SECTION II

Developmental Considerations

The preschool age (3–6 years) is a unique period for development as both emotion regulation and foundational brain development are rapidly maturing. Emotions such as frustration are common during this age; however, there is extensive variability along the spectrum from typical to atypical. This juxtaposition of normative misbehaviors with stable irritable temperament presents unique challenges to the differentiation of normative variation from the onset of clinical problems. As such, recent research has focused efforts on improving methods for differentiating normative and clinically concerning behavior. Improved neuroimaging tools, in combination with behavioral and clinical assessment, have provided an additional tool for assessing pediatric irritability. The authors believe that joint consideration of brain–behavior atypicalities will enhance early identification of clinically concerning irritability. To this end, this chapter aims to summarize the rapid development occurring during the preschool years, describe advancements in developmentally appropriate irritability

assessments, and integrate these measurements within a neurodevelopmental framework.

preschool, neurodevelopment, early childhood, MAP-DB, DB-DOS, neuroimaging

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Early Childhood Irritability

Using a Neurodevelopmental Framework to Inform Clinical Understanding

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1 The preschool age (3–6), also referred to as early childhood, is a unique period for the development of emotion regulation (Carroll & Steward, 1984; Cole, Michel, & Teti, 1994; Diamond, 2002; Tsujimoto, 2008). The ability to regulate emotion during this period is a burgeoning and rapidly maturing process, with the emotions of anger and frustration, both common substrates of irritability, occurring relatively frequently (Wakschlag et al., 2007,

2012, 2017). However, although irritability is common, there is still extensive variability in irritable temperament within children. This juxtaposition of normative misbehaviors (e.g., tantrums, grumpy mood) with stable irritable temperament presents unique challenges to the differentiation of normative variation from the onset of clinical problems (Wakschlag et al., 2012). However, as technologies for measuring neural function and structure improve, neuroimaging, in combination with behavioral and clinical assessment, has provided an additional tool for assessing pediatric irritability and its relationship with common substrates of impaired psychiatric functioning. Although not yet integrated into clinical assessment, we believe that, ultimately, joint consideration of brain–behavior atypticalities will enhance early identification (Leibenluft, 2017; Wakschlag et al., 2017). Here we present the current observational, parent-report, and neuroimaging research in this young population through a neurodevelopmental framework. In this chapter, we aim to (1) summarize the relevant rapid development occurring in the preschool years and the unique challenges posed in assessing irritability in this age group, (2) describe the advancements in measuring irritability and creating developmentally appropriate diagnostic assessments for preschool children, and (3) integrate these measurements within a neurodevelopmental framework to maximize differentiation of normative and non-normative irritability.

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Challenges in the Assessment of Irritability During the Preschool Years

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Importance of the Preschool Period

2 Preschool is a significant developmental time period as children transition to increased independence from caregivers. Beginning in toddlerhood, children are expected to demonstrate increasing personal agency and self-control as they progress into school age, which requires top-down modulation of actions, thoughts, and feelings (Brownell & Kopp, 2007; McClelland & Cameron, 2011). This increased independence coincides with rapid growth in linguistic abilities (Luu et al., 2009; McCarthy, 1930; Pungello,

Iruka, Dotterer, Mills-Koonce, & Reznick, 2009), socioemotional expression (Duncan et al., 2007; Rhoades, Warren, Domitrovich, & Greenberg, 2011), and brain structural and functional development (Diamond, 2002; Giedd et al., 2009; Tsujimoto, 2008). Disruptions to the development of these systems and skills can have serious ramifications as children progress through adolescence and into adulthood, including conduct problems (Bennett et al., 1999), poorer socialization and anger control (Kochanska, Murray, & Harlan, 2000), and depression and anxiety symptoms (Phillips, Hammen, Brennan, Najman, & Bor, 2005). For these reasons, early childhood identification and treatment of behavioral and emotional concerns is of particular importance. Irritability as a dimensional symptom spans many psychiatric and behavioral concerns across development (Stringaris, 2011; Stringaris & Goodman, 2009; Wakschlag et al., 2015), can present at clinically significant levels in children as young as 2 years (Achenbach, Edelbrock, & Howelp, 1987; Wakschlag et al., 2012; Wakschlag, Tolan, & Leventhal, 2010), and is predictive of later functioning and psychiatric outcomes (Dougherty et al., 2013). Detection and treatment of clinically significant irritability is therefore a critical component of early intervention.

