DRD2, DAT1, AND COMT GENOTYPES AS MODERATORS OF THE RELATION BETWEEN MATERNAL DEPRESSIVE SYMPTOMS AND INFANT CORTISOL REACTIVITY

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Abstract

Both maternal depression and dopamine-related genotypes have been linked to the development of the HPA axis. This thesis explored whether and how DRD2, DAT1, and (from an exploratory perspective) COMT genotypes moderate the relation between maternal depressive symptoms and infant cortisol reactivity in the context of a toy frustration challenge at 16 months and in the context of a maternal separation challenge at 17 months. Buccal cells were used for the purpose of genotyping. Maternal depressive symptoms were assessed via self-report at infant age 16 months. Candidate DRD2 and DAT1 genotypes moderated the relation between maternal depressive symptomatology and infant cortisol secretion in a diathesis-stress manner in the context of the toy frustration task, and in a differential susceptibility manner in the context of the maternal separation. Results are interpreted as indicating that the nature of gene-environment interactions is context-specific.

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Maternal depressive symptomatology has been linked to atypical hypothalamic pituitary adrenal (HPA) functioning in infants, children, and adolescents (Azak, Murison, Wentzel-Larsen, Smith, & Gunnar, 2013; Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007; Brennan et al., 2008; Diego et al., 2004; Essex, Klein, Cho, & Kalin, 2002; Feldman et al., 2009; Halligan, Herbert, Goodyer, & Murray, 2004). The impact of maternal depressive symptoms on offspring stress physiology is a pertinent issue since dysregulated patterns of cortisol secretion have been linked to a range of physical and psychiatric disorders (Goodyer, Park, Netherton, & Herbert, 2001; Hostinar & Gunnar, 2013), including depression (Adam et al., 2010; Halligan et al., 2007). Thus, researchers have proposed that maternal depression is one of the most robust risk factors for youth depression (Weissman et al., 2006) because of its influence on offspring HPA function (e.g., Dougherty et al., 2013; Halligan et al., 2007). Dopamine-related genotypes have also been linked to both cortisol secretion (Bakermans-Kranenburg, van IJzendoorn, Mesman, Alink, & Juffer, 2008) and depression (Dunlop & Nemeroff, 2007; Lawford, Young, Noble, Kann, & Ritchie, 2006), and may impact the association between maternal depressive symptoms and infant HPA function. Here I examine whether i) infant dopamine receptor D2 (DRD2), dopamine transporter (DAT1) and catechol-o-methyltransferase (COMT) genotypes moderate the relation between maternal depressive symptoms and infant cortisol reactivity to psychosocial challenge, ii) these moderating effects reflect diathesis-stress or differential susceptibility, and iii) the nature of these moderating effects is context-specific.

In this introduction, I i) provide background on the HPA axis, ii) discuss the influence of maternal depressive symptomatology on the development of the HPA axis, iii) discuss the

potential moderating role of infant genetic characteristics within diathesis stress and differential susceptibility frameworks, iv) examine the importance of considering infant cortisol secretion in the context of differentially challenging circumstances, and vi) outline the objectives and hypotheses of the current study.

The HPA System

The HPA system is one of the principal regulatory systems designed to maintain homeostasis in response to internal or external environmental changes that place demands on an organism (i.e., stress; Hostinar & Gunnar, 2013; Tarullo & Gunnar, 2006). The description I provide here is based largely on Boyce and Ellis' (2005) and Tarullo and Gunnar's (2006) summaries. In response to stress, corticotropin-releasing hormone (CRH) is produced within the paraventricular nucleus of the hypothalamus and is then carried to the anterior lobe of the pituitary gland. This stimulates corticotropes to secrete adrenocorticotropic hormone (ACTH), which in turn stimulates the synthesis of cortisol, the principal and most important (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007) glucocorticoid hormone regulating immune competence, blood pressure, and metabolic function (Sapolsky, 1992). When cortisol secretion reaches a certain level, it binds to glucocorticoid receptors that inhibit the production of CRH, ACTH, and cortisol, and return the system to a basal state (see Figure 1), thus preventing the overproduction of cortisol. Both the activation of the HPA axis in response to stress and the cortisol-based negative feedback system depicted in Figure 1 are regulated by the prefrontal cortex and amygdala, which are in turn modulated by the dopamine system during stress (Alexander et al., 2011; Sullivan & Gratton, 2002).

See Figure 1

In addition to its involvement within the stress response, cortisol secretion follows a circadian rhythm, with a single morning peak, followed by a gradual decline throughout the day (Gunnar & White, 2001; Kirschbaum & Hellhammer, 1989; Levine et al., 2007). Newborns, however, show two peaks in cortisol, which occur 12 hours apart independent of the time of day (Klug et al., 2000). The diurnal pattern develops throughout infancy and early childhood, and becomes consistent with that of adults when children stop taking daytime naps (Gunnar & Quevedo 2007).

Cortisol is necessary for survival; however, adverse effects have been observed if the response is prolonged, severe, or poorly regulated (Flin & England, 2003; Gunnar & Donzella, 2002; Tarullo & Gunnar, 2006). Specifically, both elevated and blunted cortisol secretion patterns have been linked to low levels of cognitive and social competence (Blair, Granger, & Peters Razza, 2005; Davis, Bruce, & Gunnar, 2002) and to a range of physical and psychiatric disorders, including depression (Bhagwagar, Hafizi, & Cowen, 2005; Goodyer, Tamplin, Herbert, & Altham, 2000; Granger, Weisz, McCracken, Ikeda, & Douglas, 1996; Gunnar & Vasquez, 2006; Kagan, Reznick, & Snidman, 1988; King, Barkley, & Barrett, 1998; Marsman et al., 2008). Given these associations between patterns of cortisol secretion and both physical and psychiatric disorders, and the fact that the HPA system is not fully mature at birth (Gunnar & Quevedo, 2007; Tarullo & Gunnar, 2006), the developmental origins of individual differences in cortisol secretion are a pertinent issue.

Early Programming of the HPA System

The origins of individual differences in HPA function emerge from both inherited and environmentally influenced factors related to a mother's own adjustment (Laurent, Ablow, &

Measelle, 2011; Meaney, 2010). Specifically, the *HPA programming hypothesis* posits that the HPA axis is programmed by maternal stress and interactive behaviour in the antenatal and early postnatal periods, and that such programming accounts for HPA function and associated physical and psychiatric disorders later in life (Laurent et al., 2011; Meaney, 2010; Seckl & Holmes, 2007). Given that maternal depression is one of the most robust risk factors for youth depression (Weissman et al., 2006), a disorder characterized by dysregulated HPA functioning (Pariante, 2003), several researchers emphasize the role of maternal depression in early HPA programming (e.g., Dougherty et al., 2013; Halligan et al., 2007).

The influence of maternal depression on early HPA programming is supported by animal models demonstrating that maternal stress and behaviour influence offsprings' developing stress physiology via both the fetal environment and early rearing conditions (Meaney, 2010). For example, although the placental enzyme 11ß-hydroxysteroid dehydrogenase type 2 (11ß-HSD-2) blocks maternal glucocorticoids from passing through the placenta to the fetus, it is weakened by prenatal stress, and, consequently, both physical and emotional adversity during pregnancy can increase the exposure of the fetus to maternal glucocorticoids (Mairesse et al., 2007; O'Donnell, O'Connor, & Glover, 2009; Seckl & Holmes, 2007). This exposure in turn has long-lasting effects on fetal development and HPA function (Meaney, 2010; Seckl & Holmes, 2007). Postnatal maternal behaviour that simulates maternal depression, such as deprivation and reduced tactile contact, also has enduring consequences for HPA functioning (Meaney, 2010). Offspring of mothers who demonstrated heightened levels of licking and grooming (i.e., high quality maternal behaviour), relative to those of mothers who provided lower levels of licking and grooming, show a reduced corticosterone response to stress and a greater number of glucocorticoid receptors linked to the negative feedback system that regulates the HPA axis

(Champagne & Meaney, 2001; Kaffman & Meaney, 2007; Meaney & Szyf, 2005). Importantly, the differences in stress physiology between offspring of high and low licking and grooming mothers were not due to genetic differences. Specifically, offspring of mothers that showed high levels of licking and grooming had differences in DNA methylation, as compared to offspring of mothers that showed low levels of licking and grooming, and these differences were reversed with cross-fostering (Meaney & Szyf, 2005; Weaver et al., 2004). Thus, these findings speak to the causal role of psychosocial factors in altering gene expression and influencing offspring's developing stress physiology (Meaney, 2010).

Human studies utilizing both clinical and community samples further support the supposition that maternal stress and behaviour, specifically maternal depressive symptoms, impact the development of the HPA axis. For example, several studies have linked maternal depressive symptoms and cortisol during pregnancy to fetal cortisol, downregulation of placental 11ß-HSD-2, as well as cortisol and behavioural reactivity after birth (Davis et al., 2004; DiPietro, Costigan, & Gurewitsch, 2003; Gitau, Cameron, Fisk, & Glover, 1998; Laurent et al., 2011; O'Donnell et al., 2012). Other studies link postnatal maternal depression to infant cortisol secretion (e.g., Essex et al., 2002; Halligan et al., 2004; Laurent et al., 2011), and show that the behavioural insensitivity associated with maternal depression (Hatzinikolaou & Murray, 2010) can promote infant stress dysregulation in the early postnatal period (Albers et al., 2008; Gunnar & Donzella, 2002; Hostinar & Gunnar, 2013). Such dysregulation is characterized by elevated levels of cortisol (Azak et al., 2013; Hostinar & Gunnar, 2013), but, after repeated overstimulation and elevations in cortisol, the HPA axis may become downregulated and less sensitive to psychosocial and acute stress (Fernald, Burke, & Gunnar, 2008; Gump et al., 2009).

Thus, exposure to maternal depressive symptomatology in the perinatal period has been linked to dysregulated cortisol secretion patterns (Laurent et al., 2011).

In addition to the influences of maternal depression, there are heritable components in cortisol secretion (Bartels de Geus, Kirschbaum, Sluyter, & Boomsma, 2003; Bartels, van den Berg, Sluyter, Boomsma, & de Geus, 2003; Kirschbaum, Wust, Feig, & Helhammer, 1992; Steptoe et al., 2009; Van Hulle, Shirtcliff, Lemery-Chalfant, & Goldsmith, 2012). Genes related to dopaminergic function may be particularly relevant to HPA development, given that i) lower dopamine levels are a salient characteristic of 1-2 week old infants of mothers with depression (Diego et al., 2004; Lundy et al., 1999), ii) dopamine plays a critical role in the pathophysiology of depression (Antypa, Drago, & Serretti, 2013; Dunlop & Nemeroff, 2007; Elovainio et al., 2007; Rowe et al., 1998), and iii) dopamine influences the medial prefrontal cortex (mPFC) and the amygdala, which regulate HPA functioning (Alexander et al., 2011; Zhang et al., 2005). Recent evidence suggests that genes related to dopaminergic function impact the degree to which HPA development is influenced by environmental conditions (Bakermans Kranenburg et al., 2008). That is, maternal depression may have a greater influence on the development of the HPA axis for some infants more than other infants, in a manner consistent with *diathesis-stress* or *differential susceptibility*.

Genetic Moderation: Diathesis Stress and Differential Susceptibility Theories

In conceptualizing how genetic factors might moderate environmental influences, researchers have traditionally relied on the *diathesis-stress* (or *dual-risk*) framework. Diathesis-stress theory points to the synergistic effects of a risk (i.e., diathesis) within the individual interacting with an environmental characteristic to produce an outcome. For example, Nederhof, Belsky, Ormel, & Olehinkel (2012) found that the 7 repeat allele of the dopamine receptor D4

(DRD4) gene moderated the influence of parental divorce on externalizing symptoms. Relative to children without the 7 repeat allele, children with the 7 repeat allele exhibited more externalizing problems in the context of parental divorce. Thus, individuals with this diathesis allele may be the most vulnerable to developing psychopathology following environmental stress. These findings could suggest that the adverse effects of maternal depressive symptoms are heightened in some, genetically "vulnerable" children, but absent in other, "resilient" children.

In an extension of diathesis-stress theory, recent evidence suggests that the same characteristics of individuals that make them disproportionately vulnerable to adverse environments may also make them disproportionately likely to benefit from supportive environments (Belsky, 1997a, 1997b, 2005; Belsky et al., 2009; Belsky & Pleuss, 2009; Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). This idea forms the basis of *differential susceptibility theory***.** Belsky (1997a, 1997b, 2005) proposed differential susceptibility theory based on the Darwinian premise that natural selection shapes living things to survive in order to reproduce. Belsky (1997a, 1997b, 2005; Belsky & Pluess, 2009) proposed that since the future is uncertain, and parents cannot know what child-rearing practices will most likely promote the reproductive fitness of their offspring (i.e., their own inclusive fitness), natural selection shaped parents to "hedge their bets" and have children varying in levels of developmental plasticity. This would ensure that if certain environmental effects were to threaten fitness, those children least susceptible to those effects would avoid the costs. Due to inclusive-fitness, these less susceptible children's resistance to environmental effects would not only benefit themselves, but also their parents and siblings, as they share 50% of their genes. Similarly, if certain environmental aspects were to enhance fitness, the more

malleable children benefit directly from those effects, ensuring also that their parents and siblings would benefit indirectly for inclusive-fitness reasons.

Belsky and Pleuss (2009) and Ellis et al. (2011) corroborated the differential susceptibility theory with evidence from cross-species studies that support the notion that plasticity is heritable. For example, Nussey, Postma, Gienapp, and Viser (2005) found that among a Dutch population of great tits *Parus major,* selection favoring highly plastic birds with regard to the timing of reproduction has intensified over a 32 year period, when climate change caused a mismatch between the birds' breeding times and their caterpillar prey. Thus, Belsky (1997a, 1997b, 2005) proposed that children should vary in their susceptibility to parental rearing, and to general environmental influences, in a "for better and for worse" manner. That is, in contrast to diathesis stress theory, which posits that "vulnerable" children should experience the worst outcomes if reared in impoverished environments, differential susceptibility theory posits that "susceptible" children should experience *both* the least positive outcomes if reared in impoverished environments and the most positive outcomes if reared in enriched environments.

Distinguishing between diathesis stress and differential susceptibility. Roisman et al. (2012) highlighted limitations of existing practices for probing interaction effects and proposed a set of statistical procedures that reliably differentiate between diathesis-stress and differential susceptibility. Specifically, researchers should report regions of significant difference between the slopes of those with and without the susceptibility marker, the proportion of the area between the regression lines uniquely attributable to differential susceptibility in order to quantify the importance of the "for better" effects relative to the "for worse" effects, and include nonlinear regression terms to rule out nonlinear effects or significant diathesis-stress interaction effects that might masquerade as crossover (i.e., differential susceptibility) effects (Beach et al., 2014;

Roisman et al., 2012). Roisman et al. (2012) suggested that existing studies that have not utilized these statistical procedures may have reported that their data reflect differential susceptibility when in fact it is better attributable to diathesis-stress. Based on this conclusion, the conditions under which diathesis-stress and differential susceptibility operate are currently unclear.

It is also important to consider that diathesis-stress and differential susceptibility may both operate for the same GxE model, but within different contexts. For example, Roisman et al. (2012) re-analyzed data from the NICHD Study of Early Childcare and Youth Development utilizing their newly proposed statistical criteria, and found that infant temperament moderated the relation between maternal sensitivity and teacher-reported symptoms of social competence in a differential susceptibility manner across time and across different teachers. On the other hand, infant temperament moderated the relation between maternal sensitivity and mother rated social competence in a diathesis-stress manner over time from kindergarten to Grade 3. Thus, diathesis-stress may operate in certain contexts, while differential susceptibility may operate in others (e.g., at home versus at school, Roisman et al., 2012; also see Cassidy, Woodhouse, Sherman, Stupica & Lejuez, 2011 and Cicchetti, Rogosch, & Toth, 2011).

Genetic Moderators of the Relation Between Maternal Depressive Symptoms and Infant Cortisol Secretion

There are three dopamine-related genes that influence HPA functioning (Alexander et al., 2011; Armbruster et al., 2009; Belda & Armario, 2009; Pivonello et al., 2007; Propper et al., 2008; Sullivan & Dufresne, 2006) and have repeatedly been found to moderate environmental influences in both diathesis-stress and differential susceptibility manners (Belsky & Pluess, 2009); these are DRD2, DRD4, and DAT1. COMT has also been linked to HPA functioning (e.g., Alexander et al., 2011), and there is preliminary evidence that it is a diathesis-stress and

differential susceptibility marker (Belsky & Pluess, 2009; Nederhof et al., 2012). Thus, maternal depressive symptoms may influence cortisol secretion the most in infants with candidate DRD2, DRD4, DAT1, and COMT genotypes, relative to infants without these genotypes.

DRD2. The DRD2 gene encodes the D2 subtype of the dopamine receptor. The Taq1A (A1) polymorphism involves a C to T substitution in a noncoding region of the DRD2 locus, which has been linked to dopamine receptor D2 availability. As Belsky and Pluess (2009) summarized, the A1 allele of DRD2 has been associated with low dopamine density and various psychiatric disorders. It has been identified as a diathesis-stress and differential susceptibility marker by several studies (e.g., Belsky & Pluess, 2009; Propper et al., 2008; van der Zwaluw, Kuntsche, & Engels, 2011). For example, Propper et al. (2008) found that infants with the A1 allele had the most adaptive physiological regulation (measured by respiratory sinus arrhythmia reactivity) at 12 months if they had received highly sensitive parenting at 6 months, but also the least adaptive vagal regulation if they had received low sensitivity at 6 months. Since dopamine influences the HPA axis through D2 receptors (Belda & Armario, 2009), it could be suggested that the A1 allele may also confer susceptibility to the effects of maternal depressive symptoms on cortisol secretion. However, this is in need of empirical validation.

DRD4. Variants of DRD4 differ by the number of 48-base-pair repeats in exon III. The 7-repeat (long) variant has been associated with low efficiency of dopamine reception (Robbins & Everitt, 1999). Several studies have identified the 7-repeat allele as a diathesis-stress and differential susceptibility marker (e.g., Beach, Brody, Lei, & Philibert, 2010; Kegel, Bus & van IJzendoorn, 2011; Knafo, Israel, & Ebstein, 2011; Martel et al., 2011; Nederhof et al., 2012). For example, Bakermans-Kranenburg et al. (2008) gave a group of mothers a video-feedback intervention to promote sensitive parenting. They found that children who carried the DRD4-7

repeat allele not only showed the most daily cortisol production if their mothers had been assigned to the control group, but also showed the least daily cortisol production if their mothers had been given the intervention. Since the 7 repeat allele conferred susceptibility to the effects of parenting on daily cortisol production, it could be suggested that it may also confer susceptibility to the influences of maternal depressive symptoms on cortisol secretion. This has not yet been empirically explored.

