PARENTING AND ADOLESCENT HEALTH:

MECHANISMS OF STRESS-DISEASE

COMORBIDITY

by

BENJAMIN WADE NELSON

A DISSERTATION

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DISSERTATION ABSTRACT

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Title: Parenting and Adolescent Health: Mechanisms of Social Stress-Disease Comorbidity

Adolescence is partly characterized by alterations in affective functioning during which individuals are at increased risk for the onset of mental health disorders. The experience of stress during adolescence has the potential to influence health trajectories across the lifespan as comorbidity between mental health and physical disease processes start to unfold during this period. Importantly, close relationships, such as those between adolescents and their parents, have the potential to influence and moderate (i.e., buffer or exacerbate) the expression of psychopathology and associated disease processes to influence these health trajectories.

In this dissertation, I present three multimethod studies integrating clinical diagnoses, parent-adolescent interactions, self-reported affect, observed behavior, psychophysiology, inflammation, and cellular aging to better elucidate the role parent-adolescent relationships play in influencing adolescent mental and physical health trajectories. In Chapter I, the introduction elucidates the association between parent-adolescent relationships with both adolescent mental and physical health by presenting a biological cascade model from stress to disease. Chapter II presents the first study, which examines how context, specifically varying emotionally charged interactions with parents, influence the expression of adolescent depression at the level of self-report, behavior, and

psychophysiology. Chapter III presents the second study, which utilizes a multi-system

approach to investigate the effect of observed parental behavior on the relationship

between sympathetic physiology and inflammation in adolescents. Chapter IV presents the

third study, elucidating that association between maternal depression and measures of

basal stress and social stress reactivity across measures of affect, cardiovascular

functioning, and biological aging in their adolescent children. Lastly, Chapter V provides a

brief overview of each study and discusses theoretical implications of findings. In addition,

the discussion presents future directions that focus on how smartphone, wearable, and

smart home devices can provide an opportunity to advance psychological science by

providing a passive sensing ecosystem in order to bring the laboratory out into real world

environments in order to improve ecological validity, while simultaneously allowing for

the advent of a novel precision psychology approaches to prevention and intervention in

order to improve healthcare outcomes and better understand how relationships impact

health across the lifespan.

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I dedicate this dissertation to my family.

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CHAPTER I

GENERAL INTRODUCTION:

Preface

When compared to some other dominant species in the animal kingdom, homo-

sapiens are not particularly strong and exhibit few dispositional phenotypic characteristics

that enable them to combat their environment. They don't have claws and fangs for

protection from predators or fur to protect them from the elements. Rather, what has

allowed humans to prosper has been their ability to form and maintain social bonds or

relationships to work together to accomplish common goals (Cacioppo et al., 2006). In

evolutionary terms, if an individual was shunned from a group, it almost always meant that

their survival would be at risk. Therefore, social relationships, from an evolutionary point

of view, have historically been prerequisites for safety and survival. Perhaps this is why

the social environment has such a strong impact on our biological functioning, such that

relationships are salient regulators of psychological and physiological processes that allow

us to meet the homeostatic requisites for health and optimal functioning. High-quality

relationships tend to confer positive mods and well-regulated biobehavioral responses,

while relationships high in conflict lead to negative affect and dysregulated biobehavioral

functioning. When biobehavioral responses are dysregulated with high frequency,

prolonged duration, and/or elevated intensity, this can cause repeated "biochemical insults"

weakening processes of allostasis leading to "allostatic load" that can result in the early

onset of morbidity and mortality. In this dissertation I have investigated the ways in which

a specific type of critical social context (i.e., parent-adolescent interactions) can be

associated with biobehavioral dysregulation across multiple psychobiological systems in order to understand more clearly the mechanisms by which social relationship impact health and disease.

Introduction

Adolescence is a particularly dynamic and sensitive maturational period that serves as a foundation for adult health and has therefore been described as an inflection point for mental and physical health trajectories across the lifespan (Dahl, Allen, Wilbrecht, & Suleiman, 2018; Sawyer et al., 2012). Alterations in affective functioning during which individuals are at increased risk for the onset of psychopathology is one key developmental characteristic of this period of life (Allen & Sheeber, 2008; Kessler et al., 2007; Zisook et al., 2007). One downstream implication of the increased psychological stress associated with mental disorders during adolescence is the early onset of morbidity as research has begun to elucidate high comorbidity between psychopathology and physical disease (Tegethoff, Stalujanis, Belardi, & Meinlschmidt, 2016). Therefore, while adolescence is generally characterized by high physical health, a better understanding of the emergence of psychopathology during adolescence as well as relational behaviors that influence health may be important treatment targets in order to avert deleterious health trajectories. In this context, one of the critical aspects of the picture of adolescent health is the quality of adolescent-parent relationships (Dahl et al., 2018; Morris et al., 2017; Rogers, Perino, & Telzer, In Press; Schwartz et al., 2012), which have been shown to be a potent social determinant of health (Sawyer et al., 2012) that can both directly influence and indirectly

moderate (i.e., buffering or exacerbating) the risk for psychopathology and therefore the development of early health complications.

This introductory chapter will 1) outline the importance of adolescence from a health perspective, 2) briefly describe the literature on the co-occurrence of mental disorders and physical disease, 3) outline both the historical and current evidence for the social determinants of health, and 4) introduce a biological cascade model depicting the temporal and functional pathways connecting stress to psychopathology and disease.

Part 1: Adolescence: A Vital Period for the Study of Health

While infancy is a well-recognized critical period of development that can have lifelong ramifications on health for better or worse (Shonkoff et al., 2012), recent scientific advances have begun to elucidate that adolescence is a second distinct sensitive and dynamic maturational period that is a foundation for future health (Sawyer et al., 2012). Due to the fact that adolescence can serve as an inflection point for health trajectories across the lifespan (Dahl et al., 2018; Patton et al., 2016) researchers have recently proposed that one way to prevent the rise in age-related diseases that emerge in mid to late life is by focusing on the health of younger individuals (Moffitt & Caspi, 2019). Understanding factors that influence adolescent health is also vital as adolescents currently make up a quarter of the world's populations (i.e., 1.8 billion; see Sawyer et al., 2012) and adolescent health has historically received little attention (Williams, Holmbeck, & Greenley, 2002), which has resulted in blunted health gains when compared to other age groups (Patton et al., 2016).

Adolescence: A Period of Opportunity and Vulnerability

Adolescence has a clear onset that starts with puberty and a more ambiguous offset that ends with the fulfillment of culturally valued and determined social-roles (Dahl et al., 2018; Morris, Criss, Silk, & Houltberg, 2017; Sawyer et al., 2012; Schwartz, Sheeber, Dudgeon, & Allen, 2012). During this time significant development occurs across neurobiological, cognitive, social, behavioral, and emotional domains in order to prepare individuals to transition into adult roles. While numerous reviews elucidate these changes (see Dahl et al., 2018; Patton et al., 2016), each of which could fill a book in their own right, here I highlight a subset of these dramatic developmental transitions that highly overlap with the systems that are involved in processes related to health, broadly defined. In other words, below we focus on the biopsychosocial changes that characterize adolescence and highly overlap with the very processes that are related to the etiology of psychopathology and physical disease.

First, as mentioned previously, adolescence is partly characterized by alterations in affective functioning during which individuals are at heightened risk for affective disorders (Allen & Sheeber, 2008; Kessler et al., 2007; Zisook et al., 2007). In fact, in-person assessment of over 9,000 individuals shows that the peak onset of any form of psychopathology occurs during adolescence (Kessler et al., 2005), which has large implications for later health as earlier age of onset has been associated with greater severity (Kessler, Keller, & Wittchen, 2001), chronicity (Clark, Jones, Wood, & Cornelius, 2006), recurrence (Klein et al., 1999), and poor treatment response (Nierenberg, Quitkin, Kremer, Keller, & Thase, 2004). In fact, mental disorders are so debilitating that the World Health

Organization has recently classified psychopathology as a leading cause of disability worldwide (WHO, 2018).

Second, the establishment of positive (e.g., exercise and diet) and negative (e.g., substance use, unsafe sex practices) health-related behaviors tend to become established during adolescence and persist into adulthood (Sawyer et al., 2012; Williams et al., 2002) with subsequent impacts on adult health (Beaglehole et al., 2011; UN, 2010). Therefore, adolescence is a reasonable period for focused prevention and intervention efforts in order to reinforce positive health behaviors and interrupt negative health behaviors (Williams et al., 2002).

Third, adolescence marks the first time that precursors to disease, such as atherosclerosis (McGill et al., 2000; Waloszek et al., 2016), obesity (Wardle, Waller, & Fox, 2002), and signs of metabolic syndrome (Weiss et al., 2004) can be identified. These findings indicate that the ability to identify, prevent, and treat the precursors to disease that begin to emerge during adolescence might lead to better health trajectories into adulthood.

Lastly, there are dramatic social transitions in terms of social contexts, roles, affective functioning, values, motivation, and responsibilities that can impact adolescent-parent relationships as adolescents partially reorienting away from parents towards peers (Crone & Dahl, 2012; Dahl et al., 2018; de Lorme, Bell, & Sisk, 2013; van den Bos, 2013). This social transition includes significant changes to identity development (Pfeifer & Berkman, 2018) and sense of self concept (Sebastian, Burnett, & Blakemore, 2008). In addition, social-affective changes (Crone & Dahl, 2012) motivate adolescents to gain greater autonomy and independence (Dahl et al., 2018) as they engage in novel exploration and learning opportunities (Gopnik et al., 2017) that ultimately prepares them for adult

roles and responsibilities. Despite this reorientation, research clearly indicates that adolescent relationships with their parents continue to be important, potentially more important than their relationships with peers, when it comes to social determinants of health (Dahl et al., 2018; Morris et al., 2017; Rogers, Perino, & Telzer, In Press; Schwartz et al., 2012). In fact family connectedness serves as *the most significant factor* influencing adolescent health (Resnick, 1997; Viner et al., 2012) as well as having a significant impact on adult relational functioning up to 30 years later (Graves, Wang, Mead, Johnson, & Klag, 1998).

Ultimately, adolescence can be understood to be a developmental period of biopsychosocial transitions that confer both opportunity and vulnerability for trajectories of health and disease across the lifespan (Dahl et al., 2018; Moffitt & Caspi, 2019; Sawyer et al., 2012; Viner et al., 2012). This constellation of developmental alterations put adolescents at particularly heightened risk for the onset of psychopathology, which has recently been found to have high co-occurrence with physical disease (Tegethoff et al., 2016).

Part 2: Comorbidity Between Mental Health and Physical Disease

In the last decade a substantial body of research has emerged suggesting that mental health disorders, which most often emerge during adolescence (Kessler et al., 2005) are strongly linked to poor physical health outcomes (Bruffaerts et al., 2015; Iacovides & Siamouli, 2008; Mayer, Craske, & Naliboff, 2001; Niles & O'Donovan, 2019; Prince et al., 2007; Scott et al., 2007; Von Korff, Scott, & Gureje, 2009). This co-occurrence has been shown to be particularly disabling (Beutel & Schulz, 2011), impairing (Kessler, Ormel, Demler, & Stang, 2003), hard to treat, and costly to the healthcare system

(Hochlehnert et al., 2011; Lehnert, Konnopka, Riedel-Heller, & König, 2011) with real-world implications as individuals with clinical diagnoses lose a median of 10 years off their lives due to all-cause mortality (Walker, McGee, & Druss, 2015).

Both cross-sectional and longitudinal studies have elucidated this connection between psychopathology and various forms of disease, including but not limited to heart disease (Carney & Freedland, 2017; Goldston & Baillie, 2008), stroke (Jonas & Mussolino, 2000; Pan, Sun, Okereke, Rexrode, & Hu, 2011), autoimmune diseases (Aguilar-Gaxiola et al., 2016; Andersson et al., 2015; Euesden, Danese, Lewis, & Maughan, 2017; Lu et al., 2016) and cancer (Archer, Pikhart, & Head, 2015). Importantly, mental health disorders are not weakly associated with these health outcomes, but rather rival the predictive power of well-known biomedical risk factors, such as smoking and obesity (Niles & O'Donovan, 2019). This highlights the need for the serious assessment of the role mental disorders and associated stress play in the onset and progression of physical disease.

Currently, the majority of research into the co-occurrence of mental disorders and physical disease has taken place in adults, with a relative dearth of research examining these processes during earlier periods of development (Tegethoff et al., 2016), which is particularly surprising as early interventions might have the largest downstream effect on prevention and lifelong health trajectories as early experiences of stress may calibrate biological stress response systems (Young et al., 2019) and may have the largest effect on health across time (Mayer et al., 2019). More recently, research has begun to suggest that the initial comorbidity between mental and physical health begins to emerge during adolescence (Tegethoff, Belardi, Stalujanis, & Meinlschmidt, 2015; Tegethoff et al., 2016)

with temporal prospective associations found between any occurrence of affective disorders and a host of later physical diseases, including arthritis, allergies, heart disease, diabetes, digestive system diseases, and epilepsy/seizures (Tegethoff et al., 2016).

The fact that the majority of chronic noncommunicable diseases are slow to develop and are often not expressed until early to late adulthood (Moffitt & Caspi, 2019) may be one reason for the lack of research into psychopathology-disease comorbidity during adolescence. Although this makes specific disease outcomes more difficult to study in younger populations, biological markers of health that are highly predictive of future disease, such as cardiovascular psychophysiology, inflammation, and rates of cellular aging, can be utilized as important psychophysiology mechanisms representing intermediate endpoints of health that can be used to assess increased risk for the early onset of deleterious health outcomes. This area of research is particularly important as the physiological mechanisms that allow mental health to "get under the skin" to influence physical health are poorly understood as is the potential impact modifiable social determinants of health (i.e., parent-adolescent relationships) may play in buffering or exacerbating these connections across the lifespan.

Part 3: Social Determinants of Health

It is hard to overstate the evolutionary importance social connections have played in the fitness and survival of the human species. In the animal kingdom, humans are neither particularly fast or strong compared to other dominant species as homo-sapiens don't have self-protection in the form of claws or fangs for self-defense or body hair to defend against the elements. Despite these phenotypic limitations, humans have performed remarkably well (to say the least), which has often been attributed to an evolutionary drive

to coordinate complex social behaviors that take the form of relationships (Cacioppo et al., 2006). From an evolutionary perspective, social connections and the need to belong are vital to human health and survival (Baumeister & Leary, 1995; Schoebi & Randall, 2015). Quality relationships have been shown to function as key regulators of both affective (Beckes & Coan, 2011; Coan & Maresh, 2014) and physiological activity (Hofer, 1994) conferring the ability to reappraise emotions (Schoebi & Randall, 2015) and efficiency expend and reserve psychological and physiological resources as environmental demands can traded off between members and resources can be shared to increase one's own as well as one's group survival (Sbarra & Coan, 2018).

In the absence of high quality relationships, social threat is triggered by rejection, evaluation, exclusion, and isolation, which signals the potential for one to be left out in the metaphorical (or literal) woods, which historically speaking increased risk of death. Currently, in response to such social threats, evolutionarily conserved psychological, behavioral, and physiological activation is engaged in order to maximize short-term survival as have been demonstrated in both animal and human studies (Cacioppo et al., 2006). First, in terms of types of social threat, research into social exclusion has elucidates that such states are not only associated with neural activation of areas associated with physical pain (Eisenberger, Lieberman, & Williams, 2003) and distress (Masten et al., 2009), but also lead to individuals perceiving life as less meaningful (Stillman et al., 2009). Similarly, social evaluative threat is associated with increased anxiety, embarrassment, and shame as well as increased stress activation (Lehman, Cane, Tallon, & Smith, 2015). Furthermore, both objective and perceived measures of social status are associated with health (Singh-Manoux, Marmot, & Adler, 2005) with lower social status predicting

increased susceptibility to infection (Cohen et al., 1997). Lastly, feelings of loneliness and social isolation have even been shown to predict morbidity and mortality (Holt-Lunstad et al., 2015). Overall, these findings indicate that social connections strongly influence processes related to both mental and physical health.

Relational Influences on Psychopathology.

The quality of close relationships has been shown to have profound impacts on mental health trajectories across the lifespan with early sensitive periods of development having a particularly potent effect on these outcomes (Whisman & Baucom, 2012). A number of relational theories including Attachment Theory (Bowlby, 1969) and Social Baseline Theory (Coan & Sbarra, 2015) attribute these strong associations between relational functioning and mental health to the regulatory functions relationships provide across affective and physiological functioning (Beckes & Coan, 2011; Coan & Maresh, 2014; Coan & Sbarra, 2015; Hofer, 1984; Hofer, 1994; Sbarra & Coan, 2018; Schoebi & Randall, 2015). For example, supportive relational experiences that produce positive affect may be associated with favorable health outcomes (Chida & Steptoe, 2008; Sheldon Cohen & Pressman, 2006; Pressman & Cohen, 2005; Pressman, Jenkins, & Moskowitz, 2019; Stavrova, 2019), while negative affect confers increased risk for disadvantageous health outcomes (Cohen & Rodriquez, 1995; Hernandez et al., 2018; Suls, 2018). In other words, high-quality relationships confer protection by regulating affective and physiological activation, while high conflict relationships characterized by negative affect, threat, evaluation, exclusion, violence, or isolation tend to lead to deleterious health outcomes as they exacerbate affective and physiological arousal. Research over the last 40-50 years has elucidated a similar association between quality relationships and physical health

outcomes, including morbidity and mortality (Kiecolt-Glaser & Wilson, 2016; Salmoirago-Blotcher et al., 2019), which may come as no surprise given the high comorbidity between mental and physical health.

  Relational Influences on Physical Health.

  The impact relationships have on physical health is well documented and dates back to epidemiological work conducted in the 1970s and 1980s (Berkman & Syme, 1979; Blazer, 1982; House, Robbins, & Metzner, 1982). Seminal work conducted by Cassel (1976) and Cobb (1976) first suggested that social relationships played a critical role in morbidity and mortality. Soon after these foundational publications, further empirical support began to emerge connecting relationships with these outcomes (Berkman & Syme, 1979; Blazer, 1982; House et al., 1982). Specifically, Berkman and Syme (1979) elucidated links between social relationships and mortality when they found that greater social integration (i.e., engagement in a wide range of social relationships) was associated with lower rates of mortality after controlling for various confounding factors, including poorer initial health status. Subsequently, Blazer (1982) found that social roles and attachments, perceived social support, and frequency of social interaction significantly predicted 30-month mortality in older adults after controlling for various confounding variables (e.g., age, sex, race, physical health status, economic status, self-care ability, mental health, cognitive functioning, stressful life events, and cigarette smoking).

  These initial findings in human models have also replicated in animal models allowing for initial research into the underlying biological mechanisms that may account for the association between relationships and health outcomes. For example, socially isolated rat pups were found to die at higher rates than socially intact rat pups due to

adrenal cortices hemorrhages (Vaillant, 1979). Similarly, socially isolated mice exhibit greater aggression, less stable social hierarchy, higher systolic blood pressure, greater adrenal weight, and higher mortality (Ely & Henry, 1974) with other findings indicating that socially isolated non-human primates develop higher levels of atherosclerosis (Shively, Clarkson, & Kaplan, 1989). Since these early studies a significant literature has been compiled further delineating the association between relational stress with mortality and morbidity.

Relationships and Mortality. The initial prospective epidemiological studies from the 1970s and 1980s that were described above (Berkman & Syme, 1979; Berkman, 1984; Blazer, 1982; Broadhead et al., 1983; Cassel, 1976; Cobb, 1976; House et al., 1982; Vaillant, 1979) have now been replicated in diverse populations (Brummett et al., 2001; Steptoe, Shankar, Demakakos, & Wardle, 2013). For example, in terms of relational buffering effects, supportive and high-quality relationships have been shown to be health promoting (Karelina & DeVries, 2011; Seeman, 1996, 2000) and are associated with a 46-70% reduced risk for mortality (Walker, McGee, & Druss, 2015). In contrast, both poor social relationships or those composed of frequent negative social interactions (i.e., high levels of conflict and insensitivity) are associated with higher rates of morbidity and mortality (Brooks et al., 2014; Friedman et al., 1995; Priest et al., 2015; Tucker, Wingard, Friedman, & Schwartz, 1996). These findings have since been further replicated in large scale meta-analyses. For example, in a recent meta-analysis of 148 studies (308,849 participants), the quality of close relationships was found to be strongly associated with mortality and actually exceeded the risk of more traditional biomedical risk factors, such as obesity, smoking, alcohol consumption, and physical inactivity even after controlling for

initial health status, age, and sex (OR = 1.46-1.70; Holt-Lunstad et al., 2010). Other

research has even shown that the lack of social relationships has a similar risk on mortality

as diabetes (Liu, 2011). Furthermore, a second meta-analysis of 70 studies (48,673

participants) found that the lack of close relationships (e.g., social isolation, loneliness)

increased the chance for mortality (OR = 1.29-1.32; Holt-Lunstad et al., 2015). Given the

numerous associations between social connections and mortality, it comes as no surprise

that there is a parallel literature characterizing associations between relationships and

morbidity.

   Relationships and Morbidity. Over the last few decades both animal and human

models have begun to elucidate the importance close relationships have on the

development, progression, and recovery from disease as well as the susceptibility to

infection and rate of healing post-injury. The largest body of research in this area depicts a

strong association between relational health and cardiovascular disease. Specifically,

research shows that lack of social support or greater social isolation, loneliness, and acute

and chronic psychosocial stressors are associated with processes associated with

atherosclerosis (Angerer et al., 2000; Knox et al., 2000; Kop et al., 2005; Seeman & Syme,

1987; Wang, Mittleman, & Orth-Gomer, 2005), coagulation before and after an acute

stressor (Wirtz, Redwine, Ehlert, & von Känel, 2009), left ventricle hypertrophy

(Rodriguez et al., 2011), stroke (Valtorta et al., 2016), and both incidence (Angerer et al.,

2000; Everson-Rose & Lewis, 2005; Krantz & McCeney, 2002; Williams, 2008; Valtorta

et al., 2016) and progression of coronary artery disease (Berkman, Leo-Summers, &

Horwitz, 1992; Brummett et al., 2001; Low, Thurston, & Matthews, 2010). In contrast,

those with less social isolation and greater social support have less cardiovascular

morbidity, fewer hospitalizations, and survive longer (Knox & Uvnäs-Moberg, 1998),

while also having more favorable recovery from cardiovascular disease (Seeman, 2000).

Furthermore, primate and non-primate animal models replicate these findings by

elucidating that greater social isolation (Nerem, Levesque, & Cornhill, 1980; Shively et al.,

1989), social instability (Kaplan, Manuck, Clarkson, Lusso, & Taub, 1982), and higher

social stress (Shively, Register, & Clarkson, 2009) increases atherosclerosis.

In terms of early life relationships, poor psychosocial environments during infancy

have been shown to be associated with increased cardiometabolic risk during adolescence

(Doom et al., 2019) and adverse early life interactions are associated with higher

cardiometabolic risk (i.e., high-density lipoprotein cholesterol) in young adults (Buchmann

et al., 2010). In contrast, higher parental emotional care quality is associated with lower

10-year coronary heart disease risk in offspring (Almeida et al., 2010).

While the association between relational quality and other forms of morbidity are

more scarce, research does indicate that social connectedness is related to various other

forms of disease. Specifically, human studies indicate relational quality is associated with

survival rates from cancer (Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi,

2006; Marcus, Illescas, Hohl, & Llanos, 2017; Reynolds & Kaplan, 1990), diabetic glucose

control (Trief et al., 2006), cognitive decline (Amieva et al., 2010; Wilson et al., 2007),

atopic disorders (Chida, Hamer, & Steptoe, 2008), neurological and musculoskeletal

problems (Wegman & Stetler, 2009) as well as development of metabolic syndrome

(Whisman, 2010). In addition, social connections have been found to be associated with,

with quality of adolescent-parent relationships predicting metabolic risk in young

adulthood (Ehrlich, Hoyt, Sumner, McDade, & Adam, 2015). Animal models further show

an association between relationships and the development of obesity and diabetes (Nonogaki, Nozue, & Oka, 2007) as well as the protective effects of reciprocal affiliation against tumor development (Yee, Cavigelli, Delgado, & McClintock, 2008).

Relationship quality has also been found to predict rate of infection, healing, and occurrence of somatic symptoms. Specifically, greater sociability (Cohen, Doyle, Turner, Alper, & Skoner, 2003) and diversity within social networks (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997) have been found to be associated with lower rates of developing a cold after inoculation even after taking demographics and health practices into account. Furthermore, increases in intimacy predict reduced somatic symptoms in a time-lagged fashion (Stadler, Snyder, Horn, Shrout, & Bolger, 2012). In contrast, chronic interpersonal stress is associated with increased risk for a cold after inoculation (Cohen et al., 1998), while greater relational hostility and conflict are associated with slower wound healing (Kiecolt-Glaser et al., 2005). Similarly, both high and increasing levels of loneliness are associated with greater depressive symptoms, greater frequency of doctor visits, and lower perceived health during adolescence (Qualter et al., 2013).

Overall, this literature provides strong evidence that relationships have a potent, yet non-specific effect on both mental and physical health. These findings also point to initial evidence of a potential pathophysiological basis for the development of health outcomes, with relationships triggering alterations across common underlying mechanisms of disease including cardiovascular activity, inflammation, and rates of cellular aging, which may ultimately compromise physiological systems. In other words, while the associations between relationships and health are unequivocal, the next questions turn to mechanisms.

Specifically, what biological processes translate relational health or conflict into mental and physical health outcomes?

Part 4: Biological Cascade Model From Stress to Disease

As described above, the quality of close relationships has been strongly and reliably associated with mental and physical health outcomes across the lifespan, yet relatively little is understood about the underlying psychobiological mechanisms that allow relationships to "get under the skin" to translate relational quality into mental and physical health outcomes (Uchino, 2006). One mechanisms that has been proposed to translate relational stress to processes of psychopathology and disease is the chronic activation of stress response systems (McEwen, 2006, 2008; Miller, Chen, & Cole, 2009), which has been shown to directly relate to leading worldwide causes of death, including cardiovascular disease, infection, and cancer (Uchino, Holt-Lunstad, Uno, Campo, & Reblin, 2007). Importantly, the effect sizes of these biological mechanisms on health outcomes are on par with those of health-related behaviors, such as diet (Robles, Slatcher, Trombello, & McGinn, 2015).

Initial research into this area has found that stress responses that occur within social relationships are associated with risk for psychopathology (Cicchetti & Walker, 2001) and disease (Cacioppo & Hawkley, 2003; Dickerson, Gruenewald, & Kemeny, 2004; Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004; Holt-Lunstad et al., 2015; Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016). While these studies have begun to elucidate biological pathways involved in disease (Cohen, 1988; Cohen, Doyle, et al., 1997; Uchino, Cacioppo, & Kiecolt-Glaser, 1996; Uchino, Uno, & Holt-Lunstad, 1999), the current review will outline three main physiological systems influenced by psychosocial stressors–

– the cardiovascular system, inflammatory system, and telomere system (see Figure 1.1)

without discussion of the role of the hypothalamic-pituitary-adrenal axis (due to space

limitations and less relevance to the studies in this dissertation). These seemingly disparate

biological mechanisms are intricately temporally and structurally interconnected through a

temporal biological cascade that can be activated in the face of acute and chronic

psychosocial stress.

Allostatic Load.

Allostasis is the process by which stress response systems, such as the

cardiovascular and immune systems (Priest et al., 2015), respond to environmental

demands in order to achieve biological stability thereby allowing an organism to maintain

homeostasis (McEwen, 1998). When stress response systems are efficiently activated in

response to environmental demands (i.e., acute reactivity followed by timely recovery)

organisms are able to flexibly meet environment and psychosocial pressures. In contrast,

both *overactive* stress responses in the form of greater frequency, duration, and intensity

and *underactive* responses in the form of blunted activation, which may result from

downregulation of stress systems after prolonged periods of overactivation (Souza et al.,

2015), can lead to allostatic load, which is the biological cost that incurs when allostatic

mechanisms are overworked to the point of breaking down and failing to maintain

organism homeostasis (McEwen & Stellar, 1993). Over long periods of time dysregulated

stress responses can lead to repeated biological insults causing cumulative adverse effects

on health (McEwen & Stellar, 1993) and ultimately disease (McEwen, 1998). In other

words, allostatic load shifts the set point of stress systems into either hyper- or hypo-

activation, which leads to biological wear and tear that can result in psychopathology and

disease. It is important to note that this concept is not particularly novel as it was first proposed 80 years ago by Selye (1936) who found that the very physiological systems that preserve and repair the body, can also have damaging effects if activated for prolonged periods of time.

While relationships can directly influence stress reactivity, social relationships can also buffer stress reactivity in the context of supportive relationships or exacerbate stress reactivity in the context of poor relational functioning (Cohen & Wills, 1985; Hostinar, 2015). This stress reactivity has been proposed to have downstream repercussions on both mental health and physical disease (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen & Stellar, 1993). Below a biological cascade model from stress to disease is presented that depicts how shortly after a stressor is encountered there is an immediate cardiovascular response in order to meet environmental demands, followed by a slower acting immune response that ultimately, in the long-term, triggers increased cellular turnover (i.e., biological aging) that makes an individual more susceptible to the early onset of disease. Throughout this process close relationships, such as those between adolescents and their parents, have the potential to buffer or exacerbate the activation of these underlying stress responses thereby increasing or decreasing the propensity for deleterious mental and physical health outcomes.

Psychosocial Moderator:
Parent-Offspring Relationship Quality

Biological Mechanisms

Psychosocial/ Environmental Stress

Cardiac Response: Autonomic Nervous System

Inflammation: C-Reactive Protein

Accelerated Aging: Telomere Length

Psychopathology

Disease

Time
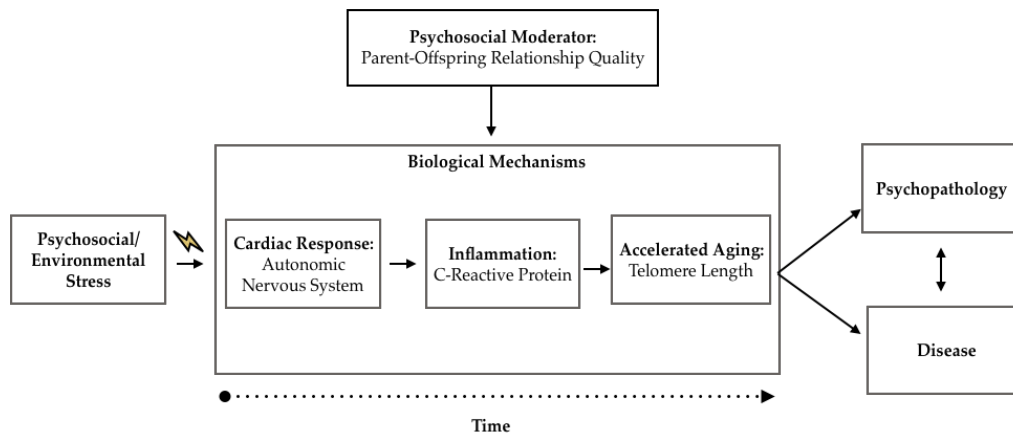
Figure 1.1. Cascade Model from Stress to Disease

Cardiovascular Psychophysiology.

Shortly after the onset of a stressor the cardiovascular system is activated. The cardiovascular system is primarily regulated by the autonomic nervous system (ANS), which is composed of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). These branches of the ANS innervate organs throughout the body to influence homeostatic functions, including heart rate, hormonal release, vasculature smooth muscle, respiration, water balance, and psychophysiological stress response to internal and external demands (Berntson, Quigley, & Lozano, 2007; Cacioppo, Tassinary, & Berntson, 2017).

