DRD2, DAT1, COMT, and OXTR GENES AS POTENTIAL MODERATORS OF THE RELATIONSHIP BETWEEN MATERNAL HISTORY OF MALTREATMENT AND INFANT EMOTION REGULATION

by

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Abstract

DRD2, DAT1, COMT, and OXTR Genes as Potential Moderators of the Relationship between Maternal History of Maltreatment and Infant Emotion Regulation

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Background: Gene-environment (GXE) interaction models have demonstrated that DRD2, DAT1, COMT, and OXTR SNPs moderate parental factors (i.e., maternal depression, parenting) to predict outcomes related to emotion regulation (e.g., affective problems, attentional control). No studies have investigated the connections between maternal maltreatment history and infant dopamine and oxytocin gene variants as they relate to infant emotion regulation. The current study addresses these gaps, evaluating the interaction of selected genes as they interact with maternal history of maltreatment to predict infant emotion regulation.

Method: I investigated five infant genotypes (DRD2, DAT1, COMT, OXTR rs53576, and OXTR rs2254298) as they interacted with maternal history of self-reported maltreatment to predict observed infant emotion regulation behaviours. Self-reported maternal depressive symptoms were covaried. Infant emotion regulation was observed in the context of a potent stressor. I assessed three potential models of interaction, diathesis-stress, differential sensitivity, or vantage sensitivity.

Results: Analyses demonstrated that, over and above maternal depressive symptoms, DRD2 and COMT significantly interacted with self-reported maternal maltreatment scores in a 'vantage sensitivity' model and DAT1 significantly interacted with maternal maltreatment history in a

'diathesis-stress' model. A cumulative vantage sensitivity (CVS) index significantly interacted with maternal maltreatment history to predict emotion regulation scores, consistent with a vantage sensitivity model.

Conclusions: Findings indicated that infants with the "vantage" DRD2 (A1+) and COMT (Met) alleles, when exposed to mothers with lesser histories of maltreatment, fair better in terms of regulation than their non-susceptible counterparts. Infants with the "risk" DAT1 (presence of the 9-repeat) allele, when exposed to a parent with a greater history of maltreatment, tended to fare worse in terms of regulation behaviours. These differences in genetic interaction models suggest that an adaptive *variation* in genetic vulnerability and vantage-sensitivity, across an infant's genome, can increase the possibility for optimal self-regulation outcomes, whether the environment is favourable or less favourable (i.e., lower versus higher history of maternal maltreatment, respectively).

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DRD2, DAT1, COMT, and OXTR Genes as Potential Moderators of the Relationship between Maternal History of Maltreatment and Infant Emotion Regulation

Modifying and coping with varying levels of emotion has been referred to as emotion regulation (Rothbart & Derryberry, 1981). A crucial aspect of infant socioemotional development involves acquiring strategies to manage emotional arousal. Mother's history of maltreatment and trauma have been linked to some child outcomes related to emotion regulation difficulties, such as conduct problems, affective symptoms, hyperactivity, and peer problems (i.e., Collishaw, Dunn, O'Connor, and Golding, 2007; Miranda, de la Osa, Granero, & Ezpeleta, 2013; Roberts, O'Connor, Dunn, & Golding, 2004). In terms of biological influence, dopamine (DRD2, DAT1), catechol-o-methyltransferase (COMT), and oxytocin (OXTR) genes have been linked to attention, behaviour, and emotion regulation (e.g., Beaver & Belsky, 2012). However, no studies have investigated the connections between maternal maltreatment history, and variations in dopamine and oxytocin genes, with infant emotion regulation. The current study addresses these gaps, evaluating the interaction of selected genes (DRD2, DAT1, COMT, OXTR) as they interact with maternal history of childhood maltreatment to predict infant emotion regulation.

Emotion Regulation in Infancy

Emotion regulation involves the ability to exert self-control and modulate emotional arousal to achieve goals and adapt to the social environment (Thompson, 1994). Emotion regulation processes can be understood as a set of behaviours, skills, and strategies used to modulate, inhibit, and enhance emotion related experiences, whether these processes are conscious or unconscious, reactive or effortful (Calkins, Gill, Johnson, & Smith, 1999).

Importantly, the ability to regulate emotions has positive consequences for exploration and social competence (Fox, 1994).

Emotion regulation strategies begin to develop in infancy. During early stages of development, infants utilize external support to regulate arousal. Specifically, they rely on their caregivers' strategies to regulate, since they are not yet equipped to regulate emotions on their own (Kopp, 1989). Infants learn to respond to distress by signalling to their caregivers their need for regulatory help. Strategies used to engage caregivers include seeking physical comfort, attracting assistance from caregivers, and directing attention toward caregivers (Calkins et al., 1999; Grolnick, Bridges, & Connell, 1996).

Self-regulation strategies, independent of external caregiver support, rapidly develop during the early years of life, improving slowly into adulthood (Eisenberg, Spinrad, & Eggum, 2010). Researchers have found infant temperament to be an aspect of emotion regulation; for instance, in a sample of 10-month-old infants, "fussy" infants use more self-comforting than infants experiencing higher levels of distress (i.e., Stifter & Braungart, 1995). However, Calkins and Johnson (1998) discuss that, by 18 months, temperamental frustration distress (i.e., measured as vagal tone in their study) may be more indicative of physiological regulation than emotional reactivity.

Changes from external to internal sources of regulation are suggested to occur in correspondence with motor and cognitive development (i.e., goal-directed behaviour; Kopp & Neufield, 2003). By the end of the first year, infants are more active in attempting to control arousal (Kopp, 1982). They begin to engage in organized motor behaviour to reach, redirect, and self-soothe in response to the environment. For instance, infants can actively redirect attention from distressing to non-distressing stimuli (Derryberry & Rothbart, 1988), which can effectively

alleviate emotional arousal. After the first two years of life, individual differences of self-regulation appear relatively stable (Eisenberg et al., 2010). Within the literature, typical paradigms used to measure self-regulation include physiological measures such as vagal tone, and observed behaviours (i.e., attention, self-comforting behaviours; Stifter & Braungart-Rieker, 1995), during and/or after stress and/or frustration tasks (i.e., Toy Frustration Task, TFT; Braungart-Rieker & Stifter, 1996).

According to longitudinal studies, maladaptive emotion regulation in infancy is related to adjustment problems in childhood, including externalizing (Eiden, Edwards, & Leondard, 2007) and internalizing problems (Feldman, 2009). Measures of regulation, including effortful control, have been negatively associated with externalizing problems in toddler and preschool years (Eiden, Colder, Edwards, & Leonard, 2009; Hill, Degnan, Calkins, & Keane, 2006; Kochanska, Barry, Aksan, & Boldt, 2008). For instance, reactive (i.e., emotionally driven) aggression is associated with poor emotion regulation after controlling for proactive (i.e., unprovoked, unemotional) aggression (Marsee & Frick, 2007). Furthermore, earlier self-regulation/effortful control has been inversely related to externalizing problems, including ADHD, in middle childhood and adolescence (e.g., Eisenberg et al., 2004; Eisenberg et al., 2010; Gardner, Dishion, & Connell, 2008).

Regulation of affect may be particularly difficult in the context of internalizing problems. Difficulty controlling attention, cognitions, and emotions is related to an enhanced attentional bias toward negative stimuli (Waters, Mogg, Bradley, & Pine, 2008), which can impact the development of anxiety and depression. However, effortful control may allow for flexible and adaptive behaviour in the face of challenging scenarios and may prevent internalizing problems. For instance, effortful control is negatively related to separation distress at 18 and 30 months

(Spinrad et al., 2007). In addition, effortful control has been inversely associated with internalizing problems in childhood (Eisenberg et al., 2004).

Maternal Maltreatment History and Emotion Regulation

Most of the evidence linking maternal psychopathology and infant self-regulation has focused on maternal depression (Brand & Brennan, 2009; Brummelte & Galea, 2010). Less attention has been given to the impact of maternal trauma on infant regulation (Enlow et al., 2011). Several studies, however, indicate that maternal posttraumatic stress disorder (PTSD) is linked to child self-regulation (Enlow et al., 2009; Chemtob et al., 2010). Enlow et al. (2011) assessed maternal PTSD symptoms and emotion regulation in 6-month-olds. They found that mothers' PTSD symptoms predicted poorer emotion regulation in infants, including poorer ability to recover from distress during the still-face paradigm (SFP) and, based on mothers' reports, slower rate of recovery from distress in daily life. Maternal PTSD symptoms also predicted infant internalizing, externalizing, and dysregulation symptoms at 13 months. Chemtob et al. (2010) found that children with mothers who had PTSD and depression tended to have more behaviour problems and worse emotion regulation than children with mothers who had only depression or neither disorder. In addition, Enlow et al. (2009) found that infants with mothers who had high levels of perinatal traumatic stress had poorer autonomic nervous system (ANS) recovery during the reunion after the still face episode, than infants with mothers who had low levels of perinatal traumatic stress. These studies suggest an important link between maternal posttraumatic stress and infant emotion regulation.

A mother's history of abuse in childhood influences her functioning in adulthood in several ways. The implications of child abuse on development are well known, leading to adverse consequences for neurobiological (Cicchetti, 2002), cognitive (Koenen, Moffitt, Caspi, Taylor, &

Purcell, 2003), and social (Hill et al., 2001; Nelson et al., 2002) functioning, which persist into adulthood. Furthermore, the effects of early abuse elevate risk of psychiatric disorders (i.e., depression, suicidal ideation, anxiety disorders, etc.) and substance abuse (Brown, Cohen, Johnson, & Smailes, 1999; Fergusson & Lynskey, 1997; Kendler et al., 2000; Schuck & Widom, 2001). Indeed, research suggests that emotional abuse experienced in childhood predicts difficulties with emotion regulation in adulthood (Kuo, Khuory, Metcalfe, Fitzpatrick, & Goodwill, 2014). Mothers with childhood abuse histories may not have learned how to appropriately self-regulate, given that abusive environments are characterized as emotionally invalidating, and healthy, predictable, and consistent emotional expressions are not usually modelled (Kuo et al., 2014). Consequently, these mothers, not likely utilizing adaptive emotion regulation strategies themselves, may not be effective in helping their infants regulate, nor model appropriate self-regulation strategies to their infants.