DAT1. The DAT1 clears dopamine from synapses and limits the duration of its synaptic activity (Kordas et al., 2012). A 40-bp variable number of tandem repeats (VNTR) polymorphism is present in the 15th exon of the dopamine transporter gene. The 40-bp VNTR element is repeated between 3 and 13 times and occurs most often in the 9- and 10- repeat forms (VanNess, Owens, & Kilts, 2005). Higher expression and availability of dopamine is found in individuals with the 10-repeat (10R) VNTR. The 10R variant has been identified as diathesis-stress and differential susceptibility marker (e.g., Faraone et al., 2005; Laucht et al., 2007; VanNess et al., 2005). For example, Laucht et al. (2007) found that teens with the 10R allele had the most inattention if living in high psychosocial adversity, but also the least inattention if living under conditions of low psychosocial adversity. The 10-repeat variant has also been linked to elevated cortisol reactivity and impaired stress recovery (Alexander et al., 2011); however, it has never been examined in relation to infant cortisol secretion using diathesis-stress or differential susceptibility models.

COMT. COMT is an enzyme involved in the degradation of catecholamines. The COMT gene contains a G>A single nucleotide polymorphism (rs4680) with a valine (val) to methionine (met) substitution (Alexander et al., 2011; Conway et al., 2010). The val158 allele is associated with higher COMT enzyme activity and lower levels of dopamine in the brain. In contrast, the

met158 allele is associated with a 3-4 fold reduction in COMT activity and thus a 3-4 fold increase in dopamine availability (Alexander et al., 2011; Conway et al., 2010). The met158 allele has been linked to increased stress hormone release and impaired stress recovery (Alexander et al., 2011; Jabbi et al., 2007; Oswald, McCaul, Choi, Yang, & Wand, 2004).

The role of val158 and met158 genotypes within diathesis stress and differential susceptibility frameworks is unclear. For example, Nederhof et al. (2012) found that met carriers (i.e., A/A or A/G genotypes), relative to those with val/val (G/G) genotypes, have the highest levels of externalizing problems in the context of parental divorce. Although there was a trend for met carriers, relative to those with G/G genotypes, to also have the lowest levels of externalizing behaviour if their parents did not divorce, this trend did not reach statistical significance. Thus, these findings are more consistent with diathesis-stress than with differential susceptibility. On the other hand, van IJzendoorn, Bakermans-Kranenburg, and Mesman (2008) documented significant differential susceptibility effects of COMT genotype, but identified the val158 allele (as opposed to the met158 allele) as the susceptibility marker. Specifically, in parents with G/G or G/A alleles, as compared to parents with A/A alleles, more daily hassles were associated with less sensitive parenting, while fewer daily hassles were associated with more sensitive parenting. Nederhof et al. (2012) provided one possible explanation for the inconsistent findings regarding which of the val158 or met158 alleles is the marker of environmental susceptibility. Nederhof et al. (2012) proposed that children with different COMT genotypes may not be *generally* more and less sensitive to environmental experience, but, rather, some genotypes promote sensitivity within certain contexts and other genotypes promote sensitivity in other contexts. Thus, with regard to COMT genotype, the val158 and met158 alleles may operate as susceptibility markers within different contexts.

Intra-Individual, Between-Challenge Variability in Cortisol Secretion

When examining associations between maternal depressive symptoms, infant genotype, and infant cortisol secretion, in addition to considering both diathesis stress and differential susceptibility models, it is also important to examine intra-individual, between-challenge variability in cortisol secretion (Atkinson et al., 2013; Goldberg et al., 2003; Jansen et al., 2010; Lauren et al., 2011; Laurent, Ablow, & Measelle, 2012). Specifically, conclusions about an infant's vulnerability to psychosocial stress are frequently made without considering differential cortisol secretion in response to differentially challenging circumstances (Laurent et al., 2012). This between-challenge variability in cortisol secretion is relevant to the challenges utilized in the current study: the toy frustration procedure (TFP, the denial of access to an attractive toy; Braungart-Rieker & Stifter, 1996), and the strange situation procedure (SSP, a mother-infant separation paradigm; Ainsworth, Blehar, Waters, & Wall, 1978). In a meta-analysis, Jansen et al. (2010) found that challenges inducing anger correspond to a *d* (standardized difference between pre- and post- stressor cortisol concentrations) of .13, whereas the SSP precipitated cortisol increases corresponding to a *d* of .34. As Atkinson et al. (2013) argued, although sample limitations precluded formal comparisons of effect sizes within the meta analysis, Jansen et al.'s (2010) *d* discrepancy suggests that the SSP may be the more potent challenge. Accordingly, Laurent et al. (2012) found that infant cortisol trajectories were higher in the context of the SSP than in the context of a clean-up task.

Atkinson et al. (2013) observed infants in the TFP and the SSP. Demonstrating the importance of considering challenge context, Atkinson et al. (2013) showed that infants of more sensitive mothers, relative to infants of less sensitive mothers, had larger declines in cortisol concentrations in the context of the TFP (attributed to a decline in cortisol following an

anticipatory anxiety- related increase in cortisol), and larger increases in cortisol concentrations in the context of the SSP. Atkinson et al. (2013) suggested that healthy HPA function involves flexible reactivity, i.e., a buffered increase in cortisol concentrations or a strong decrease in cortisol concentrations in the context of common, day-to-day stressors, and a robust increase in cortisol concentrations in the context of more potent stressors. Thus, Atkinson et al. (2013) suggested that infants of more sensitive mothers showed a more flexible cortisol response across challenges, relative to infants of less sensitive mothers. Variation in the infant cortisol response across differentially challenging circumstances has never been examined in relation to maternal depressive symptoms or infant genotype.

Moreover, given that i) infant challenge paradigms differ in the degree to which they elicit adrenocortical activation (Atkinson et al., 2013; Jansen et al., 2010; Laurent et al., 2012), and ii) diathesis-stress and differential susceptibility may both operate for the same GxE model, but within different contexts (Roisman et al., 2012), one GxE framework (i.e., diathesis-stress or differential susceptibility) cannot be expected to operate uniformly for infant cortisol secretion across different challenge paradigms. That is, diathesis-stress may emerge within the context of one challenge paradigm, and differential susceptibility may emerge within the context of another. At present, research pertinent to how differential context associates with each of these GxE models is extremely rare, such that it is impossible to make specific hypotheses in this regard. Thus, studies are needed to explore whether infant genotype moderates the association between maternal depressive symptoms and infant cortisol reactivity in a diathesis-stress or differential susceptibility manner, while considering different stressor contexts. Here I utilize the differential impact of the TFP and SSP to examine these questions.

The Current Study

This study longitudinally followed 314 mother-infant dyads to examine the hypothesis that dopamine-related genetic polymorphisms moderate the relationship between postnatal maternal depressive symptoms and infant cortisol reactivity to psychosocial challenge. I also explored whether these moderating effects reflect diathesis-stress or differential susceptibility, and whether the nature of these moderating effects is context-specific. Genotyping DRD4 was unsuccessful, likely due to buccal cell degradation (see Livy et al., 2012). Several attempts were made to repeat PCR amplification to no avail; therefore, the DRD4 marker was removed from the current study. DRD2, DAT1, and COMT appear to have resisted degradation and were successfully genotyped.

To elicit a stress response, infants were presented with the TFP (Braungart-Rieker & Stifter, 1996) at age 16 months and at 17 months were exposed to the SSP (Ainsworth et al., 1978). As reviewed, maternal separation results in greater cortisol increases than frustration challenges at this age (Atkinson et al., 2013; Jansen et al., 2010; Laurent et al., 2012). Indeed, the differential impact of the SSP, as compared to the TFP, has been demonstrated with the sample used here (Atkinson et al., 2013). The proven difference between these challenges with respect to cortisol response renders their joint use ideal for assessing whether diathesis-stress and differential susceptibility apply under different circumstances. Measuring cortisol in the context of two different challenging tasks also addressed Ellis et al.'s (2011) suggestions to aggregate data across settings (in this instance, home and lab) and measures in order to increase power and reliability of GxE findings.

Potential confounds. Several variables are linked to both infant cortisol secretion and maternal depressive symptoms that may serve to obfuscate findings. These include family socioeconomic status (e.g., Fernald et al., 2008), and the quality of parenting (Albers et al., 2008;

Atkinson et al., 2013; Blair et al., 2008; Blair et al., 2005; Coyne, Low, Miller, Seifer, & Dickstein, 2007; Dozier et a., 2006; Dougherty, Tolep, Smith, & Rose, 2013; Field, 2010; Fisher, Gunnar, & Chamberlain, 2000; Hatzinikolaou & Murray, 2010; Hoffman, Crnic, & Baker, 2006; Lovejoy, Grazyk, O'Hare, & Neuman, 2000; Murray, Halligan, Goodyer, & Herbert, 2010; Spangler, Schieche, Ilg, Maier, & Ackerman, 1994). Moreover, infant sex (Davis & Emory, 1995; Sanchez et al., 2010), feeding times (Levine et al., 2007; Magnano, Diamond, & Gardner, 1989), and exposure to maternal breastmilk (Beijers, Riksen-Walraven, & De Weerth, 2013) and smoke (Granger et al., 2007) may influence infant cortisol secretion. Thus, I included these variables as potential covariates. To represent the potential covariate of quality of parenting, I used maternal sensitivity (Albers et al., 2008; Atkinson et al., 2013; Gunnar & Donzella, 2002). Both family income and education were examined as measures of socioeconomic status.

Hypotheses. I hypothesized that DRD2, DAT1, and COMT variants interact with maternal depressive symptoms to predict cortisol reactivity in the context of the TFP and SSP. Since the TFP and SSP are differentially challenging (Atkinson et al., 2013), I posit different hypotheses for each. Moreover, the gene-environment interactions were exploratory in two respects, to determine whether: i) these interactions reflect diathesis-stress or differential susceptibility in the context of the TFP and SSP, and ii) the met158 or val158 genotype of COMT promotes susceptibility to the influences of maternal depressive symptoms on infant cortisol secretion.

In the context of the TFP, infants in the current sample show declines in cortisol, which is attributed to anticipatory anxiety (Atkinson et al., 2013). I hypothesized that infants with i) the A1 allele of DRD2, ii) the 10/10 allele of DAT1, and/or iii) either the met158 or val158 allele of COMT, relative to infants without these alleles, have buffered cortisol reactivity (i.e., buffered declines) if the mother endorses high depressive symptomatology (reflecting diathesis-stress), or

both buffered cortisol reactivity if the mother endorses high depressive symptomatology *and* the most robust cortisol reactivity if the mother endorses low depressive symptomatology (reflecting differential susceptibility).

In the context of the SSP, infants in the current sample show increases in cortisol (Atkinson et al., 2013). I hypothesized that infants with i) the A1 allele of DRD2, ii) the 10/10 allele of DAT1, and/or iii) either the met 158 or val158 allele of COMT, relative to infants without these alleles, have buffered cortisol reactivity (i.e., buffered increases) if the mother endorses high depressive symptomatology (reflecting diathesis-stress), or *both* buffered cortisol reactivity if the mother endorses high depressive symptomatology *and* the most robust cortisol reactivity if the mother endorses low depressive symptomatology (reflecting differential susceptibility).

Method

Participants

The Research Ethics Boards at the Centre for Addiction and Mental Health and Ryerson University granted approval to recruit families through postings in community centers and in-person visits to mother-infant activity centers and consumer baby shows in the Greater Toronto Area (GTA). This study utilized the Toronto Longitudinal Cortisol (TLC) sample (Atkinson et al., 2013; Pereira et al., 2012), which consists of 314 mother-infant dyads (52% male infants). Included infants were full term and healthy, and all mothers were 18 years or older at childbirth, had no known hormonal or psychiatric disorders, had pregnancies over 32 weeks, and had sufficient knowledge of English to complete questionnaires. The current study examines data collected during a home visit when infants were 16 months (M = 15.97; SD = 1.34) and a lab visit when infants were 17 months (M = 17.25; SD = 1.92). Maternal age at the 16-month visit ranged from 21 to 46 years (M = 32.94; SD = 4.51). The sample is demographically low risk.

The median family income was $114,000-149,999 Canadian, with 25th and 75th percentiles of $92,000-113,999 and $150,000-199,999. Participants were predominantly Caucasian (75%), with a smaller proportion of participants identifying as Asian (9%), Afro-Canadian (3.4%) and other (12.7%). The majority of mothers were highly educated, and reported post-graduate (21.2%), undergraduate (47.8%), community college (22.4%), secondary school (7.7%), and primary school (1.0%) as their highest level of education.

The percent of missing values ranged from 0.06% for maternal education to 27.40% for infant cortisol samples during the SSP (as a result of reluctance to participate in saliva sampling). Participants with missing data did not significantly differ from participants with complete data with regard to any focal variables (DRD2, DAT1, and COMT genotypes, maternal depressive symptoms, and infant cortisol samples during the TFP and SSP), family income, maternal age, maternal breastfeeding status, maternal smoking status, maternal education, or infant sex. However, infants with complete data ate breakfast significantly earlier before the 16 month visit, ate breakfast significantly earlier before the 17 month visit, and woke up significantly earlier before the 17 month visit, relative to infants without complete data (see Table 1). However, breakfast time was not significantly correlated with infant cortisol samples during the 16 month visit, $r = .11$, $p = .11$, or the 17 month visit, $r = -.07$, $p = .34$, and infant wake time at 17 months was not significantly correlated with infant cortisol samples at 17 months, $r = -.07$, $p = .34$[1].

See Table 1

Procedure

[1] For the purpose of analyses, temporal variables were coded as the number of minutes since 12am.

Two research assistants coded maternal sensitivity in vivo during a home visit involving a two-hour observation of mother-infant interaction when the infant was 16 months old. Mothers were instructed to go about their daily activities and to then complete questionnaires while the infant was in the room. During the same visit, the research assistants observed the infants in the TFP and collected saliva samples. The mothers completed the Beck Depression Inventory, Second Edition (BDI-II; Beck, Steer, & Brown, 1996) at this time. One month later, the mother-infant dyads visited the lab and participated in the SSP. On completion of the SSP, the mothers and infants were shown to a second room, not associated with the separations, where post-challenge cortisol was collected. At the end of each visit, buccal (cheek) cells were collected. In accordance with standard practice (Gunnar & White, 2001), all visits commenced between 0900h and 1000h. Morning collection of cortisol for infants is ideal so that perturbations of routine do not impact cortisol levels (e.g., effects of daytime stressors, meals, and naps are variable in infancy).

Measures

Beck Depression Inventory, Second Edition. Mothers completed the BDI-II (Beck et al., 1996), which assesses the presence and severity of unipolar depressive symptomatology. The questionnaire includes 21 items that are each rated on a 4-point scale from 0 (*indicating a lack of depressive symptomatology*) to 3 (*indicating high depressive symptomatology*). Ratings are totaled to create a summary score. The BDI-II is frequently used to assess depressive symptoms in mothers sampled from the community (Allen, Manning, & Meyer, 2010; Gardner & Epkins, 2012; Stuart, Couser, Schilder, O'Hara, & Gorman, 1998). It has good internal consistency, split-half reliability, test-retest reliability, and validity (e.g., Beck, 1999; Sprinkle et al., 2002; Teti, Gelfand, Messinger, & Isabella, 1995). In the current sample, Cronbach's alpha was 0.89.

Buccal cell collection and assessment. DNA was assessed from infant buccal cells at each visit. Four paper buccal swabs (Whatman Omniswab, Fisher Scientific Company) were collected from each infant. The tip of each swab was then expelled into a 15mL polypropylene tube (sealed to prevent contamination) and stored at 4°C until extracted. DNA isolation and analysis of buccal cells was conducted at the Neurogenics Laboratory at the Center for Addiction and Mental Health (CAMH; James Kennedy, Director) in Toronto, Canada. Total genomic DNA was extracted using the Qiagen QIAamp DNA Mini and Blood Mini kit as per manufacturer's instructions with the reagents used prior to the spin steps (Protease, PBS, buffer AL and 95% ethanol) doubled. Genotyping of 10% of samples from each run were replicated for quality control purposes for each marker.

Two SNPs across two genes were genotyped using commercially available TaqMan SNP genotyping assays: COMT Val158Met (rs4680; assay ID C__25746809_50); DRD2 (rs1800497; assay ID C__7486676) (LifeTechnologies, Burlington, ON). For each reaction, 1 uL of the genomic DNA was amplified as per manufacturer's directions scaled to a total volume of 10 μL in an Applied Biosystems (AB) 2720 thermal cycler. Post-amplification products were analyzed on the AB ViiA7 Real-Time PCR System and genotype calls were determined manually by comparison to six No Template Controls.

For the DAT1 VNTR, 3 μL total genomic DNA was combined with 1X MBI Fermentas PCR buffer containing KCl, 1.5 mM $MgCl_2$ (MBI Fermentas), 0.13 μg each primer (Vandenbergh et al 1992; forward primer labeled with 5' NED fluorescent tag), 10% DMSO (Sigma-Aldrich), 0.16 mM each dNTP (MBI Fermentas) and 2 U Taq polymerase (MBI Fermentas) to a total volume of 25 μL. The PCR reactions were subjected to an initial denaturation for 5 min at 95°C, followed by 35 cycles of amplification in an AB 2720

(Thermofisher Scientific Burlington, ON) thermal cycler: denaturing for 30 sec at 95°C, annealing for 1 min at 65°C and extension for 30 sec at 72°C, and a final extension at 72°C for 10 min. One microlitre of the PCR product was electrophoresed on an AB 3130-*Avant* Genetic Analyzer as per manufacturer's directions, and product sizes determined by comparison to GeneScan 1200 LIZ size standard using GeneMapper (version 4.0).

Similarly the DRD4 exon III variant was genotyped as follows: 4 μL total genomic DNA was combined with 1X MBI Fermentas PCR buffer containing KCl, 1.5 mM $MgCl_2$ (MBI Fermentas), 0.1625 μg each primer (Lichter et al 1993; forward primer labeled with 5' 6-FAM fluorescent tag), 10% DMSO (Sigma-Aldrich), 0.16 mM each dATP, dCTP, dTTP, 0.08 mM dGTP (MBI Fermentas) , 0.08mM 7'deaza-dGTP, and 1 U Taq polymerase (MBI Fermentas) to a total volume of 25 μL. The PCR reactions were subjected to an initial denaturation for 5 min at 95°C, followed by 4 cycles of amplification in an AB 2720 (Thermofisher Scientific Burlington, ON) thermal cycler: denaturing for 20 sec at 95°C, annealing for 20 sec at 62°C and extension for 1 min at 72°C, and a final extension at 72°C for 10 min. One microlitre of the PCR product was electrophoresed on an AB 3130-*Avant* Genetic Analyzer as per manufacturer's directions, and product sizes determined by comparison to GeneScan 1200 LIZ size standard using GeneMapper (verison 4.0).

Genotyping DRD4 was unsuccessful, likely due to buccal cell degradation (DRD2, DAT1, and COMT appear to have resisted degradation). Several attempts were made to repeat PCR amplification to no avail; therefore, the DRD4 marker was removed from the current study. Buccal DNA appears vulnerable to degradation, reducing the total yield and performance of DNA to a greater degree than blood DNA (Livy et al., 2012). Nevertheless, non-invasive DNA collection methods (i.e., buccal DNA) are preferred over more invasive techniques (e.g., blood

DNA) in infant studies for ethical reasons and to increase participation and compliance (Livy et al., 2012).