3 Developmental Considerations

3 The rapid pace of maturation across the early childhood period introduces unique challenges to the definition and measurement of key constructs. Of particular relevance to contextualizing pediatric irritability is the rapid development of executive function during the preschool years, which is at the heart of emotion regulation and correlates with specific changes in neural function in this age group (Bernier, Carlson, & Whipple, 2010; Denham et al., 2017; Hofmann, Schmeichel, & Baddeley, 2012; Perlman, Huppert, & Luna, 2016).

4 Second only to the first 2 years of life, the preschool years include the most rapid neural development as the brain reaches approximately 95% of its final size by age 6 (Giedd et al., 2009). Timing for peak development varies by region and index of brain development (Giedd et al., 2009; Gogtay et al., 2004;

Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Shaw et al., 2008). In terms of synaptic density, the visual cortex peaks during the first year of life with a rapid decrease in density in early childhood and a slower decrease into adolescence and adulthood (Huttenlocher et al., 1982). In terms of cortical thickness and volume, however, peak development of both the parietal and frontal regions occurs in middle childhood (9–12 years) and temporal cortex development peaks during adolescence (16–17 years), while occipital regions increase steadily into adulthood without a clear single peak (Giedd et al., 1999; Lenroot & Giedd, 2006). The greatest relative gains made in early childhood are therefore made in the frontal cortex, regions of the brain associated with executive function (Diamond, 2002; Tsujimoto, 2008). Peak developmental age in frontal cortical thickness varies within functionally and structurally defined subregions (Shaw et al., 2008). Most of the frontal cortex, including the dorsolateral prefrontal cortex (DLPFC) and the medial prefrontal cortex (MPFC), peaks in thickness from 9 to 11 years of age, while the anterior cingulate cortex (ACC) peaks further in puberty, between 11 and 14 years of age (Shaw et al., 2008).

5 Of particular note, there is evidence that orbitofrontal cortex (OFC) thickness peaks before age 5 (Shaw et al., 2008). The OFC is associated with top-down control over social and emotional regulation and has innervations from visceral sensation signaling regions of the midbrain and brainstem (Pessoa, 2017) making it strategically placed to relate feelings to socioemotional context. Additionally, the prefrontal cortex peaks in synaptogenesis at around age 2–4 years, and synaptic pruning continues into mid-adolescence (Casey, Tottenham, Liston, & Durston, 2005). Taken together, this evidence supports the notion that the preschool years are an important period for development of neural regions associated with socioemotional regulation and executive function.

6 Concurrent with these changes in frontal cortex structure, the preschool years are marked by dramatic improvements across major domains of executive function including working memory,

inhibitory control, and cognitive flexibility (Diamond, 2002; Garon, Bryson, & Smith, 2005; Luciana & Nelson, 1998; Tsujimoto, 2008). The success that children have in developing these cognitive skills relates to their abilities to identify and regulate emotion (Carroll & Steward, 1984). Taken together, it seems that the preschool years are a sensitive period for foundational frontal lobe development, which not only sets the stage for selective pruning and refinement of the structure throughout preschool development, but also provides neurodevelopmental support for changes in executive function that can contribute to improved emotion regulation. Since irritability is associated with poor emotion regulation (i.e., temper tantrums and irritable mood), these cognitive measures and the associated neural structures and functional pathways are of particular interest in examining preschool irritability and in delineating developmentally expectable versus clinically concerning irritable behavior (Wakschlag et al., 2007).

