsible for executive control and self-referential behaviors.

2.3.3 With sensorimotor networks.

Functional connectivity between the somatosensory networks has been found to vary according to anger and irritability. The variability in self-reported anger, a proxy for irritability, among healthy adults was found to relate to individual differences in the functional connectivity between several sensorimotor networks and the DMN (Weathersby et al., 2019). Further, in a connectome-wide search, the functional connectivity between the precuneus (part of the DMN) and the supplementary motor area (part of the somatomotor networks) was found to distinguish individuals with ASD with and without symptoms of dysregulation (Lin et al., 2020). In another connectome-wide search, a variety of networks related to irritability were identified, but the strongest associations with irritability were noted within motor and sensory regions, as well as between sensory-motor regions and subcortical and salience networks (Scheinhorst et al., 2021). This aberrant functional connectivity may be indicative of the atypically linked self-regulation and initiation of complex motor plans (e.g., tantrums).

2.3.4 Among control networks.

Reduced functional connectivity among regions within the CO network has been observed in children with the combination of ADHD and severe temper outbursts (Roy et al., 2018) and in children with autism who had increased emotional lability (Bennett et al., 2017). This elevated irritability in autism was also associated with reduced functional connectivity between different executive control networks (CO and FP), particularly indicating the importance of the coordination of different executive control networks. Taken together, these findings suggest that aberrant executive control, even separate from emotional processing, also relates to an individual's irritability.

2.4 Summary

Variation in how the amygdala coordinates with functional networks important for self-referential behaviors (DMN), executive control (CO, FP), production and representation of facial expressions (SM), and perception of faces (VIS) contributes to an individual's irritability. By combining findings across the whole brain, an interconnected picture of the functional connectivity related to irritability emerges, which links the internalization supported by the DMN with brain structures and functional networks important reward processing (ventral striatum), externally-driven executive control (CO, FP), and motor output (SM). Independent of the interactions involving the amygdala and DMN, the integrity and coordination of executive control networks (CO, FP) also factors into variation in irritability. Taken together, these findings support the idea that the construct 'irritability' is made up of many components and the neural underpinnings of irritability draw from a diverse set of functional networks.

Part 3: Current limitations and opportunities to expand understanding of the functional connectivity linked to irritability.

The growing body of work linking functional networks with irritability makes strides to align with RDoC and has many strengths, including the fact that irritability is a transdiagnostic phenotype present in more than 20 different DSM disorders. Further strengths are the developmental focus on the emergent phase of the clinical sequence rather than frank disorders at older ages, and research efforts to examine not only the continuous variation in typical samples, but also samples enriched for irritability. However, this growing field also has key gaps that, if not addressed as the field moves forward, may limit the interpretability and utility of the identified functional networks. Here, we discuss these limitations as we point to opportunities to better align and improve upon the RDoC framework by (1) better characterizing and capturing the full normal:abnormal dimensional spectrum of irritability, (2) better delineating functional networks, and (3) expanding consideration of maturation and developmental context.

3.1 Characterization and measurement of irritability.

As mentioned previously, interrogating irritability dimensionally and transdiagnostically may be crucial to revealing the neural substrates underlying various mental health problems. Most of the works summarized in this review were not designed for this specific purpose, and thus used a broad array of irritability measures and constructs. Measures of irritability varied in complexity (i.e., from a few survey items to an in-depth interview), dimensionality (i.e., 4-point scale vs. 100s of survey questions), range of sensitivity (i.e., capturing typical variation vs. symptom severity), epoch of measurement (i.e., behaviors/frequency in the last hour, week, 3 months, or year), and construct features (i.e., emotion reactivity vs. emotion regulation). Variation in findings across studies may in part stem from how irritability was operationalized. Some studies using measures of irritability that focused on emotional reactivity (e.g., emotional lability, anger, emotionality) illuminated different neural circuitry than those using measures that focus on emotion regulation (e.g., self-regulation), potentially suggesting that different functional networks contribute to different aspects of irritability. Leveraging measurements of irritability as a multi-dimensional, developmentally-based construct (as in the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB) (Kaat et al., 2019; Wakschlag et al., 2017)) may provide a standard tool for cross-study comparability across ages designed to capture its full dimensional spectrum. Further, the use of direct observational measures designed to capture irritability regulation and reactivity across demand and interactional contexts may add further clarity; the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS) (Wakschlag et al., 2008) was designed for this purpose. The DB-DOS shows alignment with functional neural measures collected during parent-child interactions when frustration was induced with a task (Quiñones-Camacho et al., 2020).

