The Dopamine D4 Receptor Gene, Birth Weight, Early Maternal Care, Maternal Depression Over the Postnatal Time Period and the Prediction of Disorganized Attachment at 36 Months of Age: A Prospective Gene x Environment Analysis.

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Abstract

Background: Efforts to understand the developmental pathways for disorganized attachment reflect the importance of disorganized attachment on the prediction of future psychopathology. The inconsistent findings on the prediction of disorganized attachment from the dopamine D4 receptor (DRD4) gene, birth weight, and maternal depression as well as the evidence supporting early maternal care as a mediator or moderator of more distal environmental effects, suggest the importance of exploring a Gene by Environment model. **Methods:** Our sample is from the Maternal Adversity, Vulnerability and Neurodevelopment project; consisting of 655 mother–child dyads. Birth weight was cross-referenced with normative data to calculate birth weight percentile. Infant DRD4 genotype was obtained with buccal swabs and categorized according to the presence of the 7-repeat allele. Maternal depression was assessed with the Center for Epidemiologic Studies Depression Scale at the prenatal, 6-, 12-, 24-, and 36-month assessments. Early maternal care was measured at 6-months using a videotaped session of a 20-minute non-feeding interaction. Attachment was assessed at 36-months using the Strange Situation Procedure. **Results:** Logistic regression models indicated the significant main effects of DRD4 genotype, chronic maternal depression, and maternal education, as well as the significant two-way interaction between maternal depression and one measure of early maternal care, looking away frequency, in the predication of disorganized attachment at 36 months. Specifically, the presence of the DRD4 7-repeat allele was associated with less disorganized attachment, $\beta = -1.11$, OR = 0.329, $p = 0.000828$, while chronic maternal depression was associated with more disorganized attachment, $\beta = 1.01$, OR = 2.74, $p = 0.00911$. Maternal looking away frequency showed significant interactions with maternal depression at the prenatal assessment, $\beta = 0.00312$, OR = 1.003, $p = 0.0228$, and at 24-months, $\beta = 0.00367$, OR = 1.004, $p = 0.0214$, as at both time

points, only women suffering from depression showed a decreased probability of disorganized attachment when maternal looking away frequency was low and an increased probability when maternal looking away frequency was high. Finally, maternal education showed a separate contribution to the prediction of disorganized attachment, as maternal education at the college level and the university or higher level were both associated with less disorganized attachment (college level, $\beta = -1.76$, OR = 0.173, $p = 0.0000928$, and university level or higher, $\beta = -1.15$, OR = 0.316, $p = 0.00284$). **Conclusions:** Our models support the contribution of biological and multiple environmental factors in the complex prediction of disorganized attachment at 36 months.

Contexte: La recherche sur la trajectoire développementale à l'origine de l'attachement desorganisée (D) s'explique par l'importance de D dans la prédiction de la psychopathologie future. Les résultats contradictoires quant à la prédiction de D par le gène récepteur de la dopamine D4 (DRD4), le poids à la naissance et la dépression maternelle postnatale et le rôle médiateur ou modérateur de la relation parent-enfants précocesuggèrent l'importance d'un model explication d'interaction gène-environnement. **Méthodes:** Notre échantillon provient du projet de l'adversité, de la vulnérabilité et du neuro-développement maternelles (MAVAN); il consiste de 655 dyades mère-enfant. Le poids de naissance a été comparé avec des données normatives pour calculer le pourcentage du poids à la naissance. Le génotype infantile DRD4, obtenu avec un frottis buccal, est classé en fonction de la présence de l'allèle 7-répétition du gène DRD4. La dépression maternelle a été évaluée avec le 'Center for Epidemiologic Studies Depression Scale' (CES-D). Les soins maternels précoces ont été mesurés à l'aide d'une session enregistrée sur bande vidéo d'une interaction de non-alimentation de 20 minutes. L'attachement a été évalué à 36 mois en utilisant la procédure du 'Strange Situation'. **Résultats:** Les modèles de régression logistique ont montré les principaux effets significatifs du génotype DRD4, de la dépression maternelle chronique, et de l'éducation maternelle, ainsi que l'importante interaction bidirectionnelle entre la dépression maternelle et une mesure de soins maternels précoce, la fréquence du détournement du regard, dans la prédiction de l'attachement désorganisé à 36 mois. Plus précisément, la présence de l'allèle DRD4 7 - répété a été associé à l'attachement moins désorganisé, $\beta = -1.11$, OU = 0.329, $p = 0.000828$, tandis que la dépression maternelle chronique a été associée à l'attachement plus désorganisé, $\beta = 1.01$, OU = 2.74, $p = 0.00911$. La fréquence du détournement du regard maternel a montré des interactions significatives avec la dépression maternelle à l'évaluation prénatale, $\beta = 0.00312$, OU = 1.003, $p = 0.0228$, et à 24 mois, $\beta =$

0.00367, OU = 1.004, p = 0.0214, puisque, aux deux points de temps, seules les femmes souffrant de dépression ont montré une diminution de la probabilité d'attachement désorganisé lorsque la fréquence du détournement du regard maternel était faible et une probabilité accrue quand la fréquence du détournement du regard maternel était élevée. Finalement, l'éducation maternelle a montré une contribution spécifique à la prédiction de l'attachement désorganisé, parce que l'éducation maternelle au niveau collégial et universitaire ou de niveau supérieur ont été, toutes les deux, associées à un attachement moins désorganisé (niveau collégial, $\beta = -1.76$, OU = 0.173, p = 0.0000928, et au niveau universitaire ou de niveau supérieur, $\beta = -1.15$, OU = 0.316, p = 0.00284). **Conclusion:** Nos modèles soutiennent la contribution de facteurs biologiques et de facteurs environnementaux multiples dans la prédiction complexe de l'attachement D à 36 mois.

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Preface

This dissertation is based on data previously collected by members of the MAVAN team. Co-authors of this project include: Ellen Moss,[1] Alexis Jolicoeur-Martineau,[2] Gal Moss,[4] Vanessa Lecompte,[3] Katherine Pascuzzo,[2] Vanessa Babineau,[2] Cathryn Gordon-Green,[2] Viara R Mileva-Seitz,[5] Klaus Minde,[2] Roberto Sassi,[6] Normand Carrey,[7] Meir Steiner, [8] James L. Kennedy,[9] Helene Gaudreau,[10] Robert Levitan,[9] Michael Meaney,[2,10] and Ashley Wazana[2,3]. Co-authors' contributions included the collection of the data used for this dissertation as well as reviewing and editing the manuscript. The student's contributions to this dissertation included a review of pertinent literature, construction of a model, data analysis and the writing of the manuscript.

My undergraduate dissertation was published in the McGill Science Undergraduate Journal, and focused on the main effects of infant DRD4 genotype and birth weight. However, this preliminary research was a building block towards the construction of the more complex models that were examined in the present paper and should be viewed as a stepping-stone toward the more developed topics of this dissertation.

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The Dopamine D4 Receptor Gene, Birth Weight, Early Maternal Care, Maternal Depression Over the Postnatal Time Period and the Prediction of Disorganized Attachment at 36 Months of Age: A Prospective Gene x Environment Analysis.

Background

Introduction

Attachment between a child and the primary caregiver is considered to be an important predictor of infant socio-emotional outcomes and development of psychopathology later in life (Carlson, 1998; van Ijzendoorn et al., 1999), as the primary caregiver provides the child with an initial support system and this relationship influences the development of an infant's emotional regulation (Fox & Calkins, 2003). Of the four attachment classifications (Ainsworth & Bell, 1970; Main & Solomon, 1990), disorganized (D) attachment has been highlighted as a predictor of future psychopathology (van Ijzendoorn et al., 1999). D attachment is characterized by a child lacking a coherent strategy to deal with the stress of separation and reunion with the mother (Main & Solomon, 1986). Previous research has interpreted these behaviours to represent the child's confusion, as the attachment figure paradoxically serves both as the child's source of fear and as the only source of reassurance (Main & Solomon, 1986, 1990). The conflicting influences of the caregiver cause the child to be in a perpetual state of high arousal, which interferes with the development of effective relational capabilities, communication skills, and internal organizational structures related to emotion regulation (Lyons-Ruth & Spielman, 2004).

D attachment has been studied because of its association with internalizing disorders (e.g. Groh et al., 2012; Shaw et al., 1997), externalizing disorders (e.g. Fearon et al., 2010; Lyons-Ruth et al., 1997), and personality disorders (e.g. Blatt & Levy, 2003; Liotti, 1999). D attachment contributes to behavioural problems throughout a child's development as well as psychopathology in adolescence (e.g. Carlson, 1998; van Ijzendoorn et al., 1999). Researchers have hypothesized that the impaired development of emotional self-regulation in children with D attachment contributes to the negative developmental outcomes that infants with D attachment experience (Calkins & Leerkes, 2004). Infants in two-parent, middle-class families show an incidence of 15% of D attachment; however, the incidence of D attachment increases to a high of 82% among infants in maltreating families (Lyons-Ruth, 1996). The discrepancy between the incidence of D attachment in low and high-risk samples has led to questions of how environmental factors interact with genetic susceptibility factors to cause a child to be more at risk of developing D attachment.

According to the theory of biological sensitivity to context, an organism has an integrated system of central and peripheral neuroendocrine responses designed to prepare the organism for a challenge or threat according to the environment they are in (Ellis & Boyce, 2008). Accordingly, prenatal and early postnatal risk factors may interact with genetic influences to prepare an infant to calibrate their biological and behavioural systems to their postnatal environment (Ellis & Boyce, 2008). In this fashion, perinatal and early postnatal environmental risk factors may interact with heritable factors to shape a child's early behavioural and emotional patterns, which may in turn have an effect on future developmental outcomes, such as D attachment.

Numerous studies have focused on the potential genetic, prenatal and postnatal environmental factors that may be associated with D attachment. A candidate gene that has been focused upon is the Dopamine D4 Receptor (DRD4) gene. Initial reports on the relationship between the DRD4 gene and D attachment found that individuals with the 7-repeat (7R) allele of the DRD4 gene were more likely to develop D attachment (Lakatos et al., 2000). However this finding has not been consistently replicated (e.g. Bakermans-Kranenburg & van Ijzendoorn, 2004).

Furthermore, early maternal care and more specifically maternal sensitivity, has been implicated with child attachment security since the beginnings of attachment theory (Bowlby, 1969). Maternal sensitivity has been shown to be positively associated with secure attachment security (Ainsworth et al., 1978) and evidence has also supported the notion that maternal sensitivity may act as a mediator or moderator of more distal environmental factors in their relation to child attachment security (e.g. Campbell et al., 2004; Dannemiller, 1999).

In addition to early maternal care, other environmental factors have been studied as indicators of prenatal and early postnatal influences and examined for their relation to child attachment security. Infant birth weight and maternal postnatal depression are two factors that have been well studied in relation to child attachment status. While researchers have found that infant low birth weight is associated with a host of negative developmental outcomes, (e.g. Barre et al., 2011; Roberts et al., 1989), it has shown inconsistent results in regards to its relationship with D attachment (Korja et al., 2012). Similarly, researchers have found that maternal postnatal depression is associated with lower maternal sensitivity (e.g. Pyszczynski & Greenberg, 1987);

however, previous research has also found inconsistent results in regards to its relationship with D attachment (van Ijzendoorn et al., 1999). This trend of unreplicated findings for potential risk factors has led researchers to focus less on the main effects of various risk factors for D attachment and instead on the interplay of Gene x Environment (GxE) effects (Bakermans-Kranenburg & van Ijzendoorn, 2011).

To make matters more complex, previous research has indicated that the DRD4 gene exhibits differential susceptibility, as evidenced by the different outcomes people with DRD4 polymorphisms are likely to have after being in either a positive or negative environment (Bakermans-Kranenburg & van Ijzendoorn, 2011). Following the publication of the differential susceptibility hypothesis (Belsky, 1997a), the scientific community no longer considers the DRD4 gene simply as a 'risk gene', but as a 'susceptibility gene'.

The complex relationships D attachment has with the DRD4 gene, infant birth weight, maternal postnatal depression, and early maternal care allow these factors to be well suited for exploring a GxE effect on D attachment. The aim of the present paper is to explore these relationships further using several GxE models to clarify the relationship between these factors and D attachment.

History of Attachment Disorganization

Research has shown that the nature of the early nurturance between a caregiver and their child has a predictive relationship with numerous developmental outcomes, including infant

physiological responsiveness to stressors (e.g. Liu et al., 1997; Nachmias et al., 1996; Spangler et al., 2009) as well as later cognitive and social development (e.g. Ainsworth et al., 1974; Bohlin et al., 2000; Jacobsen et al., 1994). Attachment is defined as "the affectional tie that one person forms between himself and another specific one – a tie that binds them together in space and endures over time" (Ainsworth & Bell, 1970, pg. 50). Attachment is observable through the expression of proximity-seeking and -maintaining behaviours with the object of attachment. From a young age, an infant is able to show proximity-seeking behaviours, typically through actions such as crying, smiling, or vocalizations (Ainsworth & Bell, 1970). During the first period of life, these actions are not directed at anyone in particular; however, as an infant continues to grow and learn about his/her surroundings, these behaviours may become directed at the primary caregiver; typically the mother. Once this occurs, the actions are considered to be organized and the infant can be described as having an attachment toward the mother (Ainsworth & Bell, 1970).

The Strange Situation Procedure (SSP) is the most widespread method of assessing a child's attachment status with their primary caregiver. The SSP is designed to emulate an experience a child may encounter in their everyday-life. The SSP consists of eight episodes that are intended to be novel enough to stimulate exploratory behaviour but ordinary enough to avoid causing fear and disturbance in a child. Ainsworth and Bell (1970) found that upon reunion between the child and their mother in the SSP, proximity-seeking and contact-maintaining behaviours varied in children, with some children actually demonstrating contact-resisting and proximity-avoiding behaviours.

Upon further investigation, Ainsworth et al. (1978) classified three distinct categories of attachment according to infant behaviour in the SSP: insecure-avoidant, secure, and insecure-anxious. Children classified as insecure-avoidant exhibit overt avoidance of proximity to or interaction with the mother in the return episodes. Children classified as secure seek out proximity and contact with their mother in the return episodes; when established they attempt to maintain it. Finally, while children classified as insecure-anxious display overt contact- and interaction-resisting behaviour, they do not show a tendency to ignore their mother during reunion episodes; when contact and/or interaction is established they attempt to maintain it (Ainsworth et al., 1978).

While the classifications stipulated by Ainsworth et al. (1978) have been successful in distinguishing between different types of behavioural and emotional regulation profiles, there have been difficulties classifying each child under only one of these domains (Main & Solomon, 1986). Questions about the classification system first became apparent when groups of children in middle-class samples were deemed to be unclassifiable and were only able to fit into the classifications outlined by Ainsworth et al. (1978) if 'forced' into one of the categories (Main & Weston, 1981). These 'forced' children displayed the typical behaviours of children in each respective type of attachment classification; however, they also displayed particular atypical behaviours. For example, children who were considered 'forced secures' fit the Ainsworth criteria for the secure classification but they also presented several other atypical behaviours, such as: showing the same secure-type proximity-seeking and -maintaining behaviours both toward the mother and toward a stranger; combining extreme avoidance and extreme distress

throughout the situation; and showing the physical behaviours of a securely attached infant but being affectless with signs of depression (Main & Solomon, 1986).

Further inconsistent evidence was presented from studies that were conducted on high-risk cohorts of infant-mother dyads consisting of low socioeconomic status (SES) individuals, neglecting or abusing mothers, and or mothers with emotional disorders (Crittenden, 1985, 1988; Egeland & Sroufe, 1981; Radke-Yarrow et al., 1985). Given that a secure classification is considered to be dependent on a history of sensitive and responsive interactions with the mother (Main & Solomon, 1986), it was expected that high-risk samples would have high levels of insecurely attached children. However, many of the high-risk samples had a similar prevalence of securely attached children as low-risk samples (Crittenden, 1985, 1988; Egeland & Sroufe, 1981; Radke-Yarrow et al., 1985). Additionally, in the high-risk samples many children were labeled as 'unclassifiable' under the original Ainsworth classification system or were classified according to a modification of the original Ainsworth classification system (Crittenden, 1985, 1988; Egeland & Sroufe, 1981; Radke-Yarrow et al., 1985).

This evidence led to Main and Solomon (1986) examining a D classification in a review of the empirical evidence and eventually D attachment being validated as a fourth attachment category (Main & Solomon, 1990). Given the wide variety of behaviours that D infants tend to show (Main & Solomon, 1986) further subgroups were labeled as D/secure, D/avoidant, and D/ambivalent (Main & Solomon, 1990). Each subgroup shows disordered, incomplete, or undirected sequencing of movements and confusion or apprehension in the presence of the

attachment figure. The subgroups of infants, however, vary in their emotion regulation profiles (Moss, Bureau, et al., 2004).

Longitudinal studies that focused on the reunion behaviour of older children and the evolution of infant attachment patterns have been able to identify three types of D attachment: controlling-punitive, controlling-caregiving, and behaviourally D or insecure-other (Cassidy, 1988; Cassidy & Marvin, 1992; Moss, Cyr, et al., 2004). Previous research has shown that by age 6 in low-risk samples, two thirds of D children reorganize their attachment behaviour into a controlling pattern (Cassidy, 1988; Wartner et al., 1994). Most children of the same age in a high-risk sample are classified as behaviourally D or insecure-other (Cicchetti & Barnett, 1991; Speltz et al., 1990). Researchers describe the shift from D to an organized-controlling strategy as an attempt by the child to resolve the paradox of a frightening attachment figure by assuming the role of the caregiver (Cassidy, 1988). However, children classified as controlling tend to focus on maintaining engagement with the parent on the parent's terms instead of seeking comfort, protection, and meeting their own needs (Moss, Cyr, et al., 2004). Therefore, children who reorganize their attachment behaviour into the controlling type are still at an increased risk of developing child externalizing and internalizing problem behaviour profiles (Greenberg et al., 1991; Moss et al., 1998; Moss, Cyr, et al., 2004; Moss, Bureau, et al., 2004; Solomon et al., 1995; Speltz et al., 1990).

Attachment Disorganization and The Dopamine D4 Receptor Gene

Dopamine is an important neurotransmitter in the brain; the role it plays in motor control, cognition, reward/motivation, and psychiatric disease is well-studied (e.g. LaHoste et al., 1996; Moore et al., 1999; Nestler & Carlezon, 2006; Pickering & Gray, 1999; Vallone et al., 2000). Additionally, studies show that dopamine influences early maternal care and the mother-infant interaction (e.g. Insel, 2003; Pruessner et al., 2004). Five different dopamine receptors have been isolated and characterized (Vallone et al., 2000), and of these five receptor types, previous research have focused on the DRD4 because of its associations with novelty seeking, attention deficit hyperactivity disorder (ADHD), externalizing disorders and substance abuse (e.g. Auerbach, Benjamin, et al., 2001; Bakermans-Kranenburg & van Ijzendoorn, 2006; Kluger et al., 2002; Kreek et al., 2005).

The DRD4 gene is located near the telomere of chromosome 11 (Gelernter et al., 1992) and is preferentially expressed in cortical and limbic regions that are involved in cognitive and emotional processes. Two functional polymorphisms of the DRD4 gene have been focused upon: a 48 base-pair variable number tandem repeat (VNTR) in Exon III (Van Tol et al., 1992) and a single nucleotide polymorphism −521C/T in the upstream region of the gene (Mitsuyasu et al., 1999). In the VNTR, the common functional variants range from 2-11 repeats (2-11R) (Ding et al., 2002; Oak et al., 2000); the 2R, the 4R and the 7R are the most common variants seen in humans (Chang et al., 1996). The longer variants have been found to be associated with lower dopamine receptor efficiency (Asghari et al., 1995).

In numerous samples, children with the DRD4 7R allele appear to be at a greater risk of developing ADHD (e.g. Holmes et al., 2002; LaHoste et al., 1996; Muglia et al., 2000). While the exact biological mechanism of this relationship is not clear, the lower dopamine receptor efficiency of the longer DRD4 variants is thought to be implicated (Faraone et al., 2001). There have been similar, but inconsistent, results with the relationship between the DRD4 gene and novelty seeking behaviour (Kluger et al., 2002). While several reports have found that individuals with the long form alleles have higher scores of novelty seeking (e.g. Benjamin et al., 1996; Ebstein et al., 1996), others have not found an association (Jonsson et al., 1997; Malhotra et al., 1996; Sullivan et al., 1998). Furthermore, other studies have found that the long form alleles are actually associated with a lower score of novelty seeking (Gelernter et al., 1997; Malhotra et al., 1996). Researchers have theorized that the inconsistency of results can be accounted for by one of three reasons: it can be due to a moderator of the relationship between the DRD4 gene and novelty seeking; it can be due to a different DNA variant in the DRD4 gene; or it can be due to another gene in linkage disequilibrium with the DRD4 (Ekelund et al., 1999). Similar to the VNTR in Exon III, the cytosine variant of the −521C/T polymorphism has been associated with greater novelty-seeking behaviour and extroversion (Munafò et al., 2008).

As molecular genetic studies began to focus on child attachment, the DRD4 gene was an ideal candidate to explore the genomic influences on the relationship between the mother and the child for three reasons: the mesolimbic dopaminergic system is involved with attentional, motivational and reward mechanisms; the DRD4 gene is preferentially expressed in the cortical and limbic regions of the brain; and the DRD4 is implicated with levels of novelty seeking and infant temperament. Lakatos et al. (2000) was the first group to study the relationship between

the DRD4 gene and infant D attachment. The study found that in a middle-class, ethnically homogenous Hungarian sample, D attachment was four times more frequent among children carrying at least one 7R allele of the DRD4 gene. In a follow-up study of the same sample, Lakatos et al. (2002) found that the odds ratio for D attachment increased tenfold in the presence of both the 7R allele and the -521 thymine allele.

Follow-up investigations of the DRD4 7R allele and D attachment have only replicated the results found by Lakatos et al. (2000) and Lakatos et al. (2002) once, and it was in a study using the same Hungarian sample. Gervai et al. (2005) conducted extended transmission disequilibrium tests to determine whether biased transmission of the VNTR in exon III occurred to infants who were displaying D or secure attachment behaviour with their mothers. The study found that there was a trend for preferential transmission of the 7R allele to D-classified infants and non-transmission of the same allele to securely attached infants. Interestingly, Cicchetti et al. (2011) also found an association between the DRD4 gene and D attachment, though, in the opposite direction. Namely, the study found that children without the 7R allele were more likely to develop D attachment. Cicchetti et al. (2011) focused on a sample consisting of children exposed to abuse and maltreatment, and this exposure may have moderated the relationship between the DRD4 gene and attachment disorganization.

Most notable in this field of research, other studies on the relationship between the DRD4 gene and D attachment have failed to report a main effect of the DRD4 polymorphisms (Bakermans-Kranenburg & van Ijzendoorn, 2004; Gervai et al., 2007; Lee Raby et al., 2013; Luijk et al., 2011; Spangler et al., 2009; van Ijzendoorn & Bakermans-Kranenburg, 2006).

Additionally, a meta-analysis conducted by Bakermans-Kranenburg and van Ijzendoorn (2007) on the DRD4 gene and D attachment found a very small effect size, (d=0.05). While the negative findings likely mean that the DRD4 7R allele does not have a consistent main effect on D attachment, they have led researchers to focus on why the initial findings by Lakatos et al. (2000) may have been due to potential moderating or mediating variables of the relationship between the DRD4 gene and D attachment.

van Ijzendoorn and Bakermans-Kranenburg (2006) examined the interaction between DRD4 gene polymorphisms and maternal unresolved loss or trauma. The study found that maternal unresolved loss or trauma was associated with D attachment only in the presence of the DRD4 7R allele. The increase in risk was 18 fold for D in infants exposed to maternal unresolved loss/trauma with the 7-repeat allele when compared to infants without the combined risks. Similarly, Luijk et al. (2011) found a significant effect of the interaction between parental sensitivity and the DRD4 gene on D attachment. The study's sample consisted of two different cohorts, one of children from the Netherlands and another of children from the United States. Strangely, Luijk et al. (2011) actually found opposite trends in each cohort. In the American cohort, infants without the 7R allele developed higher levels of security if their mother was more sensitive but in the Dutch cohort, the trend was in the opposite direction.