Cardiovascular functioning has been implicated in both psychopathology (Alvares, Quintana, Hickie, & Guastella, 2015; Beauchaine, 2012; Latvala et al., 2016) and disease, most notably cardiovascular disease. Both exaggerated and suppressed cardiovascular responses to stress have been identified as risk factors for atherosclerosis and hypertension in adolescent and adult populations (Carney et al., 1995; Jennings et al., 2004; Matthews, Salomon, Brady, & Allen, 2003), while various indices of cardiac functioning including

heart rate and heart rate variability are strongly related to mortality (Dekker et al., 2000; Zhang, Shen, & Qi, 2015).

Relationships and Cardiac Activity. A large proportion of research investigating relational influences on biological mechanisms of disease have focused on cardiovascular functioning (Uchino, 2006). Specifically, the social-support reactivity hypothesis of disease states that social support buffers psychobiological reactivity, which is protective for health as high levels of cardiovascular reactivity may be associated with development and progression of cardiovascular disease (Lepore, 1998), although this is still debated (Manuck, 1994). In terms of early family relationships, greater family social support is associated with lower catecholamine levels (Grewen, Girdler, Amico, & Light, 2005), while greater family strain is associated with higher catecholamine levels (Seeman, Gruenewald, Cohen, Williams, & Matthews, 2014). This may serve as one mechanism connecting greater sympathetic activity in response to psychosocial stress to disease as catecholamines have been shown to cause "biochemical insult" leading to atherogenic processes, such as arterial wall injury (Krantz & Manuck, 1984), which can in turn trigger processes of inflammation.

Other research clearly establishes that poor relational quality in the form of high conflict adolescent-parent relationships is associated with heightened sympathetic arousal (Salomon, Matthews, & Allen, 2000), while increasing experiences of stress, including family stress, during adolescence has immediate impacts on cardiovascular reactivity and intima-medial thickness or subclinical signs of atherosclerosis during adolescence (Low, Salomon, & Matthews, 2009). Furthermore, greater levels of subjectively experienced

social evaluative threat, indexed through experience sampling, has been shown to be associated with increased cardiovascular activity (Lehman, Cane, Tallon, & Smith, 2015).

In contrast to the stress inducing effects of poor relational quality, strong and supportive relationships have been shown to have a stress-buffering effect. For example, responsive parenting has been shown to protect against dysregulated heart rate activity and negative affect in infants by allowing for greater autonomic regulation during a laboratory social stressor (Haley & Stansbury, 2003). Other research confirms this in older adult populations by demonstrating that having a supportive other can blunt cardiovascular reactivity during a social stressor (Glynn, Christenfeld, & Gerin, 1999). Therefore, the buffering effects that social support have on cardiovascular reactivity may be one way in which relationships have cardioprotective effects against stress (Uchino, 2006).

Moving forward through the biological cascade model, one way that dysregulated autonomic activity may influence health across time is by influencing processes of inflammation. When considering the pathway from stress to disease, the autonomic nervous system directly innervates the slower acting inflammatory system (Fagundes & Way, 2014; Kemeny & Schedlowski, 2007; Thayer & Sternberg, 2006) regulating immune activity (Chrousos, 1995; Nance & Sanders, 2007a; Thayer & Sternberg, 2006) with the sympathetic branch having a pro-inflammatory effect (Jänig, 2014; Nelson, Byrne, Simmons, et al., 2017) and the parasympathetic branch having an anti-inflammatory effect (Borovikova et al., 2000). This ANS- inflammation relationship is thought to serve as a critical biological pathway connecting stress (i.e., increased sympathetic tone and decreased parasympathetic tone) with inflammation (Miller & Blackwell, 2006) as has been demonstrated in animal models (Felger, Haroon, & Miller, 2015).

The Inflammatory System.

While the immune system can be activated in response to viral infection and physical threat, recent research has demonstrated that the immune system can also respond to psychological factors such as perceived, imagined, or real conditions that involve social threat, conflict, isolation, rejection, and exclusion (Slavich & Irwin, 2014). Research indicates that similar to cardiovascular functioning, inflammation may play a role in psychopathology, particularly depression (Copeland, Shanahan, Worthman, Angold, & Costello, 2012; Horn et al., 2018; Howren, Lamkin, & Suls, 2009), while the literature is much more clear that inflammation plays a key role in a host of diseases including cardiovascular disease (Danesh et al., 2004; Ridker, 2001), cancer (Kinoshita, Ito, & Miki, 1999), autoimmune disorders (Koopman et al., 2011), and obesity (Visser, Bouter, McQuillan, Wener, & Harris, 1999).

Relationships and Inflammation. Stressors, especially social stressors (Sheridan, Stark, Avitsur, & Padgett, 2000), can influence immune functioning in both animal and human models. For example, supportive and functional relationships buffer against higher systemic inflammation in adolescents (Byrne et. al., 2016) and sensitive parents, positive parental behaviors, and supportive role models for adolescents have all been shown to buffer the effect of low socioeconomic status against inflammation (Chen, Miller, Kobor, & Cole, 2011; Chen, Lee, Cavey, & Ho, 2013). In contrast to the inflammation buffering effects of positive relationships, research shows that the opposite is true for those with unsupportive, stressed, and dysregulated relationships (Fagundes, Bennett, Derry, & Kiecolt-Glaser, 2011). For example, parental harshness and stress are associated with increased current levels of adolescent inflammatory response and prospectively predict

adolescent inflammatory response 1.5 years later (Miller & Chen, 2010; Wolf, Miller, & Chen, 2008).

A recent meta-analysis of 41 studies with over 73,000 participants have confirmed these individual studies by finding that social support and social integration were related to lower levels of inflammation (Uchino et al., 2018). Therefore, the lack of social support or overt social threat may influence autonomic activity leading to up-regulated inflammatory activation, that may result in a dysregulated phenotype driving disease pathogeneses (Slavich & Irwin, 2014). In contrast, quality relationships may act as a buffer (i.e., protective factor, see Hostinar, 2015) against the effects of dysregulated autonomic activity on inflammation.

Moving forward through the biological cascade model, heightened inflammation has been shown to be associated with increased rates of cellular turnover (Rode, Nordestgaard, Weischer, & Bojesen, 2014), which provides a mechanism to understand biological aging and the early onset of disease. Therefore, the inflammation-telomere connection may serve as a second critical biological pathway connecting psychosocial stress to disease.

The Telomere System.

One final pathway from relationships to health are the underlying molecular processes of cellular aging. Telomeres are repeated nucleotide sequences (TTAGGG) at the end of eukaryotic chromosomes that protect chromosomes from deterioration and enable cellular integrity (Blackburn & Epel, 2012). During somatic cell division DNA polymerase is not able to fully replicate the 3' end of linear DNA resulting in a progressive loss of telomeric repeats (Blackburn, 1991). Telomere length is affected by age

(approximately 10% of telomere length variation; see Blackburn, Epel, & Lin, 2015) and

genetics (accounts for 30-80% of telomere length variation; see Blackburn, Epel, & Lin,

2015), indicating that telomere length is part of a "biological clock", which can be

accelerated by environmental factors, such as exposure to environmental toxins and

cumulative exposure to lifetime stressors (Aviv, 2008; Mayer et al., 2019; Olovnikov,

1996). Therefore, telomere length has been conceptualized as a "psychobiological" marker

representing processes of aging (Epel, 2009).

Shorter telomere length is associated with psychopathology (Darrow et al., 2016;

Kiecolt-Glaser & Wilson, 2016; Lindqvist et al., 2015; Shalev et al., 2014; Simon et al.,

2006; Verhoeven et al., 2014) and a range of negative physical health outcomes in both

human and animal model, notably including cardiovascular disease as well as dementia,

diabetes, cancer, obesity, and early mortality. In contrast, longer telomere length is

associated with favorable health outcomes (Blackburn & Epel, 2012; Heidinger et al.,

2012; Vera, Bernardes de Jesus, Foronda, Flores, & Blasco, 2012). In fact, research shows

that telomere length is a large mechanistic contributor to disease phenotypes and strongly

predicts future incidence of disease (Blackburn, Epel, & Lin, 2015), which has led to some

to propose that telomeres might be able to be used as a biological marker for disease

progression (Houben, Moonen, van Schooten, & Hageman, 2008).

Telomere Length and Relationships. Relational stressors are associated with

telomere length. Specifically, low social support (Carroll, Diez Roux, Fitzpatrick, &

Seeman, 2013) and social status (Cohen et al., 2013; Needham et al., 2013) as well as

greater number of ambivalent social ties (Uchino et al., 2012) are associated with shorter

telomere length. In terms of parent-offspring relationships, greater maternal psychosocial

stress starting in utero (Entringer et al., 2013) and continuing into infancy (Nelson, Wright, Allen, & Laurent, In Press) as well as insecure attachment between infants and their mothers (Nelson, Bernstein, Allen, & Laurent, Revise and Resubmit) is associated with shorter telomere length. Furthermore, lack of parental responsiveness (Asok, Bernard, Roth, Rosen, & Dozier, 2013), early social deprivation (Drury et al., 2012), experiences of maltreatment (Tyrka et al., 2010), and exposure to violence (Shalev et al., 2013) during childhood are all associated with shorter telomere length. Interestingly, parental mental health, has also been shown to influence telomere length in offspring with maternal depressive symptoms and disorder predicting shorter telomere length in both infant and adolescent offspring (Gotlib et al., 2014; Nelson, Allen, & Laurent, 2018), which may be due to heightened relational stress due to greater negative parenting behaviors exhibited by depressed mothers (Goodman, 2007).

Summary

In the past few decades, research has begun to delineate high levels of comorbidity between mental disorders and physical disease in adult populations. Moreover, there is evidence that some of the common underlying etiological factors may have their origins early in life. Although health psychology research has tended to focus on infant and adult populations, researchers have begun to understand that adolescence is a particularly important developmental period that signals an inflection point, for better or worse, in mental and physical health trajectories across the lifespan (Dahl, Allen, Wilbrecht, & Suleiman, 2018; Sawyer et al., 2012) and many of the psychobiosocial changes that characterize this period of life highly overlap with underlying stress physiology that has been implicated in processes of psychopathology and disease. One such factor that

undergoes significant developmental change during this period is close personal relationships, which has important implications for psychopathology and disease as social determinant of health have been found to rival well-known biomedical predictors of mortality, including physical inactivity, alcohol consumption, diabetes, obesity, smoking, diabetes, and high blood pressure (Holt-Lunstad et al., 2015; Holt-Lunstad et al., 2010). One particularly vital relationship during adolescence is that between adolescent children and their parents, which has been shown to be the largest predictor of adolescent health outcomes.

Overall, there are a number of gaps in the literature examining how psychological stress leads to disease. First, researchers have called for a lifespan perspective to better understand the emergence of health and disease. Historically, adolescent health has received less attention than other key ages, which is reflected in fewer gains made in adolescent health when compared to other stages of life. Second, research has suggested that future studies take into account the ways in which developmental processes influence social connections (Uchino, 2006). Adolescence is a prime candidate for study as dramatic social changes occur during this time. Lastly, there is also a need for research into relevant multilevel mechanisms (i.e., physiology, behavior, and affect) as well as the ways different relational contexts (i.e., positive and negative interactions) influence underlying biological pathways to disease. Identifying key relational patterns and biomarkers of risk during adolescence and within the context of various relational interactions may open the door for new prevention and intervention efforts that might be able to interrupt deleterious health trajectories across the lifespan.

The following chapters will outline three original studies that are followed by a general discussion and future directions for health psychology and behavioral medicine. First, Chapter II, "Does Context Matter? A Multi-Method Assessment of Affect in Adolescent Depression Across Multiple Affective Interaction Contexts", will present the Nelson, Byrne, Sheeber, & Allen (2017) manuscript (published in *Clinical Psychological Science*), which discusses how context, specifically varying emotionally charged interactions with parents, influence the expression of adolescent depression at the level of self-report, behavior, and psychophysiology. Second, Chapter III, "Adolescent Sympathetic Activity and Salivary C-Reactive Protein: The Effects of Parental Behavior" presents the Nelson et al. (2017) manuscript (published in *Health Psychology*), which utilized a novel multi-system approach to investigate the effect of observed parental behavior on the relationship between biological mechanisms associated with disease processes (i.e., autonomic physiology and immune response) amongst their adolescent children. Third, Chapter IV, "Chronic Stress and Acute Stress Reactivity in Adolescents of Depressed Mothers" elucidates the association between maternal depression and both acute and chronic indices of stress across affect, cardiovascular functioning, and biological aging. Lastly, Chapter V will provide a summary and theoretical implications for each chapter followed by a future directions and conclusion section based on the Nelson & Allen (2018) manuscript, "Creating a Passive Sensing Ecosystem: Utilizing Passive Sensing Technologies to Translate Laboratory Findings into Real World Contexts" (published in *Perspectives on Psychological Science*) that discusses how smartphone, wearable, and smart home devices can provide an opportunity to advance psychological

science by providing a passive sensing ecosystem in order to bring the laboratory out into

real world environments in order to improve ecological validity.

CHAPTER II

DOES CONTEXT MATTER? A MULTI-METHOD ASSESSMENT OF AFFECT IN

ADOLESCENT DEPRESSION ACROSS MULTIPLE AFFECTIVE INTERACTION

CONTEXTS

This work was previously published in *Clinical Psychological Science* and was co-authored with M. Byrne, L. Sheeber, & N. B. Allen, therefore the following chapter is formatted according to the journal's publication standard. I was the lead author of this publication and established the study design, experimental methods, and data analysis with input from my co-authors.

Nelson, B. W., Byrne, M. L., Sheeber, L., & Allen, N. B. (2017). Does context matter? A

multi-method assessment of affect in adolescent depression across multiple

affective interaction contexts. *Clinical psychological science*, *5*(2), 239-258.

Introduction

Adolescence is a developmental period characterized by alterations in affective functioning during which individuals are at increased risk for the onset of depressive psychopathology (Allen & Sheeber, 2008; Zisook et al., 2007). Indeed, depression is often characterized as a disorder of *affect regulation*, a process that has been assessed at the level of self-reported affect, behavior, and physiology (e.g., Allen, Kuppens, & Sheeber, 2012; Byrne et al., 2010; Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Gross & Jazaieri,

2014; Sheeber et al., 2012), with depression being associated with impairment at each level. Disturbances in affective behavior in depression are often observed in social contexts, and during adolescence, parent-adolescent interactions are a particularly important context given that behavior during these interactions has shown strong associations with adolescent mental health and functioning (Kuppens, Allen, & Sheeber, 2010; Kuppens et al., 2012; Schwartz et al., 2013; Schwartz, Sheeber, Dudgeon, & Allen, 2012; Sheeber et al., 2012). Notably, however, most studies only examine the impact of depression within a single context and do not simultaneously assess across self-reported affect, behavior, and physiology. Indeed, research has yet to fully specify the impact of different interactional contexts, designed to elicit different types of affect, on depressed and non-depressed adolescent self-reported affect, behavior, and physiological responses. Additionally, research has yet to fully elucidate the experiential, behavioral, and psychophysiological differences between depressed and non-depressed adolescents during these interactional contexts. The present study addresses these gaps in the literature by utilizing a novel multi-method design to examine differences between depressed and non-depressed adolescents' experiential, behavioral, and psychophysiological responses across multiple emotionally evocative family interaction contexts.

Why Does Context Matter?

Contextual influences on research findings in the sciences has recently gained much attention, especially because of their relevance to scientific reproducibility (Bavel, Mende-siedlecki, Brady, & Reinero, 2016; Open Science Collaboration, 2015). Bavel et al. (2016) recently highlighted this issue by rating 100 studies from the Reproducibility Project (Open Science Collaboration, 2015) with regard to their "contextual sensitivity"

(i.e., how likely the effect reported was to vary by context—defined broadly as time, culture, location, or population) and found that the greater contextual sensitivity of a study was associated with lower likelihood of replication, suggesting that contextual factors can be "hidden" moderators of effects, and that research should address phenomena both across (context independent) and between (context dependent) environments. As related to the current project, this is notable in that the vast majority of studies on parenting factors associated with adolescent depression examine parent-adolescent interactions in only one context, most typically a "problem solving task", which is then used to draw general conclusions about adolescent functioning. In the current study, we address this issue by investigating the impact of adolescent depression on affective functioning during various parent-adolescent interactions that vary in affective tone.

Affect, Behavior, and Psychophysiology of Depression

Emotion is often conceptualized as consisting of coordinated alterations at the level of experience, behavior, and psychophysiology (Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005). Research has demonstrated that depression is characterized by alterations in emotion, which tend to negatively impact psychosocial functioning and adjustment (Allen & Badcock, 2003). Therefore, a greater understanding of emotional processes in depressed adolescents across multiple social interactional contexts requires measures in the domain of self-reported affect, observed behavior, and psychophysiology.

Self-Reported Affect in Depression

Individuals with depression tend to experience higher levels of negative affect and lower levels of positive affect as compared to their non-depressed peers (Watson, 2000), a finding that is especially true for depressed adolescent females (Forbes, Williamson, Ryan,

& Dahl, 2004). Depressed adolescents also tend to have deficits in the regulation of affective states (Silk, Steinberg, & Morris, 2003). These mean level differences in emotional states appear to be associated with abnormal temporal dynamics of emotion in depression, whereby young adults with depression tend to experience "emotional inertia" - the tendency to have affective states that are self-sustaining rather than sensitive to environmental changes (Koval, Kuppens, Allen, & Sheeber, 2012; Kuppens et al., 2010, 2012), which is the antithesis of emotional flexibility, which has been shown to be associated with resilience from adolescence throughout adulthood (Waugh, Thompson, & Gotlib, 2011).

Psychosocial Behavior in Depression

Another measure of affective functioning in depression that provides further evidence of affective impairment is behavioral observation of social interactions. Depressed adolescents tend to experience interpersonal difficulties that result from reduced social activity and engagement, deficits in social skills, and rigid responses to environmental demands (Rottenberg, 2005; Stark et al., 2006). Adolescents experiencing depression tend to exhibit higher levels of negative behaviors (e.g., behavioral disengagement and self-blame; Horwitz, Hill, & King, 2011), including aggression (Knox, King, Hanna, Logan, & Ghaziuddin, 2000), anger (Sheeber et al., 2009), and dysphoria in interpersonal interactions (Puig-Antich et al., 1985), while also displaying decreased positive behaviors (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Similarly to emotional inertia in self-reported affect described above, behavioral emotional inertia of both negative and positive behaviors predict the emergence of clinical depression (Kuppens et al., 2012). Also, we have previously shown increased behavioral reactivity to negative

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parental behavior and reduced reactivity to positive parental behavior amongst depressed adolescents (Sheeber, Allen, Davis, & Sorensen, 2000). However, the broader emotional and/or interpersonal context may play an important role in how depressed adolescents behaviorally respond to interactions with their parents. Indeed, the study of contextual effects in depressed adolescents, especially in studies using cross method analyses that include behavioral observation, is a matter that still requires further examination.

Psychophysiology in Depression

Physiological activity is another component of emotion that may differ between depressed and non-depressed adolescents. In comparison to other indices of emotion, it may be less subject to measurement biases and thus allow for a more objective measure of affect, though it needs to be noted that no psychophysiological index has been shown to directly map onto specific emotion states in a one-to-one fashion (Cacioppo & Tassinary, 1990). One potentially important physiological correlate of depression is the autonomic nervous system (ANS) stress response (Allen et al., 2012; Byrne et al., 2010). The ANS is composed of both the energy expending sympathetic nervous system (SNS) and the energy conserving parasympathetic nervous system (PNS). ANS components are activated when an organism faces environmental threat and challenge as well as psychosocial stress. Unlike survival threat and physical exertion, which are often transient and acute in nature, ongoing psychosocial and relational stress characterized by conflict, low social support, and social threat, particularly when it occurs in the context of close relationships, may have more chronic impacts on both psychological and physical health over time (Kiecolt-Glaser, Gouin, & Hantsoo, 2010).

There are many methods of indexing overall ANS activity as well as specific components of the ANS response (i.e., SNS or PNS). Heart rate and blood pressure are two overall indices of ANS activity that are influenced by a combination of sympathetic and parasympathetic innervation with depression being associated with higher resting heart rate and hypertension (Byrne et al., 2010; Davidson, Jonas, Dixon, & Markovitz, 2000). In contrast, finger pulse transit time (FPTT), which is the time interval between the previous R-wave and the systolic upstroke of the peripheral pulse at the finger (i.e., time between the heart's contraction and the pulse reaching the end of a finger), is influenced by the force of heart contraction and blood vessel dispensability created by SNS activity (Kang & Gruber, 2013; Mauss et al., 2005). Similarly, pre-ejection period (PEP) or the time interval between depolarization of the heart's left ventricle and the subsequent ejection of blood through the aortic valve indicates sympathetic response (Light, Kothandapani, & Allen, 1998). Research demonstrates that increased sympathetic activity, as indexed by shorter PEP time intervals, has been associated with depressive symptomatology in women (Light et al., 1998).

Respiratory sinus arrhythmia (RSA), or respiratory coupled heart rate variability, on the other hand, is an index of PNS activity via vagal control that has been shown to have associations with various forms of psychopathology throughout the lifespan (Beauchaine, 2015; Beauchaine, Gatzke-Kopp, & Mead, 2007; Porges, 2007). In addition, a recent systematic meta-analysis found that clinically depressed adolescents displayed lower resting parasympathetic activity, but do not exhibit associations between depressive symptom severity and parasympathetic activity, which is found in adults (Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). In particular, increasing RSA trajectory (i.e., greater

parasympathetic tone) over adolescence is associated with lower risk for depression (Gentzler, Rottenberg, Kovacs, George, & Morey, 2012), while depression in adults has been associated with low parasympathetic activity (i.e., low cardiac vagal tone or deficits in cardiac control) as characterized by lower resting RSA as compared to healthy controls (Rottenberg, Clift, Bolden, & Salomon, 2007). Similar findings have also been reported for infants of depressed mothers (Field & Diego, 2008). Research also indicates that depression in adulthood as well as depression with childhood onset is associated with blunted RSA reactivity (Bylsma, Salomon, Taylor-Clift, Morris, & Rottenberg, 2014; Yaroslavsky, Bylsma, Rottenberg, & Kovacs, 2013; Yaroslavsky, Rottenberg, & Kovacs, 2013). By contrast, states of positive emotion (which are especially low in clinically depressed states; (Watson, 2000) are associated with higher resting RSA in first year university students (Oveis et al., 2009).

Parent-Child Interactions in Depression

There are a small number of studies that have measured emotional, behavioral, and physiological responses in depressed adolescents during parent-child interactions with few, if any, investigating all measures simultaneously. Research has found that during interpersonal conflict with parents exhibiting aversiveness, depressed adolescents display increased dysregulation of both behaviors and physiology (RSA), while control peers displayed greater physiological (RSA) regulation (Crowell et al., 2014). Allen et al. (2012) found that non-depressed adolescents had deceleration in heart rate in response to maternal angry and dysphoric behaviors, which was not observed in depressed adolescence. In contrast, depressed adolescents had significant heart rate accelerations when father's

displayed angry behavior and heart rate decelerations when father's displayed dysphoric behaviors, findings that were not displayed by non-depressed peers.

In adolescent-parent interactions devoid of adolescent depression, research has found that parent-adolescent conflict discussions are associated with increased physiological and emotional responses, such that negative parenting has been associated with higher blood pressure and angry responses among adolescents (Chaplin et al., 2012). Another study looking at child-parent interactions found that children had lower heart rate increases from baseline to non-threat tasks, than from baseline to threat (i.e., conflict, anxiety) tasks (Gonzalez, Moore, Garcia, Thienemann, & Huffman, 2011), indicating greater sympathetic activation to conflictual discussions with parents. Furthermore, aversive behavior among both adolescents and their mothers is associated with low RSA during interactions (Crowell et al., 2013). Similarly, negative maternal behavior is associated lower physiological regulation, maladaptive emotion regulation strategies, and noncompliant behaviors in toddlers (Calkins, Smith, Gill, & Johnson, 2001) and negative and controlling parental behaviors are associated with lower RSA, while lower parasympathetic activity (i.e., lower vagal tone) is associated with harsh parenting practices in young children (El-Sheikh & Erath, 2011; Kennedy, Rubin, Hastings, & Maisel, 2004). Other studies have reported shortened PEP and decreased RSA in families with higher reported child-parent conflict during reactivity tasks (Salomon et al., 2000), indicating greater SNS and lower PNS response in high family conflict environments. While many of these studies address associations between psychophysiology indices and emotion with reported family interaction behavior, many studies fail to simultaneously address self-reported affect, observed behavior, and psychophysiology during actual

varying live parent-child interactions, or the variations of these effects associated with clinical depression.

The Current Study

While we have previously described the overall dynamics of affective experience and behavior, averaged across interaction contexts, in depressed adolescents in this sample (Sheeber et al., 2009), here we add multiple psychophysiology indices and uniquely address not only *general* dynamics of affective experience, behavior, and physiology (i.e., those that are found across contexts), but also explicitly explore the pattern of these variables across various affectively charged interactional contexts, in order to elucidate how these components of emotion and their interaction with depressive states are influenced by contextual differences in affective interpersonal situations. As noted earlier, attention to contextual influences has potentially significant implications for the reproducibility of findings (Bavel et al., 2016). This study therefore uniquely expands our understanding of abnormalities of the different components of emotion in adolescent depression in two ways. First, it examines these processes in a highly ecologically relevant, emotion eliciting contexts – various affectively charged parent-child interactions. As noted, few studies have addressed differences in observed behavior as a function of different interactional contexts. Second, we examined multiple components of emotional responses – self–report, behavior, and physiology – during these interactions, allowing for a thorough assessment of differences in the components of emotion between depressed and non-depressed teenagers across different systems of response.

We hypothesized that in general (i.e., across contexts) depressed adolescents would show greater negative and less positive self-reported affect, greater frequency and duration

of aggressive and dysphoric behavior and less frequency and duration of happy behavior, greater overall ANS response (i.e., higher heart rate and blood pressure) as well as greater SNS activation (i.e., PEP and FPTT) and lower PNS activation (i.e., RSA), than their non-depressed peers. Moreover, variations in these responses across interpersonal contexts will be examined, to evaluate whether the patterns hypothesized above are general in nature, or vary as a function of the nature of the parent-adolescent interaction context. Due to research indicating greater negative affect and sympathetic response during negative contexts (Chaplin et al., 2012), we hypothesized that putatively negative interpersonal interactions (i.e., the Problem Solving Task; PSI, which pulls for negative affect) would elicit the greatest difference in negative affect, negative behavior, and sympathetic response between depressed vs non-depressed adolescents, followed by collaborative interactions (i.e., the Family Consensus Interaction; FCI, which pulls for a mix of affects), and positive interactions (i.e., Event Planning Task; EPI, which elicits more positive affect). By contrast, due to research indicating that depressed persons are less responsive to rewarding or positive stimuli (e.g., Bylsma, Morris, & Rottenberg, 2008), we hypothesized that deficits in positive affect, positive behavior, and parasympathetic response amongst depressed adolescents (when compared to non-depressed adolescents) would be greatest during the putatively positive task (i.e., EPI).

Methods

Participants

Participants were 152 adolescents (52 males), aged 14-18, and their parents, who were participating in a study of emotional processes associated with depressive disorder during parent-adolescent interactions (see Table 2.1 for participant demographics).

Inclusion criteria required that adolescents had to live with at least one parent or permanent guardian, and fulfill research criteria for placement in one of two groups (depressed vs. non-depressed). Adolescents who were depressed met DSM IV (APA, 1994) diagnostic criteria for a current unipolar depressive disorder during a diagnostic interview. Consistent with guidelines for establishing the offset of depressive episodes, a diagnosis was considered current if it was ongoing or had an offset within two months preceding the diagnostic interview (APA, 1994). Non-depressed adolescents had no current or lifetime history of psychopathology, and no history of mental health treatment. Adolescents were excluded if they evidenced comorbid externalizing or substance dependence disorders, were taking medications with known cardiac effects, or reported regular nicotine use.

Recruitment, Assessment Measures, and Procedures

Families were recruited using a two-gate procedure consisting of an in-school screening and an in-home diagnostic interview. In order to facilitate recruitment of a representative sample of students, we used a combined passive parental consent and active student assent protocol for the school screening (Biglan & Ary, 1990; Severson & Ary, 1983). Active parent consent and adolescent assent for the full assessment were obtained prior to the diagnostic interview.

Gate 1: School Depression Screener

The Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977) was used as the initial gate of a two-stage recruitment and screening procedure. The CES-D is a widely used, self-report measure of depressive symptoms that has acceptable psychometric properties for use with adolescents (e.g., Roberts, Andrews, Lewinsohn, & Hops, 1990) and has a well-established record of use as a screener for depressive

symptoms in adolescent samples (e.g., Asarnow et al., 2005; Sheeber, Davis, Leve, Hops, & Tildesley, 2007).

Students from area high schools completed the CES-D and a demographic data form during class. Approximately 70% of enrolled students who were living with at least one parent or permanent guardian participated (4182 of 5975), 12% (n = 695) declined or had parents decline their participation, and 18% (n=1098) were absent or off campus on the day of the assessment. CES-D cut-off scores for selecting potential participants were based on the distribution of scores obtained in an earlier screening of high school students (N = 4495) in the same area (Sheeber et al., 2007). Relatively high scores (≥31 for males and ≥38 for females) were selected to maximize the positive predictive power to identify adolescents experiencing depressive disorder. Approximately 8% (n = 372) of the students scored above these cut-offs. The pool for the healthy group was defined as students not more than 1/2 SD above the mean in the earlier sample (<21 for males and <24 for females).

Gate 2: Diagnostic Interview

As the second screening procedure, interviewers conducted the Schedule of Affective Disorders and Schizophrenia- Children's Version (K-SADS, Orvaschel and Puig-Antich, 1994) with adolescents who had elevated CES-D scores. The K-SADS interview was conducted with the adolescents to obtain current and lifetime diagnoses. Interviewers, who were bachelor-and masters-level research staff, participated in a rigorous training program and demonstrated agreement with a senior interviewer ($\kappa \geq .80$) on at least two interviews before conducting independent interviews. All interview-derived

Table 2.1. Participant Characteristics by Group

Variable	Depressed			Non-Depressed		
	N	Mean (SD)	Percentage	N	Mean (SD)	Percentage
Age	75	16.21 (1.11)		77	16.13 (1.05)	
Grade	75	10.15 (1.11)		77	9.94 (1.02)	
BMI	74	24.03 (4.69)		76	23.08 (4.09)	
PDS	75	3.51 (.53)		75	3.39 (.50)	
Sex						
Male	23		30.7	29		37.7
Female	52		69.3	48		62.3
Race						
White	61		81.3	64		83.1
Black	2		2.7	2		2.6
Asian	1		1.3	2		2.6
Native American/ Alaskan	4		5.3	2		2.6
Hispanic	5		6.7	6		7.8
Other	1		1.3	1		1.3

Note: BMI = body mass index; PDS = pubertal development scale

diagnoses were confirmed by supervisors who reviewed both item-endorsement and interviewers' notes. Questions regarding the accuracy of diagnoses were resolved based upon discussion with the interviewer and review of the audiotaped interview as needed. Reliability ratings were obtained on approximately 20% of the interviews, chosen at random. The average agreement was $\kappa = .94$.

Subsequent to the interviews, families of adolescents who met criteria for MDD were invited to participate in the lab-based assessment. After each adolescent in the depressed group completed the laboratory assessment, a healthy, demographically matched comparison participant was recruited from the pool of students who scored within the normal range on the CES-D.

