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Empathy and Consistency in Parenting: A Biopsychosocial Model for the Transmission of Depression

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Abstract

Depression in children and adolescents is a prevalent, recurrent, and frequently chronic disorder, representing a considerable public health burden (Birmaher, Ryan, Williamson, Brent, & Kaufman, 2005; Costello et al., 2002). Consequently, an understanding of the disorder is critical for future intervention and prevention efforts. Previous research attempting to clarify family factors implicated in the transmission of depression from parents to youths has tended to focus on impairments in caregiving quality (such as parental warmth or harshness) for conferring risk. However, less work has examined dispositional characteristics of parents or considered other aspects of parenting behaviors beyond quality that might affect physiological and psychological processes implicated in depression. Across four studies, the current work sought to address this gap by exploring parental empathy as a dispositional characteristic of parents and interaction consistency as a structural component of families—two novel dimensions of family life—in relation to cellular inflammatory and emotion regulatory pathways emphasized in a biopsychosocial model of the transmission of depression. In a sample of children with asthma, the first study found that children whose parents demonstrated greater empathy (in the form of perspective-taking) had fewer internalizing symptoms and showed smaller asthma-relevant proinflammatory responses across a variety of functional immune assays. In a sample of medically healthy families, the second study then considered how youth depression and parental empathy might affect *parents*, revealing that parents who were higher in empathy showed greater inflammatory cytokine production when their children reported high levels of depressive symptoms, whereas less empathic parents showed the opposite pattern. Given this hidden physiological cost of empathy, the third study turned to an investigation of behavioral consistency in families as another potential contributor to youth depression, finding that greater

variability in daily interactions between parents and youths predicted youths' depression-relevant stimulated production of proinflammatory cytokines. Lastly, the fourth study tested a combined model for the transmission of depressive symptoms from parents to children through disruptions to behavioral consistency (in the form of family routines) and effects on inflammation and emotion regulation, showing that family routines accounted for part of the association between parent- and youth-depressive symptoms. Together, this set of studies identified new dimensions of family life implicated in the development of youth depression, while simultaneously exploring connections to important inflammatory and emotion regulatory processes.

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Chapter 1: General Introduction

Depression in Youths

Depression in children and adolescents (hereafter referred to as 'youths') is a prevalent, recurrent, and frequently chronic disorder, representing a considerable public health burden (Birmaher, Ryan, Williamson, Brent, & Kaufman, 2005; Costello et al., 2002). Approximately 20% of individuals will meet full diagnostic criteria for major depressive disorder at least once by age 18 (Lewinsohn, Rohde, Seeley, & Fischer, 1993). Once diagnosed, these youths also have a cumulative probability of recurrence of 40% by two years and 70% by five years (Birmaher et al., 1996; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000), as well as a two-fold increased chance of developing major depression as adults (Weissman et al., 1999). The extent of youth depression is clearly considerable. Moreover, its impact can be tragic. Depression places youths at greater risk for psychiatric comorbidity, substance use, and suicide, the third most common cause of death among individuals aged 10-24 (Angold & Costella, 1993; Galaif, Sussman, Newcomb, & Locke, 2007; Miniño, 2010; Rohde, Lewinsohn, & Seeley, 1991). It may also compound comorbid medical problems. For asthma—one of the most common chronic illness of childhood (National Center for Health Statistics (U.S.). Division of Health Interview Statistics, 2013) —depressive symptoms are associated with more frequent hospital visits (Ahmedani, Peterson, Wells, & Williams, 2013), greater medication non-compliance (DiMatteo, Lepper, & Croghan, 2000), greater social and educational impairment (Gutstadt et al., 1989), and increased risk of dying from asthma-related causes (Strunk, Mrazek, Fuhrmann, & LaBrecque, 1985). A better understanding of the etiology of depression in youths who have chronic illnesses as well as in those who do not is therefore vital to developing and expanding interventions aimed at its prevention and treatment (Howe, 2003).

Parental depression is one key factor that predicts risk for youth depression (Goodman et al., 2011; Halligan, Murray, Martins, & Cooper, 2007; Hammen & Brennan, 2003), and, as such, it offers valuable insight into pathways that may contribute to the development of the disorder. Here, work on intergenerational transmission mechanisms highlight the significance of environmental factors in conveying risk. Although shared genes certainly play a critical role in depression (Lahey, van Hulle, Singh, Waldman, & Rathouz, 2011; P. Sullivan, Neale, & Kendler, 2000), genetics do not wholly, or even largely, account for risk. For example, work examining the children of twins by Silberg, Maes, & Eaves (2010) and Singh et al. (2010) revealed that the best fitting model of intergenerational transmission of depression was one that included environmental impairments only, rather than genetic predispositions or even joint genetic and environment liability. Similarly, Tully, Iacono, & McGue (2008) demonstrated that exposure to parental depression increased risk for youth depression regardless of shared genetic profiles. Thus, while the role of genetics in depression is clearly important, the focus of the current research is on the social environment factors that contribute to childhood depression.

A primary pathway for environmental risk for depression in children is through impairments to parenting behaviors (Lim, Wood, & Miller, 2008). Indeed, Hammen, Shih, & Brennan (2004) found that impoverished parenting behaviors, in the form of greater hostility/control and less warmth/acceptance—in conjunction with greater interpersonal stress—accounted for links between maternal depression and depression in youths. Drawing on multiple informants, Ge et al. (1994) similarly showed that harsher and more inconsistent parenting behaviors mediated the association between parental depressed mood and depressive symptoms in adolescents. Meta-analyses confirm that parents with depression demonstrate significantly more negative parenting behaviors, including more frequent hostile or intrusive behaviors and

expressions of negative affect (Lovejoy, Graczyk, O'Hare, & Neuman, 2000), and in turn, that behaviors relating to parental warmth, withdrawal, aversiveness, and over-involvement are reliably associated with youth depression (McLeod, Weisz, & Wood, 2007).

In this way, the *quality* of parental behaviors has generally been the focus of prior research on environmental effects in the intergenerational transmission of depression (Carroll et al., 2013). However, less work has examined dispositional characteristics of parents that may inform the expression of these parental behaviors or considered other aspects of parenting behaviors beyond their valence. This dissertation seeks to address some of these gaps by exploring an interpersonally-focused dispositional trait—*parental empathy*—and an additional dimension related to the structure (rather than quality) of family behaviors—*interaction consistency*—in relation to the transmission of depression.

New Mechanisms for Risk

Parental Empathy

Dispositional psychological traits of parents' likely shape the parenting behaviors they engage in and thus may also contribute to mental health outcomes in children. This notion has been supported by substantial research attesting to connections between parental personality characteristics and youth outcomes (Goldberg, 1990; Laible, Murphy, & Augustine, 2013), and is especially bolstered by work linking traits to particular parenting behaviors. Here, Mangelsdorf et al. (1990) have demonstrated that mothers' trait-levels of positive emotionality were associated with more positive parenting behaviors such as greater observed warmth and supportiveness during interactions with their infants. Wilson and Durbin (2012) have similarly found that higher trait-levels of orientation toward social interactions ("social closeness") were linked to greater observed parental responsiveness during interactions with young children.

Although there are many possible dispositional factors to investigate in the context of the intergenerational transmission of psychopathology, empathy may represent a key characteristic that incorporates the potent elements of the other constructs while focusing on narrowly-defined abilities (Morelli, Lieberman, & Zaki, 2015). Coming from the German word *Einfühlung*, meaning "feeling into" (Wispé, 1986), empathy refers to the trait tendencies of a person to both *affectively* experience emotions of concern at the suffering of others and to *cognitively* adopt the perspective of another (Davis, 1983). Across species and age groups, exhibitions of empathy are seen when there is greater 1) familiarity between individuals, 2) similarity between individuals, 3) implicit or explicit learning about empathy, 4) past experience with distress, and 5) salience of distress (Preston & de Waal, 2002). Thus, although empathy is not unique to the parenting environment, the parent-child relationship may be an especially germane context for displays of dispositional empathy because of overlap with many of these dimensions. Conceptually, empathy may be thought of as a higher-order trait that informs more proximal parenting behaviors, such that the ability to empathize and take the perspective of others may allow parents to be attuned to the needs of their children, and, as a result, provide more efficient and effective care. In these ways, aspects of dispositional empathy may overlap with parenting concepts, such as attachment (Bowlby, 1988) or mind-mindedness (Meins et al., 2002), or other personality constructs, like social closeness or positive affect (Morelli et al., 2015), while offering a more parsimonious construct (Preston & de Waal, 2002).

Parents' dispositional empathy may shape the family environment in ways that are relevant to youth mental health by facilitating greater parental responsiveness. For example, highly empathic parents may be more accurate in their assessment of their children's abilities and skilled at anticipating their needs. Accordingly, parents who are better able to empathize with

their children provide more attuned caregiving (Dix, 1992). They also show more harmonious interactions with their children, characterized by greater shared positive affect and mutual responsiveness (Kochanska, 1997). Impairments in empathy, in contrast, may obscure parents' ability to understand their children's experiences and to calibrate caregiving appropriately. At its most extreme, this lack of empathy may manifest in the maltreatment of children (Wiehe, 2003). However, even in more mild forms, impairments in parental empathy and perspective-taking abilities may have ramifications for the psychological and biological processes implicated in youth mental health. Indeed, lower parental empathy has been linked to children's higher internalizing and externalizing psychopathology symptoms (Feshbach, 1987), worse emotion regulation (Manczak, DeLongis, & Chen, 2016), and worse empathy (Eisenberg, Fabes, Schaller, Carlo, & Miller, 1991; Soenens, Duriez, Vansteenkiste, & Goossens, 2007; Strayer & Roberts, 2004).

Empathy may be especially relevant to the intergenerational transmission of depression because deficits in empathy are frequently found in depressed individuals. Schreiter, Pijnenborg, & Rot (2013) suggest that poor empathic abilities may account for the social impairment widely documented in depression (e.g. Joiner & Timmons, 2002). Compared to healthy controls, individuals with depression evince greater difficulty perceiving and understanding the mental states of others (L. Lee, Harkness, Sabbagh, & Jacobson, 2005; Y.-G. Wang, Wang, Chen, Zhu, & Wang, 2008) and interpreting social interactions correctly (Zobel et al., 2010). Moreover, these impairments persist even after depression has remitted and are associated with increased risk of relapse (Inoue, Yamada, & Kanba, 2006). Importantly, these deficits may have intergenerational effects. Thoma et al. (2011) suggest that impairments in empathy may explain why depressed mothers are less responsive to their infants' crying and, in turn, have children

who are less receptive to emotional cues than children of healthy mothers (Field, Diego, & Hernandez-Reif, 2009). Apter-Levy and colleagues (2013) have demonstrated that 6-year-old children of depressed mothers show lower behavioral empathy and social engagement than children of non-depressed mothers. Together, this research suggests that empathic deficits are associated with depression and that these deficits may have intergenerational consequences.

Consistency in Parent-Child Interactions

In addition to considering dispositional traits that may affect the quality of caregiving, investigating additional features of these caregiving behaviors themselves is also warranted in the study of the intergenerational transmission of depression. Here, another novel component of the risk pathway may come from disruptions to *structural* aspects of family relationships. In contrast to previous work focusing on the quality of family behaviors (such as warmth or harshness), the *consistency* of those behaviors may also be important for links between parenting and youth mental health. Here, consistency refers to the amount of variability in parenting interactions across time. For example, are interactions between parents and youths almost always positive, almost always negative, or do they vacillate between being positive and negative? Do they occur at predictable times each day? Is there an anticipated structure to interactions, such as around meals or after school? Across these various dimensions, more consistent contact between parents and youths may establish predictability within family relationships, which in turn is considered an important stabilizing dimension of family life (Boyce, Jensen, & James, 1983). Indeed, popular parenting literature frequently stresses the importance of cultivating consistent ways of interacting with children (e.g., S. H. Gookin & Gookin, 2011; Steinberg, 2004) and several lines of research support the notion that experiences that are predictable—even if uncontrollable—are less detrimental to mental and physical health processes than experiences

that are unpredictable (Abramson, Seligman, & Teasdale, 1978; Sapolsky, 1994; Tetrick & LaRocco, 1987; Tiggemann & Winefield, 1987). For these reasons, chaotic or capricious parenting styles are held as maladaptive forms of caregiving (F. E. M. Gardner, 1989; Ross & Hill, 2002).

Moreover, evidence is emerging that disruptions to consistency in family behaviors are linked to youth social/emotional functioning relevant to depression. Benson, Buehler, & Gerard (2008) demonstrated that sixth-grade children with mothers who were less consistent with rule-enforcement showed higher levels of both internalizing and externalizing symptoms. Similarly, Brody and Flor (1997) found that children in families with fewer predictable routines had worse behavioral self-control, which in turn was associated with more internalizing and externalizing symptoms and worse educational attainment. Furthermore, inconsistent disciplinary practices have been shown to hinder executive functioning and to predict more aversive parent-child interactions (C. H. Hughes & Ensor, 2009; Wahler & Dumas, 1986). Lastly, longitudinal work by Hightower (1990) has found that adolescents' reports of parental rule-setting inconsistency predicted more negative ratings of their mental health by expert judges at age 50. Together, parental empathy and behavioral consistency may represent novel affective and structural components of parent-child relationships that contribute to the intergenerational transmission of depression.

Psychological and Biological Pathways

Parental empathy and behavioral consistency may confer risk for youth depression both by affecting psychosocial processes and by shaping internal biological factors, such as calibration of children's stress response systems (Del Giudice, Ellis, & Shirtcliff, 2011). Indeed, the most prominent models of how environmental factors associated with parental depression

lead to youth depression include both psychological and physiological mechanisms (Goodman & Gotlib, 1999). By providing more attuned care and fostering consistency, parental empathy and behavioral consistency may exert a stabilizing force for youths that facilitate more adaptive biological and psychological profiles. I suggest that disruptions to these processes may "get under the skin" through primary risk pathways that transduce external experiences into psychological and biological processes within youth, specifically, proinflammatory signaling and impairment to emotion regulation abilities. By focusing on these pathways, the current project not only extends research on family characteristics associated with youth depression but contributes to a mechanistic account of how these factors operate as well.

Inflammatory Processes

One important biological process implicated in the etiology of depression that may be affected by parents' traits and behaviors is inflammation. Two primary areas of research support this hypothesis: first, work suggesting that inflammatory processes play a critical role in depression and, second, research finding that chronic inflammation in children can be linked to psychosocial characteristics of their family environment. Briefly, when the body's inflammatory response is activated (such as by infection or injury), proinflammatory cytokines, such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are released and help coordinate responses of immune cells to destroy the infection or repair tissue damage (Kiecolt-Glaser & Glaser, 2002; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). (Anti-inflammatory cytokines, such as interleukin 10, are also released to dampen immune response and synthesize other cytokines.) Although acute immune activation is necessary to destroy infections and repair tissue damage, these processes can also be triggered and compounded by psychological threats (M. Maes et al., 1998; Segerstrom & Miller, 2004; Zapf, Seifert, Schmutte,

Mertini, & Holz, 2001), and over-activation of these responses across a prolonged period of time can lead to negative health consequences, including cardiovascular disease, diabetes, and death (Kiecolt-Glaser et al., 2002; Kiecolt-Glaser & Glaser, 2002). Indeed, working in conjunction with neuroendocrine processes, proinflammatory tendencies resulting from exposure to stress constitute one important pathway through which psychological adversity is believed to lead to greater incidence of diseases, including vascular diseases and autoimmune disorders (G. E. Miller, Chen, & Parker, 2011).

Within the context of psychological research, inflammation can be measured several ways. One approach is to assess the quantities of these cytokines that exist in peripheral blood, capturing levels of chronic, low grade inflammation (such as levels of circulating IL-6). Another approach is to examine inflammation functionally by assessing how primed immune cells are to respond to threats. Here, blood cells are cultured with mitogens that cells recognize as threats, such as a bacterial endotoxin like lipopolysaccaride (LPS), and then the magnitude with which these cells produce proinflammatory cytokines in response to the exposure is measured. Conceptually, the acute responses indexed by functional immune assays are believed to presage and contribute to levels of low-grade inflammation measured by circulating cytokines.

Depression and Inflammation

Corroborating the interconnected nature of inflammation and psychological experience, several converging findings suggest that depression and inflammation are intimately linked. First, individuals with depression who are otherwise medically healthy have been found to have elevated levels of systemic inflammation, indexed by circulating proinflammatory cytokines and acute-phase proteins (Dowlati et al., 2010; Ford & Erlinger, 2004; Gimeno et al., 2008; Herbert & Cohen, 1993; Howren, Lamkin, & Suls, 2009; Liu, Ho, & Mak, 2012; M. Maes et al., 1995;

Suarez, Krishan, & Lewis, 2003). In particular, individuals with depression have higher levels of IL-1, IL-6, TNF-α, and C-reactive protein (CRP) compared to individuals without depression. Second, rates of depression are disproportionately elevated in individuals with inflammatory diseases (Bruce, 2008). For example, depression is recognized as frequently comorbid with cardiovascular disease (McConnell, Jacka, Williams, Dodd, & Berk, 2005) and children with asthma have a two-fold higher prevalence of depressive/anxiety symptoms compared to children without asthma (Katon et al., 2007). Third, stimulation of inflammatory responses, such as by injecting healthy individuals with a bacterial endotoxin or administering cytokine-therapy for the treatment of cancers and certain infections, induces low mood and other depressive symptoms (Eisenberger, Inagaki, Mashal, & Irwin, 2010; Raison, Capuron, & Miller, 2006). Together, these results are consistent with the theory that proinflammatory signaling may not only result from—but may actually contribute to—the development of depression (Cicchetti, Wollman, Vitkovic, & Yirmiya, 1999; Felger & Lotrich, 2013; Raison & Miller, 2011).

Family Characteristics and Inflammation

In support of the potential role of parental empathy and behavioral consistency in predicting inflammatory processes, other characteristics of the family environment have been shown to relate to offspring's inflammation. For example, adults who grew up in conditions of low socioeconomic status showed a buffering of proinflammatory signaling if they also received high levels of maternal warmth and support (E. Chen, Miller, Kobor, & Cole, 2010). In contrast, adolescents raised by families characterized by high harshness and low support exhibited increasingly elevated proinflammatory profiles over 1.5 years (G. E. Miller & Chen, 2010). With regard to parental psychological characteristics, research by Wolf, Miller, and Chen (2008) demonstrated that parental depressive symptoms predicted increases in inflammatory markers in

both healthy children and children with asthma, even after statistically adjusting for children's own psychological states. Moreover, parental behavioral consistency has also been preliminarily linked to inflammatory processes. Prior research has demonstrated that greater family chaos—in concert with lower socioeconomic status—predicted greater IL-6 in youth (Schreier, Roy, Frimer, & Chen, 2014), and conversely, that in a sample of children with asthma, greater use of family routines was associated with decreases in stimulated production of an asthma-relevant cytokine, interleukin 13 (IL-13), over an 18-month period (Schreier & Chen, 2010). Importantly, causal inferences regarding family relationship and offspring inflammation have been strengthened by work suggesting that a parenting-focused intervention in an at-risk population of African American youth reduced six biomarkers of low-grade inflammation in the children (G. E. Miller, Brody, Yu, & Chen, 2014).