While the DRD4 gene has been the focus of several molecular genetic studies, most researchers have focused on its genetic effects in adverse rearing environments and have not focused on the same effects in positive rearing environments (Bakermans-Kranenburg & van Ijzendoorn, 2007). For this reason, the DRD4 has been labeled as a 'risk gene'. Researchers have

hypothesized that the focus on the effects of risk genes in negative environments has led scholars to mischaracterize genetic influences of particular developmental processes (Belsky & Pluess, 2009). Counter to this, researchers have hypothesized that instead of some genes making individuals at risk for negative outcomes, they make individuals more susceptible to their environment, '*for better or for worse*' (Belsky et al., 2007). Two theories of note have advanced the notion that individuals vary in their susceptibility to environmental influences. Both Belsky's differential-susceptibility hypothesis (Belsky, 1997b, 1997a, 2005) and Boyce & Ellis's biological-sensitivity-to-context hypothesis (Ellis & Boyce, 2008) have argued that natural selection processes promote phenotypic plasticity, which allows for a single genotype to have various phenotypes depending on the environment the organism is in. Through this selection mechanism, subsets of individuals will be more reactive to their environment, and, consequently, to *both* adverse- and beneficial-rearing conditions.

Since finding that the 7R allele of the DRD4 is under positive selective pressure (Ding et al., 2002), researchers have speculated about how the 7R allele has affected the evolution and adaptability of human functioning. This has led researchers to implicate the DRD4 gene as a candidate gene for exemplifying differential susceptibility. The DRD4 gene has been shown by several studies to exemplify differential susceptibility in interactions with several different environmental influences. van Ijzendoorn and Bakermans-Kranenburg (2006) showed that children with the DRD4 7R allele who were exposed to low maternal sensitivity showed significantly more externalizing behaviours when compared to the children without the DRD4 7R allele who were exposed to low maternal sensitivity and all children who were exposed to high maternal sensitivity. However, children with the DRD4 7R allele who were exposed to high

maternal sensitivity showed significantly less externalizing behaviours when compared to all other groups of children. Similarly, Sheese et al. (2007) showed that children with the 7R DRD4 allele exhibited the highest aggregate scores of sensation seeking when exposed to low quality parenting but also the lowest scores when exposed to high quality parenting. Interestingly, in an exclusively African-American sample, Propper et al. (2007) found that instead of the 7R allele, the small-form alleles of the DRD4 gene were associated with differential susceptibility to parental warmth and responsiveness in predicting externalizing behaviour.

Given the inconsistent results that link the DRD4 gene and D attachment together, as well as the evidence supporting the hypothesis that polymorphisms of the DRD4 gene may make individuals more susceptible to environmental influences, we considered the DRD4 gene to be an ideal candidate gene to observe in different GxE models. Previously, we examined the relationship between the DRD4 gene and D attachment in other GxE interaction models. We showed that in the MAVAN sample, the DRD4 gene 7R acts as a protective factor against D attachment (Graffi et al., 2015; Wazana et al., 2015). In the current study we wish to analyze this relationship further and examine potential moderating and mediating relationships between D attachment, indicators of a child's environment, and the DRD4 gene.

Attachment Disorganization and Infant Birth Weight

Infant birth weight influences long-term developmental outcomes and is considered to be an indication of intrauterine growth retardation (IUGR) (Kramer, 1987). IUGR is suggestive of an adverse prenatal environment and high prenatal maternal stress levels as it is associated with

high maternal and fetal concentrations of glucocorticoids (Goland et al., 1995; McTernan et al., 2001). Infants born with a weight of less than 2,500 grams are termed low birth weight (LBW), those born with a weight of less than 1,5000 grams are termed very low birth weight (VLBW) and those born with a weight of less than 1000 grams are termed extremely low birth weight (ELBW). At any gestational age, LBW infants have relatively high morbidity and mortality compared to children of birth weights higher than 2,500 grams (McIntire et al., 1999). However, with more advanced medical treatment, more of these children are surviving and are being sent to a Neonatal Intensive Care Unit (NICU) for the first days of their life (McCrea & Ment, 2008).

LBW children typically are less physically developed than infants born with a birth weight above 2,500 grams (Vohr et al., 2000). Additionally, due to having a fragile and/or a less developed nervous system, LBW infants are more reactive to stimuli in their environment and less able to self-regulate when compared to normal birth weight infants (Eckerman et al., 1994). In turn, LBW infants are more sensitive to stimuli in their proximity (Gardner et al., 2015). LBW infants may also be exposed to different treatment depending on how their birth process affects their caregivers. Having a LBW infant may be a traumatizing experience for the caregivers as they are afraid for the health of their infant (Calam et al., 1999). Research has shown that caregivers may start a grieving process before they know the actual health of their LBW infant. This compounded with the separation from their infant that is caused by the infant's admittance to the NICU can cause added anxiety, worry and even premature detachment from the infant (Brisch et al., 2003).

The relationship between an infant and its caregivers is bidirectional, as the infant reacts to how its caregivers are treating it, and the caregivers react to how the infant is behaving. This may affect a LBW infant, as its caregivers may respond to the infant differently because: the infant's health is under question; because the infant is less developed; or because the infant has a reduced ability to regulate its environment (Brisch et al., 2003). This transactional relationship may have long-term developmental implications on the LBW infant, as its relationship with the caregiver is critical for the development of emotional regulation (Fox & Calkins, 2003).

In addition to being more likely to acquire behavioural difficulties, LBW infants are also at risk of developing cognitive, language, and motor delays. For example, almost one fifth of VLBW children develop major cognitive disabilities by 8 years of age (Horwood et al., 1998; Taylor et al., 2000). Barre et al. (2011) showed that very preterm / VLBW children performed between 0.38 and 0.77 standard deviations below control subjects in the areas of overall expressive language, overall receptive language, as well as expressive and receptive semantics. Additionally, Roberts et al. (1989) found that VLBW children showed significantly poorer motor skills, as VLBW children in their cohort attained lower scores in tests of fine motor, ball and balancing skills. Previous research has debated whether these developmental delays are maintained into adulthood (Saigal & Doyle, 2008); however, it is clear that LBW children are affected during their developmental years.

LBW is also associated with an increased risk of psychopathology in the teenage and adult years. For example, LBW children have higher prevalence rates of psychiatric disorders and ADHD in the teenage years (Indredavik et al., 2004). LBW children have an increased odds

of psychological distress in later adult life (Wiles et al., 2005). As well, research has shown that adults who were born with a birth weight under 3 kilograms are more at risk of developing depression (Gale & Martyn, 2004). This evidence demonstrates how the effect of LBW on children during their developing years can have long-term socio-emotional effects.

The less developed nervous system of LBW children makes these children more susceptible to both positive and negative environments. Nomura and Chemtob (2007) showed that individuals with both LBW and subsequent childhood abuse, relative to those with neither risk, were at a substantially elevated risk for several psychological problems, including: depression, social dysfunction, and somatization. Whiteside-Mansell et al. (2009) found that preterm / LBW children with difficult temperaments who were exposed to family conflict during their childhood were more at risk of developing externalizing behaviour problems compared to children with less difficult temperaments. Laucht et al. (2001) found that VLBW children were susceptible to the quality of early caregiving, as VLBW children exposed to high levels of maternal sensitivity were at less of a risk of developing internalizing and hyperkinetic problems at the ages of 2, 4, and 5 when compared to VLBW children exposed to low levels of maternal sensitivity. Similarly, Weiss et al. (2000) found that the degree of infant vulnerability (i.e., perinatal complications, birth weight, and responsiveness) moderated the effects of nurturing touch; specifically, nurturing touch was associated with more secure classifications for low-risk infants but with less secure classifications for highly vulnerable infants.

The risk for negative developmental outcomes associated with birth weight is not restricted to infants born with LBW. Similar to evidence for other disorders such as diabetes

(Wei et al., 2007), there is an indication that the relationship between birth weight and psychopathology is curvilinear and that infants at both ends of the birth weight spectrum are at an elevated risk. It has been shown that macrosomia (excessive birth weight) also is a predictor of internalizing and externalizing disorders later in life (Van Lieshout & Boyle, 2011). Additionally, birth weight at either end of the spectrum has been associated with higher risk of attention problems (Van Mil et al., 2015), anxiety, and depression (Broekman et al., 2011).

The relationship between child attachment status and birth weight is a topic of interest because of the potential affect of the complications associated with low birth weight on the relationship between an infant and its caregivers. To date, the results from papers focusing on this relationship have yielded inconclusive results (Buchheim et al., 1999). The majority of investigations about the relationship between birth weight and attachment status have focused on samples of LBW children who were also born preterm (born before 37 weeks of gestational age; premature / LBW children).

Rode et al. (1981) examined a sample consisting of children aged 12-19 months who were separated at birth from their parents because of their prematurity or because of a serious illness. The study found that there were no significant differences in birth weight between children classified as secure or insecure. Similarly, Frodi (1983) found that a sample of premature / LBW children had a similar distribution of secure and insecure attachment classifications as term children. Goldberg et al. (1986) replicated the finding of no association between birth weight and attachment status in a preterm / VLBW sample. Additionally, Easterbrooks (1989) (in a preterm / VLBW sample) as well as Poehlmann and Fiese (2001) (in a

preterm / LBW sample) replicated the finding of no association between birth status and attachment status while specifically focusing D attachment.

In contrast, Mangelsdorf et al. (1996) found evidence that preterm / VLBW children were more likely to be classified as insecurely attached at 14 months old according to the Attachment Q-Sort (AQS) and at 19 months old according to the SSP. Significant associations between birth weight and attachment status have also been found in preterm / LBW samples at 12 months old by Weiss et al. (2000) using the AQS and by Wille (1991) using the SSP. Interestingly, Wolke et al. (2014) found that preterm / VLBW infants did not have a different amount of insecure attachment classifications at 14 months old compared to term infants; however, they did have significantly more D classifications. In addition, associations between attachment status and birth weight have been found in studies focusing on high-risk infants. Specifically, Plunkett et al. (1986) and Plunkett et al. (1988) found that high-risk preterm / LBW infants were more likely to be classified as insecure compared to low-risk preterm / LBW infants. Similarly, Brisch et al. (2005) found that in a sample of preterm / VLBW children, birth weight was only associated with attachment status if the child had a neurological impairment.

Of note, the majority of the evidence on the relationship between birth weight and attachment status describes preterm children who were born with a LBW. However, the individual effects of prematurity and birth weight are not separated in these samples. This is typical in the birth weight literature, as most preterm children are born with a LBW (Wilcox, 2001). However, this presents a possible confounding effect, as it allows for the effects of gestational term to confound the individual effect of birth weight. Additionally, several of the

studies examining the relationship between birth weight and attachment status were conducted before the development of D attachment (Main & Solomon, 1986, 1990) or are based on an instrument that does not assess D attachment, e.g. the Attachment Q-set (Waters & Deane, 1985). Accordingly, there is very little research focusing on the unconfounded effect of birth weight in term children on the development of attachment, especially in the D subtype.

However, despite the potential confounding effect of prematurity, the evidence presented above does exemplify the inconsistent nature of the association between birth weight and child attachment status. This leads to the question of whether there are genetic or postnatal factors that may affect the relationship between birth weight and child attachment status.

Attachment Disorganization and Maternal Depression

While the prevalence of postnatal depression varies according to the diagnostic criteria employed, it is generally reported to affect 13% of women in developed countries (O'Hara & Swain, 1996). This is of particular concern because of how the symptoms of postnatal depression may interfere with the developing mother-infant relationship (Murray & Cooper, 1997; Radke-Yarrow et al., 1985). Depressive symptoms such as sadness, withdrawal, loss of interest, inability to concentrate and irritability may affect how a mother interacts with her child (Murray et al., 1993). Other depressive symptoms such as thoughts of death or suicide, may expose the child to adverse circumstances during its early life (Martins & Gaffan, 2000).

Weissman et al. (1972) proposed that the symptoms of depression may prevent a mother from interacting with her child in the most sensitive and psychologically available manner. Specifically, maternal depression is associated with reduced parenting responsiveness; reduced affection and reciprocity; and increased intrusion and punitiveness (Broth et al., 2004; Goodman & Gotlib, 1999). Additionally, depressed mothers are less likely to engage in important interactions with their child such as playing, reading and establishing routine; all of which are critical in the development of the child's social interaction, learning and self-regulation (Lyons-Ruth et al., 2002). For example, in a cohort of depressed mothers, Lyons-Ruth et al. (2002) found that for each additional depressive symptom the increase in risk associated with reading to the child less than several times a week rose by 21%, increase in risk of playing with the child less than once a day rose by 33%, and the increase in risk of engaging in low levels of two or more positive behaviours increased by 40%.

Children of women suffering from postnatal depression are at risk of a variety of developmental delays (e.g. Goodman & Gotlib, 1999; Wan et al., 2008). Goodman and Gotlib (1999) proposed four potential mechanisms for the transmission of risk for negative developmental outcomes from a depressed mother to a child: heritability of depression; innate dysfunctional neuro-regulatory mechanisms; negative maternal cognitions, behaviours, and affect; and the stressful context of the children's lives. Specifically, maternal postnatal depression has been associated with negative outcomes in infant cognitive, behavioural and emotional development (e.g. Fihrer et al., 2009; Grace et al., 2003; Murray & Cooper, 1997; Reissland & Shepherd, 2006). For example, Cornish et al. (2005) found that chronic maternal postnatal depression was associated with lower infant cognitive and psychomotor development. Trapolini

et al. (2007) found that children exposed to chronic maternal postnatal depression were rated by their parents as significantly more problematic in regards to internalizing and externalizing behaviours. Additionally, Mäntymaa et al. (2008) showed that mother's current depressive symptoms increased the infant's risk of social withdrawal.

Previous research also has indicated that maternal postnatal depression increases the child's risk for psychopathology during teenage and adult years (e.g. Barker et al., 2012; Goodman et al., 2011). For example, Pawlby et al. (2008) found that the risk for psychiatric disorder at 11 years of age was four times greater among children whose mothers suffered from postnatal depression, compared to children whose mothers were not depressed. Similarly, Halligan et al. (2007) showed that maternal postnatal depression was associated with higher rates of affective disorders in adolescent offspring.

Evidence for the effect of maternal postnatal depression on the mother-infant relationship has led to the investigation of the relationship between maternal postnatal depression and infant attachment. Maternal depression has been linked to D attachment during both the prenatal time period (e.g. Hayes et al., 2013; Perry et al., 2011) and the postnatal time period (e.g. Martins & Gaffan, 2000; Tomlinson et al., 2005). This has made it difficult to separate the effects of maternal depression during different time periods because mothers who have depression during the postnatal time period often have a long term history of depression or mood disorder before or during pregnancy (Robertson et al., 2004).

There is evidence that prenatal maternal depression may have independent effects on infant developmental outcomes and that some of the effects attributed to maternal postnatal depression are caused in part by depressive symptoms during pregnancy (e.g. Deave et al., 2008; O'Connor et al., 2002; Pearson et al., 2013). As well, previous research has focused on the theory of a sensitive period for children to be affected by maternal depressive symptoms. However, inconsistent evidence exists that demonstrates that the first few months after birth may be a particularly sensitive period (e.g. Bagner et al., 2010; Goldberg, 1983; Moehler et al., 2006). The research design implications of a potential independent effect of prenatal maternal depression and a potential sensitive period for an infant to be vulnerable to the symptoms of maternal depression emphasize the importance of a longitudinal design while studying the effects of maternal depression. To measure the unconfounded effect of maternal postnatal depression, the effects of prenatal and postnatal maternal depression must be separated. Additionally, to help determine whether there is a time period that the mother-infant relationship is particularly sensitive to, researchers should measure maternal depressive symptoms at several times after birth.

Several studies have focused on the effects of maternal depression on infant attachment exclusively in the postnatal period. Murray (1992) and Murray et al. (1996) examined the relationship between maternal postpartum depression at 6 weeks postpartum and infant attachment measured at 18 months postpartum. The studies found that infants whose mothers had been depressed in the postnatal period were significantly more likely to be insecurely attached to their mothers. Donovan and Leavitt (1989) found similar results in depressed women measured at 16 months postpartum. Dawson et al. (1992) measured depressive symptoms in mothers at a

single time-point, with infants ranging from 11-17 months of age. The study found that infants of mothers who reported more depressive symptoms were more likely to show D attachment during the SSP.

Lyons-Ruth et al. (1986) examined the relationship between maternal postnatal depression and infant attachment in a low-income sample at 18 months postpartum. The study found a curvilinear relationship between reported maternal depressive symptoms and infant attachment, as women who reported mild to moderate depressive symptoms were more likely than the other groups of women to have securely attached infants, while women who reported the least depressive symptoms and women who reported the most depressive symptoms were more likely to have infants with an insecure attachment. In a community sample, also at 18 months postpartum, Righetti-Veltema et al. (2003) found that infants of depressed mothers were more likely to be insecure and that non-depressed mothers were more likely have securely attached children.

Teti et al. (1995) focused on a cohort of women who were tested for postnatal depression at two separate time-points. In the first assessment, the mothers being tested for depression had children of varying ages; however, the second assessment was always approximately a year after the initial recruitment. The study found that maternal postnatal depression was significantly associated with higher rates of insecure attachment at both time-points. Similarly, Tomlinson et al. (2005) also studied the relationship between maternal postnatal depression at two separate time-points; each mother was tested at 2 months and 18 months postpartum while infant attachment was measured at 18 months postpartum. The cohort consisted of black South African

women living in extreme poverty. The study found that mothers who were classified as depressed at the 2 months postpartum time-point were more likely to have insecure infants; however, this was not the case for women classified as depressed at the 18 months postpartum time-point. McMahon et al. (2006) assessed maternal postnatal depression at three time-points: 4, 12 and 15 months postpartum. The study categorized women into groups according to when they were depressed; a 'brief' group represented mothers who were depressed only the 4-month assessment and a 'chronic' group represented mothers who were found to be depressed at the 4-month assessment and one of the 12- or 15-month assessments. McMahon et al. (2006) found that infants of chronically depressed mothers were significantly more likely than infants of never depressed mothers to be classified as insecure at 15 months postpartum. Additionally, infants of briefly depressed mothers did not differ from infants of never depressed mothers. Interestingly, the study also found that there was no difference in the three groups in terms of D attachment.

Despite the wealth of evidence supporting the notion of a positive relationship between maternal postnatal depressive symptoms, some papers have not found evidence of the relationship. Frankel and Harmon (1996) collected a community sample and measured mothers' depressive symptoms at one time-point when their children were between 3 and 4 years old. The study found no difference between the distributions of infant attachment in the depressed and non-depressed groups. This study provides evidence that the window of vulnerability for infant attachment to be affected by maternal postnatal depression may be closed by the time children enter their preschool years. Additionally, Campbell and Cohn (1997) measured maternal postpartum depression at seven separate time-points between 2 and 24 months postpartum. Attachment security was measured at 12 and 18 months postpartum. Based upon their scores at

each time-point, women were categorized into a 'never depressed' group, a 'subclinical' group, a 'remitted' group and a 'chronic' group. Campbell and Cohn (1997) found that neither chronicity of depression, nor depression assessments concurrent with time of attachment assessments predicted higher rates of insecure attachment.

Atkinson et al. (2000) conducted a meta-analysis on maternal depression and attachment security and found a significant effect size of (d=0.18). This finding, as well as the findings in the aforementioned research, describes a positive relationship between maternal postnatal depression and incidence of D attachment. However, it is also clear that the effect of maternal postnatal depression on attachment status is not synonymous over time. The inconsistencies reported by Frankel and Harmon (1996) as well as by Campbell and Cohn (1997) illustrate how the results of a study may be affected by the timing of assessment as well as the method of measuring maternal postnatal depression; whether it be measuring continuous scores of depressive symptoms or categorizing participants into groups of clinically depressed women and non-depressed women. Additionally, although all of the studies described above exclusively measured maternal symptoms during the postnatal period, the studies did not measure maternal prenatal depression to see whether women diagnosed during this period had a different effect than those only diagnosed postnatally. This indicates a potential confound to the results presented. Furthermore, while some studies (Campbell & Cohn, 1997; McMahon et al., 2006; Teti et al., 1995; Tomlinson et al., 2005) measured maternal postnatal depression at more than one time-point, the majority of studies (Dawson et al., 1992; Frankel & Harmon, 1996; Lyons-Ruth et al., 1986; Murray, 1992; Murray et al., 1996; Righetti-Veltema et al., 2003) only

examined maternal postnatal depression at a single time-point. This does not allow for a sensitive time period of infant attachment to maternal postnatal depression to be examined.

The strong evidence demonstrating that maternal postpartum depression affects several different components of the infant-mother relationship makes maternal postnatal depression an excellent variable to study in a more complex GxE interaction study. Additionally, the longitudinal design of the MAVAN sample makes it an ideal cohort to observe whether there is a time-sensitive effect of maternal postnatal depression and to properly differentiate the independent effects of prenatal and postnatal maternal depression.

Attachment Disorganization and Early Maternal Care

Maternal sensitivity is defined as a mother's ability to perceive her child's signals appropriately and respond to them promptly and contingently (Ainsworth et al., 1978). Maternal sensitivity has been linked to child attachment since the beginning of attachment theory. Ainsworth et al. (1978) was the first group to study the relationship between parental behaviour in the home and child attachment security. The study found that four rating scales (sensitivity, cooperation, availability and acceptance) were the most strongly associated with attachment security. Ainsworth et al. (1978) identified the core maternal characteristics of sensitivity in their definition of an optimally sensitive mother: the mother is aware of the infant's signals, the mother interprets the infant's signals accurately, and the mother responds to the infant's signals both appropriately and promptly. While the results of subsequent studies examining the relationship between maternal sensitivity and attachment security have presented heterogeneous

findings, likely due to varying sample characteristics and the use of different techniques to measure maternal sensitivity, a meta-analysis of the existent literature established a statistically significant relationship, albeit with a medium effect size (De Wolff & van Ijzendoorn, 1997).

Maternal sensitivity is a global assessment of a mother's ability to promptly and adequately respond to infant cues (Mileva-Seitz et al., 2012). When maternal sensitivity is measured, several caregiving behaviours and responses are observed and scored in order for an accurate measurement to be taken (Ainsworth, 1969). While most researchers use the definition created by Ainsworth (1969), many others have expanded on it to show that maternal sensitivity encompasses a wide array of behaviours. As Nicholls and Kirkland (1996, pg. 64) state, "maternal sensitivity seems to be a complex and multi-faceted construct; it is by no means a clearly-defined and tightly-bounded set of behaviours."

In previous research, maternal behaviour has been measured using macroanalytic or microanalytic techniques. Macro-level coding refers to a summary score that is assigned based on the observation of the total interaction time while micro-level coding refers to procedures in which maternal behavioural states are coded in very small time segments (Mesman, 2010). In terms of maternal sensitivity, the scales developed by Ainsworth et al. (1978) are an example of a macroanalytic score and are the most often studied. However, microanalytic measures provide complementary information such as specific dimensions of maternal responsiveness that may affect the mother-infant relationship (Mesman, 2010; Mileva-Seitz et al., 2012).