Approximately 9% (n = 52) of families contacted by phone were not eligible to participate as per the criteria described above (e.g., due to medicine regimen; moved out of family home). Of families invited to participate, approximately 26% ($n = 131$) declined. Rates of decline did not vary as a function of pre-interview group status (i.e., elevated or healthy CES-D score), age, or race, though more males than females declined (31.6% versus 23%), $\chi^2(1, n = 498) = 4.57, p < .05$. Of adolescents with elevated CES-D scores who participated in the interview, 38% ($n = 81$) met criteria for MDD. Of these, 13.9% ($n = 10$) had a comorbid anxiety disorder and were retained in the MDD group given the high rate of comorbidity between mood and anxiety disorders. Five individuals were excluded due to psychotic diagnoses (mania or schizophrenia). Of adolescents with CES-D scores in the healthy range, approximately 76% ($n = 84$) met criteria for inclusion.

Lab assessment

Families who met criteria for the investigation after the diagnostic interview were invited to participate in the lab assessment. Approximately 4% (n = 7) of families declined. The decline rate did not vary as a function of group status, age, race, or gender. Additionally, 11 participants were excluded from this report due to missing physiological data. In approximately 93% of two-parent families, both parents participated in the assessments. The average time between the diagnostic assessment and the lab assessment was 33.2 days (SD = 20.1; no between group differences).

The lab assessment included three family interaction tasks. Each task lasted 18 min, evenly divided across two discussions. The first task consisted of two fun-focused interactions (EPI) in which families were asked to first plan a fun family activity and then to reminisce about a fun time they had in the past. The second task consisted of a problem-solving interaction (PSI) in which families were asked to discuss and resolve two areas of conflict. The third task, consisted of a family consensus interaction (FCI) in which families were asked to discuss two areas of family life; one focused on identifying and describing the best and most difficult years the adolescent had experienced, and the other focused on the most challenging and most rewarding aspects of parenting the adolescent. The EPI and PSI tasks have been shown to preferentially elicit positive and aggressive behavioral responses, respectively (Allen et al., 2012; Sheeber et al., 2012), yet each task has the capacity to elicit a wide range of affective behavior. The FCI was designed to equally elicit positive and negative behaviors. Including a positive, negative, and an emotionally mixed context is particularly important in order to cover the types of affective interactions in which adolescents and parents are likely to engage and to understand

whether behavior within these diverse interactional contexts have implications for adolescent well-being. Interactions were video recorded for subsequent behavioral coding. Participants were instructed to abstain from alcohol and illicit drugs on the day of the assessment. Compliance with this instruction was confirmed on the day of the assessment via self-report.

Physiological Measures and Procedures

All data were acquired using software and equipment from the James Long Company (www.jameslong.net) except where otherwise noted. Electrocardiograph (ECG) was input to an isolated bioelectric amplifier custom built for research (''Bioamp''). Impedance cardiogram (ICG) signals were amplified and processed by a Hutchinson Impedance Cardiograph model HIC-2000 produced by Bio-Impedance Technology Inc. (Chapel Hill, NC). Blood pressure was monitored via a Portapres portable continuous blood pressure monitor produced by Finapres Medical Systems (Amsterdam, The Netherlands). The Portapres blood pressure monitor measured systolic and diastolic blood pressures, and over time calculated the mean blood pressure from the aggregate blood pressure waveform.

The ECG and ICG signals were recorded using Ag-AgCl electrodes. To record the ECG signal, we used a three-lead system to maximize the r-wave amplitude and minimize movement artifact and t-wave amplitude. The ECG signals were amplified with the Bioamp, with a gain of 250 and bandpass of frequencies between 0.1–1,000Hz. ICG signals were produced using two current electrodes placed on the back at thoracic vertabra T9 and on the neck at cervical vertabra C4 (Bosch et al., 2009) through which a 2mA RMS current was passed. The basal thorax impedance (Z0) was measured (in ohms) by two

electrodes placed between the current electrodes between the shoulder blades and in the mid back, and the rate of change in impedance waveform (dZ/dt) was calculated.

The ECGRWAVE program from the James Long Company identified r-waves from the ECG signal with an automated, multiple-pass, self-scaling algorithm. These signals were then visually inspected to see if the program identified the morphology of the r-wave correctly and manually corrected for missed or misrepresented r-waves. Sections of movement, noise artifact or flat line artifact were removed. Overall, this accounted for only 0.5% (in seconds) of the total data that had to be marked and removed as artifact. Other physiological data such as blood pressure were visually inspected to ensure signal quality, and quantitative data were examined to ensure that values fell within a biologically plausible range (e.g. values of 0 in any signal were removed as artifact).

Mean heart rate values were derived for each one-second epoch, based on a weighted average of the heart rate values associated with each of the inter-beat intervals (IBI) to fall either fully or partially within the epoch, with each of these intervals being weighted according to the time proportion of the epoch that each IBI constituted.

RSA reflects the variation in heart rate due to changes in respiration. We calculated a ''time-domain'' RSA variable by measuring the difference in milliseconds between the maximum inter-beat interval (IBI, or r-r interval) during expiration and the minimum IBI during inspiration (peak-to-trough method; (Goldston & Baillie, 2008b). Because the RSA variable had a non-normal distribution, we transformed it to log(RSA). Log(RSA) has been used as a time-domain measure of RSA in previous research (Lehofer et al., 1997; Moser et al., 1998).

Pre-ejection period (PEP) estimates the period of time commencing with onset of ventricular depolarization as represented by the ECG Q wave and ending with the onset of left ventricular ejection as indicated by the B point of the dZ/dt signal (Cacioppo, Uchino, & Berntson, 1994). The positions in time of the Q peak in the ECG and the B point in the dZ/dt signal were detected automatically and were subsequently checked visually and edited where the detection was incorrect.

Finger pulse transit time (FPTT) were derived from the systolic time interval (in msec) between the closest previous R-wave of the heart beat as measured by the ECG (reflecting the contraction of the heart), and the peripheral finger pulse as it was measured by the finger cuffs associated with the Portapres blood pressure monitor, averaged over each interaction type.

Prior to the interactions tasks a two-minute resting baseline measure of all psychophysiological variables were collected, during which adolescents were instructed to sit quietly and with minimal movement. These baseline measures were used as covariates for all analyses.

We considered RSA to be a measure of vagal tone, and therefore of PNS functioning. We used FPTT and PEP as indicators of SNS functioning. Lastly, we used heart rate and blood pressure as overall indicators of ANS functioning (Cacioppo et al., 1994).

Behavioral Observations

The Living in Family Environments coding system (LIFE; Hops, Biglan, Tolman, Arthur, Longoria, 1995) was used to code parent behavior during the video-recorded family interactions. The LIFE is an event-based, microanalytic coding system in which a

new code is entered each time there is a change in a participant's verbal content or affective behavior. As such, duration of each behavior (i.e., the proportion of time spent engaging in this behavior across the task) can be calculated as the time between onset of one code and onset of the next code, for each person in the interaction. In addition, frequency of each behavior can be calculated as the rate per minute of each behavior across each interaction task. Each entry is comprised of several components which identify the: (a) target (i.e., whose behavior is being coded); (b) verbal content; and (c) nonverbal (or para-verbal) affect. These micro-level data are then combined into mutually exclusive constructs, which are operationalized as particular combinations of content and affect codes (Hops et al., 1995). Three binary constructs, angry, dysphoric, and happy were derived from individual affect and content codes (with 1 indicating presence of the behavior and 0 otherwise). The angry, dysphoric, and happy constructs were used in this report. Angry behavior included aggressive (e.g., raised voice; clenched teeth) or contemptuous (e.g., eye rolling; sneering) nonverbal behavior and cruel (e.g., mocking; insults; threats) or provoking (e.g., taunts; dares) statements. Dysphoric behavior was defined by sad nonverbal behavior (e.g., tearfulness, sighing) or complaining statements. Happy behavior was defined by happy nonverbal behavior (smiling; laughing) and humorous statements.

Extensively trained observers, with over a decade of experience, coded the adolescents' nonverbal affect and the content of verbal statements. These data were coded into frequency (i.e., rate per minute) and duration (i.e., the proportion of time spent engaging in this behavior across the task). Observers were blind to diagnostic status. Approximately 25% of the videos were coded by an additional observer for reliability.

Kappas for adolescent angry, dysphoric, and happy behavior ranged from .72 to .84 (Average = .79) which reflect good agreement (Fleiss, 1981; Landis & Koch, 1977). The validity of the LIFE system as a measure of family processes has been established in numerous studies of adolescent depression (e.g., Katz & Hunter, 2007; Sheeber et al., 2007).

Self-Reported Affect

The Positive and Negative Affective Scale (PANAS; Watson & Clark, 1994) was used to assess adolescents' self-reported affect both before and after each interaction task. The post-interaction assessment queried how the adolescent was feeling during the interaction. The measure has demonstrated acceptable psychometric properties in adolescent samples and all subscale scores demonstrated acceptable reliability (i.e., $\alpha >$ .80). To assess positive and negative affect prior to the beginning of the first task, we used pre-positive and pre-negative PANAS scores. In order to examine emotional change during each task specifically (i.e., controlling for the effect of baseline affect before each task), we ran a series of regression analyses using the pre-task affect ratings to predict the post-task affect ratings for each task (i.e., EPI, PSI, FCI) and then created unstandardized residual scores representing the change unique to each task period.

Data Analysis

The data reflect information on depressed or non-depressed adolescents' observed behavior, self-reported affect, and psychophysiology averaged across each of the three interaction tasks. Using SPSS Version 23, a series of repeated-measures analyses of variance (ANOVAs) were performed with independent variables reflecting a between-subjects group factor (i.e., depressed vs. non-depressed) and within-subjects factors

reflecting the 3 interaction tasks/contexts (i.e., EPI, PSI, FCI). Dependent variables included measures of observed behavior, self-reported affect, and physiology (averaged within each condition). For physiological variables, measures of baseline individual differences in the resting values of the variables were included in analyses as covariates in order to control for the effect of baseline individual differences (i.e., heart rate, PEP, RSA, BP, FPTT). The self-reported affect measures were taken both immediately before and immediately after each interaction task, two sets of analyses. For post positive and negative scores, unstandardized residual change score between pre-positive to post-positive and pre-negative to post-negative were derived in order to index change in affect. The "outlier labeling rule" was used to assess outliers and biologically implausible values (Hoaglin, Iglewicz, & Tukey, 1986; Hoaglin & Iglewicz, 1987; Tukey, 1977).

Results

Adolescent Self Rated Affect

Main Effects of Group

As presented in Table , there was a significant main effect of group for both pre-task negative affect as well as during-task negative affect, such that depressed adolescents exhibited greater negative affect in anticipation of each interaction task and greater during-task negative affect when compared to their non-depressed peers ($ps < .001$). There was also a significant main context effect for both positive affect and negative affect in anticipation of the specific interaction contexts. Specifically, there was significantly decreasing positive affect across all contexts ($ps < .001$). In addition, there was the greatest negative affect prior to the PSI ($p < .001$), while there was no significant difference between these measure taken prior to the EPI and FCI.

Table 2.2: Self-Reported Affect

Affect	Group	Context (Task)	Gender	Group x Task	Group x Task x Gender
Pre-Positive Affect	2.491	53.913***	1.607	.168	1.288
Pre-Negative Affect	17.235***	23.764***	.153	3.439*	.670
Post-Positive Affect	2.180	.097	3.201†	.788	.961
Post-Negative Affect	16.817***	.076	.838	1.692	1.404

Note: $* = p < .05$, $** = p < .01$, $*** = p < .001$, $† = p < .10$.

Interaction Effects for Context

The second set of analyses for affect focused on interaction effects (see supplementary material for Figures 2.1a and 2.1b). Results indicated a significant interaction effect of Group by Context for pre-task negative affect, such that depressed adolescents exhibited greater pre-task negative affect. Contrasts showed that for depressed adolescents there was the greatest negative affect before the PSI as compared to the EPI ($p < .001$) and the FCI ($p < .01$), while there was no significant difference in pre-task context negative affect between the EPI and FCI. In addition, contrasts showed that for non-depressed adolescents there was greatest negative affect before the PSI compared to both the EPI ($p < .001$) and the FCI ($p < .01$), while there was also greater negative affect before the FCI compared to the EPI ($p < .05$). There were no significant effects for pre- or during-task positive affect by group, nor a significant effect for during-task negative affect by group.

Adolescent Affective Behavior

Main Effects for Group

As is presented in Table 2.3, there was a significant group effect for the frequency of aggressive and happy behavior ($p < .05$), such that across interaction contexts depressed participants showed higher frequency of aggressive behavior, lower frequency of happy behavior, and marginally higher dysphoric behavior than did the healthy controls. In contrast, when duration of behavior was examined, there was a group effect for duration of aggressive behavior ($p < .001$), but not for the duration of dysphoric or happy behavior. Specifically, depressed participants showed longer duration of aggressive behavior than did their non-depressed peers across interaction contexts. Next we examined the main effect of context on each of these affective behaviors and found a significant main effect of context for both the frequency and duration of aggressive, dysphoric, and happy behavior.

Contrasts revealed that there was significantly increased *frequency* of aggressive behavior during the PSI as compared to the EPI and the FCI (ps $< .001$), but not between the EPI and the FCI. Similarly, contrasts revealed that there was increased *duration* of aggressive behavior during the PSI compared to the EPI and FCI (ps $< .001$) as well as greater *duration* of aggressive behavior during the FCI compared to the EPI ($p < .05$). In terms of dysphoric behavior, contrasts revealed differences in *frequency* and *duration* of dysphoric behavior across contexts, such that there was greater frequency and duration of dysphoric behavior during the PSI and FCI as compared to the EPI (ps $< .001$) and greater frequency and duration of dysphoric behavior during the FCI compared to the PSI ($p < .01$). In terms of happy behavior, contrast revealed greater *frequency* and *duration* of happy behavior during the EPI compared to the PSI and the FCI (ps $< .001$) and greater *frequency*

51

and *duration* of happy behavior during the FCI compared to the PSI ($p < .05$ and $p < .001$, respectively).

Interaction Effects for Context

The second set of analyses focused on interaction effects (see supplementary material Figures 2.2a, 2.2b, 2.3a, 2.3b). Results indicated that there was a Group by Context interaction effect for the duration of aggressive and dysphoric, but not happy behavior. Contrasts showed that both depressed and non-depressed adolescents had greater duration of aggressive behavior during PSI compared to the EPI and FCI (ps $< .001$) with depressed adolescents exhibiting significantly greater duration of aggressive behavior during the PSI compared to non-depressed adolescents ($p < .001$). In addition, there were no differences in duration of aggressive behavior between the EPI and FCI. Similarly, contrasts showed that depressed adolescents, demonstrated differential duration of dysphoric behavior across the interaction tasks, such that there was greater duration of dysphoric behavior during the PSI compared to the EPI ($p < .001$), greater duration dysphoric behavior during the FCI compared to the PSI ($p < .01$), and greater duration of dysphoric during the FCI compared to the EPI ($p < .001$). In addition, for non-depressed adolescents, contrasts showed that there was greater duration of dysphoric behavior during the PSI and the FCI as compared to the EPI ($p < .001$) and there was no difference in duration of dysphoric behavior between the PSI and the FCI.

a

b
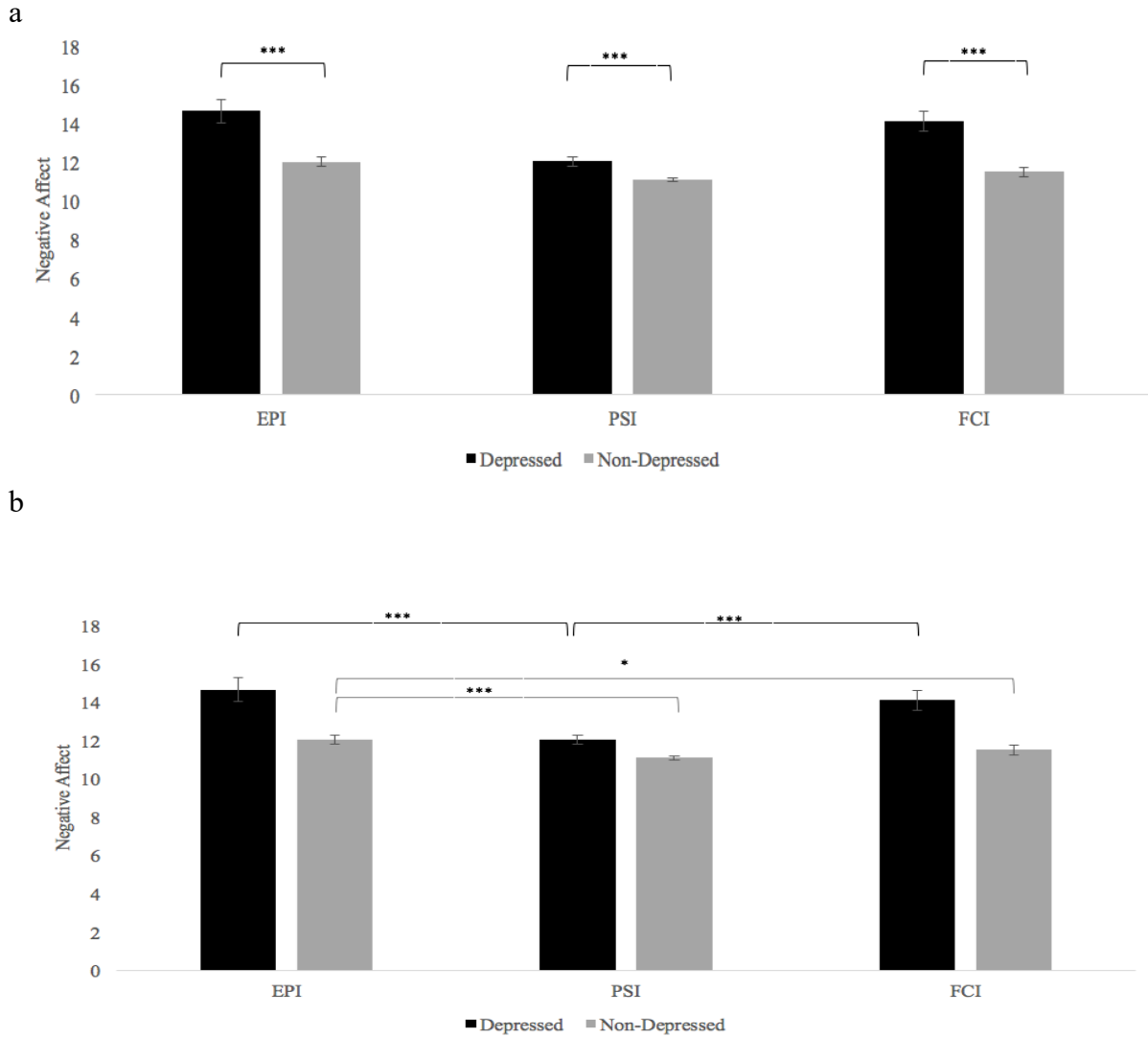
Figure 2.1. (a) Between-Subjects and (b) Within-Subjects Self-Reported Negative Affect

Across Tasks in Depressed and Non-Depressed Adolescents. Note: EPI- Event Planning

Task, PSI- Problem Solving Task, FCI- Family Consensus Interaction; * = *p* < .05, *** = *p*

< .001.

Table 2.3: Observed Affective Behavior

Behavior	Type	Group	Task	Gender	Group x Task	Group x Task x Gender
Aggression	Frequency	5.783*	25.070***	3.435†	1.122	.581
	Duration	12.422***	40.535***	3.784†	5.062**	.311
Dysphoric	Frequency	3.798†	16.080***	.123	.932	1.096
	Duration	.558	64.581***	.003	3.623*	.154
Happy	Frequency	4.122*	64.151***	.802	1.200	.714
	Duration	.384	93.337***	.002	.148	.114

Note: $* = p < .05$, $** = p < .01$, $*** = p < .001$, $† = p < .09$.

Adolescent Psychophysiology

Main Effects for Group

As presented in Table 2.4, when quiet baseline measures of psychophysiology were included as a covariate, there was a significant main group effect for PEP ($p < .05$), such that depressed adolescents had shorter PEP times, indicating greater sympathetic activation, and a significant main group effect for BP ($p < .05$), such that depressed adolescents had higher BP than non-depressed peers. Interestingly, there were no main group effects for any other physiological variables (see Table 2.4).

In addition, a significant main context effect emerged for PEP, such that PEP intervals were slower during the EPI compared to the FCI ($p < .05$). Lastly, there was a significant gender effect for FPTT, such that females had faster transit times (i.e., greater sympathetic

activity) than males (there were no other gender effects for any other physiological variables).

Interaction Effects for Context

The second set of analyses focused on interaction effects (see supplementary material Figure 2.4 for RSA withdrawal during contexts from resting baseline). Interaction effects revealed a significant Group by Context interaction for RSA, with post hoc analyses revealing that despite this significant interaction effect, the main effect of context was not statistically significant within either the depressed or non-depressed groups when run separately. However, inspection of the pattern of means suggested that depressed adolescents had *greater* RSA withdrawal during the PSI than did non-depressed adolescents, whereas during the EPI depressed adolescents showed *less* RSA withdrawal than did the non-depressed adolescents. Finally, there was also a three-way interaction between Group, Context, and Gender for RSA. Post hoc analyses, run for each depression group separately showed that this effect was driven by the fact that depressed males showed significantly less RSA withdrawal during the EPI than did depressed females (there was no significant Context x Gender effect amongst the non-depressed participants).

Discussion

These findings demonstrate significant differences between clinically depressed and non-depressed adolescents in terms of both context independent and context specific effects on self-reported affect, observed behavior, and psychophysiology during various affectively charged parent-adolescent interactions.

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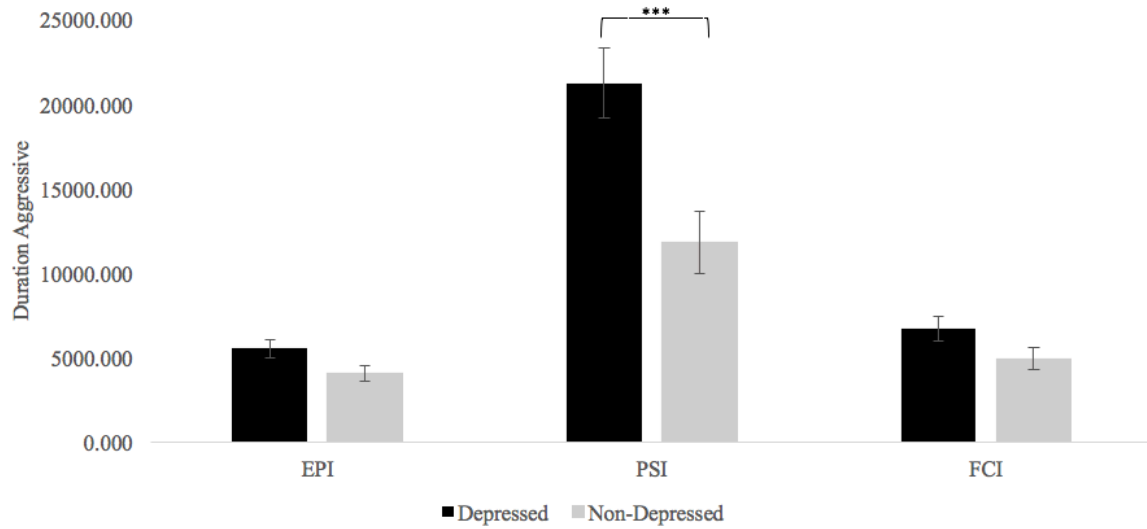
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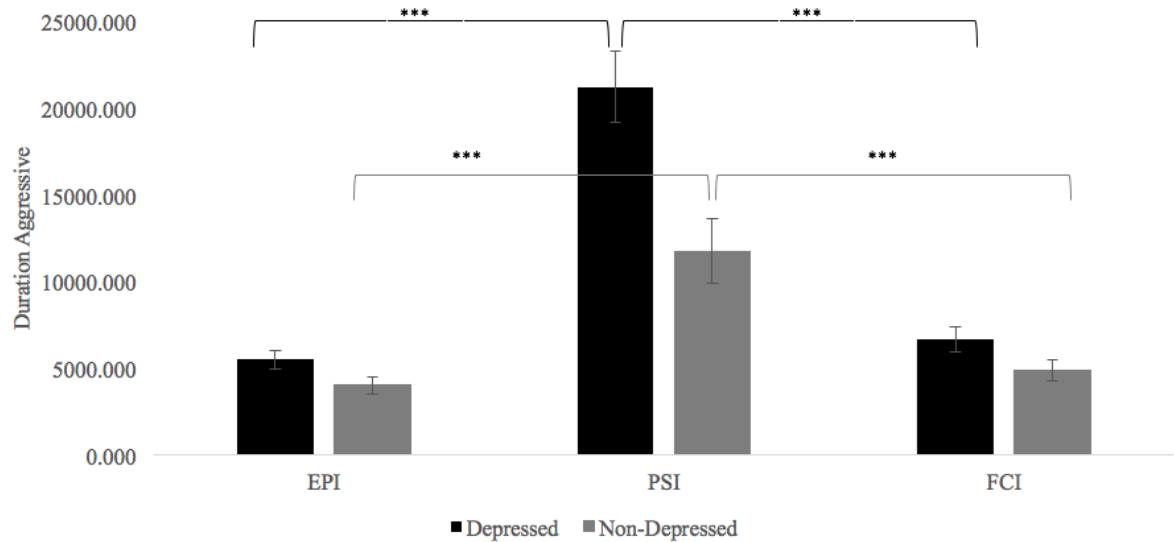
Figure 2.2. Duration of (a) Between-Subjects and (b) Within-Subjects Duration of
Aggressive Behavior Across Tasks in Depressed and Non-Depressed Adolescents. Note:
EPI- Event Planning Task, PSI- Problem Solving Task, FCI- Family Consensus
Interaction; *** = $p < .001$.

a
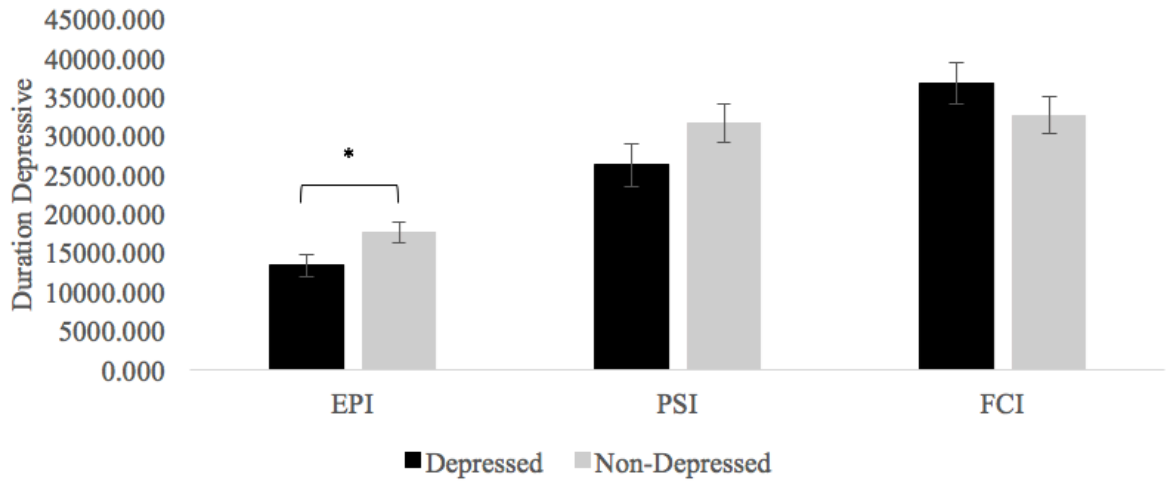
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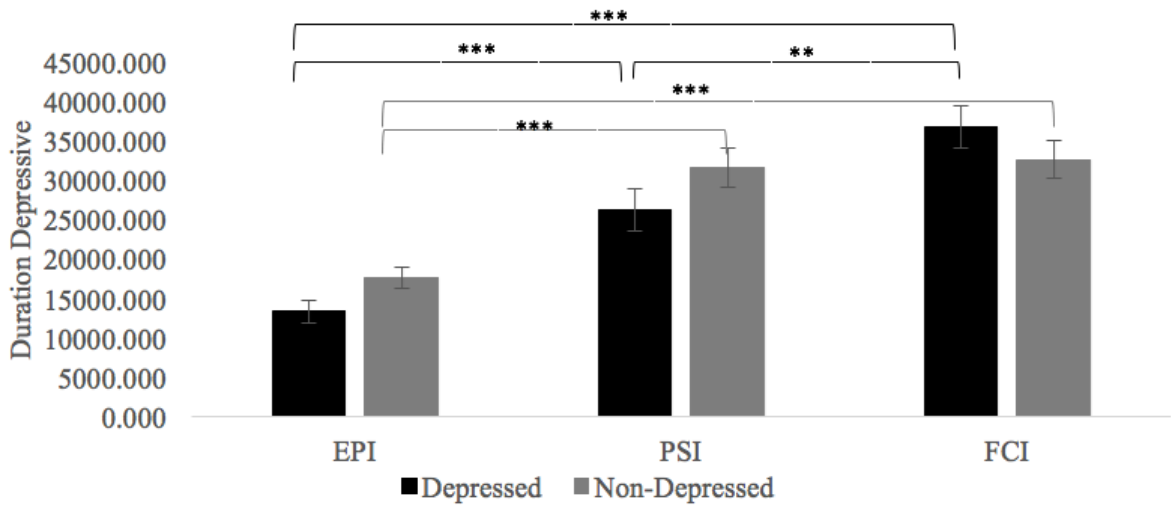
Figure 2.3. Duration of (a) Between-Subjects and (b) Within-Subjects Duration of

Depressive Behavior Across Tasks in Depressed and Non-Depressed Adolescents. Note:

EPI- Event Planning Task, PSI- Problem Solving Task, FCI- Family Consensus

Interaction; * = $p < .05$, ** = $p < .01$, *** = $p < .001$.

Table 2.4: Psychophysiology

Variable	Group	Task	Gender	Group x Task	Group x Task x Gender
HR	.012	.683	2.252	1.477	2.550†
PEP	4.01*	3.859*	.503	.434	.040
RSA	.148	1.032	2.559	4.705**	4.613**
FPTT	.007	.427	12.006***	1.545	2.795†
BP	4.048*	3.040†	0.000	1.418	1.727

Note: $* = p < .05$, $** = p < .01$, $*** = p < .001$, $\dagger = p < .09$. HR = heart rate, PEP = pre-ejection period, RSA = respiratory sinus arrhythmia, FPTT = finger pulse transit time.
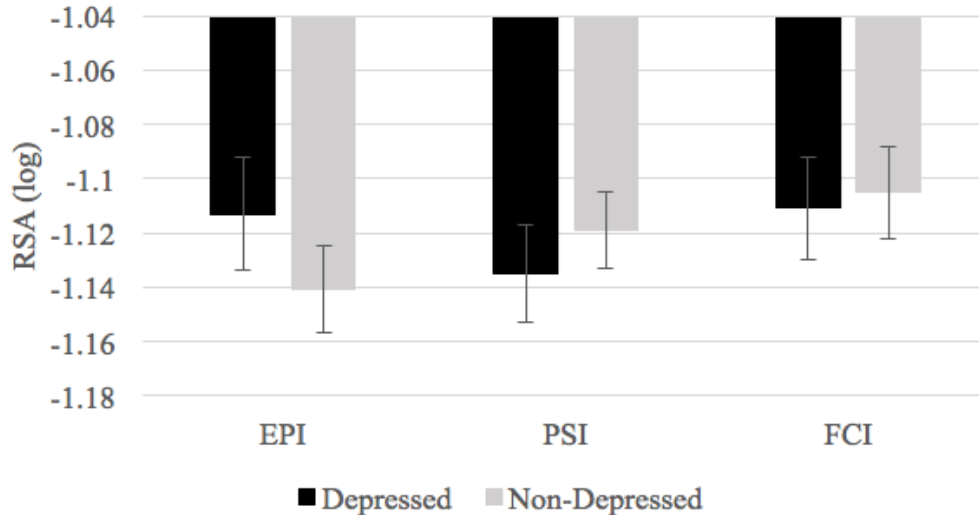
Figure 2.4. RSA (log) Across Tasks in Depressed and Non-Depressed Adolescents. Note: EPI- Event Planning Task, PSI- Problem Solving Task, FCI- Family Consensus Interaction.

