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Childhood Irritability: A Developmental Psychopathology Perspective

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Abstract

Irritability, defined as a low threshold for anger, is a transdiagnostic feature of diverse forms of psychopathology and a rapidly growing literature implicates it in child maladaptation. Existing literature has focused on characterizing irritability in children with psychopathology, using conceptualizations and methods designed to assess more severely maladaptive behavior, usually via parent report. However, emerging work suggests that, even in the absence of dysfunction, normative variations in irritability are associated with increased risk for disorder, suggesting that irritability in childhood is a quantitatively distributed trait that covaries with vulnerability to psychopathology. Additionally, parent-report methods may be subject to an array of biases. Thus, our understanding of the development of irritability in typically developing children is limited by heterogeneity in conceptualizations of this important construct and the questionable psychometric properties of existing measures. As such, there is a clear need for a framework and complementary measures that conceptualize irritability as a quantitative trait that may go awry in development, giving rise to clinically significant maladaptation. Further, the interplay between childhood irritability and early contextual influences in shaping mental health outcomes is poorly understood. I address these gaps in this dissertation by examining irritability within a developmental psychopathology framework in a longitudinal sample of 409 (201 boys) typically developing children ($M_{age\ at\ baseline}$ = 3.43 years) and their families. In Study 1, I examined the utility of an observational measure that conceptualizes irritability as a temperamental trait that reflects proneness to anger in contexts in which it is neither provoked nor appropriate. In Study 2, I examined the temporal stability of observationally assessed irritability across early

childhood and interactions between early irritability and other influences in predicting later irritability. In Study 3, I examined the adolescent neural correlates of early irritability and its association with activity in brain regions implicated in emotion regulation. Findings support the validity and utility of observer-rated irritability, and shed light on the associations of irritability with external correlates that shape its development across childhood. Implications of this work for the measurement of irritability across its quantitative spectrum are discussed.

Keywords: irritability, children, measurement, observational, parent report, stability, psychopathology, neuroimaging, parenting, temperament

Summary for Lay Audience

Irritability, described as a proneness to anger and frustration that manifest as severe and frequent temper outbursts, is a symptom of many childhood mental health disorders. However, even healthy children who do not meet criteria for a psychiatric diagnosis vary in their proneness to anger. Recent research has found that irritable children, even in the absence of a mental health disorder, are also at a higher risk for developing a mental health problem later in life. Understanding the nature of early irritability and elucidating the processes that shape its development across childhood are important towards predicting risk and identifying targets for early intervention. However, most of the research that has been conducted on irritability has focused on children who already have a mental health disorder, making it difficult to separate irritability from other symptoms of disorder so that we can study its normal development. Additionally, most of the measurement tools used to assess childhood irritability have been developed for capturing extreme manifestations and do not adequately measure irritability in typically developing children. Observing children's behaviors while they engage in tasks that resemble everyday activities can provide more accurate information about the nature of irritability in healthy children. I investigated the validity of assessing irritability using an observational laboratory measure of child behavior in a sample of 409 healthy, 3-year-old children, and tested whether irritability measured this way is predictive of later symptoms of psychopathology (Study 1). In Study 2, I examined whether observer-rated irritability remains relatively stable at age 5 years and studied the contribution of within-child and contextual factors (e.g., parenting) in predicting its trajectory. In Study 3, I investigate the association between early irritability and functioning of brain regions involved in

emotion control, during adolescence. Across these studies, I found evidence for the validity of irritability measured observationally and found associations between irritability in healthy children and markers of risk implicated in psychopathology. These findings highlight the importance of studying irritability in healthy children towards informing our understanding of the mechanisms that lead to the development of mental health disorders.

Co-Authorship Statement

Several co-authors participated in the development and writing of the three original studies that comprise this dissertation. The primary author listed on these three studies is Ola Mohamed Ali. Also listed are: Ms. Lindsay Gabel, Dr. Kasey Stanton, Dr. Erin A. Kaufman, Dr. Daniel N. Klein, Dr. Matthew R. J. Vandermeer, Dr. Pan Liu, Dr. Marc F. Joanisse, Dr. Deanna M. Barch, and Dr. Elizabeth P. Hayden.

As the primary author, Ms. Mohamed Ali contributed to the design of each study, formulation of research questions and hypotheses, data collection, data analyses and interpretation, and preparation of manuscripts for publication. Dr. Hayden is the principal investigator of the longitudinal research project from which these data were drawn. Additionally, Dr. Hayden served as the primary author's doctoral advisor and has been essential in guiding her in formulating hypotheses, interpreting results, and conceptualizing findings within the broader research field of developmental psychopathology. Ms. Gabel and Dr. Vandermeer assisted in data collection and cleaning. Dr. Stanton provided support in selecting the data analytic procedures of studies 1 and 2. Dr. Kaufman and Dr. Klein consulted on the formulation of the research questions and hypotheses of study 1. Dr. Vandermeer, Dr. Liu, Dr. Joanisse, and Dr. Barch provided support in analyzing neuroimaging data and conceptualizing results of study 3. All co-authors supported manuscript preparation through review and editing.

Dedication

To my father (1959 – 1993).

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Chapter 1 – General Overview

Almost 2000 years ago, Greek philosopher and physician Galen (AD 129 – 200) proposed the first typology of personality, in which he described a "choleric" type characterized by ease of emotional arousal, ill-temper, and irritability (Dammeyer & Zettler, 2018; Flaskerud, 2012; Kagan, 2018). Toward providing a physiological account of personality, Galen proposed that an excess of yellow bile led to a proneness to emotional reactivity that underlies the choleric temperament. Despite its inaccuracies, this ancient work highlights an age-old interest in irritable temperament; however, whether irritability reflects a stable personality trait, a symptom of disorder, or a commonly experienced mood state continues to be debated. Contemporary research on irritability has largely conceptualized it as chronic anger and frequent temper outbursts occurring in the context of mental illness (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017; Leibenluft, 2017; Leibenluft & Stoddard, 2013), yet emerging work suggests that otherwise healthy individuals vary in their experience of irritability, and that these differences are predictive of later adjustment. In this dissertation, I present a developmental psychopathology perspective on irritability, conceptualizing it as a temperamental trait that reflects a low threshold for anger such that it is expressed in situations in which is neither provoked nor expected, and offer findings that demonstrate the validity of this conceptualization.

I begin with a brief review of contemporary interest in irritability in our field and summarize emerging work that points to the relevance of normal variations in irritability to later dysfunction. I then discuss how a developmental psychopathology perspective should be applied to outstanding questions in the field regarding the phenomenology of irritability, and end Chapter 1 with an introduction of the three original research studies that comprise this dissertation. These studies are described in detail in Chapters 2, 3, and 4. In Chapter 5, I present an integrated summary of these studies and suggest directions for future research.

Childhood irritability has long garnered interest as a clinically significant manifestation of psychopathology, and as such, has been primarily studied in psychiatry, notably in the context of disruptive mood dysregulation disorder (DMDD), a condition that was introduced in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). Although it has now been 10 years since DMDD first appeared in the DSM, challenges in the characterization of irritability have led to the ongoing scrutiny of the disorder (Bruno et al., 2019; Gupta & Gupta, 2022; Havens, Marr, & Hirsch, 2022). The addition of DMDD to the DSM resulted from longstanding debate about the role of irritability within child psychiatric diagnoses, especially pediatric bipolar disorder. Although historically thought rare in childhood, diagnoses of bipolar disorder, a condition episodic in its presentation, increased 40-fold among youth seen in outpatient settings between 1994 and 2003 (Moreno et al., 2007). This increase appeared to arise in part due to flexibility in how

pediatric bipolar disorder was being defined, with some clinicians contending that the presentation of bipolar disorder among youth differed from that in adults such that it manifested as chronic irritability, rather than acute shifts in mood and other behavior (Biederman et al., 2004; Wozniak et al., 1995). In contrast, others maintained that, while episodic irritability in children might reflect bipolar disorder, chronic irritability combined with hyperarousal was indicative of attention-deficit hyperactivity disorder (ADHD; Krieger et al., 2013; Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006; McGough, 2014).

Work by Ellen Leibenluft and others proposed that pediatric bipolar disorder could be expressed as either "narrow" or "broad" (Biederman et al., 2001; Leibenluft, 2011; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). The narrow phenotype described classic bipolar disorder, which is characterized by discrete episodes of euphoria and/or irritability. In contrast, the broad phenotype, which later became DMDD, captured presentations of irritability that manifested as severe rages with chronic abnormal mood states between episodes (Leibenluft, Charney, et al., 2003). Thus, much of the discussion about the nosology of irritability centered around symptom course toward understanding whether the distinction between episodic and chronic irritability had meaningful implications for diagnosis and treatment. Empirical research on the nature, course, and clinical significance of childhood irritability was therefore needed.

Emerging work on irritability in childhood provided some support for the utility of the chronic-episodic distinction in that chronic and episodic irritability differed in their course and clinical correlates (Dickstein & Leibenluft, 2012; Krieger et al., 2013; Leibenluft et al., 2006; Rich et al., 2007; Thomas et al., 2013; Wiggins et al., 2016). For example, in a longitudinal study of irritability in a community sample of youth, episodic irritability showed linear associations with age, whereas chronic irritability exhibited a curvilinear trajectory with a peak in adolescence (Leibenluft et al., 2006). Moreover, episodic irritability predicted later diagnoses of mania, generalized anxiety disorder, and simple phobia, while chronic irritability predicted diagnoses of ADHD, and later depression (Leibenluft et al., 2006). With respect to neural correlates, clinically referred youth with diagnoses of bipolar disorder and severe mood dysregulation, a syndrome characterized by chronic irritability, exhibited differences in brain structure and function during processing of emotionally valenced stimuli (Rich et al., 2007; Thomas et al., 2013; Wiggins et al., 2016).

These findings highlight nuances in the conceptualization of irritability; however, most of this work focused on manifestations of irritability appearing in the context of bipolar and severe mood dysregulation, a phenotype of DMDD. However, aside from bipolar disorder, irritability is a symptom of many childhood disorders. That is, irritability is a cardinal feature of major depressive disorder in youth, and is a symptom descriptor in GAD, ADHD, oppositional-defiant disorder (ODD), post-traumatic stress disorder (PTSD), and borderline personality disorder (BPD). Controlling for other

features of psychopathology is a notable challenge in attempting to characterize irritability using samples of youth who already exhibit these disorders. Moreover, it is well-established that psychopathology, more often than not, is preceded by signs, traits, or risk markers that, although not clinically impairing, robustly predict the development of illness (Cicchetti, 1984). Understanding the normative development of irritability is therefore critical towards characterizing it in the context of psychopathology.

The much smaller literature on the nature of irritability in community samples of youth has provided useful descriptive information (Carlson, Danzig, Dougherty, Bufferd, & Klein, 2016; Copeland et al., 2015; Leibenluft et al., 2006; Stringaris, Cohen, Pine, & Leibenluft, 2009). Children clearly differ in their propensity to anger and frustration and show normative decreases in associated behaviors (e.g., temper outbursts, aggression) during development (Copeland et al., 2015). A study of 1,490 community dwelling preschoolers found that almost all (i.e., 83.7%) experienced temper tantrums in the past month (Wakschlag et al., 2012). Thus, in addition to being a symptom of disorder, irritability is also a normative developmental phenomenon that is quantitatively distributed (Beauchaine & Tackett, 2019; Copeland et al., 2015; Klein, Dougherty, Kessel, Silver, & Carlson, 2021; Leibenluft & Stoddard, 2013). Moreover, emerging work suggests that, even in the absence of dysfunction, irritability in typically developing children is associated with later maladjustment (Copeland et al., 2015; Dougherty et al., 2013, 2015; Vogel, Jackson, Barch, Tillman, & Luby, 2019), indicating its utility as a vulnerability marker for psychopathology (Beauchaine & Tackett, 2019; Klein et al.,

2021). In addition, parental psychopathology is associated with the severity of childhood irritability in typically developing children (Wiggins, Mitchell, Stringaris, & Leibenluft, 2014), suggesting that irritability and psychopathology "run together" or aggregate within families, a characteristic of vulnerability markers. The association between normative irritability and later psychopathology is in line with advances in psychopathology research that demonstrate the dimensional nature of trait-disorder associations, such that disorder can be understood as an extreme manifestation of normal processes and traits (Berenbaum, 2013; Sanislow, Pine, Quinn, & Garvey, 2013). Thus, studying the typical development of irritability across its quantitative spectrum, rather than focusing solely on its expression in youth with disorder, may yield important information on etiological mechanisms that underlie disorder and inform our understanding of the nature, course, and correlates of irritability itself.

The notion that maladaptation is best understood in relation to adaptive development is a fundamental tenet of developmental psychopathology, a framework that takes a lifespan approach to identifying the origins and processes that underlie psychological disorders (Cicchetti, 1984; Cicchetti & Rogosch, 2002; Masten & Cicchetti, 2010; Rutter & Sroufe, 2000). Within this framework, psychopathology is understood as normative developmental processes gone awry, and characterizing normative development, as well as the complex interplay of within-person and environmental factors that leads to maladaptation, are central goals of developmental psychopathologists. Thus, traits and symptoms are viewed dimensionally, such that they represent a continuum from normal

to abnormal (Berenbaum, 2013; Sanislow et al., 2013). Additionally, maladaptation is seen as multifactorial, arising from the dynamic and transactional interplay between person and environment over the course of development. As such, the developmental psychopathology framework emphasizes a lifespan approach, and, relatedly, the use of longitudinal designs that include healthy participants and integrate an array of endogenous and exogenous factors as well as their interplay over development to study etiological processes.

Thus, the objective of the studies described in the following chapters is to explore the conceptualization of irritability from a developmental psychopathology perspective. As operationalization and measurement of constructs are crucial steps in any scientific study, I begin with addressing a notable gap that exists in the current literature on irritability: its measurement. That is, extant work has largely examined irritability in clinical samples, and commonly used measures for assessing this construct are those that have been developed for use with such samples. Indeed, a small body of work finds that existing measures do not adequately capture irritability of lower intensity (Dougherty et al., 2021). Thus, in Chapter 2, I present my first study in which I review existing measures of irritability, discuss their limitations, and present an alternative assessment of this construct that may be better suited to capturing normative variations in irritability in typically developing children. Specifically, I discuss the value of observational laboratory measures in the study of child behavior and present findings that support the predictive validity of an observational measure of irritability drawn from methods that are well-

established in the developmental psychopathology literature. Towards further exploring the validity of this measure, my second study (Chapter 3) examines its stability across early childhood, and its association with factors that show robust relationships to temperamental traits, namely other facets of child temperament and parenting. Study 3 (Chapter 4) provides further convergent validity of the novel observer-rated irritability scale by demonstrating associations between irritability measured this way and neural markers of risk previously implicated in psychopathology.

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Chapter 2 - Observational Measures of Early Irritability Predict Children's Psychopathology Risk

Introduction

All children display anger and frustration, especially in early childhood. However, despite the ubiquity of such behaviors, previous work shows that irritable children (i.e., those who are easily annoyed, show persistently irritable mood, and have frequent temper outbursts) are at risk for a range of psychopathologies later in development (Beauchaine & Tackett, 2019; Brotman, Kircanski, & Leibenluft, 2017; Leibenluft & Stoddard, 2013; Stringaris, 2011; Stringaris et al., 2009). Irritability is also a core feature of disruptive mood dysregulation disorder (DMDD), as well as a diagnostic criterion common to several *DSM-5* disorders (e.g., major depressive disorder, oppositional defiant disorder). For these reasons, interest in early irritability as a transdiagnostic construct has grown dramatically.

However, this interest has outpaced methodological work on how irritability should be conceptualized and assessed. Much of the work on childhood irritability to date has been conducted using clinical populations; a review of this literature shows extensive variability in terms of how this construct is conceptualized. While some researchers frame irritability as excessive negative reactivity characterized by anger and possibly aggression (Brotman, Kircanski, & Leibenluft, 2017; Copeland et al., 2015; Leibenluft, 2011; Leibenluft & Stoddard, 2013), others emphasize chronic grumpiness and ill-tempered mood (Craig, Hietanen, Markova, & Berrios, 2008). Additionally, some

investigators distinguish between “phasic” and “tonic” irritability, where phasic irritability refers to acute temper outbursts that peak and decline rapidly and tonic irritability refers to chronic, relatively low-grade angry mood (Beauchaine & Tackett, 2019; Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017; Moore et al., 2019). In contrast, behavioral neuroscience approaches conceptualize irritability in context; that is, as a response to blocked goal attainment or frustrative nonreward (Beauchaine & Tackett, 2019; Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Tseng et al., 2017), with “irritable” children having a relatively low threshold for exhibiting anger when goal attainment is thwarted or otherwise challenging.

The varying conceptualizations of irritability have, unsurprisingly, given rise to various approaches to its assessment. In studies of child psychopathology, investigators often use items taken from parent-reported child symptom questionnaires or clinical interviews to assess irritability. For example, the widely used Child Behavior Checklist (CBCL; Achenbach, 1991) is frequently used to assess irritability based on three items from the Aggressive Behavior scale that reflect mood lability (e.g., “sudden changes in mood or feelings”; Evans et al., 2019; Roberson-Nay et al., 2015; Savage et al., 2015; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014). Although these items are included in scales assessing oppositional-defiant problems, Stringaris and colleagues (2012) argued that they tap aspects of irritability relevant to depressive symptoms in particular and that irritability assessed in this way accounts for the heterotypic continuity between oppositionality and depression,

highlighting the transdiagnostic relevance of the construct as measured by these items. Similarly, using the CBCL irritability scale, Wiggins and colleagues (2014) found associations between longitudinal trajectories of irritability and parental psychopathology, such that children whose parent-reported irritability increased in early childhood were more likely to have a parental history of depression and substance use problems.

Less frequently, *ad hoc* irritability scales have been derived from semi-structured parent interviews of child psychopathology, such as the Preschool Age Psychiatric Assessment (PAPA; Egger, Ascher, & Angold, 1999) and the Child and Adolescent Psychiatric Assessment (CAPA; Angold et al., 1995). Here, items assessing irritability are drawn from the depression and ODD sections, and reflect both a proneness to experience angry mood and excessive temper episodes (Dougherty et al., 2013). Similar to the literature using parent-report measures of irritability, these studies find both cross-sectional and longitudinal associations between child irritability and parent psychopathology. Additionally, interview-based irritability indices predict children's later symptoms also assessed via these interviews (Dougherty et al., 2013, 2015; Vogel et al., 2019).

Toward developing a concise measure designed specifically to assess irritability, Stringaris and colleagues (2012) developed the Affective Reactivity Index (ARI), a questionnaire consisting of six symptom items and one impairment item about irritability for use with youth between ages 6 and 18. While this brief measure is easy to use for

screening purposes in clinical settings, its single-factor structure has not been well-supported (Mulraney, Melvin, & Tonge, 2014; Stringaris, Goodman, et al., 2012). That is, certain items show high covariance and may be redundant (i.e., "lose temper easily" and "often lose temper"), although they are intended to assess different aspects of irritability, i.e., threshold and frequency of temper loss, respectively. Furthermore, the ARI was specifically designed to be completed by youth *and* parents, rendering it less useful when the goal is to assess childhood irritability prior to the age when youth can accurately self-report.

The lack of irritability questionnaires focused more specifically on children's emotions and related behavior, rather than psychopathology symptoms, is problematic (Wakschlag et al., 2015). The Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB; Wakschlag et al., 2012), a rare example of a behaviorally focused questionnaire, offers a developmentally sensitive parent-report questionnaire for the measurement of temper dysregulation, but whether it captures irritability as a transdiagnostic construct is unclear. In particular, the Temper Loss scale is composed of 22 items that assess mood dysregulation and tantrums, capturing information about frequency (i.e., number of days in the previous month), quality (e.g., "has a tantrum until exhausted"), interactional context (e.g., loss of temper with parent vs. other adults), and triggers (e.g., "lose temper or have a tantrum to get something he or she wanted"). However, existing work links the temper loss scale to aggression and impulsivity

(Wakschlag et al., 2012), suggesting that this scale may not capture aspects of mood dysregulation relevant to internalizing symptoms.

This literature review, while not exhaustive, captures the diverse perspectives in the field regarding the conceptualization and measurement of irritability. Given the current status of the field, it would be premature to emphasize one conceptualization over another, as studies of the relations between these different conceptualizations and measurement approaches are needed to optimize the valid assessment of irritability. The small available literature on the convergence of existing measures indicates that different ways of assessing children's irritability have distinct correlates and yield potentially conflicting findings, as is typical of studies of measurement of child psychopathology. For example, Deveney and colleagues (2019) found that child irritability was differentially related to neural responses to facial stimuli during a dot-probe task depending on whether it was assessed via semi-structured clinical interview or observer ratings. Unfortunately, most studies rely on a single, usually parent-reported index of irritability, although basic psychometric theory favors a multimethod approach, particularly for the assessment of child behavior (Majdandžić & Van Den Boom, 2007; Pavlova & Uher, 2020; Stifter, Dollar, & Cipriano, 2011). Further, while affordable and capable of covering child behavior in a broad array of contexts, parent report has several key limitations, including potential biases related to parent disorder (Goodman et al., 2011), as well as parent personality traits and stress exposure (Clark, Durbin, Donnellan, & Neppl, 2017; De Los Reyes & Kazdin, 2005). Finally, as noted in my earlier review of

studies of child irritability and psychopathology risk, it is standard practice to use extant child symptom measures to derive parent-reported irritability scales, which are in turn used to predict children's symptoms (Dougherty et al., 2013; Evans et al., 2019; Vogel et al., 2019; Wiggins et al., 2014). Although overlapping items in measures of irritability and symptoms can be eliminated or otherwise addressed, this approach nevertheless introduces undesirable circularity to the extent that measures of irritability are often drawn from the very same tools used to measure child psychopathology. This approach also introduces common method variance, potentially artificially inflating associations between children's risk factors (e.g., irritability) and outcomes (e.g., psychopathology symptoms).

As previously mentioned, research on child irritability has not typically capitalized on the developmental literature on child temperament and its assessment. Measures of child temperament may tap behaviors potentially more clearly differentiated from clinical symptoms, at least compared to measures of irritability drawn from symptom checklists; thus, these measures may help address the significant conceptual and methodological question of how to best distinguish between traits and clinical symptoms (Goldsmith & Lemery, 2000). Although developmental approaches to child temperament may provide useful insights and assessment approaches for the study of early irritability, these have rarely been used in the field, despite irritability's strong heritability and stability across development, features that partially define temperament constructs (Clifford, Lemery-Chalfant, & Goldsmith, 2015; Copeland et al., 2015; Moore et al., 2019; Riglin et al.,

2017; Roberson-Nay et al., 2015). Temperament research has also yielded observational paradigms designed to provide an ecologically valid, contextual method for capturing normative and atypical variation in children's behavior. Further, standardized laboratory paradigms and coding systems have been developed to provide systematic and objective assessment of children's emotions, independent of informant biases which overcome some of the inherent limitations of parent report (Gagne, Van Hulle, Aksan, Essex, & Goldsmith, 2011b). These paradigms also expose children to the same stimuli, thereby reducing situational influences on behavior and emphasizing individual differences in emotion.

Although behavioral paradigms exist for use with children, these, to my knowledge, have not been used to study irritability as a temperamental trait[1]. For example, the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS; Wakschlag et al., 2008) has been developed specifically for the assessment of anger regulation and other dimensions of disruptive behavior. The DB-DOS was therefore validated on youth oversampled for significant externalizing problems, raising the concern that it is less appropriate for tapping the full range of behaviors related to irritability. Also, the DB-DOS examines anger only in interpersonal contexts (e.g., parent-child interactions) involving anger-provoking stimuli (Wakschlag, Briggs-Gowan, et al., 2008; Wakschlag,

[1] We note that observational paradigms in the assessment of irritability have been used with infants (e.g., Owens, Shaw, & Vondra, 1998); however, the coding schemes used focus on infant fussiness and crying behavior, which may not be developmentally appropriate in assessing childhood irritability.

Hill, et al., 2008); thus ratings of children derived from interactions with the parent may conflate child characteristics with problematic caregiver-child relationships. Also, while considering child behavior during anger-eliciting contexts may index anger that is extreme in its intensity, this approach is limited in its ability to tap other aspects of maladaptive anger expression, such as context-inappropriate anger. This is potentially problematic given that context-inappropriate anger (e.g., anger expressed during tasks designed to be enjoyable) appears to capture difficulties in emotional processing and regulation (Locke, Davidson, Kalin, & Goldsmith, 2009), a mechanism identified in the pathophysiology of irritability (Brotman, Kircanski, & Leibenluft, 2017). Consistent with this, context-inappropriate affect, primarily anger, has been associated with children's behavioral and biological maladaptation (Buss, Davis, Ram, & Coccia, 2018; Locke et al., 2009; Locke, Miller, Seifer, & Heinze, 2015). Thus, children's observed anger in contexts not designed to elicit this emotion per se may prove to be a valuable index of maladaptive irritability (i.e., irritability expressed in situations in which it is neither adaptive nor expected).

The Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995) is a well-established observational paradigm designed to assess child temperament across a range of contexts. Lab-TAB episodes are designed to elicit a broad array of children's emotions, in addition to anger. Typically, child temperament indices from the Lab-TAB are derived from relevant behavior during episodes intended to elicit the emotion of interest only (Gagne, Van Hulle, Aksan, Essex,

& Goldsmith, 2011a; Goldsmith et al., 1995), although our group and others have derived child temperament indices based on aggregated ratings of the emotion of interest across *all* Lab-TAB episodes, regardless of the emotion targeted by individual tasks (Durbin, Hayden, Klein, & Olino, 2007; Hayden, Klein, & Durbin, 2005; Mackrell et al., 2014). Both approaches have advantages; while the former approach benefits from the use of tasks in which the relevant behavior occurs frequently, the latter strategy is better equipped to capture child behavior across a variety of contexts. However, neither approach captures child anger expressed during non-provocative or neutral contexts, although such contexts may be especially useful toward identifying children with a low threshold for experiencing anger, an important aspect of irritability. For example, in late childhood, observer-rated context-inappropriate anger has been related to variations in children's cortisol stress reactivity and externalizing problems above and beyond what is predicted by context-appropriate anger (Locke et al., 2009, 2015), suggesting the potential value of this approach to defining childhood irritability. Thus, in the current study, we operationalized irritability as child anger expressed during Lab-TAB tasks designed to elicit emotions and traits other than anger (i.e., tasks in which anger displays were somewhat unusual and contextually inappropriate).

The current study had several goals. With the goal of providing descriptive information for future studies aimed at optimizing the assessment of irritability, we examined associations between children's symptoms and irritability conceptualized as individual differences in the tendency to express anger with little or no provocation,

assessed using observational ratings from the Lab-TAB. This index of irritability was contrasted with children's anger expressed during tasks specifically designed to evoke anger. We referenced these approaches to the CBCL irritability scale, one of the most widely used measures of childhood irritability (Evans et al., 2019; Stringaris, Zavos, et al., 2012), and also included the anger scale from the Child Behavior Questionnaire (CBQ; Rothbart, 1989). The CBQ uses parent report to assess reactive and self-regulatory aspects of childhood temperament, with the anger scale particularly tapping reactivity to blocked goal attainment (Rothbart, 1989; Rothbart, Ahadi, Hershey, & Fisher, 2001). While widely used to assess child temperament, the CBQ, specifically the anger scale, has not been previously used to measure childhood irritability to the best of my knowledge. I used these indices to provide broad, descriptive information concerning associations between different assessment approaches to childhood irritability at age 3 and children's internalizing and externalizing symptoms at ages 5 and 8 years.

Methods

Participants

A sample of 409 families was recruited from the community using advertisements placed in local daycares, preschools, recreational facilities, and the University of Western Ontario's developmental participants pool to participate in a longitudinal study of children's development. At baseline (T1), children were 3 years old (M = 3.43; SD = .30; 208 girls), had at least one biological parent who could participate in the study, and were

free of significant medical and psychological problems. Children were also screened using the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn, 1997), and were of average cognitive ability (*M* = 112.00; *SD* = 14.05). Families were predominantly White (93.2%), and the majority were in the middle class: 15.4% reported an annual family income less than CAD $20,000, 53.3% reported an annual income between CAD $40,000 and CAD $100,000, and 31.4% reported an annual income greater than CAD $100,000. Most of the children came from two-parent homes (87.6%); 64.8% of mothers and 95% of fathers had a job that required them to work outside the home. At baseline, mothers' mean age was 33.3 years (SD = 4.62 years) and 78.6% had attained college or university level education. Similarly, fathers' mean age was 35.01 years (SD = 4.89 years); 71.1% had attained college or university level education. These demographic characteristics are consistent with that of the population of Southwestern Ontario from which participants were recruited (Statistics Canada, 2017). Study procedures were approved by the University of Western Ontario's Research Ethics Board. The primary caregiver provided consent for their own and their child's participation.

Procedure

Data used here were collected over a 6-year period. At T1, children completed observational tasks in the laboratory, described below. In addition, the primary caregiver (mothers for 93% of children) completed questionnaires assessing child symptoms and temperament. Primary caregiver report on child symptoms was again collected 2.5 (T2; N

= 394; mean child age = 5.93 years), and 5 years (T3; N = 365; mean child age = 8.59) after baseline.

Measures

Parent-reported irritability

I indexed irritability in four different ways, two derived from parent report and two derived from observational ratings. As has been done in previous studies of childhood irritability (Evans et al., 2019; Stringaris et al., 2012), three items ("temper tantrums or hot temper," "stubborn, sullen or irritable," and "sudden changes in mood or feelings") from the Child Behavior Checklist (CBCL; Achenbach, 1991) were used to create a brief irritability scale ($\alpha = .76$). I also used the Anger/Frustration subscale of the Children's Behavior Questionnaire (CBQ; Rothbart, 1989), in which parents rate their child's characteristic reactions to circumscribed situations on a 7-point scale. The Anger/Frustration subscale ($N_{items} = 13$; $\alpha = .79$) is part of the higher-order factor *negative affectivity* (Rothbart et al., 2001) and includes items such as "gets angry when told to go to bed," "has temper tantrums when s/he doesn't get what s/he wants," and "gets angry when s/he can't find something s/he wants to play with."

Observational measures

Children participated in the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995). The Lab-TAB consists of 12 emotionally evocative tasks, each two to six minutes long, designed to elicit behaviors relevant to child temperament (see Durbin, Hayden, Klein, & Olino, 2007; Johnson et al.,

2016; Mackrell et al., 2014). Specifically, each Lab-TAB task, described subsequently, is designed to elicit an emotion such as positive affect, sadness/anger, or fear, although children typically exhibit multiple emotions during each task regardless of its nature. Children's behavior during these tasks was video recorded and subsequently coded for facial, vocal, and bodily expressions of affect, using a standardized coding procedure. Briefly, for each episode, instances of facial, vocal, and bodily positive affect, sadness, fear, and anger were recorded by trained coders. As examples, eyebrows being drawn together, irritable or cranky tone of voice, and forceful movements such as stomping feet would be coded as expressions of anger. For the different expressions of affect in each episode, each instance of relevant facial, vocal, and bodily behavior was coded as low (multiplied by 1), moderate (multiplied by 2), or high (multiplied by 3). Ratings for each affect were then aggregated across selected episodes to derive scales of interest as described below. Undergraduate, postbaccalaureate, and graduate student raters were trained by a "master" coder and had to reach 80% agreement before coding independently. Intermittent reliability checks were conducted to maintain an ICC of .80 and prevent coder drift. Coders were blind to information concerning children's psychopathology symptoms and parent-reported temperament.

Although the Lab-TAB is designed to tap multiple aspects of child emotionality, I know of no study using it to assess irritability; thus, there is no extant irritability scale derived from the Lab-TAB. Some operationalizations of irritability emphasize a low threshold for experiencing anger (Brotman, Kircanski, & Leibenluft, 2017; Toohey &

DiGiuseppe, 2017); I therefore chose to index irritability based on child behavior during nine non-frustrative Lab-TAB tasks in which anger was *not* the emotion the task was intended to elicit, thereby tapping anger that is context-inappropriate or expressed in response to little-to-no provocation (e.g., annoyance in response to waiting for a toy). This operationalization is also consistent with the methodology used in work that demonstrates associations between context-inappropriate anger during the Lab-TAB and other indices of emotion dysregulation (Locke et al., 2009, 2015). While these studies focused specifically on anger during episodes designed to elicit positive affect, I aggregated affect ratings across a wider range of non-provoking tasks; thus, my first observational index of irritability was an aggregate of ratings of facial, vocal, and bodily anger across tasks designed to elicit non-anger emotions ($N_{items} = 81$; $\alpha = .78$). I refer to this scale as observed irritability.

Observed Irritability. The nine tasks used for this scale are listed below, along with the intended target emotion and typical length of the episode:

Risk room (fear; 7 min). The child was left alone in a room with a set of novel and ambiguous stimuli (e.g., a short staircase, a balance beam, a mattress). The child was allowed to play freely with these items for 5 minutes, after which the experimenter returned to the room and asked the child to approach each object.

Tower of patience (effortful control; 6 min). The child and the experimenter took turns building a tower using carboard blocks. The experimenter followed a schedule of

delays of increasing length before placing her block such that the child had to wait to take his or her turn.

Puzzle with parent (positive affect; 4 min). In this parent-child play task, the dyad were presented with block puzzle pieces that can be solved in multiple ways, and pictures of 6 completed puzzles. The dyad was instructed to work together as a team to arrange the blocks to make each of the puzzles.

Stranger approach (fear; 2 min). The child was left alone in the room with a toy. After a few moments, a friendly male research assistant unknown to the child entered the room and spoke to the child while slowly walking closer.

Make that car go (positive affect; 5 min). The experimenter and the child raced with two remote-controlled race cars.

Pop-up snakes (positive affect; 4 min). The experimenter introduced the child to what appears to be a can of potato chips, actually containing coiled spring snakes. The child was encouraged to surprise his or her caregiver with the snakes.

Jumping spider (fear; 2 min). The child was introduced to a terrarium containing a fuzzy, fake, black spider. The experimenter asked the child to touch the spider. As the child approached it, the experimenter manipulated the spider using an attached wire making it appear to jump. At the end of several trials, the experimenter showed the child that it was a fake spider.

Snack delay (effortful control; 5 min). The child was seated in front of desirable snacks and told to wait for a signal before eating them.

Popping bubbles (positive affect; 6 min). The child and experimenter played with a bubble-shooting toy.

Observed Anger. As a basis for comparing the utility of the above-described irritability scale based on child behavior during non-anger-eliciting tasks, and following common practice (Gagne et al., 2011b; Goldsmith et al., 1995), I used a second observational index of child irritability based on behavior during tasks specifically designed to elicit child anger (N_{items} = 27; α = .74). The tasks used to form this scale were:

Transparent box (anger; 4 min). The child was brought to a locked transparent box that contains an appealing toy. The experimenter handed the child a set of inoperable keys to use to open the box. The experimenter returned after a brief interval, and explained that she had given the child the wrong keys and allowed the child to unlock the box and play with the toy.

Impossibly perfect green circles (anger; 2 min). The child was asked to draw a green circle on a piece of paper and was mildly criticized by the experimenter and told repeat the drawing several times.

Box empty (anger; 7 min). The child was given an elaborately wrapped box that was in fact empty, under the pretense that it contained an appealing toy and was left alone to open it. After a brief interval, the experimenter returned with several small toys for the child to keep, explaining that she forgot to put the toy in the box.

Child symptoms

I used scales drawn from the CBCL, excluding items that constituted the irritability scale to prevent redundancy. The primary caregiver completed the preschool version of the CBCL at T1 and T2 (i.e, child ages three and five; Achenbach, 1992) and the school-aged version at T3 (i.e., child age eight; Achenbach, 1991). The CBCL asks the parent to rate the frequency and intensity of their child's emotional and behavioral problems over the past 6 months. I used scales indexing broadband internalizing (N_{items} = 29), and externalizing problems (N_{items} = 33). Alphas for these scales across the three waves of data collection waves ranged from .78 to .88. I also used the relatively short, empirically derived subscales of CBCL items relevant to specific disorders (Lengua, Sadowski, Friedrich, & Fisher, 2001). The specific subscales were: depression (N_{items} = 12; α = .52 - .71), oppositional-defiant (ODD; N_{items} = 3; α = .50 - .70; AIC = .41 - .50[2]), attention problems/hyperactivity (ADHD; N_{items} = 3; α = .68 - .75; AIC = .25 - .45), and conduct problems (CD; N_{items} = 17; α = .76 - .80).

Statistical analyses

I first examined bivariate associations between all major study variables. To examine the utility of indices of irritability in predicting children's risk, I used linear hierarchical regressions predicting children's broadband internalizing and externalizing symptoms, as well as children's depressive, oppositional-defiant, attention-deficit hyperactivity, and conduct disorder symptoms at child ages 5 and 8 years. The equivalent

[2] As Cronbach's α is influenced by scale length, we provide average interitem correlations (AIC) for scales with fewer than 10 items (Clark & Watson, 2019).

baseline symptom measure was entered in the first step as a covariate (e.g., age 3 depressive symptoms when predicting age 5 or age 8 depressive symptoms), followed by parent-reported irritability measures in the second step[3]. To determine the whether the observed irritability index had incremental validity over observed anger, these observational indices were entered in separate steps. That is, observed anger was entered in the third step, and finally, observed irritability in the fourth step. In total, I conducted 12 regression analyses. I did not apply a *p*-value adjustment given the broad descriptive goals of my analyses, which are intended to provide comprehensive information concerning irritability-symptom associations with the goal of informing future assessment practices in this field. All analyses were conducted on SPSS v.24.

Results

Descriptive Statistics and Bivariate Correlations

Descriptives of all major study variables and their bivariate correlations with one another are presented in Tables 2-1 and 2-2. Parent-reported irritability on the CBCL and the CBQ anger scale were highly correlated, as were observed irritability and observed anger (Table 2-1). CBQ anger was weakly correlated with observed irritability and

[3] I used report from the primary caregiver, almost always the mother, in these analyses, based on the fact that this person had more opportunities than secondary caregivers to observe relevant child behaviors. However, in analyses not reported here but available upon request, I found that the same measures obtained from the secondary caregiver, almost always the father, were unrelated to child symptoms. Therefore, I acknowledge that my findings may not generalize to father-reported child behavior.

observed anger, and associations between the CBCL irritability scale and observational indices were absent.

Broadband internalizing and externalizing problems at child ages 3, 5 and 8 years were correlated with questionnaire measures of irritability. However, only externalizing problems were associated with observational indices of irritability, i.e., observed irritability and observed anger. With respect to specific symptom scales, correlations with parent-reported irritability (i.e., CBCL irritability and CBQ Anger/Frustration) ranged from small to large (Cohen, 1988), and were significant for all syndrome scales assessed (i.e., depression, oppositional-defiant, attention problems/hyperactivity, and conduct problems). Symptom scales were weakly correlated with observed irritability and observed anger (Table 2-2).

Hierarchical Regressions

Broadband Internalizing/Externalizing symptoms

The CBQ, but not the CBCL irritability scale, predicted broadband internalizing symptoms at child age 5, even after controlling for age 3 symptoms (Table 2-3). Observational indices of irritability were not associated with age 5 internalizing symptoms. Parent-reported and observational indices of irritability were unrelated to broadband internalizing symptoms at age 8 (Table 2-3).

Similarly, the CBQ Anger/Frustration subscale predicted children's broadband externalizing problems at age 5, but not age 8 (Table 2-4). The CBCL irritability scale was associated with age 5 externalizing problems, although this relationship was negative

and became non-significant when observed irritability was added to the model. Although the CBCL irritability scale was significantly correlated with age 8 broadband externalizing symptoms (Table 2-2), it did not predict symptoms when entered with the CBQ Anger/Frustration in the same step. While neither observational measure (i.e., observed anger and irritability) predicted age 5 broadband externalizing problems, the observed irritability scale contributed to the prediction of age 8 externalizing problems, above and beyond parent-report (Table 2-4).

Specific syndrome scales

CBQ Anger/Frustration subscale predicted age 5 depressive symptoms, even when observational indices of irritability were added to the model (Tables 2-5, 2-6). Observed irritability predicted age 5 depressive symptoms above and beyond parent-report, whereas observed anger did not. At age 8, the CBCL irritability scale, but not the CBQ, predicted depressive symptoms (Table 2-7), despite significant zero-order correlations (Table 2-2). Observed anger did not contribute to the prediction of age 8 depressive symptoms (i.e., step 3); however, when observed irritability was added (step 4), both observed anger and irritability predicted age 8 depressive symptoms above and beyond parent report, although in opposite directions. That is, observed anger was negatively associated with age 8 depressive symptoms, likely reflecting a suppression effect[4], while symptoms were positively correlated with observed irritability.

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[4] Observed anger did not predict age 8 depressive symptoms when entered alone in a linear regression model and observed irritability was a significant predictor of age 8 depressive symptoms in models that did

The CBQ Anger/Frustration, but not the CBCL, predicted age 5 oppositional-defiant, inattention/hyperactivity, and conduct disorder symptoms (Tables 2-5, 2-6). Although observed anger showed significant zero-order correlations with age 5 ADHD symptoms, it did not contribute to models predicting any of the specific externalizing symptom scales at age 5 above and beyond parent-report. Observed irritability uniquely predicted *all* specific externalizing syndromes, above and beyond parent-report and observed anger. For age 8 symptoms, parent-report measures of irritability were unrelated to ODD, ADHD, and CD symptoms (Table 2-7, 2-8). Observed anger did not contribute to the prediction of these symptom scales. Observed irritability predicted age 8 oppositional-defiant and ADHD symptoms at age 8, above and beyond parent report and observed anger (Tables 2-7, 2-8).

Discussion

My findings provide initial support for observed irritability, conceptualized as a low threshold for anger/context-inappropriate anger, as a predictor of later child depressive symptoms and externalizing problems above and beyond other measures of irritability, including parent report. Moreover, I found that associations between irritability and children's symptoms were often dependent on the measure used to assess irritability. This

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not include observed anger (albeit with a reduced coefficient). Thus, observed anger was a suppressor variable in this model (i.e., it appears to strengthen the association between an independent and a dependent variable by accounting for residuals left in the model when it is not included, rather than due to its own association with the DV (Tzelgov & Henik, 1991).

pattern is unsurprising based on similar multimethod studies of child behavior (Hayden et al., 2005; Majdandžić & Van Den Boom, 2007); however, given that current research on irritability has relied heavily on parent report, my findings highlight the need for dedicated study of the construct and convergent validity of current measures of irritability. My findings also provide preliminary support for the notion that child irritability expressed in non-provocative or neutral contexts may be especially relevant to youth adjustment compared to more normative expressions of anger that are context-appropriate. Irritability assessed using this approach was associated with depressive, oppositional-defiant, ADHD, and conduct disorder symptoms in regression models, even after accounting for symptoms' associations with several other indices of irritability.

Observational measures of children's context-inappropriate anger demonstrated incremental validity above and beyond parent report in predicting children's symptoms. In particular, preschoolers' observed irritability, expressed in response to little-to-no provocation, explained additional variance in depressive (2%) and hyperactivity (30%) symptoms, particularly at age 8 years, even after removing the variance in these symptoms predicted by other measures of irritability and the same symptoms assessed at baseline. These findings are consistent with previous work demonstrating that laboratory temperament paradigms capture aspects of behavior that are not readily detected by questionnaire measures or by parents as informants, and that observational indices have unique associations with children's psychopathology symptoms and risk (Hayden et al., 2005; Karp, Serbin, Stack, & Schwartzman, 2004).

Across measures of irritability, I found associations with both internalizing and externalizing problems, supporting the transdiagnostic relevance of this construct (Beauchaine & Tackett, 2019; Brotman, Kircanski, & Leibenluft, 2017; Dougherty et al., 2015). However, I found that the observational measure of irritability consistently predicted depressive and, to a greater extent, hyperactivity symptoms, respectively explaining 2% and 30% of the variance in these symptoms. Although irritability characterizes several disorders, researchers have questioned whether its phenomenology varies between disorders. For example, Leibenluft and colleagues (2006) demonstrated that tonic irritability predicted ADHD and depressive disorders whereas phasic irritability was linked to phobias and mania. In contrast, Copeland and colleagues (2015) found little evidence for the distinction between tonic and phasic irritability components in normative samples. Stringaris and colleagues (2012) demonstrated that the irritability component of childhood oppositional problems accounted for its heterotypic continuity with later depressive problems, in that it may manifest differently in these disorders. Similarly, in clinical samples of children with ADHD, varying operationalizations of irritability predicted different patterns of comorbidity (Mick, Spencer, Wozniak, & Biederman, 2005).

This mixed literature illustrates the need for research dedicated to comparing the validity of different conceptualizations as well as different assessment approaches to irritability. That is, the transdiagnostic nature of irritability has been argued such that irritability leads to increases in diverse symptoms of psychopathology (Beauchaine &

Tackett, 2019; Brotman, Kircanski, & Leibenluft, 2017); however, it is unclear how the strength of irritability-symptom associations vary based on how the construct is defined and assessed. Systematic study of this issue is needed to permit strong conclusions concerning irritability's transdiagnostic nature.

Distinguishing irritability from near-neighbor constructs such as anger, aggression, and general negative affectivity is challenging (Avenevoli, Blader, & Leibenluft, 2015; Beauchaine & Tackett, 2019; Malhi, Bell, & Outhred, 2019; Toohey & DiGiuseppe, 2017). In this study, I distinguished between irritability and context-appropriate anger; that is, I compared anger responses to little-or-no provocation with observed anger in frustrating tasks that are expected to elicit this emotion. My findings suggest that considering the context in which irritability occurs may be useful in conceptualizing this construct; in the current study, behavioral expressions of irritability disproportionate to the context were more consistently linked to children's later symptoms compared to anger expressed during tasks designed to elicit this emotion. This finding complements and builds upon previous work (Locke et al., 2009) linking context-inappropriate anger to children's cortisol expression, assessed concurrently. Although my battery of tasks was not designed specifically to differentiate between irritability and closely related constructs, an important goal for future research, my findings suggest that child anger expressed in situations that are not inherently anger-provoking may be especially relevant to maladaptive expressions of irritability. Future studies using factor analytic approaches may be useful in determining the extent to which irritability expressed in non-provocative

contexts, irritability that is context-appropriate, anger, and other facets of negative affectivity are distinguishable.

While observed irritability predicted children's later depressive and hyperactivity symptoms, symptom associations with parent report were mixed. The CBCL irritability scale predicted age 8 depressive symptoms only, while the CBQ Anger scale predicted age 5, but not age 8, depressive, oppositional-defiant, hyperactivity, and conduct symptoms. The CBCL irritability scale has been used widely in the literature to predict later symptoms, often assessed using the CBCL as well (Evans et al., 2019; Savage et al., 2015; Stringaris et al., 2012). Surprisingly, I found very few associations between CBCL irritability and CBCL symptoms in my study; rather, the CBQ anger scale tended to account for more variance in later CBCL symptoms than the irritability scale derived from the CBCL itself. Although the CBQ and CBCL scales had bivariate correlations with later symptoms of comparable magnitude, it may be that the CBQ scale, as a measure of temperament, is better equipped than the CBCL to capture broad variation in irritability in typically developing children. It is also possible that associations between the CBCL irritability scale and symptoms reported in the literature (Evans et al., 2019; Savage et al., 2015; Stringaris et al., 2012) reflect variance attributable to the measurement tool, rather than veridical associations between irritability and outcomes, even with accounting for overlapping items. If so, including a superior irritability measure in multivariate models would have reduced the predictive power of the CBCL irritability scale.

The low convergence I found between observed and parent-reported irritability is unsurprising, and consistent with previous work (Durbin & Wilson, 2012; Gagne et al., 2011b; Gartstein & Marmion, 2008; Majdandžić & Van Den Boom, 2007; Pavlova & Uher, 2020; Stifter, Willoughby, & Towe-Goodman, 2008). Extant work supports the utility of multi-method, multi-informant approaches in the assessment of psychopathology, citing unique predictive contributions from these various sources (Pavlova & Uher, 2020). Nevertheless, despite meager intercorrelations between my four measures of irritability, there were consistent associations between these and child symptoms, particularly in the prediction of depressive and hyperactivity symptoms. The observation of consistent patterns despite lack of convergence between measures supports the importance of irritability for child adjustment, and renders focused psychometric study of the construct especially compelling.

The current study has several strengths, including the use of multiple methods of assessing irritability, ecologically valid laboratory tasks, and a longitudinal design. In addition, my sample was fairly large with minimal attrition over the 6-year data collection period. However, my study also had a number of limitations. Perhaps the most serious of these is the use of measures not specifically designed to assess irritability, although one (the 3-item CBCL scale) is possibly the most widely used approach in the field to date. While my use of extant measures has benefits (e.g., the Lab-TAB is a widely used child temperament measure with well-developed coding procedures), this likely constrained my ability to answer important questions about how irritability is best

operationalized and assessed. That is, my methodology precludes conclusions about which conceptualization of irritability is most valid; studies directly comparing various conceptualizations are needed to accomplish this important goal. Similarly, the development of new measures of both parent-reported and observed child irritability "from the ground up" is almost certainly needed. However, I note that my current goal was to generate preliminary hypotheses regarding the nature of the construct and its assessment in service of the development of new measures. My finding that atypical anger expressions are more consistently associated with children's later psychopathology may be useful in ongoing work on this important issue.

I studied early irritability as a predictor of *symptoms* of internalizing and externalizing disorders, rather than its association with actual diagnoses in later childhood. This approach is justified considering the low-risk nature of this sample and literature demonstrating the continuity between normative and maladaptive traits in relation to psychopathology (Clark, 2005; Krueger & Piasecki, 2002; Wakschlag et al., 2015). I also note that families in this study were mostly in the middle to upper-middle class, parents were highly educated, and children were of average to above average cognitive ability; these demographic characteristics may limit the generalizability of my findings and replication in high-risk samples where clinical diagnostic measures may be more appropriately used is an important direction for future work. Finally, I did not correct for multiple tests, given that the goal of this descriptive study was to provide broad

information characterizing associations between different irritability assessment tools and youth symptoms.

My findings corroborate previous work underscoring the importance of multimethod approaches in the study of child behavior. In particular, I demonstrate the promise of observational laboratory measures of irritability in predicting children's adaptation. Importantly, despite limitations of the current assessment approaches, my work lends additional support for the role of irritability in shaping youth outcomes. The field will benefit greatly from extensive psychometric work dedicated to the study of different conceptualizations and assessment approaches to irritability.

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Tables

Table 2-1 *Bivariate Correlations among Measures of Irritability*

		1	2	3	4	5	6	7	N	Mean	*SD*
1.	CBCL irritability	-	.50**	.05	.06	.10*	-.08	-.12*	406	1.58	1.50
2.	CBQ Ang/Frust.		-	.17**	.14*	-.05	-.12*	-.11*	406	57.76	9.99
3.	Observed Irritability			-	.49**	-.19**	-.17**	-.14**	409	.20	.19
4.	Observed Anger				-	-.16*	-.04	-.09	409	1.24	.95
5.	Child sex					-	.06	.07	409	-	-
6.	Child age at T1						-	.05	409	3.43	.30
7.	PPVT							-	399	112	14.05

Note. ** $p < .01$; * $p < .05$; Child sex: boys = 1, girls = 2; CBCL = Child Behavior Checklist; CBQ Ang/Frust = Anger/Frustration subscale of the Child Behavior Questionnaire; PPVT = Peabody Picture Vocabulary Test.