From a parenting perspective, it is likely that symptoms of posttraumatic stress (i.e., avoidance, hyperarousal, irritability, re-experiencing traumatic events, etc.) may interfere with a mother's ability to provide sensitive and responsive care (Enlow et al., 2011). Furthermore, other symptoms associated with history of traumatic experiences, including difficulty modulating emotions, difficulty interpreting emotions, and disruptions in attention and memory (Hien, Cohen, & Campell, 2005), may lead to disruptions in parenting, including avoidant, intrusive, irritable, and hostile parenting behaviours (Enlow et al., 2011). Children of traumatized caregivers exhibit attentional bias to danger and distress, avoidance of and withdrawal from conflicts (Schechter et al., 2007), and poorer emotion regulation (Elliot et al., 2014). Possibly, unresolved trauma may impede a mother's ability to accurately identify (Elliot et al., 2014) and respond sensitively to an infant's emotional cues (Schechter et al., 2012), and help the infant

learn to appropriately regulate emotions.

Parental experiences of child abuse have been found to result in elevated risks for mental illness and adjustment problems in children of the subsequent generation, in both selected (e.g., single parent, low SES; parental/offspring mood disorders; parental history of sexual abuse/assault; Bifulco et al., 2002; Brent et al., 2004; Roberts et al., 2004) and community samples (Collinshaw et al., 2007). The intergenerational transmission of psychological risk associated with maternal childhood abuse (Collishaw et al., 2007) may explain such a link. That is, mothers who have experienced maltreatment and/or abuse will be more likely to endure challenges with a variety of other risk factors, including parental mental illness, family instability, and other stressful events, which places a child at increased risk to develop adjustment problems. In a study by Collinshaw et al. (2007), children of mothers with histories of child abuse were more likely to experience negative life events, including changes in family composition, separation from parents, and physical assaults. These negative life events would also greatly influence the child's development. Therefore, risk factors associated with history of maltreatment in mothers may account for the link between maltreatment history and infant emotion regulation.

Only few studies have investigated the relationship between maternal history of maltreatment and its influence on child psychological outcome(s). For instance, studies conducted with the Avon Longitudinal Study of Parents and Children demonstrated strong associations between maternal history of sexual abuse and offspring adjustment problems, including conduct problems, emotional symptoms, hyperactivity, and peer problems, at ages 4 (Roberts et al., 2004) and 7 (Collishaw et al., 2007). Miranda, de la Osa, Granero, and Ezpeleta (2013) also found a link between maternal history of child abuse and intimate partner violence,

and child psychopathological problems. No known studies, however, have looked at the link between maternal childhood maltreatment history and infant emotion regulation in a community sample. The question remains whether the occurrence of childhood maltreatment, even at relatively low levels, in a mother's past has influence on her infant's emotion regulation behaviour.

Genetic Influences on Emotion Regulation

Emotion regulation has a hereditary basis, evidenced by behavioural genetic and molecular genetic research. For instance, Lemery-Chalfant, Doelger, and Goldsmith (2008) found a shared additive genetic influence that accounted for covariance between self-regulation and psychopathology. In addition, in a twin study, Young et al. (2009) found a primarily genetic relation between response inhibition (i.e., stop-go tasks) and behavioural disinhibition (i.e., substance use, novelty seeking, etc.) in 12- and 17-year-olds. Aspects of emotion regulation, including effortful control, attention, and affective problems, have been linked to candidate genes that are implicated in affect synaptic neurotransmitter availability. Genes related to these areas include the serotonin transporter gene (5-HTTLPR), dopamine receptor and transporter genes (DRD2, DRD4, and DAT1), monoamine oxidase A (MAOA), catechol-o-methyltransferase (COMT), and the oxytocin receptor gene (OXTR).

Serotonin is a neurotransmitter that acts as an inhibitor in the central nervous system. It has been related to regulation of mood and emotions through behavioural inhibition and emotional responses in adult samples (Sourbie, 1986). In individuals with the short allele (s), as opposed to the long allele (l), there is less transcription and less protein production (Greenberg, Tolliver, Huang, Li, Bengal, & Murphy, 1999), which can lead to low serotenergic function. In the case of the serotonin transporter gene, 5-HTTLPR has been related to regulation of mood and

attention (Lucki, 1998), executive attention involved in self-regulation (Posner, Rothbart, & Sheese, 2007), emotion regulatory capacities in children (Kochanska, Philibert, & Barry, 2009), and negative emotionality in 2-month-olds (Auerbach et al., 1999).

Dopamine has been suggested to be an underlying neurotransmitter that influences behavioural system of approach in adults (Cloninger, 1987). It is associated with active exploration and approach toward novel stimuli, behaviours favourable for adaptive infant self-regulation (Rothbart & Derryberry, 1981), as well as response in reward situations (Panskepp, 1986). Several dopamine genes have been linked to outcomes that may be related to emotion regulation. For instance, DRD2 has been significantly associated with alcoholism (Ferguson & Goldberg, 1997), conduct disorder (Lu, Lee, Ko, & Lin, 2001), and affective problems (Mills-Koonce et al., 2007), areas associated with emotion regulation (i.e., Klanecky, Woolman & Becker, 2015; Cappadocia, Desrocher, Pepler, & Schroeder, 2009; Fussner, Luebbe, & Bell, 2015). DRD2 has also been associated with novelty seeking/reward dependence (Noble et al., 1998) and alcohol/drug dependence (i.e., MA dependence; Han et al., 2008). Of note, substance dependence can be considered a maladaptive regulation strategy (i.e., self-medication through negative reinforcement; Blume, Schmaling, & Marlatt, 2000). DRD4 has been found to relate to human personality trait of novelty seeking in adults (Ronai et al., 2001), and avoidant and obsessive personality disorder symptoms (Joyce et al., 2003). Also, DAT1 homozygous 10-repeat genotype has been linked to inattention and hyperactivity-impulsivity symptoms in adolescents (Laucht et al., 2007). Importantly, *attention* is an important aspect of independent emotion regulation strategies, with shifting attention from distressing stimuli to neutral or positive stimuli being an adaptive skill, which may be difficult for individuals with ADHD. More recently, several studies have investigated the influence of dopamine on infant

temperament (Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Lakatos et al., 2000) and self-regulation (Propper & Moore, 2006; Propper et al., 2008). DRD2 (A1+) has been linked to lower infant vagal tone in response to a distressing task, a physiological indicator of poorer emotion regulation (Propper et al., 2008). In addition, DRD4 (exon III) has been related to toddler temperament (i.e., intensity of reaction in toddlers; De Luca et al., 2003), which may also be related to difficulty with self-regulation, where infants with 4/7 genotypes exhibited worse responses to new stimuli than 4/4 genotypes.

Monoamine oxidase A (MAOA) is an enzyme that deaminates norepinephrine, epinephrine, serotonin, and dopamine. MAOA has also been linked to outcomes presumably related to emotion regulation. For instance, MAOA has been related to depression in adults (Du, Bakish, Ravindran & Hrdina, 2004; Meyer et al., 2010), with depressed individuals possessing maladaptive emotion regulation strategies. Also, low MAOA activity genes have been associated with other mental health issues (e.g., ADHD; Kim-Cohen et al., 2006) and antisocial behaviours (Caspi et al., 2002).

Catechol-o-methyltransferase (COMT) is another enzyme that degrades catecholamines. The valine expression of the COMT gene has been related to cognitive tasks assessing executive functioning, such as shifting and response inhibition (Bruder et al., 2005), foundational cognitive functions that are important to self-regulation (Rothbart & Derryberry, 1981). In addition, in a sample of 2-year-olds, the COMT haplotype was related to anticipatory attention, an aspect of early emotion regulation, with valine relating to better performance (Voelker, Sheese, Rothbart, & Posner, 2009).

Finally, oxytocin is a neurotransmitter with central action in the limbic system, forebrain, and automatic centres of the brainstem (Costa et al., 2009). It plays a role in attachment

processes in animals (Insel, 1997) and humans (Carter, 1998), including social approach behaviour (Heinrichs & Domes, 2008). Given the substantial reliance in earlier infancy on caregivers for regulating emotions, oxytocin may have a crucial influence on the developing self-regulation strategies. For instance, effects of oxytocin may have implications for early emotion regulation abilities, like signalling caregivers in times of distress for comfort; in turn, these experiences may be internalized in a system of self-regulation strategies when encountered with future distress (i.e., learning to self-sooth). With regard to oxytocin receptor genes, OXTR polymorphisms have been associated with unipolar depression in adult patients (Costa et al., 2009), temperament (Tost et al., 2010), adult emotion dysregulation (Bradley et al., 2011), and loneliness in adolescents (Lucht et al., 2009).

Overall, the literature indicates specific genes linked to emotion regulation and constructs related to emotion regulation (i.e., temperament, affective problems). These genes included 5-HTTLPR, DRD4, DRD2, DAT1, MAOA, COMT, and OXTR SNPs. Specifically, 5-HTTLPR is related to regulation of mood and attention, executive attention involved in self-regulation, and emotion regulation in children. DRD4 is related to novelty seeking in adults and avoidant and obsessive personality disorder symptoms, where emotion regulation is likely related to these outcomes. DRD2 has been linked to novelty seeking/reward dependence and alcohol/drug dependence, aspects of possible maladaptive emotion regulation strategies. DAT1 has been linked to inattention and hyperactivity-impulsivity symptoms in adolescents, where attention is an important aspect of emotion regulation. MAOA has been linked to depression and other mental health issues (i.e., ADHD), conditions where emotion regulation is considered less adaptive. COMT has been linked to executive functioning, such as shifting and response inhibition, foundational cognitive functions that are important to self-regulation. Finally, OXTR

has been associated with depression, temperament, and adult emotion dysregulation. In a comprehensive effort to examine genetic influence on infant emotion regulation, these genes were selected a priori to investigate GXE interactions on emotion regulation. However, I encountered amplification issues in genotyping 5-HTTLPR, DRD4, and MAOA (see method section for further explanation), leading to inclusion of DRD2, DAT1, COMT, and OXTR SNPs.