However, method variance in measurement of irritability alone cannot explain variation in findings across studies. Even studies using the same measure yielded different results—three studies using the same measurement of emotional lability found that different functional

connectivity varied according to irritability in children with autism (Bennett et al., 2017), children with ADHD (Hulvershorn et al., 2014; Posner et al., 2013), and healthy controls. It is possible that different sampling techniques and different psychiatric syndromes play a role in which functional networks vary according to irritability. Assessing irritability consistently across studies in addition to the characterization of psychiatric/developmental context could help resolve these discrepancies.

One of the main advantages of studying irritability is that it is transdiagnostic, a central feature of the RDoC framework. As evidenced by this review, many studies evaluate irritability by studying clinical populations, as several disorders (including anxiety disorders, ASD, and ADHD) involve experiencing irritability, even beyond those disorders that are more explicitly defined by higher irritability (DMDD, ODD). These types of clinical group approaches reveal functional connectivity that distinguishes individuals with irritability symptoms from those without (e.g., ASD+dysregulation vs. ASD-dysregulation) in a variety of disorders. This can be important as the neural circuitry supporting irritability can interact with other symptoms and/or cognitive abilities; for example, the relationship between amygdala functional connectivity and irritability is altered depending on level of anxiety (Stoddard et al., 2017; Tseng et al., 2019) and level of cognitive control (Davis et al., 2019). Studying irritability, which is a common component of many different psychiatric disorders, might illuminate shared circuitry as well as highlight the complex nature of mental health problems. It is equally important to examine how irritability-linked functional networks might differ across disorders to disentangle the different mechanisms underlying the different manifestations of irritability. However, the functional networks that vary with clinically impairing irritability symptoms may not be the same as those that vary with less-severe typical variation in irritability. For example, functional connectivity involving the amygdala only varied according to the receipt of reward in individuals with high irritability, but not medium or low irritability (Dougherty et al., 2018). This suggests there may be a complex, non-linear relationship between functional connectivity and irritability and it is worth knowing how alterations in functional

networks vary across the entire normal:abnormal spectrum. In addition to operationalizing irritability in way that better captures typical variation in irritability, there is also a need to improve sampling strategies in order to capture a broad distribution of irritability. By better understanding how irritability and functional networks vary in the typically developing population, we might be able to better detect when irritability or brain networks are indicative of vulnerability to developing more severe mental health problems.

Prediction of psychopathology in young children may also require richer measurements of irritability beyond a single “snap-shot’, both because there is substantial heterogeneity in course and because impairment must be taken into account (Wakschlag et al., 2020). For example, we have shown that approximately 1/3 of young children with higher irritability will not show persistently high levels years later. On the other hand, preschoolers with persistently high irritability that is impairing are at significantly higher risk for subsequent psychopathology (odds ratio=11.52) (Wiggins et al., 2020). Examining irritability in tandem with other developmental domains that may amplify or mitigate risk (e.g., language delay (Manning et al., 2019)) may also capture meaningful individual differences in relations to functional connectivity. It is possible that atypical variation in functional networks (or other neural measures) may aid in predicting which irritable children will be impaired. Dorsolateral prefrontal cortex function measured with functional infrared spectroscopy while completing a frustrating task distinguished irritable children who were and were not impaired (Grabell et al., 2018); in that study, neural and survey-derived (on the MAP-DB) prediction of impairment yielded similar thresholds to discriminate normal:abnormal, pointing to the utility of dimensional measurement. Since functional connectivity can capture variation in function across the whole brain rather than within a single region, it is possible that information across many functional networks may aid in the prediction of impairment related to irritability. Further, because both functional connectivity and irritability can be measured early in the lifespan, combined information from the two may reveal whether a young child with irritability may be at greater risk for internalizing disorders, externalizing disorders, or both.