Microanalytic maternal caregiving behaviours also have been studied in relation to child attachment security. For example, it has been shown that mothers of securely attached infants are more responsive and encouraging in face-to-face interactions with their children (Blehar et al., 1977); are more affectionate (Bates et al., 1985), are gentler with their children (Londerville & Main, 1981), are more accepting (Main et al., 1979) and are more positive in their vocalizations with their child (Roggman et al., 1987) when compared to mothers of insecurely attached infants. Additionally, controlled attention has been shown to be of particular importance in the context of maternal sensitivity and D attachment (Atkinson et al., 2009). Controlled attention is the ability to concentrate on consciously selected stimuli and inhibit focus on potential distractors (Engle et al., 1999). Mileva-Seitz et al. (2013) found that less sensitive mothers tend to orient away from the infant more frequently and for longer durations than do more sensitive mothers and that there is a significant negative correlation between infant-directed vocalizing and frequency of orienting away from the infant. This finding has been exhibited in other samples as well (Atkinson et al., 1995; Atkinson et al., 2000; Pederson et al., 1990).

Maternal sensitivity and specific maternal caregiving behaviours may be two mechanisms that link maternal depression to negative child outcomes (Campbell et al., 2007). The symptoms that define depression, (e.g. sad mood, loss of interest, disengagement, fatigue, and irritability), conflict with the definition of a highly sensitive mother, and clinically it would be expected that maternal depression would be associated with lower maternal sensitivity. Lower maternal sensitivity, would in turn, be expected to predict lower rates of attachment security in young children. Pyszczynski and Greenberg (1987) hypothesized that depressed mothers interact less sensitively with their children because of their preoccupation with their own negative cognitions

and feelings detracts from their ability to respond appropriately to their infant's cues. Indeed, several studies demonstrate the relationship between the presence of maternal depressive symptoms and decreased maternal sensitivity (e.g. Campbell et al., 2004; Cicchetti, 1990; Crockenberg & Leerkes, 2003; Dannemiller, 1999; Mills-Koonce et al., 2008; Trapolini et al., 2008; van Doesum et al., 2007). Regardless of whether the symptoms of maternal depression reach diagnosable levels, the infant may interpret depressive behaviours as the mother being unresponsive, inconsistent, unavailable, or rejecting care (Carlson & Sroufe, 1995; Cummings et al., 2002).

Depressed mothers also are more likely to display different maternal caregiving behaviours than non-depressed mothers. Campbell et al. (1995) showed that women who were chronically depressed were less positive with their babies during face-to-face interactions, were less competent when they were observed feeding their babies; and showed less positive affect during toy play at 4 months when compared with women in the subclinical or remitted groups. Murray et al. (1996) found that depressed mothers expressed fewer affirmations of their infants' behaviours and more negations in response to their children. Additionally, Field (2002) found that compared to non-depressed mothers, depressed mothers showed less frequent positive facial expressions, more frequent negative facial expressions, less frequent vocalizations, lesser amounts of time spent looking at the infant, and lesser amounts of time providing tactile/kinesthetic stimulation.

Previous research has examined the degree to which maternal sensitivity and caregiving behaviours may explain the association between maternal depressive symptoms and negative

developmental outcomes. Harnish et al. (1995) found that maternal harshness mediated the association between maternal depressive symptoms and child adjustment in the first grade in a high-risk sample. Dannemiller (1999) observed that the effects of maternal depression on cognitive and language outcomes were partially accounted for by levels of maternal sensitivity. Furthermore, Campbell et al. (2004) specifically looked at the possible mediation effect of maternal sensitivity on the association between maternal depression history and D attachment at 36 months. The study found that when the effect of maternal sensitivity was controlled for, the association between both chronic and intermittent depressive symptoms and attachment were attenuated. However, the odds ratios of the two maternal depression groups only showed modest decreases. Therefore, the results found by Campbell et al. (2004) provides evidence of a weak mediation effect of maternal sensitivity on the association between maternal postnatal depression and D attachment.

In the present study, based upon the evidence presented above, we decided to investigate early maternal care in two ways. The first involves assessing maternal sensitivity through macroanalytic observational rating scales, as developed by Ainsworth et al. (1978) and typically used in attachment research. The second assessment, a microanalytic measure, focuses more specifically on observed maternal caregiving behaviours that have been shown to be different in groups of depressed and non-depressed women. Specifically we examined the following observed maternal behaviours: the frequency that the mother's attention is directed at something not infant-related; the frequency of any kind of soft tactile affection which is not exploratory or arousing; the frequency of maternal laugh or smile that occurs in a way directed towards the

infant; and the frequency of vocalizations towards the infant, including adult voice, 'motherese', quiet voice and nonsense words.

Models and Hypotheses

We believe that the evidence described above illustrates how infant DRD4 genotype, infant birth weight, maternal postnatal depression, and early maternal care provide an excellent GxE model to observe the interplay of several risk factors on child D attachment at 36 months. The evidence provided demonstrates how DRD4 polymorphisms are associated with an individual being more sensitive to their environment. Especially negative prenatal (as indicated by birth weight) or postnatal environments (as indicated by maternal depression and early maternal care) may exacerbate this susceptibility. The relationship between early maternal care and both infant attachment security as well as maternal depression indicates that early maternal care may mediate the relationship, if any, between postnatal maternal depression and child D attachment.

We aim to explore the interplay between all of these factors by examining several different models. Firstly, the main effect of infant DRD4 genotype, infant birth weight and maternal postnatal depression will be examined for their relationship with D attachment at 36 months. We hypothesize that infants with the DRD4 7R allele will be less likely to have D attachment; that birth weight will operate with a curvilinear effect such that children with extreme birth weight (low and high) will be more likely to have D attachment; and that children exposed to postnatal depression will be more likely to have D attachment.

Secondly, we will examine the two-way interactions between DRD4 polymorphisms and both birth weight and maternal postnatal depression, as well as the two-way interaction between birth weight and maternal postnatal depression. We hypothesize that DRD4 genotype will moderate the effects of birth weight and maternal postnatal depression such that children with the 7R allele and negative prenatal (extreme birth weight) or postnatal (exposed to maternal postnatal depression) environments will be more likely to have D attachment. Additionally, we hypothesize that birth weight and maternal postnatal depression will interact such that children exposed to maternal postnatal depression with extreme birth weights will be more likely to have D attachment.

Thirdly, we will look at the three-way interaction between the DRD4 gene, birth weight and maternal postnatal depression. We hypothesize that children with the 7R allele, extreme birth weight and mothers who are postnatally depressed will be the most likely to have D attachment. Finally, we will test to see whether early maternal care mediates the relationship, if any, between maternal postnatal depression and D attachment. We hypothesize that the effects of maternal postnatal depression will be attenuated when early maternal care is controlled for. Refer to Figure 1 for a diagram of the relationships between birth weight, DRD4 genotype and maternal postnatal depression we will be inspecting. Refer to Figure 2 for a diagram of how early maternal care will be added to the first model.

Upon examining the mediation model and observing the limited extent of its ability to examine the relationship between maternal depression, early maternal care, and child D attachment at 36 months, we decided to further examine the relationship between these variables

by conducting a post-hoc analysis. Specifically, we conducted a separate analysis from the mediation model which examined the interaction between maternal depression and early maternal care. This analysis was exploratory in nature and no hypotheses were made.

Methods

Participants

Participants were mother–child pairs from the ongoing longitudinal Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) project. MAVAN is a Canadian community-based birth cohort composed of more than 750 women recruited from Montreal (QC) and Hamilton (ON). Women 18–43 years of age were recruited between 2003 and 2009 during routine ultrasound examinations and from prenatal care clinics in maternity hospitals. Eligibility criteria for women were: 18 years of age or over at the expected date of delivery, singleton and term pregnancy (≥37 weeks), and fluency in English or French. Exclusion criteria included the presence of severe chronic maternal illness, past obstetrical complications, or major fetal/infant anomaly. Children exhibiting significant developmental delays, identified with the Bayley scale, were excluded from the study. A detailed description of the recruitment, procedure and measures has been published (O'Donnell et al., 2014).

Retention rates for the MAVAN subjects are 97.4% at 6 months, 84.0% at 18 months, and 80.6% at 36 months, with the majority of subjects dropping out when the parent returned to work. Compared to mothers who remained in the study, mothers who left did not differ significantly on measures of age at delivery, depression, or education. Compared to children who remained in the study, children lost to follow-up did not differ significantly on measures of birth weight. Of the original 750 dyads, the present study includes 655 mother–child dyads in the final imputation model excluding women who attended the initial prenatal screening and dropped out of the study before the birth of their child.

A priori power calculations were examined before the final sample of 655 dyads used in the present paper was collected. Power calculations were based on expected correlation in a multivariable linear regression model that included 450 subjects expected at the 12-year protocol of the MAVAN. Calculations were examined for models including various combinations of covariates, main effects, two-way interaction effects, and three-way interaction effects. Calculations were made for models including up to ten variables. Using the expected sample size of 450, each model demonstrated a partial correlation of 0.15 or greater, allowing for a 90% power to detect a significant effect. As the sample size in the present paper has surpassed the expected sample size at the 12-year protocol of the MAVAN, the models described have more than satisfactory power.

In the present sample, there were slightly more boys than girls, women were on average 30.4 years of age at the birth of their child, 36.9% of the women had at least one 7R DRD4 allele, and approximately half of the women were a university graduate or higher (Table 1). The demographic and socioeconomic distribution of women in this study was similar to that of women from the Generation R Study and the Avon Longitudinal Study of Parents and their Children, two comparable prenatal cohort studies (Van Batenburg-Eddes et al., 2013).

Procedure

Women consenting to participate were interviewed at 24–36 weeks of pregnancy to obtain data on demographic, medical and obstetric history, stressors, social support, and pregnancy. Birth outcomes were extracted from the chart of the birthing unit. Mothers and their

children were seen at each study time-point (3, 6, 12, and 18 months and yearly from age 24 months onward). Mothers were assessed using extensive sociodemographic and psychological measures, while children were assessed using neurodevelopmental and socioemotional measures. Early maternal care was assessed at 6 months in a 20-min videotaped non-feeding and unstructured home interaction session followed by a 10-min divided attention task. Mothers were asked to interact normally with their infants. During the last 10-min period, mothers completed scales while still caring for the infant. The purpose of this task was to place the mother in a situation that divides attention. Behaviour under these conditions augments the predictive capacity of sensitivity ratings (Atkinson et al., 2000). A macroanalytic (Ainsworth sensitivity scales) and a microanalytic (Behavioural Evaluation Strategies and Taxonomies) measure were used to code observed maternal behaviour.

Measures

Birth weight: As fetal growth may differ by race, gender, socioeconomic environment, geographical area, and altitude, birth weight from the chart was cross-referenced with Canadian normative data (Kramer et al., 2001) to calculate birth weight birth weight appropriate for gestational age (AGA), measured as a percentile. Infant birth weight ranged from 1.71 to 5.34 kg (M = 3.53 kg; SD = 0.46 kg), while birth weight AGA ranged from 0 to 100 percentile (M = 45.91, SD = 27.25) (Table 1). An initial analysis found no association between birth weight and D attachment. Consistent with recent publications (Alati et al., 2009; Broekman et al., 2011; Van Mil et al., 2015) reporting a curvilinear relationship between birth weight and psychopathology, models were tested with birth weight as a quadratic term and found to be quite significant.

Accordingly, subsequent analyses are presented with birth weight centered and squared, (birth weight – 50)^2, allowing for high and low values of birth weight (e.g. extremes of 30th percentile and 70th percentile) to be treated equally.

DRD4 genotype: Child genotype was obtained with the use of buccal swabs at 36 months. The method for genotyping the DRD4 variant and for establishing reliability has been reported previously (Lichter et al., 1993; Silveira et al., 2014; Silveira et al., 2016). For each marker tested, 10% of samples were re-typed as a form of quality control. If there was conflict between the original genotype and the QC genotype, a new working dilution of the sample was made from stock, and the test was run again using both the old and the new dilution to resolve the conflict. DRD4 was coded dichotomously for the presence or absence of the 7R allele. The genotype distribution represented that of a predominantly white population sample. For both the Montreal and Hamilton samples, the distribution of DRD4 conformed to the Hardy–Weinberg equilibrium ($p = 0.58$; $p = 0.95$, respectively). There were no gender differences between infant or maternal DRD4 genotype, $X^2(1) = 0.01$, $p = 0.92$; $X^2(1) = 0.4$, $p = 0.52$ (lab of J. Kennedy). Of the sample, 35.8% of the children and 36.9% of the mothers were carriers of the 7R allele (Table 1).

Maternal Depression: Assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) at the prenatal assessment as well as at the assessments at 6, 12, 24, and 36 months. The CES-D, a 20-item self-report measure of depressive symptomatology (Radloff, 1977) has been validated for assessment during pregnancy (e.g. Davis et al., 2011) and postnatally (e.g. Campbell et al., 2004). The CES-D items are rated on a 4-point Likert scale that ranges from rarely or none of the time to most or all of the time. The highest score is 60, and a

score of 16 or higher is suggestive of a depressive disorder. CES-D scores were examined using two methods. Firstly, CES-D scores were examined at each time-point (prenatal, 6 months, 12 months and 24 months, excluding the 36-month assessment). In order to establish causality, a measure should precede an outcome. As the 36-month measure was concurrent with the assessment of attachment, it was not examined as a separate variable. Using the scores from each time-point (prenatal, 6 months, 12 months, 24 months, and 36 months), an area under the curve (AUC) score was calculated. CES-D scores from each time of assessment and AUC scores were centered to facilitate interpretation of regression coefficients. Secondly, mothers were categorized as 'Never Depressed', 'Prenatally Depressed', 'Postnatally Depressed' or 'Chronically Depressed' according to their CES-D scores. This variable was considered to represent each woman's history of depression. Women who did not score higher than 16 at any of the assessments were categorized as 'Never Depressed' (48.8%); women who had a score of 16 or above at the prenatal assessment, but did not score 16 or higher at any of the postnatal assessments were categorized as 'Prenatally Depressed' (3.2%); women who had a score of 16 or above for at least one of the postnatal assessments, but did not score at 16 or higher at the prenatal assessment were categorized as 'Postnatally Depressed' (26.6%); and women who had a score of 16 or higher at the prenatal assessment and for at least one of the postnatal assessments were categorized as 'Chronically Depressed' (21.4%), (Table 1).

Maternal Sensitivity: Mothers were assessed using the Ainsworth Maternal Sensitivity Scales (Ainsworth et al., 1978) at the 6-month assessment. The Ainsworth Maternal Sensitivity Scales are a reliable and validated gold standard measure of sensitivity. The measure includes four 9-point Likert rating scales: cooperation, accessibility, acceptance, and sensitivity.

Videotaped mother–child interactions were coded by research assistants and then compared to videos coded by an expert coder. Interclass correlation for the Ainsworth mean score at 6 months was 0.88 (N = 28; lab of L. Atkinson). The average Ainsworth mean score was 5.74 (SD = 1.8), (Table 1). The scores of the four subscales as well as the mean score were inspected in our analyses. Scores for each subscale as well as the mean score were centered to facilitate interpretation of regression coefficients.

Maternal behaviour: Second-by-second behaviours observed during mother–infant interaction were coded at the 6-month assessment using the Behavioural Evaluation Strategies and Taxonomies coding system (Educational Consulting, Inc.; S & K NorPark Computer Design, Toronto). This analysis generated duration and frequency data for multiple maternal behaviours by use of a computer keyboard with keys indexed for each behaviour. Coded behaviours used in this analysis include frequency of looking away from the infant (mother's attention is directed at something not infant-related), frequency of stroke/pat/palm (any kind of soft tactile affection which is not exploratory or arousing, often soft, and appearing somewhat absent-minded), frequency of laugh or smile (maternal laugh or smile, occurring in a way directed toward the infant), and frequency of vocalization towards the infant (quiet talk, 'motherese', singing, and adult talk in a way direct towards the infant). These behaviours and coding schemes have been used in previous research (Giardino et al., 2008; Krpan et al., 2005; Mileva-Seitz et al., 2011). Inter-rater reliability was obtained by having two observers code the same 18 videos of mother–infant interactions twice. Inter-rater reliability was high, with r-values ranging from 0.67 to 0.96 across all behaviours. In addition, the intra-rater reliability was computed, based on the second observer independently coding 10 videotapes of mothers interacting with their infants on two

separate occasions. All of the behaviours analyzed were highly correlated, with r-values ranging from 0.821 to 1.0 (lab of A. Fleming). On average, mothers looked away from the infant 21.5 times, engaged in a soft tactile stimulation of the infant 5.7 times, laughed or smiled towards the infant 11.8 times and vocalized towards the infant 32.1 times during the videotaped interaction, (Table 1).

The looking away frequency scores have been validated against dimensional ratings of maternal sensitivity (Mileva-Seitz et al., 2013). Mileva-Seitz et al. (2012) concluded that orienting away, infant-directed vocalizing, and sensitivity are likely separate but overlapping components of the complex maternal phenotype, akin to endophenotypes in psychiatric research. Mileva-Seitz et al. (2012) argued that lower rates of orienting away are indicative of lesser maternal distractibility and greater maternal sustained attention on the infant, an argument strengthened by the negative correlation between orienting away and maternal sensitivity (Mileva-Seitz et al., 2013). Scores were centered to facilitate interpretation of regression coefficients.

Attachment: At the 36-month assessment, the modified separation–reunion procedure described by Cassidy and Marvin (1992) for preschool-age children was followed. It consisted of four episodes lasting 5 min each: (a) separation between mother and child; (b) reunion; (c) second separation; and (d) second reunion. During both separations, the child was left alone. Following the separations, the mother was told to rejoin the child but received no specific instructions concerning the reunions. The separation–reunion sequence took place in a room in which age-appropriate toys were scattered. The attachment classifications (insecure-avoidant,

secure, insecure-anxious, or D) were based on behaviour observed in both reunions, with details of coding criteria for each classification provided in Moss, Bureau, et al. (2004). The criteria for identifying D attachment at preschool age are similar to those identified in Main and Solomon (1990) with the additional criteria of role-reversed behaviour with the caregiver of a punitive or caregiving type. Children are sub-classified as behaviourally D if they display inexplicable, contradictory, or odd behaviour in the presence of the caregiver similar to infant D behaviours. Children are sub-classified as controlling–punitive if they attempt to control their parent's behaviour in a hostile, role-reversed punitive manner. Those who show role reversal in a helpful, attentive, caregiving manner are sub-classified as controlling–caregiving. Because children in all three D sub-classifications lack a coherent strategy to organize emotions and behaviours toward the caregiver at the time of the reunion, they are typically combined into a D group for analyses (Moss et al., 2005).

Overall agreement between the two coders for the major classifications was calculated on 20% of the tapes, and excellent inter-rater reliability was obtained (89%, $k = 0.83$, $p < 0.01$). Coding is based on information gathered from five modalities: physical proximity and contact, body positioning, speech, gaze, and affect. The validity of this procedure for classifying attachment behaviour in children of this age range has been demonstrated in several studies (Moss, Cyr, et al., 2004; Moss et al., 2005). In many studies primarily focused on D attachment, insecure-avoidant, secure, and insecure-anxious categories are combined into an organized category (based on the assumption that they involve organized attachment strategies for seeking proximity to the caregiver), enabling a dichotomous comparison with the D group. Attachment was available for 304 children as follows: 20 insecure-avoidant, 167 secure, 43 insecure-anxious,

and 74 D (Table 1). Breakdown of the D group in the behaviourally D, controlling–punitive, and controlling–caregiving groups was 52, 3, and 19 respectively. As is common practice, children in all three D sub-classifications were combined into one group. This was justified based on both sample size limitations and the idea that for both behaviourally D and controlling children, the internal working model underlying the behavioural strategy is characterized by disorganized in socio-emotional regulation as evidenced by performance on doll-play and other representational measures of attachment (Moss, Bureau, et al., 2011).

Covariates: Covariates were obtained from the Health and Well Being of Mothers and Their Newborns questionnaire (Kramer et al., 2009) administered prenatally and at 6, 12, 24, and 36 months postnatally. Maternal education, yearly household income, infant gender, birth location, maternal age at birth and maternal DRD4 genotype were all examined based upon a priori selection. Maternal education and yearly household income were extracted from the questionnaire administered during the prenatal assessment. Prenatal maternal education was categorized as 'Less Than College', 'College', or 'University Graduate or Higher.' Yearly household income and maternal age at birth were centered to facilitate interpretation of regression coefficients.

Analyses

Logistic Regression: Intra-class correlation, which depicts the proportion of variance in attachment accounted for by site of recruitment, was estimated to be 0 in all analyses. Therefore, a mixed model was not used. Furthermore, site was not correlated with D attachment. All

assumptions for regression were respected. Outliers were assessed with the use of standardized Pearson residual values and were removed if their value was greater than 2.8 (or, –2.8) or greater than 2.00 (or, –2) with a Mahalanobis Distance greater than the respective critical value (Penny, 1996). Covariates were identified by preliminary analyses driven by theoretical conception. Variables were retained as covariates for the final analyses when they were associated with both a predictor and the outcome. All results are adjusted for the relevant covariates.

To inspect main effects, two-way interaction effects, and three-way interaction effects, several logistic regression models were created. The models included the retained covariates, birth weight AGA, infant DRD4 genotype, maternal depression (separate models for each maternal depression measure: maternal depression history, prenatal CES-D scores, CES-D scores at 6 months, CES-D scores at 12 months, CES-D scores at 24 months and AUC of all CES-D scores), and D attachment as the outcome. To assess the effect size of our models, we used a McFadden Pseudo R^2. To assess the accuracy of our models, we used the area under the curve, which is the probability of correctly determining which children are D, or not. A value between 0.9 and 1 is considered outstanding, a value between 0.8 and 0.9 is considered excellent, a value between 0.7 and 0.8 is considered acceptable, and a value below 0.7 is considered poor. AUC scores were calculated for each model within the subset of subjects who had complete measures. All scores were in the acceptable (0.7 – 0.8) range.

Using the causal steps approach outlined in Baron and Kenny (1986) as well as Judd and Kenny (1981) to inspect the potential mediation effect of early maternal care, four relationships were considered: (1) the main effects of maternal depression measures; (2) the associations

between early maternal care and maternal depression; (3) the associations between early maternal care and D attachment; and (4) models with both maternal depression and early maternal care predicting D attachment. As well, in order for a mediating effect to be established, the causal effect must precede the mediating effect. As each early maternal care measure was assessed at 6 months, only prenatal CES-D scores and CES-D scores at 6 months fulfill this requirement. Therefore, only these measures of maternal depression were considered in the mediation models. Separate models for each early maternal care measure (Ainsworth mean score, Ainsworth sensitivity, Ainsworth cooperation, Ainsworth availability, Ainsworth acceptance, looking away frequency, stroke/pat/palm frequency, laugh/smile frequency and vocalization frequency) as well as for each maternal depression measure (prenatal CES-D scores and CES-D scores at 6 months) were considered.

As mentioned previously, the mediation model described above was limited in its ability to examine the relationship between maternal depression, early maternal care, and child D attachment at 36 months. The model was limited for two reasons: firstly, only prenatal CES-D scores and CES-D scores at 6 months could be examined as they were the only times of assessment which preceded the measurement of early maternal care. Secondly, neither the prenatal CES-D scores nor the CES-D scores at 6 months exhibited a main effect in the prediction of D attachment at 36 months. For this reason, we decided to conduct post-hoc analysis which focused on the potential moderation effect between maternal depression and early maternal care in the prediction of D attachment.

While mediation and moderation represent two separate relationships between sets of variables, at times the terms have been confused for one another and have been used interchangeably (Baron & Kenny, 1986). However, the effects of a mediator and a moderator are quite different from one another. A mediator is considered to be a mechanism through which an independent variable is able to affect a dependent variable (Baron & Kenny, 1986). In a causal pathway between a predictor and an outcome, a mediator is considered to lie directly between a predictor and the respective outcome (Holmbeck, 1997). Contrastingly, a moderator indicates what conditions are necessary for an independent variable to have an effect on a dependent variable (Baron & Kenny, 1986). In a causal pathway between a predictor and an outcome, a moderator is considered to lie outside of the causal pathway on the same level as the predictor variable (Kim et al., 2001). Indeed, mediation and moderation are also tested for by using different techniques, as mediation is examined by using path analysis such as the causal steps approach described above; whereas moderation is examined by testing the interaction effects between sets of variables.