4 Data Collection Challenges

7 Acquiring neurodevelopmental data in preschool children requires a developmentally sensitive approach (Perlman, 2012; Wakschlag & Danis, 2012). First, preschool children are limited in their ability to express abstract concepts, such as intentions, thoughts, and feelings, making standard clinical interviews inappropriate for this young age. Young children are also limited in fine motor skills and vocabulary, limiting the tasks they can perform to simple experiments requiring decisions between few responses. By nature of the developmental stage, preschool children have limited attention spans and limited ability to take complex direction, requiring assessments to be administered in a highly engaging manner with rapid pacing. Finally, and a significant concern for neuroimaging research, preschool age children possess limited motor control and often are unable to stay still for extended periods for functional magnetic resonance imaging (fMRI) scans or neuropsychological testing (Johnson, 2001; Perlman, 2012).

8 Although modifications can be made to accommodate verbal challenges, such as simple and short questionnaires

administered orally, language level and density of questioning achieved is not comparable between preschoolers and older children. Thus, many questionnaires cannot be adapted without compromising the measurement of the intended construct. Irritability is an emotion with both self and social components, and there is evidence that preschool children are still developing self and socially conscious emotional vocabulary (Bosacki & Moore, 2004). A more fruitful modification that can retain construct integrity for behavioral symptoms includes a behavior-based, rather than interview-based, clinical assessment. This might include a clinician observing a child interacting with a caregiver and coding behaviors of clinical interest (Campbell et al., 1986; Wakschlag, et al., 2008) or a child interacting with an experimenter who elicits desired emotional behavior through child-appropriate probes (Gagne, Van Hulle, Aksan, Essex, & Goldsmith, 2011). As a result, direct observation is a critical aspect of early childhood irritability assessment (Wakschlag et al., 2005). To evaluate specific developmental constructs such as executive function, developmental scientists may employ colorful, animated, and child-appropriate computerized games based on classic assessment techniques in order to acquire needed data in a developmentally engaging manner. A classic go/no-go paradigm or Stroop task, for example, can be adjusted to include cartoon characters or animals rather than words (Briggs-Gowan et al., 2014; Li, Grabell, Wakschlag, Huppert, & Perlman, 2017; Perlman, 2012).

9 One final data collection challenge in assessing preschool irritability is the strong dependence on parent report. Due to a child's difficulties in accurately reporting past events or emotional information, parent report is weighed heavily in assessing irritability, which introduces both richness and limitations to the data. Parents have the ability to respond to many more questions and at a more abstract level than their young children and to provide historical context and greater ecological validity than laboratory assessments. Furthermore, parents can also provide clinicians with a richer insight into both the home and school

environments as well as to certain events that may act as a precipitant to concerning behavior, such as the loss of a loved one or moving to a new home. Particularly important is that parents spend more time with children of this age than any other adult in their environment and thus can comment on difficulties in the home environment that may not be present in a clinician's office (i.e., challenges with bedtime). However, as with any self-report data, parent-reported data are filtered through the lens of the informant and may vary based on differences in parent knowledge of what is developmentally normative. Furthermore, given the nascent literature on the genetic basis of irritability (Coccaro, Bergeman, Kavoussi, & Seroczynski, 1997; Coccaro, Bergeman, & Mcclearn, 1993; Roberson-Nay et al., 2015; Savage et al., 2015) and intergenerational transmission (Sparks et al., 2014; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014), the parent may be struggling with his or her own challenges with irritability or mental illness and thus may experience the child's irritability within a heightened emotional context. As a result, the integration of parent report with performance-based assessments is especially key in early childhood, when the differentiation of normative misbehavior from clinical patterns is especially challenging (Wakschlag et al., 2005).

Defining What's Normal

Clinical irritability criteria comprise phasic lapses in emotion regulation (e.g., temper tantrums) as well as persistent irritable or angry mood. While irritability may present as a symptom of multiple disorders, severe irritability has recently been included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) as a unique disorder—*disruptive mood dysregulation disorder* (DMDD)—to be diagnosed when irritability presents as the primary cause for clinical concern (American Psychiatric Association, 2013). Currently, however, children under 6 are excluded from this diagnosis despite evidence of its validity at younger ages (Dougherty et al., 2017). A central challenge to differentiating normal from abnormal irritability in preschoolers is the fact that many of the behaviors that define irritability are quite common during this developmental stage. This illustrates the complicated nature of making psychiatric determinations in preschool children when symptoms and normative behaviors are so overlapping. The issue of developmentally appropriate clinical criteria has been the subject of much psychiatric research over the past few decades, with recent investigations seeking to delineate developmentally expected misbehaviors (those elicited from the context) and clinically concerning behavior (unexpected or unprovoked temper loss) (Wakschlag et al., 2012, 2017).