Table 2-2 *Bivariate Correlations between Measures of Irritability and Symptoms*

		5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	CBCL Irritability	.54**	.33**	.28**	.63**	.34**	.28**	.45**	.28**	.33**	.51**	.30**	.24**	.38**	.18**	.14**	.49**	.25**	.19**
2	CBQ Ang/Frust	.35**	.29**	.19**	.48**	.40**	.28**	.32**	.28**	.27**	.46**	.36**	.25**	.39**	.31**	.21**	.38**	.33**	.19**
3	Observed Irritability	-.07	-.07	.01	.13**	.19**	.20**	.00	.10*	.12*	.12*	.17**	.15**	.21**	.25**	.25**	.21**	.22**	.18**
4	Observed Anger	-.08	-.04	-.02	.10*	.12*	.07	-.03	-.01	-.08	.16**	.09	.05	.12*	.15**	.09	.11*	.09	.05
5	Age 3 Int Symptoms		.51**	.42**	.51**	.24**	.26**	.57**	.32**	.33**	.31**	.17**	.20**	.30**	.10	.04	.38**	.18**	.16**
6	Age 5 Int Symptoms			.56**	.38**	.51**	.33**	.37**	.62**	.46**	.27**	.33**	.21**	.24**	.24**	.17**	.34**	.39**	.26**
7	Age 8 Int Symptoms				.33**	.36**	.55**	.35**	.40**	.71**	.21**	.23**	.36**	.24**	.25**	.39**	.32**	.27**	.44**
8	Age 3 Ext Symptoms					.54**	.48**	.40**	.33**	.40**	.66**	.43**	.35**	.53**	.35**	.31**	.82**	.50**	.42**
9	Age 5 Ext Symptoms						.61**	.23**	.55**	.44**	.43**	.80**	.53**	.43**	.61**	.45**	.53**	.85**	.52**
10	Age 8 Ext Symptoms							.25**	.33**	.57**	.32**	.51**	.77**	.39**	.48**	.62**	.51**	.56**	.86**
11	Age 3 Depression								.37**	.38**	.27**	.18**	.17**	.27**	.09	.09	.28**	.13**	.16**
12	Age 5 Depression									.57**	.23**	.42**	.21**	.24**	.32**	.19**	.32**	.52**	.27**
13	Age 8 Depression										.27**	.33**	.40**	.25**	.29**	.44**	.37**	.38**	.46**
14	Age 3 ODD											.46**	.32**	.47**	.29**	.23**	.52**	.32**	.26**
15	Age 5 ODD												.53**	.40**	.59**	.40**	.40**	.62**	.43**
16	Age 8 ODD													.28**	.39**	.52**	.35**	.42**	.61**
17	Age 3 ADHD														.50**	.42**	.49**	.39**	.30**
18	Age 5 ADHD															.60**	.36**	.55**	.42**
19	Age 8 ADHD																.37**	.41**	.53**
20	Age 3 CD																	.62**	.51**
21	Age 5 CD																		.57**
22	Age 8 CD																		
	N	406	379	363	402	378	357	406	380	365	406	380	365	405	380	365	406	380	365

Mean	4.62	4.72	4.71	5.59	5.11	4.17	1.30	1.10	1.20	1.66	1.54	1.32	1.52	1.38	1.25	1.55	1.36	1.08
SD	4.09	4.43	5.02	4.52	4.62	4.88	1.62	1.69	1.87	1.11	1.31	1.29	1.36	1.47	1.51	2.29	2.27	1.99

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; Int = Internalizing; Ext = Externalizing; ODD = oppositional-defiant disorder; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

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Table 2-3 *Hierarchical Linear Regression Analyses of Irritability Measures Predicting Children's Internalizing Problems at Ages 5 and 8 Years*

	Age 5 Int					Age 8 Int				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.255	.255**			<.001	.176	.176**			<.001
Age 3 CBCL Int			.505**	11.3	<.001			.419**	8.76	<.001
Step 2	.269	.013*			.034	.181	.005			.326
CBCL Irritability			.048	.852	.395			.077	1.28	.202
CBQ Ang/Frust			.100	1.93	.054			.013	.225	.822
Step 3	.269	.001			.579	.181	.000			.784
CBCL Irritability			.050	.882	.378			.077	1.27	.205
CBQ Ang/Frust			.104*	2.10	.047			.010	.185	.853
Observed Anger			-.025	-.556	.579			.013	.274	.784
Step 4	.271	.002			.286	.183	.001			.424
CBCL Irritability			.050	.882	.378			.077	1.27	.206
CBQ Ang/Frust			.112*	2.11	.036			.005	.083	.934
Observed Anger			.000	-.006	.995			-.007	-.127	.899
Observed Irritability			-.055	-1.07	.286			.044	.800	.424

** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; Int = Internalizing symptoms.

Table 2-4 *Hierarchical Linear Regression Analyses of Irritability Measures Predicting Children's Externalizing Problems at Ages 5 and 8 Years*

	Age 5 Ext					**Age 8 Ext**				
	R^2	ΔR^2	β	t	p	R^2	ΔR^2	β	t	p
Step 1	.246	.246**			<.001	.232	.232**			<.001
Age 3 CBCL Ext			.496**	12.2	<.001			.482**	10.3	<.001
Step 2	277	.030**			.001	.239	.006			.231
CBCL Irritability			-.132*	-2.07	.039			-.070	-1.12	.263
CBQ Ang/Frust			.190**	3.58	<.001			.088	1.57	.116
Step 3	.280	.003			.230	.239	.000			.813
CBCL irritability			-.129*	-2.03	.043			-.069	-1.09	.276
CBQ Ang/Frust			.191**	3.43	.001			.087	1.55	.123
Observed Anger			.056	1.02	.230			.011	.237	.813
Step 4	.283	.003			.227	.261	.022**			.001
CBCL Irritability			-.124	-1.95	.053			-.049	-.783	.434
CBQ Ang/Frust			.185**	3.32	.001			.070	1.26	.207
Observed Anger			.027	.501	.616			-.063	-1.21	.229
Observed Irritability			.064	1.21	.227			.168**	3.20	.001

** p < .01; * p < .05; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; Ext = Externalizing symptoms.

Table 2-5 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's Depressive and ODD Symptoms of at age 5 Years*

	Age 5 Depression					Age 5 ODD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.139	.139**			<.001	.212	.212**			<.001
Age 3 CBCL symptoms			.372**	7.80	<.001			.460**	10.1	<.001
Step 2	.171	.032**			.001	.240	.028**			.001
CBCL Irritability			.068	1.17	.243			.025	.443	.658
CBQ Ang/Frust			.151**	2.74	.006			.180**	3.30	.001
Step 3	.171	.000			.543	.240	.000			.943
CBCL Irritability			.069	1.18	.237			.025	.445	.657
CBQ Ang/Frust			.156**	2.80	.005			.180**	3.28	.001
Observed Anger			-.029	-.608	.543			.003	.072	.943
Step 4	.182	.010*			.031	.252	.012*			.015
CBCL Irritability			.073	1.26	.209			.031	.557	.578
CBQ Ang/Frust			.141*	2.53	.012			.165**	3.01	.003
Observed Anger			-.083	-1.55	.122			-.056	-1.08	.280
Observed Irritability			.117*	2.16	.031			.126*	2.45	.015

** p < .01; * p < .05; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ODD = oppositional-defiant disorder.

Table 2-6 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's ADHD and Conduct at age 5 Years*

	Age 5 ADHD					Age 5 CD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.254	.254**			<.001	.384	.384**			<.001
Age 3 CBCL symptoms			.504**	11.3	<.001			.619**	15.3	<.001
Step 2	.273	.019**			.009	.400	.017**			.006
CBCL Irritability			-.080	-1.53	.127			-.122*	-2.44	.015
CBQ Ang/Frust			.164**	3.11	.002			.137**	2.89	.004
Step 3	.279	.006			.088	.400	.000			.780
CBCL Irritability			-.078	-1.49	.137			-.122*	-2.24	.015
CBQ Ang/Frust			.155**	2.90	.004			.136**	2.84	.005
Observed Anger			.076	1.71	.088			.011	.280	.780
Step 4	.291	.012*			.012	.408	.007*			.032
CBCL Irritability			-.068	-1.31	.191			-.110*	-2.20	.028
CBQ Ang/Frust			.145**	2.72	.007			.128**	2.68	.008
Observed Anger			.017	.341	.733			-.034	-.756	.450
Observed Irritability			.128*	2.53	.012			.100*	2.15	.032

** p < .01; * p < .05; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

Table 2-7 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's Depressive and ODD Symptoms at Age 8 Years*

	Age 8 Depression					Age 8 ODD			
	R2	ΔR2	β	t	p	R2	ΔR2	β	t
Step 1	.141	.141**			<.001	.105	.105**		
Age 3 CBCL symptoms			.375**	7.71	<.001			.324**	6.51
Step 2	.182	.041**			<.001	.121	.016*		
CBCL Irritability			.159**	2.73	.007			.052	.849
CBQ Ang/Frust			.100	1.80	.074			.116	1.96
Step 3	.188	.006			.099	.121	.000		
CBCL Irritability			.157**	2.71	.007			.053	.858
CBQ Ang/Frust			.112*	1.99	.047			.116	1.94
Observed Anger			-.079	-1.65	.099			.008	.162
Step 4	.215	.027**			.001	.134	.013*		
CBCL Irritability			.162**	2.84	.005			.059	.960
CBQ Ang/Frust			.090	1.62	.106			.102	1.71
Observed Anger			-.167**	-3.11	.002			-.054	-.956
Observed Irritability			.187**	3.48	.001			.133*	2.35

** p < .01; * p < .05; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ODD = oppositional-defiant disorder.

Table 2-8 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's ADHD and Conduct Symptoms at Age 8 Years*

	Age 8 ADHD					Age 8 CD				
	R2	ΔR2	β	t	p	R2	ΔR2	β	t	p
Step 1	.178	.178**			<.001	.258	.258**			<.001
Age 3 CBCL symptoms			.422**	8.86	<.001			.508**	11.2	<.001
Step 2	.182	.004			.445	.263	.005			.269
CBCL Irritability			-.040	-.703	.483			-.090	-1.60	.110
CBQ Ang/Frust			.072	1.26	.208			.020	.380	.704
Step 3	.184	.002			.368	.263	.000			.915
CBCL Irritability			-.036	-.647	.518			-.091	-1.60	.110
CBQ Ang/Frust			.067	1.17	.242			.021	.388	.698
Observed Anger			.043	.901	.338			-.005	-.106	.915
Step 4	.203	.030**			<.001	.271	.008			.051
CBCL Irritability			-.023	-.417	.677			-.080	-1.41	.160
CBQ Ang/Frust			.052	.926	.355			.013	.235	.814
Observed Anger			-.048	-.901	.368			-.052	-1.01	.315
Observed Irritability			.200**	3.68	<.001			.103	1.96	.051

** p < .01; * p < .05; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

Chapter 3 - Childhood Irritability: Temporal Stability and Associations with Psychopathology Risk

Introduction

Irritability broadly refers to proneness to frustration, annoyance, and anger, and can manifest as tonic (i.e., chronic, ill-tempered mood) and/or phasic (i.e., temper loss and frequent outbursts) (Beauchaine & Tackett, 2019; Brotman, Kircanski, Stringaris, et al., 2017; Copeland et al., 2015; Klein et al., 2021). Speaking to its clinical significance, irritability is a common presenting concern in pediatric psychiatric settings (Leibenluft, Blair, Charney, & Pine, 2003) and several psychiatric disorders include irritability as a core diagnostic criterion (e.g., major depressive disorder, disruptive mood dysregulation disorder, oppositional defiant disorder; *Diagnostic Statistical Manual of Mental Health Disorders,* fifth edition). Further, even in those without a clinical diagnosis, irritability is associated with functiona**l impairment and the development of psychopathology in childhood (Dougherty et al., 2015; Herzhoff & Tackett, 2016)**, adolescence (Copeland et al., 2015; Silver et al., 2023), and adulthood (Stringaris et al., 2009). Among typically developing children, tonic irritability is associated with the development of internalizing problems while phasic irritability is more strongly related to externalizing psychopathology (Moore et al., 2019; Silver et al., 2021, 2022, 2023). Thus, irritability in childhood is a multifaceted construct that, even when not clinically significant, may

reflect early emerging deficits in self-regulation and cognitive control of emotion that increase risk for maladaptive developmental trajectories.

As an antecedent of disorder that is heritable and independent of illness (Beauchaine & Tackett, 2019; Finlay-Jones et al., 2023; Moore et al., 2019; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016), irritability may serve as an endophenotype, defined as a quantitative, biologically influenced trait that exists on the pathway between disease and a distal genotype (Gottesman & Gould, 2003; Kendler & Neale, 2010; Lenzenweger, 2013). However, descriptive research on the developmental psychopathology of irritability is limited. Some degree of temporal stability is generally considered a prerequisite for vulnerability markers of psychopathology (Ingram & Price, 2010) and the limited available research varies widely with respect to the stability of irritability. Irritability measured dimensionally (i.e., using measures that provide continuous scores) appears to exhibit modest to high stability, although estimates nevertheless vary by measure and informant (Beauchaine & Tackett, 2019; Kessel et al., 2021; Klein et al., 2021; Vidal-Ribas et al., 2016), as well as which aspects of irritability are under consideration. For instance, Moore and colleagues (2019) report greater stability estimates for phasic irritability (i.e., $r = .50$) relative to tonic irritability (i.e., $r = .38$) from late childhood to adolescence. In a sample of 12-year-old youths, Stringaris and colleagues (2012) reported a stability estimate of .88 over a one-year period for parent-reported irritability using the Affective Reactivity Index (ARI). Interestingly, self-reported irritability showed longitudinal correlations of only .29 over this period.

Similarly, using a multimethod approach, Kessel and colleagues (2021) found lower stability estimates for self-reported compared to parent-reported irritability between ages 3 and 15 years. That is, age 3 irritability, assessed using semi-structured interviews, was weakly associated with self- reported irritability on the ARI at age 15 years (i.e., r = .10), and was modestly associated with parent-reported ARI irritability (i.e., r = .36).

Moreover, studies assessing irritability in typically developing children often use measures that have been designed for use with clinical populations (e.g., items from symptom questionnaires or semi-structured clinical interviews); these measures may be poorly equipped to assess the full range of variation in irritability. Using item-response theory, Dougherty and colleagues (2021) examined several commonly used parent-report and interview measures of child irritability, including the ARI (Stringaris, Goodman, et al., 2012), the irritability scale derived from the Child Behavior Checklist (CBCL; Achenbach, 1991), and the *ad hoc* irritability scale derived from the Preschool Age Psychiatric Assessment (PAPA; Egger, Ascher, & Angold, 1999), a semi-structured interview. Findings indicated that none of these yielded reliable information across the full spectrum of irritability in child and adolescent samples, highlighting that these measures may not be sensitive to normative variations in this construct (Dougherty et al., 2021). Similarly, in a community sample of children, I demonstrated that parent-reported child anger-proneness accounted for more variance in later symptoms of psychopathology than the CBCL irritability scale (Mohamed Ali et al., 2021), suggesting that measures designed to capture broad individual differences may have greater

predictive validity than symptom measures. Moreover, extant work has relied almost exclusively on parent-report measures which may be biased by parent characteristics, such as psychopathology and personality traits (Clark, Durbin, Donnellan, & Neppl, 2017; De Los Reyes & Kazdin, 2005; Durbin & Wilson, 2012; Goodman et al., 2011; Hayden, Durbin, Klein, & Olino, 2010). As such, towards better understanding developmental trajectories of early irritability, the field needs developmentally sensitive measures that capture this construct dimensionally and overcome limitations inherent to questionnaire and parent-report approaches.

To this end, I previously examined the utility of a laboratory observational measure of children's irritability operationalized as expressions of anger in context-inappropriate tasks (Mohamed Ali et al., 2021). In developmental psychopathology research, observational measures have long been the gold standard for the assessment of child behavior, as they offer an ecologically valid, contextual approach to capturing individual differences in child behavior across the normative to clinical range, and are thus better suited to discriminating between temperamental traits and symptoms (Goldsmith & Lemery, 2000). Moreover, observational measures use standardized laboratory paradigms and coding systems that allow for systematic and objective assessment of children's emotion and behavior, independent of biases that are inherent to informant report (Gagne et al., 2011b).

With these advantages in mind, I used tasks drawn from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995), aggregating children's observed expression of anger in non-anger eliciting episodes to derive an index of children's observationally rated irritability (Mohamed Ali et al., 2021). I found that observed irritability at age 3 years incrementally predicted symptoms of psychopathology at ages 5 and 8 years in typically developing children, above and beyond parent-report indices, including the commonly used CBCL irritability scale. Moreover, observed anger rated during anger provoking episodes of the Lab-TAB was unrelated to later symptoms when the observed irritability scale was included. Consistent with the transdiagnostic relevance of this construct, observed irritability predicted children's symptoms of depression, oppositional-defiant disorder, inattention/hyperactivity, and conduct problems at ages 5 and 8 years, even after accounting for these symptoms at baseline and other indices of irritability.

These findings offered preliminary evidence for the utility of observational measures in the assessment of childhood irritability; however, the stability of observational measures of irritability, an important characteristic of vulnerabilities, is unknown, as is whether associations between observed irritability and psychopathology risk vary with age. To shed light on these issues, in this study, I examined the stability of observed irritability in middle childhood and associations between observed irritability at age 5 years with concurrent symptoms, and symptoms at ages 8 and 11 years.

Additionally, the developmental psychopathology literature has identified both within-child and environmental factors that contribute to the continuity/discontinuity of children's traits over time (Ganiban, Saudino, Ulbricht, Neiderhiser, & Reiss, 2008; Putnam, Sanson, & Rothbart, 2002; Shiner & Caspi, 2003). For instance, Lengua (2006) found that negative parenting, characterized by self- and child-reported maternal rejection, predicted increases in irritability during middle childhood to adolescence in a community sample of youths. Further, Ravi and colleagues (2022) demonstrated greater continuity of irritability for adolescents whose mothers tended to respond to their expressions of negative emotions in childhood with distress, punishment, or minimization, specifically for those with elevated early irritability. Similarly, within-child characteristics play a role in determining the continuity of traits over time. For example, the development of regulatory temperamental traits (i.e., effortful control) has been linked to the discontinuity of reactive traits, such as negative emotionality, in infancy and early childhood (Braungart-Rieker, Hill-Soderlund, & Karrass, 2010; Nielsen, Olino, Dyson, & Klein, 2019). This work implicates effortful control, a trait that reflects voluntary self-regulation skills and includes functions such as the ability to reorient attention and inhibit dominant responses, in shaping the stability of early irritability. Indeed, extant work demonstrates that phasic irritability, which reflects temper loss and a low threshold for anger, is associated with low effortful control in 6-year-old children (Silver et al., 2023). Thus, while past work suggests that both extrinsic and intrinsic factors shape the longitudinal course of temperamental traits over time, limited work has

examined how these factors relate to the stability of early irritability. I therefore examined whether early parenting and children's effortful control moderate the stability of observed irritability between ages 3 and 5 years.

The goals of this study were therefore threefold: First, I explored the temporal stability of observed irritability in otherwise healthy children by examining associations between observational measures of irritability scales at ages 3 and 5 years. Second, I conducted exploratory analyses to examine factors associated with the stability of irritability measured this way between ages 3 and 5 years. That is, I tested whether early parenting and child effortful control moderated associations between age 3 and age 5 observed irritability. Finally, I sought to further validate the observed irritability scale and extend associations previously found between observed irritability at age 3 and psychopathology risk (Mohamed Ali et al., 2021) by examining the incremental contribution of the age 5 observed irritability scale, relative to parent report indices, in predicting symptoms of internalizing and externalizing psychopathology at child ages 5, 8, and 11 years.

Methods

Participants

Participants were 409 children (201 boys) and their primary caregiver who were part of a multi-wave, longitudinal study of children's development. Families were recruited from the community using advertisements placed in local daycares, preschools,

recreational facilities, and the University of Western Ontario's developmental participant pool. At baseline (T1), children were 3 years old (M = 3.43; SD = .30), had at least one biological parent who could participate in the study, were of average cognitive ability (PPVT mean score = 112.10; SD = 14.18), and free of significant medical and psychological problems. The sample consisted predominantly of White (93.2%), middle-class (15.4% reported an annual family income less than CAD $20,000, 53.3% reported an annual income between CAD $40,000 and CAD $100,000, and 31.4% reported an annual income greater than CAD $100,000), educated families (78.6% of mothers and 71.1% of fathers obtained college of university level education). Further description of the sample's demographics is provided in Chapter 2 (Study 1). The demographic characteristics of this sample are consistent with the population of Southwestern Ontario from which participants were drawn (Statistics Canada, 2017). Study procedures were approved by the University of Western Ontario's Research Ethics Board. The primary caregiver provided consent for their own and their child's participation.

Procedure

Data used in this study were collected at 4 time points, approximately 2.5 years apart. Retention was 96% at T2 (N =394), 89% at T3 (N =365), and 61% at T4 (N =250), relative to baseline. At T1, children attended a laboratory visit and completed the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995) from which the age three observational measure of irritability

previously described was derived (see Mohamed Ali et al., 2021). Children participated in another observational battery of laboratory tasks, adapted from the Lab-TAB, at T2. Tasks included at the age 5 assessment were slightly different, to match children's developmental age (described below). Additionally at T2, the primary caregiver (mothers for 93% of children) completed the Child Behavior Questionnaire, a parent-report measure of child temperament (CBQ; Rothbart, 1989). The primary caregiver also completed the Child Behavior Checklist (CBCL; Achenbach, 1991), a measure of children's symptoms, at T2, T3, and T4. Data at T3 were collected via online surveys, and those at T4 were collected via in-home visits or online surveys. Non-participants at T2, T3, and T4 did not differ significantly from T1 participants on sex, family income, ethnicity, or PPVT scores (all *p*s > .05).

Measures

I followed similar procedures to those described in Study 1 (Mohamed Ali et al., 2021) to construct the irritability scales at age 5. That is, I indexed irritability in four different ways, two derived from parent report and two derived from observational ratings.

Parent-reported Irritability

The CBCL irritability scale (Evans et al., 2019; Stringaris, Zavos, et al., 2012) consisted of three items that appear in the oppositional-defiant symptom scale of the Child Behavior Checklist (CBCL; Achenbach, 1991). These items were: "temper

tantrums or hot temper," "stubborn, sullen or irritable," and "sudden changes in mood or feelings", (α = .69). The primary caregiver also completed the CBQ, which asks the parent to rate their child's characteristic reactions to circumscribed situations on a 7-point scale. I used the Anger/Frustration subscale of the CBQ (N_{items} = 13; α = .85), which is part of the higher-order negative affectivity factor (Rothbart et al., 2001), and includes items like "gets angry when told to go to bed," "has temper tantrums when s/he doesn't get what s/he wants," and "gets angry when s/he can't find something s/he wants to play with."

Observed Irritability

Children participated in a laboratory visit at ages 3 and 5 years, during which they completed several emotionally evocative laboratory tasks (12 tasks at age 3, and 13 at age 5) that were based on the Lab-TAB (Goldsmith et al., 1995). Children's behavior during each task was video recorded and subsequently coded for facial, vocal, and bodily expressions of positive affect, sadness, fear, and anger by trained coders following a standardized coding manual. Instances of each affect were coded as low (multiplied by 1), moderate (multiplied by 2), and high (multiplied by 3). Ratings for each affect were then aggregated across selected episodes to derive scales of interest, described below. Coders were undergraduate, post-baccalaurate, and graduate students who were trained by a "master" coder and had to reach 80% agreement before coding independently. To prevent coder drift, intermittent reliability checks were conducted. Coders were blind to

other child and all parent characteristics (e.g., psychopathology, temperament) and different teams of raters coded the age 3 and 5 data.

To create the observed irritability scale at ages 3 and 5, I aggregated ratings of facial, vocal, and bodily anger across the non-frustrative tasks in which anger was not the intended emotion (Mohamed Ali et al., 2021). These tasks are described below:

Age 3 Observed Irritability. Nine non-frustrative episodes, described below, were used to derive this scale (N_{items} = 81; α = .78) along with the intended target emotion and typical length of the episode.

Risk room (fear; 7 min). The child was left alone in a room with a set of novel and ambiguous stimuli (e.g., a short staircase, a balance beam, mattress). The child was allowed to play freely with these items for 5 minutes, after which the experimenter returned to the room and asked the child to approach each object.

Tower of patience (effortful control; 6 min). The child and the experimenter took turns building a tower using carboard blocks. The experimenter followed a schedule of delays of increasing length before placing her block such that the child must wait to take his or her turn.

Puzzle with parent (positive affect; 4 min). In this parent-child play task, the dyad were presented with block puzzle pieces that can be solved in multiple ways, and

pictures of 6 completed puzzles. The dyad was instructed to work together as a team to arrange the blocks to make each of the puzzles.

Stranger approach (fear; 2 min). The child was left alone in the room with a toy. After a few moments, a friendly male research assistant unknown to the child entered the room and spoke to the child while slowly walking closer.

Make that car go (positive affect; 5 min). The experimenter and the child raced with two remote-controlled race cars.