With this in mind, our post-hoc analysis of the potential moderation effect between maternal depression and early maternal care in the prediction of D attachment at 36 months examined several logistic regression models to inspect the two-way interaction effects between the two variables. The models included the retained covariates, birth weight AGA, infant DRD4 genotype, maternal depression (separate models for each maternal depression measure: maternal depression history, prenatal CES-D scores, CES-D scores at 6 months, CES-D scores at 12 months, CES-D scores at 24 months and AUC of all CES-D scores), early maternal care (separate models for each early maternal care measure: Ainsworth mean score, Ainsworth

sensitivity, Ainsworth cooperation, Ainsworth availability, Ainsworth acceptance, looking away frequency, stroke/pat/palm frequency, laugh/smile frequency and vocalization frequency), and D attachment as the outcome.

Multiple Imputation: Missing values were imputed for the logistic regression using the MICE (multivariate imputation by chained equations) algorithm (van Buuren & Groothuis-Oudshoorn, 2011). The imputation model was used to explain the pattern of missing data and to obtain imputed values for these missing data and included all variables that were used in the regressions. No variable had to be removed because of excessive missing data. Imputed values were based on regression estimates. The quality of the imputations depends on the amount of missing data. When the amount of missing data does not exceed 50%, five imputations are enough to obtain valid estimates (Schafer, 1999). R Studio software (version 0.98.1060; R Foundation for Statistical Computing, Vienna, Austria) was used to perform imputation as well as all other analyses. Estimates were not biased by the imputation because executing the models with the subset of subjects with complete measures yielded the same results. The results of the imputed dataset are presented in this paper, with exceptions indicated.

Results

Covariates of Disorganized Attachment

Preliminary tests were conducted on each covariate that was chosen a priori. The tests were conducted on the subset of subjects with complete measures in order to evaluate which covariates should be included in multiple imputation. Variables were retained as covariates for the final analyses when they were associated with both a predictor and the outcome. A chi-square test of independence revealed that there was not a significant association between gender and D attachment, X^2 (1) = 0.801, p = 0.371, indicating that there was not a significant difference between the frequency of D males and females. A chi-square test of independence revealed that there was not a significant association between birth location and D attachment, X^2 (1) = 0.140, p = 0.708, indicating that there was not a significant difference in the frequency of D attachment between mother-infant dyads from Montreal or Hamilton. A chi-square test of independence revealed that there was not a significant association between maternal DRD4 genotype and D attachment, X^2 (1) = 1.62, p = 0.203, indicating that there was not a significant difference in the frequency of D attachment between mothers who had the 7R allele and those who did not. A chi-square test of independence revealed that there was a significant association between prenatal maternal education and D attachment, X^2 (2) = 20.6, p = 0.0000344, indicating that women in the lowest education group were more likely to have children classified as D. A Welch's t-test revealed that there was a significant association between maternal age at birth and D attachment, t(87.1) = 2.08, p = 0.0407, indicating that women with children classified as D were significantly older when their child was born. A Welch's t-test revealed a significant association between prenatal household income and D attachment, t(129) = 3.90, p = 0.000153, indicating that

women with children classified as D had a significantly higher mean prenatal household income than women with children classified as not D.

Prenatal maternal education and maternal age at birth were retained as covariates due to their associations with D attachment. Infant gender was retained as a covariate for a priori reasons. Birth location and maternal DRD4 genotype were not retained as covariates as they did not display significant associations with D attachment. Prenatal household income was not retained as a covariate because prenatal maternal education had a more robust association with D attachment. A logistic regression was then performed with all of the retained covariates using the imputed dataset. Both prenatal maternal education at the college level, $\beta = -1.76$, OR = 0.173, $p = 0.0000928$, and at the university level or higher, $\beta = -1.15$, OR = 0.316, $p = 0.00284$, remained significantly associated with D attachment. All subsequent analyses refer to the effects adjusted for the retained covariates.

Main Effect of Birth Weight

As described earlier, a preliminary logistic regression using the subset of subjects with complete measures revealed that birth weight AGA did not show a significant main effect on D attachment, $\beta = 0.00144$, OR = 1.00, $p = 0.801$, indicating that birth weight AGA was not a significant predictor of D attachment. Birth weight AGA was then transformed and squared before being entered into multiple imputation. All subsequent analyses reported include birth weight AGA as a transformed squared variable. A logistic regression revealed that the

transformed birth weight AGA did not show a significant main effect on D attachment, β = -0.0000147, OR = 1.00, p = 0.929.

Main Effect of Infant DRD4 Genotype

A logistic regression revealed that infant DRD4 genotype showed a significant main effect on D attachment, β = -1.11, OR = 0.329, p = 0.000828, indicating that children who had at least one 7R allele were less likely to have D attachment than children who did not have at least one 7R allele. See Figure 3.

Main Effect of Maternal Depression

A logistic regression revealed that 'Chronic Maternal Depression' showed a significant main effect on D attachment, β = 1.01, OR = 2.74, p = 0.00911, indicating that children whose mother was categorized as 'Chronically Depressed' were more likely to have D attachment than children who had mothers who were categorized as 'Never Depressed'. See Figure 4. Neither 'Prenatal Maternal Depression', β = -0.0209, OR = 0.979, p = 0.977, nor 'Postnatal Maternal Depression', β = 0.424, OR = 1.53, p = 0.282, showed a significant main effect on D attachment. This indicates that children whose mother was categorized as either 'Prenatally Depressed' or 'Postnatally Depressed' were not more likely to have D attachment than children who had mothers who were categorized as 'Never Depressed'.

Separate logistic regressions for the main effects of the CES-D scores at the prenatal, 6 months, 12 months, 24 months and the AUC score were analyzed. No CES-D score at any time-point showed a significant association with D attachment. This indicates that neither the CES-D scores at a single time point, nor the AUC of CES-D scores over the entire longitudinal period are a significant predictor of D attachment. See Table 2.

Moderation of Birth Weight by Infant DRD4 Genotype

In a logistic regression of the two-way interaction model examining the prediction of D attachment from birth weight AGA and infant DRD4 genotype, the interaction term of birth weight AGA and infant DRD4 genotype was not significant, $\beta = 0.000114$, OR = 1.00, $p = 0.825$, indicating that infant DRD4 genotype did not moderate the effect of birth weight AGA.

Moderation of Maternal Depression by Infant DRD4 Genotype

Separate logistic regressions models of the two-way interactions of each maternal CES-D score or the AUC score and infant DRD4 genotype in the prediction of D attachment provided no significant results, indicating that infant DRD4 genotype did not moderate the effect of CES-D score at any time of assessment or over the entire longitudinal period. See Table 3.

Moderation of Maternal Depression by Birth Weight

Separate logistic regressions models of the two-way interactions of each maternal CES-D score or the AUC score and birth weight AGA in the prediction of D attachment provided no significant results, indicating that prenatal maternal CES-D scores did not moderate the effect of birth weight AGA and that birth weight AGA did not moderate the effect of CES-D scores at any postnatal time of assessment nor over the entire longitudinal period. See Table 4.

Three-way Interaction

Separate logistic regressions models of the three-way interactions of each maternal CES-D score or the AUC score, birth weight AGA and infant DRD4 genotype in the prediction of D attachment provided no significant results. See Table 5.

Mediation of Maternal Postnatal Depression by Early Maternal Care

As described above, of the eligible assessment points, neither the prenatal CES-D scores nor the CES-D scores at 6 months showed significant main effects in the prediction of D attachment at 36 months. Therefore, a mediation model including early maternal care variables could not be examined.

Post-Hoc Analysis – Interaction between Maternal Depression and Early Maternal Care

Separate logistic regressions models of the two-way interactions of each maternal CES-D score and each early maternal care variable in the prediction of D attachment were examined. The only two-way interactions that showed an indication of trend were the models that included maternal looking away frequency. The results of the models examining the two-way interaction of maternal looking away frequency and each CES-D assessment point as well as the AUC score are presented. See Table 6.

In a logistic regression of the two-way interaction model examining the prediction of D attachment from prenatal CES-D scores and looking away frequency, the interaction term of prenatal CES-D scores and maternal looking away frequency was significant, indicating that prenatal CES-D scores moderated the effect of maternal looking away frequency. See Table 6, Table 7 & Figure 5.

In a logistic regression of the two-way interaction model examining the prediction of D attachment from CES-D scores at 24 months and maternal looking away frequency, the interaction term of CES-D scores at 24 months and maternal looking away frequency was significant, indicating that maternal looking away frequency moderated the effect of CES-D scores at 24 months. See Table 6, Table 8 & Figure 6.

In a logistic regression of the two-way interaction model examining the prediction of D attachment from the AUC of CES-D scores and maternal looking away frequency, the interaction

term of the AUC of CES-D scores and maternal looking away frequency was significant, indicating that maternal looking away frequency interacted with the AUC of CES-D scores. See Table 6, Table 9 & Figure 7.

Discussion

The evidence presented in this paper indicate three primary findings in regards to the predication of D attachment at 36 months: firstly, the main effect of infant DRD4 genotype; secondly, the main effect of exposure to chronic maternal depression over the prenatal and postnatal periods; and thirdly, the interaction effect of early maternal care, specifically maternal looking away frequency measured at 6 months, with maternal depression over the prenatal and postnatal periods. Of note, there was no indication of a main effect of birth weight AGA or any interaction effects including infant DRD4 genotype.

The lack of evidence supporting our hypothesis that birth weight AGA would have a main effect on D attachment at 36 months is consistent with the majority of previous research on this relationship. Importantly, because the MAVAN's inclusion criteria prevented any premature infants from being part of the sample, we were able to separate the effect of birth weight from that of prematurity. While previous research on the relationship between birth weight and infant attachment demonstrated some evidence of an inverse relationship between birth weight and D attachment (e.g. Wolke et al., 2014), the majority of previous research has not separated the effects of birth weight and gestational term. This is an important distinction to make, as gestational term may be a better indication of the severity of a negative intrauterine environment and prenatal stress exposure. As such, the lack of evidence supporting the relationship between birth weight AGA and D attachment at 36 months is an important distinction between the often confounded effects of gestational term and birth weight.

Our findings of the protective relationship between the DRD4 7R allele and D attachment at 36 months is contrary to the initial evidence found in the Hungarian sample, where a positive relationship between the presence of the DRD4 7R allele and the odds of D attachment was found (Lakatos et al., 2000). Our findings also are contrary to the follow-up research that found no association between the DRD4 7R allele and D attachment. In contrast to previous findings, results presented herein found that children with at least one DRD4 7R allele were less likely to have D attachment and that this relationship was quite robust (OR of 0.329). This finding has been consistent throughout all models examining the DRD4 7R in the MAVAN (Graffi et al., 2015; Wazana et al., 2015).

Evidence of the protective effect of the DRD4 7R allele against D attachment is consistent with only one other study. Cicchetti et al. (2011) found similar results in a cohort of children who suffered from maltreatment. In this sample, the study found that children who were maltreated and part of an intervention group were less likely to display D attachment only if they had the 7R allele. While the cohort of maltreated children examined in the Cicchetti et al. (2011) study is quite different than the cohort of low-risk mother-infant dyads comprising the MAVAN sample, this is the only other study that has found a protective effect of the DRD4 7R allele.

Despite the lack of precedent in terms of the protective effect of the DRD4 7R allele against D attachment, there is evidence that the DRD4 7R allele demonstrates a protective effect against other negative developmental outcomes. For example, very early in infancy (1–2 months of age), the DRD4 7R allele is associated with an easy temperament and more adaptive behaviour (Auerbach, Benjamin, et al., 2001; De Luca et al., 2001; Ebstein et al., 1996).

Contrasting evidence that shows the DRD4 acting as both a risk factor and a protective factor for D attachment supports the notion of differential susceptibility, which contends that children with 'risk genes' are more susceptible to both the adverse effects of unsupportive environments and the beneficial effects of supportive rearing (Belsky, 1997a; Boyce & Ellis, 2005). Researchers have implicated the DRD4 gene with differential susceptibility in the past and have asserted that it has a high potential to be a 'susceptibility gene' (Levitan et al., 2006).

The biological mechanism of the effect of the DRD4 7R allele on susceptibility to one's environment may be best demonstrated by its association with ADHD and decreased attentional capacity (e.g. Holmes et al., 2002; LaHoste et al., 1996; Muglia et al., 2000). The lower dopamine receptor efficiency associated with the DRD4 long-form alleles (Auerbach, Benjamin, et al., 2001) leads to lower dopaminergic signalling, which in turn impedes negative feedback-based learning (Klein et al., 2007). The impeded negative feedback-based learning is related to a stronger preference for immediate reinforcers (Tripp & Wickens, 2008). This preference may be advantageous or disadvantageous depending on specific environmental characteristics, such as SES or parental socioemotional factors. This leads to the hypothesis that positive feedback-based learning may be more prevalent in low-risk, higher SES cohorts, such as the MAVAN. The preference for immediate reinforcers and the 'tuning-out' of negative feedback-based learning in children with the 7R may be advantageous in such a sample. In turn, the preference for immediate reinforcers may be the mechanism for the protective effect of the 7R allele against D attachment.

The notion that the DRD4 7R allele may make an individual more susceptible to their environment led to our exploration of the potential interaction effects between infant DRD4 genotype and indicators of the child's environment; namely, birth weight AGA as an indication of prenatal environment and maternal postnatal depression as an indication of postnatal environment. Importantly, counter to our hypotheses, both the two-way and the three-way interactions between infant DRD4 genotype, birth weight AGA and maternal postnatal depression provided no evidence of a significant predictive effect on D attachment at 36 months. While this evidence did not support the notion of differential susceptibility, the fact that both the effects of birth weight AGA and maternal postnatal depression were not moderated by infant DRD4 genotype was an important finding. The lack of any GxE interaction effect and the finding that the protective main effect of the DRD4 7R allele was maintained throughout all of the models that we examined demonstrates the reliability of the effect of infant DRD4 genotype in the MAVAN. Overall, the finding of a protective main effect of the DRD4 7R allele against D attachment at 36 months and the lack of evidence towards an interaction effect between infant DRD4 genotype and several indicators of the child's prenatal and postnatal environment only adds to the complexity of the literature exploring the effect of the DRD4 gene on D attachment.

The MAVAN's longitudinal design allowed for the effects of maternal prenatal depression, postnatal depression and chronic depression to be separated and analyzed separately. These distinctions were important as previous literature has illustrated that prenatal depression may have an independent effect separate from the effect of postnatal depression (e.g. Deave et al., 2008; O'Connor et al., 2002; Pearson et al., 2013). Indeed, the results of our study illustrate the importance of this distinction, as only women who suffered from chronic depression had a

significantly increased odds of having a child with D attachment (OR = 2.74). This means that in the MAVAN sample, only women who had both prenatal depression and postnatal depression had a significant association with D attachment at 36 months. When examining each individual time-point of assessment, CES-D scores were not associated with D attachment at the prenatal, 6-month, 12-month or 24-month assessments. Additionally, the AUC of CES-D scores, representing the combined CES-D scores from the prenatal assessment point to the 36-month assessment, did not show a significant association with D attachment.

While this evidence does not support our hypothesis that maternal postnatal depression would have an independent effect on D attachment, the evidence does indicate that the effect of maternal depression on D attachment at 36 months depends on the chronicity of the exposure. Maternal depression over a shorter period of time, as indicated by a CES-D score above 16 at a single assessment, may not be a strong enough exposure to affect the D attachment status of the child. Additionally, the difference between the results of the 'Chronically Depressed' group and the AUC of CES-D scores may indicate that the effect of chronic depression is only strong enough in a particular subset of women who represent the most severe cases of chronic depression; namely, women suffering from depression over both the prenatal and postnatal assessments.

While a wealth of previous literature has found an association between maternal depressive symptoms at one time-point and infant attachment status, the majority of these studies were not conducted with a longitudinal design. Accordingly, several previously conducted studies have not been able to distinguish for what length of time women in their samples had

been depressed and whether they had a history of depression over both the prenatal and postnatal periods. The predictive relationship between maternal depression and child attachment status found in previous research may be consistent with the results presented in this paper; namely, that women suffering from chronic depression have increased odds of having a child with D attachment. However, because of the cross-sectional design in the majority of previous literature examining maternal depression and D attachment, the critical factor of chronicity has not been mentioned frequently.

Of note, McMahon et al. (2006) used a similar longitudinal design to the MAVAN and focused on the chronicity of maternal depression. The study found that infants of chronically depressed mothers were more likely to be classified as insecure when compared to infants of non-depressed mothers. Additionally, infants of briefly depressed mothers were not more likely to be insecurely attached when compared to infants of non-depressed mothers. Importantly, counter to the evidence we present, McMahon et al. (2006) found that there was no difference between the three groups in terms of D attachment.

Similarly, Campbell and Cohn (1997) studied the effect of the chronic maternal depression on child attachment status using a longitudinal design. Our results were consistent with their findings when examining maternal depression at each individual time of assessment; namely, there was no association between maternal depression and attachment classification at any of the individual times of assessment. However, unlike our findings, Campbell and Cohn (1997) did not report an association between chronicity of maternal depression and child attachment status.

Although both McMahon et al. (2006) and Campbell and Cohn (1997) focused on the chronicity of maternal depression and child attachment status, the designs of each study were different than the present study. Namely, Campbell and Cohn (1997) focused on a 'secure vs. insecure' paradigm while McMahon et al. (2006) focused on three assessment points during the postnatal period and defined chronic maternal depression differently compared to the present study. These differences may have led to the inconsistency of findings concerning the relationship between the chronicity of maternal depression and child attachment status.

Despite the lack of research that has specifically focused on the chronicity of maternal depression and D attachment, researchers have focused on the effect of the chronicity of maternal depression in relation to other facets of the mother-infant relationship and child developmental outcomes. For example, Campbell et al. (1995) found that at the 2-month assessment point, there were no differences between depressed and non-depressed mothers and their infants in either positive or negative interactions during feeding, face-to-face interaction, or toy play. However, Campbell et al. (1995) found that women whose depression lasted through 6 months were less positive with their infants in each of these three situations in comparison to women whose depression was short-lived. Meanwhile, Brennan et al. (2000) found that both the severity and the chronicity of maternal depressive symptoms are related to more behavioural problems and lower vocabulary scores in children. Consistent with the findings that we present in this paper, longitudinal studies on maternal depression reliably show that severity and chronicity of maternal depression are predictors of disturbances in child developmental outcomes (e.g. Cornish et al., 2005; Deave et al., 2008; Trapolini et al., 2007).

The longitudinal design of the MAVAN also allowed us to examine the question of whether or not a child has a sensitive period to the effects of maternal depression. As described in the paragraphs above, previous research has focused on this question and has provided inconsistent evidence demonstrating that the first few months after birth may be a particularly sensitive period (e.g. Eyer, 1994; Goldberg, 1983; Harmon, 1981; Lamb, 1983; Moehler et al., 2006). In terms of main effects, the lack of significant associations between the CES-D scores at each time of assessment and D attachment at 36 months prevented us from making any conclusions on the matter. However, our finding in regards to the effect of chronic maternal depression leads to the question of whether there are particular times during the infant's life that a mother must be depressed in order for chronic depression to have an effect. Future research may consider focusing on women who suffer from chronic depression and further sub-dividing analyses of these women depending on the specific times their depression was present.

Due to the limited extent of our mediation model, we decided to further examine the relationship between maternal depression and early maternal care by conducting a post-hoc analysis. Specifically, we examined the interaction between maternal depression and early maternal care. In several of our models, one measure of early maternal care, maternal looking away frequency, demonstrated a consistent trend when we inspected its interaction with maternal depression.

We were able to conclude that there was a significant interaction between these variables at the prenatal assessment, the 24-month assessment and while examining the AUC of the CES-D scores. Firstly, prenatal CES-D scores moderated the effect of maternal looking away

frequency in the prediction of D attachment at 36 months. Namely, maternal looking away frequency minimally influenced D attachment in mothers whose CES-D scores were less than 16. However, when women had prenatal CES-D scores equal to or above 16, and thus would be considered to be depressed, the probability of D attachment at 36 months was lowest when maternal looking away frequency was low and highest when maternal looking away frequency was high.

Similar results were found at the 24-month assessment, as maternal looking away frequency minimally influenced D attachment in mothers whose CES-D scores were less than 16. However, when women had CES-D scores equal to or above 16, the probability of D attachment was lowest when maternal looking away frequency was low and highest when maternal looking away frequency was high.

Finally, the model examining the AUC of CES-D scores over the entire longitudinal period demonstrated that in women who had scores lower than the median value, the probability of D attachment at 36 months showed a decreasing trend as maternal looking away frequency increased. However, similar to the trends found at the prenatal and the 24-month assessments, when women had scores above the median value, the probability of D attachment was lowest when maternal looking away frequency was low and highest when maternal looking away frequency was high.

The consistent evidence of an interaction between maternal looking away frequency and maternal depression across several times of assessment is an important finding. Each of our

models indicates that in depressed mothers, children have the highest probability of D attachment at 36 months if their mother has a high frequency of looking away. However, when depressed mothers had a low frequency of looking away from their child, indicating that they paid more attention to their child, children have a low probability of D attachment. Additionally, the longitudinal model indicates that the effect of maternal looking away frequency differs between depressed and non-depressed mothers. Specifically, the probability of D attachment in children who had mothers who showed below-median scores (low levels of depression over the longitudinal period), showed a decreasing trend with increasing maternal looking away frequency.

The symptoms that define depression, (e.g. sad mood, trouble concentrating, disengagement, fatigue, and irritability), typically conflict with the definition of a highly sensitive mother, and clinically it would be expected that maternal depression would be associated with lower maternal sensitivity, and in turn, risk of D attachment. However, our results illustrate that when the symptoms of depression do not affect the specific behaviours and traits that relate to being a highly sensitive mother, i.e. having a high attentional capacity for the child, the effects of maternal depression on D attachment are mitigated.

The interaction between maternal depression and maternal sensitivity has been demonstrated in one previous study. Campbell et al. (2004) observed that women who reported late, chronic, or intermittent symptoms of depression, and were also observed to be low in maternal sensitivity were more likely to have insecurely attached children (ambivalent or D). Similar to our findings, the study reported that the same patterns of maternal depressive

symptoms did not appear to place the child at greater risk of attachment insecurity coupled with high maternal sensitivity.

Both maternal depression and maternal sensitivity are complex, multi-faceted constructs. Our finding that maternal looking away frequency interacts with maternal depression reinforces the notion that maternal sensitivity can be reduced to a collection of observable behaviours and that maternal sensitivity or its specific behavioural components may affect the relationship between more distal environmental factors and the mother-infant relationship.

Previous research has shown that maternal looking away frequency, as a measure of maternal attentional capacity for the child, has frequently been implicated with the mother-infant relationship and attachment status (Atkinson et al., 2009). Researchers have hypothesized that the importance of maternal attention to the attachment status between a mother and her child is due to how a child is constantly monitoring the whereabouts of the attachment figure (Bretherton, 1980; Maier et al., 2005). As the child seeks to balance its exploratory and attachment behaviours, a mother's attention acts to reassure the child. Thus, a mother's ability to concentrate on consciously selected stimuli, i.e. the child, and inhibit focus on potential distractors is of particular importance (Atkinson et al., 2009). Pederson et al. (1990) found that when compared to mothers of less securely attached infants, mothers of more securely attached infants were more frequently characterized as noticing their babies' signals and using these signals to guide their behaviour. Similarly, Atkinson et al. (2009) found that when comparing mothers of D infants and non-D infants on the Stroop task, mothers of D infants responded to negative emotional stimuli more slowly than to neutral stimuli.