3.2 Characterization and measurement of functional networks.

Even the relatively limited research to date on the functional brain networks related to irritability, with its fairly focused spotlight on amygdala functional connectivity, indicates the involvement of multiple functional networks. To better characterize how other functional networks are linked to irritability, future studies need to broaden their scope and move beyond solely examining functional connectivity with the amygdala. A whole-brain approach, where the functional connectivity within each functional network and between each pair of functional networks is considered, may be best able to fully capture individual differences related to irritability. It is important that null findings are reported when conducting a connectome-wide search to further promote transparency and reproducibility. Further, multivariate descriptions that take into account patterns of variation across many functional networks (as in Lin et al., 2020 and Scheinost et al., 2021) may be best equipped to capture the complexities of irritability (Lessov-Schlaggar et al., 2016; Nielsen et al., 2020a). A recent study applying multivariate predictive approaches to functional connectivity and irritability found that many networks contribute to the prediction of individual-level irritability (Sheinost et al., 2021). Measuring brain function across multiple functional networks may also be better suited for RDoC: transdiagnostic and disorder-specific functional connectivity patterns have been identified across schizophrenia, bipolar disorder, and major depressive disorder involve many functional networks and these shared and distinct mechanisms were only revealed with a whole-brain network approach (Huang et al., 2020). As irritability is a transdiagnostic precursor and symptom of many mental health problems, its presentation in different clinical groups (e.g., ADHD + irritability, or MDD + irritability) may be supported by the involvement of different constellations of functional networks (Sylvester et al., 2012). Fully understanding the functional networks and specific functional relationships linked to irritability and how they vary in different clinical contexts might enable early detection and precision diagnostics/treatment.

Our understanding of the functional connectivity between cortex and the subcortex (e.g., amygdala and ventral striatum) is changing. The functional organization of regions within structures such as the amygdala, basal ganglia, hippocampus, thalamus, and cerebellum are complex and have non-uniform relationships with the functional networks in the cortex (Greene et al., 2020; Marek et al., 2018; Sylvester et al., 2020). For example, different sub-regions of the amygdala have stronger relationships with the default mode network, the dorsal attention network, and other functional networks; these functional sub-divisions do not necessarily align with anatomically defined sub-divisions (Sylvester et al., 2020). It is possible that one source of inconsistency across studies of amygdala functional connectivity related to irritability is the oversimplification of amygdala circuitry. The functional connectivity of the ventral striatum also has non-uniform ties to cortex that might affect our ability to detect variance related to irritability. Better defining the neural substrates that can then be mapped to dimensional indicators of psychopathology is in line with the RDoC framework.

Further, recent studies demonstrating how functional networks vary across individuals may be pertinent to our understanding of the neural circuitry related to irritability. Functional networks can vary in spatial location from person-to-person (Braga and Buckner, 2017; Gordon et al., 2017; Laumann et al., 2015). Amygdala functional connectivity also varies across healthy individuals (Sylvester et al., 2020) and this variability may be particularly pertinent to understanding how functional connectivity links to irritability. As summarized in this review, the most consistently identified connections that vary with irritability are those between the mePFC of the DMN and the amygdala, though the relationship between connectivity strength and irritability for these connections were often identified in opposing directions. Individual variability in either amygdala functional connectivity or in the spatial layout of functional networks in the mePFC may contribute to this inconsistency. In the functional networks identified in an individual, functional connectivity between the amygdala and mePFC appears to be guided by network (e.g., positive connectivity with DMN), rather than by spatial location. On average, the mePFC is well-connected

with regions in the DMN (i.e., part of the DMN), but a recent probabilistic description of individual functional networks suggests that for a portion of individuals, parts of the mePFC can be better connected to regions from other functional networks (e.g., salience network) (Dworetsky et al., 2021). If irritability is truly linked to increases or decreases in amygdala to DMN connectivity, individual variability in DMN location or more generally the location of different functional areas relevant to emotion regulation might yield the inconsistent results observed across studies. Thus, our interpretation of mePFC to amygdala connectivity related to irritability, which is derived from utilizing averaged functional networks, may be muddied by individual differences in network organization.

