MATERNAL GENOTYPES AND MOTHER-INFANT ATTACHMENT AS MODERATORS OF THE ASSOCIATION BETWEEN THE EARLY REARING ENVIRONMENT AND CORTISOL SECRETION

by

Jaclyn Ludmer

Master of Arts, Ryerson University, 2015

Bachelor of Arts (Honors Specialization in Psychology), University of Western Ontario, 2013

A dissertation

presented to Ryerson University

in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

in the program of

Psychology

Toronto, Ontario, Canada, 2019

AUTHOR'S DECLARATION FOR ELECTRONIC SUBMISSION OF A DISSERTATION

I hereby declare that I am the sole author of this dissertation. This is a true copy of the dissertation, including any required final revisions, as accepted by my examiners.

I authorize Ryerson University to lend this dissertation to other institutions or individuals for the purpose of scholarly research.

I further authorize Ryerson University to reproduce this dissertation by photocopying or by other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

I understand that my dissertation may be made electronically available to the public.

Abstract

Maternal Genotypes and Mother-Infant Attachment as Moderators of the Association Between the Early Rearing Environment and Cortisol Secretion

Doctor of Philosophy, 2019

Jaclyn Ludmer

Psychology, Ryerson University

Background: This dissertation examines maternal genotypes and mother-infant attachment as moderators of the association between the early rearing environment and cortisol secretion. Study 1 examines whether *DRD2*, *SLC6A3*, and *OXTR* genes moderate the association between maternal history of care and maternal cortisol secretion. Study 2 examines mother-infant attachment as a moderator of the associations between maternal depressive symptoms and both infant and maternal cortisol secretion.

Method: Mothers self-reported their history of care and depressive symptoms at infant age 16 months. At 17 months, mother-infant attachment was assessed in the Strange Situation Procedure (SSP). Salivary cortisol was assessed at baseline and at 20- and 40-minutes post-SSP. Buccal cells were collected for genotyping.

Results: Study 1 revealed that maternal history of low care predicts elevated cortisol secretion, but only for mothers with 10-repeat alleles of *SLC6A3* or G alleles of *OXTR*. Study 2 revealed that maternal depressive symptoms predict elevated cortisol secretion, but only for infants and mothers in non-secure attachment relationships.

Conclusions: This dissertation enhances our understanding of the complex relations between the early rearing environment and maternal and infant cortisol secretion.

Acknowledgements

Several people have been instrumental in supporting me through my work on this dissertation. Foremost, I would like to thank my academic advisor, Dr. Leslie Atkinson, for his kindness, thoughtfulness, guidance, and enthusiasm throughout my graduate school experience. Dr. Atkinson has been a mentor and role model. I would also like to thank the members of my committee, Dr. Andrea Gonzalez and Dr. Lili Ma, for their helpful and insightful feedback.

I would like to thank lab members and research assistants in the Biopsychosocial Development Lab. This dissertation would not have been possible without your contributions to participant recruitment, lab visits, and coding observations. Thank you for your time and commitment to this work.

Thank you to the Neurodevelopment Lab at CAMH, including Sajid Shaikh, Maria Tampakeras, Natalie Freeman, and Dr. James Kennedy, as well as Dr. Vanessa Villani, for your assistance with the genotyping process. Thank you to Brittany Jamieson, Dr. Glenn Roisman, and Dr. Chris Fraley for your help with the statistical analyses.

I would finally like to thank my family and friends for their unconditional love and support. You have been there for me through the good and the difficult times. Your support has meant the world to me and has allowed me to persevere and achieve my goals.

I extend my sincere gratitude to the mothers and infants who participated in this project. Your contributions to the field are invaluable.

Of note, Study 1 has been published in *Biological Psychology*, the original source.

Table of Contents

List of Tables

List of Figures

List of Appendices

Chapter 1: General Introduction

Statement of Purpose

Cortisol, a steroid hormone, is the end product of the hypothalamic-pituitary-adrenal (HPA) axis, the neuroendocrine stress response pathway. Patterns of cortisol secretion have important health implications (Jessop & Turner-Cobb, 2008). For example, cortisol secretion patterns have been linked to cognitive and social competence (Apter-Levi et al., 2016; Blair, Granger, & Peters Razza, 2005; Davis, Bruce, & Gunnar, 2002), cellular aging (Ceccatelli, Tamm, Zhang, & Chen, 2007), and a wide variety of physical (e.g., cancer, immune) and mental (e.g., depression, conduct problems) health problems (Goodyer, Park, Netherton, & Herbert, 2001; Halligan, Herbert, Goodyer, & Murray, 2007; Hostinar & Gunnar, 2013; Jessop & Turner-Cobb, 2008). As such, examining the origins of cortisol secretion patterns is a pertinent issue.

It is well-established that cortisol secretion patterns are set early in life and are shaped by the early rearing environment (e.g., Gunnar & Donzella, 2002; Halligan et al., 2007; Laurent, Ablow, & Measelle, 2011; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). Specifically, according to the *HPA programming hypothesis,* the early rearing environment, including maternal depressive symptomatology and interactive behaviour, shapes HPA function, which in turn accounts for HPA function and associated physical and psychiatric disorders later in life (Laurent et al., 2011; Meaney, 2010; Seckl & Holmes, 2007; Weaver et al., 2005). However, the early rearing environment does not predict cortisol secretion levels for all individuals (e.g., Ludmer et al., 2015; Luijk et al., 2010), pointing to the role of moderating factors.

The purpose of this dissertation is to examine potential genetic and psychosocial moderators of the associations between the early rearing environment and cortisol secretion. This dissertation is comprised of two studies in which I examine key moderating models. These two

studies build upon my Master's thesis, which found that infant dopamine-related genes moderate the relationship between maternal depressive symptomatology (a key marker of an adverse early rearing environment, as discussed below, Dougherty et al., 2013; Halligan et al., 2007; Weissman et al., 2006) and infant cortisol secretion (Ludmer et al., 2015). Study 1 attempts to replicate my Master's thesis findings in the infants' mothers, as well as examine an oxytocin-related gene as an additional moderator. More specifically, in Study 1, I examine maternal dopamine- and oxytocin- related genes as moderators of the association between mothers' own early rearing environments and maternal cortisol secretion. In Study 2, I further build upon my Master's work and I examine whether the quality of mother-infant attachment moderates the association between maternal depressive symptoms and infant cortisol secretion. I also attempt to replicate this depressive symptomatology x attachment model to predict maternal cortisol secretion.

To provide a context for these models, in this chapter I provide an overview of the main constructs in the models: i) cortisol secretion, ii) cortisol-related genes, iii) the early rearing environment, and iv) mother-infant attachment. Relevant relations between these constructs are discussed in the individual study introductions. The final chapter of this dissertation consists of a general discussion of the main findings and clinical implications of this work.

Overview of Cortisol Secretion

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine stress response pathway that releases corticotrophin releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland, and cortisol from the adrenal cortex. Cortisol then binds to glucocorticoid receptors that inhibit the production of CRH, ACTH, and cortisol, thereby restoring homeostasis (see summaries in Boyce & Ellis, 2005;

Tarullo & Gunnar, 2006). Increases in cortisol are important as they prepare the organism to function under stressful conditions by stimulating physiological and metabolic changes such as increased blood pressure and heart rate, and decreased digestive, reproductive, and immune function (see summary in Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008). The role of cortisol within the HPA negative feedback loop is also important as it facilitates down-regulation after a stressful event, which is critical for long-term survival. Repeated overstimulation and elevations in cortisol can result in a downregulation of the HPA axis such that it is less responsive to psychosocial and acute stress (e.g., Fries, Hesse, Hellhammer, & Hellhammer, 2005). As such, optimal HPA function takes an inverted U-shape: both hypo- and hyper- cortisol activity can be harmful and have been linked to physical and psychiatric disorders (e.g., Bhagwagar, Hafizi, & Cowen, 2005; Goodyer, Tamplin, Herbert, & Altham, 2000; Granger, Weisz, McCracken, Ikeda, & Douglas, 1996; Kagan, Reznick, & Snidman, 1988).

In addition to its role within the stress response, cortisol has a circadian rhythm. Specifically, cortisol peaks at about 30 minutes after awakening (the cortisol awakening response, Jessop & Turner-Cobb, 2008; Quirin, Pruessner, & Kulh, 2008), and then declines throughout the day, with the lowest levels occurring before bedtime (Gunnar & White, 2001; Jessop & Turner-Cobb, 2008; Kirschbaum & Hellhammer, 1989). As such, in the context of measuring cortisol, it is important to standardize time of assessment in order to avoid the confound of circadian fluctuations (e.g., Toth, Sturge-Apple, Rogosch, & Cicchetti, 2015). In further regard to methodology, it can be difficult to assess cortisol secretion in infants (e.g., location of sampling, compliance, provoking elevations, Jessop & Turner-Cobb, 2008). However, some laboratory stress paradigms do reliably elicit infant cortisol elevations (Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). One such paradigm is the Strange Situation

Procedure (SSP, Ainsworth, Blehar, Waters, & Wall, 1978), which involves repeated separations and reunions with mother, as well as the introduction of a stranger, in a strange room. This paradigm has allowed for the detection of significant inter-individual variability in infant cortisol reactivity (e.g., Atkinson et al., 2013; Jansen et al., 2010). Although mothers consistently downregulate cortisol secretion (following anticipatory anxiety) in the context of laboratory infant stress paradigms (e.g., Atkinson et al., 2013; Bernard, Kashy, Levendosky, Bogat, & Lonstein, 2016; Crockett, Holmes, Granger, & Lyons-Ruth, 2013; Laurent et al., 2011), inter-individual variability in maternal cortisol reactivity has also been shown in the SSP (e.g., Atkinson et al., 2013; Laurent et al., 2011). This dissertation utilizes the SSP in order to reliably elicit infant and maternal cortisol response variability (Atkinson et al., 2013; Jansen et al., 2010).

In terms of measurement, in the human body, about 90% of cortisol is bound to plasma proteins, while 10% is unbound and active (Gunnar & Donzella, 2002; Gunnar & White, 2001). Salivary cortisol is utilized in the current dissertation since it exclusively provides a measurement of active cortisol (thus better representing the degree of cortisol reactivity throughout the SSP, Hellhammer, Wust, & Kudielka, 2009). Further, salivary cortisol may be the best cortisol assessment method for infants (e.g., relative to plasma or urine) because it is non-invasive, thereby enabling frequent and rapid sampling (Kirschbaum & Hellhammer, 1994; Magnano, Diamond, & Gardner, 1989).

Overview of Cortisol-Related Genes

There are heritable components to cortisol secretion (Bartels de Geus, Kirschbaum, Sluyter, & Boomsma, 2003; Bartels, van den Berg, Sluyter, Boomsma, & de Geus, 2003). Genes related to dopamine and oxytocin function may be particularly relevant, given that these neurotransmitters influence brain regions such as the medial prefrontal cortex and the amygdala,

which regulate HPA functioning (Alexander et al., 2011; Chen et al., 2011; Pruessner, Champagne, Meaney, & Dagher, 2004; Sullivan & Gratton, 2002; Zhang, Chretien, Meaney, & Gratton, 2005). Here I provide an overview of the three genes examined in this dissertation. Relevant relations between these genes and study variables of interest are provided in the Study 1 introduction. Of note, DNA was assessed from buccal cells in this dissertation. Non-invasive DNA collection methods (i.e., buccal) are preferred over more invasive techniques (e.g., blood DNA) for ethical reasons and to increase participation and compliance (Livy et al., 2012).

Dopamine receptor (*DRD2*). The *DRD2* gene is localized to chromosome 11q23. The single nucleotide polymorphism (SNP) rs1800497 (Taq1A) resides in the overlapping *ANKK1* (ankyrin repeat and kinase domain containing 1) gene and involves a C to T substitution (Neville, Johnstone, & Walton, 2004). The A1 and A2 alleles correspond to the A and G alleles, respectively. The A1 allele has been associated with dysregulated HPA function (Belda & Armario, 2009).

Dopamine transporter (*SLC6A3*). A 40-base pair variable number tandem repeat (VNTR) downstream of the *SLC6A3* gene alters the density of the dopamine transporter protein in vitro differentially based on the presence or absence of 9- or 10-repeat alleles (VanNess, Owens, & Kilts, 2005). The 10-repeat allele (10R) is associated with dysregulated HPA function (Alexander et al., 2011).

Oxytocin receptor (*OXTR*). Located on chromosome 3p25, containing four exons and three introns, *OXTR* has been associated with stress physiology (e.g., Rodrigues, Saslow, Garcia, John, & Keltner, 2009). A SNP in the third intron, rs53576 (G/A), is of interest for this dissertation given that it has been linked to cortisol reactivity (Chen et al., 2011; Norman et al., 2012).

Overview of the Early Rearing Environment

It is well established that the quality of the early rearing environment has long lasting implications for offspring physical and mental health outcomes (e.g., Gunnar & Donzella, 2002; Herd, Whittingham, Sanders, Colditz, & Boyd, 2014; Hostinar & Gunnar 2013; Jawahar, Murgatroyd, Harrison, & Baune, 2015; Sroufe, 2005). Although there are many aspects of the early rearing environment that can impact child development, studies have indicated that maternal depressive symptomatology is a particularly salient predictor of offspring outcomes (e.g., Halligan et al., 2007; Laurent et al., 2011). Maternal depressive symptoms including, but not limited to, low affect, anhedonia, and fatigue (American Psychiatric Association, 2013) can impact offspring through a variety of mechanisms. For example, such symptoms have been linked to suboptimal parent-child interactions (Hatzinikolaou & Murray, 2010; Lovejoy, Graczyk, O'Hare, & Neuman, 2000), maternal and infant emotion regulation difficulties (Crugnola et al., 2016; Gilbert, Mineka, Zinbarg, Craske, & Adam, 2017; Khoury et al., 2015a), and, of particular importance to this dissertation, maternal and infant cortisol dysregulation (e.g., Barry et al., 2015; Brennan et al., 2008; Feldman et al., 2009; Halligan, Herbert, Goodyer, & Murray, 2004; Halligan et al., 2007; Laurent et al., 2011; Taylor, Glover, Marks, & Kammerer, 2009).

Maternal depressive symptomatology is most often assessed via self-report (Quilty & Bagby, 2008), although behavioural observation methods have been used (e.g., Forehand et al., 1988). One of the five most widely used measures of depressive severity (Quilty & Bagby, 2008) is the Beck Depression Inventory-II (BDI-II, Beck, Steer, & Brown, 1996), which is commonly used with mothers sampled from the community (e.g., Allen, Manning, & Meyer, 2010). My Master's thesis (Ludmer et al., 2015) found that maternal BDI-II scores predicted infant cortisol

secretion in the SSP, but only for infants with specific dopamine-related genotypes. Study 2 of this dissertation builds upon these findings by utilizing the BDI-II to examine whether mother-infant attachment security moderates the associations between maternal depressive symptomatology and infant and maternal cortisol secretion.

As described above, Study 1 of this dissertation attempts to replicate my Master's thesis findings within the infants' mothers. However, mothers cannot retrospectively report on their own mothers' postpartum depressive symptoms. As such, Study 1 operationalizes the maternal early rearing environment as *maternal history of care*, using the maternal care subscale of the Parental Bonding Instrument (PBI; Parker, Tupling, & Brown 1979). This subscale assesses the extent to which the mother received high quality maternal care (e.g., affection and comfort during distress). The PBI has previously been linked to offspring cortisol (e.g., Engert et al., 2009; Pruessner et al., 2004). In fact, Tyrka et al. (2012) found that, in adults, low levels of childhood parental care as assessed with the PBI are associated with increased methylation of the glucocorticoid receptor gene, which in turn predicts atypical cortisol secretion patterns. Tyrka et al.'s (2012) findings occurred over and above the effects of current depressive symptoms and perceived stress, highlighting the importance of early maternal care on cortisol secretion. As such, the use of the PBI in Study 1 allows for a psychometrically strong conceptual replication of my Master's thesis findings within the infants' mothers.

Overview of Mother-Infant Attachment

John Bowlby (1969, p. 371) defined attachment as a child's "strong disposition to seek proximity to and contact with a specific figure and to do so in certain situations, notably when they are frightened, tired, or ill". Bowlby (1969, 1973, 1980) suggested that infants are adaptively prewired to form an attachment bond with a primary caregiver in order to maximize

their chances of survival. For example, attachment-related behaviours such as smiling, crying and vocalizing have the predictable outcome of increasing proximity to the caregiver. This proximity in turn results in feeding, learning about the environment, and engaging in social interactions. Thus, throughout evolutionary history, infants who were biologically predisposed to elicit proximity to their caregivers were more likely to be protected (Bowlby, 1969; Cassidy, 2008). Due to this function of protection, Bowlby considered attachment behaviours to be behavioral adaptations analogous to the physical adaptations emphasized in Darwin's theory of evolution.

There is an important distinction between the presence of a caregiver and the *quality* of an attachment relationship (Weinfield, Sroufe, Egeland, & Carlson, 2008). Since forming an attachment relationship is built into the human repertoire through evolution, infants will form attachments with caregivers regardless of whether the infant is mistreated (Bowlby, 1969). Individual differences in the *quality* of the attachment relationship emerge in the first year of life and have been divided into two categories: *secure* and *non-secure* (Ainsworth et al., 1978). These categories do not merely describe the infant's behaviours within the attachment relationship, but rather the infant's perception of the consistency and reliability of comfort and protection from the caregiver, and the organization of the infant's behaviour with regard to such perceptions (Weinfield et al., 2008). Individual differences in attachment relationship quality arise when infants begin to anticipate caregiver behaviour and develop behavioural strategies to maintain proximity to, and optimize their sense of security with, the caregiver (Ainsworth, 1967; Ainsworth, Bell, & Stayton, 1971; Ainsworth et al., 1978).

Individual differences in infant attachment quality are typically observed in the SSP, which is designed to activate the infant's attachment system (Ainsworth et al., 1978). The pattern

of infant behaviour observed throughout the procedure, particularly during the reunions with the caregiver, is indicative of the security of the attachment relationship. More specifically, in the SSP, infants in *secure attachment relationships* explore their environment, direct attachment behaviours to their caregivers when distressed, and are comforted by the reassurance offered. Secure attachment promotes exploration and environmental mastery because the infant's confidence in the availability of their caregiver enables him or her to develop confidence in his or her own abilities (Goldberg, 2000; Weinfeld et al., 2008).

Ainsworth et al. (1978) identified two types of non-secure attachment. Infants in *resistant attachment relationships* direct many attachment behaviours to their caregivers when there is no apparent danger. In the SSP, resistant infants persistently seek contact, then resist contact when it is achieved (e.g., push away), as if to punish their caregiver for the separation episode. This pattern of behavior reflects a persistent anxiety about the caregiver's accessibility and may arise as a result of inconsistent maternal responsiveness (Ainsworth et al., 1978; Sroufe, Egeland, Carlson, & Collins, 2005; Weinfield et al., 2008). Infants in *avoidant attachment relationships* are not able to direct attachment behaviours to their caregiver in times of distress and cannot easily be comforted by their caregiver, perhaps as a result of intrusive or rejecting parenting (Ainsworth et al., 1978). In the SSP, these infants tend to avoid contact and focus on exploration as a way to minimize their own distress (Ainsworth et al., 1978).

An additional non-secure attachment classification, *disorganized attachment*, was later identified based on the fact that many infants did not fit into any of Ainsworth et al.'s (1978) organized attachment classifications. Infants in disorganized attachment relationships perform seemingly inexplicable, contradictory, and mistimed behaviours during the SSP (Main & Solomon, 1986, 1990). These behaviours may include crying at the stranger's departure and

attempting to follow the stranger out of the room, freezing or stilling, and simultaneously displaying distress and avoidance of the caregiver. Such behaviours reflect "fright without solution" (Hesse & Main, 2000, 2006), as the caregiver is both a source of fear and the only possible source of protection for the infant. Infants in disorganized attachment relationships do have an underlying organized (secure, avoidant, and, most often, resistant, Luijk et al., 2010) attachment strategy, however, in the context of fright without solution, the organized strategy breaks down.