Toy Frustration Procedure. The TFP (Braungart-Rieker & Stifter, 1996) consisted of four 90-second episodes: i) the mother engaged the infant with an attractive toy; ii) the mother placed the toy in a clear container with a lid on (but not sealed) while disengaging from the infant; iii) if the infant did not retrieve the toy him/herself, the mother returned the toy to the infant; and iv) the mother placed the toy in the clear container with the lid sealed and she disengaged again. If the infant cried continuously for 20 seconds, the episode was terminated. The final episode is the most frustrating episode for infants because the lid is fixed, making it impossible to retrieve the toy, and also because this episode captures the accumulating stress from previous episodes.

Strange Situation Procedure. The SSP (Ainsworth et al., 1978) consisted of eight episodes designed to induce increasing attachment-related distress in the infant. During these episodes, i) the infant and mother were introduced to a strange room with toys; ii) the infant was free to play with the toys for three minutes while the mother sat quietly and read, iii) a female stranger entered the room and sat quietly for one minute, then spoke to the mother for one minute, and then engaged the infant in play for one minute; iv) the mother left the infant alone in the room with the stranger for three minutes; v) the mother returned to the room, the stranger left, and the mother stayed in the room for three minutes; vi) the mother left the infant alone in the room for three minutes; vii) the stranger returned to the room for three minutes; viii) the mother returned, the stranger left the room, and the mother stayed in the room for three minutes. Mothers observed their infants throughout the procedure and separation episodes were terminated if the infant cried hard for 20 seconds. In this study, the SSP was used only as a

stressor and was not coded for attachment classification (Ainsworth et al., 1978). It is important to note that, for ethical considerations, infant challenge paradigms cannot be extremely stressful. Nevertheless, tasks that involve both social components and aspects of uncontrollability, like the SSP, are most likely to reliably elicit cortisol changes (Dickerson & Kemeny, 2004). Accordingly, the SSP has been documented as a more potent stressor, relative to the TFP (Atkinson et al., 2013; Jansen et al., 2010; Larent et al., 2012).

Salivary cortisol. 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). While cortisol can be sampled from plasma, urine, and saliva, only plasma samples contain both bound and unbound cortisol. Urine and saliva samples only contain unbound cortisol. Salivary cortisol measurement has advantages over plasma or urine, since its relatively simple chemical constituents enable superior estimation (Magnano et al., 1989). Moreover, salivary cortisol is advantageous since it exclusively provides a measurement of active cortisol and thus better represents the degree of cortisol reactivity (Hellhammer, Wust, & Kudielka, 2009). Further, salivary cortisol may be the best method for infants as it is non-invasive and enables frequent and rapid sampling (Kirschbaum & Hellhammer, 1994; Levine et al., 2007; Magnano et al., 1989). Thus, salivary cortisol has become the most common method for measuring cortisol in infancy. However, drawbacks of utilizing salivary cortisol must be acknowledged. Specifically, saliva obtained after eating or drinking, or saliva mixed with blood from oral cuts, may result in artificially elevated cortisol measurements (Levine et al., 2007; Magnano et al., 1989). To overcome such disadvantages, I controlled for feeding times within analyses.

Cortisol collection. To avoid contamination, mothers were asked to ensure that their infants did not brush their teeth, eat, or drink within 60 minutes of the procedure. Two Sorbettes

(Salimetrics, State College PA) were used to collect the saliva of each infant 5 minutes pre-challenge (baseline) and 20 and 40 minutes post-challenge, for both the TFP and SSP. These collection times were chosen since some individuals peak closer to 20-minutes, while others peak closer to 40-minutes (Goldberg et al., 2003). The Sorbettes were placed in the mouth for 60 seconds. Saliva samples were centrifuged for 10-minutes at 3000 rpm at 4°C in order to extract the saliva and then sealed and stored at -70 °C. Salivettes were thawed and centrifuged for 10 minutes at 3,000 rpm at 4°C. Each sample was assayed twice using a salivary cortisol enzyme immunoassay kit (Salimetrics, State College, PA), and average values were used in analyses. The interassay variability was 10.6%. The intraassay variation was 8.3% for samples with low values, and 6.9 % for samples with high values.

Cortisol indices. To assess infant cortisol reactivity in the TFP and SSP, Area Under the Curve increase (AUC_I) was computed from the trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) using three time points: baseline, 20-minutes post-challenge, and 40-minutes post-challenge. AUC_I measures the change in cortisol over time, thereby assessing the sensitivity of the HPA system (Fekedulegn et al., 2007), and was computed as {[(20 min value + baseline value)/ 2] x time} + {[(40 min value + 20 min value)/ 2] x time} – [baseline value x (time + time)]. The AUC_I has an advantage over a simple change computation as it encompasses more than merely two time point measurements of cortisol (Fekedulegn et al., 2007). It is important to consider both the magnitude and sign of AUC_I (Fekedulegn et al., 2007). Specifically, when cortisol concentrations escalate across challenge time points, AUC_I is positive and reflects cortisol increase. On the other hand, cortisol secretion may decrease across challenge time points in the event of anticipatory anxiety-related increases in cortisol (Atkinson et al., 2013; Jansen et al., 2010). Since, in such cases, subsequent cortisol measurements would be less

than the baseline value, the overall value of AUC_I would be lowered as the amount of cortisol decline increases (Fekedulegn et al., 2007). In other words, when cortisol concentrations decrease across challenge time points, AUC_I is negative, and lower AUC_I values reflect more robust cortisol declines (and thus more robust cortisol reactivity).

In contrast to AUC_I, Area Under the Curve ground (AUC_G) measures *total cortisol output* and takes into account both the difference between the single cortisol measurements from each other and the distance of these measurements from ground. Although AUC_G may in some cases supplement the information provided by AUC_I (Fekedulegn et al., 2007), it was not utilized in the current study. This is because the current study aimed to examine differential cortisol reactivity across differentially stressful challenges. While AUC_I provides a pure measure of cortisol reactivity to challenge, AUC_G values can confound cortisol reactivity with baseline cortisol levels. This notion is supported by findings that cortisol baseline and reactivity values are often negatively correlated (e.g., Brennan et al., 2008). Thus, in the context of challenge, infants with high baseline cortisol values and low cortisol change values could have similar AUC_G values as infants with low baseline cortisol values and robust cortisol change values. This suggests that AUC_I is the optimal measure when examining differential cortisol reactivity across challenges. As a result, only AUC_I was utilized in the current study.

Maternal Behaviour Q-Sort. The Maternal Behaviour Q-Sort (MBQS, Pederson et al., 1990), a measure of maternal sensitivity, is a set of 90 items describing mother-infant interactive behaviours. Based on a two-hour home observation of mother-infant interaction, experienced sorters who were blind to other measures 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 MBQS score represents the correlation between the scores of the observers Q-sort with those of a

theoretically derived sort of a prototypically sensitive mother. Thus, 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. The MBQS scores in the current sample ranged from -.69 to .90 (M = 0.46; SD = 0.34). The MBQS is a cross-culturally valid and reliable measure of maternal sensitivity (Atkinson et al., 2000a, 2000b; Chaimongkol & Flick, 2006; Pederson et al., 1990; Tarabulsy et al., 2009). For example, MBQS observations have been associated with infant attachment security at r = .48, whereas traditional assessments of sensitivity have an effect size of only r = .21 (Atkinson et al., 2000a, 2000b), indicating high predictive validity of the MBQS. In the current dataset, inter-observer reliability was high, *Intraclass Correlation Coefficient* = *.88*, $p < .001$. The mean sensitivity scores of both observers were used in the current study's analyses.

Statistical Analyses

Multiple imputation. To account for missing data with respect to covariates, maternal depressive symptoms, TFP AUC_I, and SSP AUC_I, multiple imputations were conducted. Multiple imputation addresses missing data by replacing it with $x > 1$ sets of simulated imputed cells, resulting in x plausible but unique versions of the complete dataset. Each of the x datasets is analyzed uniformly and then, with simple arithmetic, are combined to yield overall estimates and standard errors that reflect sample variation and missing-data uncertainty (Collins, Shafer, & Kam, 2001). In the present study, 20 imputations were conducted, exceeding the recommended minimum and sufficient to yield highly efficient inferences (Collins et al., 2001; Graham, Olchowski, & Gilreath, 2007; Schafer & Graham, 2002). The average of the 20 imputations for each model's significance and the pooled predictors were utilized. To determine if the data were suitable for imputation, Little's (1988) missing completely at random (MCAR) test was conducted. Based on Little's MCAR test, the data for the TFP, χ^2 (2) = 3.14, p = .20, and SSP, χ^2

(2) = 0.79, p = .67, analyses were missing at random, and thus imputation was appropriate (Collins et al., 2001).

Analyzing diathesis stress and differential susceptibility. Based on Belsky, Bakermans-Kranenburg, and van IJzendoorn's (2007) and Roisman et al.'s (2012) recommendations, I conducted a series of statistical procedures designed to establish and differentiate between differential susceptibility and diathesis stress. First, hierarchical multiple regression analyses were conducted with the predictor (i.e., maternal depressive symptoms) and proposed moderator (i.e., infant genotype) entered in the first step, and the interaction term (i.e., product) of the predictor and moderator variables entered in the second and final step. Six such regression analyses were conducted, given that I examined three proposed moderators (i.e., DRD2, DAT1, and COMT genotypes), and two outcome variables (i.e., the TFP AUC_I and the SSP AUC_I). Moderators were dummy coded as 0 (*candidate allele absence*) or 1 (*candidate allele presence*). As recommended by Dearing and Hamilton (2006), the continuous predictor variable (maternal depressive symptoms) was centered to reduce multicollinearity (Field, 2009) and aid in interpretation.

Adding to the visual interpretation of graphs (Figure 2), regions of significance (RoS) on X tests were conducted. The RoS on X test examines the values of X (the predictor variable, maternal depressive symptoms) for which the moderator and the outcome variable are significantly related. To support differential susceptibility, the association between the moderator and the outcome must be significant at both the low and high ends of the predictor variable within the normative range of 2 standard deviations (SD) above and below the mean of the predictor (see Figure 3). To support diathesis-stress, the association between the moderator and the outcome must be significant at only one end of the predictor variable within 2 SD.

See Figure 2

See Figure 3

In addition to the RoS on X test, the proportion of interaction index (PoI) was calculated for each analysis to represent the proportion of the interaction effect that is uniquely attributable to differential susceptibility (see Figures 4a and 4b). In other words, the PoI is the ratio of better outcomes (*b*) for the susceptibility group over the sum of better outcomes and worse (*w*) outcomes, $b/(b + w)$. Both differential susceptibility and diathesis-stress account for worse outcomes, but only differential susceptibility accounts for better outcomes among those with susceptibility factors (in the context of low maternal depressive symptomatology). Roisman et al. (2012) suggest that *w* should be equal to 100% in the prototypical case of diathesis stress (and thus the PoI should equal 0), while both *b* and *w* should equal 50% in the case of differential susceptibility (and thus the PoI should equal 0.5). They suggest that, as a *rough* marker, PoI values between 0.4 and 0.6 are highly consistent with differential susceptibility, and values close to 0 are consistent with diathesis stress.

See Figure 4

In addition to the PoI, the proportion affected (PA) index was calculated to represent the proportion of the population that is differentially affected by the moderator variable (i.e.,

candidate allele). First, the value of maternal depressive symptoms at which the regression lines cross was identified. The crossover point is the point at which the association between the moderator and outcome changes as a function of maternal depressive symptoms. To calculate the PA index, the dataset was sorted by maternal depressive symptoms and the proportion of cases that fell below the crossover point (representing better outcomes in the context of fewer maternal depressive symptoms) was determined. Roisman et al. (2012) suggest that if only 16% or less of cases fall below the crossover point, data are more consistent with diathesis-stress than with differential susceptibility. For each analysis in the current study, the RoS on X, PoI, and crossover point for the PA calculation were generated using a web-based program developed by Roisman et al. (2012) at http://www.yourpersonality.net/interaction/.

Finally, in order to prevent discovering differential susceptibility effects merely as a result of imposing a linear predictor model on a nonlinear diathesis-stress effect (see Figure 5), I examined an additional model for each analysis that included X^2, i.e., (maternal depressive symptoms)^2 and ZX^2, i.e., (moderator x maternal depressive symptoms)^2. To support differential susceptibility, none of i) X^2, ii) ZX^2, or iii) the combination of both together, can be statistically significant. If a nonlinear term is significant, then, in order to support either diathesis-stress or differential susceptibility, it must be demonstrated that the maternal depressive symptoms x moderator interaction term (i.e., the focal interaction term) remains statistically significant after controlling for these nonlinear terms.

See Figure 5

Results

Control Variables

I conducted bivariate correlational analyses to assess the relation between AUC_I and control variables. These variables included infant sex, infant feeding and wake times, family income, maternal age, maternal education, maternal breastfeeding status, maternal smoking status, and maternal sensitivity. No significant correlations emerged.

Descriptive Statistics

Genotype distributions are presented in Table 2. BDI total scores ranged from 0 to 39 (Median = 6.00, Interquartile Range = 7.00). The majority (94.4%) of mothers did not exceed the cut-off for clinical depression (see Table 3, Beck et al., 1996). Correlations between study variables are reported in Table 4. In the context of the TFP, infant AUC_I values ranged from -662.28 to 2156.40 (Median = -26.03, Interquartile Range = 68.44). An examination of the sample's overall baseline, +20 minute and +40 minute cortisol values in the context of the TFP revealed that cortisol secretion decreased throughout the TFP (see Figure 6). We attribute this decrease to a decline in cortisol following an "arrival effect", or anticipatory anxiety (Atkinson et al., 2013). In the context of the SSP, AUC_I values ranged from -3784.50 to 2338.25 nmol/L (Median = 9.09, Interquartile Range = 101.50). An examination of the sample's overall baseline, +20 minute and +40 minute cortisol values revealed that cortisol increased in the context of the SSP (see Figure 7).

See Table 2

See Table 3

See Table 4

See Figure 6

See Figure 7

TFP and SSP AUC_I values deviated from normality and were log transformed to minimize skew, which is common in the cortisol literature (e.g., Gonzalez, Jenkins, Steiner, & Fleming, 2009; Gunnar, Frenn, Wewerka, & van Ryzin, 2009; Luecken, Kraft, & Hagan, 2009). After the transformations, the AUC_I values were less leptokurtic, but not completely normal. However, Kerlinger and Pedhazur (1973) reviewed the research examining the robustness of *F* and *t* tests and argue that multiple regression resists violations of normality of the dependent variable, especially after transformations or when dependent variables do not substantially deviate from normality, as in the current study. Accordingly, Field (2009) does not consider normality of the dependent variable to be a necessary pre-requisite for multiple regression.

Main Analyses

Main analyses are presented in two sections. First are results on the prediction of infant cortisol reactivity (AUC_I) in the context of the TFP. Within this section, results are presented in relation to the interaction of maternal depressive symptoms and each of three moderators: i)

DRD2 genotype, ii) DAT1 genotype, and iii) COMT genotype. Second are results on the prediction of infant AUC_I in the context of the SSP. Within this section, results are presented similarly. Results are presented utilizing multiple imputation. Analyses were re-run utilizing the non-imputed dataset (list-wise deletion) and are also reported here.

Predicting infant cortisol reactivity in the context of the toy frustration procedure. I conducted three hierarchical multiple regression analyses to determine whether i) DRD2 genotype, ii) DAT1 genotype, and iii) COMT genotype moderate the association between maternal depressive symptoms and infant AUC_I in the context of the TFP (see Table 5). The RoS on X, PoI, PA, and linearity tests were then applied to each model (see Table 6).

See Table 5

See Table 6

DRD2 genotype as a moderator of the relation between maternal depressive symptoms and infant AUC_I in the context of the toy frustration procedure. As depicted in Table 5, the overall model was significant, F (3, 289) = 5.42, $p < .01$; adjusted $R^2 = .04$. The standardized regression coefficients shown in Table 5 indicate that only the interaction between maternal depressive symptoms and DRD2 genotype made a significant contribution to infant AUC_I. An analysis of the non-imputed dataset revealed that the moderation model remained significant, F (3, 217) = 5.08, $p < .01$; adjusted $R^2 = .05$, and that the interaction between maternal depressive symptoms and DRD2 genotype remained the only significant contributor to infant AUC_I, $\beta = .18$,

$p < .05$. Figure 8 depicts the interaction of maternal depressive symptoms and infant DRD2 genotype, as they predict infant cortisol reactivity in the TFP.

See Figure 8

The differential susceptibility/diathesis-stress indices are summarized in Table 6. The RoS on X test revealed significant differences between high and low Z (DRD2 genotype) for values of maternal depressive symptoms above 1.38. This indicates that the significant maternal depressive symptoms x DRD2 genotype interaction is driven by the higher AUC_Is of infants with the A1 allele whose mothers are higher on depressive symptomatology (as opposed to also being driven by the lower AUC_Is of infants with the A1 allele whose mothers are lower on depressive symptomatology). Thus, the RoS on X test supports diathesis-stress and is not consistent with differential susceptibility. Roisman et al. (2012) argued that if the RoS on X test supports diathesis-stress over differential susceptibility then the data do not represent differential susceptibility, even if all other proposed statistical criteria (i.e., PoI, PA, and linearity) are consistent with differential susceptibility. Nevertheless the remaining criteria were examined. The PoI was 0.15, which also supports diathesis stress and is not consistent with differential susceptibility. This PoI indicates that a higher proportion of the interaction represents worse outcomes in the context of higher maternal depressive symptoms than better outcomes in the context of fewer maternal depressive symptoms. The crossover point of the interaction (i.e., the point on maternal depressive symptoms where the regression lines intersect) was -5.44. The PA index represents the proportion of cases scoring below -5.44 on maternal depressive symptoms (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was

19.3%, which could be considered supportive of either diathesis-stress or differential susceptibility, but is more representative of diathesis-stress (Roisman et al., 2012). Finally, the nonlinearity test indicated that neither X^2, $t(287) = 0.75$, *ns*, nor ZX^2, $t(287) = 1.05$, *ns*, were significant predictors of AUC_I when included in the model.

Overall, results indicate that DRD2 genotype moderates the relationship between maternal depressive symptoms and infant cortisol reactivity in the context of the TFP in a diathesis-stress manner. That is, infants with the A1 allele, relative to infants without the A1 allele, had higher AUC_Is (reflecting buffered cortisol declines) if the mother was high in depressive symptomatology.

DAT1 genotype as a moderator of the relation between maternal depressive symptoms and infant AUC_I in the context of the toy frustration procedure. The overall model was significant, $F(3, 268) = 4.92$, $p < .01$; adjusted $R^2 = .04$ (see Table 5). The interaction between maternal depressive symptoms and DAT1 genotype approached significance ($p = .07$), which leaves some ambiguity in the findings. However, an analysis of the non-imputed dataset revealed that the overall model remained significant, $F(3, 204) = 4.34$, $p < .01$, adjusted $R^2 = .05$, and that only the interaction between maternal depressive symptoms and DAT1 genotype made a significant contribution to the model, $\beta = .26$, $p = .05$. Figure 9 depicts the interaction of maternal depressive symptoms and infant DAT1 genotype, as they predict infant cortisol reactivity in the TFP.