Another burgeoning line of investigation is the comparison of functional networks under different cognitive and emotional demands which may further illuminate functional differences in the circuitry relevant to variability in emotion regulation. The studies reviewed here included an equal mixture of functional connectivity in a “resting-state” and functional connectivity in a “task-state” (see Table 1). Some of the differences in findings across studies might be attributable to an individual’s cognitive state. As an example, functional connectivity between the amygdala and the DMN has been more consistently identified as related to individual differences in irritability during rest (Fulwhiler et al. 2012, Hulvershorn et al. 2014, Gaffrey et al. 2020) than during task (Kryza-Lacombe et al. 2019, Stoddard et al. 2017), potentially suggesting that the coordination of the networks for internalization and the amygdala may be more relevant to the dispositional aspects of irritability. In contrast, functional connectivity between the amygdala and processing networks including the somatosensory and visual networks has been more consistently linked to irritability during tasks (Kann et al. 2017, Liuzzi et al. 2020, Kryza-Lacombe et al. 2019), and may be more important for actively processing frustrating or emotional stimuli. While the magnitude of the modifications of functional networks during tasks seem to be much smaller than differences in functional connectivity across individuals (Gratton et al. 2018) and modifications to functional connectivity during task cannot be completely dissociated from the evoked task signals (Cole et

al. 2019), it is possible that these small, but significant task-induced differences carry information relevant to understanding individual differences in irritability (Finn et al. 2017).

Being able to detect the variability of network organization across individuals and across task states and assess their importance for understanding the networks related to irritability hinges upon the reliability of functional connectivity. The test-retest reliability of a single fMRI scan is fairly low and depends upon many factors (Noble et al., 2017) including scan length (median scan length for studies reviewed here: 8.7 minutes, see Table 1). Functional connectivity in highly sampled individuals (e.g., ~5 hours of resting-state scans) reveals that increasing the amount of data used to calculate functional connectivity can rapidly improve reliability and that some functional connectivity derived measures require more data to yield stable results (e.g., individualized network definitions) (Braga and Buckner, 2017; Gordon et al., 2017; Laumann et al., 2015). Disentangling the potential impact of individual network organization and task-induced changes to network organization on the neural underpinnings of emotion regulation might be facilitated by an individualized approach requiring the collection of many fMRI scans. Repeatedly scanning an irritable, pediatric population is undoubtably challenging, but there are methodologies that can help improve success (Greene et al., 2018, 2016). These efforts to better capture how neural features vary across individuals, particularly in relation to dimensional indicators like irritability, are well aligned with the goals of the RDoC framework and may contribute to precision psychiatry efforts (Gratton et al., 2020).

3.3 Influence of Development.

Beyond improving how we measure irritability and functional connectivity, expanding consideration of the unfolding neurodevelopmental context in which atypical functional connectivity occurs would benefit our understanding of the functional networks related to irritability. Most studies reviewed here did assess irritability in children and adolescents (see Table 1), but the heterogeneity of age groups studied may be another potential source for the lack of entirely consistent effects of irritability on functional networks. Seemingly equivalent emotion

dysregulation at different ages may be supported by different neural mechanisms as children mature and more sophisticated regulation strategies become available (e.g., cognitive control) (Zelazo and Cunningham, 2007). The same clinical symptoms or impairment may be associated with abnormalities present in different functional networks at different ages, a problem pertinent to the goals of RDoC. In Tourette syndrome, for example, the functional networks that best distinguish patients from controls differ between children and adults, suggesting that different neural mechanisms underlie tics and other symptoms over the course of development (Nielsen et al., 2020b). Considering age effects and how brain:behavior patterns change over time in the study of irritability may reveal different neural mechanisms that are necessary for emotion regulation at different ages. In one of the youngest samples (4-6 yrs, (Gaffrey et al., 2020)), only amygdala functional connectivity between the mePFC and fusiform gyrus was found to be related to irritability but in older children and adults, amygdala functional connectivity between executive control networks like the FP and CO were implicated (Dougherty et al., 2018; Hulvershorn et al., 2014; Kryza-Lacombe et al., 2020). It is possible that elevated irritability in adolescence and adulthood is associated with disrupted neural circuitry at the interface of emotion processing and executive control, but this circuity is not yet a factor in the irritability in early childhood. When tested directly, the strength of the relationship between the functional connectivity in the inferior frontal gyrus and irritability decreased with age (Tseng et al. 2019), suggesting that its role in the manifestation of irritability changes over the course of development. Longitudinal studies and/or cross-sectional studies examining the interaction between age and irritability are needed to determine whether the functional networks related to irritability change with age and can explain the current discrepancies in the literature.