Dissertation Objectives

The research reviewed above was provided as a general overview of each of the main constructs assessed in this dissertation. The objectives of this dissertation are outlined here. Specifically, it is well-established that cortisol secretion patterns are shaped by the early rearing environment (e.g., Gunnar & Donzella, 2002; Halligan et al., 2007; Laurent et al., 2011; Tyrka et al., 2012). However, the early rearing environment does not predict cortisol secretion levels for all individuals (e.g., Ludmer et al., 2015; Luijk et al., 2010), pointing to the role of moderating factors. An important goal of the two studies that comprise this dissertation is to identify genetic and psychosocial moderators of the associations between the early rearing environment and maternal and infant cortisol secretion. My Master's thesis showed that infant *DRD2* and *SLC6A3* genotypes moderate the association between maternal depressive symptoms and infant cortisol secretion (Ludmer et al., 2015). Study 1 of this dissertation attempts to replicate this model in the infants' mothers, as well as examine *OXTR* as an additional moderator. Specifically, in Study 1, I examine the association between a mother's own history of care and her cortisol secretion, as moderated by *DRD2*, *SLC6A3*, and *OXTR* (Figure 1). Study 2 attempts to further expand my Master's thesis findings by assessing whether mother-infant attachment moderates the

association between maternal depressive symptoms and infant cortisol secretion. It also attempts to replicate this model in the infants' mothers (Figure 2). Taken together, this dissertation examines moderators of the associations between the early rearing environment and maternal and infant cortisol secretion. This work provides insight into the complex interrelations of care, genetics, and cortisol secretion across mothers, infants, and their relationship.

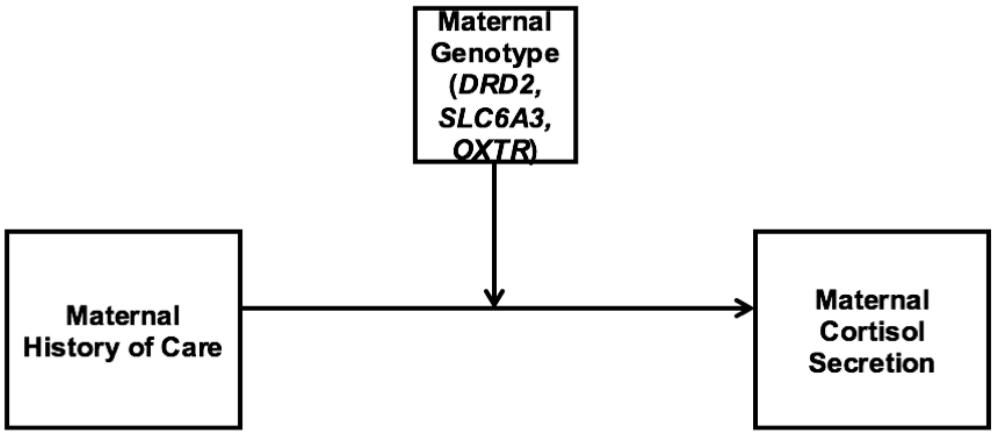

Figure 1. Examining maternal genotypes as moderators of the association between maternal history of care and maternal cortisol secretion.

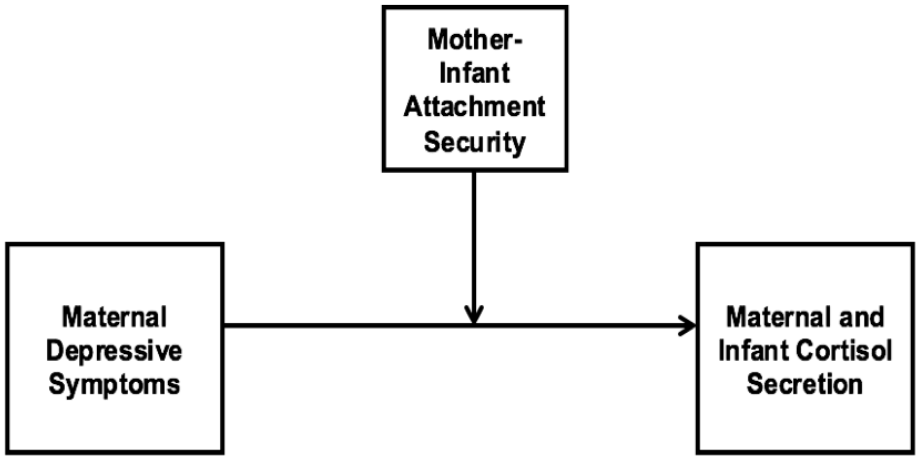

Figure 2. Examining mother-infant attachment security as a moderator of the associations between maternal depressive symptoms and maternal and infant cortisol secretion.

Chapter 2: Maternal *DRD2, SLC6A3,* and *OXTR* genotypes as potential moderators of the relation between the maternal early rearing environment and maternal cortisol secretion

Introduction

Patterns of cortisol secretion are set early in life (Gunnar & Donzella, 2002), are transmitted across generations (Yehuda et al., 2000) from mother to infant (Atkinson et al., 2013), and have important health implications, playing a role in nearly all physical and mental health conditions (Jessop & Turner-Cobb, 2008). As such, a mother's cortisol secretion is particularly important to examine, given that it has implications for her own health as well as her infant's cortisol secretion and health (Atkinson et al., 2016; Debiec & Sullivan, 2014; Gunnar & Hostinar, 2015). For example, lower levels of maternal cortisol secretion in the context of mother-infant dyadic stress are associated with lower levels of postpartum depressive symptoms, and may function to regulate and protect the infant's physiological response, i.e., buffer against infant cortisol hyperreactivity (Khoury et al., 2016). Thus, the aim of this study was to examine the early environmental and genetic predictors of maternal cortisol secretion in the context of mother-infant dyadic stress.

In terms of early environmental predictors, a mother's history of care that she received in early childhood is a well-established determinant of her cortisol secretion. For example, Tyrka et al. (2012) found that, in healthy adults, low levels of childhood parental care (as assessed with the Parental Bonding Instrument, Parker et al., 1979) are associated with increased methylation of the glucocorticoid receptor gene, which in turn predicts atypically attenuated cortisol responses to the dexamethasone/corticotropin-releasing hormone test (i.e., when dexamethasone and corticotropin-releasing hormone are administered). Tyrka et al.'s (2012) findings occurred over and above the effects of current depressive symptoms and perceived stress, suggesting the

importance of early parenting on human epigenetics and cortisol. Perhaps as a result of such epigenetic influences (e.g., Jawahar et al., 2015; Perroud et al., 2011; Perroud et al., 2014), the effects of a mother's history of care on her cortisol patterns are enduring, and can last until older adulthood (Engert et al., 2010).

The intergenerational transmission of cortisol patterns also suggests that genetic factors may play important roles in impacting cortisol secretion, and may do so in interaction with the early environment (e.g., Bakermans-Kranenburg, van IJzendoorn, Mesman, Alink, & Juffer, 2008; Ludmer et al., 2015). Pertinent to this discussion are the definitions of various theories of gene x environment (GxE) interactions. *Diathesis-stress* theory posits that individuals with specific genetic characteristics are genetically vulnerable to the adverse effects of negative rearing environments. In contrast, *differential susceptibility* theory suggests that genetically "susceptible" individuals experience *both* the worst outcomes if reared in impoverished environments *and* the best outcomes if reared in enriched environments (Belsky, 1997a ,1997b, 2005; Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011; Pluess, 2015). *Vantage sensitivity* suggests that individuals with specific genetic characteristics are exclusively susceptible to the positive effects of enriched environments. Research pertinent to how differential context associates with each of the three GxE theories is extremely rare, such that it is impossible to make specific hypotheses in this regard (Del Giudice, 2016). For example, Dalton, Hammen, Najman, and Brennan (2014) found that youth genotype interacted with family environment quality to predict youth depression at age 15 in a differential susceptibility manner, but that this same GxE interaction predicted depression after age 15 in a diathesis-stress manner. Other studies have found the GxE model to differ for the same interaction depending on the informant (i.e., parent versus teacher, Roisman et al., 2012), type of

psychosocial challenge (Ludmer et al., 2015), and adult attachment style (Cassidy, Woodhouse, Sherman, Stupica, & Lejuez, 2011).

The ambiguity regarding the contexts in which the different GxE theories emerge is compounded by lack of statistical symmetry across studies in this area. To address this issue, Roisman et al. (2012) proposed statistical criteria to differentiate between the GxE models, which have been adopted in several recent studies (e.g., Beach et al., 2014; Dalton et al., 2014; Ludmer et al., 2015). These include: i) *Regions of Significance on environmental factors* (*RoS on X*)*:* demonstration that the outcome variable and the plasticity genotype are correlated at high and/or low ends of the environmental variable (Roisman and colleagues recommend bounding by +/-2SD from the mean of the environmental variable); ii) *Proportion of interaction index (PoI):* ratio of improved outcomes for the plasticity genotype over the sum of improved outcomes and harmful outcomes; and iii) *Linearity:* apparent differential susceptibility effects can be artefacts of imposing a linear predictor model on a nonlinear diathesis stress or vantage sensitivity phenomenon, and thus analyses should be repeated when introducing quadratic effects: (environmental variable)^2 and genotype x (environmental variable)^2. While these statistics are an important step toward clarifying the contexts in which each GxE model occurs, the RoS on X test is biased by sample size, power, and environmental ranges, and the PoI index lacks clear statistical guidelines regarding which values indicate which GxE interaction type (Del Giudice, 2016; Roisman et al., 2012). Given our limited understanding of GxE models and the statistics necessary to differentiate between them (Del Giudice, 2016), it appears that, at this time, the crucial piece of information is not the type of interaction, but the fact that there is an interaction.

Additional statistical refinements to GxE research that have subsequently been proposed include presenting results without "binning" alleles (e.g., Bradley et al., 2011; Ludmer et al.,

2015; Villani et al., 2017). Binning alleles involves creating dichotomous groups of "plasticity genotype" and "non-plasticity genotype" individuals, and it is problematic because in many cases it unjustifiably assumes allele dominance in heterozygous individuals (Ludmer et al., 2015). To avoid such ambiguities, it is important to code all genes without "binning", i.e., by tallying the number of candidate alleles (an individual homozygous for plasticity alleles would be scored 2, an individual heterozygous for plasticity and non-plasticity alleles would be scored 1, and an individual homozygous for non-plasticity alleles would be scored 0).

With further regard to methodological caution, the current study focuses specifically on three candidate genes chosen a priori that may interact with maternal history of care to influence maternal cortisol secretion: dopamine receptor (*DRD2*), dopamine transporter (*SLC6A3*), and oxytocin receptor (*OXTR*). The *DRD2* gene is localized to chromosome 11q23 and the SNP rs1800497 (Taq1A) involves a C to T substitution and resides in the overlapping *ANKK1* gene (Neville et al., 2004). The A1 and A2 alleles correspond to the A and G alleles, respectively. The A1 allele has been associated with dysregulated HPA function (Belda & Armario, 2009) as well as with heightened susceptibility to environmental influences (Belsky & Pluess, 2009). With respect to *SLC6A3,* a 40-base pair VNTR downstream of this gene has been found to alter the density of the dopamine transporter protein *in vitro* differentially based on the presence or absence of 9- or 10-repeat alleles (VanNess et al., 2005). The 10-repeat allele (10R) is associated with dysregulated HPA function (Alexander et al., 2011) as well as with heightened susceptibility to environmental influences (Belsky & Pluess, 2009).

DRD2 and *SLC6A3* were selected for the current study given i) the influence of dopamine on parent-child interactions (van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008), ii) the influence of dopamine on the medial prefrontal cortex and amygdala, which regulate HPA

function (e.g., Pruessner et al., 2004; Zhang et al., 2005), and iii) our previous findings that infant *DRD2* and *SLC6A3* genotypes moderate the association between maternal depressive symptoms and infant cortisol reactivity (Ludmer et al., 2015). Conceptual replication of Ludmer et al.'s (2015) GxE findings is needed, given that only 27% of GxE replication attempts are statistically significant, compared to 96% of novel GxE studies (Duncan & Keller, 2011). As such, to conceptually replicate Ludmer et al.'s (2015) findings, the current study assesses whether *maternal DRD2* and *SLC6A3* genotypes interact with the mother's *own* early caregiving environment (i.e., history of care) to influence *maternal* cortisol secretion in the context of infant stress.

Further extending Ludmer et al.'s (2015) findings, genes related to oxytocin function may also play a role in maternal cortisol secretion, given that the two central functions of oxytocin are to enable social (e.g., parental) bonding and to reduce stress (e.g., Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Gordon et al., 2008). The *OXTR* gene, located on chromosome 3p25, containing four exons and three introns, has been found to impact social behavior and stress physiology (e.g., Rodrigues et al., 2009). A SNP in the third intron, rs53576 (G/A), is of interest given associations with cortisol reactivity (Chen et al., 2011; Norman et al., 2012), parenting (Bakermans-Kranenburg & van IJzendoorn, 2008; Bradley et al., 2011), and maternal differential susceptibility (e.g., Sturge-Apple, Cicchetti, Davies, & Suor, 2012). For example, in a low-risk community sample, mothers with GG genotypes (i.e., genotypes signifying more efficient oxytocin function) display more observable sensitivity to their toddlers (Bakermans-Kranenburg & van IJzendoorn, 2008). In a sample of healthy male students participating in the Trier Social Stress Test either alone or with social support (operationalized as having the help of a close female friend to prepare for the task), Chen et al. (2011) found that only G carriers showed lower

cortisol responses to the test in the context of social support (reflecting vantage sensitivity). In a low-income sample, Bradley et al. (2011) found that individuals with the G/G genotype, relative to individuals with other genotypes, reported the most difficulty with emotion regulation (an important correlate of cortisol reactivity, e.g., Quirin, Kuhl, & Düsing, 2011) if they reported a high history of childhood maltreatment (reflecting diathesis stress). Thus, given the role of *OXTR* in cortisol secretion, maternal bonding, and susceptibility to the influences of childhood care, *OXTR* genotypes may moderate the degree to which maternal history of care impacts maternal cortisol secretion in the context of infant stress.

As such, the aims of this study were twofold. (i) We assessed whether maternal *DRD2*, *SLC6A3*, and *OXTR* genotypes moderate the relation between maternal history of care and maternal cortisol secretion in the context of infant stress. It was hypothesized that maternal history of care would have a greater influence on cortisol secretion for mothers with more plasticity alleles of *DRD2* (A1), *SLC6A3* (10R), and *OXTR* (G), relative to mothers with fewer or no plasticity alleles. (ii) For exploratory purposes, we examined whether the GxE interactions reflect diathesis stress, differential susceptibility, and vantage sensitivity models using the Roisman et al. (2012) statistical criteria. As reviewed, specific hypotheses regarding which GxE model would emerge could not be made a priori due to the dearth of research differentiating the different models with statistical rigor and the variety of confounding variables that may impact the manifestation of the models (Del Giudice, 2016). Given that mothers consistently show declines in cortisol secretion (following anticipatory anxiety) throughout both potent and mild infant stress paradigms (Atkinson et al., 2013; Davis & Granger, 2009; Hibel, Granger, Blair, & Cox, 2009; Laurent et al., 2011; Middlemiss, Granger, Goldberg, & Nathans, 2011; Sethre-Hofstad, Stansbury, & Rice, 2002; Van Bakel & Riksen-Walraven, 2008), lower baseline cortisol

levels (i.e., intercepts in our statistical model) and/or buffered cortisol reactivity (i.e., slopes in our statistical model) to the current mother-infant separation stressor were considered to be ideal maternal cortisol patterns in this study.

Method

Participants

This study consists of a community sample of 314 demographically low-risk mother-infant dyads (52% male infants) recruited through postings in community centres and in-person visits to activity centers in Toronto (Atkinson et al., 2013). Infants were full-term and healthy. Inclusion criteria were that mothers were at least 18 years at childbirth, with no known hormonal or psychiatric disorders and with sufficient English to complete questionnaires. This study uses data obtained when infants were 16 (M = 15.97; SD = 1.34) and 17 (M = 17.25; SD = 1.92) months of age, which is a time when infants are actively calibrating their cortisol secretion patterns based on the quality of their rearing environment (Del Giudice, Ellis, & Shirtcliff, 2011). It is also a time when intra-individual cortisol secretion patterns begin to stabilize in a trait-like manner across time, location, and challenge (e.g., Atkinson et al., 2013; Goldberg et al., 2003; Laurent et al., 2012). Maternal age at the 16-month visit ranged from 21 to 46 years (M = 32.98; SD = 4.53). Median family income was $114,000-149,999 Canadian (25th and 75th percentiles were $92,000-113,999 and $150,000-199,999). Maternal highest education levels were as follows: primary (1.0%), secondary (8.2%), community college (23.8%), university (46.6%), and post-graduate degree (20.4%). Most mothers did not smoke (95.2%), did not report experiencing regular insomnia (91.3%), did not report sleep disruptions the previous night (60.2%), were not currently breastfeeding (75.2%), were not on medication (69.9%), were currently working (60.9%), and were in a relationship (94.3%). Mothers self-reported their ancestry as Caucasian

(68.0%), Asian (13.9%), African American (3.2%), Hispanic (5.7%) and Other (including Mixed, East Indian, Middle Eastern, Persian; 9.2%). Mothers self-reported their infant's ethnicity as Caucasian (74.8%), Asian (8.5%), African American (3.5%), Hispanic (2.2%) and Other (including Mixed, East Indian, Middle Eastern, Persian; 13.1%). Number of infant siblings ranged from 0 to 5 (M = 0.32, SD = 0.64), and number of hours per week in the care of people other than parents ranged from 0 to 97 (M = 5.5, SD = 12.92).

Procedure

The Research Ethics Boards at the Centre for Addiction and Mental Health and Ryerson University granted approval for this study and all procedures were performed in accordance with relevant guidelines. At infant age 16 months, two female experimenters observed the mother and infant in the home and distributed the maternal inventories to be mailed in upon completion. Mothers also completed demographic questionnaires at this time. At 17 months in the laboratory, dyads participated in the SSP. At the end of the visit, buccal cells were collected. Saliva was collected at baseline, and 20- and 40- minutes post- SSP.

Measures

Maternal history of care. Maternal history of care was assessed with the Parental Bonding Instrument (PBI; Parker et al., 1979). The PBI consists of four subscales (maternal care, maternal overprotection, paternal care, and paternal overprotection), each consisting of 12 items assessing caregiving behavior when the participant was younger than 16 years old. The current study used only the maternal care subscale because it specifically has been the focus of previous research examining offspring cortisol (e.g., Engert et al., 2009; Pruessner et al., 2004)[1]. Questions are rated on a 4-point Likert scale ranging from 0 (*Very Like*) to 3 (*Very Unlike*). Item

[1] Of note, we assessed the paternal care subscale as a post hoc analysis and results were not significant.

examples include “she could make me feel better when I was upset” and “she was affectionate to me”. Relevant items were reverse scored such that higher total scores indicate higher care. The PBI has strong psychometric properties (Parker, 1988). Cronbach’s alpha for the current study was .94.

Strange situation procedure (SSP). The SSP (Ainsworth et al., 1978) consists of eight episodes, each three minutes in duration, wherein the infant is i) introduced to an unfamiliar but child-friendly room, ii) given the opportunity to play independently while mother is in the room, iii) introduced to female stranger, iv) left alone with stranger, v) reunited with mother, vi) left alone in the room, vii) reunited with stranger, and finally viii) reunited with mother again. The HPA axis is particularly sensitive to stressors that contain elements of uncontrollability and social threat (Dickerson & Kemeny, 2004). As is conventional, SSP episodes (but not procedures) were stopped if the infant cried hard for 20 seconds or was in danger (e.g., standing on a chair while alone in the room). For example, if the infant cried hard for 20 seconds during SSP episode 6 (alone in room), episode 7 (stranger returns) would begin.

Maternal cortisol. To address time-of-day issues, all visits commenced between 0900h and 1000h. Saliva was collected at baseline, and at 20- and 40- minutes post SSP. At each time point, two Sorbettes (Salimetrics, State College PA) were placed in the mouth for 60 seconds. Saliva samples were centrifuged for 10-minutes at 3000 rpm at 4°C to extract saliva and then sealed and stored at -70 °C. Each sample was assayed twice using a salivary cortisol enzyme immunoassay kit (Salimetrics, State College, PA), and average values were used in analyses.