Pop-up snakes (positive affect; 4 min). The experimenter introduced the child to what appears to be a can of potato chips, actually containing coiled spring snakes. The child was encouraged to surprise his or her caregiver with the snakes.

Jumping spider (fear; 2 min). The child was introduced to a terrarium that contained a fuzzy, fake, black spider. The experimenter asked the child to touch the spider. As the child approached it, the experimenter manipulated the spider using an attached wire making it appear to jump. At the end of several trials, the experimenter showed the child that it was a fake spider.

Snack delay (effortful control; 5 min). The child was seated in front of desirable snacks and told to wait for a signal before eating them.

Popping bubbles (positive affect; 6 min). The child and experimenter played with a bubble-shooting toy.

Age 5 Observed Irritability. Eight tasks (N_{items} = 72; α = .78) were used for this scale, listed below, along with the intended target emotion and typical length of the episode:

Making a T-shirt (positive affect; 7 mins). The child and experimenter used paint and markers to design their own t-shirt, which the child was allowed to take home.

Exploring new objects (fear; 6 mins). The child was left alone to play in a room with unfamiliar objects (e.g., tunnel, box with "worms") for five mins. The experimenter returned and prompted the child to approach and touch each object.

Simon says (effortful control; 6 mins). The child played a game of Simon Says following prompts from a pre-recorded videotape.

Stranger approach (fear, 2 mins). The child was left alone in the room with a toy. After a few moments, a friendly male research assistant unknown to the child entered the room and spoke to the child while slowly walking closer.

Practical joke (positive affect; 3 mins). The child was shown how to operate a remote-controlled whoopee cushion and asked if he/she want to trick his/her parent. The experimenter hid the whoopee cushion under a chair and the parent was invited into the room. The child tricked his/her parent by controlling the cushion using the remote control.

Dress-up[5] ***(PA; 7 mins)****.* The experimenter brought the child into a room that contained a box of costumes (e.g., pirate, police officer, fairy princess) and a mirror. The child was given several minutes to try on different costumes and had their picture taken using an instant camera to show his/her parent.

Story time (fear; 5 mins). The experimenter walked the child into a room where a research assistant was seated and was told this was an "expert storyteller". The child was given a picture book ("A Boy, A Dog, and A Frog" by Mercer Mayer) and instructed to tell a story to the research assistant who would be grading them. The experimenter returned after 4 minutes and praised the child on their story.

Gift bag (effortful control, 3 mins). The experimenter placed a gift bag in front of the child and told him/her that she had a present for them but she would like him/her to open the gift bag with his/her parent. The experimenter left the room for 3 mins and returned with the parent.

Age 5 Observed Anger. This scale consisted of the three tasks that were designed to elicit anger (N_{items} = 26; α = .72):

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[5] Due to COVID-19 related disruptions, coding of this task was interrupted such that ratings were missing for 218 of the 394 children who completed this task. Missing data were imputed using Mplus (Muthén & Muthén, n.d.) based on the remaining seven non-anger tasks, available ratings for this task, child sex, and age. Children with missing data tended to be older than those with available ratings but did not differ on other demographic variables.

Not sharing (anger; 2 mins). A research assistant brought a bag of individually wrapped candies to the experimenter and child and instructed the experimenter to share them equally with the child. The experimenter distributed the candy unequally, eliciting responses from the child as she took more than him/her. After a few minutes, the experimenter admitted she was being unfair and gave each of them two candies, returning the rest to the research assistant.

Disappointing toy (anger; 6 mins). The experimenter showed the child three pictures: a watering can, a remote-controlled race car, and a puppet, and asked the child which toy she or he would prefer. The experimenter returned with the nonpreferred toy (generally the watering can) and left the child alone with it. After 1 min, the experimenter returned with the preferred toy (usually the race cars), and the child and experimenter played together for three minutes.

Frustrating puzzle (anger; 4 mins). The experimenter showed the child a picture of a completed puzzle and told him/her that it's an easy puzzle that even a 3-year-old can do. The child was then left alone to reproduce the puzzle; however, the pieces that the child has been given are from different puzzles. After three minutes, the experimenter returned and said they made a mistake and gave the child the correct pieces.

Parenting

Parenting was assessed at child age 3, using an observational parent-child play task conducted in families' homes. The primary caregiver was handed three numbered

bags and instructed to play with their child however they like using the items (a book, a cooking set, a farm animal set) in the bags in order. The parent and child were allowed to play for 10 minutes and were both videorecorded. Subsequently, trained graduate and undergraduate raters coded the quality of the parent-child interaction using on a standardized coding system based on the Teaching Tasks coding manual (Weinfield, Egeland, & Ogawa, 1997) and the Qualitative Ratings for Parent-Child Interactions scale (Cox & Crnic, 2003). To prevent coder drift, intermittent checks between raters and a "master" coder on 15% of all recordings, and where ICC was low, raters met with master coders to review ratings. Four dimensions of parenting were rated: parent sensitivity/responsivity (ICC = .67) towards child expressions of gestures and affect, parent supportive presence (ICC = .75) indicated by expressions of encouragement and positive emotional regard, parent intrusiveness (ICC = .83) indicated by interfering parent behaviors, and parent hostility (ICC = .81) indicated by expressions of anger or annoyance towards the child.

Child Effortful Control

Child EC was assessed observationally at child age 3 (α = .73; ICC = .94) using a subset of tasks from the Lab-TAB. Coding procedures for EC derived from these tasks are described in detail in Kochanska & Knaack (2003), Murray & Kochanska (2002), and Amicarelli, Kotelnikova, Smith, Kryski, & Hayden (2018). Briefly, failures to wait (e.g., eating the desirable snack before the signal during *Snack Delay*) and time spent seated

counted and aggregated across tasks. These codes were reversed as necessary such that higher scores indicate higher EC. The tasks used to assess EC are described below.

Tower of Patience (6 mins). The child and the experimenter took turns building a tower using cardboard blocks. The experimenter followed a schedule of delays of increasing length before placing her block such that the child has to wait to take his or her turn.

Snack Delay (5 mins). The child was seated in front of desirable snacks and told to wait for a signal before eating them.

Child Symptoms

The primary caregiver completed the preschool version of the CBCL at child age 5 (Achenbach, 1992) and the school-aged version at ages 8 and 11 years (Achenbach, 1991). The parent is asked to rate the frequency and intensity of their child's emotional and behavioral problems over the last 6 months. As was done in my previous study (Mohamed Ali et al., 2021), the three items that constituted the CBCL irritability scale were excluded from the broadband externalizing problems and oppositional-defiant scales to eliminate overlap between the irritability and symptom scales. I used six symptom scales at each timepoint: internalizing problems (N_{items} = 29; α = .80 - .87), externalizing problems (N_{items} = 33; α = .81 - .88), depression (N_{items} = 12; α = .65 - .77),

oppositional-defiant (ODD; N_{items} = 3; α = .50 -.67; AIC = .42 - .46[6]), inattention/hyperactivity (ADHD; N_{items} = 3; α = .69 - .74; AIC = .43 - .50), and conduct problems (CD; N_{items} = 17; α = .76 - .80). The specific symptom scales used here were based on those empirically derived by Lengua and colleagues (2001).

Statistical Analyses

Stability of Observed Irritability

I first conducted bivariate correlations to examine the stability of observed irritability, as well as associations between study variables. In addition, I computed a stability coefficient corrected for attenuation due to interrater unreliability. To examine factors contributing to the stability of irritability between ages 3 and 5 years, I used linear regression path analysis modelling using PROCESS macro for SPSS (Hayes, 2017) to test main effects of each of the age 3 parenting dimensions and EC, on age 5 irritability and their interactions with age 3 irritability. All analyses were conducted on SPSS v.28.

Predictive Validity of Age 5 Observed Irritability

I used linear hierarchical regressions to examine the predictive validity of the age 5 observed irritability scale, replicating procedures described in Mohamed Ali et al. (2021). Briefly, I predicted children's broadband internalizing, externalizing, depressive,

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[6] As Cronbach's α is influenced by scale length, I also provide average interitem correlations (AIC) for scales with fewer than 10 items (Clark & Watson, 2019).

oppositional-defiant, inattention/hyperactivity, and conduct symptoms at ages 5, 8, and 11 from parent-reported irritability measures, age 5 observed anger, and age 5 observed irritability entered in progressive steps. For models predicting age 8 and 11 symptoms, the equivalent age 5 symptom scale score were entered as a covariate.

Results

Descriptive Statistics and Bivariate Correlations

Descriptive statistics and bivariate correlations between age 5 observed irritability and other major study variables are presented in Table 3-1. Age 3 and age 5 observed irritability were moderately correlated; this value increased when corrected for attenuation due to interrater unreliability (r = .32)[7]. Parent-reported indices of age 5 irritability, i.e., CBCL irritability and CBQ anger, were strongly correlated. Age 5 observed irritability was weakly correlated with CBQ anger, and unrelated to CBCL irritability. Male sex was associated with greater observed, but not parent-reported, irritability. Age was negatively associated with all indices of irritability. PPVT scores were negatively associated with age 3 observed irritability and age 5 CBQ anger.

With respect to associations between age 5 irritability scales and symptoms, all symptom scales were moderately correlated with parent-reported irritability (Table 3-2).

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[7] The stability of irritability indexed using the CBCL and CBQ Anger/Frustration was high ($r_{corrected}$ = .69 and .78, respectively), reflecting "true" stability but also measurement artifacts.

Externalizing symptoms, including specific symptom scales, were consistently, although weakly (*r*s < .30), associated with age 5 observed irritability. Internalizing and depressive symptoms were correlated with age 5 observed irritability at age 11 only.

Factors Influencing the Stability of Irritability

Early Parenting

The main effect of parent sensitivity on age 5 observed irritability was not significant; however, it significantly moderated the association between age 3 and age 5 observed irritability (Table 3-3). Tests of simple slopes revealed that the association between age 3 and age 5 irritability was significantly positive at sensitive parenting 1 S.D. above and 1 S. D. below the mean. The Johnson-Neyman region of significance analysis further revealed that age 3 and 5 irritability were unrelated at very low sensitive parenting (Figure 3-1).

I observed a significant main effect of parent supportiveness on age 5 irritability but not an interaction with age 3 irritability (Table 3-3). That is, parent supportive presence was positively associated with age 5 irritability, and the association between age 3 and age 5 irritability did not depend on early parent supportive presence.

No main effect of parent intrusiveness on age 5 irritability was observed. However, the interaction between age 3 irritability and parent intrusiveness was significantly associated with age 5 irritability (Table 3-3). Tests of simple slopes showed

that the association between age 3 and age 5 irritability was positive and significant for children whose parents exhibited intrusive parenting that was 1 S.D. above and 1 S.D. below the mean. The Johnson-Neyman regions of significance analysis showed that the association between age 3 and age 5 irritability was not significant at very high levels of early intrusive parenting (Figure 3-2).

Neither the main effect of parent hostility nor its interaction with age 3 irritability significantly predicted age 5 observed irritability (Table 3-3).

Child effortful control

Despite significant negative zero-order correlations between age 3 EC and observed irritability at ages 3 and 5, no main effects or interactions were observed (Table 3-3).

Hierarchical Regressions of Age 5 Observed Irritability Predicting Symptoms

Age 5 Symptoms

The CBCL irritability and CBQ Anger/Frustration scales predicted concurrent internalizing and externalizing symptoms at age 5 (Tables 3-4 & 3-5). The observed anger scale explained an additional 1% of the variance in internalizing symptoms when added in Step 2, showing a negative association. When observed irritability was added to the model in Step 3, neither observed anger nor observed irritability were significantly associated with concurrent internalizing symptoms; only the CBCL irritability and CBQ

Anger/Frustration scales were positively associated with age 5 internalizing symptoms (Table 3-4). Although observed anger was also associated with age 5 externalizing symptoms, this association became non-significant when observed irritability was added to the model; it predicted concurrent externalizing symptoms above and beyond parent-report measures (Table 3-5). With respect to specific symptoms, CBCL irritability and CBQ Anger/Frustration consistently predicted depressive, ODD, ADHD, and CD symptoms at age 5. Observed anger further contributed to the prediction of age 5 ADHD symptoms; however, this effect became non-significant when observed irritability was added to the model. Observed irritability predicted age 5 ADHD symptoms above and beyond parent-report measures. Parent-report measures, observed anger, and observed irritability were significantly associated with age 5 conduct problems (Tables 3-6, 3-7).

Age 8 Symptoms

Parent-reported indices of irritability and observational measures were unrelated to age 8 broadband internalizing symptoms or depressive symptoms. Only CBQ Anger/Frustration predicted age 8 externalizing symptoms. Age 8 CD symptoms were unrelated to all indices of irritability. Only CBQ Anger/Frustration was significantly associated with age 8 ODD and ADHD symptoms. However, associations between the CBQ scale and age 8 ADHD symptoms became non-significant when observed irritability was added to the model (Tables 3-8, 3-9).

Age 11 Symptoms

The CBQ Anger/Frustration scale predicted age 11 internalizing symptoms; however, when observed irritability was added to the model, the effect of CBQ Anger/Frustration was no longer significant, and only observed irritability predicted age 11 internalizing symptoms (Table 3-4). CBQ Anger/Frustration was associated with age 11 externalizing symptoms, and observed irritability further contributed to the model above and beyond the CBQ scale (Tables 3-10, 3-11).

CBQ Anger/Frustration significantly predicted age 11 depressive symptoms, and observed irritability further added to the model, explaining an additional 1.2% of the variance in depressive symptoms. Only CBQ Anger/Frustration predicted age 11 ODD symptoms, and only observed irritability predicted ADHD symptoms. Both CBQ Anger/Frustration and observed irritability contributed to the prediction of age 11 conduct problems (Tables 3-10, 3-11).

Discussion

This study builds on my past work that showed support for the utility of an observational measure of child behavior that assesses early irritability as a temperamental trait reflecting a low threshold for anger/context-incongruent anger, (Mohamed Ali et al., 2021). Here, I demonstrate moderate temporal stability of observed irritability between ages 3 and 5 years. Exploratory analyses found that the continuity of observed irritability into middle childhood was moderated by early sensitive and intrusive parenting; contrary to my expectations, the stability of irritability did not differ based on children's effortful

control. I also found that age 5 observed irritability incrementally predicted concurrent and later internalizing and externalizing problems relative to parent-report measures. As with age 3 observed irritability (see Mohamed Ali et al., 2021), observed irritability at age 5 predicted externalizing problems at ages 5, 8, and 11 years, above and beyond parent-report, with robust associations with inattention/hyperactivity symptoms specifically. Associations between early irritability and internalizing symptoms were weaker than those with externalizing symptoms and varied depending on the measure used and child age.

The temporal stability estimate of irritability assessed observationally between ages 3 and 5 years was .32 (corrected for attenuation due to interrater reliability); this stability coefficient is comparable to those reported for observed temperament in early to middle childhood (Durbin et al., 2007; Dyson et al., 2015; Majdandžić & Van Den Boom, 2007), supporting the conceptualization of irritability as a temperamental trait. For instance, Durbin and colleagues (2007) report stability coefficients of trait anger assessed using the Lab-TAB at ages 3, 5, and 7 years ranging between .37 and .46. Similarly, Dyson and colleagues (2015) examined the structural and temporal stability of observed temperament between ages 3 and 6 years using a large sample of 447 children. Observed anger and sadness emerged as indicators of a higher-order latent factor of Dysphoria that showed stability estimates (i.e., .30) comparable to my observed irritability variable across both time points. The moderate stability of irritability and related constructs (e.g., anger) reported across these studies, including the present study, despite using different

laboratory tasks and coders at each timepoint, further supports the trait-like nature of these constructs; that is, they appear to remain stable despite typical neurodevelopmental changes across childhood. As such, trait irritability may prove useful in the prediction of maladaptive outcomes and early intervention efforts.

I conducted exploratory analyses examining early parenting and children's EC as moderators of the continuity of irritability. Sensitive and intrusive parenting moderated the association between ages 3 and age 5 observed irritability, such that age 3 irritability was more strongly associated with age 5 irritability in the context of high parent sensitivity and low parent intrusiveness. This appears contrary to past work showing that childhood irritability predicts adolescent irritability particularly in the context of inadequate (e.g., critical, low on warmth) parenting (Lengua, 2006; Ravi et al., 2022). However, it could be that more sensitive parents, and those who are unintrusive, show greater acceptance of their child's behavior, such that child characteristics tend to become relatively crystallized and therefore more stable over time. Relatedly, parental sensitivity and intrusiveness were assessed via a free-play task that did not require significant parental involvement. It could be that tasks designed specifically to elicit sensitivity and intrusiveness are needed to obtain better indices of typical parent behavior in these domains. In addition, examining the contribution of parenting behaviors across a range of parent-child interaction contexts in the development of irritability may also be an important area for future research. Past work suggests that associations between parenting and child temperament vary by parenting context, such that consistency of parenting

across situations is uniquely predictive of child outcomes relative to *mean* parenting (Stewart, Kotelnikova, Olino, & Hayden, 2023).

Although children's EC at age 3 was negatively correlated with ages 3 and 5 observed irritability, it did not moderate the stability of irritability. Previous work found negative cross-sectional associations between irritability and children's parent-reported, but not laboratory-assessed, EC (Silver et al., 2023). This relationship was unique to irritability characterized by temper loss and anger outbursts (i.e., phasic irritability), and not tonic irritability, which is conceptualized as chronic anger and annoyance. In addition, lower teacher-reported inhibitory control was found to predict increases in parent-reported irritability, indexed using the CBQ Anger/Frustration scale over a one-year period among otherwise healthy preschoolers, which was in turn associated with later aggression (Perhamus & Ostrov, 2023). Although these studies suggest that regulatory dimensions of temperament may attenuate the development of irritability, this appears specific to when these variables are measured using informant-report and questionnaires; I did not observe such relationships using observational measures of irritability and EC. Alternatively, it may be that EC becomes more relevant to irritability later in development.

I found that observed irritability at age 5 predicted later internalizing and externalizing symptoms, above and beyond parent report and observed context-congruent anger. This finding, generally stated, is consistent with the transdiagnostic nature of this

construct (Beauchaine & Tackett, 2019; Brotman, Kircanski, & Leibenluft, 2017; Klein et al., 2021). However, differentiation of associations between early trait irritability and symptoms emerged across childhood. That is, after removing variance in symptoms predicted by other measures of irritability and the same symptoms assessed at baseline (i.e., age 5 years), observed age 5 observed irritability predicted ADHD symptoms at all ages, but conduct problems at ages 5 and 11 years, and depressive symptoms at age 11 only. Interestingly, observed age 5 irritability was unrelated to concurrent or later oppositional-defiant symptoms in this study. These findings suggest that irritability measured as expressions in anger in contexts where it is neither provoked nor expected may reflect emotional processing deficits that are not relevant to oppositional-defiant problems, at least as measured by the CBCL. In contrast, irritability conceptualized as frequent temper outbursts and a chronic, ill-tempered mood as captured by the CBQ Anger/Frustration subscale, was more consistently associated with oppositional-defiant symptoms at all ages, although shared method variance likely contributed to this.

In the current study and in previous work (Mohamed Ali et al., 2021; Moore et al., 2019; Silver et al., 2021, 2022, 2023), associations between early irritability and later internalizing symptoms were relatively inconsistent compared to externalizing problems, regardless of irritability measure used. If my observational measure is capturing phasic irritability, this would be consistent with past work linking phasic irritability to externalizing psychopathology, and tonic irritability to internalizing problems ((Moore et al., 2019; Silver et al., 2021, 2022, 2023; Klein et al., 2021). Alternatively, associations

between observed irritability and internalizing symptoms may be indirect. For instance, Barclay and colleagues (2022) demonstrated that childhood irritability, controlling for other facets of psychopathology, uniquely predicted adolescent externalizing problems, whereas associations with internalizing problems were mediated by social factors (i.e., child social skills). Thus, it may be that irritability is more closely linked to externalizing psychopathology due to shared etiological mechanisms, while its linkages to internalizing problems are mediated by other probabilistic factors, rendering the two less consistently related.

Similar to findings from my previous study (Mohamed Ali et al., 2021), associations between parent-report measures of early irritability and child symptoms were mixed. Although the age 5 CBCL irritability scale was consistently associated with concurrent internalizing and externalizing symptoms, it failed to predict later symptoms despite shared method factors. In contrast, the age 5 CBQ Anger/Frustration scale predicted both concurrent and later symptoms, even when observational measures of irritability were added to the model. Moreover, the CBQ scale was the only measure of irritability that predicted oppositional-defiant symptoms at all ages. Thus, in a community-dwelling sample of children, the CBCL scale showed limited predictive validity for symptoms. Given past work showing its utility in predicting psychopathology in clinically impaired youths (Evans et al., 2019), the CBCL scale may therefore be more relevant for capturing severe manifestations of irritability.

The present study has several strengths: I used a well-powered, longitudinal design that capitalized on observational measures to yield a stringent assessment of child behavior to explore the temporal stability of irritability in typically developing children. However, the study also has some important weaknesses. First, my assessment of temporal stability relied on bivariate cross-time correlations, which are vulnerable to measurement error (Roberts, Caspi, & Moffitt, 2001). Families in this sample were largely White, well-educated, from middle to upper-middle class, and children were of average to high average cognitive ability. Exploration of the stability of irritability in high risk, more diverse samples is therefore needed. Longer follow-up periods are also needed toward examining associations between early irritability and the onsets of clinically significant disorders, many of which typically occur later in development (Moilanen, Shaw, & Maxwell, 2010; Rutter, Kim-Cohen, & Maughan, 2006). Finally, I did not correct for multiple tests in this exploratory research; thus, some findings may be due to chance.

This study contributes to burgeoning work on the characterization of irritability, a construct that has garnered much interest recently due to its transdiagnostic relevance. My findings support the conceptualization of irritability as anger expressed in situations where it is inappropriate or unprovoked and offers further evidence for the utility of observational measures in the assessment of irritability.

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Tables & Figures

Table 3-1 *Bivariate Correlations among Measures of Irritability, Demographic Variables, and Moderators of Stability*

		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14
1.	Age 3 Observed Irritability														
2.	Age 5 Observed Irritability	.25**													
3.	Age 5 CBCL Irritability	.10*	.07												
4.	Age 5 CBQ Ang/Frust	.18**	.18**	.53**											
5.	Child Sex	-.19**	-.21**	.01	-.10										
6.	Child Age	-.17**	-.19**	-.18**	-.15**	.06									
7.	Ethnicity	.01	-.06	.02	.01	.08	.04								
8.	Family Income	-.02	-.03	-.21**	-.16**	-.02	.06	-.12*							
9.	PPVT Score	-.14**	-.03	-.09	-.13*	.07	.05	.02	.11*						
10.	Parent Sensitivity	-.15**	-.08	-.04	.01	.01	.03	-.05	.16**	.24**					
11.	Parent Supportiveness	-.18**	-.07	-.01	-.03	.04	.09	-.03	.15**	.18**	.74**				
12.	Parent Intrusiveness	.11*	.08	.02	.00	-.08	-.05	.07	-.17**	-.22**	-.59**	-.48**			
13.	Parent Hostility	.22**	.09	.06	.04	-.11*	-.09	.00	-.16**	-.17**	-.51**	-.40**	.51**		
14.	Age 3 EC	-.35**	-.12*	-.10	-.14**	.26**	.28**	-.02	.05	.27**	.19**	.26**	-.13*	-.15**	
	N	409	394	378	380	409	409	405	389	399	409	409	409	409	409
	Mean	0.2	0.34	1.11	55.29	-	5.94	1.24	3.73	112	3.38	3.83	2.92	1.52	.92

SD	0.19	0.28	1.3	11.86	-	.31	0.79	1.13	14.05	1.03	1.59	1.56	0.9	.81

Note. ** $p < .01$; * $p < .05$; Child sex: boys = 1, girls = 2; Ethnicity: 1 = White, 2 = Black, 3 = Asian, 4 = Other; Family Income: 1 = < $20,000, 2 = $20,000 – $40,000, 3 = $40,001 - $70,000, 4 = $ 70,001 - $100,000, 5 = >$100,000; CBCL = Child Behavior Checklist; CBQ Ang/Frust = Anger/Frustration subscale of the Child Behavior Questionnaire; PPVT = Peabody Picture Vocabulary Test; EC = Effortful Control.