Emotion Regulation Processes

Of course, psychological processes are also critically important to youth depression. Although many psychological abnormalities are implicated in the disorder (such as negative cognitive biases or poor executive control), impairments in emotion regulation may be particularly relevant to the anticipated pathways involving parental empathy and behavioral consistency. Specifically, concentrating on emotion regulation unites the affective component of empathy with the focus on stability that is central to interaction regularity. Additionally, emotion regulation has implications for stress responsivity, which affects inflammatory processes previously discussed.

Depression and Emotion Regulation

As defined by Thompson (1994), emotion regulation encompasses "the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions,

especially their intensive and temporal features, to accomplish one's goals" (pp. 27-28). Perhaps not surprisingly, the selection and utilization of emotion regulation strategies are robustly linked with depression (Berking, Orth, Wupperman, Meier, & Caspar, 2008). In adults, individuals with current or remitted depression show a range of specific emotion regulation deficits, including a lack of inhibition of negative material, less use of reappraisal of situations, greater rumination, and greater use of emotional suppression (Joormann & Gotlib, 2010). Impairments are also found with regard to depression in youths (P. M. Cole, Luby, & Sullivan, 2008). For example, less inhibition of negative stimuli and greater reliance on emotional suppression have been demonstrated in samples of adolescents who are depressed (Betts, Gullone, & Allen, 2010). Additionally, Silk, Steinberg, and Morris (2003) found that depressive symptoms were correlated with emotion regulation strategies that were less effective at reducing negative affect (such as rumination and denial) in the daily lives of adolescents, as well as with greater emotional intensity and lability. For these reasons, emotion regulation is believed to be a key risk factor for the development of depression in youths, such that an inability to reduce sad affect or distress in appropriate ways presages the development of the disorder and may be seen as an important diathesis (Kovacs, Joormann, & Gotlib, 2008).

Family Characteristics and Emotion Regulation

Parental empathy may contribute to more optimal manifestations of emotion regulation by allowing parents to sensitively facilitate the development of more masterful self-regulatory strategies while signaling the availability of support (Fox & Calkins, 2003). Indeed, parent-child contact is believed to be an initial method of emotion regulation for infants (Field, 1996; Fox & Calkins, 2003; Gross & Thompson, 2006). As children grow more independent in late childhood and adolescence, the family context likely still provides important models, behaviors, and

reinforcements for emotion regulation skills and expectations (Morris, Silk, Steinberg, Myers, & Robinson, 2007). For these reasons, children with empathic parents may be more supported in their development and deployment of emotion regulation strategies, which in turn may protect them from depressive processes. In addition, regular family interactions may also affect emotion regulation abilities. In families characterized by consistent timing and quality of interactions, youth may have clear expectations for the availability of support, parental dependability, and their own behavior. In turn, these features may encourage perceptions of mastery and predictability—dimensions negatively associated with depression (Abramson et al., 1978).

Emotion Regulation and Biological Processes

By facilitating more adaptive emotional responses to stressful situations, regulation strategies may also have important ramifications for the biological processes relevant to depression discussed previously. Broadly, adaptive emotion regulation strategies, like reappraisal, reduce physiological responses to stress (Gross, 1998a; Hoyt et al., 2013). Consequently, greater use of these strategies may have protective effects on biological systems in ways that affect longer-term mental and physical health (E. Chen & Miller, 2012; E. Chen, Miller, Lachman, Gruenewald, & Seeman, 2012). With regards to inflammatory processes, research by Fuligini and colleagues has demonstrated that daily experiences of interpersonal stress and family burden among adolescents correspond to levels of low-grade inflammation (Fuligni, Telzer, Bower, Cole, et al., 2009a; Fuligni, Telzer, Bower, Irwin, et al., 2009b). Additionally, use of reappraisal (an adaptive emotion regulation strategy) has been shown to be associated with less low-grade inflammation in adults, whereas use of suppression (a maladaptive strategy) was shown to correspond to elevated levels of low-grade inflammation (Appleton, Buka, Loucks, Gilman, & Kubzansky, 2013). In these ways, inflammatory responses

and emotion regulation represent interconnected and important processes through which family characteristics of parental empathy and behavioral consistency may contribute to the development of youth depression.

The Current Studies

The current work presents a series of four studies that probe the roles of parental empathy and behavioral consistency during parent-youth interactions in contributing to risk for youth depressive symptoms via disruptions to inflammatory and emotion regulation processes. In the first study, I utilize a novel assessment of empathy to test whether parental empathy predicts youth internalizing symptoms and multiple inflammatory indicators in a sample of youth with asthma. Given the high levels of comorbidity with depressive disorders (Katon et al., 2007), higher disease impairment associated with depressive symptoms (Strunk et al., 1985), and hypothesized shared inflammatory risk pathways between asthma and depression (Van Lieshout, Bienenstock, & MacQueen, 2009), a sample of children with asthma provides a particularly relevant context in which to test links between family traits and youth psychological and physiological processes. At the same time, also examining associations in nonclinical samples allows for greater generalizability and assures that associations are not due to specific features of asthma. Thus, the remaining three studies utilize nonclinical samples. Here, in the second study, I then consider how youth depression and parental empathy may affect other family members by examining *parents'* inflammatory outcomes in light of youth depressive symptoms in a medically healthy sample. Finding that empathy may come at a cost for parents, for the third study, I turn to an investigation of behavioral consistency in families as another potential contributor to youth depression, examining whether variability in affective and temporal components of daily interactions between parents and youths predict youths' depression-relevant

stimulated production of pro-inflammatory cytokines. Lastly, the fourth study furthers an investigation of behavioral consistency by testing a combined model for the transmission of depressive symptoms from parents to children through disruptions to family routines and effects on inflammation and emotion regulation. Together, this set of studies seeks to assess parental empathy and consistency in parent-youth interactions as novel dimensions of family life implicated in the development of youth depression, while simultaneously considering inflammatory and emotion regulatory processes as focal mechanistic variables.

Chapter 2: Parental Empathy in the Context of Pediatric Asthma

As previously discussed, social environments of families leave significant legacies on the developmental trajectories of mental and physical health across the lifespan (Repetti, Taylor, & Seeman, 2002). Consequently, identifying dimensions of the parenting context that contribute to risk is a critical task of research. In this first study, I propose that parental empathy may represent an important parental dispositional trait to consider when seeking to explain connections between families and children's mental and physical health. In addition to examining youth internalizing psychopathology symptoms, I concentrate on associations with youths' inflammatory processes, as they are considered a key mechanistic pathway implicated in many of the same physical and mental health disorders that have also been associated with early family environments (Felger & Lotrich, 2013; Kern et al., 2013; G. E. Miller et al., 2011). Furthermore, I focus on a sample of youths with pediatric asthma, reflecting the significant overlap in risk between asthma and youth depression (Katon et al., 2007).

In addition to robust associations between inflammation and family characteristics previously discussed (G. E. Miller et al., 2014; G. E. Miller & Chen, 2010), preliminary support exists for the possibility that parental empathy, specifically, may relate to youth inflammation. In a study of medically healthy children, those children who had parents who reported higher levels of empathy showed lower levels of C-reactive protein (Manczak et al., 2016), an inflammatory biomarker that has been linked to depression as well as to physical health (Blake, Rifai, Buring, & Ridker, 2003; Byrne et al., 2013). Notably, these links were not accounted for by other aspects of the parenting context, including parental warmth or harshness, time spent with their child, or perceived stress. However, might similar associations with parental empathy exist within clinical populations and how might parental empathy relate to psychopathology symptoms?

Pediatric Asthma

For children with diseases driven by inflammatory processes, potential associations between family psychosocial characteristics and immune responses may be particularly consequential due to the clinical implications of heightened inflammation. Here, an examination of pediatric asthma is relevant, as it is one of the most common chronic diseases of childhood (National Center for Health Statistics (U.S.). Division of Health Interview Statistics, 2013) and is characterized by inflammation of the airways in response to allergens and other triggers. For these children, multiple aspects of the immune system work in concert to produce the inflammatory responses that underlie asthma. Briefly, exposure to antigens like dust mites or molds activates T helper (Th) cells—a key component in the adaptive immune system. Here, Th-1 cells initiate cellular immune responses and help to mobilize antiviral responses by secreting proteins known as cytokines, such as interferon-gamma (IFN –γ) and interleukin 10 (IL-10). Th-2 cells initiate humoral immune responses and include the secretion of interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), which are cytokines that promote inflammatory processes that result in airway constriction and the production of mucus. In asthma, although Th-2 pathways (and adaptive immunity) are generally the focus of research, exaggerated proinflammatory responses associated with innate immune system processes are thought to also contribute to allergic symptoms and disease responses (Jackson et al., 2008; Sigurs et al., 2005). This includes the activity of more widely studied inflammatory biomarkers like IL-6 or tumor necrosis factor-alpha (TNF-α), which are released when toll-like receptors (TLRs) on sentinel cells—like macrophages or dendritic cells—recognize conserved molecular patterns associated with pathogens or tissue damage.

In addition, inflammatory processes are regulated by glucocorticoids, such as cortisol, which are steroidal hormones that dampen inflammatory responses and contribute to metabolic functioning (Busillo & Cidlowski, 2013). Previous work has demonstrated that prolonged exposure to psychological stressors can result in reduced sensitivity to the anti-inflammatory signaling of glucocorticoids (G. E. Miller & Chen, 2010; G. E. Miller, Gaudin, Zysk, & Chen, 2009b; Rohleder, Marin, Ma, & Miller, 2009). Given that synthetic inhaled corticosteroids are commonly used as the first-line treatment for asthma flare-ups (National Heart, Lung, and Blood Institute, 2002), cortisol sensitivity represents another important biological process to study among children with asthma.

Not only may a pediatric asthma sample facilitate a consideration of links between parental empathy and multiple inflammatory processes, it may be particularly suited to investigating links with youth mental health processes as well. Like other chronic illnesses, asthma is associated with impairments and quality of life decrements for children (Merikallio, Mustalahti, Remes, Valovirta, & Kaila, 2005). Moreover, it is frequently comorbid with mental health disorders, possibly due to shared inflammatory mechanisms (Van Lieshout et al., 2009). One large representative sample found that children with asthma had significantly higher rates of depressive disorders than children without asthma (Blackman & Gurka, 2007). Indeed, children with asthma were found to have a two-fold higher prevalence of depressive/anxiety symptoms compared to healthy children (Katon et al., 2007), with co-morbid depression also associated with poorer functioning and greater mortality from asthma (Gutstadt et al., 1989; Strunk et al., 1985). For these reasons, then, a clinical sample of children with asthma provides a relevant, important test of links between parent empathy and both mental (e.g., internalizing symptoms) and physical (e.g., inflammatory biomarkers) health processes in children.

Assessment of Empathy

Thus far, parental empathy has most commonly been measured using self-report questionnaires, such as the Interpersonal Reactivity Index (Davis, 1983). One limitation to this approach, however, is that it may be subject to biased or inaccurate reporting, such as when respondents are influenced by the social desirability of their answers (Van de Mortel, 2008). A different type of assessment would be to look for evidence of empathic consideration in parents' actions or words, which might also have greater ecological validity reflecting how empathic processes operate within families. An example of such an approach would be to examine how parents describe significant life experiences as a way to reveal their values, cognitions, and meaning-making processes (E. Chen, McLean, & Miller, 2015; McAdams et al., 2008; McAdams, Dadabo, & Hanek, 2012). This procedure, which draws substantially from the narrative psychology tradition, typically involves participants describing important scenes from their lives through a semi-structured interview in which they are blind to the specific dimensions of interest. Responses are then coded for evidence of relevant psychosocial processes, such as orientation to personal growth versus security, prosocial values, or sequencing of positive versus negative components (Cox & McAdams, 2014; McAdams et al., 2012; McAdams & Guo, 2015). These types of narrative coding have been shown to contribute to the prediction of outcomes including depressive symptoms and satisfaction with life, above and beyond other self-report assessments (Manczak, Zapata-Gietl, & McAdams, 2014), and to predict mental health trajectories over the course of 7 years (Adler et al., 2015). Less work, however, has examined narrative codes in relation to physical health outcomes. For these reasons, coding evidence of parents' empathy as they discuss personal experiences would circumvent possible self-

presentation bias inherent in self-report questionnaires while also more closely reflecting empathy as it might be expressed within the family.

Thus the current study sought to test whether parental empathy—as captured during parents' conversations about challenging life experiences—would relate to psychological and inflammatory processes in a sample of youths diagnosed with asthma. I predicted that greater evidence of parents' perspective-taking during these interviews would relate to lower levels of internalizing symptoms in youths and to smaller stimulated cytokine production across a variety of antigens relevant to innate and adaptive immune responses. In addition, I hypothesized that these associations would be specific to parental empathy and would not be accounted for by more generally positive parenting behaviors, such as parental warmth.

Method

Participants

Children ages 9-17 who had physician-diagnosed asthma were recruited into a larger study of health disparities through one health care system and one federally-qualified health care center. One parent participated with each child. Families were required to be fluent in English and children were required to be free of acute respiratory illness at the time of the visit. This study was approved by the university's, the health system's, and the health center's Institutional Review Boards. Data from a baseline laboratory assessment was utilized for the present study. One hundred sixty-eight parent-child dyads participated in the psychosocial assessment (42% female children, 88% mothers), with biological data currently available for 130 dyads. Youths were on average 13.43 years old (*SD*=2.22) and parents were on average 45.54 years old (*SD*=6.00). Based on parent report, 66% percent of youths were Caucasian, 23% were African American, 13% were Hispanic, 11% were Asian, and 2% were Native American/Native

Alaskan/Native Hawaiian, with participants able to endorse multiple ethnicities. Parents had on average 16.52 years of education, with a range of 12-25 years.

Procedure

During the baseline laboratory visit, parents and youths provided written informed consent and assent and supplied demographic information. Parents and youths jointly reported on asthma medication use. Youths completed self-report questionnaires of internalizing symptoms and perceived parental warmth, and completed a blood draw. Parents completed a semi-structured interview to assess perspective-taking, described in more detail below.

Measures

Parental Empathy. Parents completed the Life Story Challenge Interview, a semi-structured interview developed for the current study, based on the "key scene" section of the Life Story Interview by McAdams (2008). Parents were asked to select two scenes from their lives that they remembered clearly in which they experienced some sort of challenge or struggle. They were asked to described the scene and discuss what they were thinking and feeling, as well as any ways in which they dealt with the experience. Following this, they were asked to reflect on how going through the experience affected their outlook on life as well as what their experiences might say about who they were as a person. They were instructed to first select one memory that involved a challenge or struggle relating to their family and then to select any other challenge or struggle from their adult life for the second scene. Common examples of challenges included the death of a loved one, losing a job, and health difficulties. These interviews were audio-recorded and then transcribed verbatim.

Using the transcribed interviews, each scene was coded for the extent to which the parent showed evidence of cognitive aspects of empathy (in the form of perspective-taking) during their

discussion, with each memory rated on a 3-point scale (0-2) for the extent to which the participant discussed the perspectives, viewpoints, or motivations of others involved in the challenging experience. (Affective dimensions of empathy, such as emotional concern, depend on nonobvious internal experiences and are not as readily visible in narrative discussions.) Here, participant responses had to demonstrate that they were moving beyond their own thoughts and feelings to acknowledge the ways in which events may be perceived by, or affect, another. Scenes that did not acknowledge perspectives of others received a score of 0, scenes that mentioned, but did not elaborate on the perspectives of others received a score of 1, and scenes that provided extensive consideration of another person's perspective received a score of 2. For example, a scene in which a mother discussed her daughter's fears about moving homes, including her daughter's mistaken belief that they would have to leave their dog behind, received a high score of 2 on perspective-taking. Importantly, parents were never prompted to consider the experiences of others during this interview, so any evidence of perspective-taking may be seen as occurring naturally. A total of 332 memories were provided.

All interviews were coded by the first author. Ninety-four memories (approximately 28%) were double coded by a trained research assistant to establish the reliability of the coding system. The intercoder correlation was .74. Disagreements within the 94 memories were resolved by discussion. Coders were blind to all participant information, including demographics, youth psychosocial responses, parental warmth, and asthma medication use. Codes on each of the two memories were averaged to create an overall empathy code for each parent (scores ranged from 0-2).

Youth Internalizing Symptoms. Youths completed the Anxious/Depressed subscale of the Youth Self Report (YSR; Achenbach & Rescorla, 2001), which assesses the extent to which

13 internalizing behaviors are characteristic of the youth for the past 6 months, including "I feel worthless or inferior" and "I cry a lot." Previous work has reported high comorbidity between anxiety and depressive disorders in children and adolescents (Brady & Kendall, 1992; Zahn-Waxler, Klimes-Dougan, & Slattery, 2000), suggesting that scales capturing internalizing symptoms may be more appropriate than considering depressive or anxiety symptoms separately for this age group. Reliability and validity of this measure are well-established, both for the YSR, broadly (Achenbach & Rescorla, 2001), and for the anxious/depressed subscale, specifically (Song, Singh, & Singer, 1994). The syndromal structure captured by the subscales has also been validated across 23 countries (Ivanova et al., 2007). Higher scores on this measure reflect greater internalizing symptoms (α =.86, current sample).

Cytokine Production. Antecubital blood was drawn into BD Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ) containing sodium heparin. Peripheral blood mononuclear cells (PBMCs) were isolated by density-gradient centrifugation according to the manufacturer's instructions and then dispensed into 12-well culture plates in the presence of several different mitogen compositions, assessing non-specific stimulation, adaptive immunity stimulation by asthma-relevant ligands, and innate immunity stimulation of proinflammatory cytokines. The extent to which glucocorticoids regulate inflammatory signaling (i.e., glucocorticoid sensitivity) was measured by repeating the innate immunity stimulation of proinflammatory cytokines in the presence of cortisol.

First, we measured Th-1 versus Th-2 cytokine production following non-specific stimulation by incubating $0.5x10^6$ PBMCs with 25 ng/mL of phorbol 12-myristate 13-acetate (PMA; Sigma-Aldrich, St. Louis, MO) + 1 ug/mL of ionomycin (INO; Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO_2, similar to previous studies (e.g., E. Chen, Fisher,

Bacharier, & Strunk, 2003; E. Chen et al., 2006). An unstimulated well with no mitogen but the same number of PBMCs was cultured under the same conditions. Following incubation, supernatants were harvested using centrifugation and frozen at -80°C until assayed in batch via electrochemiluminescence on a SECTOR Imager 2400A (Meso Scale Discovery, MSD). Assays were performed using MSD's Human Th-1/Th-2 7-Plex Tissue Culture Kit, which measures both Th-2 (IL-2, IL-4, IL-5, and IL-13) and Th-1 (IFN-γ, IL-10) cytokines in parallel. Mean inter-assay coefficients of variation ranged from 2.67-4.86%. Cytokine responses were quantified by subtracting values in the unstimulated wells from those in the PMA/INO wells.

Second, we measured Th-1 and Th-2 cytokine production in the context of asthma-specific ligands of cockroach and dust mite exposure (adaptive immunity). Here, $5x10^6$ PBMCs were dispensed into culture wells containing either 10 ug/mL of cockroach extract (50:50 mixture of American and German cockroach; Greer, Lenoir, NC) or 10 ug/mL of dust mite extract (50:50 mixture of *D. farinae* and *D. pteronyssinus*; Greer, Lenoir, NC), and incubated for 72 hours at 37°C in 5% CO_2, following protocols used in similar studies (Contreras et al., 2003; Wright et al., 2010). As before, an unstimulated well was included on the plate. Supernatants were assayed in batch using the same MSD platform and reagents as described above, capturing both Th-2 (IL-2, IL-4, IL-5, and IL-13) and Th-1 (IFN-γ, IL-10) cytokine production. Mean inter-assay coefficients of variation were 1.98-4.24%. Values in unstimulated wells were subtracted from values in active wells prior to analysis.