Maternal genotypes. DNA was assessed from maternal buccal cells at each visit. Four paper buccal swabs (Whatman Omniswab, Fisher Scientific Company) were collected from each mother (rubbed four times on each cheek) and expelled into polypropylene tubes, which were

sealed to prevent contamination and stored at 4°C. DNA isolation and analysis of buccal cells was conducted at the Neurogenics Laboratory at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada. For TaqMan assays, a 1ul volume of total genomic buccal swab DNA was amplified using the manufacturer's standard TaqMan genotyping protocol, scaled to a total reaction volume of 10 uL. For *SLC6A3*, total genomic DNA was amplified as described in Vandenbergh et al. (1992) and electrophoresed on an AppliedBiosystems 3130 Genetic Analyzer. Genotype calls were initially made in GeneMapper v4 and confirmed manually. Genotypes were in Hardy-Weinberg equilibrium and thus representative of the population.

Maternal sensitivity. As a potential covariate, maternal sensitivity was examined with the Maternal Behaviour Q-Sort (MBQS, Pederson, et al., 1990), a set of 90 items describing maternal interactive behaviour. Based on a two-hour home observation of mother-infant interaction at infant age 16 months, trained sorters arranged the items into nine piles of ten items each, ranging from pile 1 (*Least Like the Mother*) to pile 9 (*Most Like the Mother*). Each mother's final score is the correlation between the scores of her Q-sort with those of a theoretically derived sort of a prototypically sensitive mother. That is, a very sensitive mother would receive a score close to 1.0 and a very insensitive mother would receive a score close to -1.0. Sorters were blind to other measures. The mean scores of both sorters was used here. The MBQS has strong psychometric properties (e.g., Atkinson et al., 2000; Pederson et al., 1990). Inter-observer reliability was high, $ICC = .88$, $p < .001$.

Maternal depressive symptoms. The Beck Depression Inventory-II (BDI-II, Beck et al., 1996) is commonly used to assess the presence and severity of depressive symptomatology in mothers sampled from the community (e.g., Allen et al., 2010). It has strong psychometric properties (Sprinkle et al., 2002). It was used in this study as a potential covariate.

Parenting stress. Parenting stress, a potential covariate, was assessed with the Parenting Stress Index-Short Form (PSI-SF; Abidin, 1995), a self-report questionnaire consisting of three, 12-item subscales. The Parental Distress subscale examines perception of parenting competence, restriction of personal activities, depressive symptoms, and social support. The Parent-Child Dysfunctional Interaction subscale examines parent's expectations of child behaviour and level of reinforcement derived from child interaction. Finally, the Difficult Child subscale examines child behavioral characteristics that may impact parenting. The PSI-SF total score (sum of the three, 12-item subscales) was used in the current study. The PSI-SF has adequate reliability and validity (Abidin, 1995; Haskett, Ahern, Ward, & Allaire, 2006).

Perceived stress. Perceived stress, a potential covariate, was assessed with the Perceived Stress Scale (PSS, Cohen, Kamarck, & Mermelstein, 1983). The PSS is a 14-item self-report measure of perceived stress within the past month. Items such as "in the past month, how often have you been upset because of something that happened unexpectedly?" are rated on a 5-point Likert scale. The PSS is an internally consistent and predictively valid measure (e.g., Hewitt, Flett, & Mosher, 1992).

Results

Data Preparation and Analytic Approach

Maternal genotype distributions are presented in Table 1. Descriptive statistics are provided here, with means and standard deviations reported for normally distributed variables, and with medians and interquartile ranges reported for variables that deviated from normality. PBI (maternal care subscale) scores ranged from 0 to 36 (Median = 29.00, Interquartile Range = 9.25). Maternal sensitivity as assessed with MBQS ranged from -.56 to .88 (Median = .56, Interquartile Range = .44). Parenting stress scores ranged from 47 to 135 (M = 79.37, SD =

17.19). Perceived stress scores ranged from 2 to 30 (*M* = 15.17, *SD* = 5.71). Depressive symptom scores ranged from 0 to 39 (Median = 6, Interquartile Range = 7.00). Maternal cortisol values in nmol/L ranged from 1.13 to 63.70 (Median = 6.49, Interquartile Range = 6.35) at baseline, from 1.21 to 39.63 (Median = 4.21, Interquartile Range = 4.02) at +20, and from 0.99 to 34.73 (Median = 3.77, Interquartile Range = 3.24) at +40. Cortisol values were log transformed to address positive skew.

Table 1

Maternal Genotype Distributions

Number of Plasticity Alleles, *N* (%)								
DRD2 A1 allele			*SLC6A3* 10R allele			*OXTR* rs53576 G allele		
0	1	2	0	1	2	0	1	2
178(60.8)	94(32.1)	21(7.2)	27(9.2)	110(37.7)	155(53.1)	112(38.1)	133(45.2)	49(16.7)

With respect to potential covariates, maternal cortisol values were not related to maternal wake time, breakfast time, sleep disruptions (i.e., whether the mother reported that her sleep was disrupted the previous night), medication status, family income, maternal education, age, relationship status, sensitivity, depressive symptoms, parenting stress, perceived stress, insomnia status, working status, breastfeeding status, smoking status, or date of last menstruation. Nor were maternal cortisol levels associated with infant sex, number of hours in out-of-home care, or number of siblings. Thus, these variables were not included in the models. While also unrelated to maternal cortisol values, maternal ethnicity was included in all models to address population stratification (Freedman et al., 2004; Keller, 2014). Following Keller's (2014) recommendations, ethnicity x PBI and ethnicity x gene terms were also included in the models, regardless of statistical significance. Of note, *DRD2, SLC6A3,* and *OXTR* plasticity alleles were not

significantly associated with each other or with PBI scores, thus ruling out the potential confounds of gene-gene and gene-environment correlations. Correlations of main study variables are presented in Table 2.

Table 2

Correlations Amongst Main Study Variables

	1.	2.	3.	4.	5.
1. Maternal total cortisol output	-				
2. PBI	-.04	-			
3. *DRD2* number of A1 alleles[a]	-.05	-.04	-		
4. *OXTR* number of G alleles[b]	.13*	-.04	.07	-	
5. *SLC6A3* number of 10 repeat alleles[c]	-.00	-.07	.09	.03	-
6. Maternal ethnicity[d]	-.04	.07	-.31**	-.18*	-.24**

Note: PBI = Parental Bonding Instrument. [a]Coded as no A1 alleles = 0, one A1 allele = 1, two A1 alleles = 2. [b]Coded as no G alleles = 0, one G allele = 1, two G alleles = 2. [c]Coded as no 10 repeat alleles = 0, one 10 repeat allele = 1, two 10 repeat alleles = 2. [d]Coded as not Caucasian = 0, Caucasian = 1. *$p < .01$. **$p < .001$.

Data were analyzed using multilevel modelling (MLM) with maximum likelihood (*Hierarchical Linear Modeling, Version 7,* Raudenbush, Bryk, Cheong, Congdon, & du Toit, 2011) to account for interdependence of physiological measures within individuals. A two-level model was used to assess maternal cortisol across baseline, +20, and +40 time points (Level 1), nested within individual mothers (Level 2). Intra-class correlations (ICC) depicting the variance

accounted for between levels support the use of nesting procedures (ICC = .64, .62, and .63 for the *DRD2*, *SLC6A3*, and *OXTR* models, respectively). The ICC is the percentage of variance between units at different levels; thus, 62 to 64% of the variance in cortisol was between time and individual. In contrast to traditional linear regression, MLM tests and accounts for, as necessary, differential rates of change within and across individuals (growth curves, i.e., slopes), individual differences in initial status of the dependent variable (i.e., intercepts), and the effect of the predictors of interest on such factors (Singer and Willet, 2003; Hruschka, Kohrt, & Worthman, 2005).

MLM can accommodate missing data by using available participant data rather than excluding participants listwise (Garson, 2013). Thus, missing cortisol samples (127 time points total, primarily due to early termination of SSP visits due to infant fatigue) were dropped at Level 1 without the loss of an entire mother's data. While MLM estimates missing values for Level 1 variables, it deletes (listwise) individuals for which Level 2 data is not available. Due to failure to mail in questionnaires or to mailing in incomplete questionnaires, 78 PBI values were missing. Mothers who failed to mail in complete questionnaires did not differ from mothers who mailed in complete questionnaires on *DRD2, SLC6A3,* or *OXTR* genetic distributions, cortisol values, or any of the potential covariates listed above, with the exception of working status. Specifically, mothers who were currently working were less likely to mail in completed questionnaires, $\chi^2(2) = 13.50$, $p = .001$. Thus, prior to MLM analyses, the SPSS Expectation-Maximization technique was used to estimate missing values for maternal PBI scores[2]. Such imputation procedures are valid with up to 50% missing data on main variables of interest (Collins, Shafer, & Kam, 2001). PBI scores were mean-centered for main analyses.

[2] Of note, when analyses were re-run with only mothers who had complete PBI data, all results were equivalent.

Separate MLM models were run for each of *DRD2*, *SLC6A3*, and *OXTR* GxE interactions. For each model, Level 1 modeled cortisol trajectories over linear time. At Level 2, PBI (mean-centered), relevant gene (uncentered, coded as no plasticity alleles = 0, one plasticity allele = 1, and two plasticity alleles = 2), PBI x gene interaction, and ethnicity covariates (as specified above, Keller, 2014) were entered. A multi-step full maximum likelihood estimation procedure was used to determine the final model. Theoretical considerations, significance testing, a comparison of model fit using the log-likelihood ratio test, and an estimate of variance explained (for fixed effects) were used to determine final model components, including fixed and random effects (Raudenbush & Byrk, 2002). Fixed effects were interpreted using final estimation with robust standard errors. Final models were re-estimated using restricted maximum likelihood for a conservative estimation of variance-covariance structure; these results are reported. Significant MLM GxE interactions were then further analyzed with Roisman et al.'s (2012) GxE statistics. Values from the MLM variance-covariance matrix for each model were entered into Roisman et al.'s (2012) website to calculate RoS and PoI values. To assess Roisman et al.'s (2012) linearity critique, $(PBI)^2$ and genotype x $(PBI)^2$ terms were entered into the final models.

Main Analyses

***DRD2* as moderator of the relation between maternal history of care and maternal cortisol secretion.** The effect of interest (i.e., *DRD2* x maternal history of care interaction) was not significant. At level 1, the model included fixed effects for time as a linear progression (i.e., entered as 0, 1, 2) which significantly improved model fit and accounted for 39.3% of the variance. The coefficients (Table 3) reveal that cortisol decreased across time and that this decrease leveled off or became less prominent over time. The random effect of time (i.e., whether there was significant variation in cortisol trajectories across individuals) was significant

(variance = .0058, p <.001) and significantly improved model fit. At level 2, maternal history of care, *DRD2* genotype, and the maternal history of care x *DRD2* genotype interaction were entered as fixed effects (Appendix 1). The maternal history of care x *DRD2* interaction coefficient estimate was -.006, which was not significantly different from zero (p = .16). Improvement in model fit approached significance, $\chi^2(1) = 32.81$, p = .09, and 1.5% additional variance was accounted for. Since the MLM did not reveal a significant PBI x *DRD2* interaction, the model was not analyzed further.

Table 3

Fixed effect estimates from the final 2-level multilevel model with DRD2 and maternal history of care predicting maternal log transformed cortisol levels

Fixed Effect	γ	*SE*	*t*
Intercept	.82	.02	40.78***
PBI	.003	.003	0.93
DRD2 genotype[a]	-.03	.03	-1.28
PBI x *DRD2* genotype	-.006	.004	-1.40
Time	-.11	.01	-15.14***
Random Effect	**Variance**	**SD**	**Chi-Square (df)**
Intercept	.06	.24	1482.71(235)***
Time slope	.01	.08	457.20 (238)***
Level-1	.01	.11	

Note: PBI = Parental Bonding Instrument. SD = Standard Deviation. [a]Coded as no A1 alleles = 0, one A1 allele = 1, two A1 alleles = 2.

***SLC6A3* as moderator of the relation between maternal history of care and maternal cortisol secretion.** The final model fit the data significantly better than the null model, $\chi^2(1) = 221.97$, $p < .001$. The final model accounted for 80% of the variance between individuals (a 18% increase compared to the null model). Parameter coefficients and standard errors of the final model's fixed effect factors are depicted in Table 4 and the equation is displayed in Appendix 2. Similar to the *DRD2* model, at level 1, fixed effects for time as a linear progression significantly improved model fit. Random effects of time had significant variances, and significantly improved model fit. At level 2, maternal history of care, *SLC6A3* genotype, and the maternal history of care x *SLC6A3* genotype interaction were entered as fixed effects. The *SLC6A3* x maternal history of care interaction coefficient (-.01) was significantly different from zero ($p < .001$), indicating that the regression of cortisol on maternal history of care varies across levels of genotype. The addition of the *SLC6A3* x maternal history of care interaction led to significantly improved model fit, $\chi^2(1) = 7.27$, $p < .01$, and accounted for 8.5% additional variance. Covariates (i.e., ethnicity, ethnicity x *SLC6A3* genotype, and ethnicity x maternal history of care) were also added at level 2. The addition of these variables did not significantly improve model fit. The covariates were retained in the model as per guidelines (Keller, 2014). Maternal history of care, *SLC6A3* genotype, and maternal history of care x *SLC6A3* genotype were not significant predictors of the variance in the trajectory (i.e., slope) of cortisol across linear time.

Table 4

Fixed effect estimates from the final 2-level multilevel model with SLC6A3 and maternal history of care predicting maternal log transformed cortisol levels

Fixed Effect	*γ*	*SE*	*t*
Intercept	.97	.08	12.05***
PBI	.02	.01	2.49*
SLC6A3 genotype[a]	-.11	.05	-2.37*
Ethnicity[b]	-.18	.09	-2.07*
Ethnicity x PBI	.004	.005	0.73
Ethnicity x *SLC6A3* genotype	.13	.05	2.31*
PBI x *SLC6A3* genotype	-.01	.004	-3.96***
Time	-.11	.01	-15.03***
Random Effect	**Variance**	**SD**	**Chi-Square (df)**
Intercept	.06	.23	1301.35(232)***
Time slope	.01	.09	445.56 (238)***
Level-1	.12	.01	

Note: PBI = Parental Bonding Instrument. SD = Standard Deviation. [a]Coded as no 10R alleles = 0, one 10R allele = 1, two 10 R alleles = 2. [b]Coded as not Caucasian = 0, Caucasian = 1. *$p < .05$. **$p < .01$. ***$p < .001$.

To understand the significant PBI x *SLC6A3* interaction as it predicts maternal cortisol, Roisman et al.'s (2012) criteria for differentiating between diathesis stress, differential susceptibility, and vantage sensitivity were employed (see Figure 3). The RoS on X test revealed that the regression of log cortisol on *SLC6A3* was statistically significant at values of centered

PBI that fell below -19.52 and above -1.32, which is most consistent with the vantage sensitivity model as the former value is more than 2SD below the centered PBI mean. The PoI value was 0.42, indicating that 42% of the interaction is attributable to "better" outcomes in the context of high care. While Roisman et al. (2012) indicate that PoI values above 0.60 are consistent with vantage sensitivity, Del Giudice (2016) noted that it is rare to obtain such PoI values in empirical studies, even those that may best reflect vantage sensitivity. Thus, our PoI value of 0.42 is not inconsistent with vantage sensitivity. Finally, $(PBI)^2$ and *SLC6A3* x $(PBI)^2$ were added to the final MLM model and were not significant, supporting the vantage sensitivity model. Taken together, mothers with more plasticity alleles (10R) of *SLC6A3,* relative to mothers with fewer or no plasticity alleles of *SLC6A3,* had the lowest cortisol levels in anticipation of infant stress if they reported a history of high maternal care.

Although a strength of this study was to examine genetic plasticity continuously (as opposed to binning alleles and making assumptions of dominance), for exploratory purposes, we conducted simple slopes analyses to compare the association between PBI and cortisol for mothers with zero, one, and two 10 repeat alleles of *SLC6A3*. The association between PBI and cortisol was significantly stronger for mothers with two 10 repeat alleles than for mothers with no 10 repeat alleles, $t(169) = 2.21$, $p < .05$. There were no significant differences of the simple slopes between mothers with two and one 10 repeat allele, $t(247) = 1.05$, *ns*, or between mothers with zero and one 10 repeat allele, $t(126) = 1.28$, *ns*.

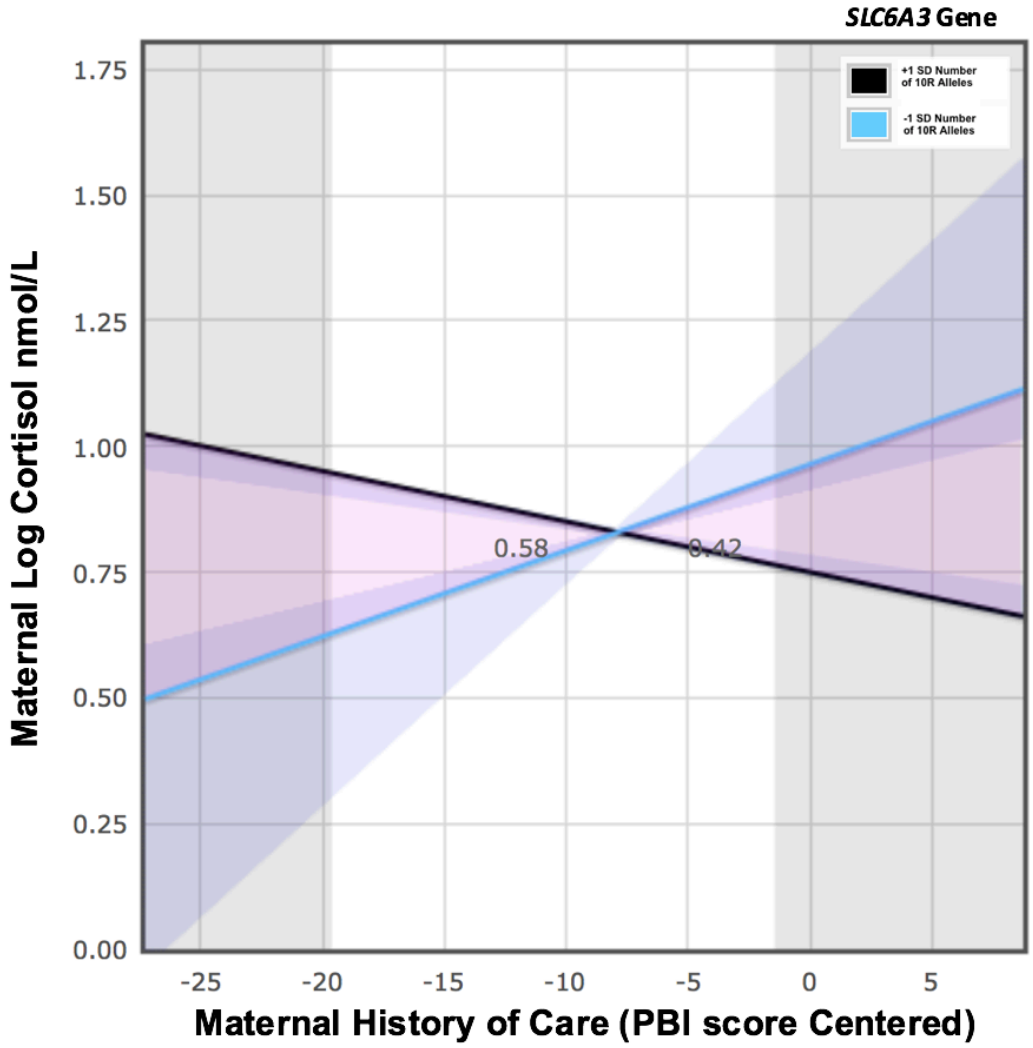

Figure 3. SLC6A3 moderating the relation between maternal history of care and maternal log cortisol (nmol/L) in a vantage sensitivity manner. Mothers with more 10R alleles, relative to mothers with fewer or no 10R alleles, had lower cortisol levels if they reported a history of high care. Side shaded (grey) rectangles depict the regions of significance (RoS) on X and denote where the two lines differ significantly. The two lines differ significantly within 2SD of the mean of maternal history of care only on the right side of the crossover, consistent with the vantage sensitivity model. Triangular (pink) shaded areas depict the proportion of the interaction (PoI), and show that, consistent with vantage sensitivity (Del Guidice, 2016), 42% of the interaction is

accounted for by "better" outcomes. Figure was generated by Roisman et al.'s (2012) calculator (http://www.yourpersonality.net/interaction/).