Table 3-2 *Bivariate Correlations between Age 5 Measures of Irritability and Symptoms*

		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.
1.	CBCL Irritability																						
2.	CBQ Anger/Frus	.53**																					
3.	Observed Anger	.15**	.18**																				
4.	Observed Irritability	.07	.18**	.33**																			
5.	Age 5 INT	.49**	.38**	-.02	-.02																		
6.	Age 8 INT	.36**	.30**	.06	.00	.56**																	
7.	Age 11 INT	.46**	.43**	.14*	.18**	.54**	.63**																
8.	Age 5 EXT	.66**	.57**	.22**	.22**	.52**	.40**	.46**															
9.	Age 8 EXT	.44**	.46**	.13*	.16**	.29**	.54**	.42**	.62**														
10.	Age 11 EXT	.48**	.50**	.07	.28**	.33**	.37**	.57**	.61**	.72**													
11.	Age 5 Depression	.46**	.42**	.07	.07	.62**	.40**	.40**	.58**	.31**	.32**												
12.	Age 5 ODD	.58**	.55**	.17**	.17**	.33**	.25**	.34**	.80**	.51**	.52**	.42**											
13.	Age 5 ADHD	.38**	.38**	.22**	.25**	.23**	.24**	.25**	.62**	.47**	.44**	.32**	.59**										
14.	Age 5 CD	.49**	.47**	.24**	.24**	.38**	.28**	.40**	.87**	.55**	.53**	.52**	.62**	.55**									
15.	Age 8 Depression	.40**	.37**	.09	.06	.44**	.70**	.48**	.46**	.56**	.42**	.57**	.33**	.29**	.38**								
16.	Age 8 ODD	.37**	.41**	.11*	.14**	.19**	.37**	.28**	.51**	.81**	.53**	.21**	.53**	.39**	.42**	.40**							
17.	Age 8 ADHD	.32**	.35**	.20**	.24**	.17**	.38**	.25**	.47**	.64**	.49**	.19**	.40**	.60**	.41**	.44**	.52**						

18.	Age 8 CD	.35**	.36**	.08	.13*	.25**	.44**	.34**	.55**	.88**	.66**	.27**	.43**	.42**	.57**	.46**	.61**	.53**				
19.	Age 11 Depression	.41**	.41**	.05	.15*	.40**	.48**	.76**	.48**	.43**	.65**	.50**	.37**	.26**	.43**	.60**	.28**	.30**	.35**			
20.	Age 11 ODD	.41**	.44**	.06	.22**	.23**	.22**	.39**	.52**	.59**	.83**	.26**	.54**	.39**	.42**	.29**	.54**	.39**	.49**	.48**		
21.	Age 11 ADHD	.32**	.36**	.14*	.29**	.22**	.28**	.36**	.47**	.57**	.65**	.18**	.45**	.55**	.41**	.35**	.44**	.70**	.52**	.39**	.54**	
22.	Age 11 CD	.39**	.41**	.09	.29**	.26**	.30**	.47**	.52**	.61**	.90**	.23**	.43**	.41**	.51**	.33**	.42**	.45**	.64**	.56**	.64**	.58**
	N	378	380	390	394	380	363	250	379	364	250	380	380	380	380	365	365	365	365	250	249	249	250
	Mean	1.1	55	.57	.34	1.6	4.8	6.0	5.3	4.5	4.3	1.1	1.5	1.4	1.4	1.2	1.3	1.3	1.1	1.6	1.2	1.1	1.2
	SD	1.3	12	.69	.28	1.4	4.9	5.9	4.9	5.0	5.1	1.7	1.3	1.5	2.3	1.9	1.3	1.51	2.0	2.4	1.3	1.3	2.1

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; INT = Internalizing; EXT = Externalizing; ODD = oppositional-defiant disorder; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

Table 3-3 *Early Parenting and Child EC as moderators of the association between age 3 and age 5 observed irritability.*

Moderator	*ß*	*SE*	*t*	95% CI (LB, UB)
1. Sensitive Parenting				
Age 3 Irr.	**.39**	.07	5.55	.25, .53
Sens.	.03	.02	1.50	-.008, .06
Age 3 Irr. x Sens.	**.23**	.09	2.61	.06, .40
2. Supportive Parenting				
Age 3 Irr.	**.40**	.07	5.56	.26, .54
Supp.	**.03**	.01	2.61	.01, .05
Age 3 Irr. x Supp.	.08	.05	1.39	-.03, .18
3. Intrusive Parenting				
Age 3 Irr.	**.44**	.07	5.94	.29, .59
Intr.	**-.03**	.01	-2.31	-.05, -.004
Age 3 Irr. x Intr.	**-.12**	.06	-2.24	-.23, -.02
4. Hostile Parenting				
Age 3 Irr.	**.39**	.07	5.51	.25, .54
Host.	-.03	.02	-1.19	-.07, .01
Age 3 Irr. x Host.	-.22	.12	-1.81	-.46, .02
5. Age 3 EC				
Age 3 Irr.	**.34**	.08	4.13	.18, .49
Age 3 EC	-.01	.01	-.68	-.04, .02
Age 3 Irr. x Age 3 EC	.00	.06	.01	-.12, .12

Note: Irr = irritability, EC = effortful control, LB = lower bound, SE = standard error, UB = upper bound. Significant regression coefficients are bolded.

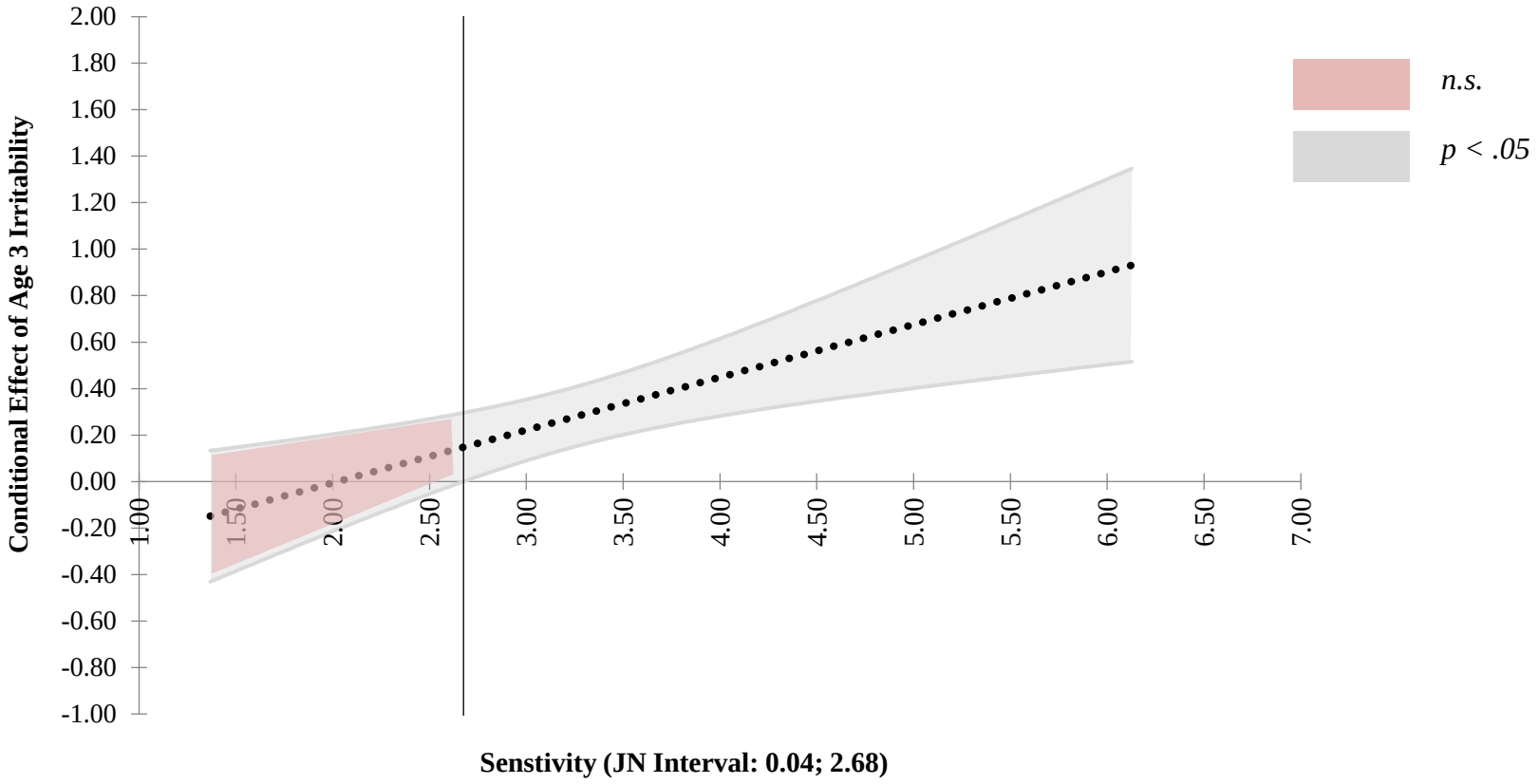

Figure 3-1 *Johnson-Neyman region of significance analysis shows that the simple slope of age 3 irritability predicting age 5 irritability is not significant at very low parent sensitivity (< 2.6).*

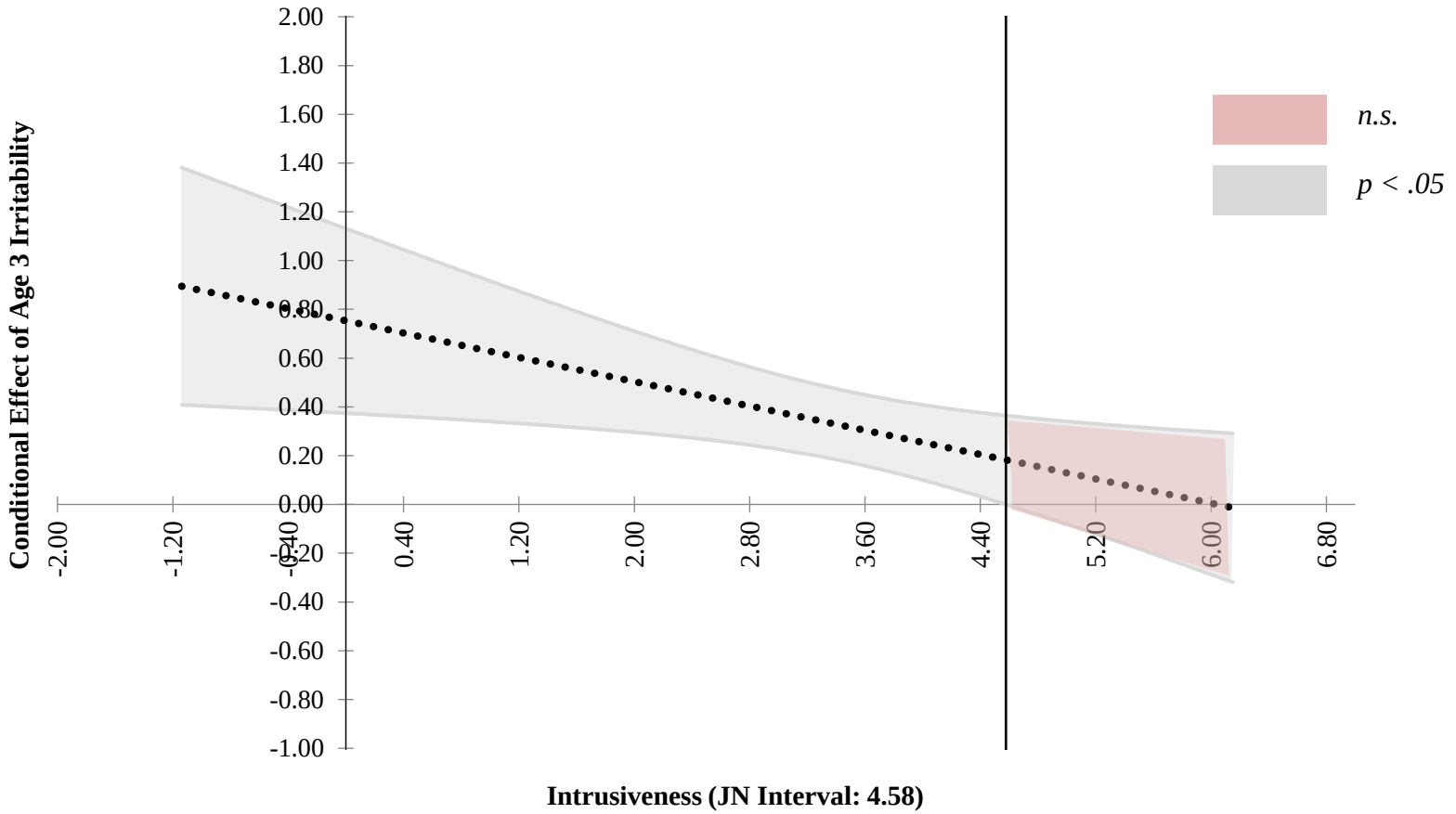

Figure 3-2 *Johnson-Neyman region of significance analysis shows that the simple slope of age 3 irritability predicting age 5 irritability is not significant at very high parent intrusiveness (> 4.6).*

Table 3-4 *Hierarchical Linear Regression Analyses of Irritability Measures Predicting Children's Internalizing Problems at Ages 5, 8, and 11 Years*

	Age 5 Int					Age 8 Int					Age 11 Int				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1						.307	.307**			<.001	.280	.280**			<.001
Age 5 CBCL Int								.554**	12.1	<.001			.529	9.48	<.001
Step 2	.259	.259**			<.001	.313	.006			.235	.324	.044**			<.001
CBCL Irritability			.396**	7.52	<.001			.047	.820	.413			.127	1.80	.073
CBQ Ang/Frust			.175**	3.33	<.001			.057	1.06	.289			.165*	2.53	.012
Step 3	.270	.010*			.023	.316	.003			.239	.333	.009			.087
CBCL Irritability			.404**	7.70	<.001			.045	.788	.431			.130	1.85	.065
CBQ Ang/Frust			.190**	3.60	<.001			.047	.870	.385			.145*	2.18	.030
Observed Anger			-.104*	-2.28	.023			.055	1.18	.239			.095	1.72	.087
Step 4	.275	.005			.111	.316	.001			.566	.349	.016*			.019
CBCL Irritability			.401**	7.65	<.001			.046	.795	.427			.132	1.90	.059
CBQ Ang/Frust			.202**	3.80	<.001			.043	.776	.438			.117	1.76	.081
Observed Anger			-.079	-1.65	.099			.046	.955	.340			.054	.945	.345
Observed Irritability			-.077	-1.60	.111			.028	.574	.566			.137*	2.37	.019

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; Int = Internalizing

Table 3-5 *Hierarchical Linear Regression Analyses of Irritability Measures Predicting Children's Externalizing Problems at Ages 5, 8, and 11 Years*

	Age 5 Ext					Age 8 Ext					Age 11 Ext				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1						.371	.371**			<.001	.367	.367**			<.001
Age 5 CBCL Ext								.609**	14.0	<.001			.605**	11.6	<.001
Step 2	.494	.494**			<.001	.386	.016*			.016	.399	.032*			.003
CBCL Irritability			.498**	11.4	<.001			.006	.110	.913			.000	-.001	.999
CBQ Ang/Frust			.301**	6.93	<.001			.149*	2.81	.005			.215**	3.42	<.001
Step 3	.504	.010*			.007	.386	.000			.676	.402	.003			.307
CBCL Irritability			.490**	11.3	<.001			.008	.135	.893			-.008	-.106	.916
CBQ Ang/Frust			.287**	6.61	<.001			.147*	2.75	.006			.224**	3.53	<.001
Observed Anger			.103*	2.73	.007			.018	.418	.676			-.054	-1.02	.307
Step 4	.515	.011*			.005	.391	.004			.135	.419	.017*			.010
CBCL Irritability			.495**	11.5	<.001			.019	.323	.747			.028	.371	.711
CBQ Ang/Frust			.270**	6.22	<.001			.141*	2.64	.009			.209*	3.31	.001
Observed Anger			.067	1.72	.087			-.001	-.027	.979			-.093	-1.73	.085
Observed Irritability			.111*	2.82	.005			.069	1.50	.135			.145*	2.59	.010

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; Ext = Externalizing

Table 3-6 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's Depression and ODD Symptoms at age 5 Years*

	Age 5 Depression					Age 5 ODD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.246	.246**			<.001	.422	.422**			<.001
CBCL Irritability			.321**	6.04	<.001			.408**	8.78	<.001
CBQ Ang/Frust			.246**	4.63	<.001			.336**	7.23	<.001
Step 2	.246	.001			.618	.424	.003			.197
CBCL Irritability			.323**	6.06	<.001			.404**	8.67	<.001
CBQ Ang/Frust			.249**	4.66	<.001			.329**	7.02	<.001
Observed Anger			-.023	-.500	.618			.052	1.29	.197
Step 3	.246	.000			.997	.428	.004			.105
CBCL Irritability			.323**	6.05	<.001			.407**	8.75	<.001
CBQ Ang/Frust			.249**	4.60	<.001			.318**	6.75	<.001
Observed Anger			-.024	-.482	.630			.030	.709	.479
Observed Irritability			.001	.029	.977			.069	1.62	.105

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ODD = oppositional-defiant disorder

Table 3-7 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's ADHD and Conduct Symptoms at age 5 Years*

	Age 5 ADHD					Age 5 CD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.209	.209**			<.001	.292	.292**			<.001
CBCL Irritability			.261**	4.81	<.001			.333**	6.47	<.001
CBQ Ang/Frust			.263**	4.83	<.001			.287**	5.57	<.001
Step 2	.221	.018*			.004	.313	.021**			<.001
CBCL Irritability			.251**	4.64	<.001			.321**	6.31	<.001
CBQ Ang/Frust			.244**	4.50	<.001			.266**	5.20	<.001
Observed Anger			.137*	2.91	.004			.148**	3.35	<.001
Step 3	.240	.021*			.001	.330	.017*			.002
CBCL Irritability			.258**	4.83	<.001			.328**	6.51	<.001
CBQ Ang/Frust			.220**	4.08	<.001			.244**	4.79	<.001
Observed Anger			.087	1.77	.078			.103*	2.23	.027
Observed Irritability			.157*	3.22	.001			.142*	3.08	.002

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

Table 3-8 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's Depression and ODD Symptoms at age 8 Years*

	Age 8 Depression					Age 8 ODD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.302	.302**			<.001	.283	.283**			<.001
Age 5 CBCL symptoms			.550**	12.0	<.001			.324**	6.51	<.001
Step 2	.326	.024*			.003	.301	.018*			.014
CBCL Irritability			.103	1.87	.063			.055	.937	.350
CBQ Ang/Frust			.105	1.96	.051			.138*	2.43	.016
Step 3	.327	.001			.542	.302	.001			.483
CBCL Irritability			.103	1.86	.063			.055	.938	.349
CBQ Ang/Frust			.101	1.85	.065			.134*	2.32	.021
Observed Anger			.028	.611	.542			.033	.703	.483
Step 4	.328	.001			.502	.308	.006			.094
CBCL Irritability			.104	1.89	.060			.063	1.08	.283
CBQ Ang/Frust			.096	1.75	.081			.125*	2.18	.030
Observed Anger			.017	.362	.718			.006	.132	.895
Observed Irritability			.033	.672	.502			.083	1.68	.094

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ODD = oppositional-defiant disorder

Table 3-9 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's ADHD and Conduct Symptoms at age 8 Years*

	Age 8 ADHD					Age 8 CD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.359	.359**			<.001	.320	.320**			<.001
Age 5 CBCL symptoms			.599**	13.7	<.001			.565**	12.5	<.001
Step 2	.374	.014*			.023	.329	.009			.101
CBCL Irritability			.048	.924	.356			.040	.723	.470
CBQ Ang/Frust			.103*	1.98	.049			.089	1.64	.102
Step 3	.378	.004			.124	.330	.001			.445
CBCL Irritability			.050	.967	.334			.038	.690	.490
CBQ Ang/Frust			.095	1.82	.070			.093	1.70	.090
Observed Anger			.069	1.54	.124			-.035	-.764	.445
Step 4	.386	.008*			.035	.331	.001			.497
CBCL Irritability			.059	1.14	.254			.042	.759	.449
CBQ Ang/Frust			.085	1.63	.104			.090	1.65	.101
Observed Anger			.040	.850	.396			-.045	-.931	.353
Observed Irritability			.099*	2.12	.035			.033	.680	.497

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

Table 3-10 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's Depression and ODD Symptoms of at age 11 Years*

	Age 11 Depression					Age 11 ODD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.216	.216**			<.001	.277	.277**			<.001
Age 5 CBCL symptoms			.465**	7.98	<.001			.526**	9.38	<.001
Step 2	.257	.041*			.002	.316	.039*			.002
CBCL Irritability			.101	1.40	.163			.083	1.16	.249
CBQ Ang/Frust			.173*	2.52	.012			.197*	2.91	.004
Step 3	.258	.001			.592	.316	.001			.619
CBCL Irritability			.099*	1.36	.175			.082	1.14	.257
CBQ Ang/Frust			.179*	2.57	.011			.203*	2.95	.004
Observed Anger			-.031	-.537	.592			-.028	-.498	.619
Step 4	.271	.012*			.050	.328	.011			.052
CBCL Irritability			.105	1.46	.147			.096	1.33	.185
CBQ Ang/Frust			.157*	2.24	.026			.187*	2.71	.007
Observed Anger			-.067	-1.11	.269			-.062	-1.07	.285
Observed Irritability			.120*	.1.97	.050			.115	1.96	.052

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ODD = oppositional-defiant disorder

Table 3-11 *Hierarchical Linear Regressions of Irritability Measures Predicting Children's ADHD and Conduct Symptoms of at age 11 Years*

	Age 11 ADHD					Age 11 CD				
	R^2	ΔR^2	β	*t*	*p*	R^2	ΔR^2	β	*t*	*p*
Step 1	.314	.314**			<.001	.261	.261**			<.001
Age 5 CBCL symptoms			.560**	10.3	<.001			.511**	9.04	<.001
Step 2	.331	.017			.056	.293*	.032			.007
CBCL Irritability			.039	.596	.552			.048	.675	.501
CBQ Ang/Frust			.123	1.86	.064			.180*	2.68	.008
Step 3	.331	.000			.834	.294	.001			.492
CBCL Irritability			.040	.609	.543			.043	.590	.556
CBQ Ang/Frust			.121	1.81	.071			.187*	2.74	.007
Observed Anger			.012	.210	.834			-.040	-.689	.492
Step 4	.352	.021*			.007	.316*	.022			.008
CBCL Irritability			.057	.883	.378			.073	1.01	.315
CBQ Ang/Frust			.101	1.53	.128			.167*	2.48	.014
Observed Anger			-.031	-.543	.588			-.081	-1.38	.169
Observed Irritability			.160*	2.72	.007			.164*	2.69	.008

Note. ** $p < .01$; * $p < .05$; CBCL = Child Behavior Checklist; CBQ Ang/Frust. = Anger/Frustration subscale of the Child Behavior Questionnaire; ADHD = attention-deficit hyperactivity disorder; CD = conduct disorder.

Chapter 4 - Associations between Adolescent's Neural Reactivity to Maternal Feedback are Moderated by Early Irritability

Introduction

Irritability reflects a proneness to anger and frustration, and is characterized by behaviors such as chronic ill-tempered mood, frequent temper outbursts, and context-inappropriate anger (Brotman, Kircanski, & Leibenluft, 2017; Copeland et al., 2015; Dougherty et al., 2013; Mohamed Ali et al., 2021). Persistent and severe irritability is a core symptom of several psychiatric disorders, including oppositional-defiant disorder and major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; *DSM-5*). Emerging work further suggests that normative variations in early irritability are linearly associated with later outcomes, with greater irritability predicting increasing impairment and greater risk for psychopathology (Beauchaine & Tackett, 2019; Copeland et al., 2015; Wakschlag et al., 2015). Although heritable neurobiological mechanisms have been implicated in the pathophysiology of irritability (Brotman, Kircanski, & Leibenluft, 2017; Riglin et al., 2017; Stoddard et al., 2014; Wiggins et al., 2016), environmental factors such as parenting also influence the trajectory of children's irritability and its associations with outcomes across development (Ezpeleta, Penelo, de la Osa, Navarro, & Trepat, 2019; Ravi et al., 2022). Thus, both endogenous (i.e., within-child) and exogenous factors play a role in the development of irritability and associated maladjustment.

Past work examining irritability has focused almost exclusively on its association with psychopathology, overlooking more proximal indicators of dysfunction (i.e., endophenotypes) that could shed light on the mechanisms that contribute to the continuity of irritability across development. For example, irritability is linked to abnormalities in the functional activity of brain regions involved in processing reward and threat, as well as those implicated in top-down emotion regulation (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Leibenluft, 2017; Nielsen, Wakschlag, & Norton, 2021; Perlman et al., 2015; Wiggins et al., 2016). Relevant research shows that, relative to typically developing children, clinically irritable youths display increased activation of the anterior cingulate cortex (ACC) during reward processing, but reduced activation in response to blocked goal attainment (Brotman et al., 2017). Clinically irritable children also show reduced activation of the amygdala, striatum, and cortical regions during frustrative non-reward tasks (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013). As such, a heightened neural sensitivity to reward and deficits in top-down regulation of emotion that manifest as pronounced negative responses to non-reward may underlie the frequent temper outbursts and context-inappropriate expressions of anger that characterize clinically significant irritability (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Perlman et al., 2015). In addition, irritable youth exhibit atypical patterns of amygdala activation in response to ambiguous faces compared to healthy controls, a finding suggestive of a tendency to interpret ambiguous social stimuli as hostile (Leibenluft, 2017; Wiggins et al., 2016). Similarly, irritable youth show decreased functional connectivity between prefrontal and limbic regions in response to

angry faces, consistent with deficits in emotion regulation during threat processing (Stoddard et al., 2017), which may underlie manifestations of irritability in social contexts (Deveney, Stoddard, et al., 2019). Together, these findings implicate abnormalities in neural reactivity to reward and deficits in cognitive control of emotion in clinically significant irritability.

Consistent with a dimensional perspective of trait-symptom associations, a small body of work finds alterations in neural function in healthy, typically developing children with elevated early irritability (Beauchaine & Tackett, 2019; Copeland et al., 2015; Wakschlag et al., 2015). Indeed, these studies find atypical patterns of activation in fronto-striatal regions during cognitive control and reward tasks associated with irritability. For example, parent-reported irritability in otherwise healthy preschool children was associated with greater functional activity of the dorsolateral prefrontal cortex (dlPFC) during inhibitory control tasks (Fishburn et al., 2019; Grabell et al., 2019; Li, Grabell, Wakschlag, Huppert, & Perlman, 2017). In addition, Dougherty and colleagues (2018) found that irritability in typically developing children was associated with aberrant patterns of functional connectivity (FC) between the amygdala and frontal regions during a reward processing task. That is, relative to low irritability children who did not show FC differences when they missed or hit rewarding and non-rewarding targets, children with elevated irritability showed decreased amygdala-frontal connectivity in response to missing a rewarding target and increased connectivity when they missed a non-rewarding target. These findings suggest that early emerging

irritability, even in otherwise typically developing children, is associated with abnormalities in response modulation during reward processing (Dougherty et al., 2018). As such, neural functioning during emotion and reward processing may serve as an endophenotype linking subclinical irritability to later psychopathology.