See Figure 9

The differential susceptibility/diathesis-stress indices are summarized in Table 6. The RoS on X test revealed significant differences between high and low Z (DAT1 genotype) for values of maternal depressive symptoms above 6.97. This indicates that the maternal depressive symptoms x DAT1 genotype interaction is driven by the higher AUC_Is of infants with the 10/10 allele whose mothers are higher on depressive symptomatology (as opposed to the lower AUC_Is of infants with the 10/10 allele whose mothers are lower on depressive symptomatology). Thus, the RoS on X test supports diathesis-stress and is not consistent with differential susceptibility. Roisman et al. (2012) argued that if the RoS on X test supports diathesis-stress over differential susceptibility then the data do not represent differential susceptibility, even if all other proposed statistical criteria (i.e., PoI, PA, and linearity) are consistent with differential susceptibility. Nevertheless the remaining criteria were examined. The PoI was 0.31. This PoI is slightly more consistent with differential susceptibility, relative to diathesis-stress, indicating that only a somewhat greater proportion of the interaction represents worse outcomes in the context of higher maternal depressive symptoms than better outcomes in the context of lower levels of maternal depressive symptoms. The crossover point of the interaction (i.e., the point on maternal depressive symptoms where the regression lines intersect) was -2.52. The PA index was 44.2%, which represents the proportion of cases scoring below -2.52 on maternal depressive symptoms (i.e., those experiencing better outcomes in the context of lower levels of maternal depressive symptoms). Finally, the linearity test indicated that neither X^2, $t(266) = 0.21$, *ns*, nor ZX^2, $t(266) = 0.87$, *ns*, were significant predictors of AUC_I when included in the model. Thus, this analysis passed the linearity test.

Taken together, findings indicate that DAT1 genotype moderates the relationship between maternal depressive symptoms and infant cortisol reactivity in the context of the TFP in

a diathesis-stress manner. That is, infants with the 10/10 allele, relative to infants without the 10/10 allele, had higher AUC_Is (reflecting buffered cortisol declines) if the mother was high in depressive symptomatology.

COMT genotype as a moderator of the relation between maternal depressive symptoms and infant AUC_I in the context of the toy frustration procedure. As depicted in Table 5, the overall model was significant, F (3, 289) = 7.35, $p < .001$; adjusted $R^2 = .06$. The standardized regression coefficients shown in Table 5 indicate that only the interaction between maternal depressive symptoms and COMT genotype made a significant contribution to infant cortisol reactivity (AUC_I). An analysis of the non-imputed dataset revealed that the moderation model remained significant, F (3, 216) = 7.90, $p < .01$; adjusted $R^2 = .09$, and that the interaction between maternal depressive symptoms and COMT genotype remained the only significant contributor to infant AUC_I, $\beta = .29$, $p < .001$. Figure 10 depicts the interaction of maternal depressive symptoms and infant COMT genotype, as they predict infant cortisol reactivity in the TFP. As illustrated in Figure 10, the G/G (val158) allele, as opposed to the A (met158) allele, is the "susceptibility" allele.

See Figure 10

The differential susceptibility/diathesis-stress indices are summarized in Table 6. The RoS on X test revealed a lower threshold of -2.95 and upper threshold of 4.59 for maternal depressive symptoms, where the regression of AUC_I on COMT genotype is statistically significant for values of maternal depressive symptoms outside this region. Since this region is within 2 SD of the mean of maternal depressive symptoms and the association between AUC_I

and COMT genotype was significant for both low and high values of maternal depressive symptoms, differential susceptibility is supported. The PoI was 0.52, which is prototypical of differential susceptibility. This PoI indicates that equal proportions of the interaction represent better outcomes and worse outcomes from the differential susceptibility effect. The crossover point of the interaction (i.e., the point on maternal depressive symptoms where the regression lines intersect) was 0.66. The PA index represents the proportion of cases scoring below 0.66 on maternal depressive symptoms (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 68%, which is consistent with differential susceptibility. Finally, the nonlinearity test indicated that X^2 was not a significant predictor of AUC_I when entered in the model, $t(287) = 0.13$, *ns*, but that ZX^2 was, $t(287) = 5.45$, $p < .001$. The maternal depressive symptoms x COMT genotype interaction did not remain statistically significant when X^2 and ZX^2 were included in the model, $t(287) = -0.67$, *ns*. Thus, this analysis failed the linearity test.

Overall, infants with the G/G allele, relative to infants without the G/G allele, had higher AUC_Is (reflecting buffered cortisol declines) if the mother was high in depressive symptomatology, and lower AUC_Is (reflecting more robust cortisol declines) if the mother was low in depressive symptomatology. However, the interaction effect can be more parsimoniously understood as driven by lower order (nonlinear) effects. Thus, the interaction is not consistent with either diathesis-stress or differential susceptibility (Roisman et al., 2012).

Predicting infant cortisol reactivity (AUC_I) in the context of the SSP. I conducted three hierarchical multiple regression analyses to determine whether i) DRD2 genotype, ii) DAT1 genotype, and iii) COMT genotype moderate the association between maternal depressive

symptoms and infant AUC_I in the context of the SSP (see Table 7). The RoS on X, PoI, PA, and linearity tests were then applied to each model (see Table 8).

See Table 7

See Table 8

DRD2 genotype as a moderator of the relation between maternal depressive symptoms and infant AUC_I in the context of the strange situation procedure. As depicted in Table 7, the overall model was significant, F (3, 271) = 16.17, $p < .001$; adjusted $R^2 = .12$. The standardized regression coefficients shown in Table 7 indicate that only the interaction between maternal depressive symptoms and DRD2 genotype made a significant contribution to infant AUC_I. An analysis of the non-imputed dataset revealed that the moderation model remained significant, F (3, 210) = 14.10, $p < .001$; adjusted $R^2 = .16$, and that the interaction between maternal depressive symptoms and DRD2 genotype remained the only significant contributor to infant AUC_I, $\beta = -.37$, $p < .001$. Figure 11 depicts the interaction of maternal depressive symptoms and infant DRD2 genotype, as they predict infant cortisol reactivity in the SSP.

See Figure 11

The differential susceptibility/diathesis-stress indices are summarized in Table 8. The RoS on X test revealed a lower threshold of -5.89 and upper threshold of 0.39 for maternal

depressive symptoms, where the regression of AUC_I on DRD2 genotype is statistically significant for values of maternal depressive symptoms outside this region. Since this region is within 2 SD of the mean of maternal depressive symptoms and the association between AUC_I and DRD2 genotype is significant for both low and high values of maternal depressive symptoms, differential susceptibility is supported. The PoI index was 0.33. This PoI is more consistent with differential susceptibility, relative to diathesis-stress, indicating that a somewhat greater proportion of the interaction represents worse outcomes in the context of higher maternal depressive symptoms than better outcomes in the context of lower levels of maternal depressive symptoms. The crossover point of the interaction (i.e., the point on maternal depressive symptoms where the regression lines intersect) was -2.33. The PA index represents the proportion of cases scoring below -2.33 on maternal depressive symptoms (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 44.2%, which is consistent with differential susceptibility. Finally, the nonlinearity test indicated that neither X^2, $t(269) = -0.87$, *ns* nor ZX^2, $t(269) = -1.84$, *ns* were significant predictors of AUC_I when added to the model. Thus, this analysis passed the linearity test.

Taken together, findings indicate that DRD2 genotype moderates the relationship between maternal depressive symptoms and cortisol reactivity in the context of the SSP in a differential susceptibility manner. That is, relative to infants without the A1 allele, those with the A1 allele had lower AUC_Is (reflecting buffered cortisol increases) if the mother was high in depressive symptomatology, and higher AUC_Is (reflecting more robust cortisol increases) if the mother was low in depressive symptomatology.

DAT1 genotype as a moderator of the relation between maternal depressive symptoms and infant AUC_I in the context of the strange situation procedure. As depicted in Table 7, the

overall model was significant, F (3, 251) = 11.96, $p < .001$; adjusted $R^2 = .12$. The standardized regression coefficients shown in Table 7 indicate that only the interaction between maternal depressive symptoms and DAT1 genotype made a significant contribution to infant AUC_I. An analysis of the non-imputed dataset revealed that the overall model remained significant, F (3, 193) = 8.58, $p < .001$, adjusted $R^2 = .10$, and that only the interaction between maternal depressive symptoms and DAT1 genotype made a significant contribution to the model, $\beta = -.33$, $p < .01$. Figure 12 depicts the interaction of maternal depressive symptoms and infant DAT1 genotype, as they predict infant cortisol reactivity in the SSP.

See Figure 12

The differential susceptibility/diathesis-stress indices are summarized in Table 8. The RoS on X test revealed a lower threshold of -11.29 and upper threshold of 2.81 for maternal depressive symptoms, where the regression of AUC_I on DAT1 genotype is statistically significant for values of maternal depressive symptoms outside this region. Since this region is within 2 SD of the mean of maternal depressive symptoms and the association between AUC_I and DAT1 genotype is significant for both low and high values of maternal depressive symptoms, differential susceptibility is supported. The PoI was 0.35. This PoI is more consistent with differential susceptibility, relative to diathesis-stress, indicating that roughly equal proportions of the interaction represent better outcomes and worse outcomes from the differential susceptibility effect. The crossover point of the interaction (i.e., the point on maternal depressive symptoms where the regression lines intersect) was -2.10. The PA index represents the proportion of cases scoring below -2.10 on maternal depressive symptoms (i.e., those

experiencing better outcomes from the differential susceptibility effect). The PA was 44.2%, which is consistent with differential susceptibility. Finally, the linearity test indicated that neither X^2, $t(249) = -0.50$, *ns,* nor ZX^2, $t(249) = -1.09$, *ns,* were significant predictors of AUC_I when added to the model. Thus, this analysis passed the linearity test.

Taken together, findings indicate that DAT1 genotype moderates the relationship between maternal depressive symptoms and infant cortisol reactivity in the context of the SSP in a differential susceptibility manner. That is, relative to infants without the 10/10 allele, those with the 10/10 allele had lower AUC_Is (reflecting buffered cortisol increases) if the mother was high in depressive symptomatology, and higher AUC_Is (reflecting more robust cortisol increases) if the mother was low in depressive symptomatology.

COMT genotype as a moderator of the relation between maternal depressive symptoms and infant AUC_I in the context of the strange situation procedure. As depicted in Table 7, the overall model was significant, $F(3, 271) = 23.28$, $p < .001$; adjusted $R^2 = .19$. As shown in Table 7, only the interaction between maternal depressive symptoms and infant COMT genotype significantly contributed to the prediction of AUC_I. An analysis of the non-imputed dataset revealed that the moderation model remained significant, $F(3, 211) = 23.90$, $p < .001$; adjusted $R^2 = .25$, and that the interaction between maternal depressive symptoms and COMT genotype remained a significant contributor to infant AUC_I, $\beta = -.49$, $p < .001$. Figure 13 depicts the interaction of maternal depressive symptoms and infant COMT genotype, as they predict infant cortisol reactivity in the SSP. As illustrated in Figure 13, the G/G (val158) allele, as opposed to the A (met158) allele, is the "susceptibility" allele.

See Figure 13

The differential susceptibility/diathesis-stress indices are summarized in Table 8. The RoS on X test revealed a lower threshold of -4.32 and upper threshold of -0.22 for maternal depressive symptoms, where the regression of AUC_I on COMT genotype is statistically significant for values of maternal depressive symptoms outside this region. Since this region is within 2 SD of the mean of maternal depressive symptoms and the association between AUC_I and COMT genotype was significant for both low and high values of maternal depressive symptoms, differential susceptibility is supported. The PoI was 0.35. This PoI is slightly more consistent with differential susceptibility, relative to diathesis-stress, indicating that somewhat equal proportions of the interaction represent worse outcomes in the context of higher maternal depressive symptoms and better outcomes in the context of lower levels of maternal depressive symptoms. The crossover point of the interaction (i.e., the point on maternal depressive symptoms where the regression lines intersect) was -2.09. The PA index represents the proportion of cases scoring below -2.09 on maternal depressive symptoms (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 44.2%, which is consistent with differential susceptibility. Finally, the linearity test indicated that X^2 was not a significant predictor of AUC_I, $t(269) = -1.38$, *ns*, but that ZX^2 was, $t(269) = -10.16$, $p < .001$. The maternal depressive symptoms x COMT genotype interaction did not remain statistically significant when X^2 and ZX^2 were included in the model, $t(269) = 0.37$, *ns*. Thus, this analysis failed the linearity test.

Overall, infants with the G/G allele, relative to infants without the G/G allele, had lower AUC_Is (reflecting buffered cortisol increases) if the mother was high in depressive symptomatology, and higher AUC_Is (reflecting more robust cortisol increases) if the mother was

low in depressive symptomatology. However, the interaction effect can be more parsimoniously understood as driven by lower order (nonlinear) effects. Thus, the interaction is not consistent with either diathesis-stress or differential susceptibility (Roisman et al., 2012).

Discussion

This study examined whether i) DRD2, DAT1, and COMT genotypes moderate the relation between maternal depressive symptoms and infant cortisol reactivity to psychosocial challenge, ii) these moderating effects reflect diathesis-stress or differential susceptibility, and iii) the nature of these moderating effects differs in the context of two infant challenge paradigms, the TFP and SSP. In the context of the TFP, infant DRD2 and DAT1 (but not COMT) genotypes moderated the relation between maternal depressive symptoms and infant cortisol reactivity in a diathesis-stress manner. Infants with the i) A1 allele of DRD2 and ii) 10/10 allele of DAT1, relative to infants without these alleles, show buffered cortisol reactivity (specifically buffered declines in cortisol) if the mother endorses high depressive symptomatology. In the context of the SSP, infant DRD2 and DAT1 (but not COMT) genotypes moderated the relation between maternal depressive symptoms and infant cortisol reactivity in a differential susceptibility manner. Infants with the i) A1 allele of DRD2 and ii) 10/10 allele of DAT1, relative to infants without these alleles, show buffered cortisol reactivity (specifically buffered increases in cortisol) if the mother endorses high depressive symptomatology, and more robust cortisol reactivity if the mother endorses low depressive symptomatology. These findings were established utilizing Roisman et al.'s (2012) statistical guidelines for differentiating between diathesis-stress and differential susceptibility (i.e., RoS on X, PoI, PA, and linearity tests). A discussion of findings is presented here, followed by acknowledgments of the

limitations of the current study, suggestions for future research, theoretical implications, and clinical implications.

The Influences of Maternal Depressive Symptoms and Dopamine-Related Genetic Variation on Infant Cortisol Reactivity

The *HPA programming hypothesis* indicates that the HPA axis is programmed by maternal stress and interactive behaviour in the antenatal and early postnatal periods. Given that maternal depression is a robust risk factor for youth depression (Weissman et al., 2006), a disorder characterized by dysregulated HPA functioning (Pariante, 2003), maternal depression has been hypothesized to play a key role in early HPA programming. Accordingly, Oberlander et al. (2008a) found that exposure to maternal depression was associated with increased methylation of the glucocorticoid receptor gene, which in turn was associated with increased salivary cortisol stress responses at 3 months of age. While there are several pathways through which maternal depressive symptoms may impact the development of the HPA axis, researchers have predominantly argued that i) maternal stress weakens the placental enzyme 11ß-HSD-2, thus enabling maternal glucocorticoids to pass through the placenta to the fetus and disrupt HPA development (O'Donnell et al., 2012; O'Donnell et al., 2009; Seckl & Holmes, 2007), and ii) maternal depressive symptoms compromise the mother's ability to provide sensitive caregiving (Hatzinikolaou & Murray, 2010; Murray et al., 2010), which in turn disrupts the development of the infant's HPA system (Albers et al., 2008; Gunnar & Donzella, 2002).

The current results, linking postnatal maternal depressive symptoms to dysregulated infant cortisol reactivity, further support the significant influence of maternal depression on infants' developing stress physiology. Given that these findings emerged while utilizing maternal sensitivity as a covariate, two speculative possibilities are that i) maternal depression impacts

infant HPA function predominantly through pathways other than parenting, such as fetal programming (Glover, O'Connor, & O' Donnell, 2010), poor marital functioning (Pendry & Adam, 2007), and maternal-infant cortisol attunement (Laurent et al., 2011), or ii) maternal depressive symptoms do not impact infant HPA function via sensitivity per se, but hostility (Dougherty, Tolep, et al., 2013) and withdrawal (Murray et al., 2010) may play more of a role. The precise mechanisms through which maternal depression impacts infant HPA development is a fruitful area for future research.

Importantly, the current results showed that dopamine-related genetic variation moderates the relation between maternal depressive symptoms and infant cortisol reactivity. Dopamine affects stress reactivity by impacting the mPFC and the amygdala, which regulate HPA functioning (Alexander et al., 2011; Zhang et al., 2005). In fact, the correlation between dopamine and cortisol release in response to psychosocial stress is $r = .78$ (Pruessner et al., 2004). Thus, the current findings further speak to the influential role of dopamine within the human stress response. Moreover, the identification of genetic moderators supports the notion that the origins of individual differences in HPA function emerge from the interaction of inherited and environmentally influenced factors related to maternal mental health (Bakermans-Kranenburg et al., 2008; Laurent et al., 2011; Meaney, 2010).

While dopamine-related genes do play a moderating role within the relationship between maternal depressive symptoms and infant cortisol reactivity, the current findings also revealed that the nature of that role depends on the context in which the infant is challenged. Specifically, diathesis-stress emerged in the context of the TFP, and differential susceptibility emerged within the context of the SSP. These findings are consistent with studies identifying DRD2 and DAT1 as both diathesis stress- and differential susceptibility- related moderators (Belsky & Pluess,

2009; Laucht et al., 2007; van IJzendoorn et al., 2008), and with Roisman et al.'s (2012) finding that diathesis-stress and differential susceptibility can both operate for the same GxE model, but within different contexts (also see Cassidy et al., 2011, and Cichetti et al., 2011). It is not entirely clear, however, why the patterns of moderation (i.e., differential susceptibility versus diathesis stress) differ by challenge context. At present, research pertinent to how differential context associates with each of these GxE models is extremely rare. Given that maternal separation results in greater cortisol increases than frustration challenges at this age (Atkinson et al., 2013; Jansen et al., 2010; Laurent et al., 2012), one speculative possibility is that diathesis-stress operates in the context of relatively mild stressors, whereas differential susceptibility operates in the context of higher challenge conditions.

Further exemplifying the importance of context, the interactions of maternal depressive symptoms and i) infant DRD2 genotype and ii) infant DAT1 genotype both account for 5% of the variance in cortisol reactivity in the context of the TFP, but 13% and 12% (respectively) of the variance in cortisol reactivity in the context of the SSP. Thus, both GxE models account for more than double the variance in cortisol reactivity in the context of the SSP, relative to the TFP. This indicates that the magnitude of the influence of GxE on child development may be context specific, and calls for future studies to incorporate these methodological considerations.