Potential Covariates of Emotion Regulation

Maternal depression. Children with mothers who are depressed tend to experience a range of socioemotional difficulties (Campbell et al., 2004) and, in particular, less effective emotion regulation strategies (Hoffman, Crnic, & Baker, 2006). Mothers who are depressed postnatally exhibit less sensitive caregiving with their infants (Hatzinkolaou & Murray, 2010), have poor communication with their children (Cox, Puckering, Pound, & Mills, 1987), exhibit low warmth (Cummings, Keller, & Davies, 2005) and high criticism (Rogosch, Cicchetti, & Toth, 2004), and are less emotionally responsive to their infants' bids for attention and cues for assistance (Cox et al., 1987; Righetti-Veltema, Conne-Perreard, Bousquet, & Manzano, 2002). Depressed mothers may experience difficulties with their own emotion regulation abilities, thereby modeling inadequate regulation strategies to their children (e.g., Feldman & Eidelman, 2007). Furthermore, depressed mothers may not have the skills to teach and reward their child's positive emotion regulation strategies (Silk, Shaw, Skuban, Oland, & Kovacs, 2006), which may reduce the child's development of adaptive strategies (Hoffman et al., 2006). Furthermore, similar to maternal history of maltreatment, there are several other factors, aside from parenting, associated with maternal depression that might impede development of emotion regulation in infants (e.g., genetics, poor emotional control, disruptions in family composition). Given the

link between maternal depression and infant emotion regulation, self-reported maternal depression is included as a covariant in the current study.

Maternal sensitivity. Parenting is a source of influence on the development of emotion regulation (Eisenberg et al., 2010). Infants learn about modulating distress with the help of their caregivers (Kopp, 1989). Parents influence how infants interpret situations in the way they help alleviate negative emotions, reinforce positive emotions, and structure the environment in which infants experience emotion (Thompson, 1994). Over time, infants may eventually internalize strategies and processes used by caregivers as regulators of their arousal (Kopp, 1982). That is, these early experiences may set a foundation for the development of self-regulation (i.e., how to independently manage emotions). Various aspects of parenting have been linked to emotion regulation, including parenting styles (e.g., authoritarian, negative, and punitive parenting; Gartstein & Fagot 2003; Hofer, Eisenberg, & Reiser, 2009; Kochanska & Knaack, 2003), maternal scaffolding (Lengua, Honorado, & Bush, 2007), attachment (Kochanska et al. 2009), and maternal sensitivity (Propper et al., 2008).

Maternal sensitivity refers to timely and effective responses to infant signals of distress and bids for attention (Pederson & Moran, 1996). Sensitive and responsive maternal behaviours effectively reduce negative emotions in the child and have been found to play a crucial role in the infant's ability to regulate their own emotions (Crockenberg & Leerkes, 2008). In several studies, sensitive and responsive parenting is related to lower negativity and more regulatory behaviours (e.g., Kochanska, Murray, & Harlan, 2000; Propper et al., 2008). In addition, maternal interactions that are categorized as warm and supportive have been associated with fostering emotion regulation skills (Eisenberg et al., 2010), particularly with regard to self-

regulation (Eiden et al., 2007). Given the link between maternal sensitivity and infant emotion regulation, maternal sensitivity is included as a potential covariate in the current study.

Gene by Environment (GXE) Interactions

In the past few years, researchers have begun to examine 'Gene by Environment' (GXE) interactions that predict emotion regulation in infancy (e.g., Kochanska et al., 2009; Propper et al., 2008). A GXE interaction occurs when genotype moderates an environmental factor, or when some environmental experience moderates the effect of genotype on a mental or physical outcome (i.e., phenotype). In line with a diathesis-stress model, certain variants of candidate genetic polymorphisms have been considered risk factors in the development of maladaptive emotion regulation (e.g., short allele of 5-HTTLPR), whereas others have been considered protective (e.g., homozygous long alleles of 5-HTTLPR). However, some of these "risky" genes have been linked to even better developmental outcomes than "protective" genes, only when paired with opportune environmental circumstances (i.e., high maternal sensitivity) or the absence of adversity (i.e., no maltreatment). Belsky et al. (2009) termed this phenomenon *genetic plasticity*, in which plasticity genes increase an individual's susceptibility to environmental influence, in a '*for-better-and-for-worse'* manner.

An individual possessing plasticity genes, therefore, would be most susceptible to environmental influences, be they positive or negative, which would influence psychological outcomes positively or negatively, respectively. This view is consistent with a "differential-susceptibility" model (Beaver & Belsky, 2012), rather than a diathesis-stress model of environmental action. There is also a "vantage-sensitivity" model (Pluess & Belsky, 2013) to consider, which essentially acts in the opposite direction of a diathesis-stress model. Vantage sensitivity reflects a variation in response to exclusively *positive* experiences, as a function of

individual endogenous characteristics (i.e., genetic composition). The gene-environment interaction models depend greatly on the interplay of the specific gene, environmental factor, and outcome of interest.

To illustrate genetic plasticity for emotion regulation, consider the following findings involving the genes that are the focus of the present research. Consistent with the "differential susceptibility" model, Taylor et al. (2006) found that adults with the 5-HTTLPR s/s allele had more depressive symptoms than other allelic variants when exposed to early adversity and recent negative events, and fewest depressive symptoms, compared to other genotypes, when exposed to a supportive childrearing environment or recent positive experiences. Kuepper et al. (2012) also found that the short allele of 5-HTTLPR was associated with overall increased reactivity to environment, whether positive or negative. Specifically, high and low life satisfactions were associated with number of positive and negative life events, respectively, in S-allele carriers only. Also, for women, neuroticism was higher and lower for S-allele carriers when preponderance of life events was negative and positive, respectively.

Consistent with the "differential susceptibility" model, genetic plasticity has also been demonstrated in dopamine genes. For DRD4, Bakermans-Kranenburg and van IJzendoorn (2006) found that maternal sensitivity at 10 months predicted externalizing problems more than 2 years later for children with the 7-repeat allele. Children who carried the 7-repeat allele and experienced insensitive mothers demonstrated the most externalizing behaviour, whereas children with this allele and highly sensitive mothers demonstrated the least externalizing behaviour. For DRD2, Mills-Koonce et al. (2007) found that infants with the A1+ allele who experienced more and less sensitive mothers had fewer and more affective problems at age three, respectively, compared to other genotypes. For DAT1, Laucht et al. (2007) found that 15-year-

olds with the homozygous 10-repeat genotype exhibited the most and least inattention when living in high and low psychosocial adversity, respectively. Other studies have proposed association between the 10-repeat allele and ADHD symptoms and independent association with poorer performance in selective attention and response inhibition in both high and low risk samples (Cornish et al., 2005). Conversely, neuroimaging studies in adults with the 10-repeat allele have shown a more efficient neural response in the prefrontal cortex during working memory tasks (Bertolino et al., 2006; Caldu´ et al., 2007). Variations in DAT1 behavioural effects may result from differences in outcomes and/or populations being studied.

With regard to COMT, Nederhof, Belsky, Ormel, and Oldehinkel (2012) found that COMT genotype suggests diathesis-stress rather than differential susceptibility when looking at its interaction with parental divorce on externalizing problems in adolescence. That is, the A-carriers (i.e., Met), rather than G/G carriers (i.e., Val), only experienced susceptibility to *negative* environmental circumstance (i.e., parental divorce). However, there are several other studies that indicate differential susceptibility for the "G" or Val allele (e.g., Caspi et al., 2005; Conway, Hammen, Brennan, Lind & Najman 2010), which may relate to differential environmental influences. This may indicate that some genotypes are more sensitive to some contextual exposures and other genotypes are more sensitive to others (Nederhof et al., 2012). Therefore, an investigation of COMT genetic plasticity variants will be partly exploratory in the current study.

Also consistent with the "differential susceptibility" model, MAOA acts as a plasticity gene. Kim-Cohen et al. (2006) found that 7-year-old boys with low MAOA-activity variant exhibited more mental health issues (i.e., ADHD symptoms) if they also suffered abuse, but fewer problems if they had not, compared to boys with the high-MAOA-activity variant. In

addition, Caspi et al. (2002) showed that males with the less active version of MAOA genotype were most antisocial in adulthood when they also experienced maltreatment in childhood, but engaged in the least amount of antisocial behaviour when not exposed to child maltreatment.

Lastly, Bradley et al. (2011) investigated the impact of childhood maltreatment and OXTR, and their interaction, on emotional dysregulation in adulthood in a low-income African American sample. There was a significant interaction between OXTR (rs53576) and childhood maltreatment on emotional dysregulation. That is, G/G carriers who were exposed to abuse had high levels of emotional dysregulation; however, G/G carriers who were not abused experienced adequate emotion regulation, with levels similar to A/A and A/G carriers. Therefore, differential susceptibility was not demonstrated in this study. This could have occurred because the entire sample was low-income, which is an environmental risk factor for many psychological outcomes. Socioeconomic status of this sample may have limited G/G carriers without abuse from having superior emotion regulation than other genotypes. In another study, Thompson, Parker, Hallmayer, Waugh, and Gotlib (2011) examined the interaction of OXTR (rs2254298) and quality of parental environment in predicting psychosocial functioning in girls. Adverse parental environment, operationalized as the mother's history of major depressive disorder, interacted with OXTR to predict daughters' symptoms of depression and anxiety. Girls with the A/G allele and a mother with a history of depression had highest levels of depression and anxiety; however, they appeared to have lowest symptom levels if their mothers did not have a history of depression compared to other genotypes (although this was not tested statistically). This may indicate genetic plasticity of the A/G variant of the OXTR gene, which is contrary to findings for the G/G carriers in Bradley et al.'s (2011) study. Again, contrary findings may be related to variant specificity for different environmental contexts (i.e., abuse verses maternal

depression). Following these inconsistencies, an investigation of OXTR plasticity variants will be exploratory.