Although parenting is a well-established and robust predictor of child outcomes, limited work has explored how it relates to the neural markers of risk that underlie irritability. A well-developed literature links parenting to offspring emotional competence, particularly self-regulation (Eisenberg et al., 2001; Eisenberg, Cumberland, & Spinrad, 1998; Thompson & Meyer, 2007; Zahn-Waxler, 2010), which is impaired in youths high in irritability (Brotman, Kircanski, & Leibenluft, 2017). This work finds that parents' self-expression and reactions to their children's emotions shape youths' own emotion regulation skills (Dallaire et al., 2006; McKee, Colletti, Rakow, Jones, & Forehand, 2008), in part via neurobiological mechanisms (Belsky & De Haan, 2011; Whittle et al., 2014, 2016; Yap et al., 2008). For instance, Romund and colleagues (2016) found that adolescent-reported maternal warmth and support, but not control, were associated with decreased activity in the amygdala in response to fearful faces, suggesting that youth-perceived maternal care may attenuate reactivity to negatively valenced emotional stimuli. In contrast, Cosgrove and colleagues (2022) did not find associations between youth-reported parenting quality and their neural activation during passive viewing of emotional pictures; rather, parenting was related to neural reactivity only during dyadic tasks that involved the parent. Specifically, youths who reported low

parental support of their emotion expression exhibited decreased neural reactivity in the amygdala and increased activation in the anterior insula and dlPFC in response to parental errors that were associated with loss to both parent and youth during a dyadic monetary reward task (Cosgrove et al., 2022). Given the involvement of the amygdala, insula, ACC, and dlPFC in emotional reactivity and regulation, these findings point to the role of the parent-child relationship in shaping children's neural reactivity. Moreover, these associations appear particularly salient when indexed in the context of parent-child interactions, relative to more general tasks of emotional processing.

Irritable children, for whom emotion regulation is particularly challenging, may be especially sensitive to parental influences relative to children without this temperamental vulnerability (Slagt, Dubas, Dekovic, & van Aken, 2016). For instance, Ravi and colleagues (2022) demonstrated that offspring with elevated irritability in childhood showed elevated irritability in adolescence, particularly in the context of critical or minimizing parental responses to child expressed negative emotion. Similarly, Lengua (2006) demonstrated that low parental warmth and rejection predicted the growth of irritable temperament as children transitioned into adolescence (Lengua, 2006). However, whether interactions between parenting and irritability influence irritable children's subsequent development via neural functioning in regions relevant to self-regulation has not, to my knowledge, been investigated.

Adolescents' experience of parental influences may be partly determined by the overall caregiving environment that unfolds over development. That is, parents'

behaviors may differentially impact children's outcomes depending on the emotional climate in which they are expressed, thus distinguishing between the overall parenting style and specific parenting behaviors that are circumscribed to a particular context (Darling & Steinberg, 1993; Lee, Daniels, & Kissinger, 2006). For instance, Van Petegem and colleagues (2017) demonstrate that in the context of perceived supportive parenting, adolescents appraise parental demands positively, relative to youth who perceive the parenting context as controlling. Thus, exploring how youth-reported parenting moderates their processing of parental feedback may inform our understanding of the individual differences in youths' responsivity to parental influences, particularly irritable youths who may be more sensitive to parental feedback.

My review of the current literature points to the involvement of neurobiological mechanisms that underlie reward, threat, and emotion processing in irritability. However, tasks of general emotion processing may fail to elicit neural processes relevant to processing interpersonal feedback. Moreover, while parenting interacts with children's irritability to predict youth outcomes, investigations that measure parenting broadly fall short of informing our understanding of how youth with elevated irritability process parental feedback specifically. These are critical gaps in the literature as, particularly during adolescence, youth in general exhibit a heightened sensitivity to interpersonal feedback, evidenced by findings of elevated emotional responsivity during processing of social cues and internal states of others at the neural and behavioral levels (Blakemore & Mills, 2014; Somerville, 2013).

Maternal feedback challenge tasks (MFC; Hooley et al., 2009; Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005) may be especially useful in understanding neural development in the context of irritability and caregiving. The MFC is an ecologically valid task that has been shown to evoke neural responses in regions involved in processing interpersonally relevant stimuli, emotional reactivity, and emotion regulation that have been implicated in the pathophysiology of irritability. While undergoing a functional magnetic resonance imaging (MRI) scan, youth listen to audio recordings of praising, neutral, and critical feedback from their own mothers, allowing researchers to examine the neural correlates of valenced parental feedback. Lee and colleagues (2014) used the MFC in a sample of healthy adolescents finding that maternal criticism, relative to neutral maternal comments, was associated with increased activation in brain regions implicated in processing of affective stimuli (i.e., putamen, insula), and decreased activation in regions involved in the cognitive control of emotion (i.e., dlPFC, ACC). These patterns of activation in healthy adolescents are reflective of increased emotional reactivity and decreased executive control of emotion that are typical during this developmental stage (Casey, Heller, Gee, & Cohen, 2019; Lee et al., 2015). Moreover, in a sample of high-risk youth (i.e., with a history of anxiety disorder), adolescents who perceived their mothers to be warm and supportive showed less activation in the amygdala as well as regions of the emotion regulation circuitry (i.e., insula, subgenual anterior cingulate [sgACC], right ventrolateral prefrontal cortex [vlPFC], and the ACC) in response to maternal criticism (Butterfield et al., 2021). This lower activation of the sgACC in response to maternal criticism further mediated the association between

maternal warmth and reduction of adolescent internalizing symptoms two years later, suggesting that youth perceptions of positive parenting may support healthy development via influences on offspring neural development (Butterfield et al., 2021). The aforementioned studies support the ecological validity of the MFC task in evoking neural networks involved in processing interpersonally relevant feedback from parents, yet limited work has explored how youths' individual differences relate to their neural processing of parental feedback.

I therefore examined whether childhood irritability predicted adolescent processing of maternal feedback, and, toward further characterizing this association, whether adolescent-reports of parent-child relationship quality moderated neural responsivity to their mothers' affectively valenced feedback. I used youth-reported caregiving given that parents and youth show low agreement on measures of caregiving (Korelitz & Garber, 2016) and some work suggests that adolescents' perception of the parent-child relationship is associated more strongly with later outcomes relative to parent-report (Bolkan, Sano, de Costa, Acock, & Day, 2010; Guion, Mrug, & Windle, 2009). I capitalized on observational measures of irritability, which predict outcomes above and beyond parent-report (Mohamed Ali et al., 2021, Mohamed Ali et al., in preparation), allowing a multi-method approach for examining interrelations between children's early emerging temperament and parenting during adolescence. I expected that early irritability would be associated with atypical patterns of neural reactivity to maternal criticism and praise, particularly in the dlPFC based on past work linking

functional activity in this region to irritability (Cosgrove et al., 2022; Fishburn et al., 2019; Grabell et al., 2019; Li et al., 2017). I expected that perceived positive parenting would moderate these associations for irritable youth, such that adolescent-reported positive parenting would be associated with greater activity of regions that underlie self-regulation in irritable youths, who may be especially sensitive to parental influences (Kiff, Lengua, & Bush, 2011; Oldehinkel, Veenstra, Ormel, de Winter, & Verhulst, 2006). However, given the lack of studies linking irritability to neural reactivity to parental feedback, I also conducted exploratory whole-brain analyses following ROI analyses.

Methods

Participants

A sample of 81 community-dwelling youths (44% girls) and their mothers were drawn from a larger sample of 409 families (50.1% girls) who were part of a larger, ongoing, multi-wave study of child development. At baseline, families were recruited from the community using advertisements in local daycares, recreational facilities, and the University of Western Ontario's developmental participant pool. Children included in the larger longitudinal study had at least one biological parent who could participate in the study, were free of significant medical and psychological problems, and were of average cognitive ability (M = 112.00; SD = 14.05) as assessed by the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn, 1997) at baseline. The larger sample was

predominantly White (93.2%), well educated (> 70% of parents had attained college or university level education), middle-class families (53.3% reported an annual household income between CAD $40,000 and CAD $100,000), consistent with the demographic characteristics of the region from which they were drawn (Statistics Canada, 2017). Most children came from two-parent homes (87.6%). Participants in the current study did not differ from the larger sample on any demographic variables (i.e., age, sex, ethnicity, family income, PPVT scores; all $p > .05$). Study procedures for all waves of data collection were approved by the University of Western Ontario's Research Ethics Board. The primary caregiver provided consent for themselves and their child's participation, and assent was obtained from youths.

Participants in the current study were originally invited for a follow-up study that examined associations between maternal depression and youth risk for psychopathology (Liu et al., 2020, 2022; Vandermeer et al., 2020, 2022). Given the expense of imaging data, for the current study (T2), families were drawn from the larger sample based on a maternal depression history, assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Nonpatient Edition (First, Spitzer, Gibbon, & Williams, 1996), to increase power. Of these 102 families, 82 youth participated in the MRI portion of the study, and the remaining youth either declined (n = 9), were unable to finish the MRI visit due to discomfort in the scanner (n = 4) or dropped out of the follow-up prior to the MRI visit (n = 7). Imaging data from one youth was dropped due to excessive motion in the scanner. As such, the current sample consists of 81 youth: Twenty-six high-risk

children whose mothers had a lifetime history of recurrent major depression, or a single major depressive episode and an anxiety disorder, and 55 low-risk children with no maternal history of major depressive or anxiety disorder. This sample size is comparable to that reported in past fMRI studies that tested adolescents' neural activity during the MFC (i.e., Range of Ns = 23 - 63; Butterfield et al., 2021; Hooley et al., 2009, 2005; Lee et al., 2015; Silk et al., 2017). Children were screened for both past and current depressive disorder using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (KSADS-PL; Kaufman et al., 1997) conducted with both the primary caregiver and the child; no child was excluded based on as history of depression (detailed recruitment procedures are described in Vandermeer et al., 2020).

Procedure

Data used here were collected at two time points, approximately 8 years apart. At T1, children (M_{age} = 3.43, *SD* = .28) completed observational measures in the laboratory to assess child temperament. In the current study, referred to here as T2, youths (M_{age} = 11.1, *SD* = .63) completed questionnaire measures assessing perceived mother-child relationship quality during a visit conducted in the child's home. Audio recordings of maternal feedback was also collected during this visit (described below). Approximately 4 weeks later youths attended an MRI visit during which functional neural reactivity to maternal feedback was recorded.

Measures

Observed Irritability

At age 3, children participated in the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995), which consists of 12 emotionally evocative tasks, each two to six minutes long, designed to elicit behavior relevant to child temperament. Children's behavior is video-recorded and later coded for expressions of emotion by trained undergraduate and graduate student raters. Coders were trained by a "master" coder and had to reach 80% agreement before coding independently. Intermittent reliability checks were conducted to maintain an interclass correlation (ICC) of .80 and prevent coder drift. Typically, children's facial, vocal, and bodily expressions of positive affect, sadness/anger, or fear are aggregated across all 12 tasks, although different tasks are designed to elicit a particular emotion (e.g., in one task designed to elicit positive affect, the child and experimenter race with two remote-controlled cars). There is no single agreed-upon operationalization of irritability (Beauchaine & Tackett, 2019; Brotman, Kircanski, Stringaris, et al., 2017; Copeland et al., 2015; Craig et al., 2008; Leibenluft & Stoddard, 2013); in the current study, I conceptualized irritability as a low-threshold, context-inappropriate anger by aggregating children's expressions of anger across Lab-TAB tasks that were not typically anger-eliciting (α = .78). As previously described, findings from my past work support the construct validity of this approach to indexing childhood irritability.

Perceived Mother-Child Relationship Quality

At age 11 (T2), with the assistance of a trained research assistant, youths completed the Parental Bonding Instrument (PBI; Parker, Tupling, & Brown, 1979) during a home visit. The PBI is a 25-item self-report questionnaire that assesses offspring perceptions of their mother's and father's care and overprotection, separately, during the past year. As mothers were the primary caregivers in this sample, and given research pointing to the significance of maternal care to youth outcomes (Bornstein, 2002; Braza et al., 2015; Milevsky, Schlechter, Netter, & Keehn, 2007), I used youths' report of their mothers' parenting styles in this study. As overprotective parenting is less relevant to current study questions[8], and because maternal warmth and affection are strongly implicated in youth development (Morris, Criss, Silk, & Houltberg, 2017; Morris, Silk, Steinberg, & Robinson, 2009), I used the 12-item maternal care subscale of the PBI (α = .77), which taps offspring perceptions of mothers' affection and nurturance (e.g., "spoke to me in a warm and friendly voice") and did not include the overprotection scale in the current study.

Functional Activity during Maternal Feedback

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[8] "Overprotection" assessed by the PBI describes perceived parental enforcement of control that undermines child autonomy. While this parenting style is generally considered to be associated with maladaptive child outcomes, evidence supporting this notion has been modest. That is, associations between youth-reported parental overprotection and related constructs (e.g., involvement) and their outcomes appears to depend on culture (Hiramura et al., 2010; Jackson-Newsom, Buchanan, & McDonald, 2008), parent and youth gender (Hiramura et al., 2010), and parental use of discipline (McKinney, Milone, & Renk, 2011).

Maternal Feedback Challenge. At child age 11, samples of maternal feedback were acquired during a visit to the child's home, prior to the MRI visit. Mothers were instructed to write two brief feedback stimuli for each of three valence conditions: neutral, critical, and praising, for a total of six stimuli. Mothers were given a standardized sentence stem specific to each condition; neutral (i.e., "[*Child's name*], one thing I want to talk to you about today is …"), critical (i.e., "[*Child's name*], one thing that really bothers me about you is …"), and praising (i.e., *"*[*Child's name*], one thing I really like about you is …"). For the neutral condition, mothers discussed mundane topics they believed their child would not feel strongly about, such as grocery shopping or the weather. As my interest was in exploring youths' neural responses to valenced interpersonal feedback, I do not discuss the neutral condition further. Stimuli were collected by trained graduate students and research assistants who ensured that mothers gave feedback on topics frequently discussed with the child to ensure their relevance and that there was sufficient material for a 30 s audio recording.

Next, mothers read each of their written statements while being audio recorded using NESSIE adaptive USB condenser microphone (Blue Microphones, Westlake Village, CA, USA) and Audacity software (Version 2.1.2). Raw audio clips were then edited to ensure consistency across participants in terms of length and volume: extended periods of silence were cropped so that all clips were exactly 30 s in length, amplitude was adjusted using Audacity's "Amplify" effect so that clips had a maximum amplitude of -1.0 dB and compressed to have a consistent dynamic range using Audacity's

"Compressor" effect. Two strategies were used as a validation check for these stimuli: First, two undergraduate research assistants blind to other study data rated how positive or negative each stimulus was on a 10-point scale (1 = "Not at all" and 10 = "Very"). Second, while in the scanner, youths provided a mood rating on a 5-point visual Likert-type scale after each condition.

MRI Acquisition. Prior to undergoing the MRI scan, children completed a "mock scan" session in a replica MRI system to familiarize them with the MRI environment and to determine whether they would be likely to be compliant with the imaging data collection procedures (De Bie et al., 2010). During the mock scan, children were explained the MRI session procedures and invited to ask questions. fMRI data were acquired on a 3T Siemens Magnetom Prisma scanner with a 32-channel head RF coil (Siemens, Erlangen, Germany). Separate runs were completed for each of the three MFC conditions (i.e., praise, neutral, critical). Each run of the MFC task consisted of 89 T_2^*-weighted volumes collected using an echo-planar imaging (EPI) sequence with the following parameters: voxel size = 3 x 3 x 3 mm, repetition time (TR) = 1000 ms, echo time (TE) = 30 ms, field of view (FOV) = 210 mm, yielding 48 axial slices. T_1-weighted anatomical scans were also collected for the purpose of co-registration, using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: voxel size = 1 x 1 x 1 mm, TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm, yielding 192 sagittal slices per participant.

During fMRI scanning, youths listened to their individualized MFC audio stimuli over MRI-safe in-ear headphone. Stimuli were presented in a block design using E-prime 2.0 (Version 2.0.10.242), for a total of three runs. Each run consisted of the two blocks of the 30-second audio clips of that condition (e.g., praise) separated by a 12-second rest period. A run of neutral feedback was always presented first, followed by either praise or criticism runs, counterbalanced between participants. Youths were instructed to listen to the MFC stimuli while fixating their gaze on a black cross against a white background. At the end of each run, youths were asked to rate their emotional response using a 5-point Likert scale depicted as 5 emotionally valenced cartoon faces (i.e., "1" depicting a frowning "sad" face, "3" depicting an emotionally neutral face, and "5" depicting a smiling "happy" face).

fMRI Preprocessing. Raw DICOM images were converted to NIFTI format using MRIcron software (Rorden, Karnath, & Bonilha, 2007). Quality assurance and preprocessing were performed separately for each functional run condition and conducted using SPM12 (Version 7847) and MATLAB R2018a (Version 9.4.0.813654; Mathworks, Inc., Natick, MA, USA). T_1-weighted images were manually oriented so that the anterior commissure was the point of origin for all participants. Quality assurance procedures were performed using the ArtRepair toolbox (Mazaika, Hoeft, Glover, & Reiss, 2009; Mazaika, Whitfield-Gabrieli, Reiss, & Glover, 2007; Mazaika, Whitfield, & Cooper, 2005). Individual scans with frame-wise displacement > 0.9 mm or frame-wise global signal intensity > 1.3% deviation from the mean were flagged and interpolated using the

nearest unrepaired scan before or after the flagged scan (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Siegel et al., 2014). Based on parameters provided by Siegel et al. (2014) for motion censoring to improve the quality of fMRI data, scanner runs with excessive repair, i.e., ≥ 20% (18 TR), or frame-wise displacement > 0.9 mm were dropped from further analyses. This resulted in one subject being dropped due to high mean framewise displacement. Functional images were preprocessed using a standard pipeline that included realignment to a mean image, co-registration to T_1-weighted anatomical scans standardized in MNI space with 2 x 2 x 2 mm voxels, and spatial smoothing using a 6 mm x 6 mm x 6 mm full-width at half-maximum (FWHM) Gaussian kernel. Registration was manually checked by comparing participants' mean functional images with T1-weighted anatomical scans.

Data Analyses

Analyses were conducted using SPM12 and SPSS. fMRI data were modelled using mixed effects models, such that single-subject analyses were first conducted on individual children's data using a fixed effects model (i.e., Level One), followed by group-level analyses using a random effects model (i.e., Level Two).

Level One Analyses

Individual functional responses to each maternal feedback condition were modeled separately using a 30s boxcar function convolved with a canonical hemodynamic response function (Poldrack, Mumford, & Nichols, 2011). Motion

parameters (i.e., three translational and three rotational per scanner per run) were treated as covariates. Main effects of each MFC condition were modeled by contrasting functional activity during that condition to activity during rest, i.e., Criticism vs. Rest and Praise vs. Rest.

Level Two Analyses

Second-level analyses were conducted to examine associations between early irritability and functional activity in the Criticism and Praise conditions, testing moderations by youth's perceived parent-child relationship quality (Figure 4-1). As such, relative neural activation (as modelled in single-subject analyses) was regressed on observed age 3 irritability (scores on observed irritability), child-reported perceived parenting (i.e., scores on PBI care), and their interaction (observed irritability x PBI care score). Child age was included as a covariate in all level two analyses[9]. Based on the literature on the neural correlates of irritability and parenting (Brotman, Kircanski, & Leibenluft, 2017; Deveney et al., 2013; Deveney, Grasso, et al., 2019; Dougherty et al., 2018; Perlman et al., 2015; Stoddard et al., 2017), I used a voxel-wise small volume correction approach (Nieto-Castanon, Ghosh, Tourville, & Guenther, 2003) within *a priori* anatomical Regions-of-Interest (ROI) to examine neural activation in regions previously implicated in childhood irritability. *A priori* ROIs were defined using the

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[9] As participants were oversampled for a maternal history of depression (Liu et al., 2020, 2022; Vandermeer et al., 2020, 2022), this was also included as a covariate. Given that doing so did not change the pattern of results, maternal risk was dropped from analyses to conserve statistical power.

WFU PickAtlas toolbox (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) and the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002), tested separately. ROIs were bilateral amygdala, dlPFC, ACC, and putamen (see Appendix for ROI definitions). I then extracted subject-wise average values of % signal changes from clusters in which the interaction effect was significant using the MARSeille Boîte À Région d'Intérêt toolbox for SPM (MarsBaR; Brett, Anton, Valabregue, & Poline, 2002) and imported these into SPSS (v.28) to probe interaction effects. Finally, I conducted exploratory whole-brain analyses examining associations between variables of interest and neural functional activity. I applied a cluster-level significance threshold of $p < .05$, family-wise error corrected during all analyses.

Results

Bivariate Correlations

Correlations between all major study variables are presented in Table 4-1. Perceived maternal care was positively associated with self-reported emotional response to maternal praise during the fMRI task. Age 3 irritability was positively correlated with youth's self-reported emotional response to maternal criticism, such that youth with higher irritability scores reported more positive mood following critical maternal feedback. Age 3 irritability was unrelated to adolescent-reported maternal care at age 11.

fMRI Results

Neural activation to maternal criticism

I found a significant main effect of age 3 irritability on neural reactivity to maternal criticism in a cluster in the right dlPFC, a region implicated in top-down emotion regulation (MNI peak coordinates: 48, 30, 38; T = 3.95; k = 31; p_{FWE} < .05; SVC applied; Figure 4-2). Specifically, irritability was negatively associated with activation in this region. No main effect of maternal care was observed. Further, the interaction between age 3 irritability and perceived maternal care was significant in a right dlPFC cluster that overlapped with the cluster of the significant main effect of age 3 irritability (MNI peak coordinates: 48, 30, 38; T = 3.87; k = 33; p < .05; SVC applied; Figure 4-2). Probing interaction patterns in SPSS based on the mean values of % signal changes of the significant cluster for the interaction effect showed that the association between early irritability and neural activation in this region was significant for youth who reported high maternal care only (β = .92; t(77) = 2.53; p = .01; Figure 3). That is, for these youth, irritability was associated with smaller % signal change to maternal criticism relative to rest. The association between irritability and neural reactivity in the criticism condition was not significant at mean (β = .16; t(77) = .63; p = .53), or low maternal care (β = -.59; t(77) = -1.63; p = .11)[10]. The Johnson-Neyman region of significance analysis further showed that the association between irritability and neural reactivity to maternal criticism became significant at very high perceived maternal care (> 34; Figure 4-4). No

[10] Although the slope of irritability was also significant at very low maternal care (< 26.5), I do not interpret this finding further as the test of simple slopes for this group was not significant.

associations between variables of interest and functional activity to maternal criticism were observed in other ROIs, or during whole-brain analyses.

Neural activation to maternal praise

Neither early irritability, maternal care, nor their interaction were associated with neural responses to maternal praise in any of the ROIs or during whole-brain analyses.

Discussion

Childhood irritability, an established marker of risk for psychopathology, has neural correlates (Brotman, Kircanski, & Leibenluft, 2017; Copeland et al., 2015; Leibenluft, 2017; Leibenluft & Stoddard, 2013) that may be shaped by maternal care. However, extant research on irritability has almost exclusively focused on child psychopathology as an outcome, overlooking more proximal indicators of dysfunction, such as youths' functional brain reactivity in regions relevant to the development of disorder. Despite the importance of parenting to predicting child outcomes, to my knowledge, no work has investigated associations between early irritability and youths' neural reactivity to their parents' feedback. I found that, in response to maternal criticism, early irritability was negatively associated with activation in the right dlPFC, a region implicated in cognitive control of emotion (Ochsner & Gross, 2005). However, youth-reported parenting moderated this association such that early irritability predicted decreased dlPFC reactivity to maternal criticism relative to rest, particularly among youths reporting relatively high maternal care.

The dlPFC is a key region within the affective salience circuitry that is involved in processing emotionally salient stimuli, playing a role in the top-down modulation of amygdala reactivity to negatively valenced stimuli (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; Golkar et al., 2012; Ochsner & Gross, 2005; Uchida et al., 2014). In particular, the dlPFC is involved in processes such as response inhibition, diverting attention from threatening stimuli, and reappraisal of emotion (Banks et al., 2007; Golkar et al., 2012), and is therefore a critical structure in the development of emotion regulation competence. Decreased dlPFC activation in response to negatively valenced stimuli has been demonstrated among depressed individuals, where a persistent negative mood state is prevalent (Hooley et al., 2009). Similarly, alterations in dlPFC activity have also been implicated in the pathophysiology of irritability (Brotman, Kircanski, & Leibenluft, 2017; Leibenluft, 2017; Nielsen et al., 2021). My finding that irritability was associated with decreased neural activation to maternal criticism is consistent with previous work that implicates reduced dlPFC activation among at-risk individuals (Hooley et al., 2009, 2005; Koenigs & Grafman, 2009b).