Importantly, maternal attention and specifically eye gaze towards the infant, has bi-directional effects on the mother-infant interaction. Since the mother acts as the child's protective figure and an infant often uses the mother's gaze as an indication of incoming threats to the environment, the mother is considered to be the child's centre of attention (Bakeman & Adamson, 1984). Typically, this leads to a child responding to maternal gaze by directing their own attention towards the mother (e.g. Lavelli & Poli, 1998). Accordingly, previous research has also studied attachment status in relation to child eye gaze toward the mother. At age 4 months, Koulomzin et al. (2002) found that compared to securely attached children, infants categorized as insecure-avoidant spent less time focusing their visual attention to the mother's face. In terms of D attachment, researchers have posited that organized attachment in a child represents the strategic allocation of attention, as organized children are able to successfully attend to their environment and explore while also displaying attachment behaviour towards the mother. Meanwhile, D attachment reflects the collapse of strategic allocation of attention, often under the conditions of perceived emotional threat (Atkinson et al., 2009).

Our finding of an interaction between maternal looking away frequency and maternal depression at several time-points provides evidence that maternal attention is a critical component of maternal sensitivity that is affected by maternal depression. Indeed, this has been a consistent finding in previous literature. Field (2002) found that depressed mothers spent less time looking at their child when compared to non-depressed mothers. Mileva-Seitz et al. (2013) found that mothers with postpartum depression were more intrusive and irritable and responded with less attentiveness and sensitivity to their infants. Goldsmith and Rogoff (1997) found that women suffering from dysphoric symptoms attended to their children less when compared to

non-dysphoric mothers, both when their children were the primary focus of attention and when they were primarily attending to a competing event. Similarly, Pearson et al. (2010) showed that maternal depressive symptoms are associated with differential attentional processing of infant emotion during the antenatal period as the authors found that non-depressed pregnant women took longer to disengage attention from distressed infant faces when compared with non-distressed infant faces while depressed pregnant women did not. Additionally, previous research has shown that maternal depression is associated with deficits in joint attention between the child and the mother (e.g. Henderson & Jennings, 2003; Jameson et al., 1997; Raver & Leadbeater, 1995).

The evidence demonstrating the importance of maternal attention to the mother-infant relationship and how maternal depressive symptoms may interfere with a mother's ability to pay attention to her child support the findings cited herein. Specifically, a mother's attentiveness towards her child may be a critical mechanism for how maternal depression affects the attachment between the mother and her child. If the symptoms of depression do not affect a mother's ability to attend to her child, the probability of D attachment will not be affected by the presence of maternal depression.

Our models were able to illustrate the complexity of genetic, child, and parental factors in the prediction of D attachment at 36 months. Importantly, our results show that three aspects of a child's environment, namely prenatal maternal education, maternal depression and early maternal care, have significant and separate effects from infant DRD4 genotype in the prediction of D attachment. Throughout our models, prenatal maternal education continued to be the most

robust predictor of D attachment at 36 months. This illustrates the importance of examining relatively distal factors such as social status and social conditions as underlying predictors of disease. Despite the medical field's focus on more proximal factors predicting outcomes (e.g. diet or lifestyle choices), distal factors such as SES continue to demonstrate robust associations with the development of disease. As such, distal factors likely serve as more significant predictors than they would as mere proxies for the factors lying closer to disease in the causal chain (Link & Phelan, 1995). The relationship between prenatal maternal education and D attachment at 36 months in the MAVAN illustrates how social status can affect complex outcomes such as D attachment, while also taking into account the effects of more proximal genetic and environmental factors.

The present study is the first molecular genetic study that has focused on the relationship between the DRD4 gene, maternal depression, and maternal sensitivity in the prediction of D attachment. While we did not find any evidence to indicate an interaction with the DRD4 gene, our models illustrated that the effects of maternal depression on D attachment interact with maternal looking away frequency in infants with and without the 7R allele. Importantly the DRD4 7R allele exhibited its protective effect against D attachment regardless of maternal CES-D scores or maternal looking away frequency. The model that included the main effect of prenatal maternal education, the main effect of infant DRD4 genotype, and the interaction effect between maternal depression and maternal looking away frequency provided the best fitting model at each time-point, including the model examining the AUC of CES-D scores over the entire longitudinal time period. While a GxE interaction was not found, there are separate and

significant genetic and environmental effects contributing to the development of D attachment at 36 months.

Limitations

The interpretation of our findings should be made in light of certain limitations. Our results indicate that early maternal care and maternal depression interact to predict D attachment. Although many confounding pathways were not significant in our analyses, it still remains possible that other unmeasured aspects of the child evoked changes in maternal behaviour (identified or not), thus leading to D attachment. When compared to other genetic studies, the MAVAN has a relatively smaller number of participants. Our power, however, is strengthened by the accuracy of our genotyping method (Wong et al., 2003), precise functional sub-categorization of the DRD4 allele (7R or not), and observational measures of maternal care.

While the DRD4 gene proved to be an excellent candidate gene to study its relationship with D attachment due to the extensive amount of previous research conducted by other groups on the topic, focusing on a monogenic model does provide some limitations. The obvious limitation of the candidate gene approach is that it does not allow for new pathways nor novel mechanisms to be discovered as the choice of gene variants is determined by previous observations. This limits the gene variants that are studied in relation to a particular outcome and biases the field of results to reflect only that of those specific variants. Another limitation of the candidate gene approach is that small sample size and low statistical power are also frequent repercussions of the approach (Lohmueller et al., 2003). However, this was not an issue for the

present study as it consisted of 655 mother-infant dyads and had adequate statistical power to detect even modest associations.

Recently, there has been an increased amount of attention focused on the interaction of genes (GxG), specifically the interaction between the DRD4 gene and the serotonin transporter promoter gene (5HTTLPR) as well as the dopamine D2 receptor polymorphism (DRD2) (Auerbach, Faroy, et al., 2001; Beaver et al., 2007). These findings have demonstrated that the effect of the DRD4 gene on developmental trajectories may be influenced by other genetic factors. Therefore, polygenic models also should be inspected in order to determine whether epistasis had any effect on the findings of the models reported in the present paper. One interesting possibility, for example, would involve norepenephrine-related genes, given that norepenephrine acts in concert with dopamine to influence attentional processes and likely D attachment (Atkinson et al., 2009).

Our use of the CES-D scores to make a categorical maternal depression history variable was conducted with our research question in mind, with the clear separation of prenatal, postnatal, and chronic depression the driving influence in creating the variable. While a chronic depression variable has been categorized in many different ways in previous literature, this categorization was the most appropriate given our interest in separating the individual effect of maternal postnatal depression from maternal prenatal depression. While the categorization of each group was decided upon given the design of the MAVAN, this categorization may not be reproducible in other samples with different longitudinal designs.

Additionally, in our preliminary analysis that used the subset of individuals with no missing values, the percentage of women in the 'Prenatally Depressed' group consisted of less than five percent of the sample. While this number rose to just under ten percent in the imputed sample, we did not include the maternal depression history variable in the two-way and three-way interaction models because of the rare category. While the finding of chronic maternal depression's main effect is not affected by the rare category, as comparisons were only made to mothers in the 'Never Depressed' group, the results of the effect of maternal prenatal depression on D attachment at 36 months should be considered with this in mind.

Finally, given the restraints of considering a mediation model, we were only able to consider the main effects of CES-D scores at the prenatal and 6-month assessment points. This was because the MAVAN measured each early maternal care variable during the 6-month assessment. Future research may consider a similar mediation model, one that measures early maternal care longitudinally in order to examine the relationship between these variables at each time of assessment.

Future Implications

Our findings demonstrate the complexity of a model predicting D attachment, and more generally, future psychopathology. This illustrates the necessity to consider genetic, parental, and child factors when considering D attachment and the mother-infant relationship. Our findings have both research-based and clinical implications for future endeavors.

Firstly, our novel results on the protective effect of the DRD4 7R allele against D attachment indicate the importance of continuing research on the relationship between the DRD4 genotype and D attachment in cohorts of individuals with different socioeconomic levels, ethnicities and other demographic characteristics. The evidence provided by the MAVAN's low-risk cohort compared to previous literature illustrates how demographic characteristics may have important influences on the effect of the DRD4 genotype. Secondly, our findings on the effect of chronic maternal depression on D attachment indicates that future research on this relationship should focus on the chronicity and severity of maternal depression using a longitudinal design, instead of using cross-sectional designs which focus on mothers who show symptoms of depression at a single time-point.

Finally, our findings on the interaction between maternal depression and early maternal care demonstrate the influence of specific depressive symptoms that affect the mother-infant relationship. These results support early interventions models for women suffering from depression that focus on improving specific facets of the mother-infant relationship. In turn, interventions may educate mothers about particular maternal behaviours such as maternal attention and the implications of these behaviours in terms of their child.

Previous research has shown that programs targeting the mother-infant relationship have been successful in improving child developmental outcomes. Moss, Dubois-Comtois, et al. (2011) demonstrated the efficacy of a home-visiting intervention aimed at improving maternal sensitivity, child attachment, and behavioural outcomes for maltreated children. Specifically, the study found that when comparing pre- and post-test scores, there were significant improvements

for the intervention group in parental sensitivity, child attachment security, and a reduction in child disorganization. Furthermore, a meta-analysis conducted by Bakermans-Kranenburg et al. (2003) illustrated the efficacy of interventions targeting maternal sensitivity and attachment status with the child, as these interventions were effective in changing insensitive parenting ($d = 0.33$) and infant attachment insecurity ($d = 0.20$).

Previous research has also examined interventions that focus on depressed mothers and improving maternal sensitivity. Cicchetti et al. (2000) reported the efficacy of a preventative psychotherapeutic intervention for depressed mothers that aimed specifically at improving the early mother–child relationship in terms of positive interaction and maternal affect. By improving these aspects of the interaction, the negative impact of postnatal depression on infant IQ was mitigated. Similarly, in a group of depressed mothers, van Doesum et al. (2008) examined the effect of a mother–baby intervention on the quality of mother–child interaction, infant–mother attachment security, and infant socio-emotional functioning. The study found that the intervention had positive effects on the quality of mother–infant interaction, as infants in the experimental group had higher scores for attachment.

Interventions specifically focusing on improving maternal attention towards their child also have demonstrated positive results in regards to the mother-infant relationship. Video feedback of recorded mother-infant interactions has been used to coach parents in becoming more attentive to their child's responses and to help parents adjust their behaviour in an individualized child-sensitive manner (Juffer et al., 2008; Moss et al., 2014). These interventions

have shown effectiveness by improving both attentiveness and overall sensitivity to the child and their needs.

Based upon our findings, video-based interventions that allow parents to see an interaction between themselves and their children could be critical for improving the mother-infant relationship between depressed mothers and their children. Within these videos, parents could watch themselves respond to their child's signals and note how attentive they, as parents, are towards their children. These interventions could be tailored for women suffering from depression in order to have the most significant impact on a subset of women that are at risk of having a D attachment with their child. Ultimately, as indicated by the complexity of our models, interventions should be individualized for each mother / child dyad in order to consider the various genetic, parental, and child factors that have been indicated to have an impact of the organization of attachment between a mother and her child. Given the known deleterious outcomes for children with D attachment, the merits of such interventions cannot be underestimated.

Figures and Tables

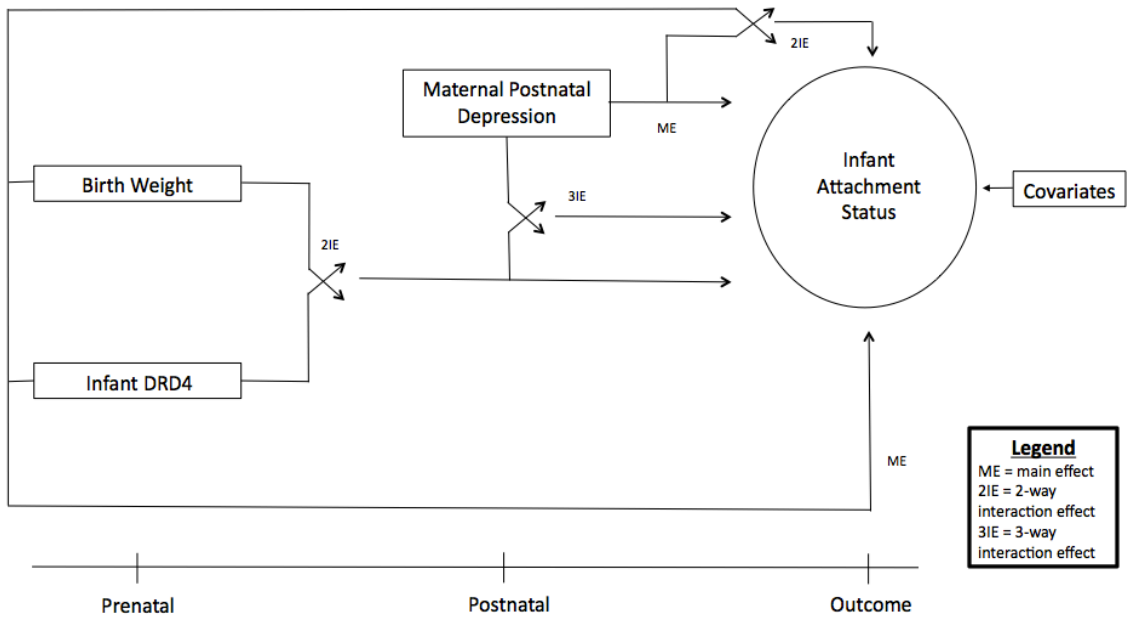

Figure 1. A summary of the main effects, the two-way interaction effects and the three-way interaction effect in Model 1.

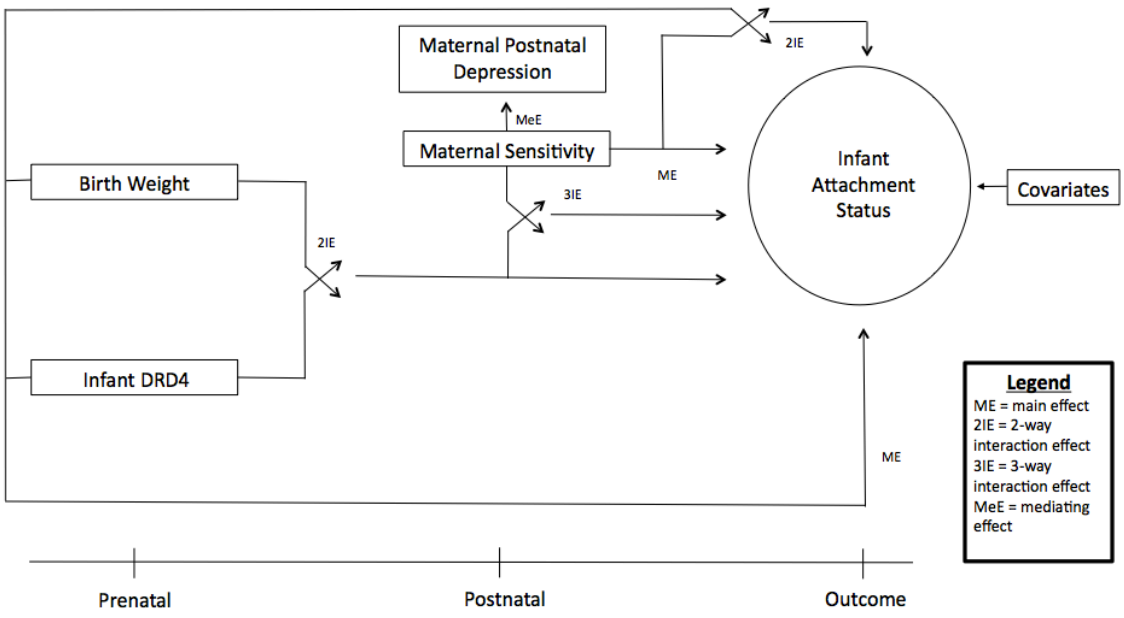

Figure 2. A summary of the main effects, the mediation effect, the two-way interaction effects and the three-way interaction effect in Model 2.

Table 1.

Descriptive statistics of MAVAN mother and child at 36 months (N=655 pairs)

Demographic Characteristics of Subjects		
Variables	Montreal (N = 389)	Hamilton (N = 266)
Mothers		
Age[a]	M = 29.8, SD = 5.02	M = 31.2, SD = 5.09
Education		
High school or less and Partial College	18.9%	17.6%
Completed College or some University	30.0%	38.3%
University graduate or more	51.1%	44.1%
Income[a]		
< 15,000	11.9%	3.5%
15,000 - <30,000	17.4%	10.6%
30,000 - <50,000	23.9%	20.1%
50,000 - <80,000	19.7%	27.6%
> 80,000	27.1%	38.2%
Genotype DRD4		
No 7 Repeat	62.3%	63.9%
7 Repeat	37.7%	36.1%
CES-D Scores		
Prenatal Depression	M = 12.2, SD = 8.58	M = 13.9, SD = 11.4
Postnatal Depression at 6mo	M = 11.3, SD = 9.16	M = 11.2, SD = 10.4
Postnatal Depression at 12mo	M = 11.0, SD = 8.18	M = 11.0, SD = 10.2
Postnatal Depression at 24mo	M = 11.2, SD = 8.16	M = 12.3, SD = 10.2
Postnatal Depression at 36mo	M = 11.4, SD = 8.74	M = 11.4, SD = 10.3
AUC of CES-D Scores	M = 383, SD = 231	M = 401, SD = 304
Ainsworth Sensitivity Scales		
Ainsworth Mean Score	M = 5.84, SD = 1.77	M = 5.59, SD = 1.94
Ainsworth Sensitivity Subscale	M = 5.63, SD = 1.92	M = 5.40, SD = 2.10
Ainsworth Cooperation Subscale	M = 5.40, SD = 1.91	M = 5.28, SD = 2.08

Ainsworth Availability Subscale	M = 6.14, SD = 1.79	M = 5.86, SD = 1.94
Ainsworth Acceptance Subscale	M = 6.18, SD = 1.65	M = 5.91, SD = 1.84
Observed Maternal Behaviours		
Looking away frequency[a]	M = 19.2, SD = 10.6	M = 23.5, SD = 13.2
Stroke/pat/palm frequency[a]	M = 6.27, SD = 6.63	M = 10.0, SD = 11.3
Laugh/smile frequency	M = 11.1, SD = 14.6	M = 12.5, SD = 12.3
Vocalization frequency[a]	M = 22.9, SD =20.6	M = 40.3, SD = 35.8
	Children	
Gender		
Male	50.4%	59.8%
Female	49.6%	40.2%
Birth weight (percentile)[a]	M = 41.2, SD = 25.9	M = 52.8, SD = 27.8
Genotype DRD4		
No 7 Repeat	66.5%	61.5%
7 Repeat	33.5%	38.5%
Attachment Style		
Avoidant	6.40%	6.90%
Secure	53.2%	57.2%
Ambivalent	15.0%	13.0%
D	25.4%	22.9%

[a]Significant differences between Montreal and Hamilton

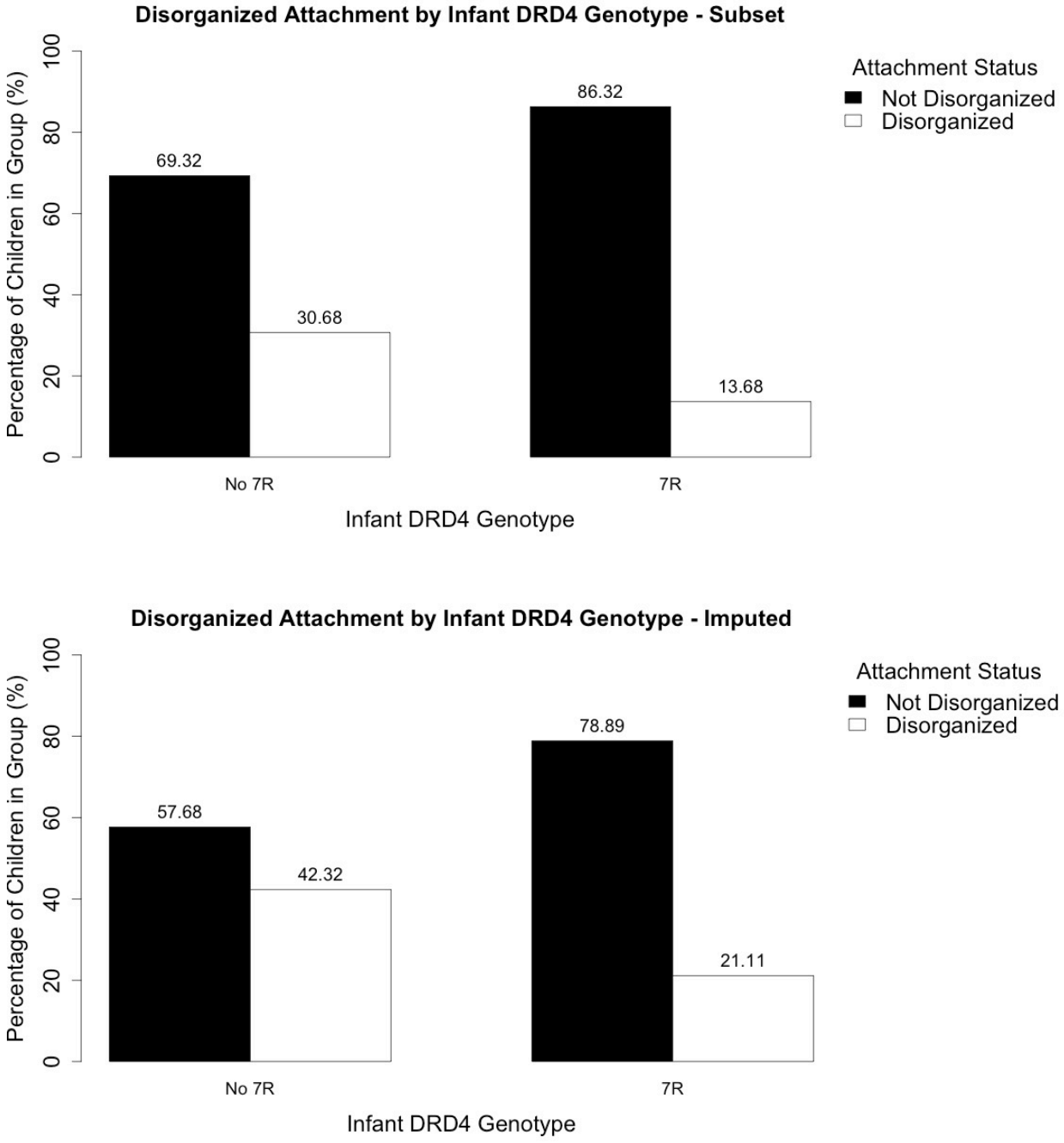

Figure 3. Disorganized attachment by infant DRD4 genotype – subset and the imputed sample.