Further, expanding consideration of typical maturation and developmental context may further clarify our understanding of the functional brain networks related to irritability. The definition of functional networks (i.e., which regions comprise the DMN) appears to be fairly similar between adults and children (Marek et al., 2019), but patterns of functional connectivity within and

between functional networks across the brain vary according to age (Cui et al., 2020; Marek et al., 2015; Nielsen et al., 2019; Satterthwaite et al., 2013). Many of the studies detailed in this review identified functional connectivity related to irritability in school-age or pre-school children, but these findings were not explicitly compared to age-related and/or maturational functional connectivity differences observed in typical development. Considering functional networks related to irritability in a maturational context can reveal whether elevated irritability reflects an atypical developmental trajectory (e.g., delayed, anomalous) of functional connectivity. For example, functional connectivity between the amygdala and mePFC becomes increasingly positive throughout childhood and adolescence in typical development (Gabard-Durnam et al., 2014). It's possible that the pattern of reduced functional connectivity strength observed between the amygdala and mePFC in preschoolers with poorer emotion regulation (Gaffrey et al., 2020), in children and adolescents with elevated irritability and anxiety (Stoddard et al., 2017), and in adults with increased trait anger (Fulwiler et al., 2012) is indicative of immature or incomplete maturation of this circuitry. Throughout childhood and adolescence, the organization of executive control networks like the FP and CO is continuously refined, such that these networks become more distinct from one another but also act to integrate other types of functional networks (Cui et al., 2020; Fair et al., 2007; Marek et al., 2015). Reduced functional connectivity between the FP and CO observed in children with autism with elevated emotional lability (Bennett et al., 2017) may reflect an atypical developmental trajectory; revealing atypical development requires placing these observed differences in the context of developmental differences or longitudinal differences. It may also be important to consider that functional networks related to irritability do not develop in isolation. Many other properties of the brain's functional network architecture are modified over the course of development in a complex, yet subtle way (Marek et al., 2015; Nielsen et al., 2019). The developmental status of functional networks not directly linked to irritability may be a risk factor or protective factor for the healthy development of emotion regulation. Specifically considering the developmental context of functional networks or other neural features in the RDoC

may provide a better description of mechanisms underlying psychopathology (Mittal and Wakschlag, 2017).

Because neuroplasticity is greater early in life (e.g., language development (Vicari et al., 2000)), consideration of the variability of the ecological context (i.e., environmental influences) may be essential to characterize the functional networks related to irritability. For example, stress and its biological correlates may affect functional connectivity (for a review, see VanTieghem and Tottenham, 2018); elevated baseline cortisol has been associated with stronger negative functional connectivity between the amygdala and mePFC in adults (Veer et al., 2012). Early life stress exposure stemming from institutionalization (Gee et al., 2013), childhood maltreatment and trauma (van der Werff et al., 2013), hostile parenting (Kopala-Sibley et al., 2020), and other adverse childhood experiences (Pagliaccio and Barch, 2016) has been associated with altered amygdala functional connectivity in childhood and adolescence. Many mental health problems involving irritability are often a potential consequence of adverse childhood experiences or early life stress (Kalmakis and Chandler, 2015). It is possible that differences in functional networks thought to be related to irritability may also include differences related to ecological context. Further, if ecological context impacts a child's other abilities (e.g., language) that influence emotion regulation, these complex interactions may further alter functional networks. Because functional connectivity is thought to reflect a history of brain function over the course of the lifespan (Dosenbach et al., 2010; Harmelech et al., 2013), a concurrent (Graham et al., 2015a) or retrospective characterization of a child's early life experiences (Demir-Lira et al., 2016) may be necessary to disentangle the functional connectivity related to irritability from that associated with early environmental experience (Graham et al., 2015c; McLaughlin, 2016).