***OXTR* as moderator of the relation between maternal history of care and maternal cortisol secretion.** The final model fit the data significantly better than the null model, $\chi^2(1) = 208.18$, $p < .001$. The final model accounted for 81% of the variance between individuals (a 19% increase compared to the null model). Parameter coefficients and standard errors of the model's fixed effect factors are depicted in Table 5 and the equation is displayed in Appendix 3. Similar to the *DRD2* and *SLC6A3* models, at level 1, fixed effects for time as a linear progression significantly improved model fit. Random effects of time had significant variances, and significantly improved model fit. At level 2, maternal history of care, *OXTR* genotype, and the maternal history of care x *OXTR* genotype interaction were entered as fixed effects. Only the *OXTR* x maternal history of care interaction coefficient (-.01) was significantly different from zero ($p = .01$), indicating that the regression of cortisol on maternal history of care varies across levels of genotype. The addition of the *OXTR* x maternal history of care interaction led to significantly improved model fit, $\chi^2(1) = 7.27$, $p < .01$, and accounted for 3.1% additional variance. Covariates (i.e., ethnicity, ethnicity x *OXTR* genotype, and ethnicity x maternal history of care) were also added at level 2. The addition of these variables did not significantly improve model fit. The covariates were retained in the model as per guidelines (Keller, 2014). Maternal history of care, *OXTR* genotype, and maternal history of care x *OXTR* genotype were not significant predictors of the variance in the trajectory (i.e., slope) of cortisol across linear time.

Table 5

Fixed effect estimates from the final 2-level multilevel model with OXTR and maternal history of care predicting maternal log transformed cortisol levels

Fixed Effect	*γ*	*SE*	*t*
Intercept	.77	.05	16.82***
PBI	-.00	.00	-0.20
OXTR genotype[a]	.02	.04	0.39
Ethnicity[b]	.03	.05	0.50
Ethnicity x PBI	.01	.00	2.81**
Ethnicity x *OXTR* genotype	-.01	.05	-0.18
PBI x *OXTR* genotype	-.01	.00	-2.34*
Time	-.11	.01	-14.88***
Random Effect	**Variance**	**SD**	**Chi-Square (df)**
Intercept	.06	.25	2328.91(228)***
Time slope	.01	.08	757.77 (234)***
Level-1	.01	.12	

Note: PBI = Parental Bonding Instrument. SD = Standard Deviation. [a]Coded as no G alleles = 0, one G allele = 1, two G alleles = 2. [b]Coded as not Caucasian = 0, Caucasian = 1. *$p < .05$. **$p < .01$. ***$p < .001$.

To understand the significant PBI x *OXTR* interaction as it predicts maternal cortisol, Roisman et al.'s (2012) criteria were employed (see Figure 4). The RoS on X test revealed that the regression of log cortisol on *OXTR* was statistically significant at values of centered PBI that fell below -15.2, which is most consistent with the diathesis stress model, although slightly

below -2SD of the mean of PBI (14.2). The PoI value was 0.04, indicating that 4% of the interaction is attributable to "better" outcomes in the context of high PBI values. This is consistent with the diathesis stress model. Finally, $(PBI)^2$ and *OXTR* x $(PBI)^2$ terms were added to the final model and were not significant, supporting the diathesis stress model. Taken together, mothers with more plasticity alleles of *OXTR*, relative to mothers with fewer or no plasticity alleles of *OXTR*, had the highest cortisol levels in anticipation of infant stress if they reported a history of low maternal care.

As above, for exploratory purposes, we performed simple slopes analyses to compare the association between PBI and cortisol for mothers with zero, one, and two G alleles of *OXTR*. The association between PBI and cortisol was significantly stronger for mothers with two G alleles than for mothers with no G alleles, $t(149) = 1.97$, $p < .05$. There were no significant differences of the simple slopes between mothers with two and one G allele, $t(167) = 1.08$, *ns*, or between mothers with zero and one G allele, $t(230) = 1.14$, *ns*.

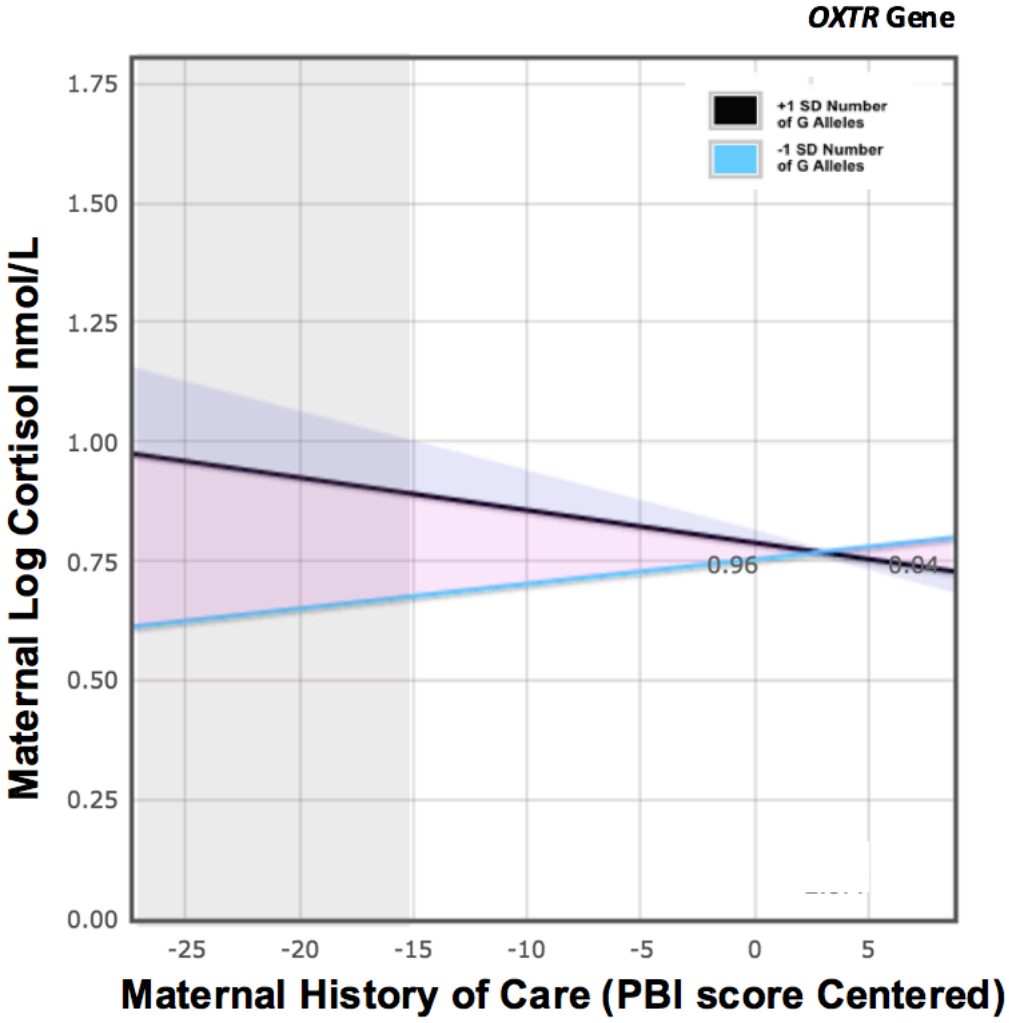

Figure 4. OXTR moderating the relation between maternal history of care and maternal log cortisol (nmol/L) in a diathesis-stress manner. Mothers with more G alleles, relative to mothers with fewer or no G alleles, had higher cortisol levels if they reported a history of low care. Side shaded (grey) rectangle depicts the regions of significance (RoS) on X and denotes where the two lines differ significantly. The two lines differ significantly at values of PBI below -15.2, which is just below 2SD from the mean of maternal history of care (14.2). Triangular (pink) shaded areas depict the proportion of the interaction (PoI), and show that, consistent with the diathesis-stress model (Roisman et al., 2012), 4% of the interaction is accounted for by "better"

outcomes. Figure was generated by Roisman et al.'s (2012) calculator (http://www.yourpersonality.net/interaction/).

Discussion

This study (i) assessed the hypotheses that maternal *DRD2*, *SLC6A3*, and *OXTR* genotypes moderate the relation between maternal history of care and maternal cortisol secretion in the context of infant stress, and (ii) explored whether the GxE interactions reflect diathesis-stress, differential susceptibility, or vantage sensitivity models. Results partially supported hypotheses: maternal history of care had a greater influence on initial (baseline) cortisol secretion (but not cortisol slopes) for mothers with more plasticity alleles of *SLC6A3* (10R) and *OXTR* (G) (but not *DRD2*), relative to mothers with fewer or no plasticity alleles of *SLC6A3* and *OXTR*. Exploratory analyses revealed that the maternal care x *SLC6A3* interaction best reflected the vantage sensitivity model of GxE and that the maternal care x *OXTR* interaction best reflected the diathesis-stress model of GxE. Specifically, mothers with more plasticity alleles of *SLC6A3,* relative to mothers with fewer or no plasticity alleles of *SLC6A3,* had the lowest cortisol levels in anticipation of infant stress if they reported a history of high maternal care. Mothers with more plasticity alleles of *OXTR*, relative to mothers with fewer or no plasticity alleles of *OXTR*, had the highest cortisol levels in anticipation of infant stress if they reported a history of low maternal care.

Our finding that the GxE interactions predicted maternal baseline cortisol but not cortisol trajectories is consistent with the "narrow definition" of attachment, which involves protection (Goldberg, Grusec, & Jenkins, 1999). That is, mothers have an evolved biobehavioural system that functions to protect the infant. This system includes *anticipatory* cortisol secretion and *proactive* behaviour to manage *potential* threat to the infant. It is possible that mothers who

received low maternal care may find the notion of an impending stressor to the baby to be more threatening (i.e., less controllable) than mothers with more positive histories of maternal care. This may be reflected in the arrival or anticipatory maternal cortisol levels. Arrival effects are common in cortisol studies (Ruttle, Serbin, Stack, Schwartzman, & Shirtcliff, 2011). However, as mothers become familiar with the actual procedures, perceived threat diminishes, as reflected in cortisol decline that is not significantly linked to maternal history of care. This may be due to several factors that contribute to the controllability of the stressor on behalf of the child: mothers participate in or observe all aspects of the SSP, episodes are terminated early if the baby is in a potentially dangerous situation or communicates prolonged (20 s) distress, and mothers are explicitly instructed that they may terminate the procedure at any time (of note, no mother did terminate, indicating behaviorally that they did not find the procedure threatening).

With respect to potential underlying mechanisms of the GxE interaction findings, we can only speculate, given the dearth of research in this area. One possibility involves the influences of dopamine (Zhang et al., 2005) and oxytocin (Fan et al., 2014) on the medial prefrontal cortex and amygdala, which regulate HPA functioning. Epigenetic mechanisms may also play a role (Oberlander et al., 2008; Pluess & Belsky, 2011; Puglia, Lillard, Morris, & Connelly, 2015). As speculated in Ludmer et al. (2015), dopamine may increase susceptibility to the impact of the early caregiving environment on cortisol secretion through its influence on attentional, motivational, and reward processes (Bakermans-Kranenburg & van IJzendoorn, 2011; Bakermans-Kranenburg et al., 2008; Pluess & Belsky, 2011). For example, the *SLC6A3* 10R allele has been linked to altered dopaminergic efficiency in the striatum (Alexander et al., 2011), and has therefore been hypothesized to impact sensitivity to immediate feedback (whether positive or negative, Bakermans-Kranenburg & van IJzendoorn, 2011). This may in turn impact

the degree to which individuals attend to and react to caregiving quality, with cortisol secretion as corollary (Bakermans-Kranenburg et al., 2008). With respect to the *OXTR* G allele, it has been associated with more efficient oxytocin function, heightened physiological reactivity to infant distress (Riem, Pieper, Out, Bakermans-Kranenburg, & van IJzendoorn, 2011), and more sensitive parenting (Bakermans-Kranenburg & van IJzendoorn, 2008). We speculate that, in the context of poor caregiving histories, mothers with G alleles may experience heightened proactive sensitivity concerned with the management of infant safety (Goldberg et al., 1999; Raval et al., 2001), which may be reflected in their cortisol secretion in anticipation of their infants being faced with potential attachment-related stress.

Of note, the addition of the *SLC6A3* x maternal history of care interaction in the model accounted for 8.5% additional variance, whereas the addition of the *OXTR* x maternal history of care interaction in the model accounted for 3.1% additional variance. This difference may be attributable to the fact that *SLC6A3* can impact the HPA axis more directly (e.g., Alexander et al., 2011), whereas *OXTR* is part of a different system and we speculate that its influence on the HPA axis may occur more indirectly, based on social-contextual factors (e.g., Chen et al., 2011). Further research is needed, however, to empirically explore the specific mechanisms by which dopaminergic and oxytocinergic function impact maternal cortisol secretion.

Although dopamine- and oxytocin-related genes do moderate the association between maternal history of care and maternal cortisol secretion, we also found that the nature of these moderations depends on the gene in question. Specifically, the vantage sensitivity model best explained the *SLC6A3* GxE interaction, and the diathesis-stress model best explained the *OXTR* GxE interaction. Given that dopamine and oxytocin may be differentially connected to cortisol response as speculated above, perhaps it is not surprising that a different GxE mechanism is

involved across genes. An alternative explanation is that the precise differentiation between diathesis-stress, differential susceptibility, and vantage sensitivity models is limited by statistical issues and confounding variables such as a restricted power, environmental ranges, and reliability of developmental cues (Del Giudice, 2016; Roisman et al., 2012). The current study's classifications of the GxE interactions as vantage sensitivity and diathesis-stress may be artifacts of limited theory, power, and statistical precision (Del Giudice, 2016), and should therefore be regarded as preliminary. For example, our *OXTR* RoS analysis fell just short of Roisman et al.'s (2012) recommended boundaries of 2SDs from the mean of the environmental variable, which was likely an artifact of the RoS test being biased by sample size and skew of the environmental variable (Roisman et al., 2012). As summarized by Del Giudice (2016), future studies are needed to integrate evolutionary theory with statistical methodology to develop a statistical procedure that more reliably differentiates between the three GxE models. Thus, the crucial piece of information here may not be the type of interaction, but rather the fact that there is an interaction.

With respect to previous work, the current findings conceptually replicate Ludmer et al.'s (2015) findings that infant *SLC6A3* genotype moderates the relation between infant early rearing environments (operationalized as maternal depressive symptoms) and infant cortisol secretion. While this is a within-sample conceptual replication (e.g., with potential genetic or familial confounds), it is remarkable that the current study assessed mothers in the context of the very same challenge and found a comparable *SLC6A3* x early rearing environment interaction to predict cortisol levels. The majority of GxE studies fail to replicate (Duncan & Keller, 2011), and thus the replicated findings highlight the important role of *SLC6A3* in interaction with the early rearing environment for shaping cortisol patterns. Future studies are needed to confirm the roles of *DRD2* and *OXTR* in impacting cortisol secretion, given that we failed to conceptually

replicate Ludmer et al.'s (2015) *DRD2* findings, and that this is the first study (to our knowledge) to examine *OXTR* as it interacts with the early rearing environment to predict cortisol secretion.

Several study limitations warrant consideration. Foremost, our method relied on maternal reports of history of care. However, the PBI maternal care subscale has been specifically linked to offspring cortisol (e.g., Engert et al., 2009; Pruessner et al., 2004). In further regard to the PBI, our low risk community sample reported a relatively positive maternal history of care, so results may not generalize to higher-risk samples. Moreover, future research can examine other potential genetic and epigenetic influences relating to glucocorticoid receptor function (Oberlander et al., 2008; Tyrka et al., 2012). Another limitation is that the sample size used here is relatively small for GxE work (Duncan & Keller, 2011). Nevertheless, our within-sample replication across candidate genes (*OXTR* and *SLC6A3*) and our conceptual replication of Ludmer et al.'s (2015) *SLC6A3* infant GxE findings with mothers does go some way to attenuating the probability of Type I error. Furthermore, we used non-binned genetic terms, which reduces potential error due to unjustifiable assumptions of allele dominance.

Conclusions

In summary, maternal *SLC6A3* and *OXTR* genotypes moderate the relation between maternal history of care and maternal cortisol secretion in anticipation of infant stress. Maternal history of care has a greater influence on cortisol secretion for mothers with more plasticity alleles of *SLC6A3* (10R) and *OXTR* (G), relative to mothers with fewer or no plasticity alleles of *SLC6A3* and *OXTR*.

Chapter 3: Mother-infant attachment security as a potential moderator of the relations between maternal depressive symptoms and maternal and infant cortisol secretion

Introduction

In both clinical and non-clinical samples, maternal depressive symptoms are associated with suboptimal infant and maternal hypothalamic-pituitary-adrenal (HPA) function (Brennan et al., 2008; Feldman et al., 2009; Laurent et al., 2011; Taylor et al., 2009). Typically, such symptomatology is initially associated with hypercortisolism, and subsequently, after prolonged overstimulation, with hypocortisolism, in order to conserve resources under conditions of chronic stress (Fries et al., 2005). The association between maternal depressive symptoms and cortisol secretion is important because cortisol secretion plays a role in cognitive and social competence (Apter-Levi et al., 2016; Blair et al., 2005; Davis et al., 2002), cellular aging (Ceccatelli et al., 2007), and nearly all human physical (e.g., cancer, immune) and mental (e.g., depression, conduct problems) health conditions (Goodyer et al., 2001; Halligan et al., 2007; Hostinar & Gunnar, 2013; Jessop & Turner-Cobb, 2008). Exposure to maternal depressive symptoms in the postnatal period is particularly important as it predicts elevated basal cortisol levels (Halligan et al., 2004) and cortisol reactivity (Barry et al., 2015) in offspring in adulthood, regardless of subsequent exposure to maternal depressive symptomatology (Barry et al., 2015). Furthermore, the disturbances in offspring cortisol associated with postnatal maternal depressive symptoms mediate the relation between maternal depressive symptoms and offspring depressive symptoms (thus accounting for the intergenerational transmission of depression; Halligan et al. 2007).

Although the relation between maternal depressive symptoms and cortisol secretion is well established, some studies fail to find main effects (e.g., Ludmer et al., 2017; Luijk et al.,

2010), as this association is moderated by several variables, including child internalizing symptoms (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002), attachment (Luijk et al., 2010), and temperament (i.e., positive emotionality, Mackrell et al., 2014). For example, maternal depressive symptoms are more strongly associated with elevated child cortisol secretion for children with higher levels of internalizing symptoms, relative to children with lower levels of internalizing symptoms (Ashman et al., 2002), for children in non-secure attachment relationships, relative to children in secure attachment relationships (e.g., Luijk et al., 2010), and for children with less positive emotionality, relative to children with more positive emotionality (Mackrell et al., 2014). As Khoury et al. (2015a), proposed, these moderating factors are conceptually associated with the ability to regulate emotions. Accordingly, Khoury et al. (2015a) showed that infant emotion regulation strategy moderated the association between maternal depressive symptoms and infant cortisol secretion during a challenge in which the mother repeatedly denied the infant an attractive toy. Specifically, infants with mothers high in depressive symptomatology who employed more independent regulatory behaviours (i.e., did not rely on their mothers to help regulate their emotions) showed higher cortisol secretion than infants who employed fewer independently regulatory behaviors.

As mentioned in the context of Khoury et al.'s (2015a) argument regarding emotion regulation as a moderating factor, mother-infant attachment classifications can be conceptualized as emotion regulation strategies (e.g., Malik, Wells, & Wittkowski, 2015; Moutsiana et al., 2014). Based on mother-infant interactions during the SSP, Ainsworth et al. (1978) delineated three classifications of mother-infant relationships. In secure relationships, infants feel confident in relying on their caregiver to consistently respond to their cues, so they signal for their caregiver upon becoming distressed and down-regulate emotion to maternal soothing. In

contrast, infants in resistant attachment relationships do not trust that their caregiver will be consistently responsive, and thus they engage in hyperactivation of emotions and evince difficulty in down-regulating in response to maternal soothing efforts. Infants in avoidant attachment relationships are theorized to expect rejection and thus refrain from signaling to their caregiver for regulatory help (i.e., they engage in emotional hypoactivation). Main and Solomon (1990) identified disorganized attachment based on the observation that some infants did not meet criteria for any of Ainsworth et al.'s (1978) organized attachment classifications as assessed in the SSP. Dyads with disorganized attachment do have an underlying organized strategy (secure, avoidant, or, most often, resistant, Luijk et al. 2010), but this strategy breaks down as a result of the infant being either fearful of or feared by the caregiver (i.e., the disorganized infant is unable to rely on a consistent strategy to regulate their emotions in the context of their attachment relationship, Main & Hesse, 1990).