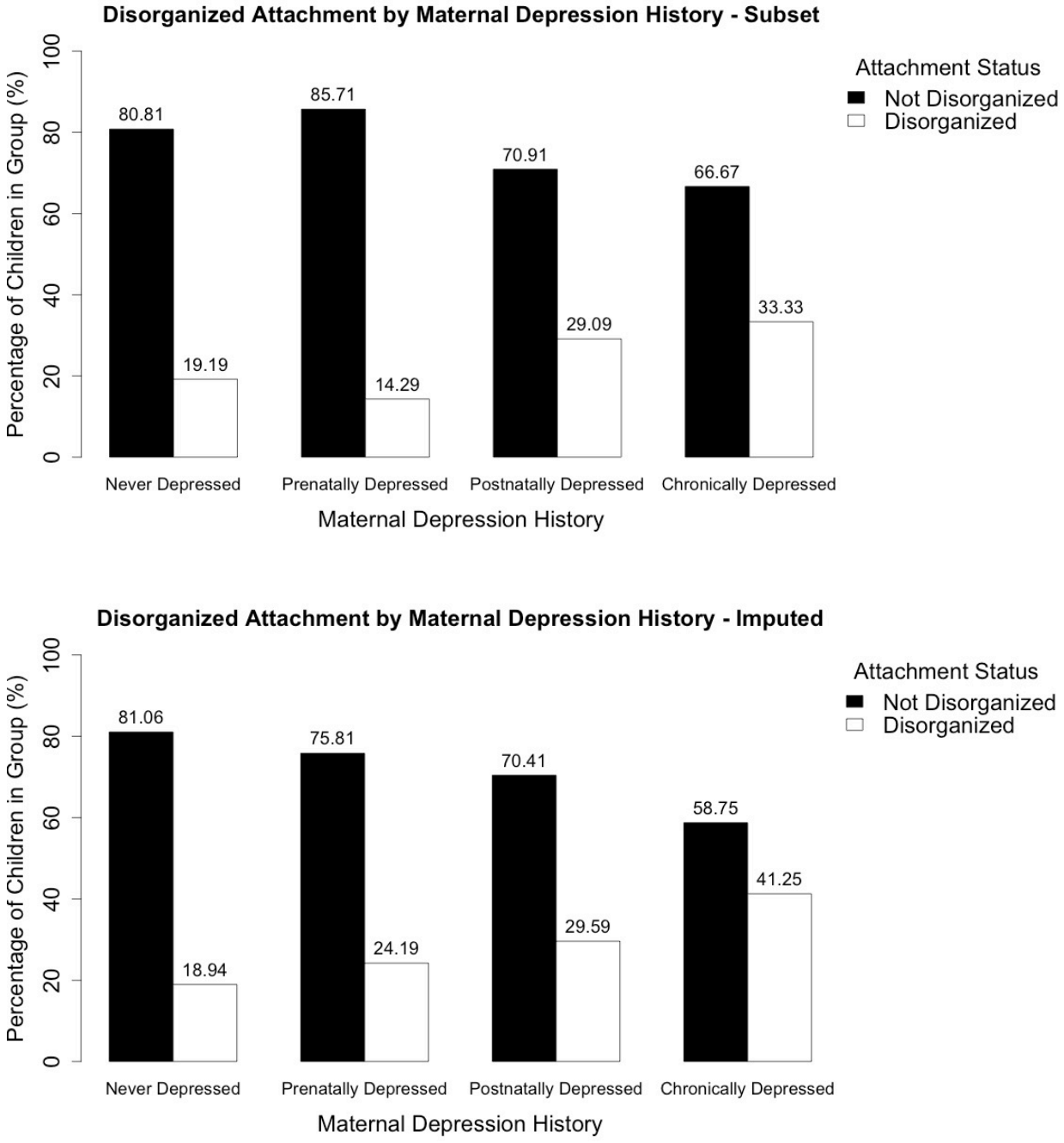

Figure 4. Disorganized attachment by maternal depression history – subset and the imputed sample.

Table 2.

Main Effect of Each CES-D Time-point on D Attachment

Variable	β	Standard Error	Odds Ratio	p
Prenatal CES-D	0.006940	0.01400	1.007	0.6210
CES-D at 6 Months	0.003413	0.01457	1.003	0.8153
CES-D at 12 Months	0.01495	0.01554	1.015	0.3384
CES-D at 24 Months	0.02303	0.01490	1.023	0.1249
AUC of CES-D Scores	0.0009408	0.0005283	1.001	0.07718 †

†p < .10 *p < .05 **p < .01 ***p < .001

Table 3.

Interaction Effect of Each CES-D Time-point and Infant DRD4 Genotype on D Attachment

Variable	β	Standard Error	Odds Ratio	p
Prenatal CES-D x DRD4	-0.03988	0.04242	0.9609	0.3504
CES-D at 6 Months x DRD4	0.005492	0.03709	1.006	0.8827
CES-D at 12 Months x DRD4	0.01330	0.04506	1.013	0.7686
CES-D at 24 Months x DRD4	0.03863	0.04151	1.039	0.3541
AUC of CES-D Scores x DRD4	0.0005732	0.001570	1.001	0.7159

†p < .10 *p < .05 **p < .01 ***p < .001

Table 4.

Interaction Effect of Each CES-D Time-point and Birth Weight AGA on D Attachment

Variable	β	Standard Error	Odds Ratio	p
Prenatal CES-D x Birth Weight AGA	-0.000002177	0.00001999	1.000	0.9135
CES-D at 6 Months x Birth Weight AGA	0.00001218	0.00002157	1.000	0.5736
CES-D at 12 Months x Birth Weight AGA	0.00001852	0.00002145	1.000	0.3900
CES-D at 24 Months x Birth Weight AGA	0.00001717	0.00002460	1.000	0.4871
AUC of CES-D Scores x Birth Weight AGA	-0.0000002293	0.0000007577	1.000	0.7629

†p < .10 *p < .05 **p < .01 ***p < .001

Table 5.

Interaction Effect of Each CES-D Time-point, Birth Weight AGA and Infant DRD4 Genotype on D Attachment

Variable	β	Standard Error	Odds Ratio	p
Prenatal CES-D x Birth Weight AGA x DRD4	0.00004816	0.00004582	1.000	0.2955
CES-D at 6 Months x Birth Weight AGA x DRD4	0.0000005208	0.00004805	1.000	0.9914
CES-D at 12 Months x Birth Weight AGA x DRD4	0.00006147	0.00005946	1.000	0.3040
CES-D at 24 Months x Birth Weight AGA x DRD4	0.00009413	0.00007308	1.000	0.2015
AUC of CES-D Scores x Birth Weight AGA x DRD4	0.000002636	0.000001848	1.000	0.1567

†p < .10 *p < .05 **p < .01 ***p < .001

Table 6.

Interaction Effect of Each CES-D Time-point and Looking Away Frequency on D Attachment

Variable	β	Standard Error	Odds Ratio	p
Prenatal CES-D x Looking Away Frequency	0.003118	0.001346	1.003	0.02278 *
CES-D at 6 Months x Looking Away Frequency	0.001800	0.001332	1.002	0.1817
CES-D at 12 Months x Looking Away Frequency	0.001577	0.001180	1.002	0.1847
CES-D at 24 Months x Looking Away Frequency	0.003665	0.001559	1.004	0.02138 *
AUC of CES-D Scores x Looking Away Frequency	0.0001354	0.00005609	1.0001	0.02119 *

†p < .10 *p < .05 **p < .01 ***p < .001

Table 7.

The prediction of D attachment from the interaction of prenatal CES-D scores x maternal looking away frequency using multiple imputation - β values presented

Predictors	Step 1	Step 2	Step 3
Birth weight (centered and squared)	0.00007434	0.0001096	0.00007123
DRD4	-0.9253 **	-0.9276 **	-1.008 **
Prenatal CES-D scores	0.007457	0.009431	0.003963
Looking away frequency	0.01990 †	0.02091 †	0.01805
Prenatal CES-D scores x looking away frequency	-	0.003214 *	0.003118 *
Covariates			
Maternal education, college	-	-	-1.841 ***
Maternal education, university	-	-	-1.245 **
Infant gender	-	-	0.1783
Mother age at birth	-	-	-0.02220
McFadden Pseudo R^2	0.04799	0.07302	0.1533

†p < .10 *p < .05 **p < .01 ***p < .001

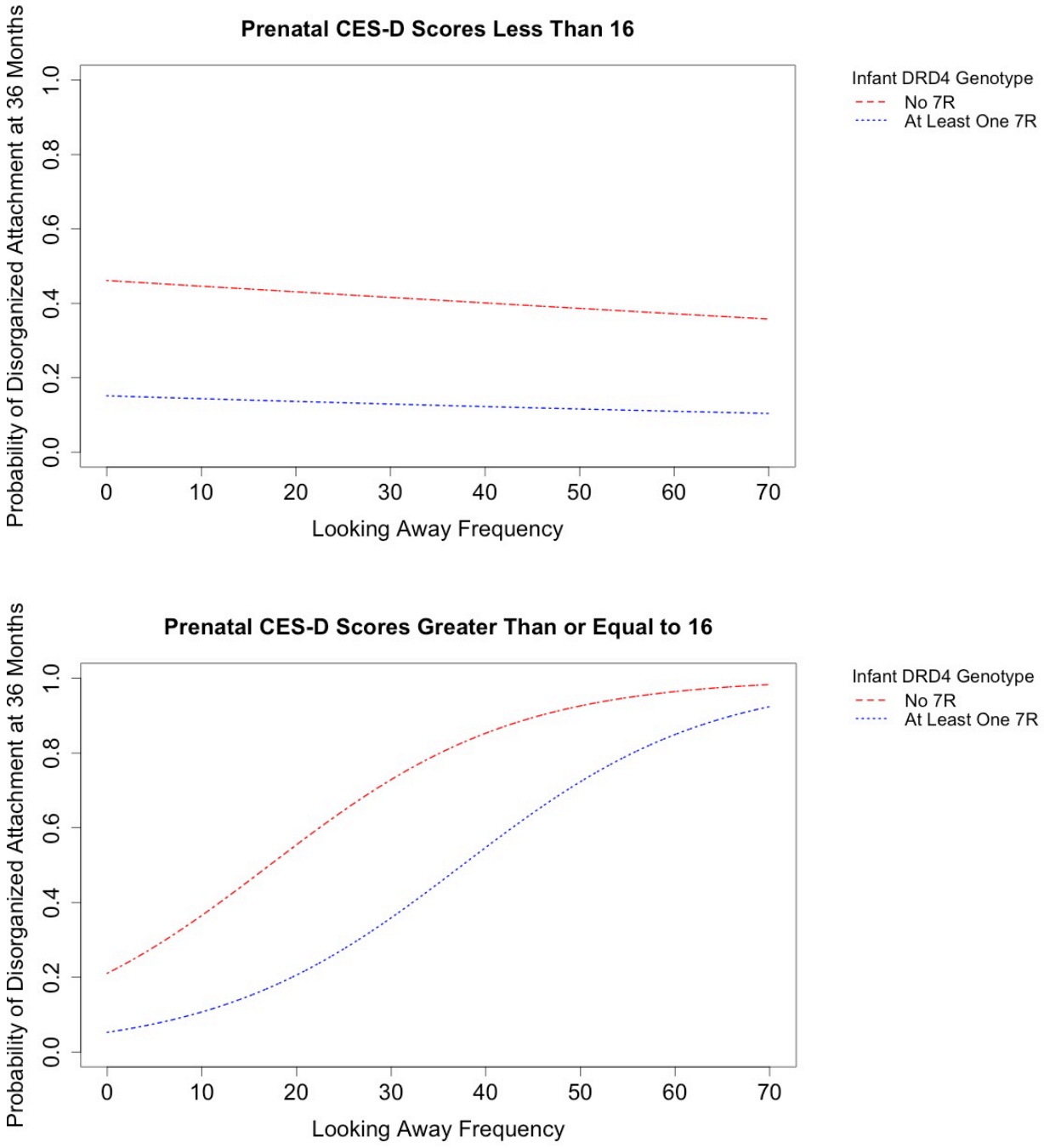

Figure 5. The prediction of D attachment at 36 months from maternal looking away frequency at 6 months, prenatal maternal CES-D scores, and infant dopamine receptor D4 (DRD4) seven-repeat (7R) allele status – subset.

Table 8.

The prediction of D attachment from the interaction of CES-D scores at 24 months x maternal looking away frequency using multiple imputation - β values presented

Predictors	Step 1	Step 2	Step 3
Birth weight (centered and squared)	0.00004586	0.00009089	0.00004995
DRD4	-0.8934**	-0.9333 **	-1.016 **
CES-D scores at 24 months	0.03773**	0.04028 *	0.003224 †
Looking away frequency	0.02075	0.02077	0.01777
CES-D scores at 24 months x looking away frequency	-	0.003299 *	0.003665 *
Covariates			
Maternal education, college	-	-	-1.874 ***
Maternal education, university	-	-	-1.061 *
Infant gender	-	-	0.1162
Mother age at birth	-	-	-0.03711
McFadden Pseudo R^2	0.06466	0.08871	0.1712

†p < .10 *p < .05 **p < .01 ***p < .001

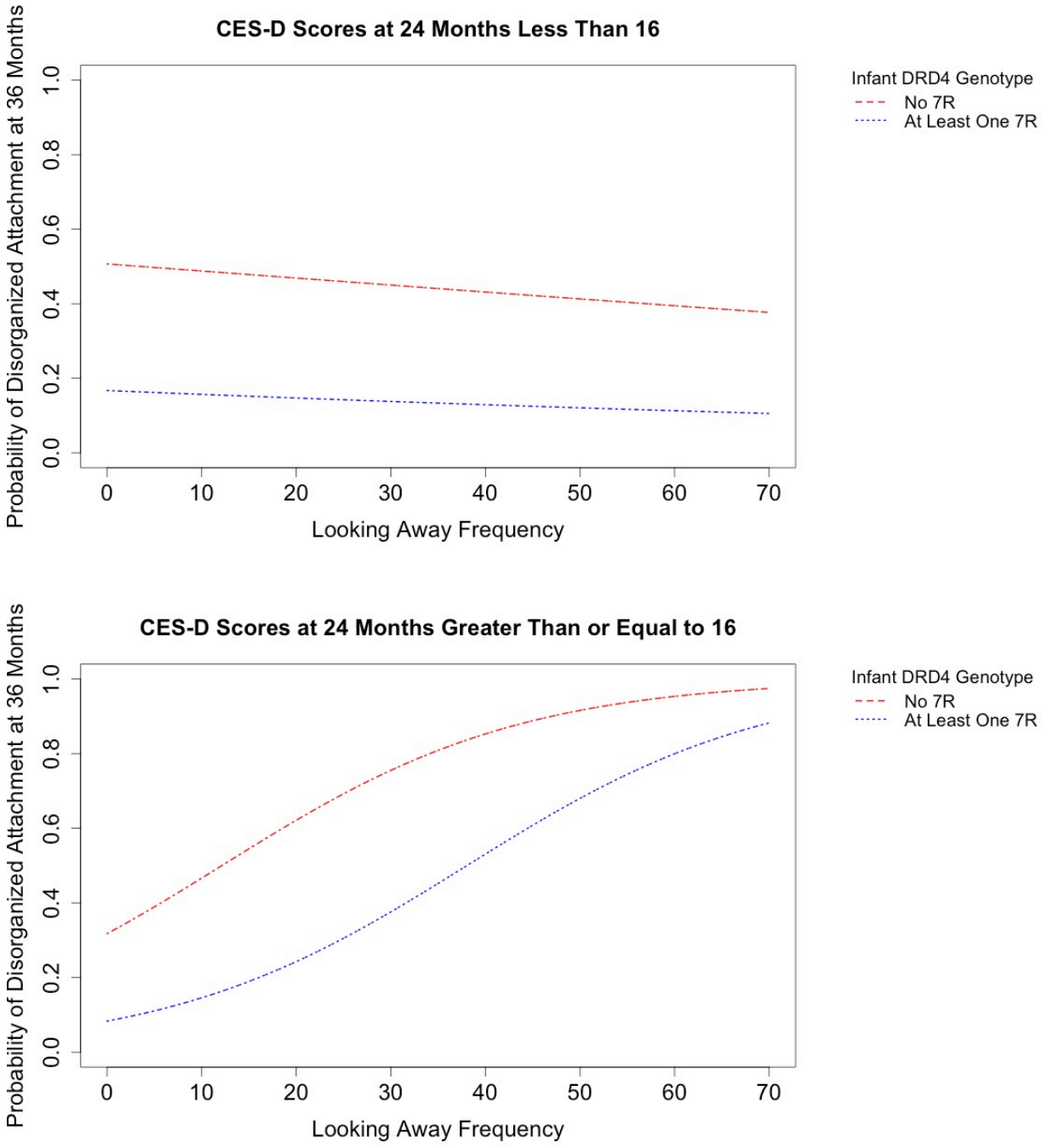

Figure 6. The prediction of D attachment at 36 months from maternal CES-D scores at 24 months, maternal looking away frequency at 6 months, and infant dopamine receptor D4 (DRD4) seven-repeat (7R) allele status – subset.

Table 9.

The prediction of D attachment from the interaction of the AUC of longitudinal CES-D scores x maternal looking away frequency using multiple imputation - β values presented

Predictors	Step 1	Step 2	Step 3
Birth weight (centered and squared)	0.00003214	0.00007910	0.00006318
DRD4	-0.8529 *	-0.8362 *	-0.9540 *
AUC of CES-D scores	0.001335 **	0.001382 **	0.0009485
Looking away frequency	0.01949 †	0.01805	0.01452
AUC of CES-D scores x looking away frequency	-	0.0001086 *	0.0001354 *
Covariates			
Maternal education, college	-	-	-1.968 ***
Maternal education, university	-	-	-1.174 *
Infant gender	-	-	0.1761
Mother age at birth	-	-	-0.02250
McFadden Pseudo R^2	0.06040	0.08955	0.1722

†p < .10 *p < .05 **p < .01 ***p < .001

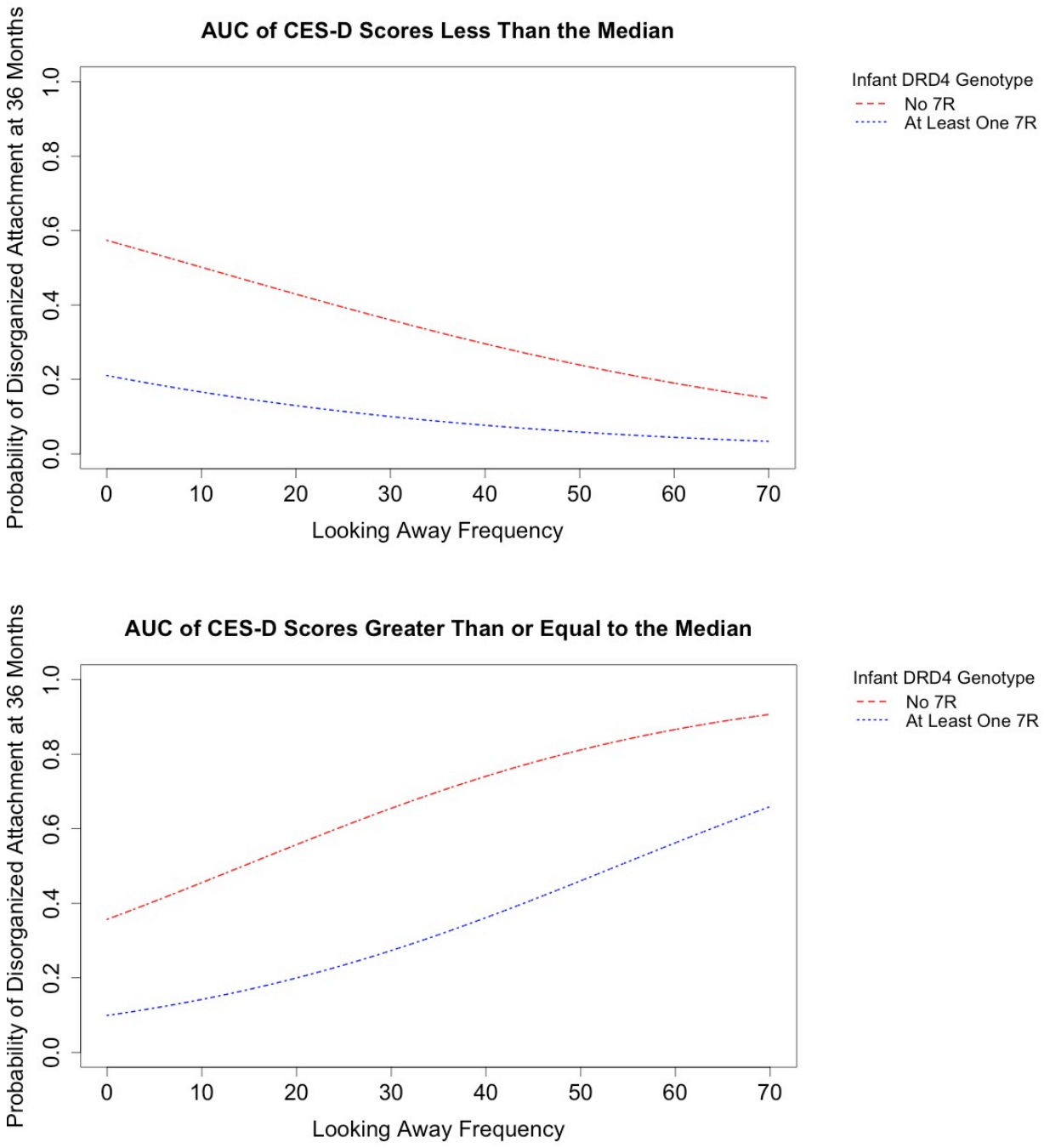

Figure 7. The prediction of D attachment at 36 months from the area under the curve (AUC) of longitudinal CES-D, maternal looking away frequency at 6 months, and infant dopamine receptor D4 (DRD4) seven-repeat (7R) allele status – subset.

References

Ainsworth, M. (1969). *Maternal sensitivity scales*. Unpublished manuscript, John Hopkins University.

Ainsworth, M., & Bell, S. (1970). Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. *Child Development, 41*(1), 49-67.

Ainsworth, M., Bell, S., & Stayton, D. (1974). Infant-mother attachment and social development: 'Socialisation' as a product of reciprocal responsiveness to signals. In M. Richards (Eds.), *The Integration of a child into a social world* (pp. 99-135). Cambridge: Cambridge University Press.

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

Alati, R., Najman, J., O'Callaghan, M., Bor, W., Williams, G., & Clavarino, A. (2009). Fetal growth and behaviour problems in early adolescence: Findings from the Mater University Study of Pregnancy. *International Journal of Epidemiology, 38*, 1390–1400.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., & Van Tol, H. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry, 65*(3), 1157-1165.

Atkinson, L., Scott, B., Chisholm, V., Blackwell, J., Dickens, S., Tam, F., & Goldberg, S. (1995). Cognitive coping, affective distress, and maternal sensitivity: Mothers of children with Down syndrome. *Developmental Psychology, 31*(4), 668-676.

Atkinson, L., Paglia, A., Coolbear, J., Niccols, A., Parker, K., & Guger, S. (2000). Attachment security: A meta-analysis of maternal mental health correlates. *Clinical Psychology Review, 20*(8), 1019-1040.

Atkinson, L., Leung, E., Goldberg, S., Benoit, D., Poulton, L., Myhal, N., . . . Kerr, S. (2009). Attachment and selective attention: Disorganization and emotional Stroop reaction time. *Development and Psychopathology, 21*(01), 99-126.

Auerbach, J., Benjamin, J., Faroy, M., Geller, V., & Ebstein, R. (2001). DRD4 related to infant attention and information processing: A developmental link to ADHD? *Psychiatric Genetics, 11*(1), 31-35.

Auerbach, J., Faroy, M., Ebstein, R., Kahana, M., & Levine, J. (2001). The association of the dopamine D4 receptor gene (DRD4) and the serotonin transporter promoter gene (5-HTTLPR) with temperament in 12-month-old infants. *Journal of Child Psychology and Psychiatry, 42*(06), 777-783.

Bagner, D., Pettit, J., Lewinsohn, P., & Seeley, J. (2010). Effect of maternal depression on child behavior: A sensitive period? *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(7), 699-707.

Bakeman, R., & Adamson, L. (1984). Coordinating attention to people and objects in mother-infant and peer-infant interaction. *Child Development, 55*(4), 1278-1289.

Bakermans-Kranenburg, M., van Ijzendoorn, M., & Juffer, F. (2003). Less is more: Meta-analyses of sensitivity and attachment interventions in early childhood. *Psychological Bulletin, 129*(2), 195.

Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2004). No association of the dopamine D4 receptor (DRD4) and-521 C/T promoter polymorphisms with infant attachment disorganization. *Attachment & Human Development, 6*(3), 211-218.

Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*(5), 406-409.

Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2007). Genetic vulnerability or differential susceptibility in child development: The case of attachment [Research review]. *Journal of Child Psychology and Psychiatry, 48*(12), 1160-1173.

Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: New evidence and a meta-analysis. *Development and Psychopathology, 23*(01), 39-52.