A *composite measure* of genes from significant GXE interactions has been found to provide an even stronger demonstration of genes moderating environmental effects (Sonuga-Barke et al., 2009). Beaver and Belsky (2012) created a cumulative genetic plasticity index of 5 putative plasticity alleles: 10R allele of DAT1, A1+ allele of DRD2, 7R allele of DRD4, short allele of 5-HTTLPR, and 2R/3R alleles of MAOA. They examined the moderating effect of the resultant index (ranging from 0 to 5) and parenting on adolescent self-regulation. Consistent with what was expected, based on the differential susceptibility model, the more plasticity alleles carried, the more and less self-regulation manifested under supportive and unsupportive parenting conditions, respectively; however, this result was only the case for males. According to Beaver and Belsky (2012), the composite measure allows for the possibility of examining additive genetic effects. The majority of the genes reviewed in their study are involved in dopaminergic and/or serotonergic activity, which raises the possibility that these genes function collectively to make an individual susceptible to positive and negative environmental circumstances by influencing sensitivity to pleasure and rewards, or displeasure and punishment (Belsky & Pluess, 2009; Beaver & Belsky, 2012).

Gene-environment studies reviewed here did not employ statistics recommended by Roisman, Newman, Fraley, Haltigan, Groh, and Haydon (2012) to determine type of GXE interaction model (i.e., differential susceptibility, vantage sensitivity, diathesis stress). This leaves the reviewed studies' conclusions to be uncertain, with a necessity for researchers to re-evaluate such GXE interactions using Roisman et al. (2012) criteria. The current study is one of few to examine GXE interactions with this higher level of statistical rigour. In addition, the vast

majority of the studies reviewed were focused on older children and adolescents, whereas the current study investigates GXE in infants. Presumably, environmental influence is even more influential during infancy than childhood/adolescence, as the infant's brain has a greater propensity for plasticity in response to favourable or unfavourable environmental conditions (Cirulli, Berry, & Alleva, 2003). Therefore, the current study will address early GXE interactions during a critical time for emotion regulation development (i.e., infancy) where the individual may be particularly susceptible to environmental influence.

The Current Study

To my knowledge, no study has looked at COMT or OXTR polymorphisms, as they interact with maternal maltreatment history to predict emotion regulation in infants. Furthermore, no study has examined these five genetic markers together (DRD2, DAT1, COMT, OXTR rs53576, and OXTR rs2254298)[1] in the context of GXE cumulative genetic indices. In addition, no study has investigated cumulative risk, genetic plasticity, or vantage sensitivity indices, interacting with maternal maltreatment history to predict infant emotion regulation. First, I examine specific genotypes of candidate gene polymorphisms to predict emotion regulation behaviour. Second, I examine maternal maltreatment history as it predicts emotion regulation. Third, I test the interaction of each genetic polymorphism with maternal maltreatment history as it predicts emotion regulation behaviour. Maternal depressive symptoms are controlled for in each instance. Following differential susceptibility criteria (Roisman et al., 2012; described in further detail in analysis section below), genes are classified as risk, plasticity, or vantage sensitivity genes. Next, I test whether a composite measure of genetic risk

[1] Genotyping the complete sample for MAOA, DRD4, and 5HTTLPR was unsuccessful, likely due to buccal cell degradation. Several attempts were made to repeat PCR amplification to no avail; therefore, these markers were removed from the current study.

(cumulative genetic risk index score) interacts with maternal maltreatment history in predicting regulation. I test whether a composite measure of genetic plasticity (cumulative genetic plasticity index score) interacts with maternal maltreatment history in predicting regulation. Then, I test whether a composite measure of genetic vantage sensitivity (cumulative vantage sensitivity index score) interacts with maternal maltreatment history in predicting regulation. See Table 1 for a description of candidate gene polymorphisms and polymorphism-based comparison groups, with risk/susceptibility/vantage sensitivity genes listed.

Hypotheses. In examining genotypes with maternal maltreatment history, I expect there to be significant interactions between gene variants and maternal maltreatment history to predict infant emotion regulation. Through evaluating GXE interactions using Roisman et al.'s (2012) statistical criteria, I will determine whether genes follow diathesis-stress, differential susceptibility, or vantage sensitivity models to environmental factors. In a diathesis-stress model, infants possessing "risk" genes would have poor emotion regulation when mothers score high on maternal history of maltreatment. Along the lines of the *for-better-and-for-worse* effect of "plasticity" genes (Belsky et al., 2009), infants possessing plasticity genes are expected to exhibit very good and poor emotion regulation when mothers score low and high, respectively, on maternal maltreatment history. In a vantage sensitivity model, infants with "vantage sensitivity" genes would have very good emotion regulation with mothers who score low on maternal history of maltreatment.

Finally, since individual genes have a small effect on a given outcome (Harlaar et al., 2005), I hypothesize that the higher an infant's cumulative genetic risk index score, the stronger the effect of high scores of maternal maltreatment history on poor emotion regulation (i.e., diathesis-stress). The higher an infant's cumulative genetic plasticity index score, the stronger

the effect of low and high maternal maltreatment history on positive and worse emotion regulation, respectively (i.e., differential susceptibility). The higher the vantage sensitivity index score, the stronger the effect of low maternal maltreatment on positive emotion regulation (i.e., vantage sensitivity).

Method

Participants

Participants were a community sample of mother-infant dyads recruited from Ontario Early Years programs and from postings and in-person "Baby Time" convention shows in the Greater Toronto Area (GTA; Pereira et al., 2012, Atkinson et al., 2013). Participants were included if infants were healthy, with no major developmental disorders, and pregnancy was over 32 weeks. Mothers in this study were 18 or older at the time of the infant's birth, spoke English fluently, and had no hormonal disorders. This is a demographically low risk sample. This sample is part of a larger longitudinal study, the Toronto Longitudinal Cohort (TLC), which consists of 314 mother-infant dyads. This study examines data collected during a home visit, where mother-infant dyads participated in a Toy Frustration Task (TFT; Braungart-Rieker & Stifter, 1996), which was scored for emotion regulation.

Of the 314 dyads in the larger study, 193 dyads participated in the video-recorded Toy Frustration Task (TFT). This subsample is much smaller than the larger study sample because we began videotaping part way through the study. This smaller sample included 51.8% female infants. At the time of the home visits, infants were approximately 15 months old (M = 15.41months; SD = 1.00) and mothers ranged from 21 to 46 years (M = 33.03 years; SD = 4.67). The majority of the sample was Caucasian (72.3%), with a smaller proportion of Asian (10.1%), Afro-Canadian (3.9%) and "other" ethnicities (13.6%). The majority of mothers were highly educated, with post-graduate (24.5%), undergraduate (45.3%), community college (22.2%), secondary school (7.1%) and primary school (0.9%) as their highest level of education. Family income was as follows: >$200, 000 (23.7%), $150,000-200,000 (18.5%), $114,000-150,000

(22.2%), $92,000-114,000 (16.9%), $70,000-92,000 (10.1%), $35,000-70,000 (5.3%), and $20,000-35,000 (3.2%).

From the N = 193 sample, there were 21 missing or incomplete BDI questionnaires, and 28 participants that could not be genotyped because DNA samples failed to amplify, reducing the sample, with all study variables available, to 144 dyads. In order to not limit sample sizes for a particular gene-environment interaction because of missing data from another gene, the current study consists of samples that represent each GXE analysis. The samples for each GXE analysis are as follows: DRD2 (N = 157), DAT1 (N = 147), COMT (N = 157), OXTR rs53576 (N = 158), and OXTR rs2254298 (N = 159). These subsets of infant-mother dyads, compared to the sample of 314 dyads, did not differ significantly on infant emotion regulation, DRD2, DAT1, COMT, OXTR SNPs, CTQ, or BDI, or majority of demographic variables (Table 2). However, infants in the DRD2 (N = 157) sample were significantly younger, with a higher percentage of females, and had mothers with higher level of education, compared to infants in the larger sample. Infants in the COMT (N = 157) sample were significantly younger and had with mothers with higher level of education, compared to infants in the larger sample. Infants in the DAT1 (N = 147), OXTR rs53576 (N = 158), and OXTR rs2254298 (N = 159) samples were significantly younger with a higher percentage being female, compared to infants in the larger sample (all aforementioned statistics provided in Table 2).

Procedure

Two research assistants video recorded mothers and infants interacting during the Toy Frustration Task (TFT; Braungart-Rieker & Stifter, 1996) in the home. After the TFT, mothers completed a questionnaire package, including a demographic information questionnaire, the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996), and the Childhood Trauma

Questionnaire (CTQ; Bernstein & Fink, 1998). Also after the TFT, to assess maternal sensitivity, the two research assistants observed mothers and infants interacting during a free-play and divided attention task over the span of two hours. Mothers were instructed to interact with their children during play with toys (provided by the observers), play with no toys, and to complete questionnaires while the infants were in the room (unattended by observers). After the visit, the observers each described the quality of mother-infant interactions using the MBQS and calculated a sensitivity score (inter-observer reliability was attained).

Demographic information, including maternal and infant age, the infant's gender, maternal and paternal income, and maternal education were also determined during the visit. DNA was obtained from buccal cells of the infants. At the end of the home visit, a research assistant used a swab to collect cells from the inner cheeks of the infants. The research assistant rubbed the end of the swab approximately four times on the inside of each cheek. Then, the tip of the swab was expelled into a tube, which was sealed to protect cells from contamination. Infants and mothers also participated in the Strange Situation Procedure (SSP) one month after the TFT; however, since infants were not assessed for self-regulation in this context, only the TFT was included in the current study.