6 The Normal–Abnormal Boundaries of Irritability

7 Defining Irritability Dimensionally and Contextually

11 The differentiation of normative from clinically salient irritability at a behavioral level requires a developmental specification approach. The central feature of this approach is pinpointing those features that enhance normal/abnormal distinctions within a developmental period (Wakschlag et al., 2010). For example, since temper tantrums occur in the vast majority of preschool children, the mere presence of tantrums is not clinically salient at this age,

and the DSM symptom “often loses temper” may overidentify young children. The DSM typically emphasizes the presence or absence of a symptom rather than its qualitative features; the latter have been determined as key to accurate clinical identification in young children (Wakschlag et al., 2007).

12 To address these issues, we have generated a developmentally sensitive toolkit specifically designed to differentiate early childhood normative misbehavior from emergent disruptive behavior (Biedzio & Wakschlag, 2018). Specifically, these are the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB) survey and the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS) standardized clinical observation (Wakschlag et al., 2008a, 2008b, 2014). Both measures are derived from a shared developmental specification framework emphasizing features that more effectively enable a normal–abnormal irritability distinction within the developmental context (e.g., frequency, (dys)regulation, and developmental expectability in context) (Bufferd et al., 2016;

Wakschlag et al., 2007a; Wakschlag et al., under review). *Frequency* assesses the regularity with which irritable behaviors occur since, while most children exhibit these behaviors, they are not the defining feature of day-to-day behavioral patterns (Wakschlag et al., 2014). For example, while 83.7% of preschoolers have had a tantrum over the past month, less than 10% of children at this age tantrum daily (Wakschlag et al., 2012). *Regulation* encompasses the intensity, flexibility, and organization of irritable behavior. *Expectability in context* assesses whether it is typical for a context to elicit an irritable response or not (Cole, Martin, & Dennis, 2004; Goldsmith & Davidson, 2004). The MAP-DB has the efficiency advantages of a survey, enabling population-level norms. In contrast, the DB-DOS is a more intensive, performance-based assessment designed for laboratory administration. Table 5.1 provides examples of information derived from the MAP-DB and DB-DOS for irritability. Ideally, information from these instruments could be combined for clinical assessment, but they are also designed to be administered independently for utility across varied settings and research designs.

[INSERT TABLE 5.1 HERE]

Questionnaire Assessment: the MAP-DB

[INSERT FIGURE 5.1 HERE]

The MAP-DB translates many of the qualitative constructs and importance of contextual variation gleaned from the DB-DOS into a survey tool. For each MAP-DB dimension, the survey includes both normative misbehaviors (e.g., has a temper tantrum) and dysregulated behaviors (e.g., tantrums until exhausted). The temper loss spectrum is depicted in Figure 5.1. Behaviors are queried across a range of contexts (e.g., with parents, with other adults) and eliciting triggers (e.g., “when tired, hungry or sick,” “out of the blue”). The MAP-DB framework emphasizes a dimensional approach that characterizes behavior across an ordered spectrum from normative, commonly occurring behaviors to severe, rarely occurring behaviors using item response theory (IRT) methods. To enable generation of empirically derived parameters of abnormality, the MAP-DB uses a 6-point objective frequency scale (from 0 = never in past month to 5 = many times/day) (Wakschlag et al., 2014). The MAP-DB has been administered to more than 5,000 parents of diverse infants, toddlers, and preschoolers, demonstrating a robust severity spectrum from mild, normatively occurring irritable behaviors to severe, dysregulated irritability (Biedzio & Wakschlag, 2018; Wakschlag et al., 2017). Most strikingly, we have demonstrated normal–abnormal differentiation of irritability in two independent samples of preschoolers based on developmental features (Wakschlag et al., 2017). These patterns demonstrated that (1) tantrums and mild irritability normatively occur in most young children (83.7%) and under expectable circumstances (e.g., when frustrated, hungry, at times of transition) (Wakschlag et al., 2017). However, dysregulated tantrums (e.g., until exhausted) and prolonged irritability (e.g., stays angry for a long time) occur in less than 10% of young children, and (2) objective frequency is a meaningful metric for differentiating normal versus abnormal expression. For example, daily or near daily occurrence of irritable behaviors is not normative and occurs in less than 10% of preschoolers. Recently, we have used a mixed-methods approach to demonstrate interesting qualitative differences in these MAP-DB patterns (Shaunfield et al., in preparation). While daily irritability is not normative for any sociodemographic group, at “normative” (milder) levels there are distinct differences. Specifically, relative to white and Hispanic mothers, African American mothers showed less tolerance for tantrum behavior and explained that it was the parent’s role to set limits which would prevent tantrums from occurring in the first place (Shaunfield et al., in preparation). While needing replication, these findings have implications for socioculturally tuned assessments.