Barker, E., Copeland, W., Maughan, B., Jaffee, S., & Uher, R. (2012). Relative impact of maternal depression and associated risk factors on offspring psychopathology. *The British Journal of Psychiatry, 200*(2), 124-129.

Baron, R., & Kenny, D. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182.

Barre, N., Morgan, A., Doyle, L., & Anderson, P. (2011). Language abilities in children who were very preterm and/or very low birth weight: A meta-analysis. *The Journal of Pediatrics, 158*(5), 766-774.

Bates, J., Maslin, C., & Frankel, K. (1985). Attachment security, mother-child interaction, and temperament as predictors of behavior-problem ratings at age three years. *Monographs of the Society for Research in Child Development*, 167-193.

Beaver, K., Wright, J., DeLisi, M., Walsh, A., Vaughn, M., Boisvert, D., & Vaske, J. (2007). A gene × gene interaction between DRD2 and DRD4 is associated with conduct disorder and antisocial behavior in males. *Behavioral and brain functions, 3*(1), 3-30.

Belsky, J. (1997a). Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: The case of mothering and attachment. *Child Development, 68*(4), 598-600.

Belsky, J. (1997b). Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry, 8*(3), 182-186.

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

Belsky, J., Bakermans-Kranenburg, M., & van IJzendoorn, M. (2007). For better and for worse differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16*(6), 300-304.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135*(6), 885.

Benjamin, J., Li, L., Patterson, C., Greenberg, B., Murphy, D., & Hamer, D. (1996). Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nature Genetics, 12*(1), 81-84.

Blatt, S., & Levy, K. (2003). Attachment theory, psychoanalysis, personality development, and psychopathology. *Psychoanalytic Inquiry, 23*(1), 102-150.

Blehar, M., Lieberman, A., & Ainsworth, M. (1977). Early face-to-face interaction and its relation to later infant-mother attachment. *Child Development, 48*(1), 182-194.

Bohlin, G., Hagekull, B., & Rydell, A.-M. (2000). Attachment and social functioning: A longitudinal study from infancy to middle childhood. *Social Development, 9*(1), 24-39.

Bowlby, J. (1969). *Attachment, Vol. 1 of Attachment and loss*. New York, NY: Basic Books.

Boyce, W. T., & Ellis, B. (2005). Biological sensitivity to context: An evolutionary–developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17*(02), 271-301.

Brennan, P., Hammen, C., Andersen, M., Bor, W., Najman, J., & Williams, G. (2000). Chronicity, severity, and timing of maternal depressive symptoms: Relationships with child outcomes at age 5. *Developmental Psychology, 36*(6), 759-766.

Bretherton, I. (1980). Young children in stressful situations: The supporting role of attachment figures and unfamiliar caregivers. In G. V. Coelho & P. Ahmed (Eds.), *Uprooting and development* (pp. 179-210). New York, NY: Plenum Press.

Brisch, K. H., Bechinger, D., Betzler, S., & Heinemann, H. (2003). Early preventive attachment-oriented psychotherapeutic intervention program with parents of a very low birthweight premature infant: Results of attachment and neurological development. *Attachment & Human Development, 5*(2), 120-135.

Brisch, K. H., Bechinger, D., Betzler, S., Heinemann, H., Kachele, H., Pohlandt, F., . . . Buchheim, A. (2005). Attachment quality in very low-birthweight premature infants in relation to maternal attachment representations and neurological development. *Parenting: Science and Practice, 5*(4), 311-331.

Broekman, B., Chan, Y. H., Goh, L., Fung, D., Gluckman, P., Saw, S. M., & Meaney, M. (2011). Influence of birth weight on internalizing traits modulated by serotonergic genes. *Pediatrics, 128*(5), e1250-e1258.

Broth, M., Goodman, S., Hall, C., & Raynor, L. (2004). Depressed and well mothers' emotion interpretation accuracy and the quality of mother—infant interaction. *Infancy, 6*(1), 37-55.

Buchheim, A., Brisch, K., & Kächele, H. (1999). Die klinische Bedeutung der Bindungsforschung für die Risikogruppe der Frühgeborenen: Ein überblick zum neuesten Forschungsstand. *Zeitschrift für Kinder-und Jugendpsychiatrie und Psychotherapie, 27*, 125-138.

Calam, R., Lambrenos, K., Cox, A., & Weindling, A. (1999). Maternal appraisal of information given around the time of preterm delivery. *Journal of Reproductive and Infant Psychology, 17*(3), 267-280.

Calkins, S., & Leerkes, E. (2004). Early attachment processes and the development of emotional self-regulation. In R. F. Baumeister & K. D. Vohs (Eds.), *Handbook of self-regulation: Research, theory, and applications* (pp. 324-339). New York, NY: Guilford.

Campbell, S., Cohn, J., & Meyers, T. (1995). Depression in first-time mothers: Mother-infant interaction and depression chronicity. *Developmental Psychology, 31*(3), 349.

Campbell, S., & Cohn, J. (1997). The timing and chronicity of postpartum depression: Implications for infant development, *Postpartum depression and child development* (pp. 165-197). New York, NY: Guilford Press.

Campbell, S., Brownell, C., Hungerford, A., Spieker, S., Mohan, R., & Blessing, J. (2004). The course of maternal depressive symptoms and maternal sensitivity as predictors of attachment security at 36 months. *Development and Psychopathology, 16*(02), 231-252.

Campbell, S., Matestic, P., von Stauffenberg, C., Mohan, R., & Kirchner, T. (2007). Trajectories of maternal depressive symptoms, maternal sensitivity, and children's functioning at school entry. *Developmental Psychology, 43*(5), 1202-1215.

Carlson, E., & Sroufe, L. A. (1995). Contribution of attachment theory to developmental psychopathology. In D. Cicchetti & D. Cohen (Eds.), *Developmental psychopathology, Vol: 1: Theory and methods* (pp. 581-617). New York, NY: Wiley.

Carlson, E. (1998). A prospective longitudinal study of attachment disorganization/disorientation. *Child Development, 69*(4), 1107-1128.

Cassidy, J. (1988). Child-mother attachment and the self in six-year-olds. *Child Development, 59*(1), 121-134.

Cassidy, J., & Marvin, R. (1992). *Attachment organization in preschool children: Coding guidelines*. Unpublished Manuscript, University of Virginia.

Chang, F.-M., Kidd, J., Livak, K., Pakstis, A., & Kidd, K. (1996). The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Human Genetics, 98*(1), 91-101.

Cicchetti, D. (1990). Towards a transactional model of relations between attachment and depression. In M. T. Greenberg, D. Cicchetti & E. M. Cummings (Eds.), *Attachment in the preschool years: Theory, research and intervention*. Chicago, IL: University of Chicago Press.

Cicchetti, D., & Barnett, D. (1991). Attachment organization in maltreated preschoolers. *Development and Psychopathology, 3*(04), 397-411.

Cicchetti, D., Rogosch, F., & Toth, S. (2000). The efficacy of toddler-parent psychotherapy for fostering cognitive development in offspring of depressed mothers. *Journal of Abnormal Child Psychology, 28*(2), 135-148.

Cicchetti, D., Rogosch, F., & Toth, S. (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*(02), 357-372.

Cornish, A., McMahon, C., Ungerer, J., Barnett, B., Kowalenko, N., & Tennant, C. (2005). Postnatal depression and infant cognitive and motor development in the second postnatal year: The impact of depression chronicity and infant gender. *Infant Behavior and Development, 28*(4), 407-417.

Crittenden, P. (1985). Maltreated infants: Vulnerability and resilience. *Journal of Child Psychology and Psychiatry, 26*(1), 85-96.

Crittenden, P. (1988). Relationships at risk. In J. Belsky & T. Nezworski (Eds.), *Clinical implications of attachment* (pp. 136-174). Hillsdale, NJ: Erlbaum.

Crockenberg, S., & Leerkes, E. (2003). Parental acceptance, postpartum depression, and maternal sensitivity: Mediating and moderating processes. *Journal of Family Psychology, 17*(1), 80.

Cummings, E. M., Davies, P., & Campbell, S. (2002). *Developmental psychopathology and family process: Theory, research, and clinical implications*. New York, NY: Guilford Press.

Dannemiller, J. (1999). Chronicity of maternal depressive symptoms, maternal sensivitiy, and child functioning at 36 months. *Developmental Psychology, 35*(5), 1297-1310.

Davis, E., Glynn, L., Waffarn, F., & Sandman, C. (2011). Prenatal maternal stress programs infant stress regulation. *Journal of Child Psychology and Psychiatry, 52*(2), 119-129.

Dawson, G., Klinger, L., Panagiotides, H., Hill, D., & Spieker, S. (1992). Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms. *Child Development, 63*(3), 725-737.

De Luca, A., Rizzardi, M., Torrente, I., Alessandroni, R., Salvioli, G. P., Filograsso, N., . . . Novelli, G. (2001). Dopamine D4 receptor (DRD4) polymorphism and adaptability trait during infancy: A longitudinal study in 1-to 5-month-old neonates. *Neurogenetics, 3*(2), 79-82.

De Wolff, M., & van Ijzendoorn, M. (1997). Sensitivity and attachment: A meta-analysis on parental antecedents of infant attachment. *Child Development, 68*(4), 571-591.

Deave, T., Heron, J., Evans, J., & Emond, A. (2008). The impact of maternal depression in pregnancy on early child development. *BJOG: An International Journal of Obstetrics & Gynaecology, 115*(8), 1043-1051.

Ding, Y.-C., Chi, H.-C., Grady, D., Morishima, A., Kidd, J., Kidd, K., . . . Swanson, J. (2002). Evidence of positive selection acting at the human dopamine receptor D4 gene locus. *Proceedings of the National Academy of Sciences, 99*(1), 309-314.

Donovan, W., & Leavitt, L. (1989). Maternal self-efficacy and infant attachment: Integrating physiology, perceptions, and behavior. *Child Development, 60*(2), 460-472.

Easterbrooks, M. A. (1989). Quality of attachment to mother and to father: Effects of perinatal risk status. *Child Development, 60*(4), 825-830.

Ebstein, R., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., . . . Belmaker, R. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. *Nature Genetics, 12*(1), 78-80.

Eckerman, C., Oehler, J., Medvin, M., & Hannan, T. (1994). Premature newborns as social partners before term age. *Infant Behavior and Development, 17*(1), 55-70.

Egeland, B., & Sroufe, L. A. (1981). Attachment and early maltreatment. *Child Development, 52*(1), 44-52.

Ekelund, J., Lichtermann, D., Järvelin, M.-R., & Peltonen, L. (1999). Association between novelty seeking and the type 4 dopamine receptor gene in a large finnish cohort sample. *American Journal of Psychiatry, 156*(9), 1453-1455.

Ellis, B., & Boyce, W. T. (2008). Biological sensitivity to context. *Current Directions in Psychological Science, 17*(3), 183-187.

Engle, R., Kane, M., & Tuholski, S. (1999). Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (pp. 102–134). New York, NY: Cambridge University Press.

Eyer, D. (1994). Mother-infant bonding. *Human Nature, 5*(1), 69-94.

Faraone, S., Doyle, A., Mick, E., & Biederman, J. (2001). Meta-Analysis of the association between the 7-repeat allele of the dopamine D4 receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry, 158*(7), 1052-1057.

Fearon, R. P., Bakermans-Kranenburg, M., van Ijzendoorn, M., Lapsley, A.-M., & Roisman, G. (2010). The significance of insecure attachment and disorganization in the development of children's externalizing behavior: A Meta-analytic study. *Child Development, 81*(2), 435-456.

Field, T. (2002). Prenatal effects of maternal depression. In S. H. Goodman, & I. H. Gotlib (Eds.), *Children of depressed parents: Mechanisms of risk and implications for treatment* (pp. 59-88). Washington, DC: American Psychological Association.

Fihrer, I., McMahon, C., & Taylor, A. (2009). The impact of postnatal and concurrent maternal depression on child behaviour during the early school years. *Journal of Affective Disorders, 119*(1), 116-123.

Fox, N., & Calkins, S. (2003). The development of self-control of emotion: Intrinsic and extrinsic influences. *Motivation and Emotion, 27*(1), 7-26.

Frankel, K., & Harmon, R. (1996). Depressed mothers: They don't always look as bad as they feel. *Journal of the American Academy of Child & Adolescent Psychiatry, 35*(3), 289-298.

Frodi, A. (1983). Attachment behavior and sociability with strangers in premature and fullterm infants. *Infant Mental Health Journal, 4*(1), 13-22.

Gale, C., & Martyn, C. (2004). Birth weight and later risk of depression in a national birth cohort. *The British Journal of Psychiatry, 184*(1), 28-33.

Gardner, S., Goldson, E., & Hernández, J. (2015). The neonate and the environment. In Gardner, S., Carter, B., Enzman-Hines, M., & Hernandez, J. (Eds.), *Merenstein & Gardner's handbook of neonatal intensive care* (8 ed., pp. 262-314). London, UK: Elsevier Health Sciences.

Gelernter, J., Kennedy, J., Van Tol, H., Civelli, O., & Kidd, K. (1992). The D4 dopamine receptor (DRD4) maps to distal 11p close to HRAS. *Genomics, 13*(1), 208-210.

Gelernter, J., Kranzler, H., Coccaro, E., Siever, L., New, A., & Mulgrew, C. (1997). D4 dopamine-receptor (DRD4) alleles and novelty seeking in substance-dependent, personality-disorder, and control subjects. *The American Journal of Human Genetics, 61*(5), 1144-1152.

Gervai, J., Nemoda, Z., Lakatos, K., Ronai, Z., Toth, I., Ney, K., & Sasvari-Szekely, M. (2005). Transmission disequilibrium tests confirm the link between DRD4 gene polymorphism and infant attachment. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 132B*(1), 126-130.

Gervai, J., Novak, A., Lakatos, K., Toth, I., Danis, I., Ronai, Z., . . . Bronfman, E. (2007). Infant genotype may moderate sensitivity to maternal affective communications: Attachment disorganization, quality of care, and the DRD4 polymorphism. *Social Neuroscience, 2*(3-4), 307-319.

Giardino, J., Gonzalez, A., Steiner, M., & Fleming, A. (2008). Effects of motherhood on physiological and subjective responses to infant cries in teenage mothers: A comparison with non-mothers and adult mothers. *Hormones and Behavior, 53*(1), 149-158.

Goland, R., Tropper, P., Warren, W., Stark, R., Jozak, S., & Conwell, I. (1995). Concentrations of corticotrophin-releasing hormone in the umbilical-cord blood of pregnancies complicated by pre-eclampsia. *Reproduction, Fertility and Development, 7*(5), 1227-1230.

Goldberg, S. (1983). Parent-infant bonding: Another look. *Child Development, 54*(6), 1355-1382.

Goldberg, S., Perrotta, M., Minde, K., & Corter, C. (1986). Maternal behavior and attachment in low-birth-weight twins and singletons. *Child Development, 57*(1), 34-46.

Goldsmith, D., & Rogoff, B. (1997). Mothers' and toddlers' coordinated joint focus of attention: Variations with maternal dysphoric symptoms. *Developmental Psychology, 33*(1), 113-119.

Goodman, S., & Gotlib, I. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review, 106*(3), 458-490.

Goodman, S., Rouse, M., Connell, A., Broth, M., Hall, C., & Heyward, D. (2011). Maternal depression and child psychopathology: A meta-analytic review. *Clinical Child and Family Psychology Review, 14*(1), 1-27.

Grace, S., Evindar, A., & Stewart, D. (2003). The effect of postpartum depression on child cognitive development and behavior: A review and critical analysis of the literature. *Archives of Women's Mental Health, 6*(4), 263-274.

Graffi, J., Moss, E., Jolicoeur-Martineau, A., Moss, G., Lecompte, V., Pascuzzo, K., . . . Wazana, A. (2015). Preschool children without 7-repeat DRD4 gene more likely to develop disorganized attachment style. *McGill Undergraduate Research Journal, 10*(1), 31-36.

Greenberg, M., Speltz, M., Deklyen, M., & Endriga, M. (1991). Attachment security in preschoolers with and without externalizing behavior problems: A replication. *Development and Psychopathology, 3*(04), 413-430.

Groh, A. M., Roisman, G. I., van Ijzendoorn, M. H., Bakermans-Kranenburg, M. J., & Fearon, R. P. (2012). The significance of insecure and disorganized attachment for children's internalizing symptoms: A meta-analytic study. *Child Development, 83*(2), 591-610.

Halligan, S., Murray, L., Martins, C., & Cooper, P. (2007). Maternal depression and psychiatric outcomes in adolescent offspring: A 13-year longitudinal study. *Journal of Affective Disorders, 97*(1), 145-154.

Harmon, R. (1981). Perinatal influences on the family: Some preventive implications. *J Prevent Psychiatry, 1*(1), 132-139.

Harnish, J., Dodge, K., & Valente, E. (1995). Mother-child interaction quality as a partial mediator of the roles of maternal depressive symptomatology and socioeconomic status in the development of child behavior problems. *Child Development, 66*(3), 739-753.

Hayes, L., Goodman, S., & Carlson, E. (2013). Maternal antenatal depression and infant disorganized attachment at 12 months. *Attachment & Human Development, 15*(2), 133-153.

Henderson, E., & Jennings, K. (2003). Maternal depression and the ability to facilitate joint attention with 18-month-olds. *Infancy, 4*(1), 27-46.

Holmbeck, G. (1997). Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: Examples from the child-clinical and pediatric psychology literatures. *Journal of Consulting and Clinical Psychology, 65*(4), 599-610.

Holmes, J., Payton, A., Barrett, J., Harrington, R., McGuffin, P., Owen, M., . . . Kirley, A. (2002). Association of DRD4 in children with ADHD and comorbid conduct problems. *American Journal of Medical Genetics, 114*(2), 150-153.

Horwood, L. J., Mogridge, N., & Darlow, B. (1998). Cognitive, educational, and behavioural outcomes at 7 to 8 years in a national very low birthweight cohort. *Archives of Disease in Childhood-Fetal and Neonatal Edition, 79*(1), F12-F20.

Indredavik, M., Vik, T., Heyerdahl, S., Kulseng, S., Fayers, P., & Brubakk, A. (2004). Psychiatric symptoms and disorders in adolescents with low birth weight. *Archives of Disease in Childhood-Fetal and Neonatal Edition, 89*(5), F445-F450.

Insel, T. (2003). Is social attachment an addictive disorder? *Physiology & Behavior, 79*(3), 351-357.

Jacobsen, T., Edelstein, W., & Hofmann, V. (1994). A longitudinal study of the relation between representations of attachment in childhood and cognitive functioning in childhood and adolescence. *Developmental Psychology, 30*(1), 112-124.

Jameson, P., Gelfand, D., Kulcsar, E., & Teti, D. (1997). Mother–toddler interaction patterns associated with maternal depression. *Development and Psychopathology, 9*(03), 537-550.

Jonsson, E., Nothen, M., Gustavsson, J. P., Neidt, H., Brené, S., Tylec, A., . . . Sedvall, G. (1997). Lack of evidence for allelic association between personality traits and the dopamine D4 receptor gene polymorphisms. *American Journal of Psychiatry, 154*(5), 697-699.

Judd, C., & Kenny, D. (1981). *Estimating the effects of social intervention*. New York, NY: Cambridge University Press.

Juffer, F., Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2008). *Promoting positive parenting: An attachment-based intervention*. Mahwah, NJ: Erlbaum.

Kim, J.-S., Kaye, J., & Wright, L. (2001). Moderating and mediating effects in causal models. *Issues in Mental Health Nursing, 22*(1), 63-75.

Klein, T., Neumann, J., Reuter, M., Hennig, J., von Cramon, D. Y., & Ullsperger, M. (2007). Genetically determined differences in learning from errors. *Science, 318*(5856), 1642-1645.

Kluger, A., Siegfried, Z., & Ebstein, R. (2002). A meta-analysis of the association between DRD4 polymorphism and novelty seeking. *Molecular Psychiatry, 7*(7), 712-717.

Korja, R., Latva, R., & Lehtonen, L. (2012). The effects of preterm birth on mother–infant interaction and attachment during the infant's first two years. *Acta Obstetricia et Gynecologica Scandinavica, 91*(2), 164-173.

Koulomzin, M., Beebe, B., Anderson, S., Jaffe, J., Feldstein, S., & Crown, C. (2002). Infant gaze, head, face and self-touch at 4 months differentiate secure vs. avoidant attachment at 1 year: A microanalytic approach. *Attachment & Human Development, 4*(1), 3-24.

Kramer, M. (1987). Determinants of low birth weight: Methodological assessment and meta-analysis. *Bulletin of the World Health Organization, 65*(5), 663-737.

Kramer, M., Platt, R., Wen, S. W., Joseph, K., Allen, A., Abrahamowicz, M., . . . Bréart, G. (2001). A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics, 108*(2), e35-e35.

Kramer, M., Lydon, J., Séguin, L., Goulet, L., Kahn, S., McNamara, H., . . . Sharma, S. (2009). Stress pathways to spontaneous preterm birth: The role of stressors, psychological distress, and stress hormones. *American Journal of Epidemiology, 169*, 1319-1326.

Kreek, M.-J., Nielsen, D., Butelman, E., & LaForge, K. S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience, 8*(11), 1450-1457.

Krpan, K., Coombs, R., Zinga, D., Steiner, M., & Fleming, A. (2005). Experiential and hormonal correlates of maternal behavior in teen and adult mothers. *Hormones and Behavior, 47*(1), 112-122.

LaHoste, G., Swanson, J., Wigal, S., Glabe, C., Wigal, T., King, N., & Kennedy, J. (1996). Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. *Molecular Psychiatry, 1*(2), 121-124.

Lakatos, K., Toth, I., Nemoda, Z., Ney, K., Sasvari-Szekely, M., & Gervai, J. (2000). Dopamine D4 receptor (DRD4) gene polymorphism is associated with attachment disorganization in infants. *Molecular Psychiatry, 5*(6), 633-637.

Lakatos, K., Nemoda, Z., Toth, I., Ronai, Z., Ney, K., Sasvari-Szekely, M., & Gervai, J. (2002). Further evidence for the role of the dopamine D4 receptor (DRD4) gene in attachment disorganization: Interaction of the exon III 48-bp repeat and the-521 C/T promoter polymorphisms. *Molecular Psychiatry, 7*(1), 27-31.

Lamb, M. (1983). Early mother-neonate contact and the mother-child relationship. *Journal of Child Psychology and Psychiatry, 24*(3), 487-494.

Laucht, M., Esser, G., & Schmidt, M. (2001). Differential development of infants at risk for psychopathology: The moderating role of early maternal responsivity. *Developmental Medicine & Child Neurology, 43*(05), 292-300.

Lavelli, M., & Poli, M. (1998). Early mother-infant interaction during breast-and bottle-feeding. *Infant Behavior and Development, 21*(4), 667-683.

Lee Raby, K., Cicchetti, D., Carlson, E., Egeland, B., & Collins, W. A. (2013). Genetic contributions to continuity and change in attachment security: A prospective, longitudinal investigation from infancy to young adulthood. *Journal of Child Psychology and Psychiatry, 54*(11), 1223-1230.

Levitan, R., Masellis, M., Lam, R., Kaplan, A., Davis, C., Tharmalingam, S., . . . Kennedy, J. (2006). A birth-season/DRD4 gene interaction predicts weight gain and obesity in women with seasonal affective disorder: A seasonal thrifty phenotype hypothesis. *Neuropsychopharmacology, 31*(11), 2498-2503.

Lichter, J., Barr, C., Kennedy, J., Van Tol, H., Kidd, K., & Livak, K. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Human Molecular Genetics, 2*(6), 767-773.

Link, B., & Phelan, J. (1995). Social conditions as fundamental causes of disease. *Journal of Health and Social Behavior, extra issue*, 80-94.

Liotti, G. (1999). Disorganization of attachment as a model for understanding dissociative psychopathology. In J. Solomon, & C. George (Eds.), *Attachment Disorganization* (pp. 39–70). New York, NY: Guilford Press.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., . . . Meaney, M. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science, 277*(5332), 1659-1662.