Measures

Demographic variables. Several demographic variables were gathered from participants and dummy coded. Infant sex was coded as 1= male and 2 = female. Highest level of maternal education was coded as: 1 = primary (grades 1-8), 2 = secondary (grades 9-13), 3 = community college, 4 = university, and 5 = post-graduate degree. Maternal and spousal salary ranges were coded separately, as: 1 = < $20,000, 2 = $20,000-$35,000, 3 = $35,001-$70,000, 4 = $70,001-

$92,000, 5 = $92,001-$114,000, 6 = $114,001-$150,000, 7 = $150,001-$200,000, 8 = > $200,000. Ethnicity was coded as: 1 = White, 2 = other.

Infant regulatory behaviours. Mother-infant dyads participated in a Toy-Frustration Task procedure, which consisted of four episodes lasting 90 seconds each. The four episodes were: 1) the mother engaged the infant with a toy, 2) the mother placed the toy in a clear container with the lid on that was not sealed, while not assisting the infant in regaining possession of the toy, 3) the toy was removed from the container and the infant played with it, and 4) the mother placed the toy in the clear container, sealed the lid shut, and continued to disengage. If the infant cried continuously for 20 seconds, the episode was curtailed. The TFT was videotaped and later coded for independent infant-regulatory behaviours. Since episodes 1 and 3 involved the child simply playing with the toy without any frustrating elements, only episodes 2 and 4 were coded for emotion regulation behaviours, combined to form an emotion regulation composite score. Coders were blind to all other aspects of the study.

Infant self-regulatory behaviours were coded during the TFT. Infants self-regulate by avoiding/withdrawing from distressing stimuli (Rothbart & Derryberry, 1981), self-soothing (e.g., thumb sucking; Rothbart & Derryberry, 1981), and using distraction strategies (e.g., averting gaze; Stifter & Braungart, 1995). Infant's independent regulatory behaviours were coded in terms of the duration of time each behaviour was displayed during episodes 2 and 4. Behaviours that were coded included withdrawing from the task, distracting him/herself, wandering away from the task, orienting to another object, and scanning the environment (see Table 3 for definitions). Twenty percent of the videos were coded by a second coder to ensure inter-rater reliability. The following are reliabilities for each behaviour: Scanning, *ICC* = .69; Withdrawal, *ICC* = .79; Wandering, *ICC* = .83; Orienting to another object, *ICC* = .93; and

Distraction, *ICC* = .74. The mean reliability was *ICC* = .80 and reliability of the composite was *ICC* = .83. Cronbach's alpha was calculated for 10 behavioural items across the two frustration-task episodes (episodes 2 and 4). The Cronbach's alpha of the 10 items was $\alpha = .64$.

Maternal depressive symptoms. Mothers completed the Beck Depression Inventory (BDI-II; Beck, Steer & Brown, 1996). The BDI-II is a self-report inventory consisting of 21 items assessing symptoms and severity of depression on a 4-point rating scale. Scores from the 21 items are summed to form one total BDI-II score. The BDI-II is a reliable questionnaire, as evidenced by high internal consistency for males and females (Bos et al., 2009; Dozois, Dobson, & Ahnberg, 1998). Furthermore, the BDI-II is a valid measure for assessing depressive symptoms of mothers (e.g., Murray & Cooper, 1997). In the current sample, Cronbach's Alpha = .89.

Maternal sensitivity. Maternal sensitivity was assessed using the Maternal Behaviour Q-Set (MBQS). The MBQS is a coding system that provides a rich description of the quality of maternal interaction with the infant (Pederson & Moran, 1996). The MBQS consists of 90 items, with each item describing potential maternal behaviours. Items are sorted into nine piles on a rectangular distribution, in which pile one represents behaviours that are least like the mother and pile nine behaviours that are most like the mother. Each item is assigned a score that corresponds to the pile it is sorted into (i.e., item in pile four receives a score of four). Each maternal sensitivity score is a correlation between the mother's derived score and a prototypical sensitivity score developed by experts in the field (Pederson & Moran, 1995). Scores range from -1.0 (extremely insensitive) to 1.0 (prototypically sensitive). MBQS scores strongly predict infant security scores (Moran, Pederson, Pettit, & Krupka, 1992; Pederson, Moran, Sitko &

Campbell, 1990). For the current study, the MBQS observers attained inter-observer total score agreement of $r = .88$.

Maternal maltreatment history. Mothers completed the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). The CTQ is a self-report inventory consisting of 28 items assessing history of childhood maltreatment. The total score of the CTQ was used to include varied types of maltreatment (i.e., sexual, physical, and emotional abuse and neglect). The CTQ has good psychometric properties for clinical (Bernstein et al., 1994) and community-based populations (Paivio & Cramer, 2004). In the current sample, Cronbach's Alpha = .93.

Genotyping. Extraction and genotyping of the DNA was performed at the Neurogenetics Laboratory at the Centre for Addiction and Mental Health in Toronto, Canada. Four paper buccal swabs were collected from each subject and stored at 4°C in a 15 mL polypropylene tube until extracted. Total genomic DNA was extracted using the Qiagen QIAamp DNA Mini and Blood Mini kit as per manufacturer's instructions with the reagents used prior to the spin steps (Protease, PBS, buffer AL and 95% ethanol) doubled. A total of four single nucleotide polymorphisms (SNPs) across three genes were genotyped using commercially available TaqMan SNP genotyping assays (see Table 4; LifeTechnologies, Burlington, ON). For each reaction, 1 uL of the genomic DNA was amplified as per manufacturer's directions scaled to a total volume of 10 μL in an Applied Biosystems (AB) 2720 thermal cycler. Post-amplification products were analyzed on the AB ViiA7 Real-Time PCR System and genotype calls were determined manually by comparison to six No Template Controls.

For the DAT1 VNTR, 3 μL total genomic DNA was combined with 1X MBI Fermentas PCR buffer containing KCl, 1.5 mM $MgCl_2$ (MBI Fermentas), 0.13 μg each primer (Vandenbergh et al 1992; forward primer labeled with 5' NED fluorescent tag), 10% DMSO

(Sigma-Aldrich), 0.16 mM each dNTP (MBI Fermentas) and 2 U Taq polymerase (MBI Fermentas) to a total volume of 25 μL. The PCR reactions were subjected to an initial denaturation for 5 min at 95°C, followed by 35 cycles of amplification in an AB 2720 (Thermofisher Scientific Burlington, ON) thermal cycler: denaturing for 30 sec at 95°C, annealing for 1 min at 65°C and extension for 30 sec at 72°C, and a final extension at 72°C for 10 min. One microlitre of the PCR product was electrophoresed on an AB 3130-*Avant* Genetic Analyzer as per manufacturer's directions, and product sizes determined by comparison to GeneScan 1200 LIZ size standard using GeneMapper (version 4.0). Genotyping of 10% of samples from each run were replicated for quality control purposed for each marker.

For the current study, 5HTTLPR, DRD4, and MAOA were in the process of being genotyped. However, genotyping the complete sample for these markers was unsuccessful, likely due to buccal cell degradation (Livy, Lye, Jagdish, Hanis, Sharmila, Ler, & Pramod, 2012). Several attempts were made to repeat PCR amplification, using fresh reagents; however, the majority of samples failed to amplify. Therefore, these markers were removed from the current study.

Statistical Analysis

I conducted multiple regressions for each gene, including gene polymorphism, CTQ score, and the gene x CTQ score interaction term as predictors, and composite infant emotion regulation as outcome. The genetic expression of each gene was dummy-coded as either 0 (non-susceptible/vulnerable allelic expression) or 1 (susceptible/vulnerable allelic expression). Dearing and Hamilton (2006) have recommended that predictor variables be centered to reduce multicollinearity and aid in interpretation. The CTQ was centred for each moderation analysis, but centering was not utilized for the genetic binary categorical moderator variables because the

zero value of these moderator variables (i.e., non-susceptible/vulnerable) is a meaningful state (Dearing & Hamilton, 2006). To determine differential susceptibility, criteria from Belsky, Bakermans-Kranenburg, and van IJzendoorn (2007) and Roisman et al. (2012) were employed to test each GXE moderation model. A description of each set of criteria is found below.

A modified version of procedures was conducted for Belsky et al.'s (2007) criteria, in accordance with Roisman et al.'s (2012) suggestions. Predictor variables, including the genetic variation, environmental factor, and GXE interaction term are entered into hierarchical multiple regression to predict the outcome of interest. In graphical format, there must appear to be a "crossover" effect, whereby the two regression lines, which signify susceptibility and non-susceptibility, cross each other, covering both the positive and negative environmental conditions (step 1). Next, the susceptibility factor must be independent of the predictor (step 2) and outcome (step 3) variables. Further, differential susceptibility is supported if the slope for the susceptible group is significantly different from zero and the slope of the non-susceptible group is not significantly different from zero (step 4). If both slopes were significantly different from zero, then contrastive effects, rather than differential susceptibility, would be suggested (Belsky et al., 2007). Finally, by replacing predictor and outcome variables with other variables, the model's specificity could be tested (step 5). However, for the current study, Roisman's et al. (2012) suggestions to follow steps 1 and 2 and to disregard steps 3-5 were followed.

Roisman et al. (2012) developed a set of statistical criteria that need to be fulfilled in a differential susceptibility model. The four criteria are as follows: 1) *Regions of Significance (RoS) on maternal factors:* demonstration that emotion regulation and the proposed plasticity gene are correlated at both high and low ends of maternal variables (bounded by +/-2SD from the mean of CTQ); 2) *Proportion of interaction index (PoI):* ratio of improved outcomes for the

plasticity gene over the sum of improved outcomes and harmful outcomes. PoI values close to 0.50 suggest strong evidence for differential susceptibility. Values closer to 0.00 suggest strong evidence for diathesis–stress. Also, I determined the percentage of population above crossover point. Approximately 16% and 2% of cases should fall 1 and 2 SDs, respectively, above the mean on a normal distribution; 3) *Multilevel model averaged across developmental course*: this criterion will be left out because this is not a longitudinal dataset and we are not completing multiple analyses to risk type 1 error; and 4) *Check linearity of the model:* apparent differential susceptibility effects can be artefacts of imposing a linear predictor model on a nonlinear diathesis–stress phenomenon. It is imperative that the model be checked for linearity.