Although mother-infant attachment may moderate the association between maternal depressive symptoms and infant cortisol, the *type* of non-secure attachment that places infants at risk for the elevated cortisol associated with maternal depressive symptoms remains unclear. This is because studies using the SSP to examine attachment and cortisol are inconsistent. Some studies show that insecurely attached infants have elevated cortisol secretion relative to securely attached infants (e.g., Beijers, Riksen-Walraven, Sebesta, & de Weerth, 2017), although this may only be the case for insecurely attached infants who are also fearful (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Another study shows that it is not insecurely attached infants per se, who show elevated cortisol secretion during the SSP; rather, resistant infants show higher cortisol secretion relative to secure and avoidant infants (Luijk et al., 2010). Other studies show no differences in cortisol secretion

between securely and insecurely attached infants, but do show differences between disorganized and organized infants (Bernard & Dozier, 2010; Hertsgaard, Gunnar, Farrel, Erickson, & Nachmias, 1995; Spangler & Grossman, 1993). Two additional studies (Frigerio et al., 2009; Laurent et al., 2011), showed no associations between attachment classifications and SSP cortisol. Taken together, mother-infant attachment has not been consistently linked to infant SSP cortisol, but when studies do show associations, resistant and disorganized attachment drive the secure/non-secure differences. Based on these studies, it would be expected that resistant and disorganized attachment increase risk for the elevated infant cortisol secretion associated with maternal depressive symptoms. However, Luijk et al. (2010) only found resistant attachment to moderate the association between depressive symptoms and cortisol. As such, the current study aimed to replicate Luijk et al.'s (2010) resistant findings, and extend them to disorganized attachment.

Furthermore, studies have not yet examined the associations between maternal depressive symptoms, mother-infant attachment, and *maternal* cortisol secretion. Maternal depressive symptoms impact maternal cortisol levels (e.g., Taylor et al., 2009), but given that i) emotion regulation strategies impact cortisol secretion among adults with internalizing disorders (Gilbert et al., 2017), ii) adult emotion regulation is associated with adult attachment (Malik et al., 2015), and iii) there is concordance between maternal and infant attachment classifications (Verhage et al., 2016), it could be suggested that mother-infant attachment may moderate the association between maternal depressive symptoms and maternal cortisol secretion. In line with this idea, attachment-informed mother-child interventions result in lowered and normalized maternal cortisol secretion in samples with high levels of depressive symptoms (e.g., Field et al., 1998; Toth et al., 2015; Urizar & Munoz, 2011). As such, the current study expands Luijk et al.'s

(2010, maternal depressive symptoms x mother-infant attachment predicting infant cortisol secretion) and Khoury et al.'s (2015a, maternal depressive symptoms x infant emotion regulation predicting infant cortisol secretion) models to examine whether maternal depressive symptoms and mother-infant attachment interact to influence maternal (as well as infant) cortisol secretion in the SSP.

Of note, there are often multiple cortisol indices examined in the literature, which may account for some of the inconsistencies in findings (e.g., Dozier et al., 2008; Luijk et al., 2010). In a principal component analysis, Khoury et al. (2015b) surveyed 15 cortisol point estimates utilized in the literature and found that, for both mothers and infants, a component representing "total cortisol output" consistently accounted for the most variance. As such, total cortisol output, which takes baseline cortisol levels as well as change in cortisol levels into account, may be the more sensitive indicator, relative to, e.g., cortisol change scores (see also Hankin, Badanes, Smolen, & Young, 2015). The current study's use of total cortisol output allows us to conceptually replicate and augment confidence in Khoury et al.'s (2015a, maternal depressive symptoms x infant emotion regulation predicting infant total cortisol output) findings within the same longitudinal sample. Replication in psychological research is rare and essential (Makel, Plucker, & Hegarty, 2012), particularly replication at the level of statistical analysis (Bernard et al., 2016).

Based on findings linking maternal depressive symptoms and non-secure mother-infant attachment to higher SSP cortisol secretion (e.g., Luijk et al., 2010), and findings that an infant's ability to rely on the mother for emotion regulation protects against the elevated cortisol secretion associated with maternal depressive symptoms (Khoury et al., 2015a), it was hypothesized that maternal depressive symptoms would predict higher total cortisol output for

infants in the SSP, but only in the context of non-secure attachment relationships. Based on findings linking maternal postnatal depressive symptoms to elevated maternal cortisol secretion in the SSP (Laurent et al., 2011), and the fact that there is concordance between maternal and infant attachment classifications (Verhage et al., 2016), it was also hypothesized that maternal depressive symptoms would predict elevated maternal total cortisol output in the SSP, but only for mothers in non-secure attachment relationships with their infants. Based on the attachment-cortisol literature discussed, we hypothesized that resistant *and* disorganized classifications would drive the moderating effects in both infant and maternal models.

Method

Measures

Strange situation procedure (SSP) attachment coding. As described in Chapter 2 (Study 1), mother-infant dyads participated in the SSP at infant age 17 months (Ainsworth et al., 1978). Here I provide a summary of the coding for mother-infant attachment for the purposes of Study 2. Attachment is coded from videotaped SSPs (Ainsworth et al., 1978). Mainly due to reluctance to participate in the laboratory visit (as opposed to the home visit, as described in the Procedure section of Chapter 2), 265 SSP tapes were available for attachment coding. Nine of these tapes were only recorded on VHS tapes that had broken, or had a reunion episode that was not captured on camera and thus could not be assigned a classification. As such, attachment classifications were available for 256 dyads. Dyads without classifications did not differ from dyads with classifications with respect to marital status, maternal education, breast feeding status, self-reported ethnicity, cortisol levels, depressive symptoms, or sensitivity. They also did not differ with respect to family income, infant sex, number of siblings, and number of hours per week in out-of-home care. Dyads with classifications, relative to dyads without classifications,

were more likely to have older mothers ($t(279) = -2.04$, $p < .05$) and mothers currently working (χ^2 (1) = 10.95, $p < .01$).

For the current study, attachment was coded as 0 (*not secure: avoidant, resistant or disorganized*) or 1 (*secure*). A trained coder (JL) who achieved reliability with Dr. Elizabeth Carlson and Dr. Alan Sroufe coded the tapes. Forty-two (16.4%) tapes were independently double coded by a second trained coder who had also achieved reliability with Dr. Elizabeth Carlson and Dr. Alan Sroufe. Raters achieved 86% agreement (36/42 cases) on the 2-way (secure, not secure) classifications. Kappa was .63 ($p < .001$), which is considered "substantial" (Landis & Koch, 1977). Raters achieved 79% agreement (33/42 cases) on the 4-way (secure, avoidant, resistant, disorganized) classifications. Kappa was .68 ($p < .001$), which is considered "substantial" (Landis & Koch, 1977).

Salivary cortisol. Mothers were asked to refrain from feeding their infants 60 min before procedures to avoid salivary contamination. Two Sorbettes (Salimetrics, State College PA) were used to collect infant and maternal saliva at each time point: 5 minutes pre-challenge (baseline) and 20 and 40 minutes post-challenge (Goldberg et al., 2003). Sorbettes were placed in the mouth for 60 seconds. Saliva samples were centrifuged for 10-minutes at 3000 rpm at 4°C to extract the saliva and then sealed and stored at -70 °C. Each sample was assayed twice using a salivary cortisol enzyme immunoassay kit (Salimetrics, State College, PA) and average values were used in analyses.

As reviewed, principal component analyses have supported the use of "total cortisol output" (Khoury et al., 2015b; Fekedulegn et al., 2007). Pruessner, Kirschbaum, Meinlschmid, and Hellhammer's (2003) area under the curve with respect to ground (AUC_G) consistently loads highly on this component (Khoury et al., 2015b). AUC_G captures both the difference between

single measurement points and the distance of single measurement points from the ground. Following Pruessner et al. (2003), AUC_G was computed as {[(20 min value + baseline value)/ 2] x time} + {[(40 min value + 20 min value)/ 2] x time}. Our use of AUC_G allowed us to attempt conceptual replication of Khoury et al.'s (2015a) findings (Bernard et al., 2016).

Potential covariates. A comprehensive attempt was made to assess for impact of known covariates to ensure validity of findings. We considered the following self-reported variables as potential covariates as they have previously been linked to cortisol: family income, maternal education, and maternal relationship status (e.g., Gustafsson, Anckarsäter, Lichtenstein, Nelson, & Gustafsson, 2010), as well as maternal age (Cauter, Leproult, & Kupfer, 1996) and infant sex (Davis & Emory, 1995). We also considered maternal and infant feeding times (Khoury et al., 2015a), wake times (Wust et al., 2000), medication status (e.g., Kirschbaum, Pirke, & Hellhammer, 1995), whether or not mothers or babies had sleep disruptions the previous night (Lasikiewicz, Hendrickx, Talbot, & Dye, 2008) and maternal smoking status (Fisher et al., 2007), menstrual stage (Marinari, Leshner, & Doyle, 1976) breastfeeding status (Tu, Lupien, & Walker, 2006), and insomnia status (Lasikiewicz et al., 2008), as these variables are physiologically linked to HPA activity.

We also examined maternal sensitivity as a potential covariate using the MBQS (Pederson et al., 1990), given that parenting has been linked to maternal depression (Hatzinikolaou, & Murray, 2010), mother-infant attachment (Atkinson et al., 2000), and cortisol secretion (Atkinson et al., 2013). Given the influence of maternal history of maternal care on cortisol secretion (Ludmer et al., 2017), we examined maternal history of maternal care as an additional covariate using the maternal care subscale of the Parental Bonding Instrument (PBI; Parker et al., 1979). Furthermore, we examined the Parenting Stress Index-Short Form (PSI-SF;

Abidin, 1995) and the Perceived Stress Scale (PSS, Cohen et al., 1983) as additional covariates. The MBQS, PBI, PSI-SF, and PSS are described in Chapter 2 of this dissertation.

Statistical Analyses

The percent of missing values was 14.3% for BDI-II scores due to unreturned or incomplete questionnaires, 18.5% for attachment classification mainly due to reluctance to participate in the laboratory visit (as opposed to home visit), 27.4% for infant AUC_G, and 18.5% for maternal AUC_G. Missing infant cortisol values were primarily due to reluctance to participate in saliva sampling and missing maternal cortisol values were primarily due to early termination of the visit due to infant fatigue. Multiple imputation is a valid procedure for up to 50% missing data (Collins et al., 2001). Little's Missing Completely at Random (MCAR) test was not significant, thus permitting imputation. Using SPSS 24, 20 imputations were conducted[3]. Following recommendations (Collins et al., 2001), we conducted inclusive imputation models (Khoury et al., 2015a). Using the imputed data, we conducted two separate multiple regression analyses, predicting AUC_G for the mother and infant in the SSP. Below we report the average of the 20 imputations. Of note, AUC_G values deviated from normality and were log transformed to address skew. BDI-II scores were centered.

Results

Descriptive Statistics and Preliminary Analyses

SSP classifications were as follows: 34 (13.3%) avoidant, 121 (47.3%) secure, 51 (19.9%) resistant, and 50 (19.5%) disorganized[4]. Of the disorganized infants, four (8%) had an underlying avoidant strategy, 20 (40%) had an underlying secure strategy, 21 (41%) had an

[3] Of note, all results were equivalent when replicated without multiple imputation (i.e., with missing data deleted listwise).

[4] Attachment classification distributions in middle class, non-clinical North American samples are as follows: 62% secure, 9% resistant, 15% avoidant, and 15% disorganized (van IJzendoorn, Schuengel, & Bakermans-Kranenburg, 1999).

underlying resistant strategy, and five (10%) did not have a classifiable underlying strategy. BDI-II scores were distributed as follows: 204 (75.8%) were not depressed (score 0-9), 39 (14.5%) had mild mood disturbance (score 11-16), 11 (4.1%) had borderline clinical depression (score 17-20), 10 (3.7%) had moderate depression (score 21-30), and 5 (1.9%) had severe depression (score 31-40) (Beck et al., 1996). Descriptive statistics and correlations amongst main variables are provided in Table 6, with medians and interquartile ranges reported because variables deviated from normality.

Table 6

Descriptive Statistics and Correlations Amongst Main Study Variables

	1.	2.	3.	Median	IR
1. BDI-II Score	-			6	7
2. Attachment Security	-.01	-			
3. Infant AUC_G	.17**	-.06	-	153.39	132.60
4. Maternal AUC_G	.11	.05	.39***	199.10	164.88

Note. IR = Interquartile Range. BDI-II score = Beck Depression Inventory score, i.e., maternal depressive symptoms. AUC_G = area under the curve ground, i.e., total cortisol output. Attachment was coded dichotomously as 0 (*not secure*) or 1 (*secure*). AUC_G values were log transformed to address skew.

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

AUC_Gs were not related to family income, infant sex, infant or maternal wake times, infant or maternal breakfast end times, infant or maternal medication status, infant or maternal sleep disruptions, or maternal history of care, education, age, relationship status, smoking status, menstrual stage, insomnia status, or breastfeeding status. Infant AUC_G was associated with

MBQS scores (such that infants of more sensitive mothers had higher AUC_G values than infants of less sensitive mothers, $r = .15$, $p < .05$). As such, we included maternal sensitivity in the infant AUC_G analyses. MBQS scores ranged from -.56 to .88 (Median = .56, Interquartile Range = .44).

Main Analyses

Attachment as moderator of the relation between maternal depressive symptoms and infant cortisol secretion in the SSP. The overall model was significant, F (4, 312) = 10.02, $p < .05$, $R^2 = .11$. Maternal sensitivity (covariate), maternal depressive symptoms, and the interaction between maternal depressive symptoms and attachment security made significant contributions to AUC_G (Table 7). As depicted in Figure 5a, high maternal depressive symptoms predicted elevated infant total cortisol output in the SSP for infants in non-secure attachment relationships with their mothers, but not for infants in secure attachment relationships with their mothers. Analyses were then conducted to determine which specific attachment classifications drove this interaction (Figure 5b). There was a significant association between maternal depressive symptoms and infant AUC_G for resistant dyads ($r = .54$, $p < .01$) and disorganized dyads ($r = .39$, $p < .05$), but not for avoidant ($r = .10$, *ns*) or secure ($r = -.02$, *ns*) dyads. Luijk et al. (2010) suggested that only resistant attachment acts as a moderator between maternal depressive symptoms and infant cortisol secretion, and that if disorganized attachment is found as a moderator it is because many disorganized infants have an underlying resistant strategy. However, the association between maternal depressive symptoms and infant AUC_G was still significant when examined with only disorganized dyads who did not have an underlying resistant classification (i.e., when examined with disorganized dyads with underlying secure, avoidant, or unclassifiable classifications, $r = .50$, $p < .05$)[5]. Taken together, high maternal

[5] Furthermore, we re-ran the main analysis when controlling for ABC resistance (i.e., when controlling for whether or not dyads had a primary or secondary resistant classification). ABCD attachment security (i.e., whether or not

depressive symptoms, in combination with non-secure (specifically resistant and disorganized) attachment, predicted elevated infant total cortisol output in the SSP.

Table 7

Multiple Regression Analyses to Predict Infant AUC_G in Strange Situation from Maternal Depressive Symptoms, Mother-Infant Attachment, and their Interaction

	β(*SE*)
Maternal Sensitivity (covariate)	.13(.05)*
Maternal Depressive Symptoms	.02(.004)**
Attachment	-.04(.04)
Maternal Depressive Symptoms x Attachment	-.02(.01)**

Note. AUC_G = area under the curve ground, i.e., total cortisol output. Attachment was coded dichotomously as 0 (*not secure*) or 1 (*secure*).

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

dyads had a primary secure classification) still significantly interacted with maternal depressive symptoms to predict infant AUC_G in the SSP (data not shown).

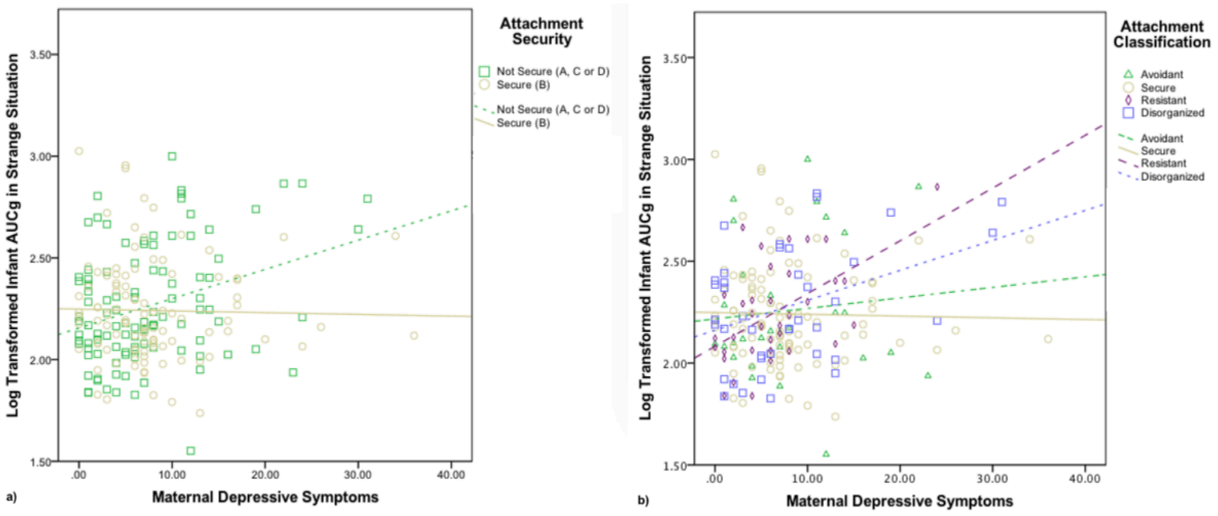

Figure 5. Mother-infant attachment security moderates the relation between maternal depressive symptoms and infant total cortisol output (AUC_G) in the Strange Situation Procedure. Maternal depressive symptoms predict elevated infant total cortisol output, but only for infants in non-secure (a), specifically resistant and disorganized (b), relationships.

Attachment as moderator of the relation between maternal depressive symptoms and maternal cortisol secretion in the SSP. The overall model was significant, F (3, 312) = 5.79, $p < .01$, $R^2 = .05$. Maternal depressive symptoms and the interaction between maternal depressive symptoms and attachment security made significant contributions to AUC_G (Table 8). Specifically, as depicted in Figure 6a, high maternal depressive symptoms predicted elevated maternal total cortisol output in the SSP for mothers in non-secure attachment relationships with their infants, but not for mothers in secure attachment relationships with their infants. Analyses were then conducted to determine which specific attachment classifications drove this interaction (Figure 6b). There was a significant association between maternal depressive symptoms and maternal AUC_G for resistant dyads ($r = .31$, $p < .05$) and disorganized dyads ($r = .45$, $p < .01$), but not for avoidant ($r = -.03$, *ns*) or secure ($r = -.11$, *ns*) dyads. As above, in order to address Luijk et al.'s (2010) suggestion that the disorganization findings may be driven by underlying

resistant strategies, we examined the association between maternal depressive symptoms and maternal AUC_G for disorganized dyads who did not have an underlying resistant classification. The association was significant, $r = .43$, $p < .05$[6]. Taken together, high maternal depressive symptoms, in combination with non-secure (specifically resistant and disorganized) attachment, predicted elevated maternal total cortisol output in the SSP.