Third, we measured pro-inflammatory cytokine production for Toll-Like Receptor stimulation (innate immunity) by dispensing $0.5x10^6$ PBMCs into wells containing 100ug/mL of Poly I:C (double stranded RNA, which stimulates the TLR-3 pathway; Invivogen, San Diego, CA), as well as an unstimulated well. The plate was then incubated for 24 hours at 37°C in 5%

CO_2. Supernatants were assayed in batch using the Sector Imager and MSD's Human Pro-Inflammatory Tissue II Culture kit, which included measurement of IL-1β, IL-6, and TNF-α. Interassay coefficients of variation were 3.33-8.81%. As above, unstimulated values were subtracted from stimulated values prior to analysis.

Lastly, glucocorticoid sensitivity was measured by co-incubating $0.5x10^6$ PBMCs with 100ug/mL of Poly I:C, and $1.38x10^{-6}$ M hydrocortisone (Sigma-Aldrich, St. Louis, MO) for 24 hours at 37°C in 5% CO_2, similar to protocols in previous studies (G. E. Miller et al., 2009b; G. E. Miller & Chen, 2010). An unstimulated well was also included on the plate. Supernatants were assayed in batch using the MSD Human Pro-Inflammatory Tissue II Culture kit to measure IL-1β, IL-6, and TNF-α, as per above, and unstimulated values were subtracted out prior to analysis. Interassay coefficients of variation were 2.78-10.14% At the dose used, cortisol suppresses production of pro-inflammatory cytokines, so higher values of cytokine production can be interpreted as reflecting greater insensitivity to glucocorticoid inhibitory signals.

Parental Warmth. To test whether associations with parental empathy simply reflected a more generally positive relationship between parents and children, youths reported on their perceptions of parental warmth over the past year using a nine-item measure developed by Brody et al (2001). Youths rated the frequency of how often parents acted lovingly or supportively toward them on a 4-point scale (from "never" to "always"), including such items as "During the past 12 months, how often did your parent tell you s/he loves you?" or "During the past 12 months, when you and your parent spent time together, how often did your parent help you with something that was important to you?" The 1-year test–retest correlation on this measure has been reported as $r = .41$ (H. Kim, Ji, & Kao, 2011) and scores on this scale has been shown to relate to nurturing caregiving behaviors as well as lower levels of child psychopathology

symptoms (Brody et al., 2001; I. J. Kim et al., 2003). Higher scores on this measure reflect greater parental warmth (α =.91, current sample).

Covariates. Demographic covariates of youth age, gender, and ethnicity, parent gender and parent's years of education were collected during the laboratory visit. Whether or not youths were prescribed a beta-agonist or an inhaled steroid medication were also recorded and coded as yes/no for each type of medication.

Statistical Approach

Statistical analyses first assessed descriptive statistics for variables of interest. Next, multiple regressions were performed in which youths' internalizing symptoms were regressed onto parent empathy scores along with youth's age, ethnicity, gender, parent's gender, and parent's years of education. Third, multiple regressions were used to regress stimulated cytokine responses onto parent empathy scores, controlling for youths' age, ethnicity, gender, parent's gender, parent's years of education, on a beta-agonist medication (yes/no), and on an inhaled steroid medication (yes/no). Lastly, multiple regression analyses were re-run while additionally controlling for parental warmth to assess whether associations with empathy remained after accounting for more general positive characteristics of the parent-child relationship.

Results

Preliminary Analyses

Descriptive statistics for study variables are presented in Table 1.

As reported in previous research (E. Chen et al., under review), principal components analyses were used to create cytokine composites. For asthma-specific stimulation of Th-1 versus Th-2 cytokines, principal components analyses of both the cockroach and dust mite stimulations revealed a 2-factor solution. Factor 1 accounted for 51.6%-53.4% of the variance,

and Factor 2 accounted for 24.7%-25.4% of the variance. Factor 1 corresponded to the Th-2 cytokines, and was comprised of IL-2 (factor loadings ranging from .86-.88), IL-4 (factor loadings .77-.87), IL-5 (factor loadings from .90-.93), and IL-13 (factor loadings from .90-.95). Factor 2 corresponded to the Th-1 cytokines, and was comprised of IFN-γ (factor loadings .70-.84) and IL-10 (factor loadings (.61-.80). Cytokine values were standardized and then IL-10 and IFN-γ values were averaged to create Th-1 composites for each ligand and IL-2, Il-4, IL-5, and IL-13 values were averaged to create Th-2 composites.

For the nonspecific stimulation of Th-1 versus Th-2 cytokines by PMA/INO, a single factor was suggested that accounted for 78.8% of the variance. However, to be consistent with the cockroach and dust mite composites and with the theoretical distinction between Th-1 and Th-2 cytokines, two factors were created reflecting Th-1 (IL-10 and IFN-γ) and Th-2 (IL-2, Il-4, IL-5, and IL-13) cytokine responses. Again, values were standardized and averaged.

For assays involving proinflammatory cytokine production from TLR stimulation (and potential regulation by glucocorticoids), single factor solutions emerged for the Poly I:C and Poly I:C+Cortisol wells, with the principal component explaining 88.5 and 84.1% of the variance, respectively. Factor loadings ranged from .93-.93 (IL-1β), .89-.95 (IL-6), and .93-.95 (TNF-α). Accordingly, we created composite indicators for each condition, by standardizing and then averaging values of IL-1β, IL-6, and TNF-α.

Parent Empathy and Youth Internalizing Symptoms

Multiple regression analyses revealed a marginally significant association between parents' empathy scores in the Life Story Challenge Interview and their children's scores on the YSR anxious/depressed subscale (β= -.15, p=.053), such that parents who demonstrated greater consideration of the perspectives of others had children with marginally lower levels of

internalizing symptoms.

Parent Empathy and Youth Cytokine Production

Multiple regression analyses revealed that children who had parents with higher levels of empathy showed significantly smaller Th-2 (β= -.20, *p*=.035), but not Th-1 (β= -.15, *p*=.135), cytokine responses to nonspecific stimulation with PMA/INO.

Regarding asthma-relevant ligands, greater parent empathy was associated with smaller child Th-1 (β =-.23, p=.010) and Th-2 (β =-.22, *p*=.014) cytokine responses following stimulation with cockroach extract. Parent empathy was also significantly associated with Th-1 (β=-.23, *p*=.011), and marginally associated with Th-2 (β=-.14, *p*=.099) cytokine responses following stimulation with dust mite extract. In each case, children with parents who engaged in more perspective-taking showed smaller stimulated cytokine responses.

With respect to TLR stimulation, higher parent empathy was associated with smaller proinflammatory cytokine responses to Poly I:C stimulation (β=-.19, *p*=.039). For assays of glucocorticoid sensitivity, parent empathy was associated with smaller proinflammatory cytokine responses to Poly I:C+ cortisol stimulation (β=-.33, *p*<.001). These associations indicate that children who had parents who demonstrated greater perspective-taking showed a greater sensitivity to glucocorticoid inhibitory signaling.

Table 2 presents a summary of multiple regression results.

Specificity of Empathy

To assess whether associations with parent empathy might be due to more general positive parenting characteristics, analyses were re-run while including parental warmth as an additional covariate in the models. Here, the contribution of parent empathy in the model predicting youth internalizing symptoms became statistically significant (β=-.15, *p*=.049).

Parental empathy continued to be associated with significantly smaller Th-2 cytokine responses to PMA/INO stimulation (β=-.20, *p*=.035), smaller Th-1 and Th-2 cytokine responses to Cockroach stimulation (β=-.24, *p*=.010 and β=-.22, *p*= .016, respectively), and smaller Th-1 cytokine responses to Dust mite stimulation (β=.24, *p*=.008). Associations between Th-2 cytokine responses to Dust mite exposure shifted slightly to non-significance (β=-.14, *p*=.103). Empathy also continued to predict significantly smaller proinflammatory cytokine responses to stimulation by Poly I:C (β =-.20, *p*=.016) and greater sensitivity to glucocorticoid inhibitory signaling (β=-.34, *p*<.001), suggesting that associations with empathy are not accounted for by broader positive parent-child relationship characteristics.

Discussion

Using a novel assessment of parental empathy in a clinical sample of children with asthma, the current study found support for the hypothesis that parents who demonstrated higher levels of empathy would have children with fewer internalizing psychopathology symptoms and better inflammatory profiles. Specifically, greater empathy was related to lower stimulated cytokine production in response to a variety of mitogens activating non-specific adaptive immune processes, asthma-specific adaptive immune processes, and proinflammatory innate immune processes in children with asthma. Greater parental empathy also was associated with greater sensitivity of youths' immune cells to the anti-inflammatory effects of glucocorticoids. Moreover, these associations with internalizing symptoms and cytokines responses could not be better accounted for by the broader positive parenting characteristic of parental warmth.

That parental perspective-taking predicted lower levels of anxious/depressive symptoms in youths (particularly after accounting for parental warmth) is in line with previous work documenting the positive psychosocial correlates of parental empathy (Soenens et al., 2007;

Strayer & Roberts, 2004). It replicates and extends Feshbach's (1987) finding that parental empathy related to parents' reports of lower internalizing symptoms in their children, here finding evidence of associations that avoid potential parental report bias by relying on researcher coding of empathy and utilizing youths' own report of symptoms. Additionally, this is the first study to assess connections between empathy and internalizing symptoms within a sample of children with asthma. While this may be a general pathways of risk across kids, regardless of chronic illness status, for this population, these associations may have even greater consequence, as co-morbid depression is associated with poorer functioning and greater mortality from asthma in youths (Gutstadt et al., 1989; Strunk et al., 1985).

Parents' tendency to acknowledge the perspectives of others also related to multiple stimulated cytokine responses in youths, revealing that children with more empathic parents show smaller inflammatory responses to both asthma-specific and nonspecific adaptive immune system stimulation, show smaller proinflammatory responses to innate immune stimulation, and show greater sensitivity to the anti-inflammatory effects of cortisol. This suggests that children who have empathic parents are mounting smaller inflammatory responses to allergens that might trigger asthmatic responses, as well as showing smaller proinflammatory responses to viruses and other possible infections that can contribute to asthma. Moreover, that these children showed greater sensitivity to cortisol indicates that the administration of synthetic glucocorticoids might have more beneficial effects for asthma control in these children.

Beyond asthma, many of these inflammatory processes are also implicated in other physical and mental disorders, suggesting that findings within the disease model of asthma may have important implications for basic psychoimmunology (G. Miller, Chen, & Cole, 2009c). For example, prolonged exposure to proinflammatory signaling is believed to result in chronic low-

grade inflammation, which is considered part of the pathogenesis of such disorders as cardiovascular disease, certain cancers, and depression (A. Gardner & Boles, 2011; Heikkilä et al., 2008; Volpato et al., 2001). Thus, these same pathways may not only place youths at greater risk for comorbid diagnoses (Blackman & Gurka, 2007), but may also represent additional pathways linking early family environments to later mental and physical health (Repetti et al., 2002).

Although the current study was unable to assess mechanisms for the observed effects, there are several possible explanations for why parental empathy was related to youths' cytokine production profiles. One possibility is that parents who are higher on empathy are better able to anticipate and respond to the general needs of their children, facilitating a more harmonious and less stressful home environment, with subsequent effects on stress-responsive physiological systems in children (E. Chen et al., 2010). More specific to asthma, it is also possible that parental empathy allows parents to more adeptly encourage healthy behaviors in their children, such as better facilitating medication compliance or limiting allergen exposure in ways that allow their child to not miss out on school or peer activities. Meta-analytic research examining the effects of social support on medical treatment fidelity is supportive of this possibility (DiMatteo, 2004).

Consistent with previous work (Manczak et al., 2016), the observed associations were not accounted for by youths' ratings of parental warmth, suggesting that there may be something unique to parents' ability and inclination to take the perspectives of others that goes beyond the effects of warmth in general. Conceptually, warmth may be seen as encompassing a wide swath of interpersonal behaviors that convey connectedness, kindness, and positivity. In contrast, empathy is best viewed as a dispositional trait that reflects an underlying tendency to care about

and understand the mental states of others. Thus, while empathy may contribute to warmth, it is not necessarily redundant with it. One possibility is that parental empathy may inform a broader range of behaviors in addition to encouraging warm interactions (Strayer & Roberts, 2004), such as curtailing use of harsh discipline or encouraging more consistent parenting responses. Another possibility is that more empathic parents may simply be more sensitive to the emotional and physical states of their children (Kochanska, 1997), allowing them to optimize and tailor their responses to the needs of the particular child in ways that are not captured by items assessing general parenting dimensions. Together, this suggests that parental empathy is not redundant with warmth, but rather may be seen as an important additional dimension to assess.

Although substantial prior work on dispositional empathy has relied on self-report measures, one strength of the current study was that it utilized coding of narrative responses to identify evidence of empathy by parents. Beyond simply offering a novel assessment technique, the use of narrative-coded empathy is in keeping with sophisticated conceptualizations of personality and identity. Here, work by McAdams (2013; 2006) asserts that personality may be represented by three layers: dispositional traits (such as those captured by self- report inventories), characteristics adaptations (such as valued goals), and life stories (such as in narrated depictions of key life experiences). By spontaneously referencing the needs, viewpoints, and perspectives of others during discussions of difficult challenges, it is likely that these parents have integrated an empathic consideration of others into their own internalized stories (McAdams, 2001). Moreover, given that empathy is generally treated as a dispositional trait, evidence of perspective-taking in parents' narratives is supportive of coherence across multiple layers of personality (McAdams et al., 2004). Thus, when considered with prior work (i.e., Manczak at el., 2016), the current study suggests that connections between empathy and youth

inflammation exist at multiple layers of personality and across multiple processes involved in the regulation of inflammation.

The current work is the first to link parents' empathy to a wide range of cytokine responses and internalizing psychopathology symptoms in children with asthma. It relied on a multi-method assessment of both psychological and biological processes and introduced a novel assessment of empathy that overcomes limits of possible bias in self-reporting. However, there are several important limitations to acknowledge. First, the research was cross-sectional and thus causality as well as directionality are impossible to determine. For example, it may be that children who are more medically ill require more empathy on behalf of their parents, which may manifest in parents' greater perspective-taking, broadly. A second limitation is that I did not look directly at asthma outcomes, such as lung functioning, which should be the focus of future work. However, substantial research on asthma has acknowledged the important mechanistic role that inflammatory processes play in disease presentation and severity (Busse & Lemanske, 2001; Chung & Barnes, 1999). In addition, youth psychopathology was assessed at the symptom level using a single self-report measure. Future work should improve on this by incorporating multiple informant ratings of psychopathology, including clinician ratings. Another limitation is that only approximately a third of parents spontaneously mentioned the perspectives of others during either one of their memory discussions. In addition to potential floor effects, it is possible that this narrative assessment of empathy is overly conservative in determining parental perspective-taking. On the other hand, by not specifically prompting for aspects of empathic consideration, such responses may better reflect dominant values and motivations as they naturally occur in the lives of participants (McAdams, Hoffman, & Day, 1996). Likewise, the topic of the interview did not specify that the parent discuss aspects of their relationship with their participating child.

Thus, it is impossible to know whether any perspective-taking that was observed is reflective of parental empathy as it occurs with regard to that child. However, if empathy is conceptualized as a dispositional trait, it is presumed that expressions of empathy would be largely stable across close relationships.

Despite these limitations, the results of the current study raise several important questions for future research. For example, how might empathy affect parents? The present work was concerned with the correlates of *receiving* empathy, but what might it mean immunologically or psychologically to *provide* empathy? Another important avenue for future work is to examine these associations in the context of the intergenerational transmission of internalizing disorders. Might parental empathy act as a pathway, or even a moderator, of risk from parents who are anxious or depressed to child symptoms? A final direction for future work is to explore mechanisms for the observed associations, such as by examining daily interactions between parents and children. Given that parental warmth did not appear to account for these associations, future research should consider links between empathy and other dimensions of parenting, such as day-to-day consistency in parenting behaviors across time.

Regardless of these unanswered questions, the present work adds to research on the importance of early family relationships for youths' mental and physical health, suggesting that parental empathy is associated with internalizing symptoms and a range of cytokine responses in children with asthma. These findings corroborate connections in previous research between parental empathy and youth psychopathology symptoms while identifying multiple asthma-relevant inflammatory markers that relate to parents' perspective-taking within a population of children with a chronic illness. Together, this work suggests that parental empathy may be able to "get under the skin" to facilitate important mental and physical health processes in children.

Chapter 3: Child Depressive Symptoms Interact with Parental Empathy to Predict Cytokine Production in Parents

Empathy is a highly valued, prosocial trait that has been shown to relate to abundant positive outcomes (Davis, 1983; Eisenberg & Miller, 1987). In the context of childrearing, the ability of parents to empathize with their children is considered fundamental to healthy, skillful parenting (Dix, 1992; Kochanska, 1997) and is believed to facilitate better psychological development for children (Eisenberg et al., 1991; Feshbach, 1987; Soenens et al., 2007; Strayer & Roberts, 2004). Moreover, as demonstrated in the previous study, greater parental empathy is associated with better inflammatory profiles and lower levels of internalizing symptoms in children. Not surprisingly, then, parental empathy is held as a prized and positive characteristic. One question that has remained largely unanswered, however, is whether parental empathy – particularly in the context of youth depression – might actually be harmful to parents?

Although the tendency of parents to understand and compassionately care about the lives of their children may be beneficial to their loved ones, it is possible that greater empathy may also make parents more sensitive to the effects of—and burdened by—times when their children are suffering. Through greater perspective-taking and more emotional investment, highly empathic parents may be better oriented to the emotional climates of their loved ones (Kochanska, 1997). However, when this climate becomes fraught with greater distress, it is possible that empathy may amplify the burden that parents experience, much as individuals in empathically demanding professions report experiences of vicarious trauma and burnout (Zapf et al., 2001).

If empathy sensitizes parents to the suffering of their children, one salient context for witnessing this phenomenon may be when children are experiencing greater distress, in the form

of elevations in depressive symptomatology. In addition to placing youths at increased risk for substance use, suicide, and other comorbid diagnoses (Galaif et al., 2007), depression also exposes youths' support systems to greater strain, including more frequent negative interactions with family members and greater emotional burden on parents (Angold et al., 1998; Kashani, Burbach, & Rosenberg, 1988).

As parents strive to support loved ones and subvert their own needs, it is possible that with greater child distress comes a greater physiological cost for empathic parents. Specifically, as greater empathy motivates parents to provide a supportive and non-reactive environment (Larson & Yao, 2005), it may require parents to suppress their own feelings, such as of judgment or frustration. Here, children with depressive symptoms may necessitate more frequent support and thus more emotional suppression by parents. Engaging in emotional suppression, however, has been found to increase physiological responses (Davis, 1983; Eisenberg & Miller, 1987; Gross, 1998b; Gross & Levenson, 1993). In addition, research by Appleton et al. (2013) has demonstrated that individuals who more frequently engage in emotional suppression as an emotion regulation strategy show higher levels of chronic, low-grade inflammation. Moreover, other seemingly positive psychological traits that require ongoing effort (such as self-control or goal-persistence) have been shown to relate to negative physiological processes, including greater physiological wear-and-tear and greater chronic inflammation (Brody et al., 2013; Eisenberg et al., 1991; Feshbach, 1987; G. E. Miller & Wrosch, 2007; Soenens et al., 2007; Strayer & Roberts, 2004). Likewise, empathic responding may require effort that ultimately comes at a physical cost.