Main Effects of Depression

Consistent with our hypotheses, across contexts depressed adolescents displayed greater negative affect in anticipation of and during interactional tasks, greater frequency and duration of aggressive behaviors, marginally greater dysphoric behaviors, and lower frequency of happy behaviors, along with shorter PEP (i.e., greater sympathetic activity) and higher BP (i.e., greater overall autonomic activity) as compared to their non-depressed peers. In contrast to our hypotheses, depressed adolescents did not differ from their non-depressed peers in terms of positive affect in anticipation of or during interaction tasks and showed no other overall autonomic or parasympathetic differences from their non-depressed peers.

These finding may have a few potential explanations. First, in terms of affect across tasks, depressed individuals, particularly depressed adolescent females, are known to demonstrate greater level of negative affect (Forbes, Williamson, Ryan, & Dahl, 2004; Watson, 2000), while there is a tendency among adults with depression for increased attentional biases resulting in greater emotional processing of negative appraisals of neutral stimuli or negative aspects of stimuli (Kan, Mimura, Kamijima, & Kawamura, 2004), and hyper-reactivity to emotional stimuli that is social in nature and indicative of threat (Allen & Badcock, 2003; Price, Sloman, Gardner, Gilbert, & Rohde, 1994) - all of which may extend the length of negative emotional responses. In contrast to our hypotheses, there was no difference between depressed and non-depressed adolescents in terms of reported positive affect either prior to or during interaction tasks generally. This is particularly surprising given that those with depression demonstrate lower levels of positive affect in prior research (Davidson et al., 2002; Watson, 2000a). Overall behavioral findings are

consistent with some previous research indicating that those with depression tend to exhibit greater aggressive behaviors (Knox et al., 2000), higher levels of negative behaviors (e.g., behavioral disengagement and self-blame; (Horwitz et al., 2011), and increased dysphoria during interpersonal interactions in prepubertal children (Puig-Antich et al., 1985). One interpretation of the strong findings for aggressive behavior in depressed adolescents is that they were experiencing more hostile parental behaviors than their non-depressed peers (McLeod, Weisz, & Wood, 2007), as parental conflict has been shown to mediate the relationship between depression and aggression (Panak & Garber, 1992). In addition, the decreased frequency of happy behavior in depressed adolescents in this sample may be related to the previously mentioned emotion context insensitivity associated with depression. For example, depressed adolescents may be having less of an emotional reaction to positive stimuli, specifically to positive interpersonal experiences as has been shown in adults (i.e., emotional context insensitivity; Bylsma, Morris, & Rottenberg, 2008; Rottenberg, 2005), as well as exaggerated/chronic negative reactions to negative stimuli in adolescence through adults (Koval et al., 2012; Koval & Kuppens, 2012). This may indeed lead to the well-known interpersonal difficulties (e.g., social rejection) experienced by adolescents experiencing depression, as they may not be expressing appropriate positive behaviors, but rather expressing depressotypic behaviors (Slavich, O'Donovan, Epel, & Kemeny, 2010). Furthermore, given the core weight given to sadness in the diagnosis of depression, it is interesting to note that there was not a significant difference between depressed and non-depressed adolescence in terms of overall dysphoric behavior, although this finding was marginally significant.

Finally, group differences in psychophysiology are consistent with prior literature indicating greater sympathetic activity in those with depressive symptomatology in adolescents and adults (Byrne et al., 2010; Rottenberg et al., 2007) as well as greater incidence of hypertension in adults with depression (Davidson et al., 2000; Jonas, Franks, & Ingram, 1997; Meng, Chen, Yang, Zheng, & Hui, 2012). It is important to note that in contrast to our hypotheses and prior research (Kemp et al., 2010; Koenig et al., 2016) - there were null group effects for heart rate, RSA, and FPTT across all contexts. In terms of heart rate and RSA, the null finding may be explained by the fact that most prior research indicating higher heart rates and lower RSA in adolescents and adults with depression have used resting baseline heart rate measurements (Byrne et al., 2010; Moser et al., 1998), rather than heart rate reactivity to interpersonal contexts as we did in the present study. It is hard to interpret the null findings in regards to FPTT as there is a dearth of research looking at the association between depression and FPTT. In addition to the main effects found by group, it is important to note that the varying interpersonal contexts strongly moderated affective, behavioral, and psychophysiological responses.

Context Specific Effects of Depression

In terms of affect experienced during interaction context and in accordance with our hypotheses, depressed adolescents displayed greater negative affect prior to each context as compared to their non-depressed peers. In addition, depressed adolescents displayed greater negative affect prior to the EPI and FCI contexts, while non-depressed adolescents displayed greater anticipatory negative affect prior to the EPI as compared to the other two contexts. These findings indicate that both depressed and non-depressed adolescents experience negative affect prior to entering a new context to begin with (i.e.,

the first interaction context), but while this negative affect diminishes for non-depressed adolescents after the initial context, it continues for depressed adolescents after they experience a negative interaction context. Specific to behavior, depressed and non-depressed adolescents showed similar increases in the duration of aggressive behavior during the PSI (negative) context as compared to the other two contexts, but depressed adolescents showed this pattern to a much larger degree. In other words, depressed adolescents displayed an exaggerated duration of aggressive behavior during the PSI (negative) context as compared to their non-depressed peers. Interestingly, while depressed and non-depressed adolescents did not differ in terms of dysphoric behavior in general, they did differ by context and across context. Specifically, depressed adolescents differed from non-depressed adolescents during the EPI (positive) context interactions during which they surprisingly showed shorter duration of dysphoric behaviors. This is an unanticipated finding, yet it reflects literature showing a "mood brightening effect" or exaggerated positive emotion reactivity to events in individuals with major depressive disorder (Bylsma, Taylor-Clift, & Rottenberg, 2011). Either way, this finding clearly requires replication before strong conclusions are drawn. In contrast, depressed adolescents differed from non-depressed adolescents in that their duration of dysphoric behavior linearly increased across all interaction contexts, while non-depressed adolescents' dysphoric behavior plateaued in duration after the PSI (negative) interaction context. Finally, in terms of psychophysiological differences between depressed and non-depressed adolescents across contexts, interaction effects revealed a group and context interaction, such that depressed adolescents showed greater RSA withdrawal during the PSI, while non-depressed adolescents showed greater RSA withdrawal during the EPI, as was

hypothesized. There was also a three-way interaction effect between Group, Context, and Gender for RSA, which was driven by the fact that depressed males showed significantly less RSA withdrawal during the EPI than did depressed females (there was no significant Context by Gender effect as amongst the non-depressed participants). In contrast to our hypotheses, there was no difference between depressed and non-depressed adolescents in terms of negative affect during, positive affect either prior to or during, and overall autonomic activity during each specific interaction context.

These findings have a number of possible explanations. First, depressed adolescents may have experienced a greater level of negative affect in anticipation of each task as compared to their non-depressed peers, because research indicates that depressed individuals experience greater overall level of negative affect (Davidson et al., 2002; Forbes, Williamson, Ryan, & Dahl, 2004; Watson, 2000), but it remains unclear why this wouldn't be true for affect experienced during the interaction. Furthermore, non-depressed adolescents had the greatest anticipatory negative affect prior to the first context, which subsequently subsided for the remainder of the interactions, indicating emotional flexibility and resilience to context (Waugh et al., 2011), while depressed adolescence had continued anticipatory negative affect prior to the FCI indicating potential emotional inertia and inflexibility due to the negative interaction of the PSI that carried over to the following task (Lougheed & Hollenstein, 2016). The ever increasing duration of depressive behavior across tasks in depressed adolescents may also be understood as a form of behavioral inertia, given that previous research has indicated that those with depression have high temporal autocorrelations between negative emotional states over time (Koval & Kuppens, 2012), indicating less emotional flexibility and the propensity for negative behavioral

spirals, specifically with dysphoric behavior during interpersonal interactions (Puig-Antich et al., 1985). Moreover, the autobiographical component of the final context, may have been more emotionally evocative for depressed than non-depressed adolescents (Williams et al., 2007). In contrast, their non-depressed peers may have had an adaptive increase in dysphoric behavior during the PSI, which stabilized and did not increase during the next consensus task context indicating a degree of behavioral flexibility, which is characteristic of resilience (Lougheed & Hollenstein, 2016; Waugh, Thompson, & Gotlib, 2011). In terms of aggressive behavior, which peaked for both depressed and non-depressed adolescents during the PSI (negative) task, depressed adolescents experienced this to a much greater degree than their non-depressed peers, which may be explained by the greater reactivity to emotional stimuli that is social in nature and indicative of threat (Allen & Badcock, 2003; Price et al., 1994) experienced by those with depression.

Finally, interpretation of the physiological effects observed depends to a certain extent on how one interprets the psychological significance of pattern of RSA findings. The data shows a dramatic reduction in RSA during all the interactions when compared to the resting baseline RSA, suggesting that the social interactions themselves prompt some type of vagal withdrawal. One parsimonious explanation for this is that the vagal withdrawal facilitates increased sympathetic control of the cardiac system, thus facilitating arousal in response to sympathetic activation. Therefore, one interpretation of these findings is that the relatively greater RSA withdrawal for non-depressed adolescents during the EPI (positive interaction) may indicate greater physiological engagement and positive sympathetic arousal, while the relatively greater RSA withdrawal exhibited by depressed adolescents during the PSI (negative interaction) may indicate the opposite (i.e., a greater

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interpretation of threat, mobilization of resources, and/or a lack of sympathetic regulatory ability) during the aversive context (Beauchaine et al., 2007). In this sense the findings may have some similarity to Schachter & Singer (1962) model which suggests that arousal can be variously interpreted or elicited depending on the affective context in which it occurs. In contrast, an alternative interpretation of these findings would be derived from the Polyvagal Theory (see Porges, 2007), which interprets RSA activation as supporting social communication and self-soothing. However, given the significant withdrawal of vagal activity during all of the interaction tasks when compared to the baseline measures, we consider the arousal interpretation as more parsimonious. More generally, what can be understood is that there was a differing RSA response between depressed and non-depressed adolescents across the different affective interpersonal interactions, suggesting that interpersonal contexts can moderate these effects. In terms of the three way interaction between RSA, group, and gender, one reason for this gender difference may be that females tend to have lower autonomic responses than age-matched men due to the possible effect of estrogen on sympathoadrenal response (Kajantie & Phillips, 2006).

Limitations and Future Directions

Though this study had significant strengths in employing a multimethod assessment of differences between depressed and non-depressed adolescents in terms of self-reported affect, observed behavior, and psychophysiology across three affectively charged interpersonal contexts, it is important to note a number of limitations. First, the present study focused solely on adolescent self-reported affective, observed behavior, and psychophysiological processes. Though this focus on adolescent processes provides a refined description of the functioning of clinically depressed adolescents, it lacks the

systemic view that could be gained by also addressing the role of parental self-reported affect, behavior, and psychophysiology. Future studies should address the role of parental processes in reactions of depressed adolescents and look at conditional responding between parents and adolescents across different tasks and groups. Previous research from our lab has addressed the importance of this systemic view, at least at the behavioral level (Hollenstein, Allen, & Sheeber, 2015). Second, the current study was limited to elucidating the impact of depression during adolescence on interactions within the context of parent-adolescent interactions. Future studies should examine the role of peer interactions in these contexts as research had elucidated that adolescence is a developmental period characterized by a "social reorientation" from parents to peers (Nelson, Leibenluft, McClure, & Pine, 2005). Third, research also indicates that depression is moderately heritable (Levinson, 2006) and therefore some of these adolescents' parents may have had a diagnosis of depression themselves, which could affect relational interactions between adolescents and their parents. Future studies should address the role parental psychopathology plays in depressed and non-depressed adolescent responses to interaction contexts. We are currently conducting a study to examine family interactions across various emotional contexts in which the mother has a diagnosis of depression in order to see how maternal, rather than adolescent depression, influences relational, affective, behavioral, and physiological dynamics during parent-adolescent interactions. Fourth, the current study focused on adolescent psychophysiology, but future research would benefit from also examining parental psychophysiology. Psychophysiological attunement or coregulation (i.e., the bidirectional synchronization of physiology between two or more individuals across time; Nelson, Laurent, Bernstein, & Laurent, 2016) is a burgeoning area

of research that may have implications for family interactions and adolescent outcomes (Timmons, Margolin, & Saxbe, 2015). As mentioned above, our lab is working on a new study to address the role of both adolescent and parental psychophysiology during interactions to elucidate the role depression plays in psychophysiological attunement in parent-adolescent dyads and how levels of attunement or lack thereof relate to adolescent mental health and adjustment. Fifth, interaction contexts were not randomized and therefore we cannot rule out priming or ordering effects. Future studies should randomize the presentation of interaction contexts in order to control for these possible effects. Fifth, our study did not differentiate between adolescents with solely clinical depression and adolescents with co-occurring clinical depression and other disorders. Future research should address co-occurring disorders, which may have also explained the lack of many psychophysiology interaction effects in the current sample, as co-occurring disorders may have had moderating influences. Sixth, we did not have a self-report measure of discrete emotions that mapped onto the dimensions measured in the observational data (i.e., anger, dysphoria, happy). Future studies should include self-report scales that more closely conceptually map onto the dimensions of observational data. Sixth, this study cannot address whether affective, behavioral, and physiological factors are risk factors for depression or concomitants of depression. We suggest that future research focus on this topic to provide a better means of understanding the etiology and subsequent manifestations of depression. Finally, future studies should incorporate measures of physical health outcomes (i.e., inflammation, chronic disease, biological aging) as research is beginning to elucidate the connection between psychopathology, specifically depression, and physical disease. Measuring physiology would be the first step as research is

elucidating the connection between autonomic alterations in depression that may lead to heart disease (Hare, Toukhsati, Johansson, & Jaarsma, 2014; Nemeroff & Goldschmidt-Clermont, 2012). The way adolescents interact with their parents during this transitional period to adulthood may be particularly important in buffering or exacerbating the physical health problems and outcomes associated with depression that may emerge in adulthood (Celano & Huffman, 2011; Pan, Sun, Okereke, Rexrode, & Hu, 2011; Valkanova, Ebmeier, & Allan, 2013; Wolkowitz et al., 2011).

Clinical Implications

Increased understanding of the ways in which context influences adolescent depression may help to provide multiple points of entry for treatment efforts to prevent the negative impacts in adulthood that are associated with adolescent depression (e.g., psychopathology, unemployment, interpersonal difficulties, and physical health problems; Bardone et al., 1998; Copeland, Shanahan, Costello, & Angold, 2009; Fergusson, Boden, & Horwood, 2007; Keenan-Miller, Hammen, & Brennan, 2007; Pine, Cohen, Cohen, & Brook, 1999).

Psychoeducation and Treatment

First, increased knowledge of how context influences the expression of depression in adolescence may also help in conceptualizing the treatment of adolescent depression. Our findings highlight that when working in mental health settings, context changes the way that psychopathology presents itself and, therefore, psychopathology may not be seen clearly in all contexts – emphasizing the importance of assessment behavior across as many contexts, and via as many observers, as possible. For example, while adolescents display greater negative affect before entering a new context, they may not be as

distinguishable from non-depressed adolescents at the behavioral level during positive or emotionally mixed contexts. Similarly, parent-adolescent interventions that incorporate psychoeducation on how context influences the expression of depression may provide grounds for better parental understanding of adolescent experience. Second, this increased knowledge of both overall differences and context influences on the expression of depression in adolescence may also help in conceptualizing the treatment of adolescent depression. For example, with regards to affect, our findings indicate that depressed adolescents may have particularly strong negative affect in anticipation of new interaction contexts. Creating treatments that incorporate the use of cognitive reappraisal (Ray, McRae, Ochsner, & Gross, 2010) and mindfulness (Keng, Smoski, & Robins, 2011) prior to entering new contexts (particularly after negative interaction contexts between adolescents and their parents) may provide for a quicker return to emotional and behavioral homeostasis. In addition, in terms of behavioral findings, the use of mindfulness (Keng et al., 2011) and relaxation techniques (Reinecke & Ginsburg, 2008) may assist in ameliorating some of the negative behavior and affect associated with negative adolescent-parent interactions as well as reduce physiological arousal, respectively. Lastly, in terms of physiology, our findings and others indicate that those with depression have greater RSA withdrawal during negative interactions, indicating greater sympathetic arousal, than their non-depressed peers. Incorporating RSA biofeedback (Karavidas et al., 2007) or vagal nerve stimulation (Sackeim et al., 2001) in the treatment of depression in adolescence may be particularly useful in upregulating parasympathetic control, which may be especially important for future negative interaction contexts. Further research is needed to fine tune these contextual differences and identify when and where to intervene in adolescent

depression in order to prevent the recurrence and duration of depressive episodes, which are associated with future negative health and adjustment outcomes as well as intergenerational transmission of risk for depression to future offspring (Lieb, Isensee, Höfler, Pfister, & Wittchen, 2002).

Conclusion

The present study provides important insights into differences between clinically depressed and non-depressed adolescents by using a multimethod approach across multiple emotionally evocative interaction contexts. Overall, our findings suggest that depressed adolescents exhibit greater negative and lower positive behaviors, higher negative affect, greater overall autonomic and sympathetic activity, and lower parasympathetic activity, particularly during emotionally charged negative interpersonal interactions as compared to their non-depressed peers. More research is needed to help refine our understanding of how these levels of analysis interact both within and between adolescents and their parents in order to provide a more comprehensive understanding of the intrapersonal and interpersonal outcomes associated with depression in adolescence.

CHAPTER III

ADOLESCENT SYMPATHETIC ACTIVITY AND SALIVARY C-REACTIVE

PROTEIN: THE EFFECTS OF PARENTAL BEHAVIOR

This work was previously published in *Health Psychology* and was co-authored with M. L. Byrne, J. G. Simmons, S. Whittle, O. S. Schwartz, E. C. Reynolds, N. M. O'Brien-Simpson, L. Sheeber, & N. B. Allen, therefore the following chapter is formatted according to the journal's publication standard. I was the lead author of this publication and established the study design, experimental methods, and data analysis with input from my co-authors.

Nelson, B. W., Byrne, M. L., Simmons, J. G., Whittle, S., Schwartz, O. S., Reynolds, E. C., O'Brien-Simpson, N. M., Sheeber, L., & Allen, N. B. (2017). Adolescent sympathetic activity and salivary C-reactive protein: The effects of parental behavior. *Health Psychology*, *36*(10), 955- 965.

Introduction

Adolescence is a developmental period during which many factors that influence health and disease trajectories across the lifespan are established (Lupien, McEwen, Gunnar, & Heim, 2009). Two potentially important biological systems that can affect these trajectories are the sympathetic nervous system (SNS) and the immune response system (Danese & McEwen, 2012; Valkanova, Ebmeier, & Allan, 2013). Furthermore, research shows that social relationships can play a significant role in the association of these

systems with poor health outcomes. For example it has been proposed that social threat (acute and chronic) up-regulates SNS activation and inflammation, leading to a dysregulated phenotype at risk for both physical and mental health problems (Slavich & Irwin, 2014), while positive social relationships may buffer against deleterious health outcomes (Chen, Miller, Kobor, & Cole, 2011; Thoits, 2011).

While previous research has examined the relationship between autonomic functioning and inflammation, as well as the connections between parenting and stress or inflammation, to our knowledge there have been no studies that have combined all these measures into a multi-system investigation (i.e., sympathetic activity, parent behavior, and inflammation) of these effects. Indeed, in general there is a dearth of research clarifying the specific mechanisms by which social relationships affect the biological systems that increase risk for poor health outcomes. Parental behavior, specifically during periods of interpersonal conflict that can provoke strong affective or stress responses, may be one important relational influence that can activate or dampen the links between sympathetic activity and inflammation (Kiecolt-Glaser, Gouin, & Hantsoo, 2010). Increased understanding that familial environmental factors influence the association between adolescent stress physiology and inflammation will help provide a deeper understanding of the ways in which the social environment can influence mechanisms of health and disease during this developmental period.

Sympathetic Activity and Inflammation

One non-invasive marker of SNS activity is pre-ejection period (PEP), or the time interval between the left ventricle's depolarization and the subsequent ejection of blood through the aortic valve. Shorter intervals are indicative of greater sympathetic response. It

has been suggested that there is a bidirectional pathway via afferent nociceptive neurons between ANS activation, specifically the SNS (Nance & Sanders, 2007), and immune functioning (Jänig, 2014). By contrast, research is more sparse when it comes to the role of parasympathetic system (PNS) activity directly innervating immune organs (Nance & Sanders, 2007), although one study does indicate that PNS activity has influences on immune function (Forsythe, 2014). Moreover, the main neurotransmitter of the SNS, norepinephrine, is thought to regulate immune cell activity by influencing cytokine and antibody gene expression to increase inflammation. Finally, sympathetic innervation of the inflammatory system has been shown to be influenced by social stress in animal (Sloan et al., 2007) and human (Kemeny & Schedlowski, 2007) models. As such, the SNS is thought to regulate the inflammation response to a greater degree than the PNS (McEwen, 2008; Nance & Sanders, 2007), and this SNS-inflammation relationship is thought to serve as a critical biological pathway connecting stress (i.e., increased sympathetic tone) with inflammation (Miller & Blackwell, 2006), as has been demonstrated in animal models (Felger, Haroon, & Miller, 2015).

Parent-Adolescent Interactions and Health

The impact relationships have on psychological and physical health is well documented (Glaser et al., 2002; Holt-Lunstad, Smith, & Layton, 2010; Jaremka, Lindgren, & Kiecolt-Glaser, 2013; Kiecolt-Glaser et al., 2010). Parent-adolescent interactions are an especially important interpersonal context that influences adolescent health (Hagan, Roubinov, Adler, Boyce, 2016) and this may be due to the chronic environmental exposure of parental behavior. For example, research shows stability of parental behavior from infancy through adolescence (Else-Quest, Clark, & Owen, 2011),

across adolescence (Sheeber, Hops, Alpert, Davis, & Andrews, 1997), as well as across generations (Neppl, Conger, Davis, & Ontai, 2010). For example, parents who experienced more warmth and support in their own childhood have been found to be more supporting in their interactions with their children (Belsky, Sligo, Jaffee, Woodward, & Silva, 2005), while parents who experienced more harsh and abusive parenting exhibit similar behavior with their own children (Pears & Capaldi, 2001). Therefore, conflictual family relational environments may provide a constant environmental input that heightens adolescent stress responses across time. The exact role that social relationships play in the association between sympathetic activity and inflammation is not yet clear, but these parent-adolescent interactions may serve as one psychosocial mechanism that may moderate the association between physiological stress (i.e., sympathetic activity) and later inflammation, thereby influencing the pathway from stress to disease (Kemeny & Schedlowski, 2007; Lupien et al., 2009; Priest et al., 2015).

Research shows that psychosocial mechanisms, such as supportive and positive interpersonal relationships, buffer against the negative impact of stress (Thoits, 2011). Specifically, research has separately demonstrated that supportive relationships protect against both dysregulated sympathetic activity as well as elevated inflammation (Byrne et al., 2016; Haley & Stansbury, 2003; Kiecolt-Glaser & Newton, 2001; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). For example, supportive and functional relationships buffer against higher systemic inflammation (Byrne et. al., 2016) as well as the deleterious effects of dysregulated physiological stress systems associated with allostatic load and psychopathology (Brooks et al., 2014; Carroll et al., 2013). Furthermore, sensitive parents, positive parental behaviors, and supportive role models for adolescents have all been

shown to buffer the effect of low socioeconomic status against inflammation (Chen, Miller, Kobor, & Cole, 2011; Chen, Lee, Cavey, & Ho, 2013). Therefore, one social signal, which may act as a relational buffer (i.e., protective factor, see Hostinar, 2015) against the effects of sympathetic activity on inflammation is positive parental behavior. Specifically, positive parental behavior, especially during negative and/or challenging interactions, may buffer against the deleterious effects of sympathetic activity on inflammation.

In addition, research shows that the opposite is true for those with unsupportive, stressed, and dysregulated relationships (Fagundes, Bennett, Derry, & Kiecolt-Glaser, 2011). For example, dysphoric or aggressive maternal behavior that is associated with social conflict has separately been shown to be associated with both increased sympathetic activity as well as inflammation (Fuligni et al., 2009; Kiecolt-Glaser et al., 2010; Miller, Rohleder, & Cole, 2009). Parent-adolescent relationships characterized by high conflict are associated with greater sympathetic arousal (Salomon, Matthews, & Allen, 2000) and parental harshness and stress are associated with increased current levels of adolescent inflammatory response as well as prospectively predicting, 1.5 years later, adolescent inflammatory response (Byrne et al., 2016; Miller & Chen, 2010; Wolf, Miller, & Chen, 2008). Indeed, social threat, including the absence of positive parental behavior, may influence sympathetic activity leading to up-regulated inflammation activation, that may result in a dysregulated phenotype driving disease pathogeneses (Slavich & Irwin, 2014).

The current study examined the association between sympathetic activity and salivary C-reactive protein (sCRP) in adolescents as well as the moderating role of parental behavior on this association. Body mass index (BMI; Gillum, 2003), gender (Bouman,

Heineman, & Faas, 2005), socio-economic status (SES; Pollitt et al., 2007), and pubertal group (Delany et al., 2016), were collected as potential confounders due to the previously identified associations with inflammation. Finally, although research suggests that CRP does not have a diurnal variation in healthy adults (Meier-Ewert et al., 2001; Miles et al., 2008), there is one study that has found the contrary with a medical patient population (Koc, Karaarslan, Abali, & Batur, 2010), so time of sCRP collection was also collected as well as parental gender as potential confounds.

The Current Study

The current study is the first to our knowledge to utilize a multi-system approach in order to address gaps in knowledge in the association between SNS activity and sCRP in adolescents, and the role that the social environment plays in this relationship, by examining: 1) the association between sympathetic activity and sCRP and 2) the moderating role of positive, dysphoric, and aggressive parental behavior during a negative interaction on the association between adolescent sympathetic activity and inflammation.

First, we hypothesized that shorter PEP (i.e., greater sympathetic activity) would, prospectively, be related to greater concentrations of sCRP approximately 3 years later (mean = 3.15, SD = .65) such that greater sympathetic arousal would predict greater levels of inflammation. Second, we hypothesized that the duration of positive parental behavior during a negative emotion-eliciting parent-adolescent problem-solving interaction would moderate the relationship between adolescent PEP and sCRP, such that shorter duration of parental positive behavior would be associated with a stronger relationship between high sympathetic arousal (i.e., shorter PEP) and higher sCRP. In addition, we hypothesized that longer duration of parental dysphoric and aggressive behavior would be associated with a

stronger relationship between high sympathetic arousal (i.e., shorter PEP) and greater sCRP.

Methods

The current study included data from the Adolescent Development Study (ADS) – a large-scale longitudinal research project conducted from 2004 to 2012 at the Orygen Centre for Youth Mental Health at The University of Melbourne, Australia. Family and electrophysiology data were collected during the first assessment at Time 1 (T1) when participants were approximately 12 years old (mean age = 12.30, SD = .68); socioeconomic status, body mass index, and pubertal development were collected at Time 2 (T2) when participants were approximately 14.85 years old (mean age = 14.85, SD = .51), whilst adolescent sCRP data from a subgroup of participants at Time 3 (T3), approximately three years after T1 (mean = 3.15, SD = .65), when participants were approximately 15 years old (mean age = 15.46, SD = .49).

Recruitment and screening of participants

The recruitment and screening of participants has been reported in detail previously (Yap, Allen, & Ladouceur, 2008). Screening was conducted to identify a community sample of 10- to 12-year-old primary-school students representing the full spectrum of risk for psychopathology as a function of temperament, as measured by the Early Adolescent Temperament Questionnaire–Revised (Ellis and Rothbart, 2001). Participants were Grade 6 students enrolled in primary schools in metropolitan Melbourne, Australia. Grade 6 corresponds to the final year of primary school, with students typically aged between 10-12 years.

The sample was defined using a one-stage cluster sampling procedure. Primary schools were selected at random with a probability proportional to the number of persons in the target population of the schools (primary sampling units). The schools were defined within a stratified frame of Government, Catholic, and Independent Private schools. These sectors contribute 65%, 22.5% and 12.5% respectively to the total school enrollment population in this geographic region. One hundred and seventy five schools were selected with 90, 44 and 24 from the Government, Catholic and Independent Private school sectors respectively. This provided a total intended sample of 4587 students.

Ninety-seven (56%) of schools approached to participate in the study did so. 2453 Grade 6 students enrolled in these schools (54% of total intended sample) became participants in the school screening study with 1730 (71%), 501 (20%) and 222 (9%) from the Government, Catholic and Private Independent schools respectively. These proportions in the sampling population within each school sector were not significantly different from those found in the total intended sampling area ($\chi^2(2) = 0.81$, $p > 0.05$).

Schools selected within the sampling frame were visited in order to administer the EATQ-R questionnaire. Research staff conducted the administration of the survey, in association with staff from the respective schools. Students completed the survey during class time in groups of approximately 18-25. Explicit consent to participate in the survey was sought from a parent or guardian and from the student himself or herself after provision of study information by letter. Any subject unavailable to complete the questionnaire during a school visit was sent the questionnaire by mail to complete at home.

A total of 2453 students (1168 male and 1280 female; 5 participants did not report their gender), completed the EATQ. The mean age of the participants was 11.62 years (SD = 0.39), and ranged between 9.35 and 13.15 years.

Based on their scores on this measure, a smaller sample of 415 students was selected to be part of the study. Adolescents at the extreme ends of the temperamental distribution were oversampled to maximize inter-individual differences in psychological well-being. Of the selected adolescents, 245 families consented to participate in the home assessment and therefore participated in the T1 data collection phase. A subset of 82 participants consented to participate in the immune analyses two to three years later at T3. The overlap between participants who completed the family interaction tasks with their parent at T1 (n=195), participants who had completed a resting electrophysiology baseline at T1 (n=109) and participants who had useable saliva samples at T3 (n=74) were 33 participants (23 male adolescents), and this comprised the final sample. This included 3 male parent/male adolescent dyads, 20 female parent/male adolescent dyads, 3 male parent/female adolescent dyads, and 7 female parent/female adolescent dyads. Informed consent was obtained from the participants, as well as a parent/legal guardian. One-way ANOVAs showed that the subgroup of 33 dyads did not differ significantly from the larger group of 195 dyads on measures of SES, BMI, age, or parent gender. The sample did differ on adolescent gender, $F(1, 244) = 6.41$, $p = .01$, from the overall sample in that there were more males in this subsample. This study was approved by the Human Research Ethics Committee at the University of Melbourne, Australia. Participants and their parents were informed that they could cease participation at any time. Table 3.1 lists the percentages of ethnicity (identified by the adolescent) and household composition (identified by the parent).