I expected that a positive parent-child relationship quality would mitigate the vulnerability associated with irritability by supporting adaptive recruitment of neural resources implicated in inhibiting emotional reactivity to negative maternal feedback (i.e., greater dlPFC activation to maternal criticism). However, among youth reporting high maternal care, irritability was associated with decreased dlPFC activation during maternal criticism. This might suggest more pronounced deficits in cognitive control of

emotion among irritable youth who perceive their mothers to be more caring. Alternatively, it may be that positive parenting supports irritable youths' disengagement from negative maternal feedback, a strategy that has been shown to be effective in managing negative emotions in the short term (Lee et al., 2015; Parsafar, Fontanilla, & Davis, 2019; Rice, Levine, & Pizarro, 2007). Future work should examine how the use of different emotion regulation strategies is associated with neural activation during interpersonally relevant tasks among irritable youth.

My findings are also relevant to previous work examining associations between irritability and activation of prefrontal regions during tasks of cognitive flexibility (Li et al., 2017) and inhibitory control (Fishburn et al., 2019; Liuzzi et al., 2020) in otherwise healthy preschool children. Past studies showed increased frontal activation during tasks of cognitive control among preschoolers with elevated early irritability in the absence of behavioral differences in performance between low and high irritability children (Fishburn et al., 2019; Li et al., 2017; Liuzzi et al., 2020). These findings suggest that currently healthy children with elevated irritability may be able to recruit more neural resources for inhibitory control, potentially reducing risk for negative mental health outcomes. In contrast, my findings suggest that different functional activity patterns characterize the neural correlates of irritability in adolescence. That is, it may be that increased dlPFC activation during tasks of cognitive control among healthy children with elevated irritability do not persist in adolescence, potentially explaining the increased prevalence of maladaptive outcomes in this developmental window. Alternatively,

patterns of dlPFC activation in irritable youth may be task dependent. That is, although the dlPFC is implicated in processing of interpersonal feedback (Butterfield et al., 2021; Lee et al., 2015; Silk et al., 2017; Vandermeer et al., 2022), irritable youth may show increased activation of this region during tasks of executive function but reduced neural reactivity to interpersonally relevant stimuli. I also note that I assessed irritability in childhood rather than concurrently to the assessment of neural reactivity to maternal feedback. Although emerging work points to the relative stability of irritability (Beauchaine & Tackett, 2019; Kessel et al., 2021; Klein et al., 2021; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016; Mohamed Ali at al., in preparation), longitudinal investigation of the neural correlates of irritability across childhood and adolescence is needed to further corroborate my findings.

I did not observe main effects of irritability or interactions between irritability and maternal care in predicting adolescents' neural reactivity to maternal praise. Past work found that typically developing youth with elevated irritability exhibited increased activation of the putamen to reward during a monetary incentive delay task, specifically in the context of poor executive function abilities (Kryza-Lacombe, Palumbo, Wakschlag, Dougherty, & Wiggins, 2022). In addition, children with elevated irritability show alterations in functional connectivity between regions of the reward circuitry during frustrative non-reward, such that they exhibit poorer regulation of the reward circuitry when anticipated reward is thwarted (Dougherty et al., 2018; Nielsen et al., 2021). These findings are indicative of hypersensitivity to reward as well as problems coping with

frustration in irritable youth. However, despite the relevance of irritability to depressive disorders, wherein blunted neural reactivity to positive parental feedback have been identified (Silk et al., 2017), to my knowledge, past work has not explored mechanisms of processing positive interpersonal feedback in irritability. The observed lack of associations between early irritability and neural reactivity to maternal praise may point to independent pathways underlying responsivity to social (e.g., evoked by parental praise) versus non-social (i.e., evoked by monetary incentive tasks) reward, in the context of irritability. This notion is supported by past work showing differential associations between different types of reward, subject-specific characteristics (e.g., age, gender, personality) and patterns of neural reactivity to reward (Delmonte et al., 2012; Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009; Rademacher et al., 2010). Alternatively, mothers' praising comments may be a common and familiar experience for the youth in this community, low-risk sample, such that there is limited variability in youths' neural reactivity to maternal praise.

This study has several important strengths. I used a multimethod approach for assessing my variables of interest, incorporating an observational measure of early irritability that is suited to its conceptualization as a temperamental trait. This approach is also useful in light of the significant limitations of parent-reported child behavior (Clark et al., 2017; De Los Reyes & Kazdin, 2005; Goodman et al., 2011). In addition, given past work implicating specific brain regions in both the pathophysiology of irritability and neural processing of parental feedback, I had strong hypotheses that permitted ROI

analysis. Relative to whole-brain voxelwise analyses, this approach limits the number statistical tests, thereby controlling for Type I error (Poldrack, 2007).

However, there are several limitations to this study. Considering the limited power, I did not examine sex differences in the relationship between irritability and neural functioning. In addition, I measured irritability in childhood only; thus, although my past work supports the stability of early irritability over several years (Mohamed Ali et al., in preparation), future longitudinal studies with repeated measures of neural activation, parenting, and youth characteristics at all waves will prove useful for testing causal links between early irritability and later neural development. My findings implicate regions within the prefrontal cortex that show protracted development across the lifespan, which is thought to underlie improvements in self-regulation capacities that typically emerge over adolescence (Casey et al., 2019; Durston & Casey, 2006). As such, although I captured an important "snapshot" of neural reactivity in early adolescence, additional follow-up is needed to adequately trace adolescent development in these brain regions. Additionally, although the patterns of neural reactivity observed should be related to adolescents' self-regulation (Ochsner & Gross, 2005; Phillips, Drevets, Rauch, & Lane, 2003), I did not include behavioral measures of self-regulation, a potentially important level of analysis to consider. Finally, my sample consisted largely of Caucasian, middle-to-upper class families who were highly educated, and youths were of average to above average cognitive ability. The homogeneity of this sample may therefore preclude the generalizability of my findings to more diverse samples.

My findings show that youth's neural reactivity to parental feedback is dependent on their early irritability and perceived parent-child relationship quality, and particularly points to shared neural pathways between irritability and processing of interpersonal feedback. These findings have important implications for understanding environmental influences on irritable youth, particularly in adolescence.

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Tables & Figures

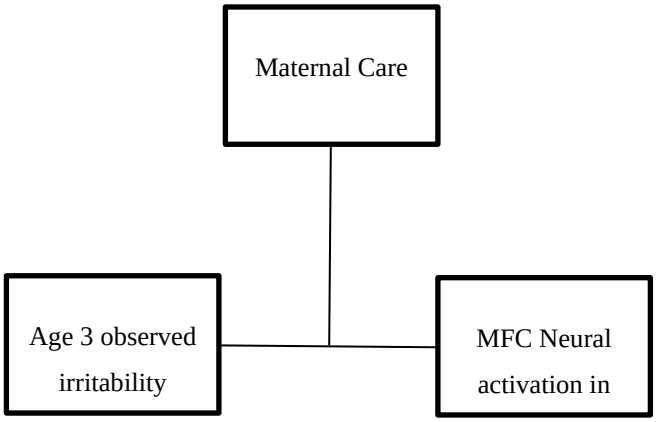

Figure 4-1 *Moderation model tested predicting neural activation in each ROI in the maternal criticism and praise conditions.*

Table 4-1 Bivariate Correlations among Major Study Variables

		M (SD)	1	2	3	4	5	6	7	8
1.	Age 3 Irritability	.21 (.21)								
2.	Age 11 PBI Mat Care	31.81 (3.82)	-.15							
3.	Mood Rating Criticism	2.68 (1.02)	.26*	.15						
4.	Mood Rating Praise	4.54 (.77)	-.18	.31**	-.02					
5.	Child Sex	-	-.12	.16	.01	.08				
6.	Family Income	-	.01	-.09	-.10	-.11	-.01			
7.	Ethnicity	-	-.01	.03	.19	.03	-.04	-.19		
8.	PPVT score	113.21 (14.31)	-.18	.01	-.18	-.01	-.08	.20	.05	

Note. ** $p < .01$; * $p < .05$; PBI = Parental Bonding Instrument; Mat = Maternal; Child sex: boys = 1, girls = 2; Family Income: 1 <$20,000, 2 = $20,000 - $40,000, 3 = $40,001 - $70,000, 4 = $70,002 - $100,000, and 5 >$100,001; Ethnicity: 1 = White, 0 = Other; PPVT = Peabody Picture Vocabulary Test.

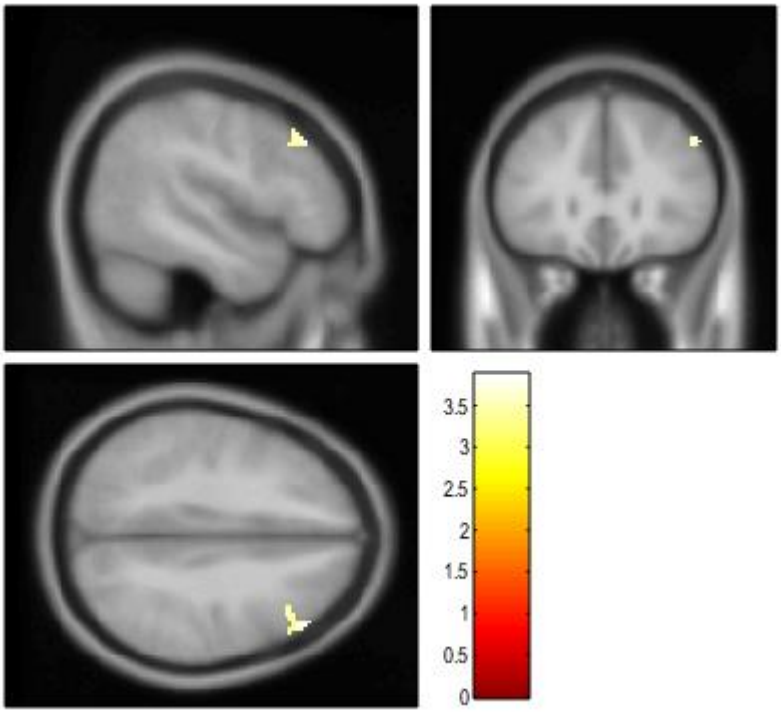

Figure 4-2 *A priori ROI analysis showing the region in the right dlPFC (48, 30, 38) where activation during the maternal criticism condition was significantly associated with the interaction of irritability and perceived maternal care.*

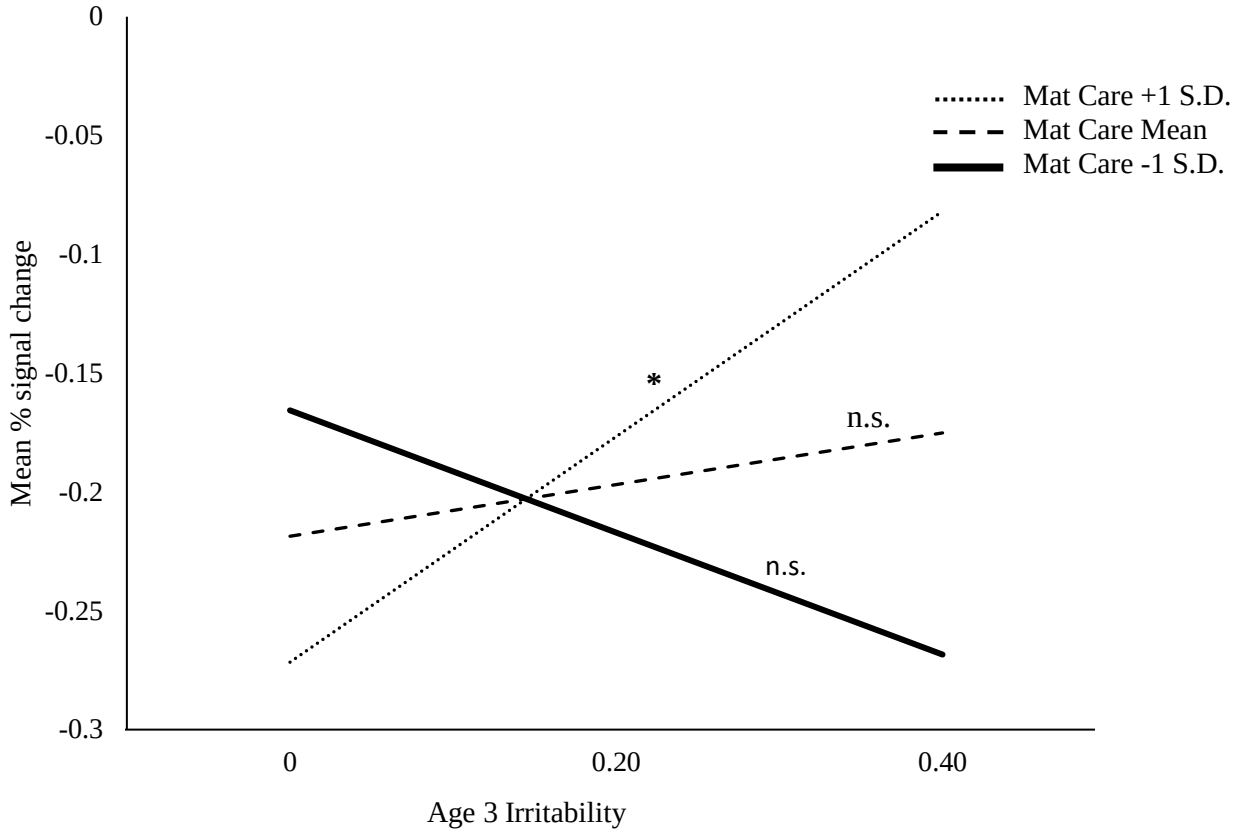

Figure 4-3 *Early irritability is associated with decreased neural reactivity of the right dlPFC during maternal criticism relative to rest among youth who reported high maternal care (*p < .05; n.s. = not significant).*

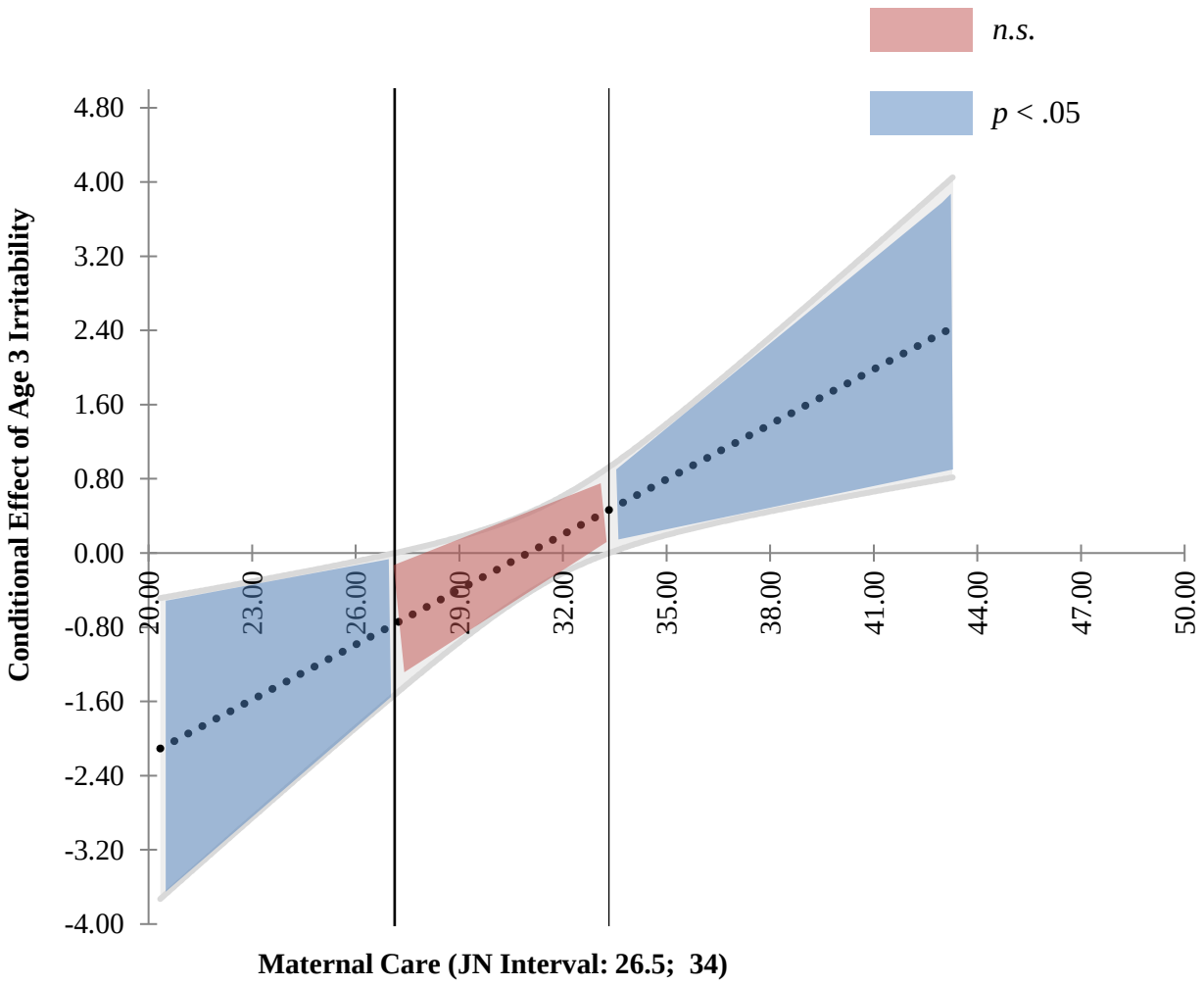

Figure 4-4 *Johnson-Neyman region of significance analysis shows that the simple slope of age 3 irritability predicting neural reactivity of the dlPFC during maternal criticism is significant at very high and very low maternal care.*

Table 4-2 *Definitions of ROIs*

ROI	Definition by Atlas Label
Bilateral amygdala	Amygdala_L, Amygdala_R
Bilateral dlPFC	Frontal_Mid_L, Frontal_Mid_R
ACC	Cingulum_Ant_L, Cingulum_Ant_R, Cingulum_Mid_L, Cingulum_Mid_R, Cingulum_Post_L, Cingulum_Post_R
Bilateral putamen	Putamen_L, Putamen_R

Note: L= Left, R = Right; dlPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex

Chapter 5 – General Summary and Discussion

All children experience annoyance, frustration, and anger; however, for some children, irritability is impairing and associated with later dysfunction. Viewed in the context of maladjustment, childhood irritability is one of the most common presenting concerns in pediatric psychiatric settings (Stringaris & Taylor, 2015). Indeed, the lifetime prevalence of severe mood dysregulation (SMD), a diagnosis characterized by severe irritability and hyperarousal, is 3.3% (Brotman et al., 2006). Moreover, irritability is a symptom of several DSM-5 childhood disorders, including major depressive disorder, oppositional-defiant disorder, and generalized anxiety disorder (American Psychiatric Association, 2013). Additionally, the presence of irritability with the cardinal symptoms of a particular disorder (e.g., low mood in depression) is associated with poorer prognosis and more severe functional impairment (Galera et al., 2021; Stringaris, Maughan, Copeland, Costello, & Angold, 2013). Irritability is also common among community-dwelling children and adolescents. For example, in a large, representative sample of community-dwelling adolescents in the U.K., around a quarter of youth (19.1% for males and 23.9% for females) reported being irritable, which strongly predicted the development of affective problems and suicidality in adulthood (Pickles et al., 2010). To date, irritability has largely been studied as a symptom of disorder among clinically referred youth; however, emerging work suggests that normative variations in irritability, even in the absence of dysfunction, mark increased risk for psychopathology across the internalizing and externalizing spectrum (Beauchaine & Tackett, 2019; Brotman,

Kircanski, Stringaris, et al., 2017; Copeland et al., 2015; Finlay-Jones et al., 2023; Klein et al., 2021). Given this literature, characterizing the phenomenology of irritability, particularly among typically developing children, may greatly enhance our understanding of the etiological mechanisms that underlie the development of psychopathology.

Summary and Review of Studies

This dissertation is comprised of three original studies that conceptualize irritability as a dimensional trait; specifically, I conceptualized irritability as a temperamental trait that reflects a low threshold for anger, operationalized as children's observed expressions of anger in situations in which it is neither provoked nor appropriate. In Study 1 (Chapter 2), in typically developing three-year-old children, I examined whether individual differences in irritability, assessed via this approach, were associated with later psychopathology, indexed as parent-reported internalizing and externalizing symptoms. In Study 2 (Chapter 3), towards further characterizing irritability as a temperamental trait, I examined its temporal stability between ages 3 and 5 years and whether early parenting and regulatory facets of temperament contributed to its continuity/discontinuity. I also investigated the associations between age 5 irritability and psychopathology symptoms. Finally, in Study 3 (Chapter 4), I examined whether age 3 irritability in typically developing children was associated with neural markers of risk, indexed by neural reactivity to maternal feedback, in adolescence. Across these three studies, I found evidence supporting the conceptualization of irritability as a

temperamental trait that reflects early emerging vulnerabilities to the development of psychopathology.

Study 1

In Study 1 (see Chapter 2 and Mohamed Ali et al., 2021), I found preliminary evidence supporting the use of observational measures of child behavior to assess irritability as a dimensional construct. I found that irritability operationalized as unprovoked, observed expressions of anger at age 3 years predicted symptoms of depression, oppositional-defiant disorder, attention-deficit/hyperactivity disorder, and conduct disorder, at ages 5 and 8 years. Importantly, the associations between observed irritability and later symptoms were significant after controlling for symptoms at baseline, variance predicted by two parent-reported indices of irritability (i.e., the CBCL irritability and CBQ Anger/Frustration scales), and observer-rated context-appropriate anger. These findings highlight the utility of observational measures of irritability and suggest that, even among young, community-dwelling children, irritability is associated with emerging symptoms of psychopathology. Past work has largely examined irritability in clinical samples, using parent-report measures specifically designed to capture extreme, functionally impairing manifestations of irritability; further, parent-report measures are limited in several key respects (Clark, Durbin, Donnellan, & Neppl, 2017; De Los Reyes & Kazdin, 2005; Durbin & Wilson, 2012; Goodman et al., 2011; Hayden, Durbin, Klein, & Olino, 2010). Using a well-established, observational paradigm for the measurement of children's behavior, my findings complement other research highlighting

the limitations of existing measures, particularly parent-report, in capturing irritability dimensionally (Dougherty et al., 2021).

Study 2

I found additional support for the validity of irritability conceptualized as a temperamental trait in the second study. That is, the stability of irritability measured observationally over a 2.5 year follow-up was .32, which is comparable to stability estimates of observer-rated temperament reported in the literature (Durbin et al., 2007; Dyson et al., 2015; Majdandžić & Van Den Boom, 2007). This finding supports the utility of early irritability as a potential marker of risk, given that vulnerability markers are thought to reflect relatively stable etiological mechanisms that underlie the development of disease (Ingram & Price, 2010).

Consistent with a developmental psychopathology framework that points to the importance of environmental factors to the trajectories of temperamental traits in development, I found that the continuity of irritability between ages 3 and 5 years was moderated by early parenting. Specifically, I found stronger associations between age 3 and age 5 irritability in the context of parenting characterized by greater responsivity to children's emotions and behaviors and less parental interference. The directionality of the association of parenting to the continuity of irritability was contrary to my expectations. That is, I predicted that responsive, highly engaged parenting would be associated with discontinuity of irritability, while negative parenting would be associated with its

continuity. There is very little research on factors that serve to heighten the stability of irritability in early childhood, so future work is needed to confirm this somewhat unexpected pattern of effects. It may be that, in a community-dwelling sample of families, children who receive sensitive, autonomy-granting parenting are more likely to exhibit greater stability of individual differences, including irritability. Thus, irritability appears relatively stable in this sample of typically developing children; this stability is associated with greater parent sensitivity and less interfering parenting behaviors.

Contrary to my hypothesis, I did not find that children's temperamental self-regulation moderated the continuity of irritability. This may be due to my focus on irritability as well as methodological factors. Past work found interactions between laboratory-assessed regulatory facets of temperament (e.g., EC) and positive, but not negative, emotionality in predicting discontinuity of symptoms in childhood (Nielsen et al., 2019). Also, irritability in typically developing 6-year-olds was negatively associated with parent-reported, but not observed, EC (Silver et al., 2023). Thus, it may be that EC is more relevant to the crystallization of positive facets of temperament when assessed observationally. Alternatively, it may be that parent-report captures aspects of EC not captured in a laboratory context. A broader multi-method investigation is needed to explore the nuanced relationship between children's self-regulation and irritability.

With respect to extending findings from Study 1, I found that age 5 observer-rated irritability was associated with concurrent and later symptoms of psychopathology, showing similar patterns reported in Study 1. Importantly, age 5 irritability predicted

symptoms into early adolescence. However, the relationship between irritability and symptoms appears nuanced, potentially depending on child age as well as the measurement approach to irritability. In my study, associations between observed irritability and internalizing symptoms were weaker relative to those with externalizing symptoms, with observer-rated irritability predicting inattention/hyperactivity symptoms at ages 5, 8 and 11. In contrast, parent-reported irritability at age 5, specifically on the CBQ, predicted concurrent and age 11 internalizing symptoms. It may be that parent-report and observer ratings are capturing different facets of irritability, which would be consistent with past work linking tonic irritability to internalizing symptoms, and phasic irritability to externalizing problems (Moore et al., 2019; Silver et al., 2021, 2022, 2023; Klein et al., 2021). That is, it may be that irritability assessed observationally captures behaviors associated with temper loss, whereas parent-reported irritability is more closely related to tonic irritability. My studies were not designed to integrate different measures of irritability, although a better understanding of how to do so toward maximizing predictive validity would be useful to the field.