Table 8

Multiple Regression Analyses to Predict Maternal AUC_G in Strange Situation from Maternal Depressive Symptoms, Mother-Infant Attachment, and their Interaction

	β(*SE*)
Maternal Depressive Symptoms	.01(.003)**
Attachment	.02(.03)
Maternal Depressive Symptoms x Attachment	-.01(.01)**

Note. AUC_G = area under the curve ground, i.e., total cortisol output. Attachment was coded dichotomously as 0 (*not secure*) or 1 (*secure*).

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

[6] Furthermore, we re-ran the main analysis when controlling for ABC resistance (i.e., when controlling for whether or not dyads had a primary or secondary resistant classification). ABCD attachment security (i.e., whether or not dyads had a primary secure classification) interacted with maternal depressive symptoms to predict maternal AUC_G in the SSP at a marginally significant level ($p = .07$, data not shown).

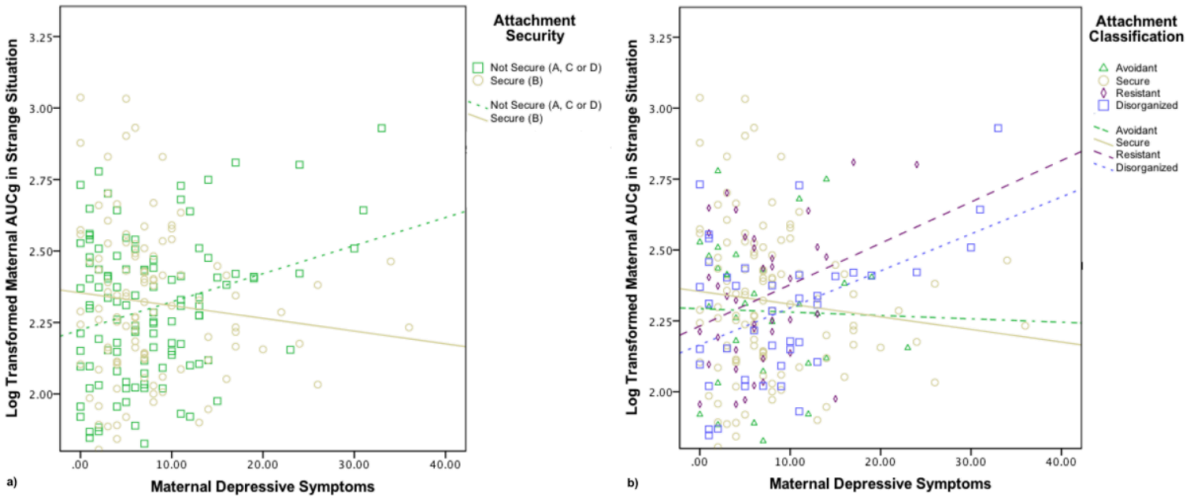

Figure 6. Mother-infant attachment security moderates the relation between maternal depressive symptoms and maternal total cortisol output (AUC_G) in the Strange Situation Procedure. Maternal depressive symptoms predict elevated maternal total cortisol output, but only for mothers in non-secure (a), specifically resistant and disorganized (b), relationships.

Discussion

The current study examined the influences of maternal depressive symptoms, mother-infant attachment, and their interaction, on infant and maternal total cortisol output in the context of the SSP. Results were consistent for both infants and mothers. Specifically, for both infants and mothers, maternal depressive symptoms significantly predicted elevated total cortisol output, and this link was moderated by mother-infant attachment. For both infants and mothers, this moderating effect was driven by resistant and disorganized attachment such that maternal depressive symptoms were associated with elevated total cortisol output only for infants and mothers in resistant and disorganized attachment relationships.

Previous research has shown that maternal depressive symptoms are associated with elevated infant cortisol secretion, and that such associations are moderated by several factors, many of which are conceptually associated with emotion regulation (Khoury et al., 2015a). For

example, the association between maternal depressive symptoms and elevated child cortisol secretion is stronger for children with less positive emotionality (Mackrell et al., 2014), higher internalizing symptoms (Ashman et al., 2002), and a tendency to utilize independent regulatory strategies (as opposed to relying on the mother, Khoury et al., 2015a). The current study conceptually replicates these studies, supporting evidence that mother-infant attachment security, which reflects an infant's strategy for regulating emotions in the context of the maternal relationship (Ainsworth et al., 1978; Malik et al., 2015; Moutsiana et al., 2014), moderates the association between maternal depressive symptoms and infant cortisol secretion in the SSP. Our results suggest that when infants are exposed to maternal depressive symptoms and are not securely attached (i.e., cannot consistently rely on their caregivers to regulate their emotions effectively), they experience over-activation of the HPA axis. Interestingly, the current findings emerged over and above the impact of maternal sensitivity. This may suggest that it is not the depressed mother's behaviour towards the child per se (or at least not her sensitivity) that places the child at risk for elevated cortisol secretion. An alternate possibility is that a mother's inability to regulate her depressed affect, which is linked to child emotion regulation ability (Pat Horenczyk et al., 2015; Gratz et al., 2014), places her child at risk for elevated cortisol secretion.

Given the inconsistencies in the literature with respect to associations between attachment classifications and infant cortisol secretion, it is notable that the current results replicate Luijk et al.'s (2010) findings that the combination of resistant attachment and maternal depressive symptoms elevates risk for high infant cortisol secretion in the SSP. On the other hand, unlike Luijk et al. (2010), and as hypothesized, we also linked disorganized attachment (in the context of maternal depressive symptoms) to elevated infant cortisol secretion in the SSP. This finding was not merely attributable to underlying resistant classifications, as suggested by

Luijk et al. (2010). Of note, Luiik et al. (2010) used an abbreviated version of the SSP in their study. It is possible that this abridged version was slightly less stressful for infants (and we know that lab challenges vary greatly in terms of impact on stress physiology; Jansen et al., 2010), thereby attenuating the disorganization effect and provoking stress primarily for resistant infants (who have a lower threshold for attachment-related distress than other classifications, Ainsworth et al., 1978). Accordingly, several studies with smaller samples have linked disorganized attachment to infant cortisol secretion utilizing the full length SSP (Bernard & Dozier, 2010; Hertsgaard et al., 1995; Spangler & Grossman, 1993).

An important contribution of the current study is that we extend our findings to maternal cortisol secretion, which has very rarely been examined in relation to maternal depressive symptoms and mother-infant attachment. Our maternal findings were equivalent to our infant findings such that both maternal depressive symptoms and the interaction of maternal depressive symptoms and mother-infant attachment security significantly predicted total cortisol output in the SSP. Given that both adult depression and adult attachment have been associated with emotion regulation (Malik et al., 2015), and that there is significant concordance between maternal and infant attachment classifications (Verhage et al., 2016), emotion regulation may be a mechanism underlying our maternal findings as well. In other words, the transactional nature of the mother-infant relationship may impact maternal cortisol secretion by serving as an important context in which a mother regulates her affect. For example, a depressed mother's secure attachment relationship with her infant may provide positive reinforcement and prevent behavioral avoidance (e.g., reduced infant interactions, McLearn et al., 2006) and depressive cognitions related to parenting (Kohlhoff & Barnett, 2013), which may in turn buffer against elevated cortisol secretion. Consistent with this hypothesis, Letourneau et al. (2011) found that

higher levels of infant interactive behaviours (i.e., clarity of cues to mother, responsiveness to caregiver) were associated with lower cortisol levels among mothers with postpartum depression.

Of note, in addition to emotion regulation, factors such as oxytocin levels (Feldman et al., 2007; Gordon et al., 2008), genetic characteristics (Ludmer et al., 2017), and glucocorticoid receptor methylation (Meaney & Szyf, 2005) may impact the associations between maternal depressive symptoms and maternal and infant cortisol secretion. However, the construct of emotion regulation appears to be the most consistently observed, and perhaps most important, moderator of the relationship between maternal depressive symptoms and cortisol secretion (Ashman et al., 2002; Khoury et al., 2015a; Luijk et al., 2010; Mackrell et al., 2014).

The impact of maternal depressive symptoms and attachment security on cortisol secretion is particularly important because chronic over-activation of the HPA axis, or allostatic load, can accelerate physical and psychological diseases processes (McEwen, 2000). Attachment-based interventions are known to be effective at improving the quality of mother-child attachment (Berlin, Zeanah, & Lieberman, 2016), as well as infant (Dozier et al., 2008) and maternal (e.g., Field et al., 1998; Toth et al., 2015; Urizar & Munoz, 2011) cortisol secretion patterns. The current findings that infants and mothers in secure attachment relationships are protected from the high cortisol levels associated with maternal depressive symptoms could be taken to suggest that attachment-based interventions may not only directly improve the quality of mother-infant relationships and cortisol secretion patterns, but may also buffer or reverse the impact of maternal depressive symptoms on both maternal and infant cortisol secretion patterns. In turn, this could potentially reduce the intergenerational transmission of depressive symptoms (Halligan et al., 2007). Furthermore, our use of a community sample supports the potential utility of population-based preventative interventions aimed at enhancing mother-infant attachment and

reducing the intergenerational transmission of dysregulated cortisol secretion patterns and depressive symptoms.

In terms of study limitations, we utilized maternal reports of depressive symptoms at a single time point. The timing of depressive symptoms (Brennan et al., 2008) as well as changes in maternal depressive symptoms across time (Laurent et al., 2011) can impact associations with cortisol secretion. Further studies are needed to determine the role of timing and symptom changes within the associations between attachment security and maternal and infant cortisol secretion. Another limitation is that, due to reluctance to attend the laboratory (as opposed to home) visit, dyads with attachment classifications, relative to dyads without classifications, were more likely to involve older mothers and mothers who were currently working. As such, results may not generalize to younger or unemployed mothers. However, all results were equivalent when analyzed with the original dataset (with missing data deleted listwise) and with the dataset with imputed variables. Future studies might also test the current model in higher risk (e.g., low income) or clinical samples, because such samples typically have high rates of non-secure attachment, and show stronger associations between maternal depressive symptoms and mother-infant attachment security (Lyons-Ruth & Jacobvitz, 2016).

Conclusions

In summary, attachment security moderates the relation between maternal depressive symptomatology and both infant and maternal total cortisol output. Specifically, higher levels of maternal depressive symptoms predict higher total cortisol output for infants and for mothers in the SSP, but only if they are in non-secure (specifically resistant or disorganized) attachment relationships. Findings suggest that secure attachment may protect both infants and mothers from

the high cortisol secretion levels associated with maternal depressive symptomatology, thus supporting the potential utility of attachment-based preventative interventions.

Chapter 4: General Discussion

Studies have indicated that the early rearing environment has an enduring influence on offspring cortisol secretion (e.g., Halligan et al., 2007; Tyrka et al., 2012). However, the early rearing environment does not predict cortisol secretion levels for all individuals, pointing to the role of moderating factors (e.g., Ludmer et al., 2015; Luijk et al., 2010). This dissertation examined potential genetic and psychosocial moderators of the associations between the early rearing environment and infant and maternal cortisol secretion.

My Master's thesis found that maternal depressive symptomatology (a key marker of an adverse early rearing environment, Dougherty et al., 2013; Halligan et al., 2007; Weissman et al., 2006) predicted infant cortisol secretion, but only for infants with 10-repeat alleles of *SLC6A3* and A1 alleles of *DRD2* (Ludmer et al., 2015). Study 1 of this dissertation attempted to replicate this model in the infants' mothers, as well as examine *OXTR* genotype as an additional moderator. Partially replicating, as well as extending, my Master's findings, Study 1 revealed that the association between maternal early rearing environment (operationalized as history of care) and maternal cortisol levels is stronger for mothers with 10-repeat alleles of *SLC6A3* and G alleles of *OXTR,* relative to mothers without these alleles. It is notable that I assessed mothers in the same sample as the infants included in my Master's thesis, and in the context of the very same challenge. As such, the conceptual replication of the *SLC6A3* x early rearing environment interaction to predict cortisol levels augments confidence in the finding and extends it across a generation. This is important given that replications in psychological research are rare (Makel et al., 2012) and that the majority of gene x environment interaction studies fail to replicate (Duncan & Keller, 2011).

Further extending my Master's work, Study 2 assessed whether the quality of mother-infant attachment moderates the association between maternal depressive symptoms and infant cortisol secretion. Results revealed that maternal depressive symptomatology predicts elevated total cortisol output, but only for infants in non-secure (specifically resistant and disorganized) attachment relationships. These results conceptually replicate several studies that identified emotion regulation (or variables closely conceptually associated with emotion regulation) as a moderator of associations between maternal depressive symptoms and infant cortisol secretion (Ashman et al., 2002; Khoury et al., 2015a; Luijk et al., 2010; Mackrell et al., 2014). Secure attachment is theorized to augment the infant's ability to manage affect and cope with stress in a variety of challenging situations, whereas non-secure attachment may interfere with the capacity to manage and regulate emotion effectively. As such, Study 2 supports the notion that the infant's ability to regulate their emotions in the context of their attachment relationship influences the degree to which their cortisol secretion is impacted by maternal depressive symptomatology.

Study 2 further extended the maternal depressive symptoms x mother-infant attachment interaction model to mothers. Specifically, it examined the association between maternal depressive symptoms and maternal cortisol secretion, and whether mother-infant attachment security moderates this association. Results were equivalent to the infant findings. That is, maternal depressive symptoms were associated with elevated maternal total cortisol output, but only for mothers in non-secure (specifically resistant or disorganized) attachment relationships with their infants. This supports the idea that the mother-infant attachment relationship serves as an important context in which mothers (in addition to infants) regulate their affect. My findings

support the notion that such regulation of affect influences the degree to which maternal cortisol secretion is impacted by depressive symptomatology.

Taken together, the two studies comprising my dissertation support the notion that the associations between the early rearing environment and maternal and infant cortisol secretion are impacted by genetic characteristics and the mother-infant attachment relationship. From a developmental psychopathology perspective (Rutter & Sroufe, 2000), genetic characteristics and mother-infant attachment may serve as risk and resilience factors, and may facilitate continuity and change in risk for the mental and physical health outcomes associated with suboptimal cortisol secretion patterns. Future longitudinal studies can build upon my work and examine my interaction models as they predict maternal and infant psychopathology and physical disease.

My dissertation results have important clinical implications. Specifically, they suggest that the effectiveness of early preventative interventions may vary based on maternal and infant genetic characteristics and attachment quality. Accordingly, preliminary studies support these ideas (Bakermans-Kranenburg et al., 2008; Cassidy et al., 2011; Bakermans-Kranenburg et al., 2008). For example, parent-child early interventions are most effective for infants with specific dopamine-related genotypes (Bakermans-Kranenburg et al., 2008) and for dyads with a "match" between maternal attachment style and infant irritability (Cassidy et al., 2011). Future studies can build upon this work to develop personalized or tailored interventions that most closely match client characteristics and presenting concerns. Furthermore, my use of a community sample supports the potential utility of population-based preventative interventions aimed at reducing the intergenerational transmission of poor mother-infant interactions, dysregulated cortisol secretion patterns, and depressive symptoms.

In conclusion, this dissertation augments our understanding of the relations between the early rearing environment and maternal and infant cortisol secretion. Findings suggest that genetic characteristics and the quality of mother-infant attachment can impact the degree to which the early rearing environment shapes maternal and infant cortisol secretion patterns. As such, genetic characteristics and mother-infant attachment may be conceptualized as markers that shape the extent of individual vulnerability and resilience.

Appendix 1: Multilevel Model Equation for *DRD2* x Maternal History of Care Interaction Predicting Maternal Log Cortisol

Level-1 Model

$$\text{Log Cortisol} = P_0 + P_1 * (\textit{Linear Time}) + e$$

Level-2 Model

$$P_0 = \beta_{00} + \beta_{01} * (\textit{PBI}) + \beta_{02} * (\textit{DRD2}) + \beta_{03} * (\textit{PBI x DRD2}) + \text{r0}$$

$$P_1 = B_{10} + r1$$

$$P_2 = B_{20} + r2$$

Mixed Model

$$\text{Log Cortisol} = \beta_{00} + \beta_{01} * (\textit{PBI}) + \beta_{02} * (\textit{DRD2}) + \beta_{03} * (\textit{PBI x DRD2})$$

$$+ \beta_{10} * (\textit{Linear Time})$$

$$+ r0 + r1 * (\textit{Linear Time}) + e$$

Appendix 2: Multilevel Model Equation for *SLC6A3* x Maternal History of Care Interaction Predicting Maternal Log Cortisol

Level-1 Model

$$\text{Log Cortisol} = P_0 + P_1 * (\textit{Linear Time}) + e$$

Level-2 Model

$$P_0 = \beta_{00} + \beta_{01} * (\textit{PBI}) + \beta_{02} * (\textit{SLC6A3}) + \beta_{03} * (\textit{PBI x SLC6A3}) + \beta_{04} * (\textit{Ethnicity}) + \beta_{05} * (\textit{PBI x Ethnicity}) + \beta_{06} * (\textit{SLC6A3 x Ethnicity}) + r0$$

$$P_1 = B_{10} + r1$$

$$P_2 = B_{20} + r2$$

Mixed Model

$$\text{Log Cortisol} = \beta_{00} + \beta_{01} * (\textit{PBI}) + \beta_{02} * (\textit{SLC6A3}) + \beta_{03} * (\textit{PBI x SLC6A3}) + \beta_{04} * (\textit{Ethnicity}) + \beta_{05} * (\textit{PBI x Ethnicity}) + \beta_{06} * (\textit{SLC6A3 x Ethnicity}) + \beta_{10} * (\textit{Linear Time}) + r0 + r1 * (\textit{Linear Time}) + e$$

Appendix 3: Multilevel Model Equation for *OXTR* x Maternal History of Care Interaction Predicting Maternal Log Cortisol

Level-1 Model

$$\text{Log Cortisol} = P_0 + P_1 * (\textit{Linear Time}) + e$$

Level-2 Model

$$P_0 = \beta_{00} + \beta_{01} * (\textit{PBI}) + \beta_{02} * (\textit{OXTR}) + \beta_{03} * (\textit{PBI x SLC6A3}) + \beta_{04} * (\textit{Ethnicity}) + \beta_{05} * (\textit{PBI x Ethnicity}) + \beta_{06} * (\textit{OXTR x Ethnicity}) + r0$$

$$P_1 = B_{10} + r1$$

$$P_2 = B_{20} + r2$$

Mixed Model

$$\text{Log Cortisol} = \beta_{00} + \beta_{01} * (\textit{PBI}) + \beta_{02} * (\textit{OXTR}) + \beta_{03} * (\textit{PBI x OXTR}) + \beta_{04} * (\textit{Ethnicity}) + \beta_{05} * (\textit{PBI x Ethnicity}) + \beta_{06} * (\textit{OXTR x Ethnicity}) + \beta_{10} * (\textit{Linear Time}) + r0 + r1 * (\textit{Linear Time}) + e$$

References

Abidin, R. R. (1995). Parenting Stress Index. Professional manual (3rd ed.). Odessa, FL: Psychological Assessment Resources.

Ainsworth, M. D. (1967). *Infancy in Uganda: Infant care and the growth of love.* Baltimore: Johns Hopkins University Press.

Ainsworth, M. D. S., Bell, S. M., & Stayton, D. J. (1971). Individual differences in the strange-situation behavior of one-year-olds. In H. R. Schaffer (Ed.), *The origins of human social relations* (pp. 17-58). San Diego, CA: Academic Press.

Ainsworth, M. D. S., Blehar, M. C., Waters, E., & Wall, S. (1978). *Patterns of attachment: A psychological study of the strange situation*. Erlbaum, Hillsdale, NJ.