Table 3.1. *Demographics*

	Percentage
Ethnicity	
White/Caucasian	90.9%
More than one race	9.1%
Household composition	
Two-parent households with siblings and/or other relatives	69.7%
Two-parent households with no siblings or other relatives	9.1%
Single-parent (mother) households with siblings and/or other relatives	15.2%
Single-parent (mother) households with no other siblings or other relatives	3.0%
Relatives other than biological parents, stepparents, adoptive parents, or grandparents (e.g., aunts or uncles as parental figures)	3.0%

Procedures and Measures

   Family-interaction assessment at T1. The parent-adolescent dyads completed two lab-based interaction tasks of 20 minutes each, designed to differentially elicit positive (Event-Planning Interaction) and negative (Problem-Solving Interaction) behavior. For the current study we only focus on the Problem-Solving Interaction due to the association of conflict with both increased autonomic (Gonzalez, Moore, Garcia, Thienemann, & Huffman, 2011) and inflammatory processes (Fuligni et al., 2009; Miller, Rohleder, & Cole, 2009). For the Problem-Solving Interaction, the interviewer selected up to five topics that both the parent and adolescent endorsed as occurring most frequently (participants were asked how many times they had discussed the issue in the last two weeks) and had the highest intensity of anger (participants filled out a Likert scale of 1 – 5 where 1 is 'calm', 3 is 'a little angry' and 5 is 'angry' for each issue) on the Issues Checklist (Prinz, Foster, Kent, & O'Leary, 1979), consisting of items representing common topics of conflict between parents and adolescents. Interactions were video-recorded with separate cameras focused on each participant.

   Affective and verbal behavior were coded using the Living in Familial Environments (LIFE) event-based observational coding system that records micro changes in social behaviors, (Hops, Davis, & Longoria, 1995). The LIFE system consists of 10 nonverbal affect codes (e.g., anger, dysphoric, positive) and 27 verbal content codes (e.g., validation, complaint, provoke), coded within an event-based protocol in which new codes are entered each time the affect or content of one of the participant's behavior changes. Composite Aggressive, Dysphoric, and Positive behavior constructs were derived from the affect and content codes. Aggressive behavior was defined as aggressive (e.g., raised

voice; clenched teeth) or contemptuous (e.g., eye rolling; sneering) nonverbal behavior and

cruel (e.g., mocking; insults; threats) or provoking (e.g., taunts; dares) statements.

Dysphoric behavior was defined by sad and anxious nonverbal behavior (e.g., tearfulness,

sighing) or complaining statements. Positive behavior was defined by positive nonverbal

behavior and humorous statements. Trained observers were blind to psychosocial

information about participants and a second observer coded 20% of interactions to provide

estimates of inter-observer consistency. Random pairs of observers were assigned to the

interactions to minimize observer 'drift'. Kappa coefficients for aggressive constructs were

.70 for mothers and .77 for fathers, positive constructs were .86 for mothers, and .84 for

fathers, and dysphoric constructs were .57 for mothers, and .54 for fathers, reflecting good

levels of agreement. Consistent with our prior research (e.g., Whittle et al., 2008; Yap et

al., 2011), average duration of each behavior (i.e., the proportion of time during the whole

interaction task that was spent engaging in a behavior) was calculated as the time between

onset of one code and onset of the next code, for each person in the interaction. The

validity of the LIFE coding system as a measure of family processes has been established

in numerous studies of adolescents (Katz and Hunter 2007; Schwartz et al. 2011; Sheeber

et al. 2007).

  Baseline Pre-Ejection Period Assessment at T1. All data were acquired using

software and equipment from Vrije Universiteit Ambulatory Monitoring System (VU-

AMS; de Geus, Willemsen, Klaver, & van Doornen, 1995; Willemsen, De Geus, Klaver,

Van Doornen, & Carroll, 1996). Simultaneous measurement of electrocardiogram (EKG)

and impedance cardiography (ICG) signals were used to assess pre-ejection period (PEP;

for methods see de Geus & van Doornen, 1996 and Willemsen et al., 1996).

Pubertal Development at T2. The Pubertal Development Scale (PDS) was used to assess pubertal development at T2 using the self-report PDS (Petersen, Crockett, Richards, & Boxer, 1988). The PDS was collected for males and females (Males: mean = 26.56, SD = 5.70; Females: mean = 21.80, SD = 4.21). For females, this measure includes 8 items assessing the stage of breast development, hair growth, acne presence, hip width and menarcheal status. For males, this measure includes 11 items assessing genitalia development, hair growth, acne presence and voice change. Reliability and validity of the PDS has been well established (Brooks-Gunn, Warren, Rosso, & Gargiulo, 1987; Petersen et al., 1988). For descriptive purposes, the PDS data was coded into a 5-point scale in accordance with the Tanner stages based on prior work (Shirtcliff, Dahl, & Pollak, 2009).

Socio-Economic Status at T2. A measure of socio-economic status (SES) was calculated for participants using the Australian National University-4 (ANU4) scale (Jones & McMillan, 2001), which provides a score between 0 and 100 based on occupation. Parents were asked about their occupation and education. For parents that had missing data or reported an occupational status that could not be coded according to ANU4 (e.g., unemployed or small business owner), data on education was used as a substitute, in number of years of education, scaled to reflect ANU4 codes. This method of measuring socio-economic status has been recommended in Australia by the National Education Performance Monitoring Taskforce (Marks, McMillan, Jones, & Ainley, 2000).

Body Mass Index at T2. BMI was measured at T2 by researchers by weighing the participant on a scale and measuring height, and calculating BMI equal to the weight (kg) divided by the height (m) squared.

Immune Assessment at T3. Two mL of whole, unstimulated saliva was collected from 82 participants at T3 (mean age = 15.45 years, SD = 0.49) using the passive drool method to analyze peripheral concentrations of sCRP. Saliva is easier and safer to collect as compared to blood in research studies (Granger et al., 2007). In particular, some studies show that saliva may be correlated with systemic or major sources of general inflammatory marker, C-reactive protein (CRP; Byrne et al., 2013; Ouellet-Morin, Danese, Williams, & Arseneault, 2011; Out, Hall, Granger, Page, & Woods, 2012). These studies have demonstrated that CRP can be detected in saliva as well as in blood, and the measures in these two tissues correlate with medium to large effect sizes. One study found that many inflammatory markers had higher detection rates in saliva compared to blood in an adolescent cohort (Byrne et al., 2013). However, there are two studies showing no significant correlation between these measures (Dillon et al., 2010; Kopanczyk et al., 2010). Therefore, it is not yet clear from the extant literature if sCRP is a measure of systemic inflammation or only oral inflammation. Nevertheless, several studies have found that sCRP is associated with measures of both psychological and physical health in children and adults (Cicchetti, Handley, & Rogosch, 2015; Goodson et al., 2014; Laurent, Lucas, Pierce, Goetz, & Granger, 2016; Lucas et al., 2016; Naidoo, Konkol, Biccard, Dudose, & McKune, 2012), and it may be a measure that is influenced by stressful family environments, as well.

Collection time varied by participant, however, research suggests that CRP does not have a diurnal variation (Meier-Ewert et al., 2001), although some research has shown diurnal variability in those with obstructive sleep apnea (Mills, Natarajan, von Känel, Ancoli-Israel, & Dimsdale, 2009). Time of day was not correlated with sCRP in our sample

($r = .04$, $p = .82$). Saliva samples were frozen immediately at -20°C after collection and stored for 24-36 months prior to analysis. After thawing to room temperature (24°C), samples were first vortexed with a protease inhibitor cocktail (PIC), "Complete, Mini" (Roche, Castle Hill; NSW, Australia) in order to protect the integrity of the acute-phase proteins. Samples were then centrifuged at 10,000 g for 10 minutes, to isolate the precipitate and debris from the supernatant. The supernatant was extracted and divided into 3 test tubes before being snap-frozen in liquid nitrogen and stored at -80°C overnight. Samples were again thawed to room temperature the following day and centrifuged once more at 10,000 g for 10 minutes and the samples were used without in this study therefore had a total of two freeze/thaw cycles. Pilot testing showed that a second centrifugation resulted in much lower viscosity, with less likelihood of clogging the Bio-Plex suspension array system. Furthermore, the lower viscosity enabled us to analyze the samples without further dilution with the Bio-Plex immunoassays.

Concentrations of sCRP were analyzed according to manufacturer's instructions, described elsewhere (Byrne et al., 2013), by the Bio-Plex multiplex bead array immunoassay system of human cytokine panel and plates read on Bio-Plex Array Reader (Bio-Plex 200 System and Bio-Plex Manager Version 4.0, Bio-Rad Laboratories, Inc., New South Wales, Australia). Saliva sample supernatant was assayed in duplicate, undiluted, and analyzed by the flow-based Bio-Plex suspension array system. Intra-assay %CV was <20%, consistent with other studies of sCRP (Byrne et al., 2013; Ouellet-Morin et al., 2011). For the assays, the test volume was 50 μL, with a range of standards from 10 – 79560 pg/mL. The mean of recovery percentages ($\frac{Observed\ Concentration}{Expected\ Concentration}$) from standards was 99.42%, S.D. = 11.31%, range: 75% - 116%. Participants that had reported taking medication (N=14) in the 24 hours

prior to saliva collection were excluded from analyses to ensure that results were not due to substances that directly affect immune functioning. These medications included antihistamines, ibuprofen, and cold and flu tablets, which can affect inflammatory processes (Assanasen & Naclerio, 2002; El-Sharrawy, El-Hakim, & Sameeh, 2006; Mainous III & Pearson, 2003; Nettis, Colanardi, Ferrannini, & Tursi, 2005; Vena, Cassano, Buquicchio, & Ventura, 2008). On the day of saliva collection, time of saliva collection was recorded and participants were asked to complete a "diary" that included questions about any medication or substance use in the past 24 hours prior to collection, and the type and dose.

Analyses

Analyses were performed using IBM SPSS statistical software, version 23 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < .05$, variables were centered, and heteroscedasticity consistent standard errors were used. Post-hoc power analyses were run using Gpower, version 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). All sCRP samples were log transformed.

Participants who participated in the parent-adolescent interaction and provided both PEP and sCRP were 33 subjects. Data was missing for PEP from one participant and PDS from one participant. To preserve statistical power lost through deletion methods, single imputation with the EM algorithm was used to estimate missing data (Little and Rubin 1987). Little's MCAR test indicated that data was missing completely at random, $\chi^2 = 32.23$ (df = 24; $p = 0.12$).

Covariates. Due to the small number of subjects that had data for both PEP and sCRP, we only included theoretically determined covariates (described above) in analyses that were correlated with sCRP (so as to remove significant variance associated with these

variables while preserving power as much as possible). BMI was the only covariate that emerged as significantly associated with sCRP and was therefore used as a covariate in all analyses (see Table 3.2).

Regression. A two-block hierarchical linear regression was run in SPSS version 23. In block one, BMI was entered as a covariate. In block two, PEP was added to test main effects.

Moderation. Moderation analyses were run using the PROCESS macro (version 2.13) for SPSS. For moderation analyses, the Johnson-Neyman Technique within PROCESS was used to derive region of significance for interpreting interaction effects (Hayes, 2013). We used PEP as the predictor, duration of parental positive, dysphoric, and aggressive behavior duration as the moderators in three separate models, BMI as a covariate, and sCRP as the outcome.

Results

Regression.

After controlling for BMI, adolescent PEP was significantly associated with sCRP (β = -.03, $t(30)$ = -2.56, p = .02, 95% CI [-.06, -.01]).

Moderation.

The duration of parental positive behavior during parent-adolescent interaction significantly moderated the relationship between resting adolescent PEP and sCRP (β = .01, $t(28)$ = 3.12, $p < .01$, 95% CI [.004, .019]; see Table 3.3), with the overall model significantly predicting sCRP, R^2 = .41, $F(4, 28)$ = 11.40, $p < .001$, and the addition of the

Table 3.2. *Variable Correlations*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. sCRP (log)	1												
2. PEP	-.38[*]	1											
3. BMI	.40[*]	.01	1										
4. Gender	.01	-.08	-.06	1									
5. Age	-.16	.26	-.05	-.14	1								
6. Family History of CVD	.17	-.08	-.12	-.02	.07	1							
7. PDS	-.09	-.02	-.04	.40[*]	.00	.19	1						
8. SES	-.07	.16	.13	-.04	-.26	-.41[*]	.06	1					
9. Time of Day	.04	-.01	-.10	.02	.13	.08	-.25	-.18	1				
10. Aggressive Behavior	.20	-.49[**]	-.03	.07	.27	-.06	-.03	-.39[*]	.13	1			
11. Dysphoric Behavior	.14	.18	-.12	.01	.08	.39[*]	-.28	-.26	.37[*]	-.06	1		
12. Positive Behavior	-.36[*]	.38[*]	-.01	.05	.27	-.03	.01	.07	.00	-.21	.13	1	
13. Parent Gender	.17	-.27	.10	.20	-.04	-.30	.03	.33	.06	.25	-.16	-.15	1

interaction term explaining significant additional variance in sCRP, $\Delta R^2 = .05$, $F(1,28)=$

9.75, $p < . 01$. Neither the duration of parental dysphoric behavior ($\beta = -.01$, $t(28) = -.80$, p

$= .43$, 95% CI [-.03, .01]) nor the duration of parental aggressive behavior during parent-

adolescent interaction ($\beta = .001$, $t(28) = .59$, $p = .56$, 95% CI [-.00, .01]) significantly

moderated the relationship between resting adolescent PEP and sCRP.

Table 3.3. *Adolescent PEP x Parent Positive Behavior Duration Effect on Adolescent*

sCRP

Variables	β	p	95% CI
Constant	-6.19	< .001***	-7.87, -4.51
Parental Positive Behavior Duration	-.17	<.01**	-.29, -.06
PEP	-.02	.11	-.04, .00
Parental Positive Behavior x PEP	.01	<.01**	.004, .019
BMI	.10	.01**	.03, .16

Note. PEP= Pre-ejection period; BMI= Body mass index.

*$p < .05$, **$p < .01$; *** $p < .001$.

The interaction was probed by testing conditional effects of PEP on sCRP at three

levels of positive parenting behavior, one standard deviation below the mean, at the mean,

and one standard deviation above the mean. Table 3.4 shows, PEP was significantly related to sCRP when positive parenting behavior was one standard deviation below the mean ($p < .001$), but not when positive parenting behavior was at the mean ($p = .11$) or one standard deviation above the mean ($p = .55$). Region of significance testing showed a significant negative association between adolescent PEP and sCRP when the duration of parental positive behavior was short (values below the 49th percentile). In other words, when there was low duration of parental positive behaviors, then lower PEP (greater sympathetic activity) was significantly associated with higher levels of sCRP. In addition, when the duration of parental positive behaviors were long (values above the 97th percentile), then adolescents had lower sCRP levels. Figure 3.1 illustrates this effect with average, +1 SD, and -1 SD duration of parents' positive behavior. This indicates that greater adolescent sympathetic activity relates to sCRP when the duration of parental positive behavior is at low levels, while adolescents' sympathetic activity is not related to sCRP when there are average or high duration of parental positive behavior.

Table 3.4. *Conditional Effects of PEP on sCRP*

Positive Parenting Behavior (Centered)	β	p	95% CI
One SD below mean	-2.18	<.001***	-.06, -.02
At the mean	.00	.11	-.04, .00
One SD above mean	2.18	.55	-.02, .04

Note. SD = Standard Deviation *$p < .05$, **$p < .01$; *** $p < .001$.
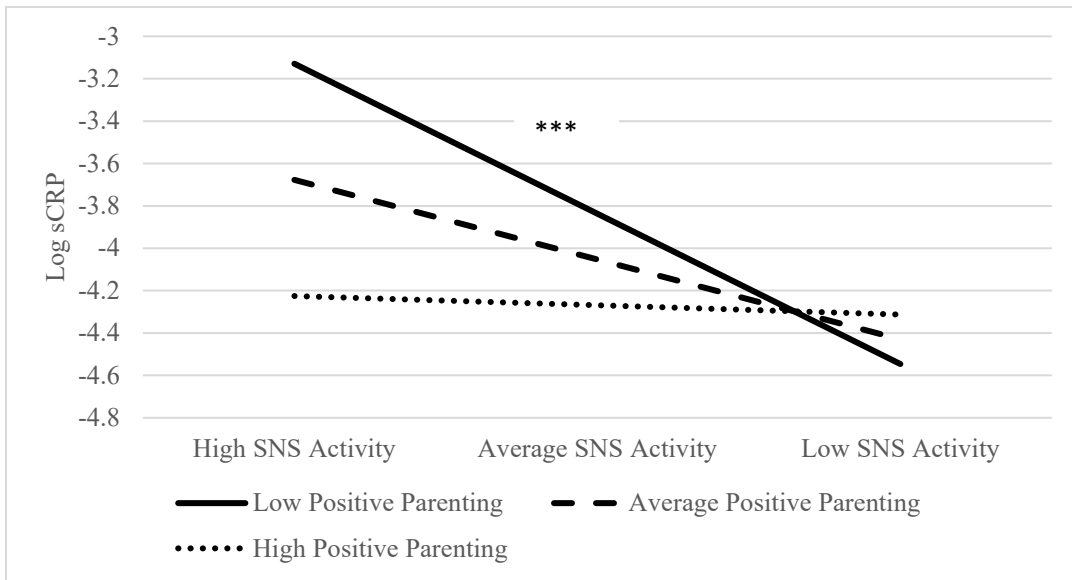
Figure 3.1. Adolescent PEP relates to higher sCRP at below average duration of positive parental behavior. Note: *** $p < .001$; Plotted at average (dashed line), +1 SD (small dotted line), and -1 SD (solid line) duration of parental positive behavior.

Post-Hoc Power Analysis. The limited sample size of the current study may have played a role in the null results for moderating effects of aggressive and dysphoric parental behavior. The observed power for the full respective models, were .94 (dysphoric), .85 (aggressive), and .96 (positive), which all surpass the recommended statistical .80 level (Cohen, 1988), indicating that there was likely sufficient power to reduce chance of a Type II error, and thus providing sufficient power to reasonably detect effects for both aggressive and dysphoric behavior.

Discussion

Consistent with our hypotheses, shorter PEP (i.e., higher sympathetic arousal) was associated with higher levels of sCRP approximately 3 years later. In addition, the duration of parental positive behavior during a negative interaction moderated the relationship

between adolescent PEP and sCRP, such that adolescents with high sympathetic arousal and whose parents displayed shorter duration of positive behavior showed the highest levels of sCRP. In contrast, duration of dysphoric and aggressive parental behavior did not moderate the relationship between adolescent PEP and sCRP.

The relationship between PEP and sCRP is a notable finding given the relatively long period of 3 years between assessments. This finding is in line with previous research indicating a relationship between sympathetic nervous system activity and inflammation (Jänig, 2014; Nance & Sanders, 2007). In the current design we cannot say whether this relationship is truly prospective, given that inflammation was only measured at one time point, an issue that is further discussed below in the limitations section. However, this finding does justify future longitudinal research that examines the moderation of this relationship by social factors. Interestingly, our findings suggest that duration of positive parental behavior during parent-child interactions moderates the relationship between adolescent sympathetic activity and sCRP, such that adolescents with parents who display average and above average duration of positive behaviors show no (or weak) associations between SNS activity and sCRP, suggesting that this form of positive parenting may buffer or inhibit the biological cascade between sympathetic arousal and inflammation. In contrast, parents who display below average duration of positive behaviors have adolescents who show significant associations between SNS activity and sCRP, indicating that lack of positive parenting may exacerbate the connection between sympathetic activity and inflammation in adolescents. Interestingly, duration of parental dysphoric and aggressive behavior did not moderate the relationship between adolescent sympathetic activity and sCRP, indicating that negative parental behaviors may be less impactful than

the absence of positive parental behaviors. The lack of association here may indicate that parents' depressive and angry tendencies may have less impact on their child's inflammation than a lack of positive behavior. Another possible explanation, outlined further in the limitations section, is that the kappas were lower for dysphoric and aggressive behavior than they were for positive behavior, which may have prevented significant findings from being found with these constructs. Overall, these findings indicate that resting adolescent sympathetic activity is associated with sCRP, however when adolescents experience average to higher than average levels of positive parental behavior during negatively charged parent-adolescent interactions this relationship is weakened, possibly inhibiting a biological cascade that can lead to greater susceptibility to stress related illness. Overall, these findings indicate that psychosocial processes may influence the activation and association between sympathetic activity with later inflammatory processes.

These findings have clinical implications for mental health providers working in the field of parent-child and parent-adolescent health. During treatment, focusing on enhancing the frequency and duration of positive parental behaviors that are already in use, such as those implemented through the Filming Interactions to Nurture Development (FIND) intervention (Fisher, Frenkel, Noll, Berry, & Yockelson, 2016) may capitalize on the strengths of positive-feedback in order to encourage more positive, warm, and nurturing parenting behaviors. Furthermore, focusing on existent positive behaviors, rather than deficits in parenting, such as the occurrence of aggressive or dysphoric behaviors, focuses on strengths and may prevent parents from feeling discouraged, which can lead to treatment dropout.

These findings suggest that parental behaviors during parent-adolescent interactions may act as a psychosocial mechanism that can moderate the biological cascade between sympathetic arousal and immune functioning, and set off mechanisms that may increase susceptibility to stress related diseases over time (Miller, Chen, & Parker, 2011). Shonkoff, Boyce, & McEwen (2009) describe how such early negative experiences can have lagged effects over years before these experiences are expressed as disease. These data provide an empirical and mechanistic basis for examining whether treatment interventions that aim to foster positive parental behaviors during negative interaction contexts provide positive health outcomes during and after adolescence.

While this study had a number of strengths, including the utilization of multi-method design with measures that do not contain tautological variance, there are some limitations that should be noted. First, this study contained a relatively small sample of 33 participants, which only allows for initial preliminary evidence of these effects. Therefore, there may not be great generalizability of these results. We are currently conducting a study of 200 parent-adolescent dyads, which will allow us to see if these results replicate at a larger scale as a means to provide greater generalizability. Second, the current study was limited in examining study measures at one time point, although it should be mentioned that CRP levels are relatively stable overtime. For example, Deverts et al. (2010) found strong stability between CRP levels collected 5 years apart ($r = .66$, $p < .001$). Future studies should provide a pre-post design to address changes in autonomic activity, parental behavior, and inflammation over the course of the study. Third, the current study only examined sCRP as the sole marker of inflammation and health. Future studies should examine multiple pro-inflammatory and anti-inflammatory biomarkers as well as other

markers of disease, such as telomere length, in order to provide a more complete understanding of how the sympathetic nervous system interacts with parental behavior to influence inflammation and general health. As mentioned above, our lab is currently working on a new study to elucidate how both parent and adolescent interactions influence psychophysiology, cortisol, inflammation, and telomere length (i.e., biological aging). Fourth, while our study excluded participants taking medication, we did not measure temperature or assess illness, or dental hygiene, which could be especially relevant for salivary inflammation. Future studies should collect this information. Fifth, the positive behavior construct, the only behavior that had a significant moderation, had a higher kappa than either the aggressive or dysphoric constructs. It is possible that the lower reliability in the aggressive and dysphoric constructs may have prevented the ability to find a moderation. Future studies should use both human observers and automated facial, language, and body language analysis (De la Torre et al., 2015) to assess parental behavior as this will likely result in greater reliability. Lastly, as would be expected, CRP concentrations in the saliva samples were low compared to those found in saliva with adult samples and as is normally found in blood (Laurent, Lucas, Pierce, Goetz, & Granger, 2016; Lucas et al., 2016; Mohamed, Campbell, Cooper-White, Dimeski, & Punyadeera, 2012; Ouellet-Morin et al., 2011; Out et al., 2012). Our samples were stored in -20°C, as is recommended for sCRP (Salimetrics, Inc.; http://www.salimetrics.com), and while degradation is possible at this temperature, CRP has been shown to be stable in saliva in previous research (e.g., at room temperature up to eight hours after collection; Ouellet-Morin et al., 2011). Therefore, the lower values in this sample were not likely a result of

degradation, but rather is more likely due to the young age of our sample, however there is a need for more research on sCRP norms in children and adolescents.

The present study is the first to our knowledge to use a multi-system approach by looking at the interaction of adolescent electrophysiology and observed parental behavior in relation to sCRP. Overall the findings suggest that exposure to low levels of parental warmth leads to a greater coupling of sympathetic activation and sCRP, which extends prior literature examining the relationship between sympathetic activity and inflammation. More research is needed to further refine the understanding that psychosocial factors, such as close personal relationships, influence both the sympathetic nervous system and inflammatory system, which serve as two biological mechanisms in disease processes. This understanding may lead to novel prevention and intervention efforts to identify adolescent physiology and family interactions patterns that may lead to decreased risk of physical and mental health problems during adolescence and beyond.

CHAPTER IV

BIOMARKERS OF CHRONIC STRESS AND SOCIAL STRESS REACTIVITY IN

ADOLESCENTS OF DEPRESSED MOTHERS

Introduction

The pathogenesis of disease can begin in early life, with risk factors in youth predicting indicators of mental and physical health that are ultimately associated with premature mortality in adulthood. Relationships are vital to health outcomes across the lifespan (Glaser, Kiecolt-Glaser, McGuire, & Robles, 2002; Jaremka, Lindgren, & Kiecolt-Glaser, 2013; Kiecolt-Glaser, Gouin, & Hantsoo, 2010) with recent meta-analyses indicating that relationships wields an influence on health outcomes that is on par with those of well-known behavioral-health variables, such as physical activity, smoking, alcohol consumption, and diet (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Holt-Lunstad, Smith, & Layton, 2010).

Exposure to maternal depression has been shown to be a particularly potent stressor, which may be partially due to greater expression of maladaptive parental behaviors (Beck, 1995; Leinonen, Solantaus, & Punamaki, 2003; Norcross, Leerkes, & Zhou, 2017) that have been shown to adversely affects relationship quality and may account for the associated deleterious outcomes in offspring across cognitive, behavioral, and emotional domains - as has been documented in various reviews and meta-analyses (Goodman, 2007; Goodman & Gotlib, 1999; Goodman et al., 2011; National Research Council and Institute of Medicine, 2009). Currently, there are three main limitations to the investigation of the impact maternal depression has on offspring health that need to be

tackled in order to push the field forward: 1) the lack of multisystem investigations; 2) the

absence of a focus on adolescent health; 3) and the failure to focus on both chronic and

acute markers of stress.

Three Limitations to Understanding the Impact of Maternal Depression on Offspring

Health

First, within the last decade the comorbidity between mental health and physical

disease has become clear (Scott et al., 2016; Tegethoff, Stalujanis, Belardi, &

Meinlschmidt, 2016), yet that the vast majority of studies on offspring health do not focus

on the multiple systems (both psychological and biological) that can be affected by

maternal depression, which prevents a systemic understanding of the impact of maternal

depression. Therefore, there is a need for multisystem investigations that include affective

and biological markers of health to better understand how maternal depression translates

into detrimental physical and mental health outcomes in offspring. Second, while there is

literature examining the association between maternal depression and offspring outcomes

in infancy, childhood, and adulthood, there is a relative dearth of research examining the

association between exposure to maternal depression and intermediate endpoints of health

during adolescence, which is particularly warranted as adolescence is understood to be a

sensitive period of development during which adolescents are strong influenced by social

environmental factors (Dahl, Allen, Wilbrecht, & Suleiman, 2018) and are at increased risk

for the first onset of mental health disorders (Kessler et al., 2005; Zisook et al., 2007).

Lastly, the research literature on maternal depression, and social stress more generally,

often only address either chronic stress or acute social stress reactivity. Therefore, there is

a need to study both biological markers of chronic basal stress as well as acute social stress

reactivity across multiple systems in order to better understand how maternal depression impacts mental and physical health targets that are associated with detrimental health.

Maternal Depression as a Form of Social Stress

Depressive disorders disproportionately affect women (Nolen-Hoeksema, 2001) and are experienced by approximately 10-15% of mothers with children younger than 18 years of age (Ertel, Rich-Edwards, & Koenen, 2011), with rates of women experiencing subsyndromal depression being far higher (Goodman, 2007). Depression is a highly recurrent disorder with 80% of individuals experiencing more than one episode within a two year window (Belsher & Costello, 1988) with increasing rates of relapse after each new episode (Keller et al., 1992). These data indicate that millions of children and adolescents are repeatedly exposed to maternal depression each year and are, therefore, at increased risk for negative developmental outcomes. For these reason we focus on maternal depression, rather than paternal or parental depression, as a model for social stress.

As noted above, maternal depression is a robust, yet non-specific predictor of offspring mental health symptoms (Betts, Williams, Najman, & Alati, 2014; Connell & Goodman, 2002; Lyons-Ruth, Easterbrooks, & Cibelli, 1997), negative maternal-child interactions (for meta-analysis see Beck, 1995), and worse physical health in offspring (Casey et al., 2004; Rahman, Iqbal, Bunn, Lovel, & Harrington, 2004; Raposa, Hammen, Brennan, & Najman, 2014). These deleterious outcomes may be due to heritability (Levinson, 2006), intrauterine exposure to stress hormones (Dunkel Schetter & Tanner, 2012), shared environmental stressors, or relational stressors in the form of maladaptive parenting behaviors (Repetti, Taylor, & Seeman, 2002) that can influence multiple

physical- as well as mental-health outcomes (Ulmer-Yaniv, Djalovski, Priel, Zagoory-Sharon, & Feldman, 2018).

Stress and Health

Stress in early life is associated with increased risk for morbidity and mortality (Ferraro, Schafer, & Wilkinson, 2016; Miller, Chen, & Parker, 2011; Murphy, Cohn, & Loria, 2017; Taylor, 2010; Danese et al., 2009; Shonkoff, Boyce, & McEwen, 2009). Underlying biological mechanisms, including the autonomic nervous (ANS) and cellular aging due to telomere shortening, have been proposed to be two pathways by which social stress exposure is translated into negative health outcomes (Hostinar, 2015; Shonkoff et al., 2009). Specifically, higher levels of allostatic load resulting from toxic stress and the excessive and repeated activation of stress response systems, especially in the absence of the social buffering effects of close and warm relationships (Shonkoff et al., 2012), may partly account for these negative outcomes. These processes may have implications for the early onset of disease, as repeated activation can compromise stress response systems (McEwen, 2006) and potentiate the pathogenic effects of later life stress (Dich et al., 2015). Indeed, human and animal models have established that stress is associated with cardiovascular disease, heightened inflammation, and shorter telomere length in adulthood (for reviews see Fagundes & Way, 2014; Murphy et al., 2017; Price, Kao, Burgers, Carpenter, & Tyrka, 2013 Taylor, Lehman, Kiefe, & Seeman, 2006).

In terms of maternal depression as a specific model of social stress, research has demonstrated that maternal depression is associated with alterations in a range of stress response systems in offspring and one reason for this may be the moderately higher rates of various negative parenting behaviors and practices displayed by depressed mothers

(Beck, 1995; Leinonen, Solantaus, & Punamaki, 2003; Norcross, Leerkes, & Zhou, 2017). For example, depressed mothers exhibit greater hostility, irritability, negative affect, intrusiveness, criticism, unpredictable behavior (e.g., inconsistent discipline), withdrawal and unresponsiveness (Leinonen, Solantaus, & Punamaki, 2003; Norcross et al., 2017) all of which are likely to be experienced as stressful by offspring.

These stressful experiences may impact underlying physiological systems as Nelson and colleagues have shown that adolescents exposed to both higher levels of parental aggressive behaviors and lower levels of positive behaviors exhibit higher sympathetic nervous system activity (Nelson, Byrne, Simmons, et al., 2017). Furthermore, parent-adolescent relationships characterized by high conflict are associated with greater sympathetic arousal (Salomon, Matthews, & Allen, 2000) and harsh family environments are associated with higher blood pressure in adulthood (Lehman, Taylor, Kiefe, & Seeman, 2009). These findings coincide with literature showing that offspring of depressed mothers show higher autonomic stress reactivity, such that infants have lower heart rate variability (i.e., parasympathetic activity) and higher heart rate (Dierckx et al., 2009). In addition, children of depressed mothers have higher resting heart rates, greater blood pressure reactivity, and slower blood pressure recovery in response to a stressor (Fan et al., 2016), while adolescents have greater sympathetic reactivity and slower recovery (Vedhara et al., 2012), although consistent findings are not observed in all studies (Rash, Campbell, Letourneau, & Giesbrecht, 2015). Repeated, sustained, and exaggerated acute cardiovascular activity during adolescence has been proposed to be pathogenic and provides one mechanism translating stress to cardiovascular health (Low, Salomon, & Matthews, 2009; Treiber et al., 2003). For example, increasing chronic life stress during

adolescence is associated with increasing cardiovascular reactivity across time, which then relates to intima-media thickness, a surrogate for atherosclerosis (Low, Salomon, & Matthews, 2009).