9 Performance-Based Assessment: The DB-DOS

14 The DB-DOS uses “presses” to increase the likelihood that irritability will actually be observed during clinical assessment (e.g., compliance demands, frustration, waiting). It provides unique information about contextual variation in the child’s

capacity to regulate behavior across varying demands and social contexts (e.g., with parental and nonparental adults). Interactions with parent maximize the ecological validity of data obtained on how child irritability naturally unfolds and is managed within the parent–child context, while interactions with the examiner provide a window on the child's capacity to make use of regulatory supports from an adult (e.g., redirecting) (Wakschlag et al., 2005). Examiner/clinician behavior is loosely standardized; specifically, a hierarchy of prompts is used for responding to disruptive behavior to ascertain the minimal level of support a child needs to reestablish equilibrium (Danis, Hill, &Wakschlag, 2009). Behaviors are coded along a qualitative continuum (0–3) ranging from normative/expectable to clinically concerning. In this way, across multiple contexts, we can systematically observe what type of demands or transitions trigger young children's irritable behavior, the extent to which its expression is proportionate to context, and their capacity to make use of both internal strategies (e.g., distraction, self-talk) and/or external supports (e.g., parental reassurance or redirection). Observed irritability is coded separately for each context within the domain of problems in anger modulation. These codes capture variations in the extent to which frustration/anger/tantrums/upset is in response to expectable demands or transitions (e.g., cleaning up toys) versus pervasive regardless of the situation (e.g., even during fun activities). Qualitative features assessed include the ease with which irritability is elicited (e.g., “reflexive response” vs. gradual build-up), its rapidity of escalation, intensity, dysregulation, pervasiveness, and observed coping strategies. Contextual variation on the DB-DOS has proved to be informative across multiple independent samples (Bunte et al., 2013; Frost et al., 2017; Gray et al., 2012; Petitclerc et al., 2015; Tseng et al., 2015). For example, young children at-risk due to family history or stressful life experiences display heightened irritability during the DB-DOS Parent Context relative to low-risk peers. Contextual variation has also proved to be clinically informative (Frost et al., 2017; Tseng et al., 2015). In particular, preschoolers who showed lower decreases in irritability with the examiner versus their parent (the tendency to be more inhibited with unfamiliar vs. familiar adults is the developmentally expectable pattern) have poorer inhibitory control relative to peers (Petitclerc et al., 2015). We and others have demonstrated clinical validity of irritability ratings on the DB-DOS and its incremental utility above and beyond DSM symptoms (Bunte et al., 2013; Wakschlag et al., 2008).

Clinical Utility and Diagnosis

This dimensional spectrum of irritability severity has demonstrated clinical utility. Dimensional patterns indicate that clinically significant irritability is not an either/or phenomenon, with children well below traditional clinical cut points having significant clinical risk. For example, preschoolers with MAP-DB Temper Loss scores typically considered normative (i.e., 1 standard deviation [SD] above the population mean) have a 67% probability of clinically impairing symptoms, a risk that increased to 83% at 2 SD above the mean (Wakschlag et al., 2015). It has been suggested that categorical approaches resting on extreme scores are adequate for identifying children with severely dysregulated irritability but less so for those children falling at the normal–abnormal boundary. While this approach has some merit, our findings about developmental variability in irritability patterning in young children suggests that such patterns are less stable than assumed. Approximately one-third of preschoolers exhibit meaningful change in level of irritability within an approximately 1-year period (Wakschlag et al., 2015). Preschoolers who are low in irritability, those with clinical levels, and those at the normal–abnormal boundary are all equally likely to exhibit meaningful changes in irritability patterns. Furthermore, of the 6.5% of children exhibiting extremely high irritability (>2 SD above the population mean), less than one-third of these preschoolers remained at this level for more than one assessment. Accounting for this developmental variability improves clinical prediction (Wakschlag et al., 2015).