One biological system of particular relevance to the psychological burdens experienced by caregivers is the immune system, which is sensitive to an individual's social and

psychological environments (Lovell & Wetherell, 2011; G. E. Miller et al., 2011; Segerstrom & Miller, 2004). Previous work suggests that caregivers of patients with chronic physical illnesses show elevations in markers of low-grade inflammation and reduced sensitivity to the regulatory effects of glucocorticoids (Lovell & Wetherll, 2011; Miller et al. 2008), and as well, increase in their levels of low-grade inflammation over time (Lewinsohn et al., 1993; Rohleder et al., 2009). These findings are believed to arise from a cascade of physiological responses in which psychological stressors prime the immune system to exhibit heightened inflammatory responses in the presence of pathogens, which lead to elevations in chronic, low-grade inflammation and to dysregulation of counter-regulatory immune mechanisms if experienced repeatedly over time (Galaif et al., 2007; G. E. Miller et al., 2011).

To the extent that empathic parents are more attuned to the suffering of their children, it is possible that this greater empathy may potentiate the effect of children's depressive symptoms on parents' own inflammatory responses. Theories of biological sensitivity to context (Boyce & Ellis, 2005) and differential susceptibility (Belsky & Pluess, 2009) propose that individuals differ in the extent to which their psychological and physiological processes are responsive to their environments. Here, for better or worse, more receptive individuals respond to *both* the positive and negative elements of their environments more than less receptive individuals, for example, becoming more impaired by stress associated with their child's depression but also more responsive to positive social environments (Hankin et al., 2011). Thus, if parental empathy is one type of trait that produces sensitivity to one's social context, it may be associated with different patterns of inflammatory responses depending on the environmental context of their child's current depressive state.

The present study sought to test whether parental empathy would amplify the physiological costs for parents of their adolescent children experiencing greater depressive symptomatology. Specifically, it examined whether child depressive symptoms and parents' dispositional empathy (assessed at baseline) interacted to predict parents' inflammatory responses one year later. Parents' blood was exposed *in vitro* to a bacterial stimulus in order to measure the magnitude of immune cells' responses to threat, based on how much pro-inflammatory cytokines their cells produced. It was hypothesized that as child depressive symptoms increased, the association between parental empathy and cytokine production would become increasingly positive, such that empathic parents would demonstrate greater pro-inflammatory cytokine production when their children were high in depressive symptoms, but less cytokine production if their children were low in depressive symptoms. Parents low in empathy were not expected to show differences in cytokine production as their children's depressive symptoms increased.

Method

Participants

Parents and their adolescent children (ages 13-16) were recruited through advertisements in local media as part of a larger study on psychosocial contributors to cardiovascular disease risk. One adolescent and one parent from each family participated. All participants were required to be free of any chronic or acute medical illness and to be English-speaking. Data from two time-points were considered: psychosocial measures taken at baseline and blood drawn one year later. Complete data on psychosocial and biomarker variables were available for 143 dyads (76% mothers; 50% daughters). The mean age for parents was 45.5 years (*SD*=5.53) and the mean age for adolescents was 14.5 years (*SD*=1.07) at baseline. Fifty-five percent of families

identified as being of European descent, 38% were Asian descent, 4% were Hispanic descent, 1% was African descent, and 2% identified as "other." Family income ranged from less than $5000 to more than $200,000, with mean income in the 50,000-75,000 Canadian dollars range. The mean level of education for parents was some college education.

Procedure

As part of the baseline laboratory visit, parents and adolescents provided written consent, as overseen by the Institutional Review Board, and completed self-report questionnaires described below. One year later, families returned for a follow-up visit, and blood samples were obtained from parents. Covariates related to inflammation, including waist circumference and demographic variables, were also recorded at this time.

Measures

Parental Empathy. Parents completed the Empathic Concern and Perspective Taking subscales of the Interpersonal Reactivity Index (Davis, 1983) at baseline, a widely used measure of dispositional empathy. This measure has previously been shown to have a two-year test-retest correlation of r=.58 and to relate to other measures of empathy, as well as to predict self-esteem and sensitivity to others (Davis, 1983; Davis & Franzoi, 1991). The Empathic Concern subscale captures affective dimensions of empathy, assessing emotional experiences stemming from sympathy or compassion for others, such as having "tender, concerned feelings for people less fortunate than me" (α=.76, current sample). The Perspective Taking subscale probes for cognitive dimensions of empathy, gauging one's tendency to adopt the psychological viewpoint of others, such as "[trying] to understand my friends better by imagining how things look from their perspective" (α=.76, current sample). A single composite score (labeled "Empathy") was

computed by summing standardized scores on each scale, as responses on the two scales were significantly correlated ($r(141)=.52$, $p<.01$), with higher scores indicating greater empathy.

Child Depressive Symptoms. During the baseline lab visit, adolescents completed the Center for Epidemiological Studies Depression Scale Short Form (Bjorgvinsson, Kertz, Bigda-Peyton, McCoy, & Aderka, 2013), a widely used self-report depression screen that assesses the frequency of ten depressive symptoms over the course of the previous week and is appropriate for use with adolescents (Bradley, McGrath, Brannen, & Bagnell, 2010). Its reliability and validity have been established in both clinical and community samples, showing convergence with other self-report measures of depression as well as clinical diagnoses of major depressive disorder (Anderson, Malmgren, Carter, & Patrick, 1994; Bjorgvinsson et al., 2013). Higher scores on this measure indicate higher levels of depressive symptoms ($\alpha=.67$, current sample).

Parenting Behaviors. To clarify the unique contribution of parental empathy versus more general parenting behaviors, child-reported positive parenting behaviors were also assessed at baseline. Using items developed by Brody et al. (2001), adolescents reported on how frequently their parents acted supportively or lovingly toward them, such as by letting their children know they appreciated them or helping them with an important task. The one-year test-retest correlation on this measure has been reported as r=.41 (H. Kim et al., 2011). Here, nine items were rated on four-point scales, with higher scores on this measure reflecting more positive parenting behaviors ($\alpha=.89$, current sample). Although formal validation studies of this measure have not been published, this collection of items has previously been demonstrated to relate positively to the frequency of nurturing caregiving behaviors as reported by both children and their parents and to relate negatively to increases in child psychopathology symptoms over time (Brody et al., 2001; I. J. Kim et al., 2003).

Inflammatory Markers. One year after the baseline visit, peripheral blood was drawn from parents using antecubital venipuncture into sodium heparin vacutainer tubes, which were diluted with 10% isotonic saline solution. Blood was then mixed with 400uL of saline solution and 50ng/mL lipopolysaccaride (LPS)—a bacterial stimulus—and then incubated for 6 hours at 37°C at 5% CO_2. The production of four cytokines were measured: Interleukin 1-beta (IL-1β), Interleukin 6 (IL-6), Interleukin 10 (IL-10), and Tumor Necrosis Factor-alpha (TNF-α). IL-1, IL-6, and TNF-α are considered classic pro-inflammatory cytokines. IL-10, although considered anti-inflammatory, is typically released when pro-inflammatory cytokines become high, and thus often relates to outcomes in the same way as pro-inflammatory cytokines. (In the current study, all four cytokines were significantly and positively correlated, *r*s(141*)*>.42, *p*s<.001.) Cytokine production was measured using Meso Scale Discovery human pro-inflammatory 7-plex base kit (Meso Scale Discovery, Gaithersburg, MD). Enzyme-linked immunosorbent assay plates were analyzed using the Sector Imager 2400 from Meso Scale Discovery. (Mean intra-assay CV=3.46.) Values were log-transformed prior to analysis in order to normalize their distribution.

Covariates. Demographic variables and variables known to affect inflammation were also assessed at the time of the blood draw and included as covariates. These included parent gender, age, ethnicity, and waist circumference (an indicator of adiposity).

Statistical Approach

Multiple regression analyses were conducted in which stimulated cytokine values were regressed onto parental empathy, child depressive symptoms, and their interaction. Parental empathy and child depressive symptoms were centered before calculating the interaction term, and recommendations for testing interactions with two continuous variables outlined by Aiken & West (1991) were followed. Models were repeated while covarying demographic and adiposity

variables. Secondary analyses examined whether similar patterns of results were obtained when substituting a more general measure of positive parenting behaviors for parent empathy, as well as simultaneously including positive parenting behaviors and its interaction with child depressive symptoms into regressions with parental empathy and its interaction.

Results

Empathy and Depressive Symptom Interactions. As presented in Table 3, regression analyses revealed no main effects of parental empathy or child depressive symptoms on stimulated cytokine production. However, significant interactions emerged across all markers, as well as their composite (created by summing z-scored cytokine values). In support of our hypothesis, parents higher in empathy showed greater cytokine production as child depression symptoms increased (see Figure 1). Parents lower in empathy showed the opposite pattern. In addition, all interactions remained significant when including covariates of parental age, gender, ethnicity, and waist circumference (Standβs>.24, *ps*<.05, semipartialr^2s>.05).

Secondary Analyses. It is possible that associations with parental empathy are not specific to empathy per se, but rather reflect more general parenting characteristics such as positive parenting behaviors. (Although not statistically significant, parental empathy and positive parenting behaviors were positively correlated $r(141)=.11$, $p=.17$.) To test for this possibility, regression analyses were first rerun substituting positive parenting for parental empathy, along with its interaction with child depressive symptoms and adiposity and demographic covariates, in predicting inflammatory markers. There were no significant main effects of positive parenting behaviors or child depressive symptoms, and no interaction effects (Standβs< .16, *ps*>.05, *spr*^{2}s<.03). Second, multiple regression analyses were run including positive parenting and its interaction with child depressive symptoms simultaneously with

parental empathy and its interaction with depressive symptoms, in addition to covariates. All interactions between parental empathy and child depressive symptoms remained significant (Standβs>.22, ps<.05, spr^2s>.04) and there were no additional independent contributions of positive parenting or its interaction (Standβs< .10, ps>.05, spr^2s<.02), suggesting that parental empathy uniquely interacts with child depressive symptoms to predict parents' cytokine production.

Discussion

These results provide support for the hypothesis that parents with higher levels of empathy may be especially affected – physiologically—by the depressive symptoms of their adolescent children. Specifically, across four markers of inflammation, parents who were higher in empathy showed heightened cytokine production to *in vitro* stimulation by a bacterial product as their children's depressive symptoms increased. In contrast, for parents lower in empathy, there was a negative association between children's depressive symptoms and stimulated cytokine production. Moreover, these associations do not appear to be accounted for by adiposity- or demographic-related variables or by more general positive parenting behaviors.

While researchers have long acknowledged the profound influences of parental depression on children (Lieb, Isenee, Hofler, Pfister, & Wittchen, 2002; A. L. Singh et al., 2010), relatively less work has examined the reverse relationship, of the effects of child depression on parents. The present work suggests that empathic parents may be especially vulnerable to these effects. Specifically, parents who are better able to take the perspective of others and are more emotionally invested may more viscerally experience and be burdened by their children's psychological distress. This mirrors research regarding the psychological costs of vicarious trauma in counselors and therapists (Schauben & Frazier, 1995), with the present study finding

evidence for physiological costs of empathy in family members. An alternative explanation is that highly empathic parents may be more self-sacrificing in their caregiving of distressed children and may neglect protective health behaviors for themselves, such as getting adequate sleep, exercise, or nutrition, consistent with work documenting the physiological toll associated with taking care of others (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991).

That parents who are higher in empathy showed reduced pro-inflammatory cytokine production when children were low in depressive symptoms but greater production when children were high in depressive symptoms suggests that empathy may confer a heighten biological sensitivity to context (Boyce & Ellis, 2005; Ellis & Boyce, 2011). In their seminal work, Boyce and Ellis (2005) suggest that individuals can differ in the extent to which their stress response systems react to input from their environments in ways that may be beneficial if the environment is good or detrimental if the environment is bad. With regards to the current work, one's tendency to take the perspective of others and react with emotional concern may similarly amplify responding to social contexts such that empathy can be either positive or negative depending on the situation.

Because we saw effects on the functioning of immune cells (how they respond to a bacterial stimulus), over the long term, it is possible that these exaggerated immunological responses will lead to higher levels of chronic inflammation (G. E. Miller & Chen, 2010). In turn, this may then put empathic parents at elevated risk for a host of physical health problems linked to inflammation, including heart disease and certain cancers (Heikkilä et al., 2008; Ridker, Hennekens, Buring, & Rifai, 2000). Chronic inflammation may have repercussions for parents' mental health as well, as several lines of research suggest that inflammation is implicated in the etiology of depression. For example, individuals with depression consistently show elevations in

pro-inflammatory cytokines (Dowlati et al., 2010) and induction of an inflammatory response is associated with the onset of several symptoms of depression, including low mood (Eisenberger et al., 2010). Through these inflammatory processes, it is possible, then, that child depression may transmit effects onto parents. Of course, the current study is limited by its single assessments of stimulated cytokine production, depressive symptoms, and empathy and is not able to address these possibilities directly. However, given that first onset of depressive disorders is often in adolescence (K. C. Burke, Burke, Rae, & Regier, 1991), it is possible that our associations are capturing the first stage in a cascade by which greater inflammatory responses lead over time to chronic inflammation more systemically and, ultimately, to health risks for parents, if children's depressive symptoms are not ameliorated.

There are several other limitations to the present investigation. For example, the present work focused on adolescents in a healthy, community sample in which depressive symptoms were generally low. Second, no formal validation study has been conducted for the parenting questionnaire, though this measure has been used repeatedly in other parent-adolescent research, has good reliability, and has been shown to predict changes in child psychopathology (I. J. Kim et al., 2003). Further, in this preliminary study, I was unable to assess possible mechanism variables—such as coping processes, enmeshment, health behaviors, or chronic strain—that may account for our results. It is also not yet clear whether these results are specific to youth depression or whether they would apply to other types of psychological symptoms as well. Lastly, it remains unclear why parents who are lower in empathy appear to show more adaptive inflammatory responses as child depressive symptoms increase.

Notwithstanding these limitations, the current work raises intriguing possibilities for future research. Although many interventions exist for treating depressive symptoms in children,

I am unaware of studies that consider the impact of children's treatment on parents. As family interventions aimed at reducing child psychological symptoms frequently seek to foment greater parental empathy (e.g. Marvin, Cooper, Hoffman, & Powell, 2002), assessing parental physiological functioning throughout these interventions would determine whether there are hidden costs embedded in expanding parents' repertoire for empathic responding. It is possible that as children get better from treatment, parents may actually get worse, and thus we would need to modify treatment interventions to consider these effects. In addition, to more firmly establish whether empathy reflects a greater biological sensitivity to context, it would be interesting for future work to examine not only negative contexts such as child depression but also positive contexts and whether high parental empathy when children have positive life experiences is associated with more beneficial inflammatory profiles. For example, what might empathic parents' immune functioning look like when positive events happen to their children, such as college acceptance, social successes, or extracurricular achievements?

Despite these unanswered questions, the present study has several important implications. Although a high level of empathy is often assumed to be an exclusively positive characteristic (e.g. Eisenberg & Miller, 1987), the current work suggests that, at least under certain circumstances, it may also make the person expressing empathy more vulnerable to inflammation-related health problems over time. Further, the present findings highlight the complex interpersonal context of depressive symptoms (not only from parent to child but also from child to parent) and emphasize important connections between physical and mental health processes in families, demonstrating that child depressive symptoms, in conjunction with parent trait qualities of empathy, "get under the skin" and relate to inflammatory processes in parents.

Chapter 4: Consistency in the Timing and Quality of Daily Interactions Between Parents and Adolescents Predicts Production of Proinflammatory Cytokines in Youths

Given that parental empathy in the context of youth depressive symptoms is associated with an immunological cost to parents, other aspects of the caregiving environment should be considered in research aimed at identifying targets for the treatment and prevention of youth depression. While much of the previous research on family contributors to risk focus on the *quality* of parenting, another important aspect of family relationships may be related to structural aspects of parenting, namely *consistency in family interactions*. That is, the variability (rather than just the valence) of behaviors as they occur across time may represent another important characteristic of family experiences for children. This is supported by research examining psychosocial correlates of various forms of family inconsistency. For example, inconsistent disciplinary practices have been shown to hinder executive functioning and to predict more aversive parent-child interactions (C. H. Hughes & Ensor, 2009; Wahler & Dumas, 1986). Intraparental inconsistency has also been demonstrated to relate to internalizing and externalizing symptoms in sixth-graders (Benson et al., 2008). Longitudinal work by Hightower (1990) has additionally found that adolescents' reports of parental rule-setting inconsistency predicted their mental health outcomes at age 50.

Could inconsistency in parent-child interactions also be related to depression-relevant inflammatory activity in youths? One possibility is that interaction variability may contribute to a sense of unpredictability, in turn amplifying experiences of stress and physiological responses to family interactions. Previous work has demonstrated that predictability represents a key psychological dimension related to physiological stress responses (Dess, Linwick, & Patterson, 1983; Hennessy, King, & McClure, 1977; Sapolsky, 1994). If less predictable parenting

interactions create more stressful environments for children, these stress experiences may contribute to how immune cells respond to challenges. Variability in social interactions may also undermine important regulatory cues to the body. For example, consistent interpersonal interactions are considered a type of social *zeitgeber*—an environmental cue that helps entrain certain biological rhythms to a 24-hour circadian cycle (Ehlers, Frank, & Kupfer, 1988). In healthy individuals, regular social interactions have been shown to predict cortisol rhythms (Stetler & Miller, 2007), a hormone that, in part, regulates inflammation.

Preliminary support for links between inflammation and family consistency come from two studies suggesting that broad indicators of stability in homes are related to inflammatory profiles in children. In the first, higher ratings of chaos in the home environment for low socioeconomic children was found to be related to youths' higher levels of circulating IL-6 and greater proinflammatory cytokine production in response to bacterial challenge (Schreier et al., 2014). In a second study, greater use of routines within the families of children with asthma were found to predict lower stimulated production of an asthma-relevant cytokine, interleukin-13, in youths (Schreier & Chen, 2010).

In previous research, however, family inconsistency has been measured by employing global self-report questionnaires that ask respondents to aggregate across experiences and time (e.g., Benson et al., 2008; C. H. Hughes & Ensor, 2009). However, with a variable such as consistency in behavior, the best approach to understanding this process may be to capture day-to-day interactions in the lives of families (Fuligni, Telzer, Bower, Irwin, et al., 2009b). A daily diary approach may also highlight the more nuanced aspects that contribute to connections between early family environments and youth inflammation, perhaps through repeated or frequent stress-system activation (Fuligni & Telzer, 2013; Repetti et al., 2002). Hence in this

study, I took a daily diary approach to measuring consistency and chose to focus on two dimensions of daily consistency in parent-youth interactions: affective and temporal. By affective consistency, I refer to whether family members consider their interactions to be positive or negative, and whether this is consistent across days. By temporal consistency, I refer to *when* interactions occur, specifically focusing on whether parents and children engage in leisure time together at the same time of day across days. These two aspects were selected because each may contribute differently to the family environment: variability in the degree of positivity of parent-child interactions may challenge a youth's ability to predict whether that parent might be a helpful source of support (Mallinckrodt, 1992), whereas variability in the timing of interactions may reflect more chaotic structural family elements that undermine anticipation of daily activities (Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005).