Identifying the neural underpinnings of irritability as early as possible (i.e., in infancy) is one way to disentangle the complexities that arise with long-term exposure and maturation and has the added benefit of providing the potential to intervene and prevent lasting neural and

psychological consequences. Even in infancy, meaningful variation in irritability can be observed when developmentally appropriate assessments are used (Wakschlag et al., 2020). Similarly, many functional networks like the default mode network are identifiable even at birth, and they can be non-invasively measured in infants using fMRI during natural sleep (Smyser et al., 2011, 2010); interest in examining the neural circuitry related to irritability in infancy using functional connectivity is growing. Concurrent measurement of functional connectivity and negative emotionality reveals that stronger functional connectivity within the default mode network correlates with greater negative emotionality in 6-12 month old infants (Graham et al., 2015b). Further, differences in neonatal functional connectivity between the amygdala and the mePFC, circuitry consistently linked to irritability, can partially explain variation in early internalizing behavior at age 2 (Rogers et al., 2017) suggesting that the neural building blocks of irritability may be present at birth and that this early biomarker may provide clinical utility to predict whether a child is on a clinical trajectory. Our group is also working to test whether improving the gestational environment (via prenatal stress reduction within a clinical trial) alters the between link functional connectivity and irritability in infancy (Wakschlag et al., n.d.). The current RDoC framework acknowledges the neurodevelopmental origins of many mental health problems, but could do more to promote the study of vulnerabilities and risk factors even earlier in the lifespan (Luby et al., 2019; Wakschlag et al., 2019). Identifying the earliest indicators of later mental health problems and understanding the earliest mechanisms that determine clinical progression and manifestation can serve as an engine for translation of scientific knowledge to clinical action (Wakschlag et al., 2017).

3.4 Other experimental design considerations

Other factors related to the experimental design of studies linking irritability and functional connectivity may also have an impact on the accuracy and reproducibility of these findings. First, many of the studies reviewed here had fairly modest sample sizes (median n = 62). Recent work suggests that very large sample sizes (n~2000) may be necessary to reproducibly identify

correlations between functional connectivity and behavior (Marek et al., 2020). Boosting sample sizes, harmonizing measures, and combining data from smaller studies may be necessary to improve the reproducibility of the functional connectivity linked to irritability. Second, many of the studies reviewed here did not account for differences in head motion in the scanner. Even sub-millimeter head movements can produce spurious, yet systematic alterations to measured functional connectivity (Power et al., 2012; Satterthwaite et al., 2012). Head motion in the scanner is frequently found in children, toddlers, and infants (Satterthwaite et al., 2012; Smyser et al., 2011), correlated with many variables related to cognition and psychopathology (Siegel et al., 2017), and importantly, reflected in individual differences in functional connectivity (Nielsen et al., 2019). Differences in head motion across studies may impact the validity of the identified relationship between functional connectivity and irritability. Improving the quality and reliability of the measurements of functional connectivity and irritability (as discussed above) would promote more accurate depictions of the neural substrates underlying differences in emotion regulation.

Lastly, it is important to keep in mind that the elemental cognitive and emotional processes underlying emotion dysregulation may not directly map on to the functional network organization of the brain. A recent meta-analysis of studies of emotion regulation using task-fMRI by Morawetz et al. reveals several sets of commonly co-activated brain regions that potentially correspond to different processes involved in emotion regulation (Morawetz et al., 2020). The brain regions identified as being involved with emotion regulation by task-fMRI align well with those identified by functional connectivity, but the groupings of co-activated regions thought to underlie different components of emotion regulation did not necessarily respect functional network organization. First, regions that comprise a single functional network were associated with multiple components of emotion regulation; different parts of the DMN including the medial prefrontal cortex, posterior cingulate cortex, and lateral parietal cortex were linked with different components of emotion regulation tasks including self-regulation, emotion generation, and emotion reactivity. Second, each identified component of emotion regulation was comprised of