Alexander, N., Osinsky, R., Mueller, E., Schmitz, A., Guenthert, S., Yvonne, K., & Hennig, J. (2011). Genetic variants within the dopaminergic system interact to modulate endocrine stress reactivity and recovery. *Behavioral Brain Research, 216*, 53-58. doi:10.1016/j.bbr.2010.07.003

Allen, J. P., Manning, N., & Meyer, J. (2010). Tightly linked systems: Reciprocal relations between maternal depressive symptoms and maternal reports of adolescent externalizing behavior. *Journal of Abnormal Psychology, 119*, 825-835.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Apter-Levi, Y., Pratt, M., Vakart, A., Feldman, M., Zagoory-Sharon, O., & Feldman, R. (2016). Maternal depression across the first years of life compromises child psychosocial adjustment; relations to child HPA-axis functioning. *Psychoneuroendocrinology, 64*, 47-56. doi:10.1016.j.psyneuen.2015.11.006

Ashman, S. B., Dawson, G., Panagiotides, H., Yamada, E., & Wilkinson, C. W. (2002). Streess hormone levels of children of depressed mothers. *Development and Psychopathology, 14*, 333-349. doi:10.1017/S0954579402002080

Atkinson, L., Gonzalez, A., Kashy, D.A., Basile, V.S., Masellis, M., Pereira, J… (2013). Maternal sensitivity and infant and mother adrenocortical function across challenges. *Psychoneuroendocrinology, 38*, 2943-2951. http://dx.doi.org/10.1016/j.psyneuen.2013.08.001

Atkinson, L., Jamieson, B., Khoury, J., Ludmer, J. A., & Gonzalez, A. (2016). Stress physiology in infancy and early childhood: Cortisol flexibility, attunement, and coordination. *Journal of Neuroendocrinology*, *28*. doi:10.1111/jne.12408

Atkinson, L., Paglia, A., Coolbear, J., Niccols, A., Poulton, L., Leung, E., & Chisholm, V. C. (2000). L'evaluation de la sensibilite maternelle dans le context de la securite d'attachment: Une meta-analyse. [Assessing maternal sensitivity in the context of attachment security: a meta-analysis] In: Tarabulsy, G. M., Larose, S., Pederson, D. R., Moran, G. (Eds.), Attachment et Developpment: Le Role des Premieres Relations dans le Developpment Humain. [Attachment and Development: The Role of First Relationships in Human Development.] Presses de l'Universite du Quebec, Quebec, pp. 27-56.

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2008). Oxytocin receptor (*OXTR*) and serotonin transporter (*5-HTT*) genes associated with observed parenting. *SCAN*, *3*, 128-134.

Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., Mesman, J., Alink, L. R., & Juffer, F. (2008). Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: A randomized control trial on 1-to 3-year-olds screened for

externalizing behavior. *Development and Psychopathology*, *20*, 805-820. doi:10.1017/S0954579408000382

Barry, T. J., Murray, L., Fearson, R. M .P., Moutsiana, C., Cooper, P., Goodyer, I. M., Herbert, J., & Halligan, S. L. (2015). Maternal postnatal depression predicts altered offspring biological stress reactivity in adulthood. *Psychoneuroendocrinology, 52*, 251-260. doi:10.1016/j.psyneuen.2014.12.003

Bartels, M., de Geus, E. J., Kirschbaum, C., Sluyter, F., & Boomsma, D. I. (2003). Heritability of daytime cortisol levels in children. *Behavior Genetics, 33*, 421-433.

Bartels, M., van den Berg, M., Sluyter, F., Boomsma, D. I., & de Geus, E. J. (2003). Heritability of cortisol levels: review and simultaneous analysis of twin studies. *Psychoneuroendocrinology, 28*, 121-137.

Beach, S. R., Brody, G. H., Lei, M. K., Kim, S., Cui, J., & Philibert, R. A. (2014). Is serotonin transporter genotype associated with epigenetic susceptibility or vulnerability? Examination of the impact of socioeconomic status risk on African American youth. *Development and psychopathology*, *26*, 289-304. doi:10.1017/S0954579413000990

Beck, A. T., Steer, R. A., Brown, G. K. (1996). *Beck Depression Inventory manual*, 2nd ed. The Psychological Corporation, San Antonio, TX.

Beijers, R., Riksen-Walraven, M., Sebesta, K., & de Weerth, C. (2017). Associations between behavioral and cortisol responses to a stressor in securely versus insecurely attached infants. *Behavioural Brain Research, 325*, 147-155. doi:10.1016/j.bbr.2016.10.008

Belda, X., & Armario, A. (2009). Dopamine D1 and D2 dopamine receptors regulate immobilization stress-induced activation of the hypothalamus-pituitary-adrenal axis. *Psychopharmacology, 206*, 355-365.

Belsky, J. (1997a). Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry, 8*, 182-186.

Belsky, J. (1997b). Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: The case of mothering and attachment. *Child Development, 68*, 598-600.

Belsky, J. (2005). Differential susceptibility to rearing influence: An evolutionary hypothesis and some evidence. In B. Ellis & D. Bjorklund (Eds.), *Origins of the social mind: Evolutionary psychology and child development* (pp. 139-163). New York: Guilford.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135*, 885-908. doi:10.1037/a0017376

Berlin, L. J., Zeanah, C. H., & Lieberman, A. F. (2016). Prevention and intervention programs to support early attachment security: A move to the level of the community. In J. Cassidy & P. R. Shaver (Eds.). Handbook of attachment: Theory, research, and clinical applications (pp 739-758). New York: Guilford.

Bernard, K., & Dozier, M. (2010). Examining infants' cortisol responses to laboratory tasks among children varying in attachment disorganization: stress reactivity or return to baseline? *Developmental Psychology*, *46*, 1771. doi:10.1037/a0020660

Bernard, N. K., Kashy, D. A., Levendosky, A. A., Bogat, G. A., & Lonstein, J. S. (2016). Do different analytic approaches generate discrepant findings when measuring mother-infant HPA axis attunement? *Developmental Psychobiology, 59*, 174-184. doi:10.1002/dev.21474

Bhagwagar, Z., Hafizi, S., & Cowen, P. J. (2005). Increased salivary cortisol after waking in depression. *Psychopharmacology, 182*, 54-57.

Blair, C., Granger, D., & Peters Razza, R. (2005). Cortisol reactivity is positively related to executive function in preschool children attending Head Start. *Child Development*, *76*, 554-567. doi:10.1111/j.1467-8624.2005.00863

Bowlby, J. (1969). *Attachment and loss: Attachment.* New York, NY: Basic Books.

Bowlby, J. (1973). *Attachment and loss: Separation*. New York, NY: Basic Books.

Bowlby, J. (1980). *Attachment and loss: Loss sadness and depression*. New York, NY: Basic Books.

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17*, 271-301. doi:10.1017/S0954579405050145

Bradley, B., Westen, D., Mercer, K.B., Binder, E.B., Jovanovic, T., Crain, D . . . Heim, C. (2011). Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: Moderation by oxytocin receptor gene. *Development and Psychopathology, 23*, 439-452. doi:10.1017/S0954579411000162

Brennan, P. A., Pargas, R., Walker, E. F., Green, P., Newport, D. J., & Stowe, Z. (2008). Maternal depression and infant cortisol: Influences of timing, comorbidity and treatment. *The Journal of Child Psychology and Psychiatry, 49*, 1099-1107. doi:10.1111/j.1469-7610.2008.01914.x

Cassidy, J. (2008). The nature of the child's ties. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research, and clinical applications* (pp. 3-22). New York, NY, US: Guildford Press.

Cassidy, J., Woodhouse, S. S., Sherman, L. J., Stupica, B., & Lejuez, C. W. (2011). Enhancing infant attachment security: An examination of treatment efficacy and differential

susceptibility. *Development and Psychopathology*, *23*, 131. doi:10.1017/S0954579410000696

Cauter, E. V., Leproult, R., & Kupfer, D. J. (1996). Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *The Journal of Clinical Endocrinology & Metabolism, 81*, 2468-2473. doi:10.1210/jcem.81.7.8675562

Ceccatelli, S., Tamm, C., Zhang, Q., & Chen, M. (2007). Mechanisms and modulation of neural cell damage induced by oxidative stress. *Physiology & Behavior*, *92*, 87-92. doi:10.1016/j.physbeh.2007.05.048

Chen, F. S., Kumsta, R., von Dawans, B., Monakhov, M., Ebstein, R. P., & Heinrichs, M. (2011). Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. *Proceedings of the National Academy of Sciences of the USA, 108*, 19937-19942.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*, 385-396.

Collins, L. M., Schafer, J. L., & Kam, C. M. (2001). A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychological Methods, 6*, 330-351.

Crockett, E. E., Holmes, B. M., Granger, D. A., & Lyons-Ruth, K. (2013). Maternal disrupted communication during face-to-face interaction at 4 months: Relation to maternal and infant cortisol among at-risk families. *Infancy, 18*, 1111-1134. doi:10.1111/infa.12015

Crugnola, C. R., Ierardi, E., Ferro, V., Gallucci, M., Parodi, C., & Astengo, M. (2016). Mother-infant emotion regulation at three months: The role of maternal anxiety, depression and parenting stress. *Psychopathology, 49*, 285-294. doi:10.1159/000446811

Dalton, E. D., Hammen, C. L., Najman, J. M., & Brennan, P. A. (2014). Genetic susceptibility to family environment: BDNF Val66met and 5-HTTLPR influence depressive symptoms. *Journal of Family Psychology*, *28*, 947. doi:10.1037/fam0000032

Davis, E. P., Bruce, J., & Gunnar, M. R. (2002). The anterior attention network: Associations with temperament and neuroendocrine activity in 6-year-old children. *Developmental Psychobiology*, *40*, 43-56. doi:10.1002/dev.10012

Davis, E. P., & Granger, D. A. (2009). Developmental differences in infant salivary alpha-amylase and cortisol responses to stress. *Psychoneuroendocrinology*, *34*, 795-804.

Davis, M., & Emory, E. (1995). Sex differences in neonatal stress reactivity. *Child Development, 66*, 14-67. doi:10.1111/j.1467-8624.1995.tb00852.x

Debiec, J., & Sullivan, R. M. (2014). Intergenerational transmission of emotional trauma through amygdala-dependent mother-to-infant transfer of specific fear. *PNAS, 111*, 12222-12227. doi:10.1073/pnas.1316740111

Del Giudice, M. (2016). The evolution of interaction shape in differential susceptibility. *Child Development*. http://dx.doi.org/10.1111/cdev.12710

Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The adaptive calibration model of stress responsivity. *Neuroscience & Biobehavioral Reviews, 35*, 1562-1592. doi:10.1016/j.neubiorev.2010.11.007

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*, 355.

Dougherty, L. R., Smith, V. C., Olino, T. M., Dyson, M. W., Bufferd, S. J., Rose, S. A., & Klein, D. N. (2013). Maternal psychopathology and early child temperament predict young

children's salivary cortisol 3 years later. *Journal of Abnormal Child Psychology, 41*, 531-542. doi:10.1007/s10802-012-9703-y

Dozier, M., Peloso, E., Lewis, E., Laurenceau, J. P., & Levine, S. (2008). Effects of an attachment-based intervention on the cortisol production of infants and toddlers in foster care. *Development and Psychopathology, 20*, 845-859. doi:10.1017/S0954579408000400

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168*, 1041-1049.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology, 23*, 7-28. doi:10.1017/S0954579410000611

Engert, V., Buss, C., Khalili-Mahani, N., Wadiwalla, M., Dedovic, K., & Pruessner, J. C. (2010). Investigating the association between early parental care and stress responsivity in adulthood. *Developmental Neuropsychology, 35*, 570-581. doi:10.1080/87565641.2010.494752

Engert, V., Efanov, S. I., Dedovic, K., Duchesne, A., Dagher, A., & Pruessner, J. C. (2009). Perceived early-life maternal care and the cortisol response to repeated psychosocial stress. *Journal of Psychiatry and Neuroscience, 35*, 370-377.

Fan, Y., Herrera-Melendez, A. L., Pestke, K., Feeser, M., Aust, S., Otte, C., ... & Grimm, S. (2014). Early life stress modulates amygdala-prefrontal functional connectivity: Implications for oxytocin effects. *Human brain mapping*, *35*, 5328-5339.

Fekedulegn, D. B., Andrew, M. E., Burchfiel, C. M., Violanti, J. M., Hartley, T. A., Charles, L. E., & Miller, D. B. (2007). Area under the curve and other summary indicators of repeated waking cortisol measurements. *Psychosomatic Medicine*, *69*, 651-659. doi:10.1097/PSY.0b013e31814c405c

Feldman, R., Grant, A., Pariente, C., Kanety, H., Kuint, J., & Gilboa-Schechtman, E. (2009). Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*, 919-927. doi:10.1097/CHI.0b013e3181b21651

Feldman, R., Weller, A., Zagoory-Sharon, O., & Levine, A. (2007). Evidence for a neuroendocrinological foundation of human affiliation plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. *Psychological Science*, *18*, 965-970.

Field, T. M., Scafidi, F., Pickens, J., Prodromidis, M., Pelaez-Nogueras, M., Torquati, J…Kuhn, C. (1998). Polydrug-using adolescent mothers and their infants receiving early intervention. *Adolescence, 33*, 117-143.

Fisher, D., Serbin, L. A., Stack, D. M., Ruttle, P. L., Ledingham, J. E., & Schwartzman, A. E. (2007). Intergenerational predictors of diurnal cortisol secretion in early childhood. *Infant and Child Development*, *16*, 151-170. doi:10.1002/icd.474

Forehand, R., Brody, G., Slotkin, J., Fauber, R., McCombs, A., & Long, N. (1988). Young adolescent and maternal depression: Assessment, interrelations, and family predictors. *Journal of Consulting and Clinical Psychology, 56*, 422-426.

Freedman, M. L., Reich, D., Penney, K. L., McDonald, G. J., Mignault, A. A., Patterson, N., ... & Pato, M. T. (2004). Assessing the impact of population stratification on genetic association studies. *Nature Genetics*, *36*, 388-393.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30*, 1010-1016. doi:10.1016/j.psyneuen.2005.04.006

Frigerio, A., Ceppi, E., Rusconi, M., Giorda, R., Raggi, M. E., & Fearon, P. (2009). The role played by the interaction between genetic factors and attachment in the stress response in infancy. *Journal of Child Psychology and Psychiatry*, *50*, 1513-1522. doi:10.1111/j.1469-7610.2009.02126

Garson, D. G. (2013). *Hierarchical linear modeling guide: Guide and applications*. Thousand Oaks, CA: Sage Publications.

Gilbert, K., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2017). Emotion regulation regulates more than emotion: Associations of momentary emotion regulation with diurnal cortisol in current and past depression and anxiety. *Clinical Psychological Science, 5*, 37-21. doi:10.1177/2167702616654437

Goldberg, S. (2000). *Attachment and development*. London: Arnold.

Goldberg, S., Grusec, J. E., & Jenkins, J. (1999). Confidence in protection: Arguments for a narrow definition of attachment. *Journal of Family Psychology, 13,* 475-483.

Goldberg, S., Levitan, R., Leung, E., Masellis, M., Basile, V., Nemeroff, C. B., & Atkinson, L. (2003). Cortisol concentrations in 12-18-month-old infants: Stability over time, location, and stressor. *Biological Psychiatry, 54*, 719-726.

Goodyer, I. M., Park, R. J., Netherton, C. M., & Herbert, J. (2001). Possible role of cortisol and

dehysroepiandrosterone in human development and psychopathology. *The British Journal of Psychiatry, 179*, 243-249. doi: 10.1192/bjp.179.3.243

Goodyer, I. M., Tamplin, A., Herbert, J., & Altham, P. M. E. (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *The British Journal of Psychiatry, 177*, 499-504.

Gordon, I., Zagoory-Sharon, O., Schneiderman, I., Leckman, J. F., Weller, A., & Feldman, R. (2008). Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. *Psychophysiology*, *45*, 349-352. doi:10.1111/j.1469-8986.2008.00649.x

Granger, D. A., Weisz, J. R., McCracken, J. T., Ikeda, S. C., & Douglas, P. (1996). Reciprocal influences among adrenocortical activation, psychosocial processes, and the behavioral adjustment of clinic-referred children. *Child Development, 67*, 3250-3262.

Gratz, K. L., Kiel, E. J., Latzman, R. D., Elkin, T. D., Moore, S. A., & Tull, M. T. (2014). Maternal borderline personality pathology and infant emotion regulation: Examining the influence of maternal emotion-related difficulties and infant attachment. *Journal of Personality Disorders, 28*, 52-69.

Gunnar, M. R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology, 27*, 199-220. doi:10.1016/S036-4530(01)00045-2

Gunnar, M. R., & Hostinar, C. E. (2015). The social buffering of the hypothalamic-pituitary-adrenocortical axis in humans: Developmental and experiential determinants. *Social Neuroscience, 10*, 479-488. doi:10.1080/17470919.2015.1070747

Gunnar, M. R., & White, B. P. (2001). Salivary cortisol measures in infant and child assessment. In: Singer, L. T., Zeskind, P. S. (Eds.), *Behavioral Assessment of the Infant.* Guilford Press, New York, pp. 167-189.

Gustafsson, P. E., Anckarsäter, H., Lichtenstein, P., Nelson, N., & Gustafsson, P. A. (2010). Does quantity have a quality all its own? Cumulative adversity and up- and down-regulation of circadian salivary cortisol levels in healthy children. *Psychoneuroendocrinology, 35*, 1410-1415. doi:10.1016/j.psyneuen.2010.04.004

Halligan, S. L., Herbert, J., Goodyer, I. M., Murray, L. (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. *Biological Psychiatry, 55*, 376-381. doi:10.1016/j.biopsych.2003.09.013

Halligan, S. L., Herbert, J., Goodyer, I. M., Murray, L. (2007). Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biological Psychiatry, 62*, 40-46. doi:10.1016/j.biopsych.2006.09.011

Hankin, B. L., Badanes, L. S., Smolen, A., & Young, J. F. (2015). Cortisol reactivity to stress among youth: Stability over time and genetic variants for stress sensitivity. *Journal of Abnormal Psychology, 1*, 54-67. doi:10.1037/abn0000030

Haskett, M. E., Ahern, L. S., Ward, C. S., & Allaire, J. C. (2006). Factor structure and validity of the Parenting Stress Index-Short Form. Journal of Clinical Child and Adolescent Psychology, 35, 302–312.

Hatzinikolaou, K., & Murray, L. (2010). Infant sensitivity to negative maternal emotional shifts: Effects of infant sex, maternal postnatal depression, and interactive style. *Infant Mental Health Journal, 31*, 591-610. doi:10.1002/imhj.20265

Hellhammer, D. H., Wust, S., & Kudielka, B. M. (2009) Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology, 34*, 163-171.

Herd, M., Whittingham, K., Sanders, M., Colditz, P., & Boyd, R. N. (2014). Efficacy of preventative parenting interventions for parents of preterm infants on later child behavior: A systematic review and meta-analysis. *Infant Mental Health Journal, 35*, 630-641.

Hertsgaard, L., Gunnar, M., Erickson, M. F., & Nachmias, M. (1995). Adrenocortical responses to the strange situation in infants with disorganized/disoriented attachment relationships. *Child Development*, *66*, 1100-1106. doi:10.1111/j.1467-8624.1995.tb00925.x

Hesse, E., & Main, M. (2000). Disorganized infant, child, and adult attachment: Collapse in behavioral and attentional strategies. *Journal of the American Psychoanalytic Association, 48*, 1097-1127.

Hesse, E., & Main, M. (2006). Frightened, threatening, and dissociative parental behavior in low-risk samples: Description, discussion, and interpretations. *Development and Psychopathology, 18*, 309-343.

Hewitt, P. L., Flett, G. L., & Mosher, S. W. (1992). The perceived stress scale: Factor structure and relation to depression symptoms in a psychiatric sample. *Journal of Psychopathology and Behavioral Assessment, 14*, 247-257.

Hibel, L. C., Granger, D. A., Blair, C., & Cox, M. J. (2009). Intimate partner violence moderates the association between mother–infant adrenocortical activity across an emotional challenge. *Journal of Family Psychology*, *23*, 615.

Hostinar, C. E., & Gunnar, M. R. (2013). Future directions in the study of social relationships as regulators of the HPA axis across development. *Journal of Clinical Child and Adolescent Psychology*, *42*, 564-575. doi:10.1080/15374416.2013.804387

Hruschka, D. J., Kohrt, B. A., & Worthman, C. M. (2005). Estimating between-and within-individual variation in cortisol levels using multilevel models. *Psychoneuroendocrinology*, *30*, 698-714.

Jansen, J., Biejers, R., Riksen-Walraven, M., & de Weerth, C. (2010). Cortisol reactivity in young infants. *Psychoneuroendocrinology, 35*, 329-338. doi:10.1016/j.psyneuen.2009.07.008

Jawahar, M. C., Murgatroyd, C., Harrison, E. L., & Baune, B. T. (2015). Epigenetic alterations following early postnatal stress: a review on novelaetiological mechanisms of common psychiatric disorders. *Clinical Epigenetics, 7*, 1-13. doi:10.1186/s13148-015-0156-3

Jessop, D. S., & Turner-Cobb, J. M. (2008). Measurement and meaning of salivary cortisol: A focus on health and disease in children. *Stress, 11*, 1-14. doi:10.1080/10253890701365527

Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240*, 167-171.