The cumulative genetic indices vary depending on how many genes are deemed risk genes, plasticity genes, or vantage sensitivity genes. If genes interacted significantly with maternal maltreatment history to predict regulation consistent with a diathesis-stress model, I included these markers in the composite diathesis-stress cumulative risk index. If genes interacted significantly with maternal maltreatment history to predict regulation consistent with a differential susceptibility model, I included these markers in the composite cumulative plasticity index. If genes interacted significantly with maternal maltreatment history to predict regulation consistent with a vantage sensitivity model, I included these markers in the cumulative vantage sensitivity index. For instance, if three of the candidate genes are deemed plasticity genes, and the remaining two are considered risk genes, then an infant can possess a cumulative plasticity score ranging from 0 (no plasticity genes) to 3 (all plasticity genes) and a cumulative risk score ranging from 0 (no risk genes) to 2 (all risk genes).

Results

Descriptive Statistics and Bivariate Correlations

In the main analyses, I report on participants with complete data, as follows: DRD2 (N = 157), DAT1 (N = 147), COMT (N = 157), OXTR rs53576 (N = 158), and OXTR rs2254298 (N = 159)[2]; in this way, sample size in a particular analysis is not limited by missing data from another gene. All genes were in Hardy-Weinberg Equilibrium (Table 5). Correlations, descriptive statistics, and multiple regression estimates for these samples are provided throughout the results section. Mean comparisons of emotion regulation by allelic expressions of each gene are presented in Table 6. Measured variables included genetic polymorphisms (DRD2, DAT1, COMT, OXTR SNPS), emotion regulation, sex of the baby, maternal education, maternal sensitivity, maternal income, spouse's income, ethnicity, and maternal depressive symptoms (i.e., BDI). Bivariate correlations were performed for all study variables (see Tables 7, 8, and 9). Out of all bivariate correlations performed, infant emotion regulation only significantly correlated with maternal depressive symptoms (BDI); therefore, the maternal BDI score was included as a covariant in multiple regression analyses.

Multiple Regression Analyses

Multiple regressions were performed for each gene to determine whether DRD2, DAT1, COMT, OXTR rs53576, and OXTR rs2254298 moderated the effect of CTQ on emotion regulation. Maternal depressive symptom (BDI) score was included as a covariate. Out of all regressions performed, DRD2, DAT1, and COMT significantly interacted with CTQ to predict

[2] Results for the *complete sample* (participants with information for each variable, including each gene; N = 144) are provided in Appendix A. This includes a summary of correlations, descriptive statistics, and multiple regression estimates, with Roisman et al. (2012) statistics and figures, which complement larger samples. Overall, trends in findings of the *larger samples* (N = 147 to 157) were replicated with the *complete sample* (N = 144).

emotion regulation, whereas OXTR SNPs did not. There were no main effects involving OXTR SNPs. Only models with significant interaction terms are tested further. See Tables 6, 7, and 8 for means, standard deviations, and correlations for each sample (i.e., DRD2, DAT1, COMT).

Multiple regression estimates are provided in Table 10 for all genes. The Roisman et al. (2012) differential susceptibility indices for genes that significantly interacted with CTQ are provided in Table 11. In addition, since the current sample had missing data for maternal depressive symptoms, maternal history of maltreatment, and infant emotion regulation, multiple imputations were conducted to compare regular hierarchical multiple regression results to imputed results (see Appendix B). Imputed multiple regression results indicated the same trends as regression analyses from samples that were not imputed. Imputed results were not employed for Roisman et al. (2012) statistics, given the inability to derive relevant parameters from the imputed data.

Belsky et al. (2007) Differential Susceptibility Criteria

Belsky et al. (2007) criteria were tested for DRD2, DAT1, and COMT. A series of linked steps were taken to determine potential differential susceptibility of the models. First, interaction effects were examined. Second, bivariate correlations were estimated between each gene and predictor variable (CTQ), and each gene and outcome variable (emotion regulation). According to Belsky et al. (2007), a lack of association indicates independence of the genetic factor and the predictor, and a possible effect of genetic plasticity. Consistent with this, all gene-CTQ correlations were non-significant.

Graphical representations of the interactions were compared to the prototypical differential susceptibility graph from Belsky et al. (2007). None of the graphs followed a differential susceptibility graphical display (Figures 1 to 4). It appeared that the DAT1 graph represented

dual risk (i.e., negative genetic and environmental influence on outcome), whereas DRD2 and COMT represented contrastive effects (i.e., valence of associations between independent and dependent variables runs in opposite direction at relatively high versus low levels of the moderator variable). That is, the DAT1 graph indicates that DAT1 9-repeat allele (genetic vulnerability) and higher maternal history of maltreatment scores leads to less effective emotion regulation in the infant (diathesis-stress); whereas, with the DAT1 10/10 genotype (protective gene), despite higher maternal history of maltreatment, more effective emotion regulation occurs in the infant. For DRD2 and COMT contrastive effects demonstrated in the graphs, the susceptible genes, A1+ for DRD2 and one Met allele for COMT, led to graphical representations of a cross-over effect. That is, for each gene, the susceptible allele appeared to be associated with more effective emotion regulation strategies in infants whose mothers had lower scores for history of maltreatment, but less effective emotion regulation strategies with mothers who had higher scores of maltreatment. I used the Roisman et al. (2012) criteria for differential susceptibility to further evaluate these graphical representations.

Roisman et al. (2012) Differential Susceptibility Criteria

DRD2 genotype as a moderator of the relation between maternal history of maltreatment and infant emotion regulation. The overall model was significant, F (4, 152) = 4.34, p = .002; adjusted R^2 = .04. Regression coefficients indicate that maternal history of maltreatment, maternal depressive symptoms, and the interaction between maternal history of maltreatment and DRD2 genotype significantly predicted infant emotion regulation. The regions of significance (RoS) on X test revealed significant differences between high and low Z (DRD2 genotype) for values of maternal maltreatment history *below* 7.51 (see Figure 1). Thus, the RoS on X test is more consistent with vantage sensitivity than with differential susceptibility. The

proportion of the interaction index (PoI) was 0.77, which is more consistent with vantage sensitivity than with differential susceptibility. This PoI indicates that a higher proportion of the interaction represents better outcomes from the differential susceptibility effect than worse outcomes from the differential susceptibility effect. The crossover point of the interaction (i.e., the point on maternal history of maltreatment where the regression lines intersect) was 7.51. The PA index represents the proportion of cases scoring above 7.51 on maternal history of maltreatment (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 86%, representative of vantage sensitivity (Pluess & Belsky, 2013). Finally, the nonlinearity test indicated that neither X^2, $t(150) = 1.37$, *ns*, nor ZX^2, $t(150) = -.387$, *ns*, were significant predictors of emotion regulation when included in the model. Findings indicate that DRD2 genotype moderates the relationship between maternal history of maltreatment and infant emotion regulation as a vantage sensitivity interaction.

DAT1 genotype as a moderator of the relation between maternal history of maltreatment and infant emotion regulation. The overall model was significant, $F(4, 142) = 7.74$, $p < .001$; adjusted $R^2 = .16$. Regression coefficients indicate that maternal history of maltreatment, DAT1 genotype, and the interaction between maternal history of maltreatment and DAT1 genotype significantly predicted infant emotion regulation. The regions of significance (RoS) on X test revealed significant differences between high and low Z (DAT1 genotype) for values of maternal maltreatment history *above* -17.45 (see Figure 2). Thus, the RoS on X test is more consistent with diathesis-stress than with differential susceptibility. The proportion of the interaction index (PoI) was 0.04, which is more consistent with diathesis-stress than with differential susceptibility. This PoI indicates that a lower proportion of the interaction represents better outcomes from the differential susceptibility effect than worse outcomes from the

differential susceptibility effect. The crossover point of the interaction (i.e., the point on maternal history of maltreatment where the regression lines intersect) was -17.45. The PA index represents the proportion of cases scoring below -17.45 on maternal history of maltreatment (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 0%, representative of diathesis-stress (Roisman et al., 2012). Finally, the nonlinearity test indicated that neither X^2, $t(140) = 1.02$, *ns*, nor ZX^2, $t(140) = -1.15$, *ns*, were significant predictors of emotion regulation when included in the model. Findings indicate that DAT1 genotype moderates the relationship between maternal history of maltreatment and infant emotion regulation as a diathesis-stress interaction.

COMT genotype as a moderator of the relation between maternal history of maltreatment and infant emotion regulation. The overall model was significant, $F(4, 152) = 5.49$, $p < .001$; adjusted $R^2 = .10$. Regression coefficients indicate that maternal history of maltreatment, maternal depressive symptoms, and the interaction between maternal history of maltreatment and COMT genotype significantly predicted infant emotion regulation. The regions of significance (RoS) on X test revealed significant differences between high and low Z (COMT genotype) for values of maternal maltreatment history *below* 6.79 (see Figure 3). Thus, the RoS on X test is more consistent with vantage sensitivity than with differential susceptibility. The proportion of the interaction index (PoI) was 0.74, which is more consistent with vantage sensitivity than with differential susceptibility. This PoI indicates that a higher proportion of the interaction represents better outcomes from the differential susceptibility effect than worse outcomes from the differential susceptibility effect. The crossover point of the interaction (i.e., the point on maternal history of maltreatment where the regression lines intersect) was 6.79. The PA index represents the proportion of cases scoring above 6.79 on maternal history of

maltreatment (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 84.7%, representative of vantage sensitivity (Pluess & Belsky, 2013). Finally, the nonlinearity test indicated that neither X^2, $t(150) = -.39$, *ns*, nor ZX^2, $t(150) = 1.15$, *ns*, were significant predictors of emotion regulation when included in the model. Findings indicate that COMT genotype moderates the relationship between maternal history of maltreatment and infant emotion regulation as a vantage sensitivity interaction.