The current results also underscore the importance of considering differential patterns of cortisol secretion in response to differentially challenging circumstances. As reviewed, the SSP provokes larger increases in infant cortisol secretion than the TFP, suggesting that the SSP is the more potent stressor (Atkinson et al., 2013). Atkinson et al. (2013) suggested that healthy HPA functioning involves flexible reactivity characterized by a robust decrease in cortisol concentrations (in the event of anticipatory anxiety) in the context of relatively mild stressors, as

well as a robust increase in cortisol concentrations in the context of more potent challenges. The current results showed that infants of mothers higher in depressive symptomatology, relative to infants of mothers lower in depressive symptomatology, have buffered cortisol declines in the context of the TFP and buffered cortisol increases in the context of the SSP. Moreover, the relationships between maternal depressive symptoms and infant cortisol reactivity are more pronounced among infants with candidate dopamine-related genotypes, relative to infants without these genotypes. Thus, the current results support that i) there are important differences in infant cortisol secretion across challenge paradigms (Atkinson et al., 2013; Jansen et al., 2010; Laurent et al., 2012), ii) healthy HPA functioning is characterized by a flexible cortisol response across differentially challenging circumstances (Atkinson et al., 2013), and iii) maternal depressive symptomatology is related to the flexibility of the infant cortisol response across differentially challenging circumstances, but particularly for infants with certain genetic characteristics.

COMT Genotype as a Marker of Susceptibility to Environmental Influences

I was the first to examine whether COMT genotype moderates the relation between environmental factors and infant cortisol secretion in a diathesis stress or differential susceptibility manner. The current analyses involving COMT genotypes were exploratory with regard to which allele (i.e., val158 or met158) would confer heightened susceptibility to the influences of maternal depressive symptoms on infant cortisol reactivity. A directed hypothesis could not be established because the met158 allele has been linked to increased stress hormone release and impaired stress recovery (Alexander et al., 2011; Jabbi et al., 2007; Oswald, et al., 2004), but both the met158 and val158 alleles have been identified as markers of heightened susceptibility to environmental influences (e.g., Nederhof et al., 2012; van IJzendoorn et al.,

2008). The current study provides some evidence that the G/G (i.e., val158) allele is the differential susceptibility-related moderator of the association between maternal depressive symptoms and infant cortisol secretion (see Figures 10 and 13). However, upon closer examination with Roisman et al.'s (2012) linearity test, the current interaction effects are more parsimoniously understood as driven by lower order (nonlinear) effects. Thus, neither diathesis-stress nor differential susceptibility are supported in the context of either the TFP or SSP. Future research is needed to clarify the nonlinear role of COMT genotype in moderating the relation between maternal depressive symptoms and infant cortisol secretion.

Limitations of the Current Research

A number of limitations of the current study warrant consideration. Specifically, the BDI-II is designed to assess depressive symptoms over the past two weeks and this study incorporates a 1-month time span, potentially weakening prediction from BDI-II to SSP findings. Studies have also suggested that the timing of maternal depressive symptoms can impact the association between maternal depressive symptoms and child cortisol secretion (Brennan et al., 2008; Diego et al., 2004; Essex et al., 2002; Laurent et al., 2011), and that prenatal maternal depression can disrupt the development of the fetus' HPA axis by weakening the placental enzyme 11ß-HSD-2 (O'Donnell et al., 2009; Seckl & Holmes, 2007). Given that the current study only examined maternal depressive symptoms at infant age 16 months, future studies might examine how antenatal, early postnatal, and later postnatal maternal depressive symptoms differentially interact with infant genotype to predict infant cortisol reactivity across challenges. Additionally, maternal psychotropic medication (Brennan et al., 2008; Oberlander et al., 2008b) and type of depression (Dougherty, Klein, Olino, Dyson, & Rose, 2009) may also impact the relationship

between maternal depressive symptomatology and infant cortisol secretion, but these were not assessed in the current study.

Furthermore, genotyping DRD4 was unsuccessful, likely due to buccal cell degradation; therefore, the DRD4 marker was removed from the current study. The DRD4 7-repeat allele has been identified as a diathesis stress and differential susceptibility marker (e.g., Beach et al., 2010; Kegel et al., 2011; Knafo et al., 2011; Martel et al., 2011; Nederhof et al., 2012) and has previously been shown to moderate the relationship between maternal participation in a sensitivity promoting intervention and infant daily cortisol production (Bakermans-Kranenburg et al., 2008). Future studies are needed to examine whether the 7-repeat allele may also promote susceptibility to the influences of maternal depressive symptoms on infant cortisol reactivity to psychosocial challenge.

In addition, the interaction of maternal depressive symptoms and i) infant DRD2 genotype and ii) infant DAT1 genotype each account for only 5% of the variance in AUC_I in the context of the TFP. However, the statistical magnitude of an effect does not necessarily reflect its theoretical or practical value. For example, aspirin has an effect size of $r = .03$ as a prophylactic against cardiac arrest (Steering Committee of the Physician's Health Study Research Group, 1988), but regardless of its statistical effect size has significant consequences for diverse populations across the lifespan. Similarly, relations between maternal depressive symptoms, infant genotype, and infant HPA functioning have universal implications (Field, 2010; Gunnar & Donzella, 2002; Kessler, 2002).

Finally, there was some ambiguity in the current findings: the interaction between maternal depressive symptoms and DAT1 genotype as it predicts AUC_I approached significance in the context of the TFP ($p = .07$). However, an analysis of the non-imputed dataset revealed that the

interaction between maternal depressive symptoms and DAT1 genotype made a significant contribution to AUC_I in the context of the TFP, thus augmenting confidence in the current findings and conclusions. It is also worth considering that this study did not have sufficient power to reduce alpha across its six main analyses for the purpose of controlling Type I error. Nevertheless, results are consistent across genes and challenges, rendering Type I error unlikely, and analyses involving COMT were exploratory, in any case. It is also worth noting that the statistical criteria utilized to differentiate between diathesis-stress and differential susceptibility represent an improvement from typical procedures (Beach et al., 2014; Roisman et al., 2012), but nevertheless leave some interpretation to subjective judgment (e.g., the PoI index).

Despite these limitations, the current study has important methodological strengths. For example, researchers have highlighted that the large number of hypotheses (due to the many variables, operational definitions, and analyses that can be conducted) within GxE research can lead to unacceptable rates of Type I error (Duncan & Keller, 2011; Ellis et al., 2011). As discussed, the within-study replication across candidate genes (i.e., DRD2 and DAT1), and differentially challenging tasks (i.e., TFP and SSP) given at two separate time points (i.e., 16 and 17 months) in two different settings (i.e., home and lab), utilizing recommended statistical procedures (Beach et al., 2014; Roisman et al., 2012), provides evidence that the current findings are not attributable to Type I error (Ellis et al., 2011). Thus, the within-study replication of results is a notable strength and serves to increase the power and reliability of the current findings.

Directions for Future Research

This study was the first to explore infant genotype as a moderator of the relation between maternal depressive symptoms and infant cortisol reactivity. Future experimental research can

build on these findings to better understand the causal factors within the relationships between maternal depressive symptoms, infant genotype, and infant cortisol reactivity. For example, studies can provide treatment for maternal depressive symptoms and then assess whether the cortisol reactivity patterns of infants with candidate genotypes are more susceptible to changing following alleviation of maternal depressive symptoms, relative to the cortisol reactivity patterns of infants without the candidate genotypes. Moreover, given that a community sample was utilized in the current study, results cannot be generalized to infants of mothers with Major Depressive Disorder. Thus, future research should examine the current model within a clinical sample of mother-infant dyads.

In addition, other variables that have previously been shown to moderate the association between maternal depressive symptoms and infant cortisol secretion, such as emotion regulation strategy (Khoury et al., in prep), internalizing symptoms (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002), attachment style (Luijk et al., 2010), and temperament (Dougherty et al., 2013; Mackrell et al., 2014), should be examined to expand on current findings. It would also be important to examine maternal cortisol reactivity, given the associations between maternal and infant cortisol secretion (e.g., Atkinson et al., 2013; Azar et al., 2007; Diego et al., 2004; Feldman et al., 2009; Lundy et al., 1999), and the idea that a depressed mother's ongoing HPA dysregulation can impact her child's HPA development via physiological attunement (Laurent et al., 2011).

Finally, it would be important for future research to examine epistasis and how this may influence the association between maternal depressive symptoms and infant cortisol secretion. Previous research has supported the notion that dopamine-related genotypes interact to influence phenotypes, including cortisol reactivity (e.g., Alexander et al., 2011; Balci et al., 2013;

Bertolino et al., 2008; Heinzel et al., 2013; Hersrud & Stoltenberg, 2009). Moreover, non-dopamine-related plasticity alleles have been identified and may also interact with dopamine-related plasticity alleles to impact the extent of environmental susceptibility. For example, the short allele of the serotonin-transporter-linked polymorphic region (5-HTTLPR) has been identified as a diathesis-stress and differential susceptibility marker (Belsky & Pluess, 2009; Caspi et al., 2003), and has been linked to cortisol reactivity (Gotlib, Joordman, Minor, & Hallmayer, 2008; Armbruster et al., 2009). Armbruster et al. (2009) found a DRD4 x 5-HTTLPR epistatic interaction such that individuals homozygous for the long allele of 5-HTTLPR demonstrate a lower cortisol response to the Triers Social Stress Test, relative to those not homozygous for the long allele, but only if they are also carriers of at least one copy of the DRD4 7 repeat allele. Thus, the dopaminergic and serotonergic systems may have both independent and epistatic effects on stress reactivity (Armbruster et al. 2009). Future studies are needed to examine how plasticity genotypes interact to influence the relation between maternal depressive symptoms and cortisol reactivity in infancy.

Theoretical Implications

The current results also carry theoretical implications regarding the role of nature and nurture in shaping developmental plasticity (Pluess & Belsky, 2011). That is, does the extent of an individual's susceptibility to environmental influence arise from *nature* or *nurture*? The current finding that susceptibility to the influence of maternal depressive symptoms is related to gene variants supports the notion that developmental plasticity is a function of nature (Nussey et al., 2005; Pigliucci, 2001, 2005). On the other hand, physiological stress reactivity also moderates environmental influences in accordance with diathesis-stress and differential susceptibility (Boyce & Ellis, 2005; Ellis et al., 2011), and, as found in the current study, is itself shaped by

environmental influences (i.e., maternal depressive symptoms). Taken together, the current findings support the notion that nature and nurture interact to shape the extent of an individual's susceptibility to environmental influences (Pluess & Belsky, 2011). In other words, as depicted in Figure 14, maternal depressive symptoms may influence the development of one susceptibility marker (i.e., cortisol reactivity), the most in children who are born with another susceptibility marker (i.e., DRD2 and DAT1 plasticity alleles), relative to children without this other susceptibility marker. Thus, for genetic reasons, some individuals may be more likely to be affected by rearing experience in ways that further contribute to the extent to which they will be susceptible to their rearing environments. Future empirical research is needed to explore these theoretical assertions.

See Figure 14

Clinical Implications

Maternal depression is one of the most robust predictors of youth depression (Weissman et al., 2006), and places children at a six-fold increased risk of depression themselves (Downey & Coyne, 1990). Research suggests that one mechanism mediating this risk is dysregulated HPA functioning (Dougherty et al., 2013; Halligan et al., 2007; Laurent et al., 2011; Meaney, 2010). This study demonstrated that infant genotype moderates the relation between maternal depressive symptomatology and infant cortisol reactivity, which indicates that maternal depression has a particularly strong influence on HPA function for children with certain genetic characteristics, relative to children without these genetic characteristics. These results speak to the potential benefits of targeting maternal depressive symptoms in order to prevent the onset of

maladaptive developmental trajectories. Additionally, the fact that the current moderation model was observed within a demographically low risk sample underscores the importance of universal, community accessible parenting intervention programs.

Summary

The current study found that dopamine-related genotypes moderate the relation between maternal depressive symptomatology and infant cortisol secretion in a diathesis-stress manner in the context of a toy frustration task, and in a differential susceptibility manner in the context of a maternal separation procedure. Specifically, in the context of the TFP, infants with the i) A1 allele of DRD2 and ii) 10/10 allele of DAT1, relative to infants without these alleles, show buffered cortisol reactivity (specifically, buffered cortisol declines from anticipatory stress level) if the mother endorses high depressive symptomatology. In the context of the SSP, infants with the i) A1 allele of DRD2 and ii) 10/10 allele of DAT1, relative to infants without these alleles, show buffered cortisol reactivity (specifically, buffered cortisol increases) if the mother endorses high depressive symptomatology, and more robust cortisol reactivity if the mother endorses low depressive symptomatology. These results suggest that maternal depressive symptomatology is related to an infant's cortisol reactivity to psychosocial challenge, but that this relation is dependent on the infant's genetic characteristics and the context of the challenge.

References

Adam, E. K., Doane, L. D., Zinbarg, R. E., Mineka, S., Craske, M. G., & Griffith, J. W. (2010). Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. *Psychoneuroendocrinology, 35*, 921-931.

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

Albers, E. M., Riksen-Walraven, J. M., Sweep, F. C. G. J., & de Weerth, C. (2008). Maternal behavior predicts infant cortisol recovery from a mild everyday stressor. *Journal of Child Psychology and Psychiatry, 49*, 97-103. doi:10.1111/j.1469-7610.2007.01818.x

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.

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.

Antypa, N., Drago, A., & Serretti, A. (2013). The role of COMT gene variants in depression: Bridging neuropsychological, behavioral and clinical phenotypes. *Neuroscience & Biobehavioral Reviews*, *37*, 1597-1610.

Armbruster, D., Mueller, A., Moser, D. A., Lesch, K. P., Brocke, B., & Kirschbaum, C. (2009). Interaction effect of D4 dopamine receptor gene and serotonin transporter promotor polymorphism on the cortisol stress response. *Behavioral Neuroscience, 123*, 1288-1295.

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

Atkinson, L., Gonzalez, A., Kashy, D. A., Basile, V. S., Masellis, M., Pereira, J.,…Levitan, R. (2013). Maternal sensitivity and infant and mother adrenocortical function across challenges. *Psychoneuroendocrinology, 38*, 2943-2951.

Atkinson, L., Niccols, A., Paglia, A., Coolbear, J., Parker, K. C. H., Poulton, L., & Chisholm, V. C. (2000a). A meta-analysis of time between maternal sensitivity and attachment assessments: Implications for internal working models in infancy/toddlerhood. *Journal of Social and Personal Relationships, 17*, 791-810.

Atkinson, L., Paglia, A., Coolbear, J., Niccols, A., Poulton, L., Leung, E., & Chisholm, V. C. (2000b). 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.

Azak, S., Murison, R., Wentzel-Larsen, T., Smither, L., & Gunnar, M. R. (2013). Maternal depression and infant daytime cortisol. *Developmental Psychobiology, 55*, 334-351.

Azar, R., Paquette, D., Zoccolillo, M., Baltzer, F., & Tremblay, R. E. (2007). The association of major depression, conduct disorder, and maternal overcontrol with a failure to show a cortisol buffered response in 4-month infants of teenage mothers. *Biological Psychiatry, 62*, 573-579.

Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., Mesman, J., Alink, L. R. A., & 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.

Balci, F., Wiener, M., Cavdaroglu, B., & Coslett, H. B. (2013). Epistasis effects od dopamine genes on interval timing and reward magnitude in humans. *Neuropsychologia, 51*, 293-308.

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. H., Brody, G. H., Lei, M. K., Kim, S., Cuit, 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

Beach, S. R. H., Brody, G. H., Lei, M., Philibert, R. A. (2010). Differential susceptibility to parenting among African American youths: Testing the DRD4 hypothesis. *Journal of Family Psychology, 24*, 513-521. doi:10.1037/a0020835

Beck, C. T. (1999). Maternal depression and child behavior problems: a meta-analysis. *Journal of Advanced Nursing, 29*, 623-629.

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

Beijers, R., Riksen-Walraven, J. M., & De Weerth, C. (2013). Cortisol regulation in 12-month-old human infants: Associations with the infants' early history of breastfeeding and co-sleeping. *Stress, 16*, 267-277.

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., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). For better and for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16*, 300-304.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry, 14*, 746-754. doi:10.1038/mp.2009.44

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

Bertolino, A., Di Giorgio, A., Blasi, G., Sambataro, F., Cafo, G., Sinibaldi, L.,…Dallapiccola, B. (2008). Epistasis between dopamine regulating genes identifies a nonlinear response of the human hippocampus during memory tasks. *Biological Psychiatry, 64*, 226-234.

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

Blair, C., Granger, D. A., Kivilighan, K. T., Mills-Koonce, R., Willoughby, M., Greenberg, M. T.,,…Family Life Project Investigators. (2008). Maternal and child contributions to cortisol response to emotional arousal in young children from low-income, rural communicties. *Developmental Psychology, 44*, 1095-1109.

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.

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

Braungart-Rieker, J. M. & Stifter, C. A. (1996). Infants' responses to frustrating situations: Continuity and change in reactivity and regulation. *Child Development, 67*, 1767-1779.

Brennan, P. A., Pargas, R., Walker, E. F., Green, P., Newport, J. D., & Stowe, Z. (2008). Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. *Journal of Child Psychology and Psychiatry, 49*, 1099-1107.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 302*, 386-389.

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*, 131-148.

Chaimongkol, N. N., & Flick, L. H. (2006). Maternal sensitivity and attachment security in thailand: Cross-cultural validation of western measures. *Journal of Nursing Measurement*, *14*(1), 5-17. doi:10.1891/jnum.14.1.5

Champagne, F., & Meaney, M. J. (2001). Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. *Progress in Brain Research, 133*, 287-302.

Cicchetti, D., Rogosch, F. A., & Toth, S. L. (2011). The effects of child maltreatment and polymorphisms of the serotonin transporter and dopamine D4 receptor genes on infant attachment and intervention efficacy. *Development and Psychopathology, 23*, 357-372.

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.

Conway, C. C., Hammen, C., Brennan, P. A., Lind, P. A., & Najman, J. M. (2010). Interaction of chronic stress with serotonin transporter and catechol-o-methyltransferase polymorphisms in predicting youth depression. *Depression and Anxiety, 27*, 737-745.

Coyne, L. W., Low, C. M., Miller, A. L., Seifer, R., & Dickstein, S. (2007). Mothers' empathic understanding of their toddlers: Associations with maternal depression and sensitivity. *Journal of Child and Family Studies, 16*, 483-497.

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.

Davis, M., & Emory, E. (1995). Sex differences in neonatal stress reactivity. *Child Development, 66*, 14-27.

Davis, E. P., Snidman, N., Wadhwa, P. D., Glynn, L. M., Schetter, C. D., & Sandman, C. A. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy, 6*, 319-331.

Dearing, E., & Hamilton, L. C. (2006). Contemporary advances and classic advice for analyzing mediating and moderating variables. *Monographs of the Society for Research in Child Development, 71*, 88-104.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*, 355-391.

Diego, M. A., Field, T., Hernandez-Reif, M., Cullen, C., Schanberg, S., & Kuhn, C. (2004). Prepartum, postpartum, and chronic depression effects on newborns. *Psychiatry, 67*, 63-80.

DiPietro, J. A., Costigan, K. A., & Gurewitsch, E. D. (2003). Fetal response to induced maternal stress. *Early Human Development, 74*, 125-138.