The present study sought to test whether variability in day-to-day interactions between parents and children would be related to the production of proinflammatory cytokines in youths one year later. I also aimed to test associations with both affective consistency and temporal consistency in these daily interactions. As an index of inflammatory processes, I exposed youths' immune cells *in vitro* to a bacterial stimulus, LPS, and then measured the amounts of several different proinflammatory cytokines that were produced. It was hypothesized that greater variability in the quality and timing of daily parent-child interactions would be related to greater production of proinflammatory cytokines in youths' immune cells. Moreover, these effects were hypothesized to be independent of overall relationship quality and frequency of parent-child interactions. An exploratory question was whether variability in quality and timing would relate independently to production of proinflammatory cytokines or would reflect shared risk.

Method

Participants

Using advertisements in local media, adolescent youths (age 13-16) and their parents were recruited as part of a larger study of psychosocial contributors to health. One parent and one child from each family participated. Both family members were required to be English-speaking and to be free of any chronic or acute medical illness. Data from three assessments were utilized in the present study: a baseline laboratory visit during which demographic and anthropometric data was gathered, two weeks of daily diary reporting following the laboratory visit, and biomarker data collected one year later. One-hundred-twenty-three dyads participated in these assessments (95 mothers and 28 fathers, 66 daughters and 57 sons) and all available data were utilized. Youths were on average 14.57 years old (*SD*=1.05) and parents were on average 46.56 years (*SD*=5.15) at baseline. Fifty-seven percent of youths identified as being of European descent, 31% identified as being of Asian descent, 5% identified as being of African descent, 3% identified as being of Latin American descent, and 4% identified as "other." Parents had on average 16.62 years of education (*SD*=2.66) with a range of 10-27 years.

Procedure

During the baseline laboratory visit, parents and youths provided informed consent and assent and supplied demographic information. Anthropometric data, including youths' waist circumference (a measure of central adiposity, which is related to inflammation) was also collected. Immediately following this visit, parents commenced two weeks of daily diary assessments where they reported on several aspects of their daily experiences with their child (described below). They were instructed to complete this diary at the end of each day just before going to bed. One year later, youths returned to the lab to have blood samples collected.

Measures

Daily Diaries. *Variability in Quality of Interactions.* For 14 days, parents rated the quality of their daily interactions with their child by responding to the item, "Overall, my day with my child was____" using a 3-point scale in which 1=negative, 2 =neutral, and 3=positive. In the case of multiple children, parents were instructed to respond with respect to the target child participating in the study. To calculate variability, each person's standard deviation of ratings across days was extracted. This was the "variability of relationship quality" variable, with higher numbers indicating greater variability in relationship quality across days. To control for the fact that variability could be related to average levels, the mean rating of quality across days was also calculated ("overall relationship quality"), with higher scores reflecting more positive overall quality of parent-child interactions.

Variability in Timing of Interactions. Over the same period, parents also recorded the time of day at which they engaged in a number of daily behaviors (e.g., eating breakfast, exercising, etc.). Relevant to the current study, they reported the time of day at which they spent leisure time with their child. If they spent leisure time with their child multiple times during the day, they were asked to only record the time of their first experience, as this would capture daily structure while being consistent across as many families as possible. The variability in the timing of leisure interactions across days was calculated by extracting the standard deviation of their onset time and was labeled "variability in timing of interactions." To control for the possibility that families who rarely spent time together might show lower variability, the number of days over the two-week period during which parents reported spending leisure time with their child was also calculated ("overall interaction frequency").

Stimulated Cytokine Production. Peripheral blood was drawn in youths using antecubital venipuncture into sodium heparin vacutainer tubes, which were diluted 10% with an isotonic saline solution. Blood was then mixed with the bacterial stimulus lipopolysaccharide (LPS) at a final concentration of 50ng/mL before being incubated for 6 hours at 37°C at 5% CO_2. The production of four proinflammatory cytokines in response to LPS were measured: Interleukin 1-beta (IL-1β), Interleukin 6 (IL-6), Interleukin 8 (IL-8), and Tumor Necrosis Factor-alpha (TNF-α). Samples were assayed using electrochemiluminescence with a Sector Imager 2400 from Meso Scale Discovery, using the Meso Scale Discovery human proinflammatory 7-plex base kit (Meso Scale Discovery, Gaithersburg, MD). Mean intra-assay CV was 3.46. Values were log-transformed prior to analysis in order to normalize their distribution. Stimulated cytokine values were significantly correlated (all *r*s(121) >.40, *p*s<.001); hence, a composite variable was created by summing z-scored values for the four cytokines.

Participant Characteristics. To statistically control for the fact that differences in cytokine production, daily relationship quality, or daily relationship timing variables may be related to participants' backgrounds, family structure, or work schedule, additional demographic variables were assessed. These included youths' age, gender, ethnicity (dummy coded for "Asian descent," "European descent," and "Other descent"), and waist circumference, as well as parents' gender, marital status (dummy coded for "married/cohabitating"), years of education, and hours worked per week.

Parental Warmth. To better gauge the role of parent-child interaction inconsistency in the context of broader family relationship characteristics, child-reported parental warmth was also assessed using items developed by Brody et al. (2001), as described in Studies 1 and 2. Using 4-point scales, nine items probed for how frequently youths believed their parents acted

supportively and lovingly toward them, such as helping them on something important or acting affectionately (α=.88, current sample). Higher scores on this scale reflect greater parental warmth.

Statistical Approach

First, associations with participant characteristics and the independent and dependent variables of interest were assessed. Variables relating to participant background, family structure, or work schedule that were significantly correlated with interaction variables or cytokine production were retained for further analyses. Second, hierarchical multiple regression analyses were conducted in which the stimulated cytokine production composite variable was predicted from retained participant characteristic variables entered at step 1, overall quality of the parent-child relationship entered at step 2, and variability of parent-child relationship quality entered at step 3. This statistical approach provides the most stringent test of the contribution of variability in relationship quality, as predictive variance shared with other variables would be assigned to earlier steps. Third, this was repeated, substituting overall frequency of parent-child interactions in step 2 and variability in timing of parent-child interactions in step 3. Fourth, to gauge the relative contribution of variability in timing versus variability in quality, both variables, as well as their mean-level counterparts, were simultaneously entered into a single hierarchical model. Finally, to test alternative explanations, the covariate of parental warmth was added to models of interaction inconsistency and stimulated cytokine production.

Results

Descriptive and Preliminary Statistics

Descriptive statistics are presented in Table 4 and intercorrelations among psychosocial variables are displayed in Table 5. Notably, dyads with female children evinced greater

variability in the quality of their interactions and parents who worked more hours per week had less frequent leisure interactions with their children. There were no other associations between participant characteristic variables and interaction or cytokine variables; thus, only youth gender and parent work hour variables were retained for subsequent analyses.

In addition, dyads with higher overall quality showed significantly less variability in their ratings of that quality and also had more frequent leisure interactions. Greater frequency of interactions was associated with greater variability in the timing of those interactions; however, there was no direct relationship between variability in timing and variability in quality of interactions.

Variability in Quality of Parent-Child Interactions and Stimulated Cytokine Production in Youths

As displayed in Table 6, hierarchical regression analyses revealed that, at step 1, participant characteristics of youth gender and parents work hours did not significantly predict stimulated cytokine production in youths and neither variable emerged as significant independent predictors. The addition of overall quality at step 2 improved the model and made a significant independent contribution to the prediction of stimulated cytokine production in youths. However, this association was no longer significant once the variability of relationship quality variable was added at step 3. Instead, variability of quality was a significant independent predictor. In other words, parents who reported greater day-to-day variability in the quality of their interactions with their child had youths who exhibited greater production of proinflammatory cytokines in response to *in vitro* stimulation by LPS, and this was not accounted for by overall relationship quality.

Variability in Timing of Parent-Child Interactions and Stimulated Cytokine Production in Youths

Similar analyses were conducted regarding the timing of parent-child interactions and are presented in Table 7. Step 1 of the analysis was identical to that for quality variability, where youth gender and parent work hours were not significantly predictive of stimulated cytokine production in youths. The inclusion of overall frequency of parent-child interactions did not significantly improve the model, nor was it independently associated with stimulated cytokine production in youths. However, at step 3, variability in timing of parent-child interactions emerged as a significant independent predictor of youths' stimulated cytokine production, such that greater day-to-day variability in when parents and children spent leisure time together was associated with greater stimulated proinflammatory cytokine production in youths.

Variability in Quality Versus Variability in Timing

To assess whether variability in affective (quality) versus temporal (timing) aspects of parent-child interactions each had unique associations with inflammation and to gauge the relative predictive power of each, both the variability of relationship quality and the variability in timing of interactions were simultaneously entered in a hierarchical model of youths' stimulated cytokine production (see Table 8). At step 2, overall quality of parent-child interactions made a significant independent contribution to the model, but this became nonsignificant once variability of quality and variability of timing variables were added at step 3. When both dimensions were considered together, variability in relationship quality continued to be significantly associated with stimulated proinflammatory cytokine production in youths and variability in the timing of parent-child interactions showed a trend-level independent contribution. These findings suggest that variability in both the affective and temporal dimensions of daily parent-child interactions

contribute independently to youths' proinflammatory cytokine production in response to stimulation, even after accounting for average levels of quality and time together.

Alternative Explanations

To test whether observed associations with stimulated cytokine production might be confounded by other characteristics of parents, analyses were re-run controlling for parental warmth. This variable was selected to represent the possibility that more loving, positive relationships between parents and youth might foster more consistent interactions and better inflammatory profiles. Variability in quality continued to significantly predict stimulated cytokine production (Standβ=.32, t=2.43, p=.02), even after controlling for parental warmth, as did variability in interaction timing (Standβ=.22, t=2.24, p=.03), supporting the assertion that associations between stimulated cytokine production and interaction inconsistency are not better accounted for by parental warmth.

Discussion

Consistency in parent-child interactions—and not solely the quality or frequency of those interactions—was significantly associated with the production of proinflammatory cytokines in youths. I found that greater variability over a 2-week period in the positivity/negativity of daily parent-child interactions related to youths' greater production of proinflammatory cytokines following *in vitro* exposure to LPS, even after controlling for average quality of interactions. Similarly, greater day-to-day variability in the time at which parents and children engaged in leisure activities together also related to greater proinflammatory cytokine production in youths, regardless of how frequently they engaged in those activities. Furthermore, the contributions of affective and temporal variability were largely independent of each other and were not accounted for by parental warmth.

There are several possible explanations for these findings. More consistent day-to-day interactions with parents may engender greater psychological predictability within youths' home life, resulting in reduced experiences of stress. This would reflect the cross-species phenomenon that greater situational predictability is associated with less physiological and psychological responses to stress (Dess et al., 1983; Tiggemann & Winefield, 1987) and would likewise be consistent with theoretical models of the psychological effects of family consistency (e.g., Boyce et al., 1983; Dickstein, 2002). These findings also parallel work documenting that less chaos in families related to reduced proinflammatory phenotypes in low SES adolescents (Schreier et al., 2014) as well as research on children with asthma demonstrating that those with more family routines showed decreasing stimulated production of an asthma-relevant cytokine over 1.5 years (Schreier & Chen, 2010).

That variability in quality and variability in timing each independently predicted proinflammatory cytokine production suggests that affective and temporal inconsistencies may operate through distinct pathways. Through affective consistency, youths may develop clearer expectations for the availability of parental support and dependability, in line with attachment theory (Bowlby, 1982). For example, consistently positive interactions may encourage coping behaviors that utilize parental help, whereas consistently negative interactions may motivate youths to seek support from other advocates. In either scenario, this may contribute to reduced proinflammatory cytokine production through the use of positive, engagement-coping, which has been shown to relate to lower levels of CRP in adolescents (Low, Matthews, & Hall, 2013). In contrast, consistency in the *timing* of interactions may foster environmental predictability by establishing expectations about schedules and may additionally serve as a social *zeitgeber* that affects several biological rhythms related to inflammatory processes, including sleep and diurnal

cortisol secretion (Stetler & Miller, 2007; Tighe, Dautovich, & McCrae, 2016). Although further research is needed to clarify the cascade, having regularly-timed activities with parents may entrain biological processes with downstream effects on inflammation.

If less consistent interactions affect how youths' immune cells respond to bacterial challenge, over the long term, these patterns may contribute to low-grade inflammation, and, ultimately, to heightened risk for a number of poorer mental and physical outcomes (G. E. Miller & Chen, 2010). Indeed, low-grade inflammation is implicated in the pathogenesis of many diseases of aging, including heart disease, cancers, diabetes, and arthritis (Heikkilä et al., 2008; Ridker et al., 2000) and is also associated with psychological disorders, including depression and schizophrenia (Dowlati et al., 2010; Fan et al., 2007). For these reasons, then, inconsistent quality and timing of interactions within families may provide an additional explanation for why individuals raised in challenging early environments evince high rates of disease later in life (e.g., G. E. Miller et al., 2011).

The current work is limited by single time-interval assessments of study variables, making it impossible to know how these associations may change longitudinally or to be confident of causality. As well, timing and quality variability indices were taken from single-item responses over the 14-day period and from the parent's perspective. Though not uncommon in daily diary studies, future work should consider additional and more thorough ways of operationalizing daily inconsistency and should also explore potential differences between parent- versus youth-reports. Reliability and validity have also not been established for these diary items; however, this is not unusual for daily diary assessments (Doane et al., 2013). Furthermore, I was unable to assess hypothesized psychological mechanisms, such as predictability or coping, that may underlie associations.

Despite these limitations, by identifying facets of daily family experiences related to inflammatory processes, the current study has implications for interventions and future research. For example, the cultivation of behavioral consistency may be safer, more cost-effective, less socially stigmatized, and more easily disseminated than specialized psychotherapy or pharmacotherapy for parents and youths at risk. Such interventions could also serve to better illuminate causal relationships among variables. Another interesting topic for future research would be to examine how the sequelae of consistency with one parent are buffered or exacerbated by the consistency of other caregivers. Youths who have at least one parent who is more consistent on quality and timing dimensions may be protected from negative physiological outcomes, whereas those with two unpredictable caregivers may have greatest risk.

The current study also has several notable strengths. For instance, the observed associations emerged across naturalistic multi-method and multi-informant assessments, minimizing the likelihood that shared measurement variance or biases in youths' perceptions of relationships account for the findings. Moreover, I believe this is first study to link dimensions of inconsistency in daily parent-child interactions to youths' production of proinflammatory cytokines. As such, it moves beyond focusing on deficits in parenting behaviors to identifying additional family characteristics that may have implications for inflammatory processes and, eventually, mental and physical health. That variability in the quality and timing of daily family interactions predicted youths' proinflammatory cytokine production beyond averaged quality and frequency of interactions also underscores the importance of considering day-to-day fluctuations in relationship features, which may be obscured through assessments that aggregate across experiences. Together, these findings highlight important and novel links between daily family interactions and inflammatory processes in youths.

Chapter 5: The Role of Family Routines in the Intergenerational Transmission of Depressive Symptoms Between Parents and Their Adolescent Children

Thus far, the present research has provided converging evidence for the possibility that novel aspects of the family environment—specifically, parental empathy and behavioral consistency—may contribute to youth internalizing symptoms and to depression-relevant inflammatory pathways. However, parental empathy was also found to come at a cost to parents. Thus, for the final study, I sought to concentrate exclusively on behavioral consistency and to test its role in the intergenerational transmission of depressive symptoms. Here, I selected family routines as one important indicator of—and contributor to—consistency within a family, which Boyce et al., (1983) define as "the predictable, repetitive patterning which characterizes day-to-day, week-to-week existence within a given nuclear family unit, the shared pattern of behavioral rhythmicity that serves as an ordering principle in the ongoing process of a family's existence" (p. 194). Although routines may play a role in fostering broadly adaptive or maladaptive family environments through different mechanisms, I propose that family routines may contribute specifically to the intergenerational transmission of depression by shaping youth emotion regulation abilities as well as cellular inflammatory processes.

Family Routines and Pathways to Depression

As previously discussed, parents with higher depressive symptomatology show a range of parenting deficits that are believed to, at least partially, account for intergenerational risk of depression (Lim et al., 2008). Disruptions to behavioral consistency in the form of fewer family routines may be one additional mechanism of risk. Indeed, research on caregiving in infancy suggests that mothers with postpartum depression enact fewer behavioral routines with their

children, such as for sleeping and feeding (Field, 2010). It is possible that similar deficits exist even in families of older children.

In turn, disruptions to behavioral consistency have been linked to youth mental health processes. For example, more consistent rule enforcement by mothers was shown to predict lower internalizing and externalizing psychopathology symptoms in sixth grade children (Benson et al., 2008). Furthermore, families with more consistent routines were found to have children with better behavioral self-control, which was itself associated with fewer internalizing and externalizing symptoms (Brody & Flor, 1997). But how might these associations between routines and depressive symptoms come about?

By fostering consistency, family routines may exert a stabilizing force for youths that facilitates both better emotion regulation abilities and reduced inflammatory activity, two mechanisms tied to depression in children and adults. Evidence supporting these possible pathways can be found in parallel work demonstrating that other types of family characteristics shape these same affective and physiological processes. For example, young adults with better parental support during childhood have been shown to utilize more adaptive emotion regulatory and coping strategies, such as greater use of positive reappraisal and problem solving (Valentiner & Holahan, 1994). In addition, in families characterized by consistent interactions through routines, youth may have clearer expectations for the availability of support, parental dependability, and their own behavior, all of which may facilitate youth self-regulation. To this end, predictable, routinized behavior has been associated with better self-control in samples of both Caucasian and African American adolescents (Brody & Flor, 1997; Fiese & Kline, 1993; Jensen, James, Boyce, & Hartnett, 1983). By extension, it is possible that the regulation of *emotions* is similarly associated with family routines.

Family routines may also help to shape inflammatory processes in youths. Indeed, other characteristics of the family environment have been shown to relate to offspring markers of inflammation. Research by Fuligini and colleagues has demonstrated that daily experiences of interpersonal stress and family burden among adolescents were related to higher levels of circulating IL-6 and CRP (Fuligni, Telzer, Bower, Cole, et al., 2009a; Fuligni, Telzer, Bower, Irwin, et al., 2009b). Maltreatment in childhood has also been associated with higher levels of CRP in adulthood (Danese, Pariante, Caspi, Taylor, & Poulton, 2007), as has lower parental empathy for adolescent children (Manczak et al., 2016). Moreover, parental behavioral consistency has been connected to inflammatory cytokine production. As demonstrated in the previous study, less variability in daily interactions between parents and youths was associated with smaller stimulated proinflammatory cytokine responses in youth. Examining the family as a unit, greater utilization of routines within families of children with asthma predicted decreases in mitogen-stimulated production of the asthma-relevant cytokine interleukin 13 over an 18-month period (Schreier & Chen, 2010). The extent to which family routines may be linked to cytokines associated with depression remains unclear, however.