Cumulative genetic composites. Since no genes interacted with CTQ in a differentially susceptible manner, a cumulative susceptibility composite score was not derived. In addition, only the DAT1 by CTQ interaction was classified as diathesis-stress, thus a cumulative risk composite score was not derived. The DRD2 and COMT by CTQ interactions were classified as vantage-sensitivity. In terms of a cumulative "vantage sensitivity" index (CVS index), each participant received a score of 0, 1, or 2 (i.e., no vantage genes, 1 vantage gene, or 2 vantage genes). I ran a multiple regression analysis, with maternal depressive symptoms (as covariate), maternal history of maltreatment, CVS index, and the CVS index by maternal history of maltreatment interaction term as predictors of emotion regulation. The overall model was significant, $F(4, 150) = 6.638$, $p < .001$; adjusted $R^2 = .13$. The regression coefficients indicate that maternal history of maltreatment, maternal depressive symptoms, and the interaction between maternal history of maltreatment and CVS index significantly predicted infant emotion regulation.

To test this model on Roisman's et al. (2012) criteria, the CVS index was centred to convert it to a continuous measure. The regions of significance (RoS) on X test revealed significant differences between high and low Z (CVS index) for values of maternal maltreatment history above and below 7.40 (see Figure 4). This RoS on X test is more consistent with a

contrastive effect, rather than differential susceptibility, particularly because the slope of the 'non-susceptible (i.e., -1SD) line is significant and the slope of the 'susceptible (i.e., +1SD) line is not significant. The proportion of the interaction index (PoI) was 0.76, which is more consistent with vantage sensitivity than with differential susceptibility. This PoI indicates that a higher proportion of the interaction represents better outcomes from the differential susceptibility effect than worse outcomes from the differential susceptibility effect. The crossover point of the interaction (i.e., the point on maternal history of maltreatment where the regression lines intersect) was 7.40. The PA index represents the proportion of cases scoring above 7.40 on maternal history of maltreatment (i.e., those experiencing better outcomes from the differential susceptibility effect). The PA was 85.7%, representative of vantage sensitivity (Pluess & Belsky, 2013). Finally, the nonlinearity test indicated that neither X^2, $t(148) = .70$, *ns*, nor ZX^2, $t(148) = .56$, *ns*, were significant predictors of emotion regulation when included in the model. Although the regions of significance were significant at both high and low CTQ scores, the overall pattern of findings, including the POI and PA index, indicate that CVS index moderates the relationship between maternal history of maltreatment and infant emotion regulation as a vantage sensitivity interaction. Overall, this result depicts that, with more vantage alleles and lower scores on maternal history of maltreatment, infants will have the most adaptive emotion regulation behaviour, whereas infants with fewer vantage alleles and lower scores on maternal history of maltreatment will have less adaptive emotion regulation behaviour. Even though this was not, overall, a differential susceptibility finding, the RoS was significant at the higher end of CTQ scores, indicating that, with higher scores on maternal maltreatment history combined with more susceptibility alleles, the infant has less adaptive emotion regulation behaviours, whereas

infants with fewer susceptibility alleles and higher scores on maternal maltreatment history fair better in terms of emotion regulation.

Discussion

The goal of the present study was to investigate interactions between genetic polymorphisms (DRD2, DAT1, COMT, and OXTR SNPs) and maternal history of maltreatment to predict infant emotion regulation behaviour. Maternal history of maltreatment was explored as an environmental factor, given the validated positive association between maternal history of trauma/maltreatment and infant emotion regulation difficulties (Chemtob et al., 2010; Enlow et al., 2009; Enlow et al., 2011). Specific genes were investigated in the current study, given that dopamine (e.g., Mills-Koonce et al., 2007; Laucht et al., 2007), catechol-o-methyltransferase (e.g., Bruder et al., 2005), and oxytocin (e.g., Bradley et al., 2011) genes have been linked to outcomes related to emotion regulation. This is the first study to examine infant genes by maternal maltreatment history interactions as they influence infant emotion regulation. Furthermore, this study evaluates three models of GXE interaction: diathesis-stress, differential susceptibility, and vantage sensitivity (Roisman et al., 2012). Findings support that child genetic factors moderate intergenerational impact of maternal maltreatment history.

Overall Findings

Previous studies demonstrated associations between maternal history of abuse and offspring adjustment problems (e.g., Collishaw et al., 2007; Roberts et al., 2004). However, no studies demonstrated the link between maternal maltreatment history and infant emotion regulation in a community sample. In the current study, history of maternal maltreatment significantly predicted infant emotion regulation behaviour, above and beyond maternal depressive symptoms. Moderation analyses were run for five gene-environment models, including DRD2, DAT1, COMT, OXTR rs53576, and OXTR rs2254298, with maternal history of maltreatment as the environmental factor, to predict infant emotion regulation behaviour.

Significant interaction terms occurred for DRD2, DAT1, and COMT. For DRD2, DAT1, and COMT genes, statistical tests were conducted to better understand the genetic-environmental relationships influencing emotion regulation. Roisman et al. (2012) analyses indicated that DRD2 and COMT interacted with maternal history of maltreatment in vantage sensitivity models. Certain genotypes, specifically the A1+ allele of DRD2 and the Met allele of COMT, combined with low levels of maternal history of maltreatment, predicted higher levels of infant emotion regulation than the A1- allele of DRD2 and Val allele of COMT, respectively. Roisman et al. (2012) analyses also indicated that DAT1 interacted with maternal history of maltreatment following a diathesis-stress model. That is, the 9-repeat allele for DAT1, combined with high levels of maternal history of maltreatment, predicted lower levels of infant emotion regulation than with the 10/10 genotype. In addition, a cumulative vantage sensitivity index score was derived for the "vantage alleles" of the DRD2 (i.e., A1+) and COMT (i.e., Met) genes, supporting a vantage sensitivity model when these vantage alleles occur in combination. This study furthers our understanding of infant emotion regulation, identifying how DRD2, DAT1, and COMT interact with maternal history of maltreatment differently; specifically, that genetic variants interacted with maternal maltreatment history in both diathesis-stress (i.e., DAT1) and vantage sensitivity (i.e., DRD2, COMT) patterns, to predict infant regulation, per Roisman et al. (2012) statistical evaluation. The following section covers further discussion and interpretation of these findings.

Interpretation of GXE Interaction Models

Diathesis-stress was demonstrated for the DAT1 and maternal history of maltreatment interaction. Consistent with hypotheses, the 9-repeat allele for DAT1, combined with high levels of maternal history of maltreatment, predicted lower levels of infant emotion regulation than did

interaction involving the 10/10 genotype. This result is consistent with findings that the absence of the 10/10 genotype for DAT1 predicted negative outcomes related to aspects of emotion regulation, such as inattention and ADHD symptoms (Cornish et al., 2005). ADHD is related to poor emotion regulation (Maegden & Carlson, 2000; Steinberg & Drabick, 2015), which may be due to executive inhibition deficits (Barkley, 1997), including difficulties with temperamental regulation and effortful control processes. However, this finding is in contrast to Laucht et al. (2007), who found that 15-year-olds with the 10/10 genotype exhibited the most and least inattention when living in high and low psychosocial adversity, respectively. That is, in the Laucht et al. (2007) study, *presence* of the 10/10 genotype demonstrated differential susceptibility for varying psychosocial adversity in the outcome of inattention, rather than the current study's finding of diathesis-stress for *absence* of the 10/10 genotype with high maternal history of maltreatment in the outcome of infant emotion regulation. Differences in the GXE model may be resultant from differing statistics, variables, and methodology, where the Laucht et al. (2007) study 1) employed less stringent statistical analyses, possibly leading to false representations of differential susceptibility (Roisman et al., 2012), 2) addressed different environmental (e.g., psychosocial adversity) and outcome (e.g., inattention) factors, and/or 3) investigated a different age group (e.g., 15-year-olds). Differences in the type of GXE model (i.e., differential susceptibility or diathesis-stress) and influential allele (i.e., 10/10 absent or present) may have occurred because of one, two or all of these differences. Overall, this finding extends the literature by identifying that the absence of the 10/10 genotype (presence of 9-repeat allele) for DAT1 acts as a *risk factor* when combined with high levels of maternal history of maltreatment, leading to lower self-regulation skills in infants.

Vantage sensitivity was demonstrated for DRD2 gene interacting with maternal history of maltreatment. The A1+ allele of DRD2, when combined with low levels of maternal history of maltreatment, predicted higher levels of infant emotion regulation than the A1- allele. Consistent with previous research, these "vantage" alleles, when combined with an optimal environment, allow individuals to thrive (Mills-Koonce et al., 2007). For example, for DRD2, Mills-Koonce et al. (2007) found that infants with the A1+ allele who experienced more sensitive caregiving had fewer affective problems at age three, compared to other genotypes. Findings, however, differ from the current study findings, as Mills-Koonce's et al. (2007) study supported a differential susceptibility effect, with A1+ infants who had less sensitive mothers expressing more affective problems, possibly based on several study differences (also discussed above for DAT1 findings): 1) less stringent statistical analyses leading to apparent differential susceptibility (Roisman et al., 2012), 2) addressing different environmental (e.g., maternal sensitivity) and outcome (e.g., affective problems) factors, and 3) investigating different age group (three-year-olds) than current study (15-month-olds). Current study findings extend the literature by identifying the A1+ allele of DRD2 as a *vantage* allele when combined with low levels of maternal history of maltreatment, leading to higher self-regulation skills in infants.