Lohmueller, K., Pearce, C., Pike, M., Lander, E., & Hirschhorn, J. (2003). Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nature Genetics, 33*(2), 177-182.

Londerville, S., & Main, M. (1981). Security of attachment, compliance, and maternal training methods in the second year of life. *Developmental Psychology, 17*(3), 289-299.

Luijk, M., Roisman, G., Haltigan, J., Tiemeier, H., Booth-LaForce, C., van Ijzendoorn, M., . . . Bakermans-Kranenburg, M. (2011). Dopaminergic, serotonergic, and oxytonergic candidate genes associated with infant attachment security and disorganization? In search of main and interaction effects. *Journal of Child Psychology and Psychiatry, 52*(12), 1295-1307.

Lyons-Ruth, K., Zoll, D., Connell, D., & Grunebaum, H. (1986). The depressed mother and her one-year-old infant: Environment, interaction, attachment, and infant development. *New Directions for Child and Adolescent Development, 1986*(34), 61-82.

Lyons-Ruth, K. (1996). Attachment relationships among children with aggressive behavior problems: The role of disorganized early attachment patterns. *Journal of Consulting and Clinical Psychology, 64*(1), 64-73.

Lyons-Ruth, K., Easterbrooks, M., & Cibelli, C. (1997). Infant attachment strategies, infant mental lag, and maternal depressive symptoms: Predictors of internalizing and externalizing problems at age 7. *Developmental Psychology, 33*(4), 681-692.

Lyons-Ruth, K., Lyubchik, A., Wolfe, R., & Bronfman, E. (2002). Parental depression and child attachment: Hostile and helpless profiles of parent and child behavior among families at risk. In S. H. Goodman & I. H. Gotlib (Eds.), *Children of depressed parents: Mechanisms of risk and implications for treatment* (pp. 89–120). Washington, DC: American Psychological Association.

Lyons-Ruth, K., & Spielman, E. (2004). Disorganized infant attachment strategies and helpless-fearful profiles of parenting: Integrating attachment research with clinical intervention. *Infant Mental Health Journal, 25*(4), 318-335.

Maier, M., Bernier, A., Pekrun, R., Zimmermann, P., Strasser, K., & Grossmann, K. (2005). Attachment state of mind and perceptual processing of emotional stimuli. *Attachment & Human Development, 7*(1), 67-81.

Main, M., Tomasini, L., & Tolan, W. (1979). Differences among mothers of infants judged to differ in security. *Developmental Psychology, 15*(4), 472-473.

Main, M., & Weston, D. (1981). The quality of the toddler's relationship to mother and to father: Related to conflict behavior and the readiness to establish new relationships. *Child Development, 52*(3), 932-940.

Main, M., & Solomon, J. (1986). Discovery of an insecure-disorganized/disoriented attachment pattern. In M. Yogman & T. B. Brazel- ton (Eds.), *Affective development in infancy* (pp. 95-125). Norwood, NJ: Ablex.

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

Malhotra, A., Virkkunen, M., Rooney, W., Eggert, M., Linnoila, M., & Goldman, D. (1996). The association between the dopamine D4 receptor (D4DR) 16 amino acid repeat polymorphism and novelty seeking. *Molecular Psychiatry, 1*(5), 388-391.

Mangelsdorf, S., Plunkett, J., Dedrick, C., Berlin, M., Meisels, S., McHale, J., & Dichtellmiller, M. (1996). Attachment security in very low birth weight infants. *Developmental Psychology, 32*(5), 914-920.

Mäntymaa, M., Puura, K., Luoma, I., Kaukonen, P., Salmelin, R., & Tamminen, T. (2008). Infants' social withdrawal and parents' mental health. *Infant Behavior and Development, 31*(4), 606-613.

Martins, C., & Gaffan, E. (2000). Effects of early maternal depression on patterns of infant–mother attachment: A meta-analytic investigation. *Journal of Child Psychology and Psychiatry, 41*(06), 737-746.

McCrea, H., & Ment, L. (2008). The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. *Clinics in Perinatology, 35*(4), 777-792.

McIntire, D., Bloom, S., Casey, B., & Leveno, K. (1999). Birth weight in relation to morbidity and mortality among newborn infants. *New England Journal of Medicine, 340*(16), 1234-1238.

McMahon, C., Barnett, B., Kowalenko, N., & Tennant, C. (2006). Maternal attachment state of mind moderates the impact of postnatal depression on infant attachment. *Journal of Child Psychology and Psychiatry, 47*(7), 660-669.

McTernan, C., Draper, N., Nicholson, H., Chalder, S., Driver, P., Hewison, M., . . . Stewart, P. (2001). Reduced placental 11β-hydroxysteroid dehydrogenase type 2 mRNA levels in human pregnancies complicated by intrauterine growth restriction: An analysis of possible mechanisms. *The Journal of Clinical Endocrinology & Metabolism, 86*(10), 4979-4983.

Mesman, J. (2010). Maternal responsiveness to infants: Comparing micro- and macro-level measures. *Attachment & Human Development, 12*(1-2), 143-149.

Mileva-Seitz, V., Kennedy, J., Atkinson, L., Steiner, M., Levitan, R., Matthews, S., . . . Fleming, A. (2011). Serotonin transporter allelic variation in mothers predicts maternal sensitivity, behavior and attitudes toward 6-month-old infants. *Genes, Brain and Behavior, 10*(3), 325-333.

Mileva-Seitz, V., Fleming, A., Meaney, M., Mastroianni, A., Sinnwell, J., Steiner, M., . . . Sokolowski, M. (2012). Dopamine receptors D1 and D2 are related to observed maternal behavior. *Genes, Brain and Behavior, 11*(6), 684-694.

Mileva-Seitz, V., Steiner, M., Atkinson, L., Meaney, M., Levitan, R., Kennedy, J., . . . Fleming, A. (2013). Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood. *PloS One, 8*(4), e61443.

Mills-Koonce, W. R., Gariepy, J.-L., Sutton, K., & Cox, M. (2008). Changes in maternal sensitivity across the first three years: Are mothers from different attachment dyads differentially influenced by depressive symptomatology? *Attachment & Human Development, 10*(3), 299-317.

Mitsuyasu, H., Ozawa, H., Takeda, Y., & Fukumaki, Y. (1999). Novel polymorphisms in the upstream region of the human dopamine D4 receptor (DRD4) gene. *Journal of Human Genetics, 44*(6), 416-418.

Moehler, E., Brunner, R., Wiebel, A., Reck, C., & Resch, F. (2006). Maternal depressive symptoms in the postnatal period are associated with long-term impairment of mother–child bonding. *Archives of Women's Mental Health, 9*(5), 273-278.

Moore, H., West, A., & Grace, A. (1999). The regulation of forebrain dopamine transmission: Relevance to the pathophysiology and psychopathology of schizophrenia. *Biological Psychiatry, 46*(1), 40-55.

Moss, E., Rousseau, D., Parent, S., St-Laurent, D., & Saintonge, J. (1998). Correlates of attachment at school age: Maternal reported stress, mother-child interaction, and behavior problems. *Child Development, 69*(5), 1390-1405.

Moss, E., Cyr, C., & Dubois-Comtois, K. (2004). Attachment at early school age and developmental risk: Examining family contexts and behavior problems of controlling-caregiving, controlling-punitive, and behaviorally disorganized children. *Developmental Psychology, 40*(4), 519-532.

Moss, E., Bureau, J.-F., Cyr, C., Mongeau, C., & St-Laurent, D. (2004). Correlates of attachment at age 3: Construct validity of the preschool attachment classification system. *Developmental Psychology, 40*(3), 323-334.

Moss, E., Cyr, C., Bureau, J.-F., Tarabulsy, G., & Dubois-Comtois, K. (2005). Stability of attachment during the preschool period. *Developmental Psychology, 41*(5), 773-783.

Moss, E., Dubois-Comtois, K., Cyr, C., Tarabulsy, G., St-Laurent, D., & Bernier, A. (2011). Efficacy of a home-visiting intervention aimed at improving maternal sensitivity, child attachment, and behavioral outcomes for maltreated children: A randomized control trial. *Development and Psychopathology, 23*(01), 195-210.

Moss, E., Bureau, J.-F., St-Laurent, D., & Tarabulsy, G. (2011). Understanding disorganized attachment at preschool and school age: Examining divergent pathways of disorganized and controlling children. In J. Solomon & C. George (Eds.), *Attachment disorganization and caregiving* (pp. 52-79). New York, NY: Guilford Press.

Moss, E., Tarabulsy, G., St-Georges, R., Dubois-Comtois, K., Cyr, C., Bernier, A., . . . Lecompte, V. (2014). Video-feedback intervention with maltreating parents and their children: Program implementation and case study. *Attachment & Human Development, 16*(4), 329-342.

Muglia, P., Jain, U., Macciardi, F., & Kennedy, J. (2000). Adult attention deficit hyperactivity disorder and the dopamine D4 receptor gene. *American Journal of Medical Genetics, 96*(3), 273-277.

Munafò, M., Yalcin, B., Willis-Owen, S., & Flint, J. (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: Meta-analysis and new data. *Biological Psychiatry, 63*(2), 197-206.

Murray, L. (1992). The impact of postnatal depression on infant development. *Journal of Child Psychology and Psychiatry, 33*(3), 543-561.

Murray, L., Kempton, C., Woolgar, M., & Hooper, R. (1993). Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. *Journal of Child Psychology and Psychiatry, 34*(7), 1083-1101.

Murray, L., Fiori-Cowley, A., Hooper, R., & Cooper, P. (1996). The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Development, 67*(5), 2512-2526.

Murray, L., & Cooper, P. (1997). *Postpartum depression and child development*. New York, NY: Guilford Press.

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development, 67*(2), 508-522.

Nestler, E., & Carlezon, W. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry, 59*(12), 1151-1159.

Nicholls, A., & Kirkland, J. (1996). Maternal sensitivity: A review of attachment literature definitions. *Early Child Development and Care, 120*(1), 55-65.

Nomura, Y., & Chemtob, C. (2007). Conjoined effects of low birth weight and childhood abuse on adaptation and well-being in adolescence and adulthood. *Archives of Pediatrics & Adolescent Medicine, 161*(2), 186-192.

O'Connor, T., Heron, J., Glover, V., & Team, A. S. (2002). Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*(12), 1470-1477.

O'Hara, M., & Swain, A. (1996). Rates and risk of postpartum depression: A meta-analysis. *International Review of Psychiatry, 8*(1), 37-54.

O'Donnell, K., Gaudreau, H., Colalillo, S., Steiner, M., Atkinson, L., Moss, E., . . . Lydon, J. (2014). The maternal adversity, vulnerability and neurodevelopment project: Theory and

methodology. *Canadian Journal of Psychiatry: Revue Canadienne de Psychiatrie, 59*(8), 497-508.

Oak, J., Oldenhof, J., & Van Tol, H. (2000). The dopamine D4 receptor: One decade of research. *European Journal of Pharmacology, 405*(1), 303-327.

Pawlby, S., Sharp, D., Hay, D., & O'Keane, V. (2008). Postnatal depression and child outcome at 11 years: The importance of accurate diagnosis. *Journal of Affective Disorders, 107*(1), 241-245.

Pearson, R., Cooper, R., Penton-Voak, I., Lightman, S., & Evans, J. (2010). Depressive symptoms in early pregnancy disrupt attentional processing of infant emotion. *Psychological Medicine, 40*(04), 621-631.

Pearson, R., Evans, J., Kounali, D., Lewis, G., Heron, J., Ramchandani, P., . . . Stein, A. (2013). Maternal depression during pregnancy and the postnatal period: Risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry, 70*(12), 1312-1319.

Pederson, D., 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*(6), 1974-1983.

Penny, K. (1996). Appropriate critical values when testing for a single multivariate outlier by using the Mahalanobis distance. *Applied Statistics, 45*(1), 73-81.

Perry, D., Ettinger, A., Mendelson, T., & Le, H.-N. (2011). Prenatal depression predicts postpartum maternal attachment in low-income Latina mothers with infants. *Infant Behavior and Development, 34*(2), 339-350.

Pickering, A., & Gray, J. (1999). The neuroscience of personality. In L. Pervin & O. John (Eds.), *Handbook of personality* (pp. 277-299). San Francisco, CA: Guilford Press.

Plunkett, J., Meisels, S., Stiefel, G., Pasick, P., & Roloff, D. (1986). Patterns of attachment among preterm infants of varying biological risk. *Journal of the American Academy of Child Psychiatry, 25*(6), 794-800.

Plunkett, J., Klein, T., & Meisels, S. (1988). The relationship of preterm infant-mother attachment to stranger sociability at 3 years. *Infant Behavior and Development, 11*(1), 83-96.

Poehlmann, J., & Fiese, B. (2001). The interaction of maternal and infant vulnerabilities on developing attachment relationships. *Development and Psychopathology, 13*(01), 1-11.

Propper, C., Willoughby, M., Halpern, C., Carbone, M., & Cox, M. (2007). Parenting quality, DRD4, and the prediction of externalizing and internalizing behaviors in early childhood. *Developmental Psychobiology, 49*(6), 619-632.

Pruessner, J., Champagne, F., Meaney, M., & 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 [11C] raclopride. *The Journal of Neuroscience, 24*(11), 2825-2831.

Pyszczynski, T., & Greenberg, J. (1987). Self-regulatory perseveration and the depressive self-focusing style: A self-awareness theory of reactive depression. *Psychological Bulletin, 102*(1), 122-138.

Radke-Yarrow, M., Cummings, E. M., Kuczynski, L., & Chapman, M. (1985). Patterns of attachment in two-and three-year-olds in normal families and families with parental depression. *Child Development, 56*(4), 884-893.

Radloff, L. (1977). The CES-D scale a self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401.

Raver, C. C., & Leadbeater, B. (1995). Factors influencing joint attention between socioeconomically disadvantaged adolescent mothers and their infants. In C. Moore & P. Dunham (Eds.), *Joint attention: Its origins and role in development* (pp. 251-271). Hillsdale, NJ: Erlbaum.

Reissland, N., & Shepherd, J. (2006). The effect of maternal depressed mood on infant emotional reaction in a surprise-eliciting situation. *Infant Mental Health Journal, 27*(2), 173-187.

Righetti-Veltema, M., Bousquet, A., & Manzano, J. (2003). Impact of postpartum depressive symptoms on mother and her 18-month-old infant. *European Child & Adolescent Psychiatry, 12*(2), 75-83.

Roberts, B., Marlow, N., & Cooke, R. (1989). Motor problems among children of very low birthweight. *The British Journal of Occupational Therapy, 52*(3), 97-99.

Robertson, E., Grace, S., Wallington, T., & Stewart, D. (2004). Antenatal risk factors for postpartum depression: A synthesis of recent literature. *General Hospital Psychiatry, 26*(4), 289-295.

Rode, S., Chang, P., Fisch, R., & Sroufe, L. A. (1981). Attachment patterns of infants separated at birth. *Developmental Psychology, 17*(2), 188-191.

Roggman, L., Langlois, J., & Hubbs-Tait, L. (1987). Mothers, infants, and toys: Social play correlates of attachment. *Infant Behavior and Development, 10*(2), 233-237.

Saigal, S., & Doyle, L. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet, 371*(9608), 261-269.

Schafer, J. (1999). Multiple imputation: A primer. *Statistical Methods in Medical Research, 8*(1), 3-15.

Shaw, D., Keenan, K., Vondra, J., Delliquardi, E., & Giovannelli, J. (1997). Antecedents of preschool children's internalizing problems: A longitudinal study of low-income families. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(12), 1760-1767.

Sheese, B., Voelker, P., Rothbart, M., & Posner, M. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology, 19*(04), 1039-1046.

Silveira, P., Portella, A., Kennedy, J., Gaudreau, H., Davis, C., Steiner, M., . . . Dubé, L. (2014). Association between the seven-repeat allele of the dopamine-4 receptor gene (DRD4) and spontaneous food intake in pre-school children. *Appetite, 73*, 15-22.

Silveira, P., Gaudreau, H., Atkinson, L., Fleming, A., Sokolowski, M., Steiner, M., . . . Dubé, L. (2016). Genetic differential susceptibility to socioeconomic status and childhood obesogenic behavior: Why targeted prevention may be the best societal investment. *JAMA pediatrics, 170*(4), 359-364.

Solomon, J., George, C., & De Jong, A. (1995). Children classified as controlling at age six: Evidence of disorganized representational strategies and aggression at home and at school. *Development and Psychopathology, 7*(03), 447-463.

Spangler, G., Johann, M., Ronai, Z., & Zimmermann, P. (2009). Genetic and environmental influence on attachment disorganization. *Journal of Child Psychology and Psychiatry, 50*(8), 952-961.

Speltz, M., Greenberg, M., & Deklyen, M. (1990). Attachment in preschoolers with disruptive behavior: A comparison of clinic-referred and nonproblem children. *Development and Psychopathology, 2*(1), 31-46.

Sullivan, P., Fifield, W., Kennedy, M., Mulder, R., Sellman, J. D., & Joyce, P. (1998). No association between novelty seeking and the type 4 dopamine receptor gene (DRD4) in two New Zealand samples. *American Journal of Psychiatry, 155*(1), 98-101.

Taylor, H. G., Klein, N., & Hack, M. (2000). School-age consequences of birth weight less than 750 g: A review and update. *Developmental Neuropsychology, 17*(3), 289-321.

Teti, D., Gelfand, D., Messinger, D., & Isabella, R. (1995). Maternal depression and the quality of early attachment: An examination of infants, preschoolers, and their mothers. *Developmental Psychology, 31*(3), 364-376.

Tomlinson, M., Cooper, P., & Murray, L. (2005). The mother–infant relationship and infant attachment in a South African peri-urban settlement. *Child Development, 76*(5), 1044-1054.

Trapolini, T., McMahon, C., & Ungerer, J. (2007). The effect of maternal depression and marital adjustment on young children's internalizing and externalizing behaviour problems. *Child: Care, Health and Development, 33*(6), 794-803.

Trapolini, T., Ungerer, J., & McMahon, C. (2008). Maternal depression: Relations with maternal caregiving representations and emotional availability during the preschool years. *Attachment & Human Development, 10*(1), 73-90.

Tripp, G., & Wickens, J. (2008). Research review: Dopamine transfer deficit: a neurobiological theory of altered reinforcement mechanisms in ADHD. *Journal of Child Psychology and Psychiatry, 49*(7), 691-704.

Vallone, D., Picetti, R., & Borrelli, E. (2000). Structure and function of dopamine receptors. *Neuroscience & Biobehavioral Reviews, 24*(1), 125-132.

Van Batenburg-Eddes, T., Brion, M., Henrichs, J., Jaddoe, V., Hofman, A., Verhulst, F., . . . Tiemeier, H. (2013). Parental depressive and anxiety symptoms during pregnancy and attention problems in children: A cross-cohort consistency study. *Journal of Child Psychology and Psychiatry, 54*(5), 591-600.

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). MICE: Multivariate imputation by chained equations in R. *Journal of Statistical Software, 45*(3).

van Doesum, K., Hosman, C., Riksen-Walraven, M., & Hoefnagels, C. (2007). Correlates of depressed mothers' sensitivity toward their infants: The role of maternal, child, and contextual characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(6), 747-756.

van Doesum, K., Riksen-Walraven, J. M., Hosman, C., & Hoefnagels, C. (2008). A randomized controlled trial of a home-visiting intervention aimed at preventing relationship problems in depressed mothers and their infants. *Child Development, 79*(3), 547-561.

van Ijzendoorn, M., Schuengel, C., & Bakermans-Kranenburg, M. (1999). Disorganized attachment in early childhood: Meta-analysis of precursors, concomitants, and sequelae. *Development and Psychopathology, 11*(02), 225-250.

van Ijzendoorn, M., & Bakermans-Kranenburg, M. (2006). DRD4 7-repeat polymorphism moderates the association between maternal unresolved loss or trauma and infant disorganization. *Attachment & Human Development, 8*(4), 291-307.

Van Lieshout, R., & Boyle, M. (2011). Canadian youth born large or small for gestational age and externalizing and internalizing problems. *Canadian Journal of Psychiatry, 56*(4), 227-234.

Van Mil, N., Steegers-Theunissen, R., Motazedi, E., Jansen, P., Jaddoe, V., Steegers, E., . . . Tiemeier, H. (2015). Low and high birth weight and the risk of child attention problems. *The Journal of Pediatrics, 166*(4), 862-869. e863.

Van Tol, H., Wu, C., Guan, H.-C., Ohara, K., Bunzow, J., Civelli, O., . . . Jovanovic, V. (1992). Multiple dopamine D4 receptor variants in the human population. *Nature, 358*, 149-152.

Vohr, B., Wright, L., Dusick, A., Mele, L., Verter, J., Steichen, J., . . . Bauer, C. (2000). Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics, 105*(6), 1216-1226.

Wan, M. W., Abel, K., & Green, J. (2008). The transmission of risk to children from mothers with schizophrenia: A developmental psychopathology model. *Clinical Psychology Review, 28*(4), 613-637.

Wartner, U., Grossmann, K., Fremmer-Bombik, E., & Suess, G. (1994). Attachment patterns at age six in south Germany: Predictability from infancy and implications for preschool behavior. *Child Development, 65*(4), 1014-1027.

Waters, E., & Deane, K. (1985). Defining and assessing individual differences in attachment relationships: Q-methodology and the organization of behavior in infancy and early childhood. *Monographs of the Society for Research in Child Development, 50*(1-2, Serial No. 29), 41-65.

Wazana, A., Moss, E., Jolicoeur-Martineau, A., Graffi, J., Tsabari, G., Lecompte, V., . . . Mileva, V. (2015). The interplay of birth weight, dopamine receptor D4 gene (DRD4), and early maternal care in the prediction of disorganized attachment at 36 months of age. *Development and Psychopathology, 27*(4pt1), 1145-1161.

Wei, J. N., Li, H. Y., Sung, F. C., Lin, C. C., Chiang, C. C., Li, C. Y., & Chuang, L. M. (2007). Birth weight correlates differently with cardiovascular risk factors in youth. *Obesity, 15*(6), 1609-1616.

Weiss, S., Wilson, P., Hertenstein, M., & Campos, R. (2000). The tactile context of a mother's caregiving: Implications for attachment of low birth weight infants. *Infant Behavior and Development, 23*(1), 91-111.

Weissman, M., Paykel, E., & Klerman, G. (1972). The depressed woman as a mother. *Social Psychiatry, 7*(2), 98-108.

Whiteside-Mansell, L., Bradley, R., Casey, P., Fussell, J., & Conners-Burrow, N. (2009). Triple risk: Do difficult temperament and family conflict increase the likelihood of behavioral maladjustment in children born low birth weight and preterm? *Journal of Pediatric Psychology, 34*(4), 396-405.

Wilcox, A. (2001). On the importance—and the unimportance—of birthweight. *International Journal of Epidemiology, 30*(6), 1233-1241.

Wiles, N., Peters, T., Leon, D., & Lewis, G. (2005). Birth weight and psychological distress at age 45-51 years - Results from the Aberdeen Children of the 1950s cohort study. *The British Journal of Psychiatry, 187*(1), 21-28.

Wille, D. (1991). Relation of preterm birth with quality of infant-mother attachment at one year. *Infant Behavior and Development, 14*(2), 227-240.

Wolke, D., Eryigit-Madzwamuse, S., & Gutbrod, T. (2014). Very preterm/very low birthweight infants' attachment: Infant and maternal characteristics. *Archives of Disease in Childhood-Fetal and Neonatal Edition, 99*(1), F70-F75.

Wong, M., Day, N., Luan, J., Chan, K., & Wareham, N. (2003). The detection of gene–environment interaction for continuous traits: Should we deal with measurement error by bigger studies or better measurement? *International Journal of Epidemiology, 32*(1), 51-57.