The Present Study

The present work sought to test the role of family routines in the intergenerational transmission of depressive symptoms via effects on emotion regulation processes and a biomarker of inflammation. As displayed in a schematic model of my hypotheses in Figure 2, I predicted that parents who were experiencing higher levels of depressive symptoms would be less able to provide a predictable family environment for their children, which would be reflected in fewer family routines. In turn, I hypothesized that, for youths, fewer family routines would be related to higher levels of the proinflammatory cytokine IL-6 in circulation and to poorer

emotion regulation abilities—two markers related to key components of risk that I anticipated would be associated with youth depressive symptoms. Finally, I predicted that fewer family routines would be related to higher levels of depressive symptoms in youths, both directly and indirectly through IL-6 and emotion regulation abilities.

Method

Adolescent children (ages 13-16) and their parents were recruited through advertisements in local media into a larger study on cardiovascular functioning and family characteristics. All participants were required to be free of chronic and acute illness and to be fluent in English. Two-hundred-sixty-one dyads composed of one adolescent and one parent from each family participated. Seventy-six percent of parents were mothers and 53% of children were female. Youths were on average 14.53 years old (*SD*=1.07) and parents were on average 45.83 years old (*SD*=5.50). Forty-nine percent of children identified as being of European descent, 36% identified as being of Asian descent, 5% identified as being of Latin American descent, 5% identified as being of African descent, and 5% identified as "other." Average family income was in the $50,000-74,999 Canadian dollars range and parents had on average some college education. Seventy-one percent of parents were married, 18% were divorced, and 11% were single.

Procedure

As part of a laboratory visit, parents and youths provided written consent and assent before independently completing a series of questionnaires, described below. In addition, peripheral blood was drawn from youths. Covariates potentially related to independent or dependent variables, including age, gender, ethnicity, and waist circumference, were also assessed.

Measures

Depressive symptoms. Parents and youths independently completed the Center for Epidemiological Studies Depression Scale Short Form (CESD; Bjorgvinsson et al., 2013). This widely-used self-report depression screen probes for the frequency of ten depressive symptoms over the course the previous week and is appropriate for use with both adolescents and adults (Bradley et al., 2010; Mojtabai & Olfson, 1999). Its reliability and validity have been established in clinical as well as community samples, showing convergence with other self-report measures of depression and with clinical diagnoses of major depressive disorder (Anderson et al., 1994; Bjorgvinsson et al., 2013). Higher scores on this measure indicate greater depressive symptomatology ($\alpha = .81$ for parents; $\alpha = .72$ for youths, current sample).

Family routines. Parents and youths also independently completed the Family Routines Inventory (Jensen et al., 1983), a 20-item measure probing for how regularly family members engage in specific behavioral routines in any given week. Participants were asked to rate the extent to which various behaviors are a routine in their family, such as "Children do the same things every morning as soon as they wake up" or "Family has certain 'family time' each week when they do things together at home." Responses follow a 4-point scale from "almost never" to "always" with specific frequencies provided as guides (for example, "3-5 days a week" or "most weekdays," depending on whether the item is appropriate across the week or for weekdays only). This scale has been shown to have good test-retest reliability and validity (Jensen et al., 1983) and to converge with other measures of child routines (Sytsma, Kelley, & Wymer, 2001). Higher scores on this inventory indicate family environments characterized by greater consistency of family routines ($\alpha = .85$ for parents; $\alpha = .79$ for youths, current sample). In the present study, youth and parent scores were significantly correlated ($r(251)=.33$, $p<.001$); consequently, reports

were standardized and then averaged to create a single, more reliable indicator of family routines. This approach of combining parent and youth reports sought to increase the reliability of the construct while reflecting the importance of considering the family as a unit (rather than only the parent's or youth's appraisal).

Youth emotion regulation. Parents reported on their child's perceived emotion regulation abilities by completing a shortened version of the Emotion Regulation Checklist (Shields & Cicchetti, 1997). They rated six statements on a 4-point scale to indicate the extent to which emotion regulation abilities were characteristic of their child, including "Is able to delay gratification" and "Can recover quickly from things that upset or distress him/her." Higher scores on this measure reflect more adaptive emotion regulation skills ($\alpha = .75$, current sample).

Inflammatory biomarker. Peripheral blood was drawn from youths using antecubital venipucture into serum separator (SST) tubes. Serum was harvested by centrifugation at 1,200g for 10 min and was then frozen at -30 °C until assays were performed. Circulating levels of interleukin 6 (IL-6) were assessed in the lab using high sensitivity ELISA kits (R&D Systems, Minneapolis, MN). This system has a lower detection threshold of .07pg/ mL. Intra- and interassay coefficients of variation were less than 10%. This marker was selected because elevations in IL-6 (and other pro-inflammatory cytokines) are believed to play a role in the pathogenesis of depression (Raison et al., 2006) and have been shown to be elevated in individuals with major depressive disorder (Dowlati et al., 2010; Liu et al., 2012). IL-6 values were log transformed prior to analysis to normalize the distribution.

Covariates. Demographic characteristics of youth age, gender, and ethnicity were assessed and retained as covariates. Ethnicity was represented using a set of dummy codes to create contrasts between being of European descent, Asian descent, or other descent. Youth waist

circumference was additionally included as a covariate for analyses with IL-6 to control for the potential contribution of adiposity to inflammatory processes (i.e., to be sure that obesity was not accounting for potential links between IL-6 and youth depressive symptoms). As a measure of adiposity, waist circumference has been shown to be a better predictor of chronic inflammation than body mass index (Festa et al., 2001; Hermsdorff, Zulet, Puchau, & Martínez, 2010).

Statistical Approach

Descriptive statistics and zero-order correlations between study variables were computed. Following this, path analyses were conducted to simultaneously test direct and indirect pathways linking the constructs of interest. I aimed to (a) test a scenario involving the role of routines as a link between parental depression and child depression, while (b) simultaneously testing the mechanisms through which routines might confer risk, both directly and indirectly through associations with emotion regulation and IL-6 production. Path analyses were conducted using the Mplus software (version 6.12, Muthén & Muthén, 2011) and used maximum likelihood estimation with robust standard errors. Given that only 3% missing data was observed, imputation was unnecessary. Model fit was evaluated using several statistics: overall model fit was assessed by examining the chi-square test of fit, in which a nonsignificant value indicates acceptable fit, the Comparative Fit Index (Bentler, 1990), in which a value above .90 is considered acceptable (Bentler & Bonett, 1980), and the root-mean-square error of approximation (RMSEA), for which a value less than .08 is considered indicative of a reasonable fit (Browne & Cudeck, 1992). Comparisons between nested models were evaluated using the chi-square test of difference, in which a nonsignificant value indicates that both models are of equivalent fit (and thus the smaller model should be used), while a significant value indicates the nested model is a worse fit for the data (Schermelleh-Engel & Moosbrugger, 2003). Although I

hypothesized specific associations between the variables (as displayed in the schematic), I began by testing a full model in which all paths were specified and then compared this to models in which paths were increasingly eliminated based on their statistical significance, stopping once the fit of the nested model was worse than the one prior. This approach allows me to determine whether the best-fitting model for the data is or is not consistent with my hypothesized model. Specific parameters of path analyses are described below and standardized coefficients (betas) are presented in all path analysis results.

Results

Descriptive statistics and intercorrelations for study variables are presented in Tables 9 and 10. There were several significant correlations between demographic covariates and study variables. Specifically, families with older children endorsed fewer routines, as did families of European descent. In contrast, families of Asian descent endorsed more routines. IL-6 levels were negatively associated with child age, but positively associated with waist circumference. Boys and youths of European descent reported lower levels of depressive symptoms.

Path Analyses of Full Model: Direct and Indirect Effects

Parent and youth depressive symptoms, routines, emotion regulation, and IL-6 variables were included in the path analyses. Across all models, each of these variables was regressed onto covariates of age, gender, and dummy codes representing being of European descent, Asian descent, or neither European nor Asian descent. IL-6 was additionally regressed onto waist circumference. The direct paths specified in the full model (Model A) were links from parental depressive symptoms to family routines, emotion regulation, IL-6, and youth depressive symptoms, from family routines to emotion regulation, IL-6, and youth depressive symptoms, from emotion regulation to IL-6 and youth depressive symptoms, and from IL-6 to youth

depressive symptoms. These pathways were specified based on previous research examining connections between aspects of family life and youth psychobiological functioning, as reviewed above. In addition to the significance of direct effects, the path analysis results also indicated significance levels of each possible indirect effect.

The standardized path coefficients for the full model are presented in Figure 3. For clarity, contributions of demographic covariates are not presented. Overall, Model A had acceptable fit, where X^2[4, N=260]=6.47, *ns;* CFI=.976, and RMSEA=.049. The simultaneous estimation of direct effects was largely consistent with the theoretical model, such that there was a significant direct path from parental depressive symptoms to family routines (β=-.20, *95% CI*=-.30, -.10, p<.01) and to emotion regulation abilities (β=-.19, *95% CI*=-.31, -.06, p<.01). Significant direct paths also existed to child depressive symptoms from family routines (β=-.20, *95% CI*=-.33, -.07, p<.01), emotion regulation abilities (β=-.17, *95% CI*=-.29, -.04, p<.01), and IL-6 (β=.14, *95% CI*=.02, .25, p<.05). Direct paths between parental depressive symptoms and child depressive symptoms (β=-.11, *95% CI* =-.02, .23, p<.10), family routines and emotion regulation abilities (β=.11, *95% CI*=-.02, .25, p<.10), and family routines and IL-6 levels (β=-.12, *95% CI*=-.24, .01, p<.10) were marginally significant. The paths from parental depressive symptoms to youth IL-6 and from emotion regulation to IL-6 were nonsignificant (β=.04, *95% CI*=-.10, .17, *ns* and β=-.05, *95% CI*=-.20, .09, *ns*, respectively).

Tests of indirect effects are presented in Table 11. These reveal a significant indirect pathway from parent depressive symptoms to youth depressive symptoms through family routines (β=.04, *95% CI*=.00, .08, p<.05). In addition, there were marginally significant indirect pathways from parental depressive symptoms to youth depressive symptoms through emotion

regulation abilities (β=.03, *95% CI*=-.01, .07, p<.10) and from parental depressive symptoms to youth IL-6 levels through family routines (β=.02, *95% CI*=.00, .04, p<.10).

Path Analyses of Trimmed Model Retaining Marginal and Significant Paths

To probe for the best fitting model, I next compared Model A to a trimmed model that retained pathways originally shown to be significant or marginally significant (Model B). Given my focus on the hypothesized role of family routines in conferring aspects of risk, I opted to retain marginally significant pathways as well as significant pathways in order to further probe connections between family routines and youth emotion regulation and between routines and youth IL-6 levels, which were marginally significant in the first model. (I also tested a model in which only significant paths were retained, described below as Model C.) Overall, Model B had acceptable fit as well, where X^2[6, N=260]=6.61, *ns;* CFI=.993, and RMSEA=.021.

As displayed in Figure 3, direct paths from parental depressive symptoms to family routines (β=-.20, *95% CI*=-.30, -.10, p<.01) and to emotion regulation abilities (β=-.18, 95%CI [-.31, -.06], p<.01) were significant. As before, direct paths to child depressive symptoms from family routines (β=-.20, *95% CI*=-.33, -.07, p<.01), emotion regulation abilities (β=-.17, *95% CI* =-.29, -.04, p<.01), and IL-6 (β=.14, *95% CI*=.02, .26, p<.05) were also significant. In contrast to Model A, the path from family routines to IL-6 was statistically significant in Model B (β=-.13, *95% CI*=-.26, -.01, p<.05). Direct paths between parental depressive symptoms and child depressive symptoms (β=-.11, *95% CI*=-.02, .23, p<.10) and between family routines and emotion regulation abilities (β=.11, *95% CI*=-.02, .24, p<.10) were marginally significant.

Similar to Model A, tests of indirect effects revealed a significant indirect path from parental depressive symptoms to youth depressive symptoms through family routines (β=.04, *95% CI*=.00, .08, p<.05). There were also marginally significant indirect effects of parental

depressive symptoms on youth depressive symptoms through emotion regulation abilities (β=.03, *95% CI*=-.01, .07, p<.10) and of parental depressive symptoms on youth IL-6 levels through family routines (β=.02, *95% CI*=.01, .05, p<.10).

An examination of the chi-square test of difference suggested that this trimmed, nested model (Model B) was equivalent in fit to the Model A (X^2_{diff}[2, N=260]=.235, *ns*), and thus superior. This determination is further supported by comparing the values of the CFI and RMSEA across the models, as well.

Path Analyses of Trimmed Model Retaining Significant Paths Only

I next compared the trimmed model retaining both marginal and significant paths (Model B) to a model in which only the significant paths were retained from the full model (Model C). Here, X^2[9, N=260]=16.75, *n.s.*; CFI=.924, and RMSEA=.058, indicating adequate fit.

All specified paths were significant, such that there were significant paths from parental depressive symptoms to family routines (β=-.20, *95% CI*=-.30, -.10, p<.01) and to emotion regulation abilities (β=-.21, *95% CI*=-.34, -.08, p<.01). Paths from family routines, emotion regulation, and IL-6 levels to child depressive symptoms were also significant (β=-.22, *95% CI*=-.36, -.09, p<.01; β=-.19, *95% CI*=-.31, -.06, p<.01; and β=.14, *95% CI*=.02, .27, p<.05, respectively).

Tests of indirect effects revealed that there were significant indirect paths from parent depressive symptoms to child depressive symptoms through both family routines and emotion regulation abilities, (β=.04, *95% CI*=.00, .08, p<.05 and β=.04, *95% CI*=.00, .08, p<.05, respectively).

A comparison of this model to the prior model using the chi-square test of difference indicated that the model retaining both marginal and significant paths was superior in fit to the

model retaining significant paths only (X^2_{diff}[3, N=260]=10.045, p<.05). Consequently, Model B (retaining both marginal and significant paths) was the best fitting model for our data and I did not test any further nested models.

Discussion

As researchers and clinicians seek to understand and thwart the intergenerational transmission of depression between parents and children, they increasingly turn to modifiable characteristics of the family environment that may confer risk (Connell & Dishion, 2008; Valdez, Mills, Barrueco, Leis, & Riley, 2010). While previous work has tended to focus on the *quality* of parenting characteristics, such as parental warmth or harshness, the current work sought to test a model in which *routines* within families may contribute to key immunologic and affective processes. In keeping with a biopsychosocial conceptualization of the intergenerational transmission of depression (Goodman & Gotlib, 1999), the results of the present study suggest that the utilization of family routines may play a role in multiple risk processes, consistent with my hypothesized model. Specifically, I found that, in the best fitting model of risk, family routines were significantly associated with both parent- and youth-depressive symptoms and youths' levels of a biomarker of low-grade inflammation, IL-6, and had a marginally significant association with youths' emotion regulation abilities. Furthermore, my model revealed that a statistically significant portion of the observed link between parent- and youth- depressive symptoms (22%) was accounted for by fewer family routines.

That parental depressive symptoms were related to fewer family routines is consistent with prior work documenting depression-related impairments in other aspects of caregiving, such as more intrusive interactions and greater hostility toward children (Ge et al., 1994; Lovejoy et al., 2000). As such, this work extends an understanding of the taxonomy of caregiving deficits

that may exist when a parent is depressed. Multiple different depressive symptoms may contribute to this particular impairment. For example, parents may find it more difficult to access the energy for engaging in consistent interactions with their children due to motivational declines or sleep disturbance (Goyal, Gay, & Lee, 2007). Even if attempted, those interactions may be less reinforcing, as greater anhedonia may result in parents deriving less satisfaction or pleasure from spending time regularly with their child (Lovejoy et al., 2000; Pizzagalli, 2014). It is also possible that if interactions with a depressed parent are more aversive, youths, too, may be less willing to participate in family routines.

In turn, families with fewer routines have youths with riskier phenotypes. In the current study, engaging in fewer family routines was associated with higher IL-6 levels in youths and showed a trend-level association with worse emotion regulation, in line with the proposal that less consistent family behaviors may undermine structure and predictability and relate to depression-relevant affective and immunologic processes (Abramson et al., 1978; Boyce et al., 1983).

That IL-6 was significantly related to youth depressive symptoms echoes the findings that individuals with depression show elevations in this biomarker, reaffirming links between psychopathology and inflammation even in adolescence (Gabbay et al., 2009; G. E. Miller & Cole, 2012). Although there was not evidence that IL-6 accounted for the association between family routines and youth depressive symptoms (contrary to my predictions), there was a marginally significant indirect effect of family routines accounting for part of the link between *parental* depressive symptoms and youth IL-6. This finding is consistent with previous work attesting to associations between impairments in caregiving and youth inflammation (G. E. Miller & Chen, 2010; Repetti, Robles, & Reynolds, 2011). Indeed, given that inflammation is

implicated not only in depressive disorders but also in a variety of physical health disorders, such as heart disease and certain cancers (Heikkilä et al., 2008; Ridker et al., 2000), this pathway from parental depression and family routines to youth inflammation may have important effects on offspring's health in the future if sustained over the long term. For example, previous work has shown that children raised in abusive or dysfunctional family environments show elevations in forms of cancers, chronic lung disease, skeletal fracture, ischemic heart disease, and liver disease (Felitti et al., 1998). It is possible that the absence of family routines, if it encourages repeated activation of the proinflammatory processes that give rise to higher IL-6, may over time impact both physical and mental health.

With regard to emotion regulation, there was a significant pathway from parental depressive symptoms to youth emotion regulation and a marginally significant pathway from family routines to emotion regulation abilities, suggesting that youths exposed to parental symptomatology or who have more chaotic home environments may have less support for learning adaptive coping strategies (Repetti et al., 2002), resulting in weaker development of emotion regulation skills and more emotional lability that confer risk for depression (Morris et al., 2007; R. J. Thompson et al., 2012). There was also a marginally significant indirect effect in which emotion regulation abilities accounted for part of association between parent depressive symptoms and youth depressive symptoms, highlighting the importance of affective processes for intergenerational transmission.

These pathways through family routines, emotion regulation, and IL-6 may represent broad risk for a range of mental and physical health problems, but they also show particular connections to youth depression. Here, I found that not only were there direct effects between family routines and youth depressive symptoms, there was also a significant indirect effect in

which parental depressive symptoms related to youth depressive symptoms through family routines. In this way, routines appear to be one mechanism that confers risk for the intergenerational transmission of depressive symptoms. Although the size of this effect is small, it may nonetheless represent an important risk factor (Prentice & Miller, 1992). Indeed, even small changes in depressive symptoms or subsyndromal depression may result in notable impairment for individuals (Rapaport & Judd, 1998). Furthermore, given that adolescence represents a time of increasing vulnerability for the onset of major depressive disorder (e.g., K. C. Burke et al., 1991), it is possible that family factors that contribute to risk during this period will have a more substantial impact than at other developmental periods. However, further work is needed to test this possibility directly.