Offspring of mothers with increasing levels of depressive symptoms in infancy and depressive disorder during adolescence have greater stress reactivity and shorter telomere length (Gotlib et al., 2014; Nelson, Allen, & Laurent, 2018). Indeed, exposure to stress in early life in a variety of forms, including intrauterine stress, childhood maltreatment, trauma, and violence have all been shown to be associated with shorter telomere length (Asok, Bernard, Roth, Rosen, & Dozier, 2013; Entringer et al., 2011; Li, He, Wang, Tang, & Chen, 2017; Shalev et al., 2013; Tyrka et al., 2010). Overall, these findings suggest that maternal depression may act as a form of social threat that may up-regulate immediate autonomic activation (Glaser et al., 2002; Kiecolt-Glaser et al., 2010) and long-term cellular aging, which may lead to allostatic load that places offspring at risk for both physical and mental health problems (Slavich & Irwin, 2014).

The Current Study

The current study was preregistered on Open Science Framework (https://osf.io/wu4y5/) and was designed to address gaps in our understanding of the association between maternal depression and both baseline (i.e., tonic, set-point, or basal) biomarkers of the adolescent stress system, as well as reactivity of these indices during social interactions with their mothers. To investigate these questions the study used a design wherein half of the adolescents studied had mothers with a history of treatment for maternal unipolar depressive disorders along with current elevations in depressive symptoms (who constituted our putative High-Risk Group), and half had mothers with no

history of treatment for depressive disorders, no current mental health treatment, and no more than mild depressive symptoms currently (who constituted our putative Lower-Risk Group), although it should be noted that both groups were high risk in terms of being from a poverty sample.

Baseline Hypotheses. In terms of baseline basal measures of stress in adolescent offspring, we hypothesized that High-Risk adolescents would have higher levels of total mental health symptoms, shorter telomere length, higher overall resting autonomic activity (i.e., heart rate), higher resting sympathetic activity (i.e., greater skin conductance level and shorter pre-ejection period), and lower resting parasympathetic activity (i.e., lower heart rate variability) compared to Lower-Risk adolescents.

Reactivity Hypotheses. Our reactivity hypotheses are based on the premise that maternal depression acts as a form of social threat for adolescents that results in increases in affective and biological reactivity, rather than taking an alternative theoretical approach which could predict that that adolescents of depressed mothers would exhibit a more blunted affective and cardiovascular reactivity profiles associated with depression (Kristen Salomon, Bylsma, White, Panaite, & Rottenberg, 2013) as might be expected through emotion socialization processes (Eisenberg, Cumberland, & Spinrad, 1998; Schwartz, Sheeber, Dudgeon, & Allen, 2012) of learned helplessness. Furthermore, we examined both negative and positive interactions as both types of interactions can be potentially stressful. In relation to the latter, we decided to look at positive interactions in addition to negative interactions 1) as positive interactions have been shown to be stressful to those with depressive tendencies and prior research shows lower levels of positive affect in those with depression (Forbes, Williamson, Ryan, & Dahl, 2004; Watson, 2000), which may be

the case of adolescents in the High-Risk group, and 2) research elucidates that it can be particularly stressful when positive interactions go poorly (i.e., high conflict during positive interactions), which has been shown to predict poor outcomes in adolescents (Schwartz et al., 2013).

In terms of reactivity hypotheses during negative interactions with parents, we hypothesize that High-Risk adolescents will have greater heart rate, shorter pre-ejection period (i.e., shortening of interval), greater skin-conductance reactivity, and less heart-rate variability reactivity during negative interactions with their mothers relative to Lower-Risk adolescents of non-depressed mothers. In addition, High-Risk adolescents are predicted to show greater negative affect reactivity and similar positive affect reactivity during a negative interaction with their mother compared to Lower-Risk adolescents. Lastly, in terms of reactivity hypotheses during positive interactions with parents, we hypothesized that High-Risk adolescents, will be less reactive to these positive contexts as indicated by lower heart rate reactivity, less shortening of pre-ejection period, greater heart rate variability, and greater skin conductance level during a positive interaction with their mother compared to Lower-Risk adolescents. In addition, we hypothesized that High-Risk adolescents, will have greater negative affect reactivity and lower positive affect reactivity during a positive interaction with their mother compared to Lower-Risk adolescents.

Methods and Materials

Participants

Participants consisted of 179 low-income women (see Table 4.1) and their adolescent children, aged 11-14 (see Table 4.2). The majority of participants (n= 131) were recruited through Trillium Community Health Plans, the organization that administers the

Oregon Health Plan (OHP; Medicaid) in the county where data collection was conducted, while the rest of the sample was collected through online advertisements (n = 48). Two groups of women were recruited: a Depressed sample, selected for currently elevated depressive symptoms and a history of treatment for depression (whose adolescent children constituted our putative High-Risk Group), and a Non-Depressed sample, selected for low levels of current depressive symptomatology, no history of treatment for depression, and no current (i.e., past month) mental health treatment for any mental health disorder (whose adolescent children constituted our putative Lower-Risk Group), although it should be noted that the participants did consist of a higher risk poverty sample.

We selected our groups based on symptom levels rather than diagnostic status given evidence that elevated maternal symptoms are associated with parenting difficulties and risk for adverse child outcomes regardless of diagnostic status (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Moreover, the inclusion of a Depressed sample with a history of treatment-seeking, selected for those who have experienced a significant level of distress and impairment. In recruiting non-depressed women, we are selecting for those not currently in treatment so as to reduce the likelihood of high levels of current distress in those included in the sampling pool. Exclusion criteria for mothers and adolescents of both groups included psychosis or other illness or cognitive impairment that would interfere with meaningful participation (e.g., substance use that would render abstinence for the assessment difficult to tolerate).

Table 4.1. Maternal Characteristics by Group

| Variable | | Depressed | | | Non-Depressed | | Group Difference |
	N	Mean (SD)	Percentage	*N*	Mean (SD)	Percentage	*p*-value
Group	90		100%	89		100%	
Age	90	40.6 (6.5)		89	41.6 (23.3)		.710
Maternal Mental Health							
Depressive Symptoms	90	12.32 (5.84)		88	2.59 (2.71)		< .001
Anxiety Symptoms	90	9.69 (5.42)		89	2.37 (2.88)		< .001
Employment							.074
Currently employed	44		48.89%	57		64.04%	
Homemaker	23		25.56%	20		22.47%	
Disabled and unable to work	9		10.00%	1		1.12%	
Underemployed, looking for a job	8		8.89%	8		8.99%	

Table 4.1. Maternal Characteristics by Group Continued

Variable	Depressed			Non-Depressed			Group Difference
	N	Mean (SD)	Percentage	N	Mean (SD)	Percentage	p-value
Currently a student	3		3.33%	1		1.12%	
Other	3		3.33%	2		2.25%	
Education Level							.061
Less than High School	3		3.33%	3		3.37%	
High School Graduate/ GED	8		8.89%	17		19.10%	
Vocational or Professional School Certificate/	7		7.78%	8		8.99%	
Some College	57		63.33%	38		42.70%	

Table 4.1. Maternal Characteristics by Group Continued

| Variable | | Depressed | | | Non-Depressed | | Group Difference |
	N	Mean (SD)	Percentage	N	Mean (SD)	Percentage	p-value
Bachelor's Degree or Higher Degree	15		16.67%	23		25.84%	
Income							.499
<$17,000	25		27.78%	16		18.39%	
$17,000 – $19,999	7		7.78%	13		14.94%	
$20,000 – $24,999	14		15.56%	8		9.20%	
$25,000 – $29,999	11		12.22%	10		11.49%	
$30,000 – $34,999	5		5.56%	6		6.90%	
$35,000 – $39,999	6		6.67%	9		10.34%	
$40,000 –	8		8.89%	10		11.49%	

$49,999				
>= $50,000	14	15.56%	15	17.24%
Don't Know	0	0.00%	2	2.25%

There were no statistically significant group differences in adolescent biological sex, age, race, and ethnicity or maternal education, employment, or income.

Recruitment

As mentioned above, we partnered with Trillium Community Health Plans, the coordinated care organization that administers OHP in Lane County to help us to identify and contact potential participants, as our primary recruitment pool. Because socioeconomic distress is a risk factor for depressive conditions in women and adverse developmental outcomes in their offspring, this partnership enabled access to a particularly at-risk population. In consultation with their chief performance officer, we developed a multi-gate recruitment approach that leveraged their population access.

Gate 1. Trillium identified 2 groups of women, aged 30-55 (that is, of an age wherein they are likely to have adolescent children) - one that had met the diagnostic and treatment-history criteria described (Depressed Group pool) above and one that had no history of treatment also as described above (Non-Depressed Group pool). These women were mailed the Patient Health Questionnaire (PHQ-8) depression screener (Kroenke et al., 2009). Because Trillium does not have access to information regarding how many of these

Table 4.2. Adolescent Characteristics by Group

Variable	High Risk			Low Risk			Group Difference
	N	Mean (SD)	Percentage	N	Mean (SD)	Percentage	p-value
Group	90		100%	89		100%	
Age	90	12.9 (1.3)		89	12.9 (1.2)		.998
Adolescent Sex							.542
Male	45		50%	49		55.68%	
Female	45		50%	39		44.32%	
Race							.248
White or Caucasian	75		83.33%	66		74.16%	
More than One Race	15		16.67%	18		20.22%	

Table 4.2. Adolescent Characteristics by Group Continued

Variable	N	Mean (SD)	Percentage	N	Mean (SD)	Percentage	p-value
		High Risk			Low Risk		Group Difference
American Indian/ Alaska Native	0		0.00%	1		1.12%	
Native Hawaiian/ Pacific Islander	0		0.00%	1		1.12%	
African American	0		0.00%	1		1.12%	
No Response/ Unknown	0		0.00%	2		2.25%	
Ethnicity							.233
Not Hispanic or Latino	7 7		85.56%	69		77.53%	

Table 4.2. Adolescent Characteristics by Group Continued

Variable	High Risk			Low Risk			Group Difference
	N	Mean (SD)	Percentage	N	Mean (SD)	Percentage	p-value
Hispanic or Latino	13		14.44%	20		22.47%	

women have children, the screener included a query about the age and number of children living in the home. An enclosed cover letter/informed-consent form briefly described the goal of the project and indicated that if mothers return the questionnaire in a pre-addressed, postage-paid envelope, Oregon Research Institute (ORI) may contact them to invite further participation. Participants received a $30 check for completion of the screener, and if appropriate, speaking briefly with ORI staff about the larger study.

Gate 2. Eligible participants in these respective pools were identified based on responses to the mail-out screener. We selected participants who scored at ≥ 10 on the PHQ, indicative of moderate symptomatology (Depressed Group) or ≤ 8, indicative of no more than minimal symptoms (Non-Depressed Group). These participants were contacted by phone who confirmed eligibility criteria (i.e., child in age range; treatment history) and invited them and their adolescent children to an informational meeting to be conducted at a place of their choosing (e.g., their home, our offices). At the informational meeting, staff provided details about the project goals and assessment components, and obtained

informed consent and assent from mothers and adolescents, respectively. Mothers and adolescents received $30 for their time attending the meeting. All procedures were approved by ORI's Institutional Review Board.

      Additional Recruitment Sources. In addition to recruiting through Trillium, we also recruited participants via Facebook pages, Craigslist, and flyers (n= 48) with interested participants completing the PHQ-8 on-line through a secure link. Participants were selected to meet the recruitment criteria described earlier for PHQ-8 scores, treatment history (self-reported), and income level (met eligibility criteria for OHP). Subsequent to screening, data collection and informed-consent procedures were identical to those described above. There was significant difference in recruitment source, such that there were more mothers in the depressed group that were recruited online, X^2 (1) = 12.236, $p <$ .001.

Assessment Procedures

      After the informed-consent meeting, mothers participated in both an online questionnaire assessment via Qualtrics through a secure link and a diagnostic interview conducted by phone by lay research assistants. Subsequently, mothers and adolescents participated in a laboratory assessment. At the lab visit, mothers and their adolescents were outfitted with ambulatory electrocardiography (ECG) and impedance cardiography (ICG) devices to record psychophysiological indices and participated in two 15-min interaction tasks. One task was the Event-Planning Interaction (EPI) in which they were asked to plan a vacation they would like to take together. The second task was the Problem-Solving Interaction (PSI), in which families were asked to discuss and try to resolve one or two areas of conflict from the Issues Checklist. Areas of conflict were chosen by using the

highest mean frequency by intensity ratings across mother and adolescent reports. These tasks have been shown to differentially elicit positive and negative affect, respectively (Allen, Kuppens, & Sheeber, 2012; Nelson, Byrne, Sheeber, & Allen, 2017; Sheeber et al., 2012). The ordering of tasks was counterbalanced and separated by a puzzle task, to reduce affect contagion or carry-over effects from one task to the next.

Measures

Self-Report Measures

Maternal Mental Health Symptoms. Mothers completed the Patient Health Questionnaire-which provides a psychometrically sound assessment of depressive symptoms and is appropriate for use as a screener. This measure was completed as an initial screener (PHQ-8; Kroenke et al., 2009), as described above, and again at the lab assessment (PHQ-9; Kroenke, Spitzer, & Williams, 2001). Mothers also complete the Generalized Anxiety Disorder-7 (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006), a well-established measure of anxious symptoms designed to minimize contamination by depressive content. The PHQ-8 has excellent sensitivity with 96.5% of respondents with a score ≥ 10 exhibiting major depressive disorder or a key depressive symptom. The PHQ-9 also has acceptable internal consistency ($\alpha = .89$) as well as high sensitivity (88%) and specificity (88%) for a score ≥ 10 for major depressive disorder.

Adolescent Mental Health. Adolescents completed the Youth Self Report (YSR; Achenbach, 1991) to determine overall levels of mental health symptoms. The YSR has acceptable test-retest reliability ($r = .79$) and internal consistency ($\alpha = .83$).

Affect Assessment. At the start and conclusion of each interaction, adolescents completed the Positive and Negative Affect Schedule for Children (PANAS-C; Laurent et

al., 1999) to provide an index of positive affect (i.e., energy, interest, and engagement) and negative affect (i.e., emotional distress) before and during the interaction in order to measure affective reactivity during interaction tasks. This measure displays good convergent and divergent validity with a high internal consistency for negative affect (α = .94) and positive affect (α = .90).

Health Records.

Maternal history of depressive disorder and treatment was obtained from her records at Trillium. We had adolescents complete a form to indicate what type of medications they used including dosage and frequency of use.

Diagnostic Measure.

Mothers completed the Structured Clinical Interview, non-patient version (SCID-NP) in order to assess current incidence of depressive, anxious, and other Axis I disorders in order to confirm that non-depressed mothers did not meet criteria for depression. The SCID has strong psychometric properties (First, 2015). Prior to conducting research interviews, interviewers demonstrated a minimum interrater reliability level of kappa = .80 on two interviews. During the study, a masters level interviewer supervised and reviewed all completed interviews for strict adherence to DSM criteria. All interviews were audio-recorded, and a second interviewer independently rated a randomly selected sample of 20%. Overall interrater reliability for this study was kappa = .80.

Biological Measures

Psychophysiology Assessment. Adolescent ECG and ICG data were acquired using Vrije Universiteit Ambulatory Monitoring System, which uses a 3-lead ECG and 4-lead ICG. Data were scored using the Data Analysis and Management Software (DAMS)

program (http://www.vu-ams.nl/). Similar to our previous work in which psychophysiological measures were obtained from adolescents during parent-child interactions (Nelson, Byrne, Sheeber, et al., 2017), in the current study indices of adolescent physiology were obtained during a resting baseline as well as during the interaction tasks to examine adolescent physiological responding to maternal affective behavior. To obtain the resting baseline assessment, adolescents were asked to sit quietly for a 2-minute period while measures of heart rate, heart rate variability (HRV), pre-ejection period (PEP), and skin conductance level (SCL) were collected. Data collected was averaged over this 2-minute period in order to obtain a measure of physiological baseline. To obtain psychophysiology reactivity measures, we collected data during the EPI and PSI tasks and averaged physiological activity during each of these tasks to index arousal during interactions. To calculate reactivity, quiet baseline physiology measures were used as covariates in models in order to index reactivity in the physiological variables.

Heart rate, a measure of overall autonomic nervous system activity, was calculated based on the time (in milliseconds) between successive R waves (R-R intervals) on the ECG.

Heart Rate Variability (HRV): HRV, a measure of parasympathetic nervous system activity, was automatically calculated using the root mean square of successive R-R interval differences (RMSSD), which has been shown to reflect vagal tone (Thayer & Lane, 2000; Kleiger et al., 2005; Laborde, Mosley, & Thayer, 2017). This measure of HRV was chosen as it provides reliable estimates of HRV across different duration of recordings (Laborde, Mosley, & Thayer, 2017), such that 1 minute recordings of the natural log of

RMSSD has good reliability relative to 5 min RMSSD (Esco & Flatt, 2014) and because recordings longer than 120 seconds have been shown to be unnecessary to record accurate measures of RMSSD (Munoz et al., 2015) allowing this measure to accurately capture HRV during the brief 2-minute baseline. Furthermore, RMSSD is highly correlated with high-frequency heart rate variability (HF-HRV; Kleiger et al., 2005) and is relatively free of respiratory influences, unlike high frequency parameters (Hill & Siebenbrock, 2009). This may be particularly important during interaction tasks like ours that require speech.

Pre-Ejection Period (PEP): PEP, a marker of sympathetic nervous system activity, was automatically calculated for each cardiac cycle as the time interval in msec between the onset of ventricular depolarization (Q wave onset of the ECG) and the opening of the aortic valves (B point in the ICG dZ/dt signal). Q and B points were visually inspected and manually adjusted in the VU-AMS program when necessary, according to DAMS Program guidelines.

Skin Conductance Level (SCL): SCL, a second measure of sympathetic nervous system activity, was automatically calculated based on the electrodermal activity of the skin, which is measured using direct current (DC) utilizing a 16 bit A/D converter. The sampling rate was 10 Hz with a signal range of 0-95 micro Siemens (µS). The SCL signal was pre-processed to remove the noise and power-line interference in the signal. A low-pass filter with cut-off frequency of 2 Hz was used to filter the signal. In order to avoid shifting of peaks, filtering was done both in forward and reverse directions. The signal was then visually inspected for artifacts. As suggested by prior research we used two measures of SNS activity as research has indicated that SNS activity is displayed differently between the heart and the skin (Goedhart, Willemsen, & De Geus, 2008).

Telomere Length. A saliva sample (DNA Genotek Oragene DISCOVER (OGR-500) collection devices) was collected at the end of the session from a subsample (n= 85) of adolescents (Low Risk = 41, High Risk = 44) using the passive drool method and then stored at room temperature. This subsample was based on ancillary funding awarded to the first author. Approximately equal numbers of participants from each group were recruited within budgetary limitations. Salivary telomere length was assayed in triplicate by The Blackburn Lab at University of California San Francisco to calculate relative telomere length (T/S ratio). The telomere measurement assay was adapted from the published original method by Cawthon (Cawthon, 2002; Lin et al., 2010). Salivary samples contain approximately 70% white blood cells and 30% buccal epithelial cells indicating that salivary telomere length indexes cellular age across tissues. Research shows a strong positive correlation between blood leukocyte telomere length and salivary telomere length (Mitchell et al., 2014), significant positive correlations between telomere length of leukocytes, skin, skeletal muscle, and subcutaneous fat (Daniali et al., 2013), and correlations between relative telomere length across different tissues in animal models (Reichert, Criscuolo, Verinaud, Zahn, & Massemin, 2013). The average CV was 2.18% in the current study. There was no difference in the telomere subgroup for any demographic or maternal variables, except there was a significant difference for adolescent age, such that adolescents were older on average in the telomere subsample, [$F(1, 171) = 12.1, p < .001$].

Covariates. We collected adolescent age and biological sex as these measures have known associations with mental health and psychophysiology measurements. In addition, a number of variables potentially related to psychophysiology were examined as potential

control variables, including body mass index, ethnicity, race, and stimulant use. The only significant association was found with stimulant use, which was included in all adjusted models.`

Statistical Analyses.

All statistical analyses were conducted with R Studio, version 1.1.463. See supplemental materials for statistical code and packages used for analyses. Statistical significance was defined using 95% confidence intervals and *p*-values. Exploratory analyses including histograms as well as skew and kurtosis statistics were run for each variable to check for normality. Any variable that had a skew of +/- was log transformed. All variables were winsorized to +/- 3 SD to correct for outliers.

Baseline Models. To assess set-point differences between the High-Risk and Lower-Risk groups of adolescents, a series of one-way analysis of covariance (ANCOVAs) procedures were performed in order to test the baseline hypotheses concerning group differences in total mental health symptoms, telomere length, and resting psychophysiology markers of heart rate, RMSSD, PEP, and SCL (averaged within each condition). All baseline model tables can be found in supplementary materials (see Appendix A).

Reactivity Models. To assess differences in reactivity between the High-Risk and Lower-Risk Groups of adolescents, a series of mixed model repeated-measures analysis of covariance (ANCOVAs) were performed with independent variables reflecting a between-subjects group factor and within-subjects factors reflecting the two interaction tasks/contexts (i.e., EPI, PSI). Dependent variables included measures of self-reported affect (PANAS-C) and psychophysiology variables (heart rate, RMSSD, PEP, and SCL)

averaged within each condition. Significant effects were explored descriptively using graphical presentation of the data. All reactivity models can be found in supplementary materials (see Appendix A).

Multiple Comparisons. We corrected for multiple comparisons by hypothesis construct. Therefore, we ran Benjamini-Hochberg Correction (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001) for positive and negative affect (emotional hypotheses) as well as pre-ejection period and skin conductance level (sympathetic nervous system hypotheses). We did not correct for multiple comparisons for adolescent total mental health symptoms, telomere length, heart rate, and heart rate variability as these were distinct constructs with independent hypotheses.

Data Exclusion. During psychophysiology recording, any impedance signal during a task that had $\geq$ 40% artifacts and any respiratory signals or skin conductance that have $\geq$ 10% artifacts within a task were coded as missing data in accordance with VU-DAMS manual instructions (de Geus, Willemsen, Klaver, & van Doornen, 1995). Descriptive statistics were run to examine the range of physiological data to determine that values were biologically plausible. If any value were not biologically plausible, then they were coded as missing data.

Missing Data. Missing data was accounted for by using maximum likelihood for reactivity models.

Results

Descriptive Statistics.

There was a significant difference in depressive symptoms for mothers, such that Depressed Mothers (M = 12.32) had significantly higher depressive symptom scores

compared to the Non-Depressed Mothers (M = 2.59), $F(1, 176) = 202.1$, $p < .00001$, 95% CI (-11.084, -8.381). In addition, descriptive statistics for each measure are presented in Supplementary Table S1 and exploratory analyses using paired-samples t-tests revealed significant increases from baseline to each interaction across most affective and psychophysiological indices (see Supplementary Table S2) verifying that interaction tasks elicited affective and physiological responses.

Chronic Stress or Baseline Models.

Mental Health Symptoms. As shown in Figure 4.1, there was a significant difference in total mental health symptoms for group, such that High-Risk Adolescents (M = 54.247) had significantly higher total mental health symptom scores compared to Lower-Risk Adolescents (M = 47.802) in the unadjusted ($b = 6.445$, $p < .001$, 95% CI [3.496 – 9.394]) and adjusted ($b = 6.351$, $p < .001$, 95% CI [3.408 – 9.294]) models (see Supplementary Table S3).
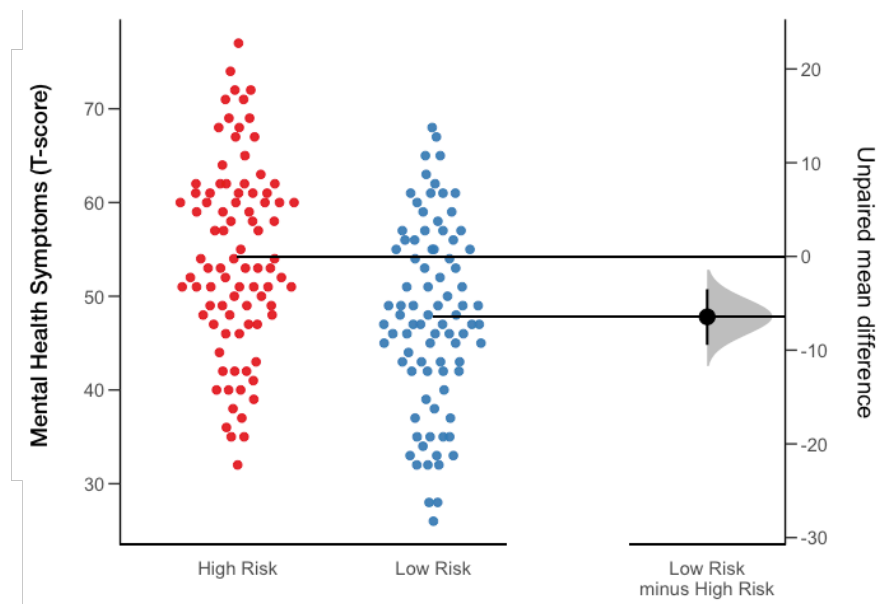
Figure 4.1. Difference Between High-Risk and Lower-Risk Adolescent Mental Health Symptoms

Telomere Length. As shown in Figure 4.2, there was a significant group effect, such that High-Risk Adolescents (M = 1.258) had significantly shorter telomere length compared to Lower-Risk Adolescents (M = 1.370) in both unadjusted (b = -0.112, p = .012, 95% CI [-0.197 – -0.026]) and adjusted (b = -0.115, p = .013, 95% CI [-0.203 – -0.027]) models (see Supplementary Material S4).
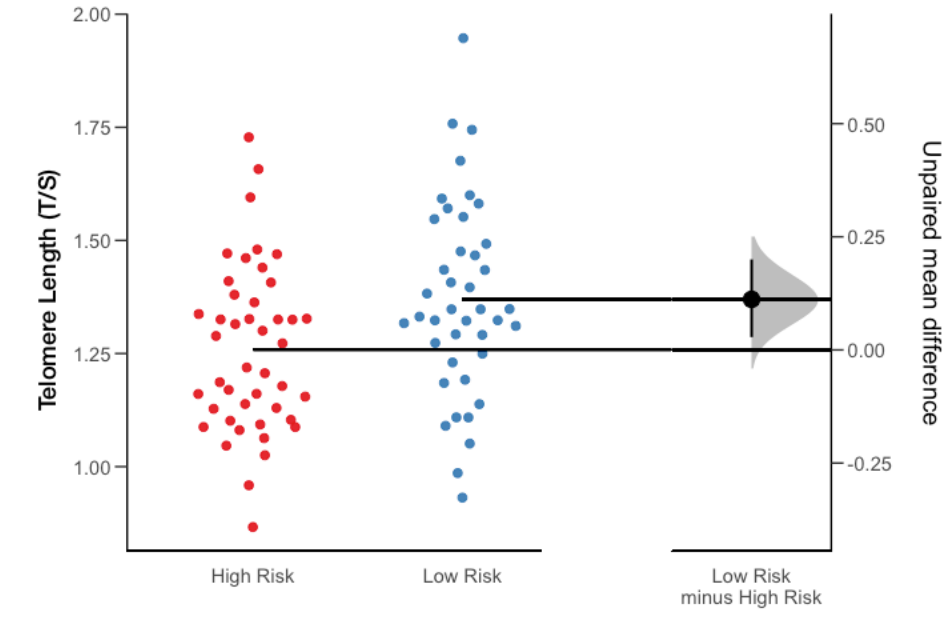
Figure 4.2. Difference in High-Risk and Lower-Risk Adolescent Telomere Length

Resting Autonomic Activity. As shown in Figure 4.3, there was a significant group effect, such that High-Risk Adolescents (M = 82.707) had significantly higher resting heart rates compared to Lower-Risk Adolescents (M = 78.563) in both unadjusted (b = 4.144, p = .028, 95% CI [0.480 – 7.808]) and adjusted (b = 3.612, p = .051, 95% CI [0.039 – 7.184]) models (see Supplementary Table S5).

Resting Parasympathetic Activity. There was not a significant group in resting RMSSD between High-Risk Adolescents (M = 63.242) and Lower-Risk Adolescents (M =

65.909) in unadjusted (b = -2.668, p = .637, 95% CI [-13.757 – 8.422]) or adjusted (b = -1.011, p = .860, 95% CI [-12.135 – 10.113]) models (see Supplementary Table S6).
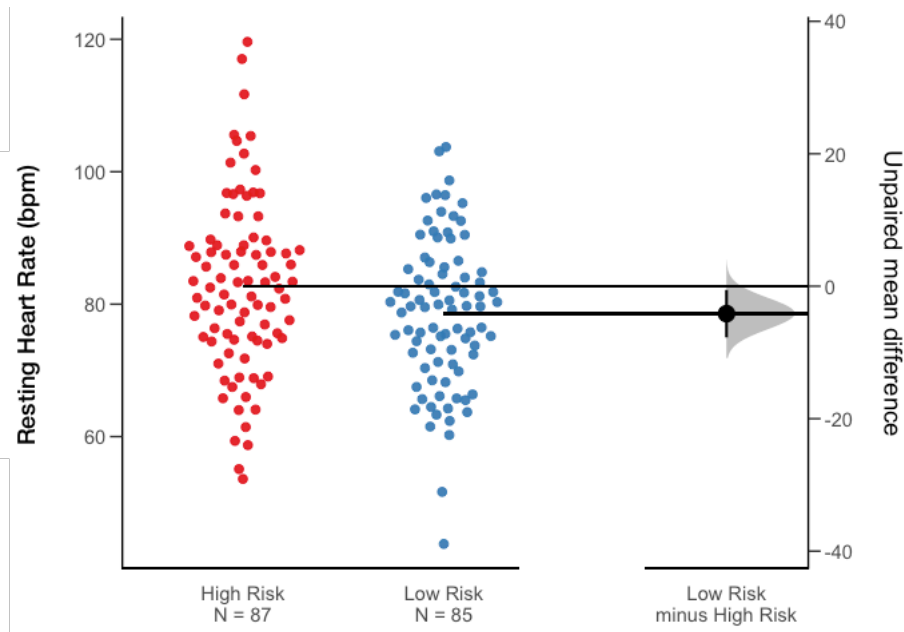
Figure 4.3. Difference in High Risk and Low Risk Adolescent Resting Heart Rate

Resting Sympathetic Activity. There was not a significant difference in resting PEP for High-Risk Adolescents (M = 89.127) and Lower-Risk Adolescents (M = 89.056) for unadjusted (b = 0.071, p = .979, 95% CI [-5.245 – 5.386]) and adjusted (b = -0.591, p = .825, 95% CI [-5.769 – 4.587]) models (see Supplementary Table S7). Similarly, there was not a significant difference in resting SCL for High-Risk Adolescents (M = 6.777) and Lower-Risk Adolescents (M = 6.252) in unadjusted (b = 0.525, p = .306, 95% CI [-0.478 – 1.528]) or adjusted (b = 0.558, p = .290, 95% CI [-0.464 – 1.579]) models (see Supplementary Table S8). We did not run multiple comparisons for sympathetic analyses as findings were not statistically significant.