16 Thus, we have rigorously demonstrated the psychometric validity of these developmentally sensitive tools. Because the

extent to which irritability interferes with young children's ability to learn, play, and engage with the world around them adaptively is crucial to clinical determination (Wakschlag et al., under review), we have also recently developed a companion impairment interview for this developmental irritability assessment toolkit (Wakschlag et al., under review). Additionally, because these patterns emerge very early in life, we have also adapted the MAP-DB for use with infants/toddlers. Preliminary findings indicate that similar developmental features are distinguishing in children as young as 12 months of age but that specific parameters defining the normal–abnormal boundary may shift (Biedzio & Wakschlag, in press). For example, 86% of infants/toddlers tantrum during daily routines versus 59% of preschoolers, but it is uncommon for young children at any age to hold their breath during a tantrum.

11 Neurodevelopment: Breakthroughs in Understanding the Neural Substrates of Preschool Irritability

17 As previously discussed, the rapid developmental growth and extensive normative variation of the preschool period present challenges to clinical and neurodevelopmental assessment. Although many of these challenges arise from short attention spans and motion-related issues, neurodevelopmental measurement techniques, such as fMRI, functional near-infrared spectroscopy (fNIRS), and event-related potentials (ERPs), often have the benefit of bypassing immature linguistic development to present a picture of the neural underpinnings of affective and cognitive function in irritable children. Most notably, fNIRS, a technique for measuring the hemodynamic blood oxygen-level dependent (BOLD) response using near-infrared light (Jobsis, 1977) has been a particularly useful tool in this pursuit (Aslin & Mehler, 2005). The fNIRS probe is placed on the child’s head in the form of a cap or headband, which limits motion sensitivity. Although measuring a similar construct as fMRI (Cui, Bray, Bryant, Glover, & Reiss, 2011), fNIRS is notably less expensive in comparison, allowing researchers to collect larger samples and, in the case of a lab-

purchased machine, more easily adapt to schedules for busy families. Further, fNIRS data can be collected in a simple research lab or the child's naturalistic location (e.g., home, school, clinic) and allows for interaction with an experimenter, computer screen, or even a family member. The following is a discussion of the emerging literature on the neural substrates of irritability. We mostly focus on the fNIRS imaging technique as it has provided the most reliable data in the preschool age range, with attention to emerging datasets using fMRI and ERP measurement.

12 Neurodevelopment of Irritability Within the Temperament Domain

18 Understanding the neural substrates of irritable temperament in preschoolers has generally taken two interwoven approaches. First, research has probed the domain of emotional reactivity, generally focusing on frustration (i.e., the negative feelings associated with a blocked goal), as this is generally considered a prominent emotion in highly irritable children. In the first fNIRS study to examine frustration in preschool children, our research team introduced 3-