There are several limitations to acknowledge in the present work. First, the study was cross-sectional in nature, making it impossible to determine directionality or causality. For example, it is possible that higher youth depressive symptoms may lead to fewer routines or may take a toll on parental mental health, rather than the reverse. Future longitudinal work will be important for determining the time course and direction of these pathways. Second, parent and youth depressive symptoms were assessed at the symptom-level using short self-report inventories, rather than clinician-administered measures or more comprehensive, multidimensional assessments. However, the CES-D has been shown to converge with clinician diagnoses and is commonly used in clinical settings, including primary care (Bjorgvinsson et al., 2013; L. R. Fischer, Wei, Solberg, & Rush, 2003). Thus, although it is brief, the measure represents an important real-world tool for the diagnosis and treatment of depressive symptoms. Moreover, a dimensional (vs. categorical) approach to depression acknowledges the substantial toll that even subthreshold depressive symptoms can take on psychosocial functioning (Rapaport

& Judd, 1998). Future work would also benefit from observational or daily diary assessment of other constructs such as family routines or emotion regulation, as well as youth reports of emotion regulation.

There are also limitations regarding the study sample. For example, the current study was conducted in a city in which the majority of the citizens are of European or Asian descent, which was reflected in the low numbers of participants of Latin American or African descent, limiting generalizability. Additionally, the sample was drawn from the community and required that participants not take medication for chronic health issues. Thus, no participants included in the study were on long-term psychotropic medication, which likely contributed to the generally low levels of depressive symptoms observed in parents and youths. However, if anything, restricted range should attenuate the magnitude of associations (Wiberg & Sundström, 2009), underestimating the contribution of family routines to these pathways. Rather, that these associations emerge in normative family environments suggest that they may represent a persistent source of influence on youths across the spectrum of functioning.

The current research also raises several important issues deserving of future study. Examinations of interventions aimed at cultivating family routines will be particularly fruitful for determining causal pathways and for testing additional implications. For example, although the focus of the current project was on how family routines may affect youths, additional research should consider how the implementation of family routines may impact *parents* with depression. Might consistently engaging with their children around dinners or homework serve as a form of behavioral activation that lessens depressive symptomatology in parents? Or might it represent an additional burden for parents that saps already limited energetic resources? Longitudinal work will be especially important for clarifying these potential effects and for examining other parent

and child characteristics that may contribute to the generation or maintenance of family routines, including assessments of family quality.

Another interesting topic for future work would be to examine how systems *outside* of the home may influence family routines and youth mental health. For example, certain religious communities have regular patterns of worship that may add consistency to weekly family behaviors, while schools can differ in whether students' class schedules are consistent or variable across days of the week. It would be interesting to see whether such community-level structures might relate to youth mental health as well or how other types of regularly-occurring family behaviors would be associated with these outcomes. With regards to this last point, the current work was guided by the conceptualization of family routines provided by Jensen et al. (1983). However, other types of behaviors, such as family prayer, seasonal vacations, or holiday traditions, could be considered family traditions or rituals and should be investigated in the future.

Additional work should also consider other forms of youth psychopathology. For example, future research might examine associations between parental depression, family routines, and youth ADHD or anxiety disorders. Previous work has shown that maternal depression is associated with broad risk for youth mental health disorders (Goodman et al., 2011). Thus, it is possible that impairments in family routines may confer risk for other forms of psychopathology. Relatedly, future research should also consider whether there might be forms of youth psychopathology for which the cultivation of family routines would be contraindicated. For example, would it be possible for families to become overly rigid about family interactions in ways that then undermine healthy youth functioning?

Despite these limitations and unanswered questions, the current work has several notable strengths and important implications. First, the present study examined a novel, integrative model for the transmission of depressive symptoms, reflecting the interconnections of social, biological, and psychological processes in the context of youth psychopathology. In doing so, it drew on multiple reporters and mixed methodology, reducing the likelihood that associations amongst variables were due to shared method variance. Second, it highlighted a dimension of family life that may be particularly conducive to modification through behavioral interventions. Promoting the cultivation of family routines may be safer, more cost effective, more palatable, and more easily disseminated than other types of interventions for depression such as specialized therapies or prescriptions for psychotropic medications, which require extensive training and expertise on the part of the care provider. Lastly, by testing multiple outcome variables, such as emotion regulation and IL-6, the current study has implications for theoretical models of the biological and psychological processes involved in youth depression. In sum, the results of this study suggest that family routines may have important consequences for youth mental and physical health and their underlying processes.

Chapter 6: General Discussion

Across four studies, the current project sought to explore the role of family characteristics in a theoretical model for the intergenerational transmission of depression by investigating how dimensions of parental empathy (one's dispositional tendency to take the perspective of others and be concerned about others' suffering) and family consistency (how much variability exists in the quality, timing, or type of parent-youth interactions) were associated with affective and physiological processes relevant to depression in youths. Briefly, the first study found that lower levels of empathy in parents' discussions of challenging experiences related to an array of worse inflammatory profiles (i.e., larger stimulated cytokine responses) and to higher levels of internalizing psychopathology symptoms in a sample of children with asthma. When examining associations between parental empathy and *parents'* inflammatory outcomes, however, Study 2 found that *greater* parental empathy predicted worse inflammatory profiles for parents themselves when their child had high levels of depressive symptoms, suggesting that providing empathy in the context of youth depression may come at a physiological cost. The third study then turned to an examination of family consistency and predictability in relation to stimulated proinflammatory cytokine profiles in a sample of healthy children, finding that youths who experienced greater affective and temporal day-to-day variability during interactions with their parents showed larger stimulated proinflammatory cytokine responses. Lastly, consistency in the family environment was further investigated in Study 4, which tested a model for the intergenerational transmission of depressive symptoms via family routines and found that fewer routines accounted for part of the association between parent- and child- symptomatology. Together, these studies suggest that impairments in parental empathy or family consistency may increase youths' risk for depressive processes, raising important questions for future research.

One such important question raised by this dissertation is: whose outcomes should be the focus of research on youth depression? The child alone or the family as a unit? The observed divergence in inflammatory outcomes between *receiving* empathy and *providing* it highlights the complicated interpersonal context of depression and has implications for treatment interventions. Substantial prior research finds that dysfunction within relationships both contributes to and results from depressive symptoms (Joiner & Timmons, 2002; Zlotnick, Kohn, Gabor, & Grotta, 2000). When an individual is depressed, supportive relationships can be critical for helping the person cope and recover (George, Blazer, Hughes, & Fowler, 1989; Goering, Lancee, & Freeman, 1992; Lara, Leader, & Klein, 1997), and yet those relationships are likely to be subjected to particular strain as a result (Coyne, Thompson, & Palmer, 2002; Davila, Hammen, Burge, & Paley, 1995). Thus, in many ways, it is unsurprising that characteristics tied to youth depressive processes may have different effects across family members. However, most research and clinical work concerning families and youth depression has concentrated exclusively on improving *child* functioning (Asarnow, Scott, & Mintz, 2002; Connell & Dishion, 2008). If adopting this perspective, then efforts to increase parental empathy should be a focus of future interventions. Indeed, the current studies and my prior work (Manczak et al., 2016) suggests that children who have parents who are more empathic show fewer internalizing symptoms, better emotion regulation, smaller stimulated inflammatory responses, and lower chronic inflammation. Thus, fostering empathy may help shape these important child outcomes. However, if we consider the family as a unit as a focus of intervention, then this approach might come at a physiological cost to parents and would not be advised. Instead, the current findings suggest that family routines and daily interpersonal interaction variability may be better targets of treatment. (Indeed, exploratory analyses not reported in the current work did not find evidence of any

immunological costs to parents of either the variability variables in Study 3 or family routines in Study 4). These processes appear to similarly foster better inflammatory profiles and lower depressive symptoms in youths, but without a hidden, physiological burden on parents.

These two focal family characteristics (empathy and consistency) draw attention to important differences between emotional and structural elements that may contribute to the transmission of depression. Although both appear to relate to depression-relevant processes for youths, it is likely they may operate—at least partially—through different mechanisms. The positive outcomes associated with consistent parent-child interactions and greater family routines signal the relevance of structural aspects of family to youth depression. These features may confer benefit by promoting psychological predictability for children, which in turn may result in less frequent or less intense activation of stress response systems (S. M. Miller, 1981). By knowing what to expect during contact with a parent and when interactions will occur, anticipatory stress arousal may be minimized (Greco & Roger, 2003; Grillon, Baas, Lissek, Smith, & Milstein, 2004) and youths may use energetic resources more efficiently—relaxing if they expect positive interactions or activating coping or defensive strategies if they anticipate conflict, for example. In contrast, affective elements of families, like parental empathy, may operate on youths' depressive processes by allowing parents to provide more attuned help, resulting in greater emotional support to youths. This support, in turn, may both shield children from experiences of stress (as parents recognize and then minimize children's exposure to stress) and act as a buffer when stressful events do occur (Calkins, Propper, & Mills-Koonce, 2013; Guan et al., 2016).

That both characteristics appear to confer risk or protection from depression-relevant processes suggests that parents may utilize multiple tools to help their children. For example, if

parents are not high on dispositional empathy, it may be possible for them to still foster better youth outcomes by concentrating on providing a consistent, predictable family environment. Alternately, if life circumstances result in structurally chaotic home lives, exhibitions of parental empathy may provide an important buffer for children. Of course, these aspects of caregiving are likely not completely independent of one another, either. Being concerned about and attuned to the needs of one's child may make a parent more likely to recognize the important stabilizing benefits of consistency. Conversely, more consistent interactions may facilitate more perceptive insights about that child's emotional states. However, future work will be necessary to determine the extent of overlap and independence of these constructs.

Although the current project was focused on physiological and psychological mechanisms that pertain to youth depression, the results have important implications for physical health problems as well. Research on psychoimmunology has long acknowledged the significance of early childhood contexts—including aspects of parent-child relationships—for affecting health trajectories (Beach, Lei, Brody, Dogan, & Philibert, 2015; Brody, Miller, Yu, Beach, & Chen, 2016; G. E. Miller & Chen, 2010). For example, a representative study of children in Sweden found that adverse family conditions in early life (such as economic hardship or family conflict) was associated with illness symptom severity 13 years later and that family conflict was the facet of this early environment that predicted illness and mortality most strongly (Lundberg, 1993). Similarly, a study of undergraduates found that men who rated themselves as having a negative relationship with one of their parents were twice as likely to have a diagnosed disease 35 years later than those with neutral or positive relationships (Russek & Schwartz, 1997). Research seeking to explain these links suggests that early developmental contexts may contribute to later health outcomes by shaping key aspects of the biological stress responses,

initiating a cascade of physiological changes that span multiple physiological systems (Repetti et al., 2002). As previously discussed, one key pathway for these effects is inflammation, which is also believed to explain the high comorbidity between depressive symptoms and physical disease (Iwata, Ota, & Duman, 2013). Thus, by identifying links between parental empathy and consistency with youth inflammatory processes, the results of the present studies highlight family characteristics that are not only relevant to youth mental health, but also to later physical health.

Although the present work was focused on understanding, rather than preventing, youth depression, the current set of studies may still have important implications for clinical interventions. Currently, many family-focused interventions for youth psychopathology encourage parents to develop greater empathy for their child (Pavuluri et al., 2004). While this may be helpful for children, the current work suggests that this may come at a cost to parents themselves. Future work incorporating the assessment of inflammation in addition to psychological functioning will be important for determining the physical and emotional trade-offs of traditional family-based treatment for youth depression across family members. In contrast, interventions that seek to increase predictability and consistency within the family (such as by encouraging the development of family routines) may be an efficient, safe, and cost-effective intervention with minimal burden or risk. Moreover, such interventions could likely be disseminated by a range of care providers or community members, reducing the need to seek specialized therapists or psychiatrists. However, if disadvantaged life circumstances make establishing consistency difficult, interventions might continue to foster greater empathy but might also include discussion of self-care, health behaviors, and stress management for parents.

Limitations

The current project has several limitations that are important to acknowledge. First, across the four studies, slightly different assessment instruments were used for constructs of interest, limiting an ability to directly compare studies. For example, empathy was assessed using self-report and narrative coding, depressive symptoms were examined through the Child Depression Inventory and by the internalizing subscale of the Youth Self Report, consistency was explored using daily diaries and reports of family routines, and inflammatory processes were indexed by both circulating inflammatory markers and stimulated production of proinflammatory cytokines in response to a variety of mitogens. It remains unclear the extent of overlap that would exist between these various measures, such as correlations between narrative perspective-taking codes and self-reported empathy scores. At the same time, I believe these differences in assessment provide convergent validity for central study hypotheses and speak to the generalizability of associations across both medically healthy children and children with asthma.

Another important limitation of the current work is that the data were taken from larger projects seeking to assess the role of social environments for youths' *physical* health, rather than mental health. Thus, the level of depressive symptoms in parents and children were relatively low and the measures used to assess psychopathology symptoms were short self-report questionnaires. More nuanced assessment of psychopathology, such as by clinician interview, and investigations within clinical populations would provide valuable insight.

A final limitation is that all analyses were conducted using data collected at single measurement periods. Consequently, it is impossible to determine directionality or causality of my findings or to understand the timescale under which these associations operate. For example, the present work was predicated on the assumption that inflammatory biomarkers are indicative

of important depression-relevant processes. Although there is substantial research linking proinflammatory processes to depression (e.g., A. H. Miller, Maletic, & Raison, 2009a; Slavich & Irwin, 2014), the current work was unable to establish causal pathways between inflammatory phenotypes and depressive symptoms in children. Future work with longitudinal assessments will be invaluable for confirming hypothesized directions of association.

Future Directions

The current set of studies was informed by a theoretical model sketched below in Figure 4. Across the four studies, I was able to examine many components of the model; however, important pieces remain untested. For example, while Study 4 tested the role of family routines in a model of the intergenerational transmission of depressive symptoms, I was unable to test a similar model examining the role of parental empathy for intergenerational transmission. Indeed, the current work does not directly examine associations between parents' depressive symptoms and their empathy, even though previous work has found that individuals with depression can have deficits in key aspects of empathy (such as identifying the emotions of others; Zobel et al., 2010). One step in examining this possibility would be for future work to assess levels of empathy in parents with current, remitted, or no history of depression and to test whether dispositional empathy differs between groups as well as whether it mediates associations with youth depression. This approach would also have the benefit of clarifying whether deficits in empathy confer risk to children in conjunction with, or independent of, parent's current mental health status.

Another direction for future research is to assess whether impairments in parental empathy affect consistency in families. In my conceptual model, I predict that lower levels of dispositional empathy in parents may make them less attuned to the importance of predictability

and consistency, conferring risk through similar pathways. One way to assess these links might be to examine whether parent's dispositional empathy makes them more or less likely to implement behavior change following a brief psychoeducational intervention regarding the benefits of establishing family routines. It will also be interesting to determine the amount of overlap between risk conveyed by empathic deficits and risk conveyed by unpredictability. Here, research that assesses empathy, family consistency, and inflammatory markers for both parents and children within a single study framework will allow researchers to determine whether these family characteristics are independent or are shared predictors of depression-relevant processes and if they operate similarly for parents and for children.

Of course, a critical task for future work is to further clarify the biological and psychological cascades that link parental empathy and consistency to youth depressive symptoms and inflammation. Developing and testing biologically plausible models that explain intermediary connections between psychological experiences and physiological stress responses will be especially fruitful. For example, considering differences in gene regulation would provide insight into an additional and important mechanistic layer. Similarly, examining associations between parental empathy and family consistency with youth reports of daily experiences of distress holds the potential to clarify how persistent, daily manifestations of these traits may accrete to contribute to indicators of stress.

Regardless of these unanswered questions, the current set of studies provides a first step in examining novel dimensions of parental empathy and family consistency in contributing to youth depression. Through a consideration of both biological and psychological pathways, and both parents and children, it contributes to a greater understanding of the complex yet critical role of the family environment in youth depression.

Tables

Table 1. *Descriptive Statistics for Study 1 Variables*

	Mean	SD	Range	%
Child Age	13.43	2.22	9-17	
Parent Age	45.54	6.00	29-63	
Parent Years Education	16.52	2.71	12-25	
Child Gender (Female)				42
Child Ethnicity (Caucasian)				66
Parent Gender (Female)				88
Beta Agonist Use				96
Inhaled Corticosteroid Use				70
Empathy	.20	.36	0-2	
Anxious/Depressed Symptoms	6.56	4.94	0-26	
Parental Warmth	29.31	5.39	9-36	

Note. Descriptive statistics for the cytokine composites are not presented because they all have a mean of zero and a standard deviation close to 1, due to how they were computed. Beta Agonist and Inhaled Corticosteroid Use refer to the percent of participants who have been prescribed that form of medication by a physician.

Table 2. *Study 1 Summary of Associations between Parent Empathy and Youth Psychosocial and Cytokine Production Outcomes*

	β	*p*
Psychosocial Outcomes		
Anxious/Depressed Symptoms	-.15	.053
Immune (Cytokine Production)		
Nonspecific Stimulation		
PMA/INO: Th-1	-.15	.135
PMA/INO: Th-2	-.20	.035
Adaptive Immune Stimulation		
CR: Th-1	-.23	.010
CR: Th-2	-.22	.014
DM: Th-1	-.23	.011
DM: Th-2	-.14	.099
Innate Immune Stimulation		
Poly I:C: proinflammatory	-.19	.039
Glucocorticoid Sensitivity		
Poly I:C+Cortisol: proinflammatory	-.33	.000

Note. PMA/ION= phorbol 12-myristate 13-acetate + ionomycin; Th-1 = T helper 1 cytokine composite (IFN- γ & IL-10); Th-2 = T helper 2 cytokine composite (IL-2, Il-4, IL-5, and IL-13); CR= Cockroach; DM= Dust mite; Proinflammatory= Proinflammatory cytokine composite (IL-1β, IL-6, & TNF-α). Standardized beta weights are presented for empathy in models that also statistically controlled for youth age, gender, ethnicity, parent gender, and parent education. Beta agonist prescriptions and inhaled corticosteroid prescriptions were included as additional covariates in models of immune outcomes.

Table 3. *Study 2 Multiple Regression Models for Parental Empathy, Child Depressive Symptoms, and Their Interaction Predicting Parent Stimulated Inflammatory Cytokines*

Predictor Variable	R	R^2	F	Sig	Standβ	*t*	*p*	sr^2
Model IL-1β	.26	.07	3.41	.02				
Empathy					-.07	-.88	.38	.01
Child Depressive Sx					-.02	-.19	.85	.00
Empathy x Depressive Sx					**.26**	**3.14**	**.00**	**.06**
Model IL-6	.27	.07	3.55	.02				
Empathy					-.06	-.76	.45	.00
Child Depressive Sx					.04	.43	.67	.00
Empathy x Depressive Sx					**.39**	**4.32**	**.00**	**.07**
Model TNF-α	.27	.07	3.69	.01				
Empathy					-.13	-1.53	.13	.02
Child Depressive Sx					.01	.16	.87	.00
Empathy x Depressive Sx					**.24**	**2.89**	**.00**	**.06**
Model IL-10	.23	.05	2.66	.05				
Empathy					-.14	-1.64	.10	.02
Child Depressive Sx					-.06	-.71	.48	.00
Empathy x Depressive Sx					**.18**	**2.13**	**.04**	**.03**
Model Inflammation Composite	.30	.09	4.59	.00				
Empathy					-.12	-1.44	.15	.01
Child Depressive Sx					-.01	-.10	.92	.00
Empathy x Depressive Sx					**.27**	**3.35**	**.00**	**.07**

Note. IL-1 β= Interleukin 1 Beta; IL-6= Interleukin 6; IL-10= Interleukin 10; TNF-α= Tumor Necrosis Factor-Alpha; sr^2=semi-partial r-squared. All inflammatory markers were log-transformed prior to analysis. The inflammation composite reflects the sum of z-scored IL-1 β, IL-6, IL-10, and TNF-α levels. Similar results were obtained when including participant age, ethnicity, gender, and waist circumference as covariates.