Acute Reactivity Models.

Physiological Reactivity.

Autonomic Reactivity. There was not a significant main effect of group on heart rate reactivity in unadjusted (b = -0.103, p = .896, 95% CI [-1.648 – 1.441]) or adjusted b = -0.297, p = .707, 95% CI [-1.846 – 1.252]) models (see Supplementary Table S9), although there was a significant main effect for task, such that heart rate reactivity was greater during the PSI when compared to the EPI in unadjusted models (b = 0.856, p = .022, 95% CI [0.129 – 1.584]), which became non-significant in the adjusted model (b = 0.679, p = .066, 95% CI [-0.041 – 1.398]). Furthermore, there was not a significant group by task effect for heart rate reactivity in unadjusted (b = 0.689, p = .191, 95% CI [-0.339 – 1.718]) or adjusted (b = 0.867, p = .095, 95% CI [-0.144 – 1.878]) models (see Supplementary Table S9).

Parasympathetic Reactivity. There was not a significant main effect of group on RMSSD reactivity in unadjusted (b = 2.437, p = .406, 95% CI [-3.301 – 8.175]) or adjusted (b = 2.215, p = .460, 95% CI [-3.648 – 8.078]) models (see Supplementary Table S10). Similarly, there was not a significant main effect for task, such that RMSSD reactivity was similar during the PSI when compared to the EPI in unadjusted (b = 0.855, p = .619, 95% CI [-2.510 – 4.220]) and adjusted (b = 1.092, p = .532, 95% CI [-2.325 – 4.510]) models. In addition, there was not a significant group by task effect for RMSSD reactivity in unadjusted (b = -3.067, p = .208, 95% CI [-7.821 – 1.687]) and adjusted (b = -3.304, p = .179, 95% CI [-8.104 – 1.496]) models (see Supplementary Table S10).

Sympathetic Reactivity. There was not a significant main effect of group on PEP reactivity in unadjusted (b = -2.251, p = .216, 95% CI [-5.805 – 1.303]) or adjusted (b = -

2.001, p = .277, 95% CI [-5.599 – 1.596]) models (see Supplementary Table S11). In

contrast, there was a significant main effect for task, such that there was a greater reduction

in PEP during the PSI when compared to the EPI in unadjusted models (b = -1.108, p =

.049, 95% CI [-2.202 – -0.013]), which became non-significant in the adjusted model (b =

-0.986, p = .083, 95% CI [-2.094 – 0.122]). Furthermore, there was not a significant group

by task effect for PEP reactivity in unadjusted (b = 0.297, p = .708, 95% CI [-

1.255 – 1.849]) or adjusted (b = 0.175, p = .827, 95% CI [-1.386 – 1.735]) models.

As shown in Figure 4.4, there was a significant main effect of group on SCL

reactivity in unadjusted (b = -1.105, p < .001, 95% CI [-1.683 – -0.527]) and adjusted (b =

-1.181, p < .001, 95% CI [-1.758 – -0.605]) models as well as after correcting for multiple

comparisons (p = .0002), such that that High-Risk adolescents had lower SCL reactivity

when compared to Lower-Risk adolescents. In contrast, there was not a significant main

effect for task, such that there was similar levels of SCL reactivity during the PSI when

compared to the EPI in unadjusted (b = -0.027, p = .853, 95% CI [-0.310 – 0.256]) and

adjusted (b = -0.034, p = .815, 95% CI [-0.321 – 0.253]) models. In addition, there was not

a significant group by task effect for SCL reactivity in unadjusted (b = 0.232, p = .247,

95% CI [-0.159 – 0.623]) or adjusted (b = 0.238, p = .238, 95% CI [-0.156 – 0.632])

models (see Supplementary Table S12).

Affect Reactivity.

Negative Affect. There was not a significant main effect of group on negative affect

reactivity in unadjusted (b = -0.032, p = .870, 95% CI [-0.419 – 0.354]) or adjusted (b = -

0.043, p = .827, 95% CI [-0.431 – 0.345]) models (see Supplementary Table S13). In

contrast, there was a significant main effect of task on negative affect reactivity in

unadjusted (b = -0.619, p = .001, 95% CI [-0.984 – -0.254]) and adjusted (b = -0.615, p = .001, 95% CI [-0.983 – -0.248]) models as well as after correcting for multiple comparisons (p = .003), such that there was greater negative affect reactivity during the
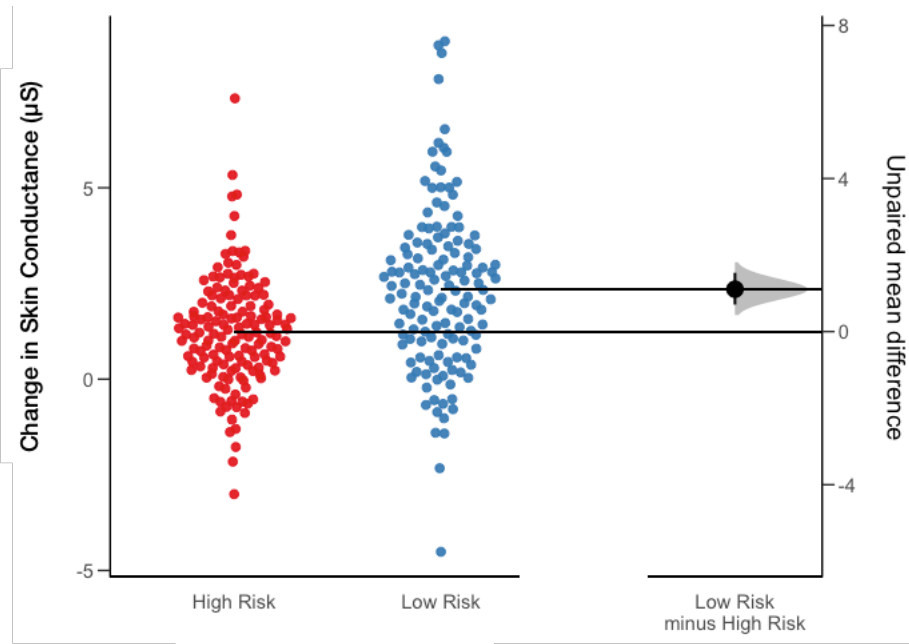
Figure 4.4. Change in SCL by Group

PSI task when compared to the EPI task. Lastly, as shown in Figure 4.5, there was a significant group by task effect for negative affect reactivity in unadjusted (b = 1.216, p < .001, 95% CI [0.705 – 1.728]) and adjusted (b = 1.213, p < .001, 95% CI [0.699 – 1.727]) models as well as after correcting for multiple comparisons (p = 0.00001), such that High-Risk adolescents had greater negative reactivity, specifically during the PSI task (i.e., negative interaction), when compared to the Lower-Risk adolescents.
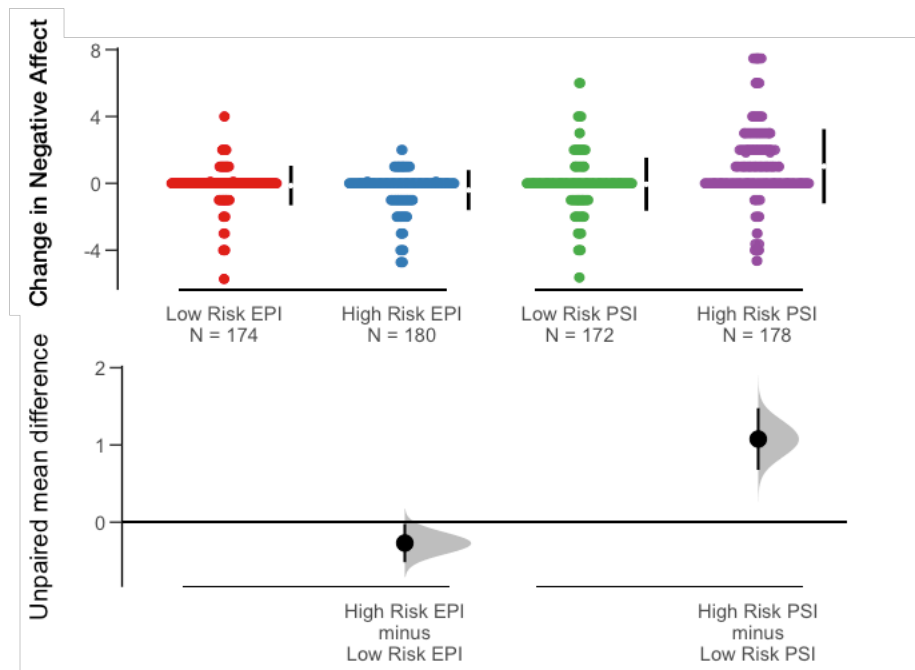
Figure 4.5. Group by Task Interaction for Change in Negative Affect

Positive Affect. There was not a significant main effect of group on positive affect reactivity in unadjusted ($b = 0.554$, $p = .338$, 95% CI [-0.577 – 1.686]) or adjusted ($b = 0.555$, $p = .339$, 95% CI [-0.581 – 1.691]) models. There was also not a significant main effect of task on positive affect reactivity in unadjusted ($b = 0.314$, $p = .590$, 95% CI [-0.827 – 1.456]) or adjusted ($b = 0.299$, $p = .610$, 95% CI [-0.849 – 1.447]) models. Lastly, there was not a significant group by task effect for positive affect reactivity in unadjusted ($b = -0.618$, $p = .450$, 95% CI [-2.221 – 0.984]) or adjusted ($b = -0.605$, $p = .461$, 95% CI [-2.213 – 1.002]) models.

Discussion

The current study was designed to investigate the association between maternal depression, adolescent mental health, and biological mechanisms (i.e., cardiovascular and mechanism of cellular aging) that may serves as distal premorbid risk factors for subsequent physical and mental health problems in a low-income sample. We also

examined the association of maternal depression with physiological and self-report indices of social stress reactivity during mother-adolescent interactions. Overall, findings demonstrate some significant differences between adolescents with depressed versus non-depressed mothers with regard to multisystem measures of chronic basal stress with fewer differences across acute stress reactivity indices.

Baseline Findings

Consistent with our hypotheses, adolescents of depressed mothers reported greater overall mental health symptoms and had, on average, shorter telomere length and higher resting heart rates, than did the children of non-depressed mothers. This suggests that adolescents of depressed mothers have comorbid mental and physical health risk profiles suggestive of higher allostatic load. Overall, our mental health findings are consistent with literature showing greater mental health symptoms among offspring of depressed mothers (Betts et al., 2014; Connell & Goodman, 2002; Lyons-Ruth et al., 1997). Similarly, shorter telomere length and higher resting heart rate are consistent with prior research indicating that offspring of depressed mothers have shorter telomere length (Gotlib et al., 2014; Nelson et al., 2018) and higher autonomic activity (Allister, Lester, Carr, & Liu, 2001; Fan et al., 2016).

In contrast, to the observed higher resting heart rate in High-Risk adolescents, both High-Risk and Lower-Risk adolescents had similar resting baseline measures of parasympathetic and sympathetic activity, which potentially indicates that activation of individual branches of the autonomic nervous system may be influenced less than overall autonomic activity in adolescents exposed to maternal depression. These significant effects for heart rate and null effects for sympathetic and parasympathetic activity are consistent

with prior literature. For example, prior research has established that there can be changes in heart rate without parallel changes to sympathetic and parasympathetic control (Moser et al., 1998). Furthermore, some research suggests that differences in parasympathetic activity, specifically respiratory sinus arrhythmia, in those with depression may be due to anticholinergic effects of medication, rather than mental health differences (Lehofer et al., 1997). Parallel findings to those presented here have also been found in a sample of depressed and non-depressed adolescents, such that depressed adolescents had higher resting heart rate, but similar sympathetic and parasympathetic activity at rest (Byrne et al., 2010).

One potential interpretation of these findings is that maternal depression may act as a form of social threat that may increase the set-point or baseline of mental health symptoms, overall autonomic activation, and rate of cellular aging, which may lead to a allostatic load putting offspring at risk for psychopathology and the early onset of disease (Epel & Prather, 2018; Slavich & Irwin, 2014). Alternatively, these effects may be mediated by genetic mechanisms, such that increased expression of biological markers may be due to shared genetic inheritance, rather than, or in addition to, wear and tear on biological systems due to repeated activation of stress response systems. Research indicates that depression is moderately (40-50%) heritable (Levinson, 2006) and when it comes to telomere length research has shown that 30-80% of telomere length variation is due to heritability (Blackburn, Epel, & Lin, 2015). In addition, it is also possible that these associations are not causally related but are epiphenomenal, such that a common factor or factors contribute to both maternal depression and child-risk profiles (e.g., shared environmental stressors).

Reactivity Findings.

Consistent with our reactivity hypotheses, adolescents displayed greater negative affect reactivity during the PSI, a task shown to differentially elicit negative affect. Negative affect reactivity among High-Risk adolescents may be contributed to either the chronic exposure to stress associated with maternal behavior, or by differential parenting behavior displayed by mothers during the interactions themselves. Subsequent analyses can address the effect of maternal behavior during the interaction after behavioral data has been coded. One other possible explanation for these findings is that High-Risk adolescents, while not necessarily having depression themselves, may have learned via emotion socialization, heightened affective responses to negative interactions that are consistent with those seen in depressed populations as prior literature demonstrates that those with depression exhibit greater reactivity to emotional stimuli that is social in nature and indicative of threat (Allen & Badcock, 2003; Price, Sloman, Gardner, Gilbert, & Rohde, 1994).

In contrast to our hypotheses, adolescents of depressed mothers had lower SCL reactivity (less sympathetic activity) across all tasks, which indicates that High-Risk adolescents may have been more withdrawn and less engaged during the interaction tasks when compared to Lower-Risk adolescents. This process would be consistent with a withdrawal pattern of learned helplessness during which there is a blunting of acute stress reactivity across time. For example, during the initial encounter of social stress and threat, adolescents may exhibit hyper-reactivity in an attempt to meet environmental demands, which leads to tolerance of the stimuli overtime, and eventually results in withdrawal or blunted (Gilbert, 1984; Solomon, 1980) activation as adolescents learn that their energy

expending acute stress reactivity fails to provide a viable solution for maternal depression. In addition, there were no differences in either positive affect reactivity nor any measure of cardiovascular reactivity, except for skin conductance, between High-Risk and Lower-Risk groups. There are a number of potential explanations for these null results. First, in terms of positive affect reactivity, it may be that the interaction tasks don't pull for the exact type of positive affect reactivity we were measuring. Perhaps an interaction task that involved more high arousal positive affect, such as those displayed more commonly among friends than between parents and adolescents would have elicited a difference (Dahl et al., 2018). Second, in terms of the lack of psychophysiology reactivity findings, research has indicated that there can be lagged (Shonkoff, Boyce, & McEwen, 2009b) or delayed (Tilders, Schmidt, Hoogedijk, & Swaab, 1999) effects of stress on underlying biological systems that are not expressed until adulthood. This may account for why we found overall resting differences in baseline autonomic activity, whereas these differences in tonic functioning may not have yet been translated to differences in phasic responses associated with cardiovascular system flexibility during positive and negative interaction contexts. Although, as noted, there may be issues with the type of affective experience elicited by the tasks, one explanation that can be ruled out, is that the interaction tasks did not elicit significant changes in affect and psychophysiological response as described above.

Limitations and Future Directions

While the present study had significant strengths such as using a multimethod assessment of differences between High-Risk and Lower-Risk adolescents in terms of both tonic (i.e., chronic or baseline) indices of mental health, cellular aging, and cardiovascular functioning as well as acute social stress reactivity indices of affect and cardiovascular

activity, there were also a number of limitations that should be noted. First, although the present study focused on adolescent self-reported mental health and affect as well as intermediate mechanisms that influence health risk across multiple biological systems, it lacked a systemic view that could be gained from also addressing the role of maternal behaviors, self-reported affect, and other biological measures. Future studies should incorporate maternal variables, beyond symptom and treatment history in order to see how they influence adolescent functioning. In particular, it will be important in ongoing research to examine parent-child relationship quality and interactional processes as predictors of health risk. Second, although we categorized adolescents as High-Risk and Lower-Risk depending on maternal symptoms and treatment history, respectively, we did not collect diagnostic status on adolescents. Future research should collect not only self-reported mental health symptoms as was done in the current study, but also utilize adolescent diagnostic status in analyses as research shows that maternal depression is a strong, yet non-specific predictor of increased rates of psychopathology among offspring (Fendrich, Warner, & Weissman, 1990; Goodman et al., 2011; McLaughlin et al., 2012; Murray, Halligan, Goodyer, & Cooper, 2011; Wickramaratne & Weissman, 1998). Third, this was a cross-sectional study, which precluded the ability to study developmental effects within adolescence (i.e., early, middle, late adolescence), which is why future studies should utilize a longitudinal design. Fourth, although the EPI and PSI tasks significantly impacted most indices of affect and psychophysiology, indicating that the interaction tasks successfully influenced variables of interest, it is not clear whether or not the baseline and interaction tasks provided an ecologically valid assessment of variables of interest. As we have argued previously, future studies should utilize passive sensing technologies (i.e.,

wearable, smartphone, and smart home devices) to increase the ecological validity of environmental contexts (Allen, Nelson, Brent, & Auerbach, 2019; Nelson & Allen, 2018, 2019) to bring this type of research out of the lab and into real world contexts. Fifth and relatedly, collecting stress reactivity on one day does not provide the level of temporal detail required to generalize one stress response in a novel laboratory environment, to a stress response during daily life in different contexts. Therefore, there is a need to address the gap between an acute stress response and chronic stress (Rohleder, 2019), which are often conflated in the stress literature. Again, utilize passive sensing technologies may allow for the unobtrusive and temporally fine grained data collection that could more accurately characterize stress response within and across contexts and time (Nelson & Allen, 2018; 2019).

Conclusion

This study was the first to investigate multisystem (affect, cellular aging, and cardiovascular activity) differences between High-Risk and Lower-Risk adolescents from lower income backgrounds across both basal stress and acute stress reactivity conditions. Overall, our findings suggest that adolescents of depressed mothers exhibit differences in basal measures of stress (i.e., greater overall mental health symptoms, faster cellular aging, and heightened autonomic activity at rest), although we observed less evidence of differences in acute affect and cardiovascular stress reactivity during positive and negative interactions with their mothers (with the exception of self-reported negative affect reactivity during the PSI task and sympathetic reactivity across both tasks). These findings are particularly noteworthy as both the High-Risk and Lower-Risk adolescents came from a poverty sample, which indicates that findings may be even stronger when comparing

Lower-Risk adolescents in a non-poverty sample to High-Risk adolescents in a poverty sample. More research is needed to further characterize the gap between null differences in acute social stress reactivity and significant differences in chronic stress differences across multiple systems in adolescents of depressed and non-depressed mothers. Passive sensing technologies, such as wearables, smartphones, and smart home devices provide one such avenue to longitudinally characterize the transition from acute to chronic stress within these populations of interest in order to provide a more comprehensive understanding of how maternal depression translates to impaired mental and physical health functioning across the lifespan.

CHAPTER V

GENERAL DISCUSSION

Overview

In this general discussion I will briefly present an integrated summary as well as

implications of the major findings from Chapters II through IV (the detailed results from

these three experiments have been extensively covered in previous chapters). Next, I will

describe the overlapping limitations across the three studies that reduce generalizability

and that should be the focus of future research. Lastly, I will then conclude by presenting

promising future directions that elucidate how using passive sensing technologies (i.e.,

wearable, smartphone, and smart home) may be able to ameliorate many of these

limitations as well as the need to dispatch these new methods in demographically diverse

samples utilizing a developmental lifespan approach.

Summary and Theoretical Implications

The main aim of this dissertation was to utilize multimethod approaches across

various psychobiological systems and affective relational contexts in order to characterize

the association between both mental disorders and relational stress with underlying

mechanisms of disease. The second aim of this dissertation was to elucidate the importance

relationships, particularly adolescent-parent interactions, play in both directly influencing

psychobiological functioning as well as modifying the association between psychological

disorders and underlying biological mechanisms of disease. Findings from the three studies

in this dissertation largely uphold the Cascade Model presented in Chapter I.

Study I: Summary and Theoretical Implications

  In the first study, a multimethod approach across self-reported affect, observed behavior, and recorded psychophysiology was utilized to investigate differences between clinically depressed and non-depressed adolescents across three distinct affective interaction contexts with their parents in order to provide an initial characterization of how adolescents with depression differ across psychobiological systems as compared to their non-depressed peers. Context independent findings showed that depressed adolescents exhibited greater negative affect and behaviors, fewer positive behaviors, and upregulated autonomic and sympathetic activity when compared to their non-depressed peers. These findings indicate that depressed adolescents have heightened negative valence systems in terms of affective, behavioral, and biological patterning as would be predicted in the Cascade Model. In terms of context specific findings (i.e., the influence of positive, negative, and mixed affective interactions with parents), we first found that depressed adolescents exhibited greater persistence of negative affect and dysphoric behavior across the sequence of tasks, whereas these phenomena declined amongst their non-depressed peers. This finding indicates that depressed adolescents may be experiencing emotional inertia and affective inflexibility to changing environmental demands (Koval, Kuppens, Allen, & Sheeber, 2012; Kuppens, Allen, & Sheeber, 2010; Kuppens et al., 2012), while non-depressed adolescents exhibit emotional flexibility, an indicator of resilience (Waugh, Thompson, & Gotlib, 2011). Second, depressed adolescents had greater increases in aggressive behaviors during negative interactions, which parallels prior literature showing that those with depression have greater reactivity to emotional stimuli that is social in nature and indicative of threat (Allen & Badcock, 2003; Price, Sloman, Gardner, Gilbert,

& Rohde, 1994). Finally, depressed adolescents had greater parasympathetic withdrawal during negative interactions, while this response characterized the non-depressed group during positive interactions. One interpretation of these findings based on an arousal framework is that the relatively greater parasympathetic withdrawal for non-depressed adolescents during the positive interaction may indicate greater physiological engagement, while the relatively greater parasympathetic withdrawal exhibited by depressed adolescents during the negative interaction may indicate the opposite (i.e., a greater interpretation of threat, mobilization of resources, and/or a lack of sympathetic regulatory ability) during the aversive context (Beauchaine, Gatzke-Kopp, & Mead, 2007). These context specific findings also coincide with the Cascade Model from Stress to Disease by elucidating the way in which psychosocial factors, particularly positive, negative, and mixed affective interaction contexts, moderate the expression of depression in an adolescent sample.

Study II: Summary and Implications

In the second study, we again utilized a novel multisystem approach to investigate the effect positive and negative parental behaviors had on the relationship between resting sympathetic activity during early adolescence and levels of systemic inflammation during middle adolescence. First, analyses revealed that higher resting sympathetic activity during early adolescence, as indexed by pre-ejection period, was associated with higher levels of systemic inflammation during middle adolescence. This initial finding parallels prior research showing that the autonomic nervous system directly innervates the inflammatory system (Fagundes & Way, 2014; Kemeny & Schedlowski, 2007; Thayer & Sternberg, 2006) with the sympathetic activity increasing inflammatory processes (Jänig, 2014a, 2014b; Nance & Sanders, 2007). Furthermore, while aggressive and dysphoric parental

behaviors did not moderate this association, adolescents whose parents displayed average to above average levels of positive behaviors buffered against the association between sympathetic activity and inflammation, suggesting that this form of positive parenting may buffer or inhibit the biological cascade between sympathetic arousal and inflammation. In contrast, adolescents whose parents exhibit lower than average levels of positive behaviors may be at for risk increased coupling and initiation of the biological cascade between sympathetic activity and processes of inflammation. These findings coincide with the Cascade Model from Stress to Disease indicating that positive behaviors during negative interactions can buffer the biological cascade from sympathetic activity to inflammation across adolescence. In addition, these findings parallel prior research indicating that more guidance and support in early childhood is associated with lower resting sympathetic activity during adulthood (Lyons et al., 2019). Overall, these findings indicate that parental behavior has the potential to influence biological mechanisms of disease for better or worse and may serve as one modifiable psychosocial factor that may be amendable to intervention in order to improve future health outcomes.

Study III: Summary and Implications

Lastly, the third study also utilized a multimethod design to investigate biomarkers of both basal stress and acute social stress reactivity in adolescents of depressed and non-depressed mothers to better understand how maternal depression may act as a form of early life social stress to influence mental and physical health processes among offspring. Baseline or basal measures representing chronic stress revealed that adolescents of depressed mothers exhibited greater mental health complaints as well as upregulated autonomic activity and accelerated telomere shortening when compared to peers with non-

depressed mothers. These findings strongly supporting the Cascade Model from Stress to Disease in that they reveal health outcomes associated with relational functioning and underlying biological mechanisms of disease, These baseline findings parallel prior literature, which describes a strong association between maternal depression and greater mental health symptoms (Betts, Williams, Najman, & Alati, 2014; Connell & Goodman, 2002; Lyons-Ruth, Easterbrooks, & Cibelli, 1997) in offspring. In addition, upregulated autonomic activity and shortened telomere length coincide prior research indicating that offspring of depressed mothers experience accelerated cellular aging (Gotlib et al., 2014; Nelson, Allen, & Laurent, 2018) and upregulated autonomic activity (Allister, Lester, Carr, & Liu, 2001; Fan et al., 2016). These findings indicate that maternal depression may act as common form of early life social stress, potentially a form of social threat, that may up-regulate the set-point of allostatic load to influence mental health, while also triggering a biological cascade that may lead to greater susceptibility to stress related illness. In terms of acute social stress reactivity findings, results indicated that adolescents of depressed mothers exhibited greater negative affect reactivity, particularly during negative interactions, when compared to their peers of non-depressed mothers, which coincides with prior literature demonstrating that those with depression exhibit greater reactivity to emotional stimuli that is social in nature and indicative of threat (Allen & Badcock, 2003; Price et al., 1994). Furthermore, adolescents of depressed mothers had lower sympathetic activity across all tasks, which indicates that stress reactivity patterning is consistent with a withdrawal pattern of learned helplessness in response to initial energy expending stress reactivity failing to provide a solution to distress triggered by maternal depression (Gilbert, 1984; Solomon, 1980).

Limitations

The primary limitation to the generalizability of the current findings involves restricted sample demographics, specifically when it comes to race and ethnicity of adolescents and parents that participated in these studies. These limitations have implications for the role parent-adolescent relationships plays in adolescent health outcomes as research has demonstrated that culturally bound social norms moderate the relationship between parenting and offspring adjustment (Lansford et al., 2018). Therefore, it is of great importance to characterize the impact parental psychopathology and behaviors play on adolescent mental and physical health outcomes. In contrast, across the studies we successfully sampled across other demographic factors including socioeconomic status and gender. Regardless of these limitations, current findings suggest that parental mental health and parenting behaviors may be particularly important social determinants of health that may be amenable to early intervention in order to protect developing adolescent's mental and physical health trajectories.

A second limitation to the current studies were the cross-sectional designs, which introduced two main flaws related to poor temporal resolution. First, the lack of a longitudinal design prevented the ability to address developmental timing effects and processes that relationships may play on health both within adolescence as well as across distinct developmental periods. Second, the cross-sectional design did not allow for an investigation of the magnitude of an effect that early precursors to disease actually played in the early onset of morbidity. Future research should be conducted across developmental periods to elucidate the times when offspring are at highest risk for alterations in health

trajectories as well as longitudinal designs that follow participants in order to determine the predictive power that intermediate health outcomes actually play on long-term health.

A third limitation is that the current studies attributed findings to mental health of mothers and adolescents as well as social determinants of health, specifically to the impact parent-adolescent interactions. While these were shown to be associated with outcomes of interest other factors, such as genetics, shared environmental influences, and prenatal environments may also contribute to outcomes presented in these studies. Future research should take a systemic approach in order to better approximate the specific variance in outcomes of interest that are influenced by these factors.

The last major flaw of the current studies was the use of laboratory paradigms, which while extremely common in this research, may reduce the ecological validity and therefore generalizability of the current findings to daily life. Research has shown that laboratory environments can introduce artificial noise that may not be observed in real-life conditions, including increased stress, which may preclude the collection of accurate baselines. Future research should utilize methods both within and outside of laboratory contexts to validate laboratory conditions, extend findings to real-world contexts, and provide novel opportunities for prevention and intervention.

The following section presents future directions for this line of research by expanding on a recent Nelson & Allen (2018) manuscript, "Creating a Passive Sensing Ecosystem: Utilizing Passive Sensing Technologies to Translate Laboratory Findings into Real World Contexts" that was published in *Perspectives on Psychological Science*.

Future Directions

For decades researchers have traditionally brought participants into laboratory settings as was done in the studies presented in this dissertation in order to better understand how relationships and other processes influence mental health as well as underlying stress response systems. Unfortunately, laboratory-based studies largely consist of novel environments that can be stressful to participants, which may confound laboratory findings. These research paradigms may include participants interacting with cumbersome equipment (e.g., electrocardiography, functional magnetic resonance imaging) that limit or prohibit naturalistic behavior. Such designs often include researchers periodically interrupting conversations and behaviors for the collection of biological samples (e.g., cortisol reactivity) and self-report measures of affect to index reactivity in these measures. While this body of research has led to a greater understanding of how relational interactions influence stress reactivity and how such processes influences mental and physical health outcomes as displayed in the prior chapters, this approach also contains some inherent limitations that prevent the generalizability of findings to day-to-day lived experience.

To begin, traditional assessment of affective, relational, behavioral, and biological functioning related to health in individuals and families relies almost entirely on questionnaires, self-report interviews, or laboratory-based measurements of physiology. Although each of these approaches have important strengths, they are also (like all methods) subject to limitations. Some of these include reporter bias, lack of ecological validity, Hawthorne effects, memory limitations, and incomplete assessment of affect, relationship behavior, and physiology (Baumeister, Vohs, & Funder, 2007; Furr, 2009;

Gosling, John, Craik, & Robins, 1998; Harari et al., 2016; McCambridge, Witton, & Elbourne, 2014; Miller, 2012; Paulhus & Vazire, 2005; Reis & Gosling, 2010). Moreover, many of these methods of assessment have not fundamentally changed for over 40 years.

Recent technological developments have become permissive of active (i.e., requiring input from participants) intensive repeated measure designs, which collect multiple time points of data using methods such as daily diaries (Repetti, Reynolds, & Sears, 2015) as well as Ecological Momentary Assessment (EMA; Shiffman, Stone, & Hufford, 2008) methods, which have been utilized to provide greater temporal resolution of data collection within an individual's daily life (Repetti et al., 2015). While, these newer methods address some of the methodological limitations mentioned above, they can still miss important gaps in assessment.

First, many laboratory paradigms as described in the prior chapters are designed to simulate phenomenon in non-laboratory environments in order to generalize findings to real-world contexts, yet laboratory designs often lack ecological validity (i.e., the degree to which a research design matches naturalistic environments in order to generalize results to real-life settings) as they occur in new environments (e.g., laboratory spaces with novel personnel and equipment) that lack the contexts of actual lived experience. This difference between simulated and actual lived experience introduces potential noise that may prevent data from accurately representing daily lived experience. Second, many laboratory studies, particularly when it comes to physiology and behavior, lack sufficient sampling resolution to accurately capture measures of interest. While, some measures can be captured with low resolution, such as demographic variables as they are relatively stable, other phenomenon, such as affect, relational behavior, and physiology can benefit from higher data resolution

in order to accurately capture within-day dynamics of relevant constructs. Classical stress paradigms collect between 3-5 saliva samples across a laboratory session or day and are assumed to capture the full variability of that physiological system to draw accurate conclusions about a complex system dynamics. Unfortunately, this may not be the case as individual variability might fluctuate dramatically within a single day. Third, many laboratory studies are cross-sectional, which precludes the ability to repeatedly follow participants over longer periods of time. These studies assume interday reliability or that data collected on day 1 would be representative of that same data collected on day 2 in the same or a different context. Other study designs provide longitudinal collection of data by following participants over years, yet they may have extremely low temporal resolution as participants may only provide data once per year when they come into the laboratory. This low temporal resolution precludes the capture of important between-day, week, and month variability in the measures of interest therefore potentially undermining theoretical assumptions.