Dougherty, L. R., Klein, D. N., Olin, T. M., Dyson, M., & Rose, S. (2009). Increased waking salivary cortisol and depression risk in preschoolers: the role of maternal history of melancholic depression and early child temperament. *Journal of Child Psychology and Psychiatry, 50*, 1495-1503.

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 oung children's salivary cortisol 3 years later. *Journal of Abnormal Child Psychology, 41*, 531-542.

Dougherty, L. R., Tolep, M. R., Smith, V. C., & Rose, S. (2013). Early exposure to parental depression and parenting: Associations with young offspring's stress physiology and oppositional behavior. *Journal of Abnormal Child Psychology, 41*, 1299-1310.

Downey, G., & Coyne, J. C. (1990). Children of depressed parents: An integrative review. *Psychological Bulletin, 108*, 50-76.

Dozier, M., Peloso, E., Lindhiem, O., Gordon, M. K., Manni, M., Sepulveda, S., & Ackerman, J. (2006). Developing evidence-based interventions for foster children: An example of a randomized clinical trial with infants and toddlers. *Journal of Social Issues, 62*, 767-785.

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.

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry, 64*, 327-337.

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

Elovainio, M., Jokela, M., Kivimaki, M., Pulkki-Raback, L., Lehtimaki, T., Airla, N., & Keltikangas-Jarvinen, L. (2007). Genetic variants in the DRD2 gene moderate the relationship between stressful life events and depressive symptoms in adults: Cardiovascular risk in young finns study. *Psychosomatic Medicine, 69*, 391-395.

Essex, M. J., Klein, M. H., Cho, E. Kalin, N. H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biological Psychiatry, 52*, 776-784.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 1313-1323.

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.

Feldman, R., Granat, 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 American Academy of Child and Adolescent Psychiatry, 48*, 919-927.

Fernald, L. C. H., Burke, H. M., & Gunnar, M. R. (2008). Salivary cortisol levels in children of low-income women with high depressive symptomatology. *Development and Psychopathology, 20*, 423-436.

Field, A. (2009). *Discovering statistics using SPSS (3rd Ed.).* Los Angeles: Sage.

Field, T. (2010). Postpartum depression effects on early interactions, parenting, and safety practices: A review. *Infant Behavior & Development, 3*, 1-6.

Fisher, P., Gunnar, M. R., Chamberlain, P., & Reid, J. B. (2000). Preventive intervention for maltreated preschool children: Impact on children's behavior, neuroendocrine activity, and foster parent functioning. *Journal of the American Academy of Child & Adolescent Psychiatry, 39*, 1356-1364.

Flin, M. V., & England, B. G. (2003). Childhood stress: endocrine and immune responses to psychosocial events. *Social & Cultural Lives of Immune Systems*, 107-147.

Gardner, C., & Epkins, C. C. (2012). Girls' rumination and anxiety sensitivity: Are they related after controlling for girl, maternal, and parenting factors? *Child Youth Care Form, 41*, 561-578.

Gitau, R., Cameron, A., Fisk, N. M., & Glover, V. (1998). Fetal exposure to maternal cortisol. *The Lancet, 352*, 707-708.

Glover, V., O'Connor, T. G., & O'Donell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehaviral Reviews, 35*, 17-22.

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.

Gonzalez, A., Jenkins, J. M., Steiner, M., & Gleming, A. S. (2009). The relation between early life adversity, cortisol awakening response and diurnal salivary cortisol levels in postpartum women. *Psychoneuroendocrinology, 34*, 76-86.

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.

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.

Gotlib, I. H., Joorman, J., Minor, K. L., & Hallmayer, J. (2008). HPA-axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry, 63*, 847-851.

Graham, J. W., Olchowski, A. E., & Gilreath, T. D. (2007). How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prevention Science, 8*, 206-213.

Granger, D. A., Blair, C., Willoughby, M., Kivlighan, K. T., Hibel, L. C., Fortunato, C. K., & Weigand, L. E. (2007). Individual differences in salivary cortisol and alpha-amylase in mothers and their infants: Relation to tobacco smoke exposure. *Developmental Psychobiology, 49*, 692-701.

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.

Gump, B. B., Reihman, J., Stewart, P., Lonky, E., Darvill, T., Granger, D. A., & Matthews, K. A. (2009). Trajectories of maternal depressive symptoms over her child's life span: Relation to adrenocortical, cardiovascular, and emotional functioning in children. *Development and Psychopathology, 21*, 207-225.

Gunnar, M. R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology, 27*, 199-220.

Gunnar, M. R., Frenn, K., Wewerka, S. S., & Van Ryzin, M. J. (2009). Moderate versus severe early life stress: Associations with stress reactivity and regulation in 10-12 year old children. *Psychoneuroendocrinology, 34*, 62-75.

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review*

of Psychology, 58, 145-173.

Gunnar, M. R., & Vazquez, D. (2006). Stress neurobiology and developmental psychopathology. *Developmental Neuroscience, 2*, 533-577.

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.

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.

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.

Heinzel, S., Dresler, T., Baehne, C. G., Heine, M., Boreatti-Hummer, A., Jacob, C. P.,…Ehlis, A. C. (2013). COMT x DRD4 epistasis impacts prefrontal cortex function underlying response control. *Cerebral Cortex, 23*, 1453-1462.

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

Hersrud, S. L., & Stoltenberg, S. F. (2009). Epistatic interaction between COMT and DAT1 genes on eating behavior: A pilot study. *Eating Behaviors, 10*, 131-133.

Hoffman, C., Crnic, K. A., & Baker, J. K. (2006). Maternal Depression and Parenting: Implications for Children's Emergent Emotion Regulation and Behavioral Functioning. *Parenting: Science and Practice, 6*, 271-295.

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 & Adolescent Psychology, 42*, 564-575.

Jabbi, M., Kema, I. P., van der Pompe, G., te Meerman, G. J., Ormel, J., & Boer, J. A. (2007). Catechol-o-methyltransferase polymorphism and susceptibility to major depressive disorder modulates psychological stress response. *Psychiatric Genetics, 17*, 183-193.

Jansen, J., Biejers, R., Riksen-Walraven, M., & de Weerth, C. (2010). Cortisol reactivity in young infants. *Psychoneuroendocrinology, 35*, 329-338.

Kaffman, A., & Meaney, M. J. (2007). Neurodevelopmental sequale of postnatal maternal care in rodents: Clinical and research implications of molecular insights. *Journal of Child Psychology and Psychiatry, 48*, 224-244.

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

Kegel, C. A., Bus, A. G., & van IJzendoorn, M. H. (2011). Differential susceptibility in early literacy instruction through computer games: The role of the dopamine D4 receptor gene (DRD4). *Mind, Brain, and Education, 5*, 71-78.

Kerlinger, F. N., & Pedhazur, E. J. (1973). *Multiple Regression in Behavioral Research*. New York: Holt, Rinehart and Winston, Inc.

King, J. A., Barkley, R. A., & Barrett, S. (1998). Attention-deficit hyperactivity disorder and the stress response. *Biological Psychiatry, 44*, 72-74.

Kirschbaum, C., Wust, S., Faig, H. G., & Hellhammer, D. H. (1992). Heritability of cortisol responses to human corticotropin-releasing hormone, ergometry, and psychological stress in humans. *The Journal of Clinical Endocrinology & Metabolism, 75*, 1526-1530.

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.

Kessler, R. C. (2002). Epidemiology of depression. In I. H. Gotlib, & C. L. Hammen (Eds.), *Handbook of depression* (pp. 23-42). New York, NY: Guilford Press.

Khoury, J. (2013). *Infant emotion regulation strategy moderates the relation between maternal depressive symptomatology and infant HPA-axis regulation.* Master's thesis. Ryerson University, Toronto, Canada.

Khoury, J. E., Gonzalez, A., Levitan, R. D., Basile, V. S., Masellis, M., Goodwill, A., & Atkinson, L. (in prep). Summary cortisol reactivity indicators: Interrelations and meaning. *Psychoneuroendocrinology*.

Klug, I., Dressendorfer, R. A., Strasburger, C., Kuhl, G. P., Reiter, A., Reich, A., …Kiess, W. (2000). Cortisol and 17-hydroxyprogesterone in saliva of healthy neonates: normative data and relation to body mass index, arterial cord blood pH and time of sampling after birth. *Biology of the Neonate, 78*, 22-26.

Knafo, A., Israel, S., & Ebstein, R. P. (2011). Heritability of children's prosocial behavior and differential susceptibility to parenting by variation in the dopamine receptor D4 gene. *Development and Psychopathology, 23*, 53-67. doi:10.1017/S0954579410000647

Kordas, K., Ettinger, A. S., Bellinger, D. C., Schnass, L., Roo, M. M. T., Hernandez-Avila, M., …Wright, R. O. (2012). A dopamine receptor (DRD2) but not dopamine transporter

(DAT1) gene polymorphism is associated with neurocognitive development of Mexican preschool children with lead exposure. *Journal of Pediatrics, 159*, 638-643.

Laucht, M., Skowreonek, M. H., Becker, K., Schmidt, M. H., Esser, G., Schulze, T. G., &Rietschel, M. (2007). Interacting effects of the dopamine transporter gene and psychosocial adversity on attention-deficit-hyperactivity disorder symptoms among 15-year-olds from a high-risk community sample. *Archives of General Psychiatry, 64*, 585-590.

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 infant's stress response profiles. *Development and Psychopathology, 23*, 521-538.

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.

Lawford, B. R., Young, R., Noble, E. P., Kahn, B., & Ritchie, T. (2006). The D2 dopamine receptor (DRD2) gene is associated with co-morbid depression, anxiety, and social dysfunction in untreated veterans with post-traumatic stress disorder. *European Psychiatry, 21*, 180-185.

Levine, A., Zagoory-Sharon, O., Feldman, R., Lewis, J. G., & Weller, A. (2007). Measuring cortisol in human psychobiological studies. *Physiology & Behavior, 90*, 43-53.

Lichter, J. B., Barr, C. L., Kennedy, J. L., Van Tol, H. H., Kidd, K. K., Livak, K. J. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Human Molecular Genetics, 2*, 767-773.

Little, R. J. (1988). A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association, 83*, 1198-1202.

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.

Luecken, L. J., Kraft, A., & Hagan, M. J. (2009). Negative relationships in the family-of-origin predict attenuated cortisol in emerging adults. *Hormones and Behavior, 55*, 412-417.

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

Lundy, B. L., Aaron Jones, N., Field, T., Nearing, G., Davalos, M., Pietro, P. A., … Kuhn, C. (1999). Prenatal depression effects on neonates. *Infant Behavior & Development, 22*, 119-129.

Mackrell, S. V. M., Shiekh, 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.

Mairesse, J., Lesage, J., Breton, C., Breant, B., Haun, T., Daraundery,M., et al… Viltart, O. (2007). Maternal stress alters endocrine function of the feto-placental unit in rats. *American Journal of Physiology-Endocrinology and Metabolism, 292*, 1526-1533.

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.

Marsman, R., Swinkels, S. H., Rosmalen, J. G., Oldehinkel, A. J., Ormel, J., & Buitelaar, J. K. (2008). HPA-axis activity and externalizing behavior problems in early adolescents from the general population: The role of comorbidity and gender: The TRAILS study. *Psychoneuroendocrinology, 33*, 789-798.

Martel, M. M., Nikolas, M., Jernigan, K., Friderici, K., Waldman, I., & Nigg, J. T. (2011). The dopamine receptor D4 gene (DRD4) moderates family environmental effects on ADHD. *Journal of Abnormal Child Psychology, 39*, 1-10.

Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*, 41-79.

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

Murray, L., Halligan, S. L., Goodyer, I., & Herbert, J. (2010). Disturbances in early parenting of depressed mothers and cortisol secretion in offspring: A preliminary study. *Journal of Affective Disorders, 122*, 218-223.

Nederhof, E., Belsky, J., Ormel, J., & Oldehinkel, A. J. (2012). Effects of divorce on Dutch boys' and girls' externalizing behavior in gene x environment perspective: Diatheiss stress or differential susceptibility in the Dutch Tracking Adolescents' Individual Lives Survey study? *Development and Psychopathology, 24*, 929-939.

Nussey, D. H., Postma, E., Gienapp, P., & Visser, M. E. (2005). Selection on heritable phenotypic plasticity in a wild bird population. *Science, 310*, 304-306.

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

Oberlander, T. F., Grunau, R., Mayes, L., Riggs, W., Rurak, D., Papsdorf, M., …Weinberg, J. (2008b). Hypothalamic-pituitary-adrenal (HPA) axis function in 3-month old infants with prenatal selective serotonin reuptake inhibitor (SSRI) antidepressant exposure. *Early Human Development, 84*, 689-697.

O'Donnell, K. J., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T. G., & Glover, V. (2012). Maternal prenatal anxiety and downregulation of placental 11ß-HSD-2. *Psychoneuroendocrinology, 37*, 818-826.

O'Donnell, K., O'Connor, T. G., & Glover, V. (2009). Prenatal stress and neurodevelopment of the child: Focus on the HPA axis and role of the placenta. *Developmental Neuroscience, 31*, 285-292.

Oswald, L. M., McCaul, M., Choi, L., Yang, X., & Wand, G. S. (2004). Catechol-o-methyltransferase polymorphism alters hypothalamic-pituitary-adrenal axis responses to naloxone: a preliminary report. *Biological Psychiatry, 55*, 102-105.

Pariante, C. M. (2003). Depression, stress, and the adrenal axis. *Journal of Neuroendocrinology, 15*, 811-812.

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. doi:10.1111/j.1467-8624.1990.tb03579.x

Pendry, P., & Adam, E. K. (2007). Associations between parents' marital functioning, maternal parenting quality, maternal emotion and child cortisol levels. *International Journal of Behavioral Development, 31*, 218-231.

Pereira, J., Vickers, K., Atkinson, L., Gonzalez, A., Wekerle, C., & Levitan, R. (2012). Parenting stress mediated between maternal maltreatment history and maternal sensitivity in a community sample. *Child Abuse & Neglect, 36*, 433-437.

Pigliucci, M. (2001). *Phenotypic plasticity: beyond nature and nurture.* Baltimore, MD: John Hopkins University Press.

Pigliucci, M. (2005). Evolution of phenotypic plasticity: Where are we going now? *Trends in Ecology and Evolution, 20*, 481-486.

Pivonello, R., Ferone, D., Lombardi, G., Colao, A., Lamberts, S. W. J., & Hoflans, L. J. (2007). Novel insights in dopamine receptor physiology. *European Journal of Endocrinology, 156*, 513-521. doi:10.1530/eje.1.02353

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

Propper, C., Moore, G. A., Mills-Koonce, W. R., Halpern, C. T., Hill-Soderlund, A., Calkins, S. D.,…Cox, M. (2008). Gene-environment contributions to the development of infant vagal reactivity: The interaction of dopamine and maternal sensitivity. *Child Development, 79*, 1377-1394.

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. *The Journal of Neuroscience, 24*, 2825-2831.

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. *Psychoneuroendocrinology, 28*, 916-931.

Robbins, T. W., & Everitt, B. J. (1999). Motivation and reward. In M. J. Zigmond, F. E. Bloom, S. C. Landis, J. L. Roberts, & L. R. Squire (Eds.), *Fundamental neuroscience* (pp. 1246-1260). San Diego, CA: Academic Press.

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.

Rowe, D. C., Stever, C., Gard, J. M .C., Cleveland, H. H., Sanders, M. L., Abramowitz, A.,…Waldman, I. D.. (1998). The relation of the dopamine transporter gene (DAT1) to symptoms of internalizing disorders in children. *Behavior Genetics*, *28*, 215-225.

Sanchez, M. M., McCormack, K., Grand, A. P., Fulks, R., Graff, A., & Maestripieri, D. (2010). Effects of sex and early maternal abuse on adrenocorticitropin hormone and cortisol responses to the corticotropin-releasing hormone challenge during the first 3 years of life in group-living rhesus monkeys. *Development and Psychopathology, 22*, 45-53.

Sapolsky, R. M. (1992). Neuroendocrinology of the stress-response. In S. M. B. J. B. Becker & D. Crews (Eds.), *Behavioral endocrinology.* Cambridge MA: MIT Press.

Schafer, J. L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods, 7*, 147-177.

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.

Spangler, G., Schieche, M., Ilg, U., Maier, U., & Ackerman, C. (1994). Maternal sensitivity as an external organizer for biobehavioral regulation in infancy. *Developmental Psychobiology, 27*, 425-437.

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 Counseling Psychology, 49*, 381-385.

Steering Committee of the Physician's Health Study Group. (1988). Findings from the aspirin component of the ongoing Physician's Health Study. *New England Journal of Medicine, 318*, 262-264.

Steptoe, A., van Jaarsveld, C. H. M., Semmier, C., Plomin, R., & Wardle, J. (2009). Heritability of daytime cortisol levels and cortisol reactivity in children. *Psychoneuroendocrinology, 34*, 273-280.

Stuart, S., Couser, G., Schilder, K., O'Hara, M., & Gorman, L. (1998). Postpartum anxiety and depression: Onset and comorbidity in a community sample. *Journal of Nervous & Mental Disease, 186*, 420-424.

Sullivan, R. M., & Dufresne, M. M. (2006). Mesocortical dopamine and HPA axis regulation: Role of laterality and early environment. *Brain Research, 1076,*, 49-59.

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.

Tarabulsy, G. M., Provost, M. A., Bordeleau, S., Trudel-Fitzgerald, C., Moran, G., Pederson, D. R.,…Pierce, T. (2009). Validation of a short version of the maternal behavior Q-set

applied to a brief video record of mother-infant interaction. *Infant Behavior & Development*, *32*(1), 132-136. doi:10.1016/j.infbeh.2008.09.006

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

Teti, D. M., Gelfand, D. M., Messinger, D. S., & Isabella, R. (1995). Maternal depression and the quality of early attachment: an examination of infants, preschoolers, and their mothers. *Developmental Psychology, 31*, 364-376.

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

Van der Zwaluw, C. S., Kuntsche, E., & Engels, R. C. M. E. (2011). Risk alcohol use in adolescence: The role of genetics (DRD2, SLC6A4) and coping motives. *Alcoholism: Clinical and Experimental Research, 35*, 756-764.

Van Hulle, C. A., Shirtcliff, E. A., Lemery-Chalfant, K., & Goldsmith, H. H. (2012). Genetic and environmental influences on individual differences in cortisol level and circadian rhythm in middle childhood. *Hormones and Behavior, 62*, 36-42.

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.

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.

Weaver, I. C. G., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R.,…Meaney, M. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*, 847-854.

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.

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. *The Journal of Neuroscience, 25*, 1493-1502.

Table 1

Comparison of Participants with Missing Data to those with Complete Data

	t (X^2)	*df*	*P*
Maternal BDI	-0.10	267	.91
DRD2 Genotype	(0.04)	1	.85
DAT1 Genotype	(2.45)	1	.12
COMT Genotype	(0.01)	1	.91
AUC_I Toy Frustration	-0.67	255	.50
AUC_I Strange Situation	-0.16	226	.88
Family Income	0.05	200	.92
Maternal Age at 16 Month Visit	-0.33	283	.74
Breastfeeding Status at 16 Month Visit	(0.05)	1	.82
Breastfeeding Status at 17 Month Visit	(0.22)	1	.64
Smoking Status	(0.01)	1	.93
Maternal Education	-1.34	310	.18
Infant Sex	(2.01)	1	.16
Infant Wake Time at 16 Month Visit	1.22	269	.22
Infant Wake Time at 17 Month Visit	1.98	255	.05
Infant Breakfast End Time at 16 Month Visit	2.62	252	.01
Infant Breakfast End Time at 16 Month Visit	2.96	229	.03

Note. BDI = Beck Depression Inventory.