cortical and subcortical regions from multiple functional networks suggesting that these elemental processes do not recruit single functional networks in isolation. An indirect mapping between functional networks and behavior is not uncommon--regions that frequently show coordinated activity while reading are linked to distinct visual, attention, and executive control networks at rest (Vogel et al., 2013). Even though spontaneous brain activity is organized by functional networks, the neural substrates underlying the different components of irritability, developmental changes in irritability, and environmental influences on irritability may have even more complex organization.

Conclusion

Here, we have discussed that functional connectivity and irritability provide important insights into the brain:behavior patterns underlying mental health problems and can potentially generate a more complete and actionable picture of psychopathology. Previous studies conducted in normative and several disease contexts suggest that irritability is linked to differences in functional connectivity involving many functional networks important for internalization, executive control, emotion generation, and emotion perception. Targeting the large-scale neural circuitry related to irritability, the earliest transdiagnostic behavioral indicator of subsequent mental health problems, has the potential to improve our understanding of heterogeneity in mental disorders and our ability to predict/prevent disease progression. Progress towards clinical translation is also facilitated by ongoing efforts to 1) improve the reliably and validity of measurements of both irritability and functional connectivity, 2) deepen the operationalization and modeling of environmental and maturational features of neurodevelopmental context, and 3) boost statistical power and reproducibility with the collection of very large samples across multiple sites. Practical insights into the etiology, progression, or treatment of mental health problems from neuroimaging may be achievable but will likely require thoughtful consideration of many factors impacting the relationship between the brain and psychopathology, such as development and environment.

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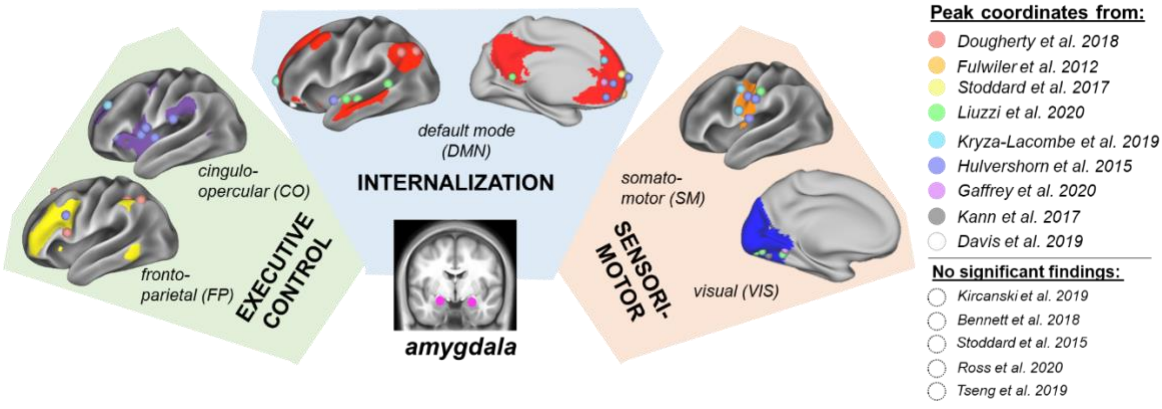
FIGURE CAPTIONS:

Figure 1. **Amygdala functional connectivity linked to irritability involves several brain networks.** Peak coordinates from the studies that identified functional connectivity involving the amygdala are depicted as spherical regions of interest. Findings are categorized by class of functional networks (i.e., executive control, internalization, sensorimotor) and displayed in relation to average definitions of functional networks defined in Power et al., 2011. Peaks identified in either the left or right hemisphere are depicted on the left hemisphere. No significant relation between irritability and amygdala functional connectivity was identified in Kircanski et al. 2019, Bennett et al. 2018, Stoddard et al. 2015, Ross et al. 2020, and Tseng et al. 2019. It is important to note that the direction of the relationship between amygdala functional connectivity and irritability identified in similar spatial locations differed across studies.



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