to 6-year-old children with no personal or parental history of psychopathology to a computer game in which they raced a "very sneaky dog" to capture bones (The Frustrative Emotion Task for Children - FETCH; Perlman, Luna, Hein, & Huppert, 2014). Children slowly built up the necessary amount of bones to win a desired prize, but rapidly lost all their earnings when the dog became faster and stole all their bones back. During the experience of frustration, we recorded increased activation in the lateral prefrontal cortex (LPFC), which was positively correlated with parent-rated irritable temperament on the Child Behavior Questionnaire (CBQ), a widely used measure of childhood temperament (Rothbart, Ahadi, Hershey, & Fisher, 2001). We reasoned that children who are more irritable than their peers, but not impaired, may engage this region, which is often related to executive function and emotion regulation, in order to modulate their intense response to frustration while playing an enjoyable game. This finding has now been replicated and extended in a larger study (n = 56) where children were taught a specific emotion regulation strategy to use during a second frustration task (Grabell et al., under review). We found that use of the strategy correlated with increased LPFC activation and decreased negative facial expressions and that, while most children were effectively able to increase LPFC activation during frustration, change from pre- to post-test was largest in children with the least irritable temperament. A recent fMRI experiment that examined general emotional reactivity neural circuitry as a function of both age and temperament scanned children aged 4–12 during naturalistic viewing of children's movie scenes (Karim & Perlman, 2017). An age by temperament interaction was found in the LPFC and striatum, a region activated during the experience of reward and frustration, such that age-related increases in activation during negative scenes were observed but only in those children high in irritable temperament. This finding supports the hypothesis that typically developing but temperamentally irritable children may develop increased function of emotional reactivity and regulatory regions when faced with negative emotional challenges.

19 The second approach to probing the development of neural circuitry as a function of irritability in children has turned to the domain of executive function, as this grouping of basic skills is thought to comprise components of regulatory behaviors (Hofmann, Schmeichel, & Baddeley, 2012). Specifically, researchers have postulated that the emerging executive function skill of cognitive flexibility, defined as the ability to mentally switch between two or more demands (Scott, 1962), forms the basis of early emotion regulation strategies (Kopp, 1982; Zelazo & Cunningham, 2007). This skill may be particularly dysfunctional in children with high irritability who cannot easily shift their attention away from an undesirable outcome when goals are blocked or toward desirable possibilities when plans unexpectedly change. A recent fNIRS study used a novel cognitive flexibility task in which 46 3- to 5-year-old children were given the task of putting the animals of an escaped pet store back into their cages (Li et al., 2017). The “tricky” animals, however, liked to pretend to be other animals in order to trick the children, thus children were

required to listen to the sound that the animal made in order to identify its true breed (e.g., a dog who says “meow” would really be a cat), creating a preschool version (The Pet Store Stroop) of the classic Stroop paradigm (Stroop, 1935). We found that LPFC activation was highest during the Stroop condition in which animals did not make their correct sound and that children highest in irritability, but still within the normative, unimpaired, range, also had the highest LPFC activation during this condition. Similar to the FETCH frustration findings described earlier, we suspected that those children who are more susceptible to frustration during challenge have developed effective use of this executive function region in order to manage challenge during a difficult task.

13 Neurodevelopment of Irritability Within the Clinical Domain

20 As extreme forms of irritability are a substrate of a range of psychopathologies, understanding its neurodevelopment in early childhood is important for uncovering the underpinnings of early childhood onset psychopathology. To illustrate, we again

measured LPFC activation during the FETCH frustration task in a separate sample of 92 children aged 3–7 (Grabell et al., 2017). In this sample, however, children were recruited from both the community and local psychiatric clinics in order to sample as many highly irritable children experiencing related impairing symptoms as possible. Replicating our earlier findings (Perlman et al., 2014), we found that LPFC activation during frustration increased as a function of irritability, but only to the point of clinical impairment. Above the 91st percentile of irritability score based on the MAP-DB (Wakschlag et al., 2012), LPFC activation decreased as a function of irritability, creating an inverted U-shaped relationship. Interestingly, the apex MAP-DB score of this inverted U was a 42.5, which corresponds to the 96th percentile score on the MAP-DB in a community sample (Wakschlag et al., 2015). This implies a correspondence between neural indicators of irritability-related impairment and parent-reported irritability severity. An example of the relationship between irritability and executive function–related neural predictors of psychopathology was found by Kessel and colleagues (2016). Among children who were high in irritability at age 3, an enhanced ΔERN during a go/no-go task at age 6 (measured through ERP) predicted the development of internalizing symptoms at age 9, while a blunted ΔERN predicted the development of externalizing symptoms. In older samples, fMRI studies suggest that school-age children and adolescents presenting with clinically salient forms of irritability experience deficits in cognitive flexibility (Dickstein et al., 2007) with underlying deficits in PFC activation (Adleman et al., 2011). Though cognitive performance was not assessed, a study of 6- to 9-year-olds with severe temper outbursts found reduced cingulate cortex functional connectivity (measured by resting state fMRI) and that reduced anterior midcingulate cortex (a frontal region associated with emotion regulation) to precuneus (a posterior region associated with thinking about the self) connectivity was related to elevated mood dysregulation (Roy et al., 2017). Taken together, these findings indicate that neural differences between irritable temperament and clinical levels of irritability can be found in the domains of modulation of frustration and deployment of executive functions, potentially predicting a transition from the normal to abnormal boundary.