Keller, M. C. (2014). Gene-by-environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. *Biological Psychiatry, 75*, 18-24.

Khoury, J. E., Gonzalez, A., Levitan, R., Masellis, M., Basile, V., & Atkinson, L. (2015a). Infant Emotion Regulation Strategy Moderates Relations between Self-Reported Maternal Depressive Symptoms and Infant HPA Activity. *Infant and Child Development*, *25*, 64-83. doi:10.1002/icd.1916

Khoury, J. E., Gonzalez, A., Levitan, R., Masellis, M., Basile, V., & Atkinson, L. (2016). Maternal self-reported depressive symptoms and maternal cortisol levels interact to

predict infant cortisol levels. *Infant Mental Health Journal, 37*, 125-139. doi:10.1002/imhj.21554

Khoury, J. E., Gonzalez, A., Levitan, R., Pruessner, J. C., Chopra, K., Basile, V. S., Masellis, M., Goodwill, A., & Atkinson, L. (2015b). Summary cortisol reactivity indicators: Interrelations and meaning. *Neurobiology of Stress, 2*, 34-43. doi:10.1016/j.ynster.2015.04.002

Kirschbaum, C., & Hellhammer, D. (1989). Salivary cortisol in psychobiological research – an overview. *Neuropsychobiology, 22*, 150-169.

Kirschbaum, C. & Hellhammer, D. H. (1994). Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. *Psychoneuroendocrinology*, *19*, 313-333.

Kirschbaum, C., Pirke, K., & Hellhammer, D. H. (1995). Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. *Psychoneuroendocrinology, 20*, 509-514. doi:10.1016/0306-4530(94)00078-O

Kohlhoff, J., & Barnett, B. (2013). Parenting self-efficacy: Links with maternal depression, infant behavior and adult attachment. *Early Human Development, 89*, 249-256. doi:10.1016/j.earlhumdev.2013.01.008

Lasikiewicz, N., Hendrickx, H., Talbot, D., & Dye, L. (2008). Exploration of basal diurnal salivary cortisol profiles in middle-aged adults: Associations with sleep quality and metabolic parameters. *Psychoneuroendocrinology, 33*, 143-151. doi:10.1016/j.psyneuen.2007.10.013

Laurent, H. K., Ablow, J. C., & Measelle, J. (2011). Risky shifts: How the timing and course of mothers' depressive symptoms across the perinatal period shape their own and infants' stress response profiles. *Development and Psychopathology, 23*, 521-538. doi:10.1017/S0954579411000083

Laurent, H. K., Ablow, J. C., & Measelle, J. (2012). Taking stress response out of the box: Stability, discontinuity, and temperament effects on HPA and SNS across social stressors in mother-infant dyads. *Developmental Psychology, 48*, 35-45. doi:10.1037/a0025518

Letourneau, N., Watson, B., Duffett-Leger, L., Hegadoren, K., & Tryphonopoulos, P. (2011). Cortisol patterns of depressed mothers and their infants are related to maternal-infant interactive behaviours. *Journal of Reproductive and Infant Psychology, 29*, 439-459. doi:10.1080/02646838.2011.649474

Livy, A., Lye, S., Jagdish, C. K., Hanis, N., Sharmila, V., Wee Ler, L., & Pramod, B. (2012). Evaluation of quality of DNA extracted from buccal swabs for microarray based genotyping. *Indian Journal of Clinical Biochemistry*, *27*, 28-33.

Lovejoy, M., Graczyk, P. A., O'Hare, E., & Newman, G. (2000). Maternal depression and parenting behavior: A meta-analytic review. *Clinical Psychology Review, 20*, 561-592.

Ludmer, J. A., Jamieson, B., Gonzalez, A., Levitan, R., Kennedy, J., Villani, V., Masellis, M., Basile, V. S., & Atkinson, L. (2017). Maternal *DRD2, SLC6A3,* and *OXTR* genotypes as potential moderators of the relation between maternal history of care and maternal cortisol secretion in the context of mother-infant separation. *Biological Psychology, 129*, 154-164. doi:10.1016/j.biopsycho.2017.09.004

Ludmer, J.A., Levitan, R., Gonzalez, A., Kennedy, J., Villani, V., Masellis, M., Basile, V.S., & Atkinson, L. (2015). *DRD2* and *SLC6A3* moderate impact of maternal depressive

symptoms on infant cortisol. *Psychoneuroendocrinology, 62*, 243-251. https://doi.org/10.1016/j.psyneuen.2015.08.026

Luijk, M.P., Saridjan, N., Tharner, A., van IJzendoorn, M.H., Bakermans-Kranenburg, M.J., Jaddoe, V.W., ... Tiemeier, H. (2010). Attachment, depression, and cortisol: Deviant patterns in insecure-resistant and disorganized infants. *Developmental Psychobiology, 52*, 441-452. doi:10.1002/dev.20446

Lyons-Ruth, K., Jacobvitz, D., 2016. Attachment disorganization: Genetic factors, parenting contexts, and developmental transformation from infancy to adulthood, in Cassidy, J., Shaver, P.R. (Eds.), Handbook of attachment: Theory, research, and clinical applications. Guildford, New York, pp. 666-697.

Mackrell, S. V. M., Sheikh, H I., Kotelnikova, Y., Kryski, K. R., Jordan, P. L., Singh, S. M., & Hayden, E. P. (2014). Child temperament and parental depression predict cortisol reactivity to stress in middle childhood. *Journal of Abnormal Psychology, 123*, 106-116. doi:10.1037/a0035612

Main, M., & Hesse, E. (1990). Parents' unresolved traumatic experiences are related to infant disorganized attachment status: Is frightened and/or frightening parental behavior the linking mechanism? In M.T. Greenberg, D. Cicchetti, & E. M. Cummings (Eds.) *Attachment in the Preschool Years: Theory, Research, and Intervention* (pp. 161-182). University of Chicago Press, Chicago.

Main, M., & Solomon, J. (1986). Discovery of a new, insecure-disorganized/disoriented attachment pattern. In T. B. Brazelton & M. W. Yogman (Eds.), *Affective development in infancy* (pp. 95-124). Norwood, NJ: Ablex.

Main, M., & Solomon, J. (1990). Procedures for identifying infants as disorganized/disoriented during the Ainsworth Strange Situation. In M. T. Greenberg, D. Cicchetti, & E. M. Cummings (Eds.), *Attachment in the preschool years: Theory, research, and intervention* (pp. 121-160). Chicago: University of Chicago Press.

Makel, M. C., Plucker, J. A., & Hegarty, B. (2012). Replications in psychology research: How often do they occur? *Perspectives on Psychological Science, 7*, 537-542. doi:10.1177/1745691612460688

Magnano, C. L., Diamond, E. J., & Gardner, J. M. (1989). Use of salivary cortisol measurements in young infants: A note of caution. *Child Development, 60*, 1099-1101.

Malik, S., Wells, A., & Wittkowski, A. (2015). Emotion regulation as a mediator in the relationship between attachment and depressive symptomatology: A systematic review. *Journal of Affective Disorders, 172*, 428-444. doi:10.1016/j.jad.2014.10.007

Marinari, K. T., Leshner, AA. I., & Doyle, M. P. (1976). Menstrual cycle status and adrenocortical reactivity to psychological stress. *Psychoneuroendocrinology, 1*, 213-218. doi;10.1016/0306-4530(76)90011-1

McEwen, B. S. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology, 22*, 108-124. doi:10.1016/S0893-133X(99)00129-3

McLearn, K. T., Minkovitz, C. S., Strobino, D. M., Marks, E., & Hou, W. (2006). Maternal depressive symptoms at 2 to 4 months post partum and early parenting practices. *Archives of Pediatrics & Adolescent Medicine, 160*, 279-284. doi:10.1001/archpedi.160.3.279

Meaney, M. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*, 41-79. doi:10.1111/j.1467-8624.2009.01381

Meaney, M. J., & Szyf, M. (2005). Maternal care as a model for experience-dependent chromatin plasticity?. *Trends in Neurosciences*, *28*, 456-463. doi:10.1016/j.tins.2005.07.006

Middlemiss, W., Granger, D. A., Goldberg, W. A., & Nathans, L. (2012). Asynchrony of mother–infant hypothalamic–pituitary–adrenal axis activity following extinction of infant crying responses induced during the transition to sleep. *Early human development*, *88*, 227-232.

Moutsiana, C., Fearson, P., Murray, L., Cooper, P., Goodyer, I., Johnstone, T., & Halligan, S. (2014). Making an effort to feel positive; insecure attachment in infancy predicts the neural underpinnings of emotion regulation in adulthood. *The Journal of Child Psychology and Psychiatry, 55*, 999-1008. doi:10.1111/jcpp.12198

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R. H., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development*, 508-522.

Neville, M. J., Johnstone, E. C., & Walton, R. T (2004). Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23. *Hum Mutat, 23*, 540-545. doi:10.1002/humu.20039

Norman, G. J., Hawkley, L., Luhmann, M., Ball, A. B., Cole, S. W., Berntson, G. G., & Cacioppo, J. T. (2012). Variation in the oxytocin receptor gene influences neurocardiac reactivity to social stress and HPA function: a population based study. *Hormones and behavior*, *61*, 134-139.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A.M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress responses. *Epigenetics. 3*, 97-106.

Parker, G. (1988). The parental bonding instrument: Psychometric properties reviewed. *Psychiatric Developments, 7*, 317-335.

Parker, G., Tupling, H., & Brown, L. B. (1979). A parental bonding instrument. *British journal of medical psychology*, *52*, 1-10.

Pat-Horenczyk, R., Cohen, S., Ziv, Y., Achituv, M., Asulin-Peretz, L., Blanchard, T. R., Schiff, M., & Brom, D. (2015). Emotion regulation in mothers and young children faced with trauma. *Infant Mental Health Journal, 36*, 337-348. doi;10.1002/imhj.21515

Pederson, D. R., Moran, G., Sitko, C., Campbell, K., Ghesquire, K., & Acton, H. (1990). Maternal sensitivity and the security of infant-mother attachment: A Q-sort study. *Child Development*, *61*, 1974-1983.

Perroud, N., Paoloni-Giacobino, A., Prada, P., Olié, E., Salzmann, A., Nicastro, R., ... & Huguelet, P. (2011). Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. *Translational Psychiatry*, *1*, e59. doi:10.1038/tp.2011.60

Perroud, N., Rutembesa, E., Paoloni-Giacobino, A., Mutabaruka, J., Mutesa, L., Stenz, L., ... & Karege, F. (2014). The Tutsi genocide and transgenerational transmission of maternal stress: Epigenetics and biology of the HPA axis. *The World Journal of Biological Psychiatry*, *15*, 334-345. doi:10.3109/15622975.2013.866693

Pluess, M. (2015). Vantage sensitivity: Environmental sensitivity to positive experiences as a function of genetic differences. *Journal of Personality.* doi: 10.1111/jopy.12218

Pluess, M., & Belsky, J. (2011). Prenatal programming of postnatal plasticity? *Developmental Psychopathology, 23*, 29-38.

Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: A positron emission tomography study using [^{11}C] raclopride. *Journal of Neuroscience, 24*, 2825-2831. doi:10.1523/JNEUROSCI.3422-03-2004

Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D.H., (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinol. 28, 916–931. https://doi.org/10.1016/S0306-4530(02)00108-7

Puglia, M. H., Lillard, T. S., Morris, J. P., & Connelly, J. J. (2015). Epigenetic modification of the oxytocin receptor gene influences the perception of anger and fear in the human brain. *Proceedings of the National Academy of Sciences*, *112*, 3308-3313.

Quilty, L. c., & Bagby, M. R. (2008). The assessment of depressive severity: A review. *Directions in Psychiatry, 28*, 135-146.

Quirin, M., Kuhl, J., & Düsing, R. (2011). Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities. *Psychoneuroendocrinology*, *36*, 898-904.

Raudenbush, S. W., & Bryk, A. S. (2002). *Hierarchical linear models: Applications and data analysis methods* (2nd Ed.). Sage.

Raudenbush, S., Bryk, A., Cheong, Y. F., Congdon, R., du Toit, M. (2011). *HLM 7 Hierarchical linear and nonlinear modelling.* Lincolnwood, IL: Scientific Software International.

Raval, V., Goldberg, S., Atkinson, L., Benoit, D., Myhal, N., Poulton, L., & Zwiers, M. (2001). Maternal attachment, maternal responsiveness, and infant attachment. *Infant Behavior & Development, 24*, 281-304.

Riem, M. M. E., Pieper, S., Out, D., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Oxytocin receptor gene and depressive symptoms associated with physiological reactivity to infant crying. *Social Cognitive Affective Neuroscience, 6*, 294-300.

Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of the National Academy of Sciences*, *106*, 21437-21441.

Roisman, G.I., Newman, D.A., Fraley, R.C., Haltigan, J.D., Groh, A.M., & Haydon, K.C. (2012). Distinguishing differential susceptibility from diathesis-stress: Recommendations for evaluating interaction effects. *Development and Psychopathology, 24*, 389-409. doi:10.1017/S0954579412000065

Rutter, M., & Sroude, L. A. (2000). Developmental psychopathology: Concepts and challenges. *Development and Psychopathology, 12*, 265-296.

Ruttle, P. L., Serbin, L. A., Stack, D. M., Schwartzman, A. E., & Shirtcliff, E. A. (2011). Adrenocortical attunement in mother-child dyads: Importance of situational and behavioral characteristics. *Biological Psychology, 88*, 104-111.

Seckl, J. R., & Holmes, M. C. (2007). Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal "programming" of adult pathophysiology. *Nature Clinical Practice Endocrinology & Metabolism, 3*, 479-488.

Sethre-Hofstad, L., Stansbury, K., & Rice, M. A. (2002). Attunement of maternal and child adrenocortical response to child challenge. *Psychoneuroendocrinology*, *27*, 731-747.

Singer, J. D., & Willet, J. B. (2003). A framework for investigating change over time. *Applied longitudinal data analysis: Modeling change and event occurrence*, 3-15.

Spangler, G., & Grossman, K. E. (1993). Biobehavioral organization in securely and insecurely attached infants. *Child Development, 64*, 1439-1450.

Sprinkle, S.D., Lurie, D., Insko, S.L., Atkinson, G., Jones, G.L., Logan, A.R., & Bissada, N.N. (2002). Criterion validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a university counseling center sample. *Journal of Counselling Psychology*, *49*, 381-385.

Sroufe, L. A. (2005). Attachment and development: A prospective, ongitudinal study from birth to adulthood. *Attachment & Human Development, 7*, 349-367. doi:10.1080/14616730500365928

Sroufe, A. L., Egeland, B., Carlson, E. A., & Collins, W. A. (2005). *The development of the person: The Minnesota study of risk and adaptation from birth to adulthood.* New York, NY: Guilford.

Sturge-Apple, M. L., Cicchetti, D., Davies, P. T., & Suor, J. H. (2012). Differential susceptibility in spillover between interparental conflict and maternal parenting practices: Evidence for OXTR and 5-HTT genes. *Journal of Family Psychology*, *26*, 431.

Sullivan, R. M., & Gratton, A. (2002). Prefrontal cortical regulation of hypothalamic-pituitary-adrenal function in the rat and implications for psychopathology: side matters. *Psychoneuroendocrinology, 27*, 99-114.

Tarullo, A. R., & Gunnar, M. R. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior*, *50*, 632-639.

Taylor, A., Glover, V., Marks, M., & Kammerer, M. (2009). Diurnal pattern of cortisol output in postnatal depression. *Psychoneuroendocrinology, 34*, 1184-1188. doi:10.1016/j.psyneuen.2009.03.004

Toth, S. L., Sturge-Apple, M. L., Rogosch, F. A., & Cicchetti, D. (2015). Mechanisms of change: Testing how preventative interventions impact psychological and physiological stress functioning in mothers in neglectful families. *Development and Psychopathology, 27*, 1661-1674. doi:10.1017/S0954579415001017

Tu, M. T., Lupien, S. J., & Walker, C. D. (2006). Multiparity reveals the blunting effect of breastfeeding on physiological reactivity to psychological stress. *Journal of Neuroendocrinology, 18*, 494-503. doi:10.1111/j.1365-2826.2006.01441.x

Tyrka, A. R., Price, L. H., Marsit, C., Walters, O. C., & Carpenter, L. L. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: Preliminary findings in healthy adults. *PloS One*, *7*, e30148. doi:10.1371/journal.pone.0030148

Urizar, G. G., & Munoz, R. F. (2011). Impact of a prenatal cognitive behavioral stress management intervention on salivary cortisol levels in low-income mothers and their infants. *Psychoneuroendocrinology, 36*, 1480-1494. doi:10.1016/j.psyneuen.2011.04.002

van Bakel, H. J., & Riksen-Walraven, J. M. (2008). Adrenocortical and behavioral attunement in parents with 1-year-old infants. *Developmental Psychobiology*, *50*, 196-201.

Vandenbergh, D. J., Persico, A. M., Hawkins, A. L., Griffin, C. A., Li, X., Jabs, E. W., & Uhi, G. R. (1992). Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. *Genomics, 14*, 1104-1106.

Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., & Mesman, J. (2008). Dopamine system genes associated with parenting in the context of daily hassles. *Genes, Brain and Behavior, 7*, 403-410. doi:10.1111/j.1601-183X.2007.00362.x

Van IJzendoorn, M. H., Schuengel, C., & Bakermans-Kranenburg, M. J. (1999). Disorganized attachment in early childhood: Meta-analysis of precursors, concomitants, and sequelae. *Development and Psychopathology, 11*, 225-249.

VanNess, S. H., Owens, M. J., & Kilts, C. D. (2005). The variable number of tandem repeats element in DAT1 regulated in vitro dopamine transporter density. *BMC Genetics, 6*, 55. doi:10.1186/1471-2156-6-55

Villani, V., Ludmer, J. A., Gonzalez, A., Levitan, R., Kennedy, J., Masellis, M., Basile, V., Wekerle, C., & Atkinson, L. (2017). *DRD2, SLC6A3*, and *COMT* genes as potential moderators of the relation between maternal history of maltreatment and infant emotion regulation. *Development and Psychopathology.* doi:10.1017/S095457941700122

Verhage, M. L., Schuengel, C., Madigan, S., Fearon, R. M. P., Oosterman, M., Cassibba, R., . . . van IJzendoorn, M. H. (2016). Narrowing the transmission gap: A synthesis of three decades of research on intergenerational transmission of attachment. *Psychological Bulletin, 142*, 337-366. doi:10.1037/bul0000038

Weaver, I. C., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., & Szyf, M. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *The Journal of Neuroscience*, *25*, 11045-11054. doi:10.1523/JNEUROSCI.3652-05.2005

Weinfield, N. S., Sroufe, A., Egeland, B., & Carlson, E. (2008). Individual differences in infant-caregiver attachment: Conceptual and empirical aspects of security. In J. Cassidy & P. R.

Shaver (Eds.), *Handbook of attachment: Theory, research, and clinical applications* (pp. 3-22). New York, NY, US: Guildford Press.

Weissman, M. M., Wickramarante, P., Nomura, Y., Warner, V., Pilowsky, D., & Verdeli, H. (2006). Offspring of depressed parents: 20 years later. *The American Journal of Psychiatry, 163*, 1001-1008.

Wust, S., Federenko, I., Hellhammer, D. H., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology, 25*, 707-720. doi:10.1016/S0306-4530(00)00021-4

Yehuda, R., Bierer, L. M., Schmeidler, J., Aferiat, D. H., Breslau, I., & Dolan, S. (2000). Low cortisol and risk for PTSD in adult offspring of holocaust survivors. *American Journal of Psychiatry*, *157*, 1252-1259. doi;10.1176/appi.ajp.157.8.1252

Zhang, T. Y., Chretien, P., Meaney, M. J., & Gratton, A. (2005). Influence of naturally occurring variations in maternal care on prepulse inhibition of acoustic startle and the medial prefrontal cortical dopamine response to stress in adult rats. *Journal of Neuroscience, 25*, 1493-1502.