Table 4. *Descriptive Statistics for Study 3 Variables*

Variable	Mean	Standard Deviation	Range
Child Age	14.57	1.05	13-16
Child Waist Circumference (cm)	75.11	9.27	59-113
Parent Years of Education	16.62	2.66	10-27
Hours Parent Works Per Week	31.16	14.35	0-70
Overall Quality Rating	2.71	.27	1.79-3.00
Quality Variability	.37	.23	.00-.84
Frequency Interaction	8.26	3.79	0-14
Timing Variability	2.40	1.09	0-4.56
Stimulated IL-1B (pg/mL)	3.74	.37	2.43-4.67
Stimulated IL-6 (pg/mL)	4.51	.17	3.64-4.89
Stimulated IL-8 (pg/mL)	4.19	.29	3.31-4.68
Stimulated TNF-α (pg/mL)	4.13	.22	3.33-4.71
Stimulated Cytokine Production	0.00	3.38	-13.16-8.36

Note. Stimulated cytokine variables are presented with log transformation. The composite stimulated cytokine production variable reflects the sum of z-scored IL-1B, IL-6, IL-8, and TNF-α values. Overall Quality Rating reflects the average of daily ratings of quality on a 1-3 scale. Frequency of Interaction reflects the number of days within a 2-week period in which parents and youths spent leisure time together.

Table 5. Intercorrelations Amongst Psychosocial Variables in Study 3

Variable	2.	3.	4	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Child Gender	-.09	-.05	-.05	.15	-.22*	.04	-.15	.07	-.10	-.13	.22*	.12	.05	-.07
2. Child Age		.03	-.03	-.01	.21*	-.09	.10	-.14	.10	-.05	.10	-.10	-.08	.08
3. European Descent			-.78 **	-.43 **	.07	.04	-.04	-.20*	-.08	-.03	.00	-.09	-.04	.03
4. Asian Descent				-.25 **	.00	-.06	.07	.06	.00	.00	.00	.01	-.04	.03
5. Other Descent					-.09	.03	-.04	.22*	.13	.05	-.10	.12	.11	-.09
6. Child Waist						.13	.04	-.15	-.09	.08	-.11	.00	.04	.13
7. Parent Gender							-.17	.07	-.28 **	.03	.04	.15	-.05	.04
8. Marital Status								-.16	-.04	.12	-.06	.14	.00	.06
9. Years of Education									.15	-.07	.02	.15	.12	-.05
10. Hours of Work										-.08	-.09	-.18*	-.13	-.05
11. Overall Quality											-.70 **	.31**	0.02	-.18*
12. Quality Variability												-.13	.15	.27**
13. Interaction Frequency													.39**	-.06
14. Timing Variability														.19*
15. Stimulated Cytokines														

Note. For parent and child gender, males were coded "0" and females were coded "1." Marital status was coded "0" for unmarried/widowed/divorced and "1" for married. European-, Asian-, and Other Descent were dummy coded "1" for endorsement and "0" for no endorsement of that ethnic status. * $p<.05$; ** $p<.01$

Table 6. *Study 3 Hierarchical Regression Model for Affective Variability of Parent-Child Interactions Predicting Youths' Stimulated Cytokine Production*

Predictor Variable	Standβ	*t*	*p*	sr^2
Step 1				
Youth Gender	-.08	-.87	.39	.01
Parent Hours Worked	-.06	-.61	.55	.00
Step 2				
Youth Gender	-.11	-1.17	.25	.01
Parent Hours Worked	-.07	-.80	.43	.01
Overall Relationship Quality	-.19	-2.14	.04	.04
Step 3				
Youth Gender	-.14	-.16	.11	.02
Parent Hours Worked	-.03	-.33	.75	.00
Overall Relationship Quality	.03	.25	.80	.00
Variability in Relationship Quality	.32	2.53	.01	.05
Model	R^2	ΔR^2	*p*	
Step 1	.01	.01	.60	
Step 2	.05	.04	.04	
Step 3	.09	.05	.01	

Note. sr^2=semi-partial r-squared. Additional potential covariates of youth age, ethnicity, waist circumference, parent gender, parent marital status, and parent years of education were not associated with cytokine production, interaction, or variability variables and were therefore not included in the models.

Table 7. *Study 3 Hierarchical Regression Model for Temporal Variability of Parent-Child Interactions Predicting Youths' Stimulated Cytokine Production*

Predictor Variable	Standβ	*t*	*p*	sr^2
Step 1				
Youth Gender	-.08	-.87	.39	.01
Parent Hours Worked	-.06	-.61	.55	.00
Step 2				
Youth Gender	-.07	-.80	.43	.01
Parent Hours Worked	-.07	-.70	.49	.00
Frequency of Interactions	-.06	-.62	.53	.00
Step 3				
Youth Gender	-.07	-.82	.42	.00
Parent Hours Worked	-.05	-.55	.58	.00
Frequency of Interactions	-.15	-1.53	.13	.02
Variability in Timing of Interactions	.24	2.51	.01	.05
Model	R^2	ΔR^2	*p*	
Step 1	.01	.01	.60	
Step 2	.01	.00	.53	
Step 3	.06	.05	.01	

Note. sr^2=semi-partial r-squared. Additional potential covariates of youth age, ethnicity, waist circumference, parent gender, parent marital status, and parent years of education were unrelated to cytokine production, interaction, or variability variables and were therefore not included in the models.

Table 8. *Study 3 Hierarchical Regression Model for Simultaneous Inclusion of Affective and Temporal Variability Predicting Youths' Stimulated Cytokine Production*

Predictor Variable	Standβ	*t*	*p*	sr^2
Step 1				
Youth Gender	-.08	-.87	.39	.01
Parent Hours Worked	-.06	-.61	.55	.00
Step 2				
Youth Gender	-.11	-1.16	.25	.01
Parent Hours Worked	-.07	-.68	.44	.00
Overall Relationship Quality	-.20	-2.03	.04	.03
Frequency of Interaction	.01	.05	.96	.00
Step 3				
Youth Gender	-.13	-1.47	.14	.02
Parent Hours Worked	-.03	-.28	.78	.00
Overall Relationship Quality	.02	.17	.86	.00
Frequency of Interaction	-.09	-.83	.41	.01
Variability in Relationship Quality	.28	2.13	.04	.03
Variability in Timing of Interactions	.18	1.88	.06	.03
Model	R^2	ΔR^2	*p*	
Step 1	.01	.01	.60	
Step 2	.05	.04	.11	
Step 3	.12	.08	.01	

Note. sr^2=semi-partial r-squared. Additional potential covariates of youth age, ethnicity, waist circumference, parent gender, parent marital status, and parent years of education were unrelated to cytokine production, interaction, or variability variables and were therefore not included in the models.

Table 9. *Descriptive Statistics for Study 4 Variables*

Variable	Mean	SD	Observed Range
Primary Variables			
CESD Parent	6.42	4.77	0-30
CESD Child	7.80	4.43	0-21
Family Routines Inventory (parent report)	38.96	8.65	12-60
Family Routines Inventory (child report)	34.61	8.60	12-53
Emotion Regulation Checklist	18.22	3.08	6-24
Interleukin 6 (pg/mL)	1.01	1.41	.05-15.58
Covariates			
Youth Age	14.53	1.07	13-16
Waist Circumference (cm)	75.73	11.82	26-123
% Female	53%		
% European Descent	49%		
% Asian Descent	36%		
% Neither European nor Asian Descent	15%		

Note. CESD= Center for Epidemiological Studies-Depression Scale (Short Form). Interleukin 6 is presented untransformed.

Table 10. *Intercorrelations Amongst Study 4 Variables*

Variable	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. CESD-Parent	.19**	-.21**	-.21**	.09	.06	.11	-.03	-.03	.10
2. CESD-Youth		-.23**	-.22**	.19**	.02	.14*	-.15*	.12	.09
3. Routines			.15*	.16*	-.13*	-.05	-.14*	.24**	-.11
4. Emotion Regulation				-.09	-.03	.02	.04	.04	-.07
5. IL-6 (log)					-.14*	.12	.01	-.07	.21**
6. Age						-.05	.04	-.05	.21**
7. Gender							.02	-.08	-.13*
8. European descent								-.74 **	.02
9. Asian descent									.00
10. Waist Circumference									

Note. IL-6 = Interleukin 6. Routines reflect the sum of z-scored parent- and child-reports of the Family Routines Inventory. IL-6 analyses were computing using $\log_{10}$ transformation of raw values. Gender was coded where 1=male and 2= female. European descent and Asian descent were dummy coded using a system of contrast coding where 0= no endorsement and 1= endorsement of racial category.
* $p<.05$; ** $p<.01$

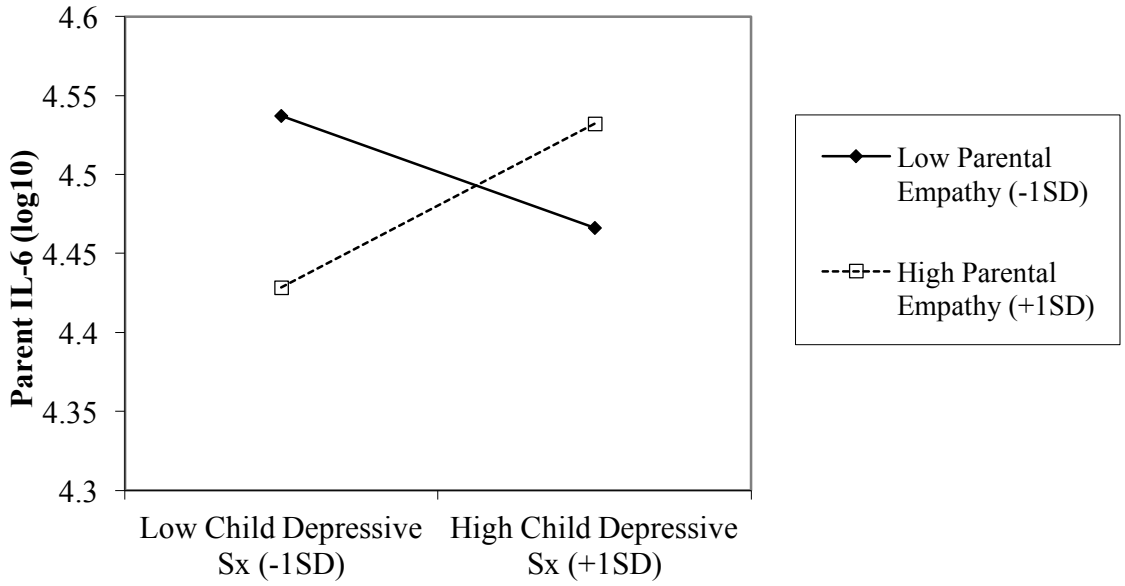
Table 11. *Study 4 Standardized Results of Indirect Effects Analyses Using Path Analysis with All Paths Estimated Simultaneously and Adjusted for Covariates*

Indirect Paths	*β*	*SE*	*p*-value	% var of total effect
Model A				
Parent CESD → Routines → Youth CESD	.04	.02	.02	22%
Parent CESD → Emotion Regulation → Youth CESD	.03	.02	.05	16%
Parent CESD → IL6 → Youth CESD	.01	.01	.62	3%
Parent CESD → Routines → Emotion Regulation	-.02	.01	.11	11%
Parent CESD → Routines → IL6	.02	.01	.09	34%
Routines → Emotion Regulation → CD	.00	.00	.55	8%
Routines → IL6 → CD	-.02	.01	.16	7%
Model B				
Parent CESD → Routines → Youth CESD	.04	.01	.03	22%
Parent CESD → Emotion Regulation → Youth CESD	.03	.02	.06	17%
Parent CESD → Routines → Emotion Regulation	-.02	.01	.11	11%
Parent CESD → Routines → IL6	.03	.01	.05	--
Routines → Emotion Regulation → CD	-.02	.01	.16	8%
Routines → IL6 → CD	-.02	.01	.12	8%
Model C				
Parent CESD → Routines → Youth CESD	.04	.02	.02	--
Parent CESD → Emotion Regulation → Youth CESD	.04	.02	.05	--

Note. % var of total effect = the percentage of the variance in the total effect of the independent variable on dependent variable accounted for by specified indirect path. Values are listed as "--" if no direct path between variables was specified in the model.

Figures

Figure 1. *Interaction between Parental Empathy and Child Depressive Symptoms Predicting Parents' Interleukin-6 (IL-6) Production in Study 2*



Note. Similar results were obtained for stimulated IL-1ra, IL-10, TNF- α, and the inflammation composite

Figure 2. *Schematic of Hypothesized Study 4 Model*

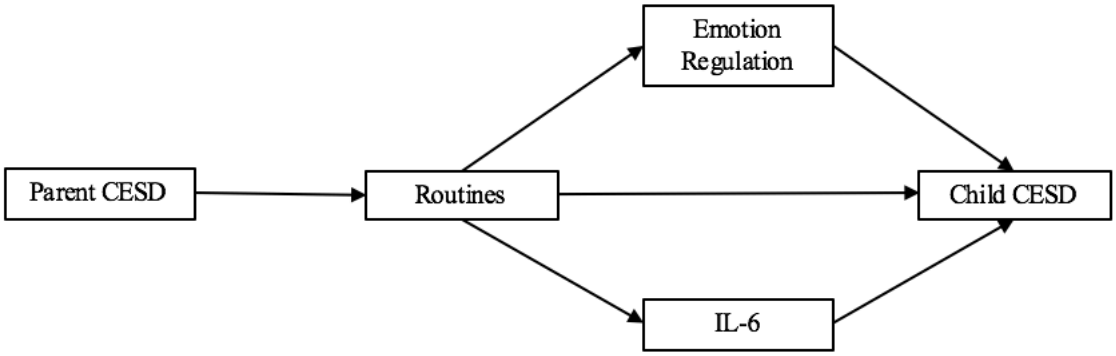
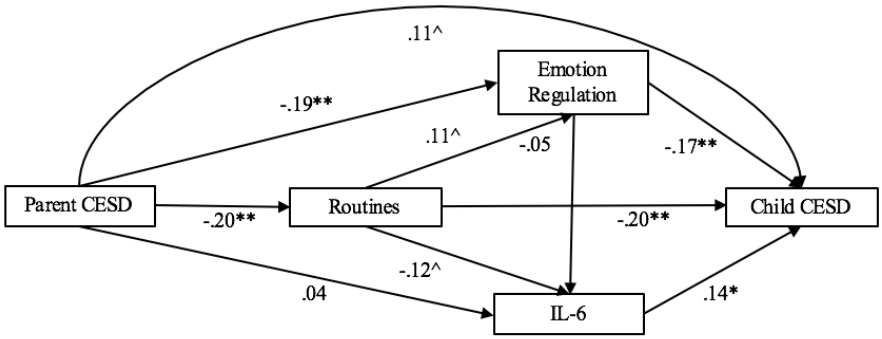
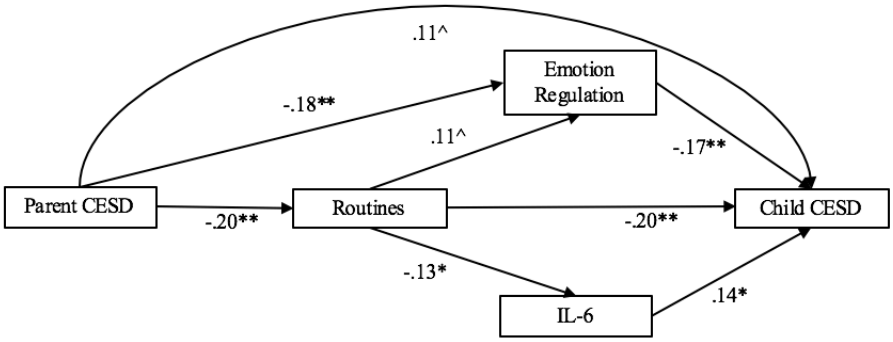


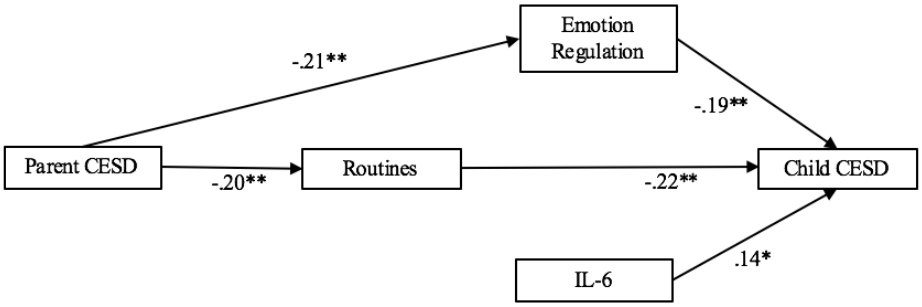
Figure 3. *Standardized Path Coefficients for Direct Pathways Across Three Nested Models in Study 4*



Model A: Full Model
$\chi^2(4)=6.471$, *ns;* RMSEA=.049; CFI=.976



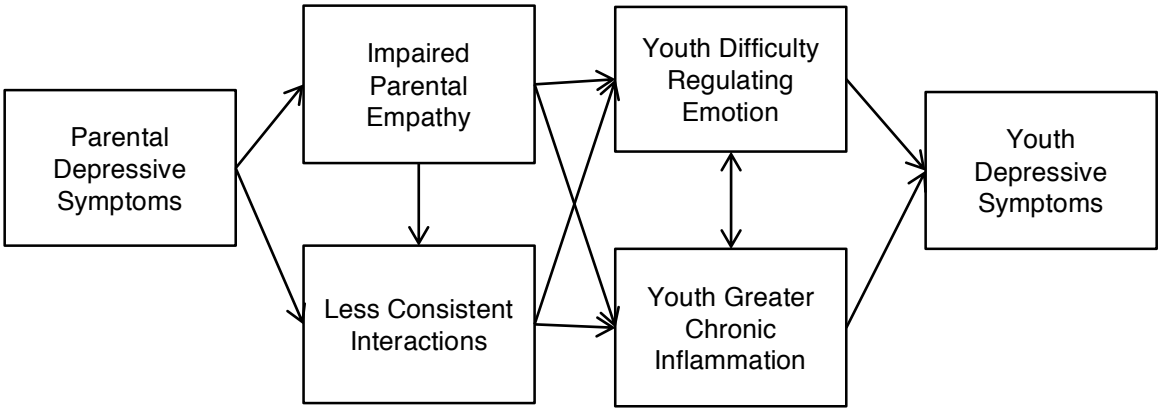
Model B: Marginal and Significant Paths Retained; *Best Fitting Model*
$\chi^2(6)=6.607$, *ns;* RMSEA=.021; CFI=.993; $\chi^2_{diff}(2)=.235$, *ns*



Model C: Only Significant Paths Retained
$\chi^2(9)=16.751$, *ns*; RMSEA=.058; CFI=.924; $\chi^2_{diff}(3)=10.045$, $p<.05$

Note. For clarity, contributions of demographic and anthropometric covariates are not presented but were included in the models.
^ $p<.10$; * $p<.05$; ** $p<.01$

Figure 4. *Conceptual Model of Intergenerational Transmission Guiding the Current Research*



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