14 Future Neurodevelopment Research Within the Family System

21 As technology improves, we propose the consideration of preschool irritability neurodevelopmental research within the family system. Parental support is a critical aspect of the development of executive function and emotion regulation during the preschool period (Hughes & Ensor, 2009). However, optimal parent support might be more challenging to achieve with highly irritable children. Furthermore, Belsky, Bakermans-Kranenburg, & IJzendoorn (2007) have proposed a differential susceptibility hypothesis in which children high in negative emotionality (e.g., irritability) are hypothesized to be more vulnerable to both positive and negative parental influences. Thus, it is critical that we examine the neurodevelopment of executive function and emotion regulation as a moderator for clinical outcome within the context

of parent–child interaction. fNIRS has the ability to examine the correlation between the rise and fall of the hemodynamic response in order to characterize “interpersonal neural synchronization” (Jiang et al., 2015). Our team is currently in the process of employing this methodology to examine parent–child interpersonal neural synchronization using an adaptation of the DB-DOS as a mechanistic measure for scaffolding the development of emotion regulation and executive function, which are likely to buffer highly irritable children from the later onset of psychopathology symptoms.

15 Conclusion

22 Recent advances in preschool irritability research have been essential for demonstrating both that the normative misbehaviors that are part and parcel of irritability in young children (e.g., tantrums) can be distinguished from clinically concerning patterns (e.g., in frequency and quality) and that neuroimaging can provide clinically relevant insight into psychiatric concern at this young age. Translation to clinical application is a critical next step,

requiring an approach that embraces the complexity of early development and also integrates these varying sources of information in a clinically feasible and meaningful manner. For example, using receiver operating curve (ROC) analyses, we have recently demonstrated that 2 of the 22 MAP-DB Temper Loss items may serve as effective irritability screeners (Wiggins et al., 2018). These two items, one a normative, commonly occurring misbehavior (i.e., becoming easily frustrated) and one an abnormal severe behavior (i.e., having destructive tantrums) identify irritability-related DSM disorders with good sensitivity (70–73%) and specificity (74–83%) as well as predict persistent irritability and elevated risk of disorders at early school age. We are also working toward algorithms for integrating the multifaceted information gathered via different irritability assessment methods as these provide unique sources of information and are only modestly correlated. Finally, we have theorized that joint consideration of brain–behavior markers of atypical irritability, as well as accounting for developmental change and parental contribution, will reduce the "developmental noise" and enhance the accuracy of early identification. Methods for incorporating this multilevel information in clinical decision-making have not yet been validated, and therein lies the next steps in preschool irritability research.

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1 Table 5.1

Exemplars of reported and observed features of preschool irritability

Temper Loss (MAP-DB)	Observed Anger Modulation (DB-DOS)
Have temper tantrums…when tired/hungry, during routines, that last > 5 min. out of the blue *Irritable mood*…, stay angry long time, have a short fuse, act irritable	*(Dys)regulation of irritability* (e.g., ease of elicitation, rapidity of escalation, capacity to make use of internal/external strategies to recover, pervasiveness across contexts)

From Wakschlag et al., 2008, 2012.

1 Figure 5.1

Psychometric severity spectrum of early childhood irritability (MAP-DB Temper Loss in Early Childhood). Measured with the

MAP-DB temper loss scale in early childhood. Data are derived from the MAPS replication sample (*N* = 1,857) and analyzed using item response theory (IRT). Theta (θ) scores (y-axis) are akin to z scores: mean = 0, SD = 1. A higher θ score indicates more reliable association the temper loss trait.