Table 2

Genotype Distributions

Gene	Susceptibility Allele (%)		Non-susceptibility Allele (%)	
DRD2	A1/A1 and A1/A2 (38.7)		A2/A2 (61.3)	
DAT1	10/10 (59.8)		10/9 and 9/9 (40.2)	
COMT	G/G (32.1)		A/G and A/A (67.9)	
Total	0 (%)	1 (%)	2 (%)	3 (%)
	17.3	42.8	32.4	7.6

Note. Due to buccal cell degradation, DRD4 genotypes were not included in analyses. Total = total number of candidate alleles.

Table 3

Distribution of Maternal BDI-II Scores.

	% of sample
None (score 0-10)	75.8
Mild mood disturbance (score 11-16)	14.5
Borderline clinical depression (score 17-20)	4.1
Moderate depression (score 21-30)	3.7
Severe depression (score 31-40)	1.9

Note. Cut off scores obtained from Beck et al. (1996).

Table 4

Correlations Amongst Study Variables

	1	2	3	4	5	6
1. BDI-II	-					
2. DRD2 Genotype	-.10	-				
3. DAT1 Genotype	.02	.12	-			
4. COMT Genotype	-.03	.03	-.12*	-		
5. AUC_I TFT	-.00	-.06	.04	-.07	-	
6. AUC_I SSP	.12	-.02	.01	-.11	.09	-

Note. BDI-II = Beck Depression Inventory; AUC_I = area under the curve; TFT = toy frustration task; SSP = strange situation procedure.
*$p < .05$.

Table 5

Hierarchical Multiple Regression Analyses Predicting Infant AUC_I in the Toy Frustration Procedure from Maternal Depressive Symptoms and Infant Genotype

	Moderator					
	DRD2 Genotype		DAT1 Genotype		COMT Genotype	
Predictor	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1	.05***		.04***		.03**	
BDI-II Score		.18***		.18***		.17***
Moderator		.08		.05		-.02
Step 2	.02**		.01*		.04***	
BDI-II Score		.08		-.00		.06
Moderator		.09		.06		-.01
BDI-II Score x Moderator		.16**		.22*		.23***
Total R^2	.05		.05		.07	
n	293		272		293	

Note. BDI-II = Beck Depression Inventory.
*$p < .10$. **$p < .05$. ***$p < .01$.

Table 6

Differential Susceptibility/Diathesis-Stress Indices for Analyses Predicting Infant AUC_I in the Toy Frustration Procedure from Maternal Depressive Symptoms and Infant Genotype

	RoS X						
	Lower Bound	Upper Bound	PoI	Crossover	PA	Linear Model?	Best Fitting Model
Moderator							
DRD2 genotype	< -2 SD	1.38	0.15	-5.44	19.3	Yes	Diathesis-stress
DAT1 genotype	< -2 SD	6.97	0.31	-2.52	44.2	Yes	Diathesis-stress
COMT genotype	-2.95	4.59	0.52	0.66	68.0	No	Neither diathesis-stress nor differential susceptibility

Note. RoS X = regions of significance on X (there are significant differences in AUC_I between infant genotype groups for all values of maternal depressive symptoms *outside* this region); PoI = proportion of the interaction attributable to better outcomes from the differential susceptibility effect; Crossover = the crossover point of the interaction (i.e., the point on maternal depressive symptoms where the genotype group regression lines intersect); PA = proportion affected index (the proportion of infants differentially affected by the crossover interaction); < -2 SD = below the normative range cutoff of ± 2 standard deviations from the mean of maternal depressive symptoms.
Note. Beck Depression Inventory-II scores were centered.

Table 7

Hierarchical Multiple Regression Analyses Predicting Infant AUC_I in the Strange Situation Procedure from Maternal Depressive Symptoms and Infant Genotype

	Moderator					
	DRD2 Genotype		DAT1 Genotype		COMT Genotype	
Predictor	Δ R^2	β	Δ R^2	β	Δ R^2	β
Step 1	.10***		.95***		.91***	
BDI-II Score		-.29***		-.29***		.29***
Moderator		-.08		-.06		-.10
Step 2	.05***		.02*		.10***	
BDI-II Score		-.13		-.02		-.10
Moderator		-.09		-.06		-.09
BDI-II Score x Moderator		-.28**		-.30*		-.37***
Total R^2	.13		.12		.20	
n	275		255		275	

Note. BDI-II = Beck Depression Inventory.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 8

Differential Susceptibility/Diathesis-Stress Indices for Analyses Predicting Infant AUC_I in the Strange Situation Procedure from Maternal Depressive Symptoms and Infant Genotype

	RoS X						
	Lower Bound	Upper Bound	PoI	Crossover	PA	Linear Model?	Best Fitting Model
Moderator							
DRD2 genotype	-5.89	0.39	0.33	-2.33	44.2	Yes	Differential susceptibility
DAT1 genotype	-11.29	2.81	0.35	-2.10	44.2	Yes	Differential susceptibility
COMT genotype	-4.32	-0.22	0.35	-2.09	44.2	No	Neither diathesis-stress nor differential susceptibility

Note. RoS X = regions of significance on X (there are significant differences in AUC_I between infant genotype groups for all values of maternal depressive symptoms *outside* this region); PoI = proportion of the interaction attributable to better outcomes from the differential susceptibility effect; Crossover = the crossover point of the interaction (i.e., the point on maternal depressive symptoms where the genotype group regression lines intersect); PA = proportion affected index (the proportion of infants differentially affected by the crossover interaction).
Note. Beck Depression Inventory-II scores were centered.

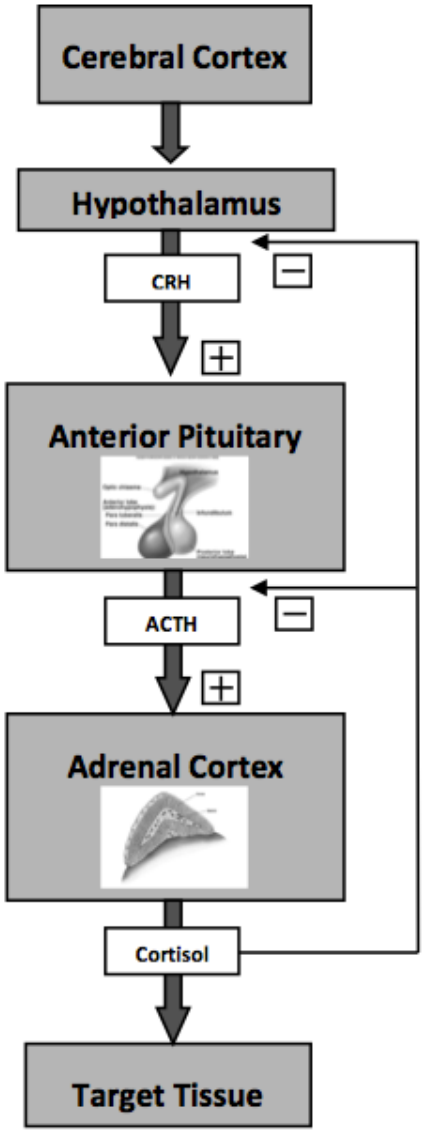

Figure 1. The cortisol mediated negative feedback loop. Reprinted with permission from Khoury (2013).

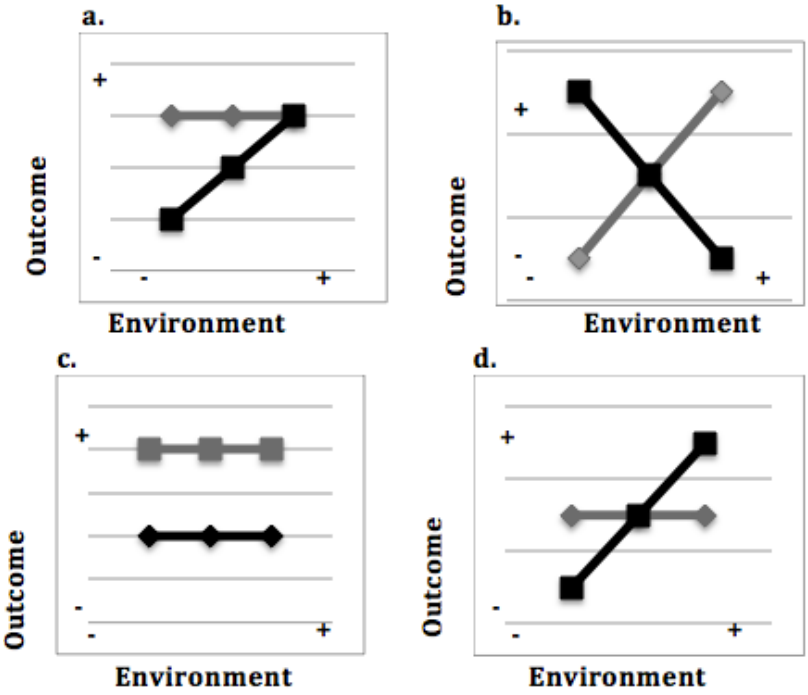

Figure 2. Graphical displays of moderation effects of a) diathesis stress, b) contrastive effects, c) absence of susceptibility, and d) differential susceptibility. The x-axis depicts variation in the environment from negative to positive; the y-axis depicts the outcome from negative to positive; and the lines depict two groups differing on the susceptibility allele (Belsky et al., 2007).

a. **b.**

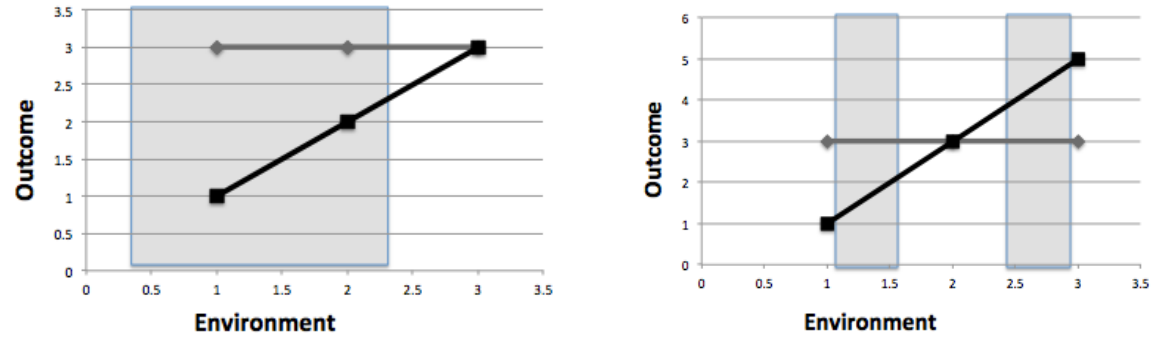

Figure 3. Regions of significance of a) diathesis stress effects, in which the association between the moderator and the outcome is significant at only one end of the environment (predictor) variable, and b) differential susceptibility, in which the association between the moderator and the outcome is significant at both the low and high ends of the environment variable (Roisman et al., 2012).

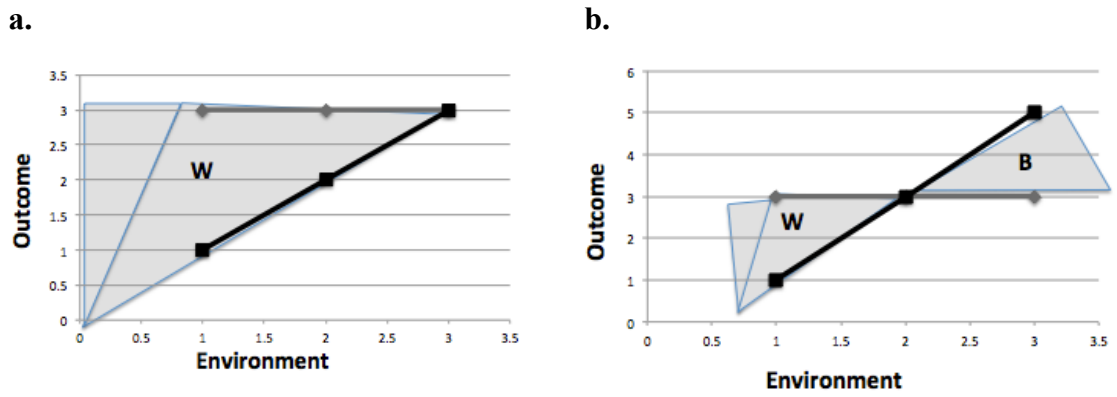

Figure 4. The proportion of the interaction (PoI) for a) diathesis-stress and b) differential susceptibility models. w = worse outcome, b = better outcome (Roisman et al., 2012).

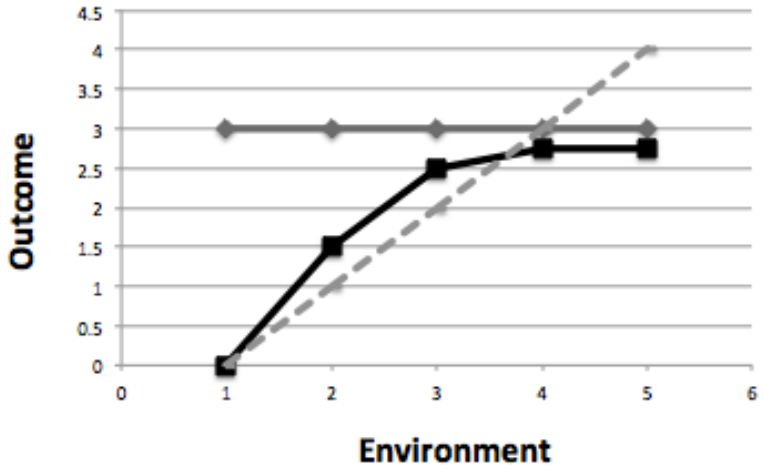

Figure 5. Nonlinear relationship masquerading as differential susceptibility. The solid lines depict predictions from a nonlinear model. The dashed line depicts predictions from a linear model (Roisman et al., 2012).

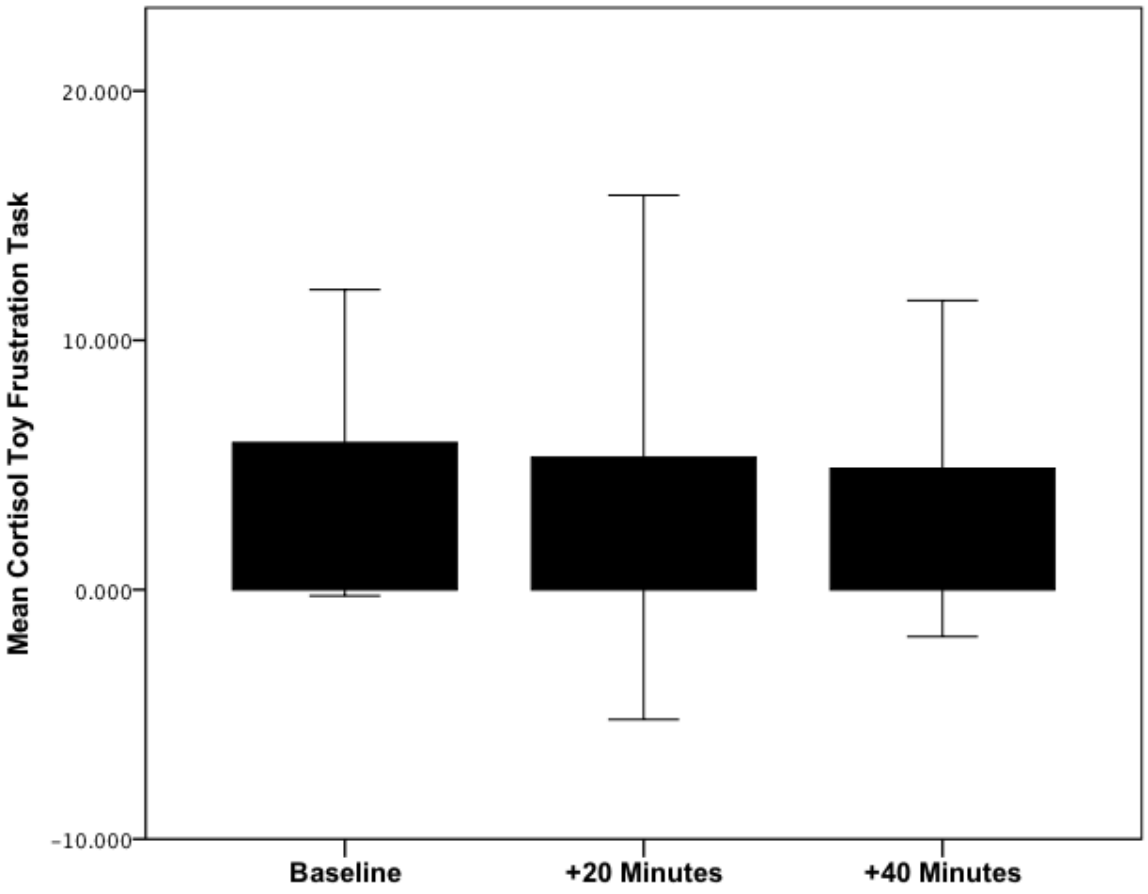

Figure 6. Mean baseline, +20 minute, and +40 minute cortisol values during the toy frustration procedure. Error bars represent SD.