A Potential Solution: Passive Sensing Technologies

A number of key limitations within psychological and intervention science can be addressed by the development of novel assessment methods that can be deployed in real-world settings. In particular, passive sensing technologies, including smartphone, wearable, and smart home devices, allow for the creation of a passive sensing ecosystem that allows for the measurement of observed behavior, relational functioning, affect, and physiology in real-time, continuously, unobtrusively, and in an eventually scalable manner that has the potential to reduce both researcher and participant burden, while simultaneously capitalizing on a collection method that utilize devices that many

participants already carry with themselves on a daily basis. The utilization of these methods may advance psychological science by allowing for more objective and multimodal (e.g., facial expression, gesture, body posture, voice, language, movement, physiology, location, interaction with people and devices) measurement of affective, behavioral, and physiology in daily lived contexts. In the last few years there has been a massive expansion of research utilizing passive sensing technologies that have successfully provided proof of concept that these devices can be utilized in studies with a high rate of success to capture data on relational functioning, mental health symptoms, and physical health.

Advancing Psychological Science.

Psychological findings across sub-disciplines from developmental and clinical psychology to cognitive neuroscience have often been severely limited by their inability to study the temporal dynamics of affect, relational functioning, physical health, observed behavior, and stress physiology over extended periods of time, especially in naturalistic settings. Current longitudinal research designs typically involve significant time gaps between waves of data collection, which are often insufficiently fine grained in order to examine the dynamics of these phenomenon that can unfold over shorter timescales (e.g., minutes, days, weeks). Recent work, as mentioned above, using EMA (Shiffman, Stone, & Hufford, 2008) or diary methods (Repetti et al., 2015) is providing some greater insight into these issues, but even EMA techniques are not able to capture any temporal dynamics of stress physiology and are typically not able to fully capture the full temporal dynamics of behaviors, affect, or relational functioning over shorter time scales (minutes, hours).

Passive sensing technologies on the other hand may be able to facilitate the development of psychological science more broadly by integrating novel types of data that have not previously been available, especially within the real-world contexts. Specifically, passive sensing devices allow for the 1) *continuous* and 2) *passive* collection of 3) *intensively longitudinal* and 4) *multimodal* data from a 5) *first-person* and a 6) *third-person observational perspective* that 7) preserves *ecological validity* by taking place outside of the laboratory and within participants' own lives. Below specific examples of how psychological science and intervention may be advanced by the collection of passive sensing data are discussed.

Targets for Passive Sensing.

Relational Health.

Given the significance of close interpersonal relationships on mental and physical health outcomes, passive sensing assessment may be especially relevant to theories of relational processes. To take one example, the theory of social buffering can be further evaluated and extended by studies incorporating passive sensing technologies. Social buffering posits that supportive social relationships can buffer (or moderate) the impact of stress on psychological and biological functioning (Nelson et al., 2017; Pietromonaco & Collins, 2017). This body of research has been largely dependent on discrete laboratory paradigms that observe individual and family functioning or use self-reported measures of perceived relational functioning. A study utilizing a passive sensing approach would allow for a novel investigation that may extend the theory of social buffering in ways that are difficult (if not impossible) to achieve with other techniques.

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First, smartphone data collection would allow for objective first person affectively-laden social information via tone of voice and affective text messages, while smart home observation allows for the objective description of third-person observation of behaviors within a key ecological environment (i.e., the home) and wearables could capture stress physiology, thereby extending the evaluation of this theory to observed behaviors in the home and during day to day activities. This may ultimately bolster the ultimate validity and translatability of the findings into what are clearly key ecological environments for these processes.

Second, it is possible that the temporal dynamics of social buffering effects may be observable at more micro-level timescales, such as when an act of social support results in an immediate reduction of behavioral or physiological indices of stress (e.g., eating behavior, sleep, heart rate, angry or dysphoric vocal affect). Smartphone devices would allow for collection of social communication via phone calls and text messages, wearable devices can collect specific joint physical activities, while smart home devices allow for observed behavior in order to advance the understanding of when and how social buffering takes place. This would provide a unique perspective that is distinct from that available from less temporally detailed EMA of subjective report on social experiences.

Third, the longer time periods over which data can be collected with passive sensing methods could help to determine the time lag between social support and buffering effects, and how long they are sustained. The ability to compare buffering effects over different timescales may help to adjudicate key mechanisms (e.g., whether the effects are mediated by immediate autonomic physiology, or longer-term changes in social and health behaviors), and ultimately, to guide interventions.

Fourth, wearable devices allow for the collection of autonomic nervous system activity in order to directly assess how processes of social buffering impact underlying stress physiology. Lastly, the passive collection of these data in real-world contexts will prevent participants from having to pause their normal activities to provide a response or enter a novel laboratory environment, therefore potentially allowing for a more natural unfolding of social buffering in a real-world context.

Mental Health.

Data that allows for intensive temporal sequencing of emotional expressions, physiology, and behaviors is essential in order to fully assess and refine theories of emotional dynamics, such as *emotional inertia* and *critical slowdowns*. Emotional inertia, is a phenomena whereby the autocorrelation of an individual's emotions over time predicts psychological maladjustment, rumination, and depressive severity (Koval, Kuppens, Allen, & Sheeber, 2012; Koval & Kuppens, 2012; Kuppens, Allen, & Sheeber, 2010; Kuppens et al., 2012) and critical slowdowns, which are partly characterized by greater variance in emotion, higher temporal autocorrelation of emotion, and greater correlation of emotions of similar and dissimilar valence, has also been shown to predict transitions toward depression (van de Leemput et al., 2014). These phenomena have thus far largely been studied in discrete laboratory settings. Utilizing passive sensing devices would allow for the collection of behavior, physiology, and affect as they unfold within the daily life, which may increase the ecological validity of laboratory studies and translate these findings into real-world settings. In addition, the temporally detailed and longitudinal collection of data may elucidate both micro- (moment to moment) and macro- (week to week) inertia of behavior and affect, which has yet to be investigated. These advantages

would address a number of significant questions regarding these phenomena, including their persistence across contexts (interpersonal and environmental), the time frames over which these phenomena are observable, and the relationship between the temporal dynamics of different measures of emotion. Furthermore, this method could be used in conjunction with self-reported methods to see how both observed and experienced inertia of affect and behaviors relate to one another across time. Indeed, smartphone and wearable devices have recently been used to predict mental health symptoms. For example, sedentary time captured with wearables (Brazendale et al., 2017) and GPS signals from smartphones have been used to predict depressive symptoms (Saeb et al., 2015) and may even be able to be used to detect early signs of depression (Saeb, Lattie, Schueller, Kording, & Mohr, 2016).

Physical Health.

While smartphones may be particularly suited to capturing affectively-laden social information relevant for mental health (Lind, Byrne, Wicks, Smidt, & Allen, 2018), wearables seem to hold particularly great promise for tracking changes in underlying stress physiology and health (Li et al., 2017). For example, wearable photoplethysmography (PPG) that allows wearable devices to collect pulse rate or volumetric changes in blood profusion that act as a surrogate for heart rate have been shown to be a valid measure of heart rate in multiple contexts (Boudreaux et al., 2017; de Zambotti et al., 2016; Shcherbina et al., 2017) as well as over 24 hour periods (Nelson & Allen, 2019) when compared to electrocardiograms, which indicates that these devices can be used to assess autonomic stress physiology changes in daily life. Indeed, recent research has shown that these signals can predict changes in cardiovascular health with high accuracy including

atrial fibrillation (Tison et al., 2018a), hypertension, and sleep apnea (Tison et al., 2018b) as well as an ability to predict flu symptoms (Bradshaw et al., 2019; Samson et al., 2018). Furthermore, wearables have been shown to predict body mass index, early indicators of Lyme disease and inflammation (Li et al., 2017) as well as gait and motor dynamics in individuals with Parkinson's Disease (Mazilu et al., 2015; Patel et al., 2015).

Interventions.

In addition to potential research applications, passive sensing devices can also be used for novel prevention and intervention techniques related to behavior change that is relevant to mental and physical health. First, in terms of assessment and prevention, researchers have already utilized smartphones to detect features of depression and smart home devices to distinguish between healthy older adults and those suffering from dementia (Dawadi, Cook, Parsey, Schmitter-Edgecombe, & Schneider, 2011; Dawadi, Member, Cook, Fellow, & Schmitter-edgecombe, 2013). Assessments of this kind could be extended to other remote populations, which could allow for diagnosis from a distance and a better understanding of the dynamics that are associated with deterioration or recovery of mental health, disease, and interpersonal functioning.

Second, in terms of treatment there are a number of remote therapeutic interventions that could be administered with such technology. One potential is a therapeutic nudge, where clients would be prompted to change an aspect of their behavior in order to increase adaptive functioning, such as modifying eating and sleep patterns (Marteau, Ogilvie, Roland, Suhrcke, & Kelly, 2011). For example, behavior and language captured using home monitoring cameras or vocal and written affect from smartphones could be analyzed, in real-time with future algorithms to determine and code for conflictual

interpersonal behavior (e.g., deviation from acoustic norms and occurrences of aggressive behavioral posturing). If such deviations from normal behavioral and acoustic functioning are positively identified, then wearable notifications, smartphone text messaging, or smart home voice-activated speakers or could initiate therapeutic "nudges" (e.g., reminders to use interpersonal skills that have been taught during face to face therapy interventions) to move individuals out of conflict and toward resolution. Similarly, passive sensing data may be able to provide actionable information for healthcare providers. Take for example a psychotherapeutic context during which a couple attends psychotherapy in order to reduce patterns of interpersonal conflict. At the start of each session, rather than the therapist relying on the couple to retrospectively report on their past week's functioning (which is highly biased and subject to faults in memory), the therapist could pull up summary descriptive charts of relational quality (i.e., frequency and duration of conflictual interactions as detected by voice tone and facial expression) as well as a host of other metrics such as sleep habits and physical activity that may be influencing a couple's mood.

Third, passive sensing technologies may allow for "just-in-time" interventions that utilize real-time data to provide interventions at the moment they are needed, which may be particularly important given that the timing of an intervention can be as important as the specific type of intervention used (Nahum-Shani et al., 2016; Nahum-shani et al., 2014). These interventions may be particularly helpful with specific psychological and behavioral processes associated with acute risk for mental health crises, such as suicide attempts. In particular, due to methodological limitations, these processes have largely been studied using distal risk factors rather than more proximal measures. For example, the onset of suicidal ideation and selection of suicide methods often occur years prior to an attempt,

whereas the proximal steps to suicide often occur within a week, and mostly within hours, prior to the attempt (Millner et al., 2017), suggesting that different risk factors may operate at different time scales. The significance of passive sensing technologies and other IRM methods is that they offer, in some cases for the first time, the opportunity to examine these issues in a non-retrospective way.

For example, recent research utilizing timeline follow-back interview approaches and EMA methods have demonstrated alterations in first-person affect prior to a suicide attempt, which elucidates that there is typically a rapid increase in emotions related to dissatisfaction, hostility, loneliness, fear, hopelessness, and burdensomeness in the hours and minutes prior to a suicide attempt (Bagge, Littlefield, & Glenn, 2017; Kleiman, Turner, Fedor, Beale, Huffman, & Nock, 2017). Utilizing passive sensing technology to collect intensively longitudinal data on behavioral processes associated with depression and suicide risk may better elucidate the behavioral patterns associated with these changes in psychological states (e.g., hopelessness, interpersonal distress), especially how these may precipitate and sustain suicidal risk. Temporally detailed data collected in real-time, rather than retrospective timeline follow-back interviews, may allow for a more accurate categorization of behavioral and affective dynamics that emerge along both discrete and longitudinal timescales leading up to suicide attempt.

In summary, data collected via passive sensing technology provides a set of tools that can make a unique contribution to psychological research, theory, and intervention by providing the 1) *continuous* and 2) *passive* collection of 3) *intensively longitudinal* and 4) *multimodal* data from a 5) *first-person* and 6) *third-person observational perspective* that 7) preserves *ecological validity* by taking place outside of the laboratory and within

participants' own lived contexts. Some of these methods may initially be labor intensive (by requiring human coding of behaviors until automated coding methods have been developed and validated), however by providing intensive longitudinal data within the real-world environments that can capture concurrent multimodal processes (facial, voice, physiology, behavior, device usage, home environment), on both individual and relational functioning, in a temporally precise and ecologically valid manner, and that is independent from, yet complimentary to, self-report, and EMA, passive sensing methods may plausibly allow us to address unique questions relevant to psychological science.

Potential Barriers and Limitations to Using Passive Sensing Technologies. Incorporating passive sensing technology into psychological research will first have to focus on device validity and reliability in order to ensure that commercially available devices are indeed measuring their intended constructs. Furthermore, feasibility research is still needed for passive sensing studies. This early research will have to detail needed sample sizes, percentage of participants accepting these devices in their homes, levels of study attrition, and how device adherence varies by participants characteristics. It is important to highlight that moving forward with this type of research will likely require interdisciplinary data integration necessitating collaboration between experts in behavioral science, affective computing, intervention, mobile sensing, mental health, signal processing, artificial intelligence, biomedical engineering, data mining, computer networks, machine learning, bioethicists, technology developers, and industry partners. In addition, combining validated forms of passive sensing technologies (e.g., smartphones, smart home devices, and wearables) with valuable self-report ecological momentary assessment methods may also allow researchers and clinicians to continuously track both

first-person subjective affect as well as third-person observed affective behavior both within the home and in participants' wider environment. Lastly, there is always the potential that these passive sensing technologies do not deliver what they promised (e.g., potential lack of use and adoption, no behavior improvement). Other potentially promising areas of research, including the translation of neuroscientific findings into new treatments (Nature Neuroscience Editorial, 2013) or using genetics to improve treatment outcomes (Joyner, Paneth, & Ioannidis, 2016), have recently been subjected to critical evaluations that have raised the question of when a direction of research should be abandoned or significantly re-directed. Likewise, passive sensing technologies will need to be subjected to regular critical evaluations of their usefulness and incremental effectiveness, in order to ensure that we do not persist with invasive and expensive procedures that do not have clear utility for science or application.

Concluding Remarks

The three studies presented in the prior chapters elucidate a connection between mental health disorders and relational stress with underlying biological mechanisms of disease (i.e., cardiovascular functioning, inflammation, and cellular aging) as well as the important role parent-adolescent relationships play in both the initiation and modification of these intermediate health outcomes. While these multimethod studies established important links between mental health, relationships, and biological markers of disease in adolescent populations, future research should incorporate a passive sensing ecosystem to track daily activity with smartphones to index social relationships and wearables to assess stress physiology and physical activity in daily life, while smart home technology can be used to collect further multimodal data on close family relationships within the home

environment. Overall, these findings indicate that adolescent-parent relationship quality may initiate and modify the biological cascade between stress, psychopathology, and disease and may serve as one modifiable psychosocial mechanism that may be amendable to intervention in order to prevent deleterious health trajectories and enhance the health of adolescent populations and beyond.

APPENDIX A: SUPPLEMENTARY MATERIAL FOR CHAPTER IV

Mean and Standard Deviation of Measures

Table S1. Mean and Standard Deviation for Baseline Measures

Measure	Lower Risk		High Risk	
	Mean	SD	Mean	SD
Total Symptoms	47.802	9.830	54.247	10.039
Telomere Length (T/S)	1.370	0.216	1.258	0.184
Heart Rate (bpm)	78.563	11.271	82.707	13.121
RMSSD (msec)	65.909	34.274	63.242	39.578
PEP (msec)	89.056	17.357	89.127	17.944
SCL (µS)	6.252	3.484	6.777	2.894

Note: T/S = Relative telomere length, RMSSD = Root mean square of successive RR interval differences, PEP = Pre-ejection period, SCL = Skin conductance level, SD = Standard deviation, msec = milliseconds.

Affective and Psychophysiological Changes Across Tasks

Table S2. Change in Affect and Psychophysiology From Baseline to Interaction Task

Measure		*t*-statistic	df	*p*
EPI Affect Change				
	Δ Positive Affect	6.917	176	**< .001**
	Δ Negative Affect	-3.004	176	**.003**
PSI Affect Change				
	Δ Positive Affect	-0.902	175	.368
	Δ Negative Affect	3.239	174	**.001**
EPI Psychophysiology				
	Δ Heart Rate	11.2	170	**< .001**
	Δ RMSSD	-6.34	170	**< .001**
	Δ PEP	1.35	159	.179
	Δ SCL	11.5	145	**< .001**
PSI Psychophysiology				
	Δ Heart Rate	12.9	170	**< .001**
	Δ RMSSD	-5.53	170	**< .001**
	Δ PEP	-.168	155	.867
	Δ SCL	11.3	141	**< .001**

Note: RMSSD = Root mean square of successive RR interval, PEP = Pre-ejection period, SCL = Skin conductance level, EPI = Event planning interaction, PSI = Problem solving interaction.

Baseline Tables

Table S3. Unadjusted and Adjusted Baseline Model for Total Mental Health Symptoms

Predictors	Unadjusted Model: Total Mental Health Symptoms			Adjusted Model: Total Mental Health Symptoms		
	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	47.802	**45.700 – 49.905**	**<0.001**	39.847	**24.143 – 55.552**	**<0.001**
Group	6.445	**3.496 – 9.394**	**<0.001**	6.351	**3.408 – 9.294**	**<0.001**
Age				0.571	-0.629 – 1.771	0.355
Sex				1.275	-1.677 – 4.227	0.400
Observations	175			175		

Table S4. Unadjusted and Adjusted Baseline Model for Telomere Length

Predictors	Unadjusted Model: Telomere Length			Adjusted Model: Telomere Length		
	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	1.370	**1.308 – 1.431**	**<0.001**	1.406	**0.948 – 1.864**	**<0.001**
Group	-0.112	**-0.197 – -0.026**	**0.012**	-0.115	**-0.203 – -0.027**	**0.013**
Age				-0.003	-0.038 – 0.031	0.848
Sex				0.023	-0.064 – 0.110	0.611
Observations	85			85		

Table S5. Unadjusted and Adjusted Baseline Model for Resting Heart Rate

Predictors	Unadjusted Model: Resting Heart Rate			Adjusted Model: Resting Heart Rate		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	78.563	**75.958 – 81.169**	**<0.001**	93.924	**75.578 – 112.270**	**<0.001**
Group	4.144	**0.480 – 7.808**	**0.028**	3.612	**0.039 – 7.184**	**0.051**
Age				-1.204	-2.607 – 0.200	0.097
Sex				-0.594	-4.172 – 2.983	0.747
Stimulant				15.576	**6.517 – 24.634**	**0.001**
Observations	172			170		

Table S6. Unadjusted and Adjusted Baseline Model for RMSSD

Predictors	Unadjusted Model: Resting RMSSD			Adjusted Model: Resting RMSSD		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	65.909	**58.022 – 73.796**	**<0.001**	111.593	**54.470 – 168.715**	**<0.001**
Group	-2.668	-13.757 – 8.422	0.637	-1.011	-12.135 – 10.113	0.860
Age				-3.243	-7.613 – 1.127	0.151
Sex				-6.530	-17.669 – 4.610	0.256
Stimulant				-29.860	**-58.064 – -1.656**	**0.041**
Observations	172			170		

Note: RMSSD = Root mean square of successive RR interval.

Table S7. Unadjusted and Adjusted Baseline Model for PEP

Predictors	Unadjusted Model: Resting PEP			Adjusted Model: Resting PEP		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	89.056	**85.275 – 92.837**	**<0.001**	90.435	**64.001 – 116.869**	**<0.001**
Group	0.071	-5.245 – 5.386	0.979	-0.591	-5.769 – 4.587	0.825
Age				-0.415	-2.438 – 1.608	0.690
Sex				10.151	**4.963 – 15.339**	**<0.001**
Stimulant				-4.134	-17.184 – 8.916	0.539
Observations	170			168		

Note: PEP = Pre-ejection period.

Table S8. Unadjusted and Adjusted Baseline Model for SCL

Predictors	Unadjusted Model: Resting SCL			Adjusted Model: Resting SCL		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	6.252	**5.541 – 6.963**	**<0.001**	8.494	**3.212 – 13.776**	**0.002**
Group	0.525	-0.478 – 1.528	0.306	0.558	-0.464 – 1.579	0.290
Age				-0.175	-0.582 – 0.231	0.403
Sex				-0.021	-1.056 – 1.015	0.969
Stimulant				0.437	-2.483 – 3.357	0.772
Observations	157			155		

Note: SCL = Skin conductance level.

Reactivity Tables

Table S9. Unadjusted and Adjusted Reactivity Model for Heart Rate

Predictors	Unadjusted Model: HR Reactivity			Adjusted Model: HR Reactivity		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	85.367	**84.277 – 86.457**	**<0.001**	85.274	**84.010 – 86.538**	**<0.001**
Baseline HR	0.793	**0.734 – 0.852**	**<0.001**	0.773	**0.712 – 0.835**	**<0.001**
Group	-0.103	-1.648 – 1.441	0.896	-0.297	-1.846 – 1.252	0.707
Task	0.856	0.129 – 1.584	**0.022**	0.679	-0.041 – 1.398	0.066
Group x Task	0.689	-0.339 – 1.718	0.191	0.867	-0.144 – 1.878	0.095
Sex				0.156	-1.292 – 1.605	0.833
Age				-0.301	-0.773 – 0.171	0.213
Stimulant				4.007	**0.224 – 7.790**	**0.039**
Random Effects						
σ^2	5.86			5.60		
τ_{00}	20.11 subject_id			19.62 subject_id		
ICC	0.77 subject_id			0.78 subject_id		
Observations	342			338		
Marginal R^2 / Conditional R^2	0.789 / 0.953			0.797 / 0.955		

Note: HR = Heart rate.

Table S10. Unadjusted and Adjusted Reactivity Model for RMSSD

Predictors	Unadjusted Model: Reactivity RMSSD			Adjusted Model: Reactivity RMSSD		
	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	53.007	**48.934 – 57.080**	**<0.001**	53.436	**48.660 – 58.212**	**<0.001**
Baseline RMSSD	0.622	**0.551 – 0.692**	**<0.001**	0.621	**0.549 – 0.694**	**<0.001**
Group	2.437	-3.301 – 8.175	0.406	2.215	-3.648 – 8.078	0.460
Task	0.855	-2.510 – 4.220	0.619	1.092	-2.325 – 4.510	0.532
Group x Task	-3.067	-7.821 – 1.687	0.208	-3.304	-8.104 – 1.496	0.179
Sex				-0.774	-6.150 – 4.602	0.778
Age				0.276	-1.454 – 2.007	0.755
Stimulant				2.151	-11.538 – 15.841	0.758
Random Effects						
σ^2	125.28			126.17		
τ_{00}	241.61 $_{subject\_id}$			243.22 $_{subject\_id}$		
ICC	0.66 $_{subject\_id}$			0.66 $_{subject\_id}$		
Observations	342			338		
Marginal R^2 / Conditional R^2	0.591 / 0.860			0.590 / 0.860		

Note: RMSSD = Root mean square of successive RR interval.

Table S11. Unadjusted and Adjusted Reactivity Model for PEP

Predictors	Unadjusted Model: Reactivity PEP			Adjusted Model: Reactivity PEP		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	91.021	**88.495 – 93.548**	**<0.001**	91.763	**88.800 – 94.726**	**<0.001**
Baseline PEP	0.827	**0.727 – 0.927**	**<0.001**	0.838	**0.733 – 0.942**	**<0.001**
Group	-2.251	-5.805 – 1.303	0.216	-2.001	-5.599 – 1.596	0.277
Task	-1.108	**-2.202 – -0.013**	**0.049**	-0.986	-2.094 – 0.122	0.083
Group x Task	0.297	-1.255 – 1.849	0.708	0.175	-1.386 – 1.735	0.827
Sex				-1.248	-4.935 – 2.438	0.508
Age				0.507	-0.629 – 1.644	0.383
Stimulant				-5.943	-14.679 – 2.793	0.184
Random Effects						
σ^2	11.74			11.70		
τ_{00}	124.48 subject_id			121.40 subject_id		
ICC	0.91 subject_id			0.91 subject_id		
Observations	316			312		
Marginal R^2 / Conditional R^2	0.604 / 0.966			0.616 / 0.966		

Note: PEP = Pre-ejection period.

Table S12. Unadjusted and Adjusted Reactivity Model for SCL

Predictors	Unadjusted Model: Reactivity SCL			Adjusted Model: Reactivity SCL		
	Estimates	*Conf. Int (95%)*	*P-Value*	*Estimates*	*Conf. Int (95%)*	*P-Value*
Intercept	8.793	**8.380 – 9.205**	**<0.001**	8.992	**8.511 – 9.473**	**<0.001**
Baseline SCL	0.910	**0.822 – 0.999**	**<0.001**	0.914	**0.827 – 1.001**	**<0.001**
Group	-1.105	**-1.683 – -0.527**	**<0.001**	-1.181	**-1.758 – -0.605**	**<0.001**
Task	-0.027	-0.310 – 0.256	0.853	-0.034	-0.321 – 0.253	0.815
Group x Task	0.232	-0.159 – 0.623	0.247	0.238	-0.156 – 0.632	0.238
Sex				-0.295	-0.842 – 0.252	0.293
Age				-0.071	-0.287 – 0.145	0.521
Stimulant				0.747	-0.756 – 2.251	0.332

Random Effects						
σ^2	0.69			0.69		
τ_{00}	2.49 subject_id			2.36 subject_id		
ICC	0.78 subject_id			0.77 subject_id		
Observations	288			284		
Marginal R^2 / Conditional R^2	0.712 / 0.937			0.726 / 0.938		

Note: SCL = Skin conductance level.

Table S13. Unadjusted and Adjusted Reactivity Model for Negative Affect

Predictors	Unadjusted Model: Negative Affect Reactivity			Adjusted Model: Negative Affect Reactivity		
	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	0.016	-0.259 – 0.292	0.907	-0.051	-0.357 – 0.254	0.742
Group	-0.032	-0.419 – 0.354	0.870	-0.043	-0.431 – 0.345	0.827
Task	-0.619	**-0.984 – -0.254**	**0.001**	-0.615	**-0.983 – -0.248**	**0.001**
Group x Task	1.216	**0.705 – 1.728**	**<0.001**	1.213	**0.699 – 1.727**	**<0.001**
Sex				0.157	-0.136 – 0.450	0.294
Age				0.016	-0.101 – 0.134	0.784
Random Effects						
σ^2	1.50			1.50		
τ_{00}	0.22 subject_id			0.22 subject_id		
ICC	0.13 subject_id			0.13 subject_id		
Observations	352			350		
Marginal R^2 / Conditional R^2	0.092 / 0.210			0.095 / 0.208		

Table S14. Unadjusted and Adjusted Reactivity Model for Positive Affect

Predictors	Unadjusted Model: Positive Affect Reactivity			Adjusted Model: Positive Affect Reactivity		
	Estimates	Conf. Int (95%)	P-Value	Estimates	Conf. Int (95%)	P-Value
Intercept	-0.282	-1.089 – 0.525	0.494	-0.043	-0.929 – 0.844	0.925
Group	0.554	-0.577 – 1.686	0.338	0.555	-0.581 – 1.691	0.339
Task	0.314	-0.827 – 1.456	0.590	0.299	-0.849 – 1.447	0.610
Group x Task	-0.618	-2.221 – 0.984	0.450	-0.605	-2.213 – 1.002	0.461
Sex				-0.479	-1.287 – 0.329	0.246
Age				-0.063	-0.389 – 0.262	0.703

Random Effects

σ^2	14.75		14.75
τ_{00}	0.00 subject_id		0.00 subject_id
ICC	0.00 subject_id		0.00 subject_id
Observations	353		351

Open Source Code

Statistical code that was used in this study can be found on Open Science Framework at https://osf.io/wu4y5/.

R Packages

The following R packages were used for data wrangling, cleaning, and analyses.

Table S16. R Packages

Package	Purpose	Citation
psych	Calculating descriptive statistics	(Revelle, 2019)
lubridate	Dealing with dates and times	(Spinu et al., 2018)
ggplot2	Creating figures	(Wickham et al., 2019)
dplyr	Data wrangling	(Wickham, François, Henry, & Müller, 2019)
tidyverse	Code grammar and data structure	(Wickham, 2017)
summarytools	Data summary statistics	(Comtois, 2019)
plyr	Data wrangling	(Wickham, 2016)
readxl	Importing excel into R	(Wickham, 2019)
zoo	Data wrangling	(Zeileis, Grothendieck, Ryan, Ulrich, & Andrews, 2019)
magrittr	Data wrangling	(Bache & Wickham, 2014)
readr	Import csv files	(Wickham, Hester, Francois, Jylänki, & Jørgensen, 2018)
naniar	Visualizing and summarizing missing data	(Tierney et al., 2019)
car	Regression	(Fox et al., 2018)
nlme	Linear and nonlinear mixed-effects models	(Pinheiro et al., 2019)

lme4	Linear mixed-effects models	(Bates et al., 2019)
reshape2	Reshape data	(Wickham, 2017a)
jmv	Common statistical methods	(Selker, Love, & Dropmann, 2018)
texreg	Format output	(Leifeld, 2017)
sjPlot	Data visualization	(Lüdecke, 2018)
sjlabelled	Label output	(Lüdecke, 2019a)
sjstats	Statistical output	(Lüdecke, 2019b)
dabestr	Data visualization and estimation statistics	(Ho & Tumkaya, 2019)

APPENDIX B: CONTENT AND STYLE REQUEST FORM

In the following chapters of my dissertation, I intend to include published and unpublished co-authored material.

I. DOES CONTEXT MATTER? A MULTI-METHOD ASSESSMENT OF AFFECT in ADOLESCENT DEPRESSION ACROSS MULTIPLE AFFECTIVE INTERACTION CONTEXTS.

Published as Nelson, B. W., Byrne, M. L., Sheeber, L., & Allen, N. B. (2017). Does context matter? A multi-method assessment of affect in adolescent depression across multiple affective interaction contexts. *Clinical psychological science*, *5*(2), 239-258.

I performed this research in collaboration with Nicholas B. Allen, Michelle Bryne, and Lisa Sheeber.

II. ADOLESCENT SYMPATHETIC ACTIVITY AND SALIVARY C-REACTIVE PROTEIN: THE EFFECTS OF PARENTAL BEHAVIOR.

Published as Nelson, B. W., Byrne, M. L., Simmons, J. G., Whittle, S., Schwartz, O. S., Reynolds, E. C., ... & Allen, N. B. (2017). Adolescent sympathetic activity and salivary C-reactive protein: The effects of parental behavior. *Health Psychology*, *36*(10), 955- 965

I performed this research in collaboration with Nicholas B. Allen, Michelle L. Byrne, Lisa Sheeber, Julian G. Simmons, Sarah Whittle, Orli S. Schwartz, Eric C. Reynolds, and Neil M. O'Brien-Simpson.

III. EXTENDING THE PASSIVE-SENSING TOOLBOX: USING SMART-HOME TECHNOLOGY IN PSYCHOLOGICAL SCIENCE.

Published as Nelson, B. W., & Allen, N. B. (2018). Extending the passive-sensing toolbox: using smart-home technology in psychological science. *Perspectives on Psychological Science*, *13*(6), 718-733.

This paper was written by me, with my coauthor providing editorial assistance.

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Chapter I

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Appendices

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