Study 3

In Study 3 (Chapter 4; Mohamed Ali et al., in press), I found associations between early irritability and neural markers of risk: Age 3 irritability predicted decreased activation in the dlPFC in response to maternal criticism, specifically among adolescents who reported a more positive relationship with their mothers. Activation of the dlPFC during emotionally evocative tasks is associated with engagement in cognitive

reappraisal, an effortful emotion regulation strategy in which one reinterprets the meaning of stimuli to modify their emotional response (Ochsner & Gross, 2005). Decreased dlPFC activation has been demonstrated in depression (Hooley et al., 2005; Koenigs & Grafman, 2009a), suggesting that alterations in the functional activity of this region may be a mechanism that underlies vulnerability to psychopathology.

While I expected irritability to be associated with decreased dlPFC activation to maternal criticism, I hypothesized that youths' perceptions of a positive parent-child relationship quality would moderate this relationship, such that it would be weaker for youths who reported more positive maternal care. This particular hypothesis was again informed by past work that emphasizes the role of positive parenting in mitigating vulnerability conferred by temperament traits characterized by negative emotionality (Slagt, Dubas, Deković, et al., 2016). Contrary to my hypothesis, I found that the negative relationship between early irritability and dlPFC activation was stronger among youth reporting greater maternal care. Although surprising at first, given that this was a nonclinical sample, this finding may reflect the use of irritable youths' disengagement, or distraction, from emotionally evocative stimuli as an emotion regulation strategy (Lee et al., 2015; Rice et al., 2007; Sheppes & Levin, 2013). Past work suggests that, under certain conditions, individuals prefer disengagement to effortful cognitive reappraisal as a regulatory strategy, and that disengagement is effective in the short-term (Rice et al., 2007; Sheppes & Levin, 2013). It may be that irritable youth, particularly in non-referred samples, respond to maternal criticism by disengaging from such stimuli. Alternatively,

in a generally positive maternal care environment, youth may be less likely to engage in effortful processing in response to negative maternal feedback. Future work that incorporates measures of emotional regulation may be especially important towards examining these possibilities. Nevertheless, this study points to neural correlates of irritability among typically developing children, further supporting the validity of conceptualizing irritability as a temperamental trait reflecting context-inappropriate anger.

Integration

I used a longitudinal, multimethod, multi-informant design to conduct three studies focused on the developmental psychopathology of irritability indexed via a novel laboratory observational measure of irritability. Across my studies, I show that early irritability viewed from a developmental psychopathology perspective is a unique predictor of later psychopathology symptoms (Mohamed Ali et al., 2021), shows relative stability in childhood, interacts with environmental factors that shape its continuity/discontinuity (Mohamed Ali, et al., in preparation), and is associated with alterations in neural functioning that have been implicated in emotion dysregulation and in the etiology of psychopathology (Mohamed Ali et al., in press). Together, my findings suggest that differences in the experience of irritability emerge early in life and may reflect etiological pathways that underlie risk and contribute to the development of psychopathology in later life.

Based on current literature supporting the transdiagnostic relevance of irritability (Beauchaine & Tackett, 2019; Brotman, Kircanski, Stringaris, et al., 2017; Klein et al., 2021), I expected irritability to be similarly associated with symptoms of many forms of psychopathology, and with alterations in neural activity of brain regions implicated in psychopathology during emotionally evocative tasks. Interestingly, the strength of associations between irritability and outcomes of interest varied by index of irritability, symptom cluster predicted, child age, and moderating variables, speaking to the complex and dynamic relationships between person and context as emphasized in a developmental psychopathology framework.

In particular, observer-rated irritability at ages 3 and 5 consistently added to the prediction of externalizing relative to internalizing symptoms. In contrast, parent-report measures, specifically the CBQ Anger/Frustration scale, were more consistently related to parent-reported symptoms of depression. Of note, converging evidence pointed to the robustness of observer-rated irritability as a predictor of symptoms of inattention/hyperactivity. While I did not design my program of research to directly compare the performance of different indices of irritability, these findings can be interpreted in the context of past work that has done so. That is, Dougherty and colleagues (2021) found that existing measures commonly used to assess irritability capture severe, or clinically relevant, manifestations of irritability, and are unreliable at lower levels of irritability. As such, it may be that unprovoked expressions of anger captured by the observational index of irritability reflect early emerging emotional

reactivity that is particularly relevant to the etiology of ADHD (Albrecht, Uebel-Von Sandersleben, Gevensleben, & Rothenberger, 2015). With respect to parent-reported irritability, it may be that such measures are capturing manifestations of irritability in interpersonal contexts, which may be more relevant to internalizing than externalizing psychopathology.

Irritability, assessed observationally, was relatively stable in early childhood, further supporting its conceptualization as a temperamental trait. While I did not examine its stability into early adolescence, observer-rated irritability was associated with alterations in prefrontal functional activity, which may represent an endophenotype of emotion dysregulation (Phillips et al., 2003; Uchida et al., 2014). In line with the role of environmental factors in shaping the development of vulnerability markers, I expected positive caregiving to predict more adaptive patterns of brain functional activity during the processing of emotionally valenced stimuli. That is, I hypothesized that the strength of the negative associations between irritability and dlPFC activation would be weaker in the context of high maternal care. However, findings from Studies 2 and 3 did not support these hypotheses. Indices of positive parenting (i.e., observed sensitive and less interfering parenting, youth-reported maternal care) were associated with indicators of maladaptation (i.e., continuity of irritability, stronger irritability-prefrontal activation during processing of maternal criticism). These unexpected findings point to nuances in the role of parenting in shaping the development of irritability. For instance, it could be that sensitive and unintrusive parenting is associated with crystallization of children's

temperament, reflected as greater stability of early irritability. Interpreting the irritability-dlPFC activation finding is challenging given the somewhat mixed literature on the implications of reduced dlPFC activation. Most past work suggests that reduced dlPFC activation reflects poorer cognitive reappraisal of emotionally valenced stimuli, and as such poorer emotion regulation (Banks et al., 2007; Golkar et al., 2012; Hooley et al., 2009, 2005; Koenigs & Grafman, 2009a). Conversely, a small body of literature suggests that decreased dlPFC activation may reflect disengagement from emotionally salient stimuli, which may serve as a short-term emotion regulation strategy (Lee et al., 2015; Parsafar, Fontanilla, & Davis, 2019; Rice, Levine, & Pizarro, 2007). Thus, it may be that irritable youth who perceive their mothers to be caring may use distraction as an emotion regulation strategy to disengage from negative maternal feedback. Exploring whether the moderating effect of perceived maternal care relates to adaptive or maladaptive behavioral outcomes could serve to clarify which interpretation is more relevant.

The studies in this dissertation contribute to the burgeoning study of irritability in several ways. The observational assessment of irritability overcomes important methodological challenges, including the potential biases of parent-reported child behavior (Clark, Durbin, Donnellan, & Neppl, 2017; De Los Reyes & Kazdin, 2005; Durbin & Wilson, 2012; Goodman et al., 2011; Hayden, Durbin, Klein, & Olino, 2010), and limited sensitivity of existing tools in capturing the full continuum of irritability (Dougherty et al., 2021). My examination of the stability of irritability contributes to bridging current gaps in our understanding of the typical development of this trait in

childhood, an area of study that has been largely overlooked to date. Further, my findings suggest a role of early irritability-parenting interactions in predicting irritability in later childhood. Additionally, to my knowledge, Study 3 is the first to examine the association between irritability and neural processing of interpersonally relevant feedback, which can greatly inform our understanding of the influence of parenting on the development of irritable youth. Past work has largely investigated irritability-neural functioning relationships during executive functioning tasks (e.g., Go/No-go task, Stroop task), and neural networks recruited during such tasks may differ from those that are recruited during processing of interpersonally relevant information (Delmonte et al., 2012; Kohls et al., 2009; Rademacher et al., 2010). Here, I offer evidence to support the relevance of trait irritability to the processing of parental feedback.

Limitations and Future Directions

The studies described herein have strengths that have been previously discussed in their respective chapters. Collectively, these studies share additional strengths that I will briefly review here. The longitudinal design of this research allowed me to programmatically build on previous findings and study the convergence of the predictive validity of observer-rated irritability. Moreover, I used a large sample of community-dwelling children across these studies which allowed me to examine the normative development of irritability. The high retention rate of this sample is also worth noting as a strength as it limits bias due to attrition and adequate power is maintained.

Despite these methodological strengths, a discussion of limitations is warranted. Most importantly, I was interested in studying irritability dimensionally and in children who were developing typically to better understand its normative development. However, although all children were free of psychiatric diagnoses at baseline, I did not examine onset of disorder at follow-ups; therefore, children who developed psychopathology in later childhood were likely included and may have influenced irritability-psychopathology associations. I did not distinguish between phasic and tonic irritability in my work, although past work suggests that these components have unique associations with psychopathology risk. In future research, examining how observer-rated irritability relates to tonic and phasic irritability would be useful. In addition, I characterized irritability during the early childhood window; exploring trajectories of irritability as children mature into adolescence and pubertal development will be important from a developmental psychopathology perspective. Examining bidirectional associations between irritability and parenting is also important, given the well-established role of the early caregiving environment in shaping children's outcomes. In particular, a cross-lagged analysis in which irritability and dimensions of parenting are assessed at multiple timepoints can serve to answer important questions raised in this dissertation. Finally, my sample was largely homogeneous and consisted of predominantly White families of middle to upper-middle socioeconomic status, which precludes the generalizability of these findings. Replication of this work in more diverse samples is needed.

Conclusions

Across the three studies described in this dissertation, I found evidence to support a novel conceptualization of irritability as a temperamental trait that reflects maladaptation in the experience and expression of anger. Irritability assessed observationally in this manner was associated with later risk for psychopathology, was relatively stable, and showed meaningful neural correlates that have previously been implicated in emotion dysregulation. Interest in irritability has rapidly grown in recent years, arguably outpacing measurement concerns; my findings highlight the need to consider measurement issues in this burgeoning field and the utility of a developmental psychopathology approach to studying this important construct.

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Appendices

Ethics Approvals

Office of Research Ethics

The University of Western Ontario
Room 00045 Dental Sciences Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. E.P. Hayden

Review Number: 15121S **Review Level:** Full Board

Review Date: May 2, 2008

Protocol Title: Gene-Environment Interplay and the Development of Child Temperament

Department and Institution: Psychology, University of Western Ontario

Sponsor: CANADIAN INSTITUTE OF HEALTH RESEARCH

Ethics Approval Date: June 11, 2008 **Expiry Date:** July 31, 2013

Documents Reviewed and Approved: UWO Protocol, Letter of Information and Consent (Parent Consent for Self), Letter of Information and Consent (Parent Consent for Child), Advertisement.

Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Non-Medical Research Involving Human Subjects (NMREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the applicable laws and regulations of Ontario has granted approval to the above named research study on the approval date noted above.

This approval shall remain valid until the expiry date noted above assuming timely and acceptable responses to the NMREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the study or consent form may be initiated without prior written approval from the NMREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the NMREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the NMREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the NMREB.

[redacted]

Chair of NMREB: Dr. Jerry Paquette

Ethics Officer to Contact for Further Information			
☑ Grace Kelly (grace.kelly@uwo.ca)	☐ Janice Sutherland (jsutherl@uwo.ca)	☐ Elizabeth Wambolt (ewambolt@uwo.ca)	☐ Denise Grafton (dgrafton@uwo.ca)

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cc: ORE File

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: Prof. Elizabeth Hayden
Department & Institution: Social Science\Psychology,Western University

Review Type: Full Board
HSREB File Number: 106617
Study Title: Children's brain and hormonal responses to mild stress
Sponsor: Ontario Mental Heath Foundation

HSREB Initial Approval Date: August 18, 2015
HSREB Expiry Date: August 18, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Questionnaire Package - Caregiver Report on Self	2015/04/06
Instruments	Questionnaire Package - Child Report on Self	2015/04/06
Instruments	Questionnaire Package - Caregiver Report on Child	2015/04/06
Assent		2015/05/15
Other	Resources for Local Mental Health Services and Other Concerns	2015/05/15
Other	Qs Child Report on Self	2015/05/15
Other	Qs Caregiver Report on Child	2015/05/15
Other	Qs Caregiver Report on Self	2015/05/15
Other	Debriefing Script for TSST	2015/05/15
Recruitment Items	Recruitment Letter Template	2015/05/15
Recruitment Items	OMHF Recruitment Email Template	2015/05/15
Recruitment Items	Recruitment Telephone Script	2015/05/15
Western University Protocol	Received May 15, 2015	2015/05/15
Letter of Information & Consent	Caregiver Consent for Child	2015/08/18
Letter of Information & Consent	Caregiver Consent for Self	2015/08/18

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Ethics Officer, on behalf of Dr. Doreen Matson, HSREB Vice Chair

Ethics Officer to Contact for Further Information

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Western Research

Research Ethics

Western University Non-Medical Research Ethics Board
NMREB Amendment Approval Notice

Principal Investigator: Prof. Elizabeth Hayden
Department & Institution: Social Science\Psychology,Western University

NMREB File Number: 5246
Study Title: Gene-Environment Interplay and the Development of Child Temperament - 15121S
Sponsor: Canadian Institutes of Health Research

NMREB Revision Approval Date: May 17, 2017
NMREB Expiry Date: June 11, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Assent	T4	2017/03/31
Recruitment Items	Telephone Script and Email Script T4	2017/03/31
Other	Child Report T4	2017/03/31
Other	Caregiver Report on Child T4	2017/03/31
Other	Caregiver Report on Self T4	2017/03/31
Revised Western University Protocol		2017/03/31
Revised Letter of Information & Consent	Caregiver Consent	2017/03/31
Revised Caregiver Letter of Information & Consent	Caregiver Consent	2017/03/31

The Western University Non-Medical Science Research Ethics Board (NMREB) has reviewed and approved the amendment to the above named study, as of the NMREB Amendment Approval Date noted above.

NMREB approval for this study remains valid until the NMREB Expiry Date noted above, conditional to timely submission and acceptance of NMREB Continuing Ethics Review.

The Western University NMREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the Ontario Personal Health Information Protection Act (PHIPA, 2004), and the applicable laws and regulations of Ontario.

Members of the NMREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The NMREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000941.

[redacted]

Ethics Officer, on behalf of Dr. Riley Hinson, NMREB Chair
EO: Erika Basile ___ Grace Kelly _V_ Katelyn Harris___ Nicola Morphet ___ Karen Gopaul ___

Curriculum Vitae

OLA MOHAMED ALI, *Hons.* B.Sc., M.Sc

Education

Doctor of Philosophy, Clinical Science and Psychopathology **2018 - Present**
University of Western Ontario, London, Ontario
Dissertation title: Childhood Irritability: A Developmental Psychopathology Perspective
Supervisor: Elizabeth P. Hayden, Ph.D.

Master's of Science, Psychology (Clinical) **2018**
University of Western Ontario, London, Ontario
Thesis: Associations between white matter microstructure of the cortico-limbic pathway and internalizing symptoms in young girls
Supervisor: Elizabeth Hayden, Ph.D.

Master's of Science, Psychiatry **2015**
McGill University, Montreal, Quebec
Thesis: Effects of Atypical Antipsychotics and Schizotypy on Indexes of Semantic Processing
Supervisor: Bruno J. Debruille, MD, FRCP

Honors Bachelor of Science, Psychology, Neuroscience & Behavior **2012**
Minor in Peace Studies
McMaster University, Hamilton, Ontario
Hons. Thesis: Coping with Chronic Pain: Retrospective analysis of the Chronic Pain Coping Inventory (CPCI)
Supervisor: Eleni G. Hapidou, Ph.D., C. Psych

Awards and Distinctions

Canada Graduate Scholarship, Doctoral ($105,000) **2020-2023**
Social Science and Humanities Research Council

Vanier Graduate Scholarship (Nominated) **2019**
The Government of Canada

Ontario Graduate Scholarship ($15,000) **2019-2020**
Ministries of Colleges and Universities, Ontario

Experiential Opportunities Fund ($200) **2019**
University of Western Ontario

Ralph S. Devereux Award in Psychology ($1600) **2017-2018**
University of Western Ontario

Graduate Research Award ($200) **2018**
University of Western Ontario

Graduate Research Fellowship ($10,000) **2016 -2019**
Children's Health Research Institute

Faculty of Medicine International Travel Award ($1900) **2014**
McGill University

Graduate Excellence award ($2025) **2013**
McGill University

Dean's Honor List **2010-2012**
McMaster University

McMaster President's Entrance Award ($6000) **2008**
McMaster University

Research Experience

Published Peer Review Articles

1. **Mohamed Ali, O.,** Vandermeer, M. R. J., Liu, P., Joanisse, M. F., Barch, D. M. & Hayden, E. P. (2023). Associations between Childhood Irritability and Neural Reactivity to Maternal Feedback in Adolescence. *Biological Psychology.*

2. Gabel, L. N., **Mohamed Ali, O.,** Kotelnikova, Y., Tremblay, P. F., Stanton, K. J., Durbin, C. E. & Hayden, E. P. (2023) Children's Early Emotional Reactivity to Standardized Laboratory Stimuli Predicts Internalizing and Externalizing Symptoms in Later Development. *Social Development*

3. **Mohamed Ali, O.,** Borg Debono, V., Anthonypillai, J., Hapidou, E. G., (2022). A Qualitative Study of the Impact of the COVID-19 Pandemic on a Sample of Chronic Pain Patients. *Journal of Patient Experience.*

4. Vandermeer, M. R. J., Liu, P., **Ali, O. M.,** Daoust, A., Joanisse, M. F., Barch, D., & Hayden, E. P. (2022). Children's Neural Reactivity to Maternal Praise and Criticism: Associations with Early Depressive Symptoms and Maternal Depression. *Development & Psychopathology*

5. **Mohamed Ali, O.**, Gabel, L. N., Stanton, K., Kaufman, E. A., Klein, D. N. & Hayden, E. P. (2021). Observational measures of early irritability predict children's psychopathology risk. *Development and Psychopathology*.

6. **Mohamed Ali, O.,** Kotelnikova, Y., Kryski, K. R., Durbin, C. E. & Hayden, E. P. (2021). Parent personality and children's inattention/hyperactivity are related via early caregiving. *Journal of Infant and Child Development*. https://doi.org/10.1002/icd.2220

7. Liu, P., Vandermeer, M. R. J., **Mohamed Ali, O**., Daoust, A. R., Joanisse, M. F., Barch, D. M., Hayden, E. P. (2021). Maternal depression, child temperament, and early life stress predict never-depressed preadolescents' functional connectivity during a negative mood induction. *Clinical Psychological Science.* https://doi.org/10.1177/21677026211016419

8. Vandermeer, M. R. J., Liu, P., **Ali, O. M**., Daoust, A. R., Joanisse, M. F., Barch, D. M., & Hayden, E. P. (2020). Orbitofrontal cortex grey matter volume is related to children's depressive symptoms. *NeuroImage: Clinical, 102395.* https://doi.org/10.1016/j.nicl.2020.102395

9. **Ali, O. M.,** Kassie, S., Luthra, V., Karrani, A., Orr, K., Alsaadi, T., & Arida, A. (2020). Repetitive transcranial magnetic stimulation in the treatment of major depressive disorder: Preliminary results from the United Arab Emirates. *Hamdan Medical Journal, 13(1), 46.*

10. **Ali, O. M.,** Vandermeer, M. R., Sheikh, H. I., Joanisse, M. F. & Hayden, E. P. (2019). Girls' internalizing symptoms and white matter tracts in Cortico-Limbic circuitry. *NeuroImage: Clinical*, 101650.

11. Alsaadi, T., Kassie, S., **Mohamed Ali, O.**, Mozahem, K., Al Fardan, S., & Ahmed, A. M. (2019). Psychiatric Comorbidity in Neurological Disorders: Towards a Multidiciplinary Approach to Illness Management in the United Arab Emirates. *Frontiers in psychiatry, 10, 263.*

12. Fernandez Cruz, A.L., **Ali, O**. **M.**, Asare, G., Whyte, M. S., Walpolla, I., Segal, J. & Debruille, J.B., (2016), Embrained drives to play extraordinary roles predict schizotypal traits in the general population. *Npj Schizophrenia (2), doi:10.1038/npjschz.2016.35*

13. Gu, V., **Mohamed Ali, O**., L'Abbée Lacas, K. & Debruille, J. B. (2014). Investigating the effects of antipsychotics and schizotypy on the N400 using event-related potentials and semantic categorization. *J. Vis. Exp.* (93), e52082, doi:10.3791/52082

Manuscripts In Preparation

1. **Mohamed Ali, O.,** Gabel, L. N., Stanton, K. & Hayden, E. P. (In Preparation). Childhood Irritability: Temporal stability and associations with psychopathology risk.

2. Vandermeer, M. R. J., Liu, P., **Mohamed Ali, O.,** Daoust, A. R., Joanisse, M. F., Barch, D. A., & Hayden, E. P. (In Preparation). Resting state functional connectivity as a putative marker of depression vulnerability in never-depressed youth.

Book Chapters

1. **Ali, O. M**. (2020). Behavioral inhibition/activation, personality correlates of. In B. J. Carducci (Editor-in-Chief) & A. Di Fabio, D. H. Saklofske, & C. Stough (Vol. Eds.), *The Wiley-Blackwell encyclopedia of personality and individual differences: Vol. III. Personality processes and individual differences*. Hoboken, NJ: John Wiley & Sons.

Conference Presentations

1. **Mohamed Ali, O.,** Vandermeer, M. R. J., Daoust, A. R., Liu, P., Joanisse, M. F., Barch, D. M. & Hayden, E. P. (September, 2021). *The association between perceived parent-child relationship quality and adolescent reactivity to maternal feedback is moderated by early irritability.* Thirty-Fourth Annual Meeting of the Society for Research in Psychopathology. Virtual.

2. **Mohamed Ali, O.,** Stanton, K., Kaufman, E. A., Klein, D. N., & Hayden, E. P. (2020). *Observational Measures of Early Irritability Predict Children's Psychopathology Risk*. Thirty Second Annual meeting of the Association of Psychological Science. Virtual.

3. **Mohamed Ali, O.,** Vandermeer, M. R., Daoust, A. R., Liu, P., Kryski, K. R., Joanisse, M. F., Barch, D. M., & Hayden, E. P. (2019). *Associations between early parenting and children's neural development*. Thirty Third Annual Meeting of the Society for Research in Psychopathology, Buffalo, NY, USA.

4. **Mohamed Ali, O.**, Vandermeer, M., R., J., Sheikh, H., I., Mackrell, S., V., M., Joanisse, M., F. & Hayden, E. P., (2018). *Associations between elevated internalizing symptoms during early childhood and integrity of white matter tracts in cortico-limbic circuitry*. Poster presented at the annual meeting of the Flux Society, Berlin, Germany.

5. **Mohamed Ali, O**., Kryski, K. R., Durbin, C. E. & Hayden, E. P., (2018). *Caregiver personality and child temperament interact to predict negative parenting.* Thirty Second Annual Meeting of the Society for Research in Psychopathology, Indianapolis, IN.

6. Vandermeer, M. R. J., Daoust, A. R., **Mohamed Ali, O**., Joanisse, M. F., Barch, D. M. & Hayden, E. P., (2018). Gray matter concentrations in never-depressed children at risk for depression. Annual Meeting of the Flux Congress 2018, Berlin, Germany.

7. Alsaadi T., Kassie S., **Mohamed Ali O.**, Mozahem K., Al Fardan S. & Ahmed A. M., (2018). Psychiatric comorbidity in neurological disorders: Towards a

multidisciplinary approach to illness management in the United Arab Emirates. *Front. Hum. Neurosci. Conference Abstract: 3rd International Conference on Educational Neuroscience.* doi: 10.3389/conf.fnhum.2018.225.00010

Teaching Experience

Psychological Assessment Practicum **2019 – 2020**
(Graduate; PSYCHOL 9900)
Clinical Science & Psychopathology, University of Western Ontario
Role: Teaching Assistant
Instructor: Elizabeth Hayden Ph.D., & Erin Kaufman, Ph.D.

Exceptional Children: Behavioral Disorders **Winter 2019**
(Undergraduate; PSYCHOL 2042)
Department of Psychology, University of Western Ontario
Role: Teaching Assistant
Instructor: Jeffrey St. Pierre Ph.D., C. Psych

Research in Developmental Cognitive Neuroscience **Winter 2018**
(Undergraduate; PSYCHOL 3485)
Department of Psychology, University of Western Ontario
Role: Teaching Assistant
Instructor: Niki Hosseini-Kamkar (Ph.D. Candidate)

Abnormal Child Psychology **Fall 2016**
(Undergraduate; PSYCHOL 2320)
Department of Psychology, University of Western Ontario
Role: Teaching Assistant
Instructor: Elizabeth Hayden, Ph.D.

Professional Service

Public Lectures

Public Speaking Anxiety – Workshop **February 2021**
Virtual
Advocacy Through Action Lecture Series

Navigating the Mental Health System **February 2021**
Virtual

Advocacy Through Action Lecture Series

For Fast Acting Relief, Try Slowing Down: Coping Effectively with Chronic Pain **March 2019**
London Public Library Central Branch
Advocacy Through Action Lecture Series

Public Speaking Anxiety – Workshop **October 2019**
University of Western Ontario
Laura Evans Public Workshops

Assertiveness – Workshop **November 2019**
University of Western Ontario
Laura Evans Public Workshops

Peer Review Experience

Reviewer **2016- 2021**
Western Undergraduate Psychology Journal- University of Western Ontario

Ad-Hoc Manuscript Reviewer **2020**
Clinical Psychological Science

Ad-Hoc Manuscript Reviewer **2020**
Development and Psychopathology

Ad-Hoc Manuscript Reviewer **2020**
Child Psychiatry and Human Development

Professional Associations

Society for Research in Psychopathology	2017 – 2022
Association for Psychological Science	2018 – 2022
Flux: Society for Developmental Cognitive Neuroscience	2018 – 2019