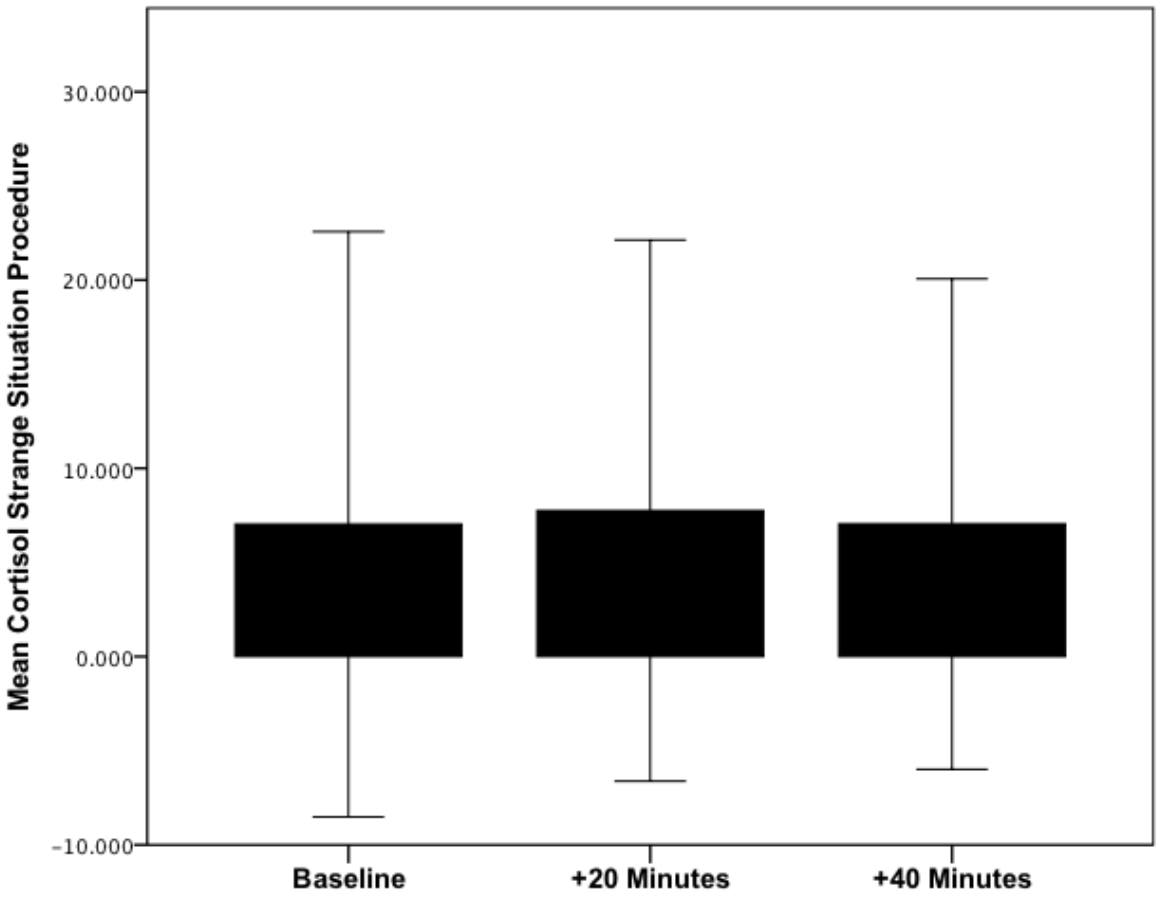

Figure 7. Mean baseline, +20 minute, and +40 minute cortisol values during the strange situation procedure. Error bars represent SD.

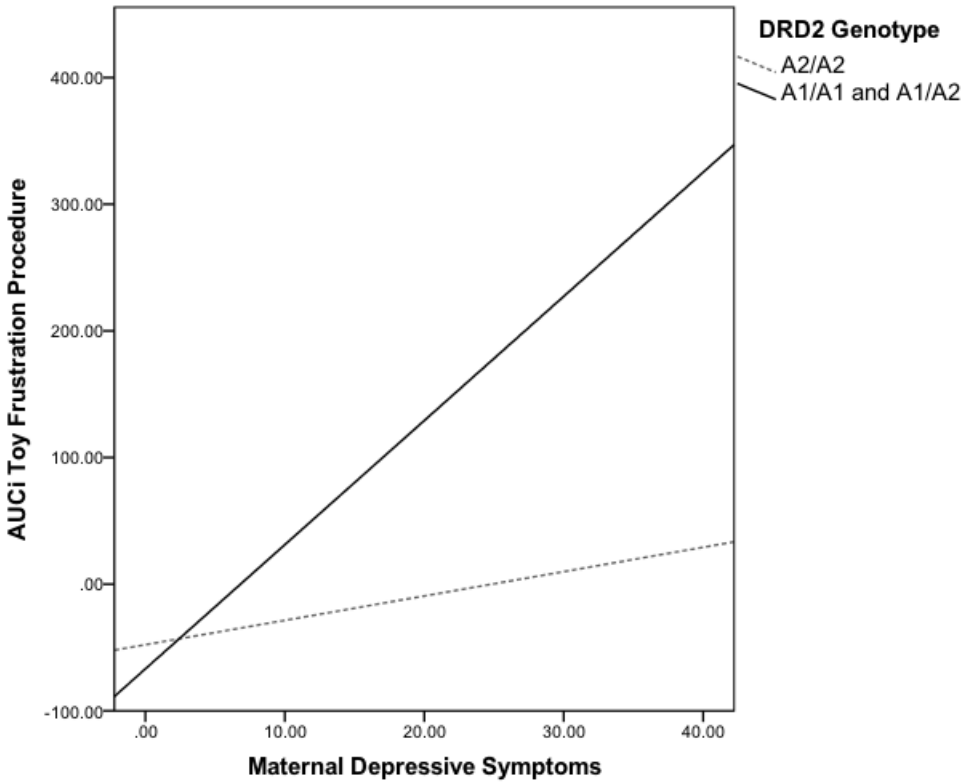

Figure 8. Infant DRD2 genotype moderating the relation between maternal depressive symptoms and infant cortisol reactivity, indicated by area under the curve with respect to increase (AUC_I, nmol/L), during the toy frustration procedure (at 16-months).

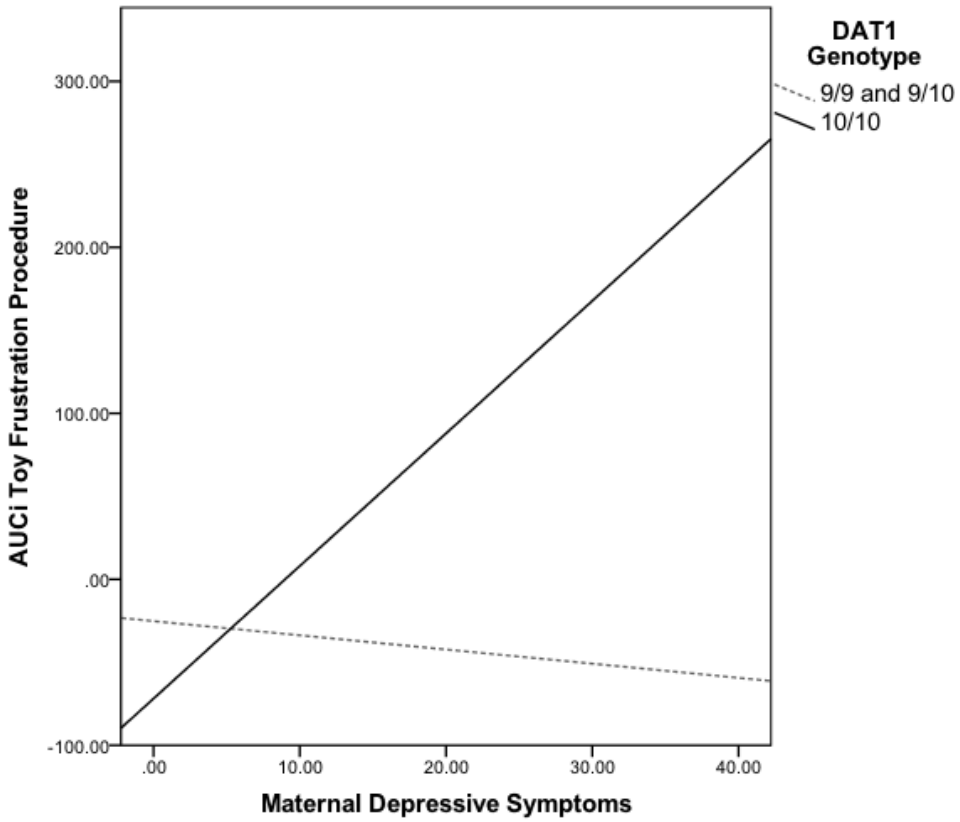

Figure 9. Infant DAT1 genotype moderating the relation between maternal depressive symptoms and infant cortisol reactivity, indicated by area under the curve with respect to increase (AUC_I, nmol/L), during the toy frustration procedure (at 16-months).

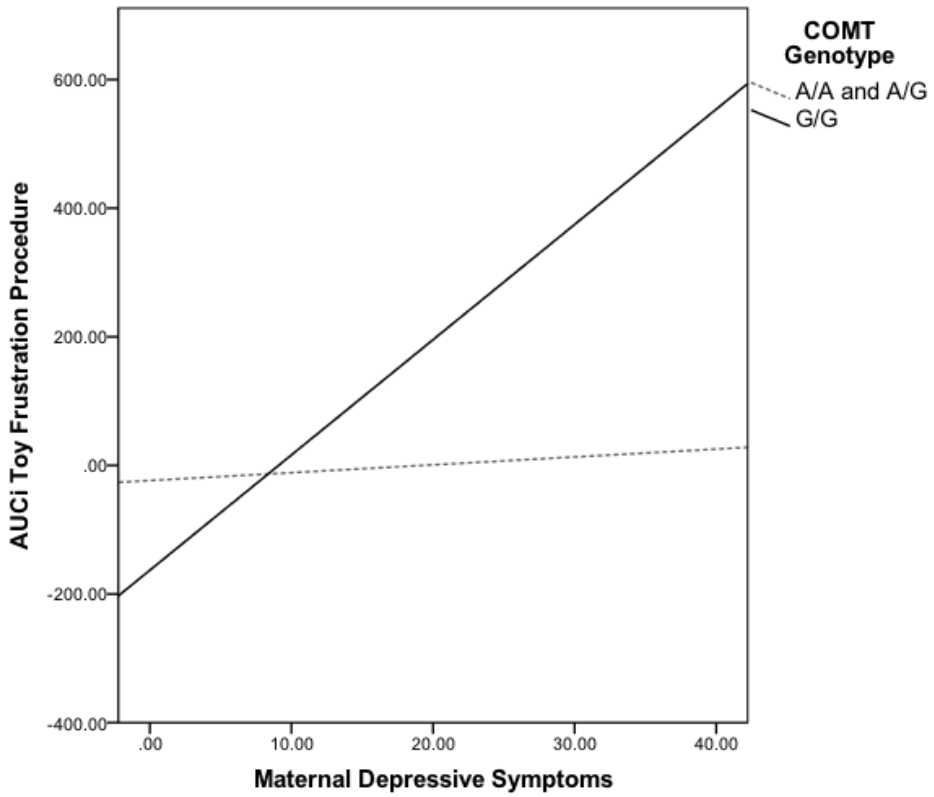

Figure 10. Infant COMT genotype moderating the relation between maternal depressive symptoms and infant cortisol reactivity, indicated by area under the curve with respect to increase (AUC_I, nmol/L), during the toy frustration procedure (at 16-months).

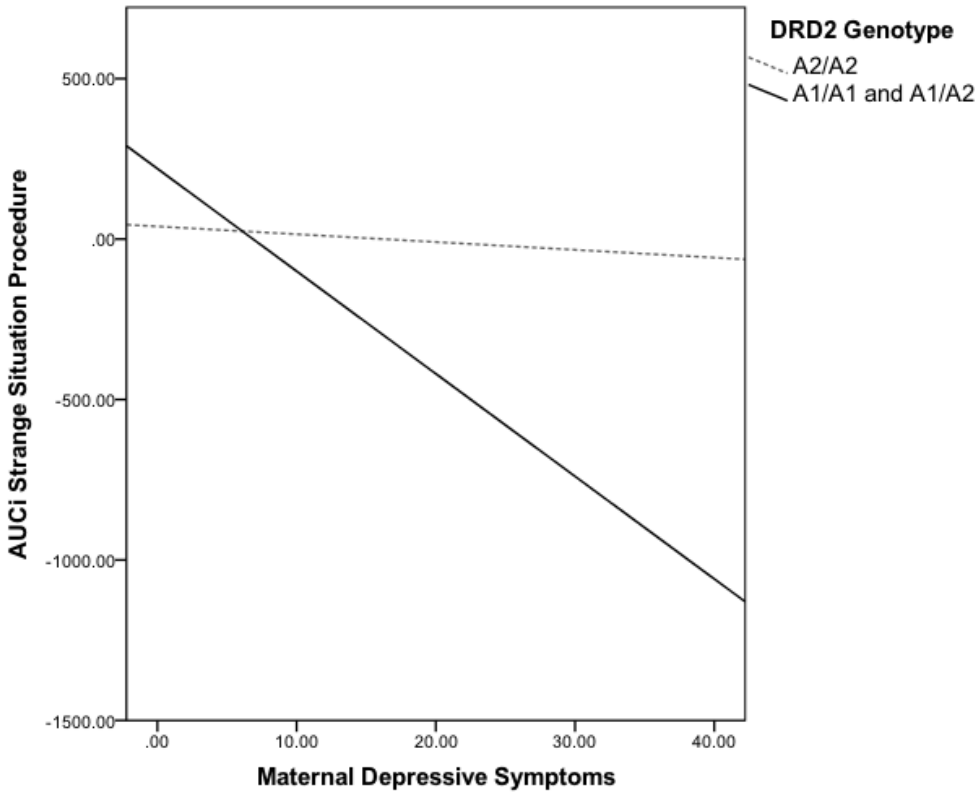

Figure 11. Infant DRD2 genotype moderating the relation between maternal depressive symptoms and infant cortisol reactivity, indicated by area under the curve with respect to increase (AUC_I, nmol/L), during the strange situation procedure (at 17-months).

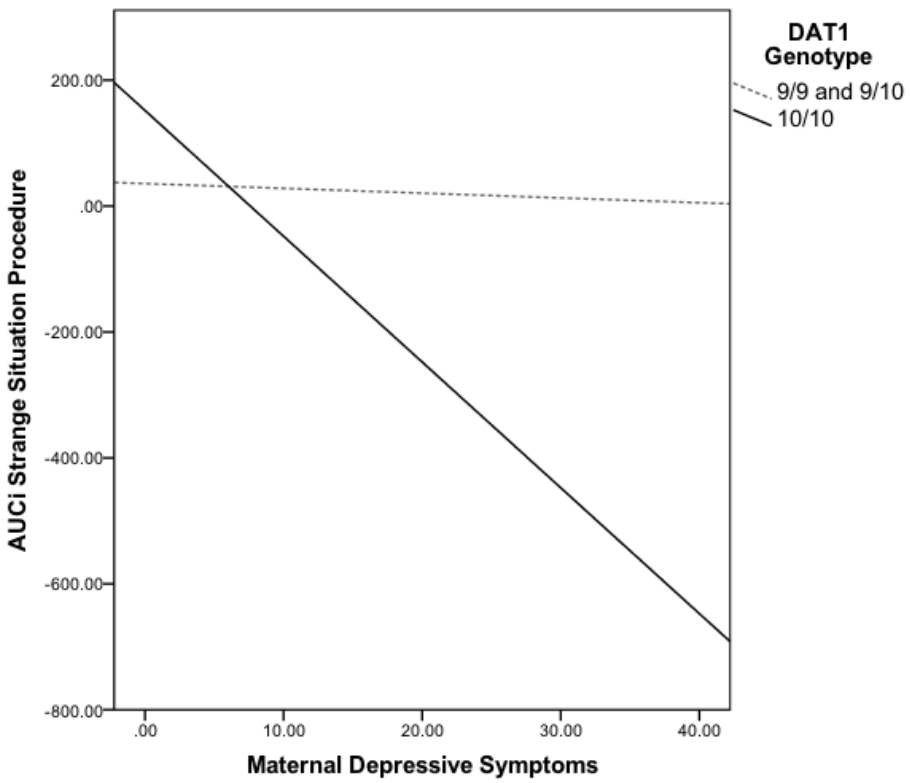

Figure 12. Infant DAT1 genotype moderating the relation between maternal depressive symptoms and infant cortisol reactivity, indicated by area under the curve with respect to increase (AUC_I, nmol/L), during the strange situation procedure (at 17-months).

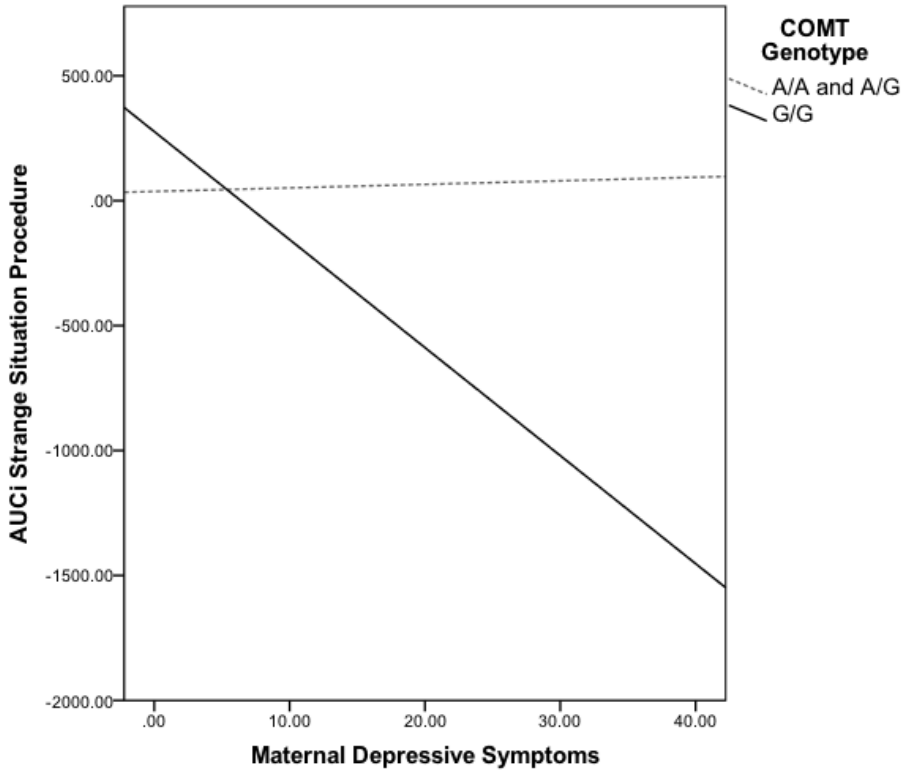

Figure 13. Infant COMT genotype moderating the relation between maternal depressive symptoms and infant cortisol reactivity, indicated by area under the curve with respect to increase (AUC_I, nmol/L), during the strange situation procedure (at 17-months).

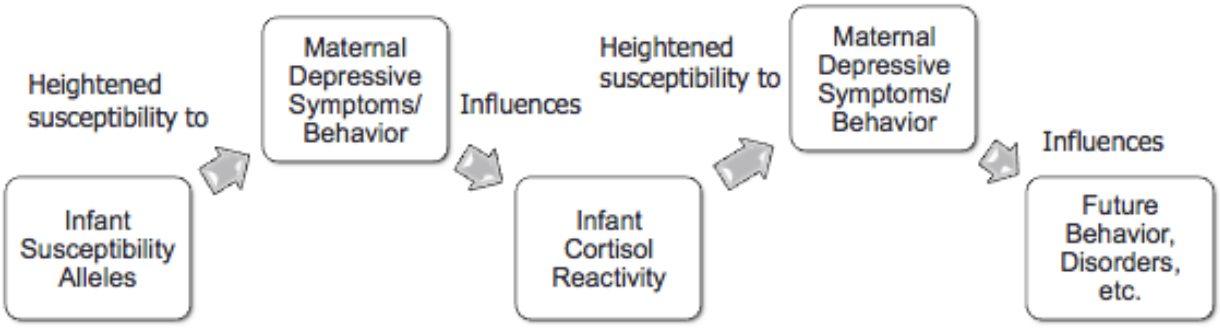

Figure 14. Environmental susceptibility as the product of a gene x environment interaction.