Vantage sensitivity was also demonstrated for the COMT gene, interacting with maternal history of maltreatment. The Met allele of COMT, when combined with low levels of maternal history of maltreatment, predicted higher levels of infant emotion regulation than the Val allele of COMT. The current study results for COMT varied from previous findings. For instance, Nederhof et al. (2012) found that the A-carriers (i.e., Met) only experienced susceptibility to *negative* environmental circumstance (i.e., parental divorce) for externalizing problems in adolescence, in a diathesis-stress model, and other studies suggested differential susceptibility

for the Val allele (e.g., Caspi et al., 2005). In making sense of these differences, the form of interaction greatly depends on the environmental factor and outcome. That is, contrastive findings, again, are likely related to differences in the type of environmental factor (e.g., parental divorce versus maternal history of maltreatment) and outcome (e.g., externalizing problems in adolescence versus infant emotion regulation) of interest. Overall, these findings extend the literature by identifying the Met allele of COMT as a *vantage* allele when combined with low levels of maternal history of maltreatment, leading to higher self-regulation skills in infants.

In the cases of GXE interactions for OXTR SNPs, there were no significant interactions for either OXTR SNP (i.e., OXTR rs53576, OXTR rs2254298) with maternal history of maltreatment in predicting infant emotion regulation. Null findings might be related to Type II error, resulting from low statistical power. It is also possible that environmental and outcome variables investigated were not connected to OXTR SNPs in GXE interaction. Of note, previous research indicated that OXTR (rs2254298) interacts with history of maternal major depressive disorder to predict psychosocial functioning (i.e., anxiety and depression) in girls (Thompson et al., 2011). Consequently, it is possible that 1) OXTR SNPs are linked to infant emotion regulation in interaction with more potent environmental moderators (i.e., maternal depressive disorders), 2) OXTR SNPs interact with maternal history of maltreatment to predict more potent outcomes (i.e., anxiety and depression) in offspring, or 3) OXTR SNPs do not interact with maternal history of maltreatment to predict infant emotion regulation in a GXE interaction model. More research in this area, with larger sample size and/or investigation of different environmental factors/outcomes, is warranted.

The cumulative genetic index was derived to understand additive genetic effects. In the current sample, DRD2 and COMT were included in forming a cumulative vantage sensitivity

index score to examine its interaction with CTQ on emotion regulation. With the cumulative index score converted into a continuous variable, Roisman et al. (2012) analyses demonstrated a vantage sensitivity response, with a higher number of vantage alleles leading to better emotion regulation. There was some evidence that the pattern of GXE interaction for the cumulative vantage sensitivity index depicted differential susceptibility (i.e., RoS significant at both high and low ends of CTQ), yet this was not the trend when these genes were examined separately. Beaver and Belsky (2012) explained that, the more differential susceptibility alleles, the stronger the effect of differential susceptibility on phenotypic outcome. Possibly, by including a larger number of putative alleles (i.e., 5-HTTLPR, DRD4) in a cumulative index, differential susceptibility could be fully supported (Beaver & Belsky, 2012). It is a limitation of the current study that the full selection of relevant alleles to predict emotion regulation could not be employed. There are multiple genetic alleles possibly interacting with multiple environmental factors to predict emotion regulation. As each gene likely has only a small effect on phenotypical outcomes (Beaver & Belsky, 2012), future research should evaluate all relevant GXE interactions to understand the overall nature-nurture impact on the development of emotion regulation.

Current study results compared with the extant literature support the notion that the nature of the genetic-environmental interaction (i.e., diathesis-stress, differential susceptibility, or vantage-sensitivity) likely depends on the specific environmental factor, genotype, and the outcome of interest (Roisman et al., 2012). Furthermore, in the current study, there were differential gene-environment effects for different genetic polymorphisms, predicting the same outcome of infant emotion regulation. This pattern of results can be considered evolutionarily adaptive in the sense that an individual can adaptively respond to environmental differences with

a variable genetic make-up (Brüne, 2012). Variation in *multiple* gene-environment interaction models for emotion regulation, within a single individual, would allow for flexibility of phenotypic expression in response to the environment, leading to possibility of better neuropsychiatric outcome (Wurzman & Giordano, 2012). In turn, favourable neuropsychiatric outcomes might allow for adaptive survival in response to environmental contingencies and would lead to increased chance of genetic replication. Genetic variation and its relation to developmental plasticity may explain the persistence of perceived risk alleles in the context of natural selection (Brüne, 2012). Findings allude to an overarching genetic variability of multiple genes on a single phenotype, where some polymorphisms act as diathesis-stress and others as vantage sensitivity to allow for increased overall plasticity in response to environment (i.e., *differential susceptibility* with multiple polymorphisms).

Of note, current study findings show that even normative variation in maternal history of maltreatment (i.e., an overall lower level of CTQ scores) in a low-risk sample predicts infant emotion regulation, and that dopamine- and catechol-o-methyltransferase-related genetic variations moderate this intergenerational transmission. Hane and Philbrook (2012) discuss how offspring phenotypic change can occur in response to even normative variations in maternal care. That is, brain adaptations are sensitively sculpted to normative variations in environment (Hane & Philbrook, 2012), shaping human behaviours in response to environmental circumstance to enhance chances of survival (e.g., strategic decision-making; Atkinson, 2012). Consistent with the intergenerational transmission of maltreatment, even mothers who experienced lower levels of maltreatment may experience challenges (Collishaw et al., 2007), placing children in environmental situations that increase risk to developing suboptimal emotion regulation.

Clinical Implications

In terms of clinical practice, study findings provide information on who might benefit most from intervention, depending on infant genetic make-up and maternal factors. Given that lower levels of maternal history of maltreatment, when paired with certain infant genetic variants (e.g., A1+ of DRD2 and Met of COMT), leads to higher levels of adaptive emotion regulation in infancy, interventions that capitalize on cultivating enriching mother-infant experiences might prove most effective for individuals with vantage allele(s). Pat-Horenczyk et al. (2015) found that *maternal emotion regulation* issues mediated the link between maternal PTSD symptoms and child dysregulation. Furthermore, Pereira et al. (2012) determined that *parental stress* mediated the relation between maternal maltreatment history and lower levels of maternal sensitivity. These findings allude to a possible explanation for low maternal maltreatment history and its influence on positive child emotion regulation in the present; specifically, that adaptive maternal emotion regulation strategies may increase a mother's ability to provide sensitive/responsive parenting, increase opportunities to model adaptive regulation to the infant, and reinforce adaptive regulation strategies exhibited by the infant, thereby increasing the probability that adaptive strategies will be continued. A possible intervention for childhood regulation, particularly for children with the vantage DRD2 and/or COMT alleles (i.e., who may benefit most from a positive environment), may be to increase adaptive maternal emotion regulation strategies in order to reduce parental stress and increase positive parenting behaviours during this critical period in infant emotion regulation development.

In addition, the concerning finding that high levels of maternal history of maltreatment, when paired with the genetic variant of the 9-repeat allele for DAT1, leads to lower levels of adaptive emotion regulation, may highlight the importance of similar interventions mentioned

above for infants with the 9R allele and mothers with such maltreatment histories. Interestingly, in the current study, the 10/10 genotype of DAT1 was related to better emotion regulation, whereas the 10/10 genotype has been linked to ADHD symptoms in adolescence (Cornish et al., 2005). Since the 10/10 allele is related to inattention (Cornish et al., 2005), it is possible that the 10/10 genotype in infancy may be a protective factor during this developmental period when the infant experiences a negative environment (i.e., less attention placed on negative environmental circumstances). However, with an accumulation of unfavourable experiences over time, this genotype may lead to maladaptive levels of inattention/hyperactivity in settings/situations where this phenotype is not as adaptive (e.g., school). Laucht et al. (2007) determined that the 10/10 genotype acts as a differential susceptibility factor in response to variations in psychosocial adversity during adolescence, indicating possible malleability at later points in development, although psychosocial adversity may be a difficult experience to ameliorate through intervention efforts in later years, as psychosocial circumstances may be more static. With regard to early prevention, similar interventions explained above might prove important for infants of mothers with significant maltreatment histories and either the 10/10-genotype or 9R allele for DAT1.

Limitations and Future Directions

The current study has several limitations that need to be addressed. Primarily, this was a small sample (i.e., ranging from 147 to 159, depending on gene) to test gene-environment interactions, increasing the risk of committing error (Types 1 and 2). Duncan and Keller (2011) note that a large interaction effect requires a sample size between 600 and 800 to detect reliability and that smaller effects require an even larger sample size. In addition, small sample size makes results less generalizable to the population at large. Furthermore, multiple

comparisons were made in this study, which increases potential for Type 1 error, a common issue in genetic association studies.

Furthermore, for purposes of Roisman et al. (2012) statistics, sample size, or more precisely, statistical power, influences the Regions of Significance (RoS) test. This is a crucial test to distinguish differential susceptibility from diathesis-stress and vantage sensitivity. Specifically, the RoS determines that emotion regulation and the proposed gene are correlated at both high and low ends of maternal history of maltreatment, CTQ scores (bounded by +/-2SD from the mean of CTQ). With less statistical power, emotion regulation and the gene might be correlated only at the high end (+2SD), only at the low end (-2SD), or neither end of CTQ scores. With less statistical power in this instance, there is a strong possibility the effects were differential susceptibility interactions, but without enough power to establish this effect, the patterns of diathesis-stress and vantage sensitivity emerged instead. However, given that the PA and PoI metrics are less influenced by sample size (Roisman, personal communication, May 20, 2014), which suggest patterns consistent with diathesis-stress for DAT1 and vantage-sensitivity for DRD2 and COMT, these metrics provided confidence in the overall patterns of gene-environment interaction models indicated by the RoS tests. In future research, it would be important to utilize larger sample sizes to increase confidence and reliability in these findings.

Another limitation in this study was the portion of missing BDI data for mothers within the sample. Scores were missing because BDI questionnaire was either unreturned or incomplete. This missing portion reduced sample size and also reduced representativeness of the community-based population. The DRD2 and COMT study samples compared with the larger sample (N = 314) significantly differed for maternal education, with study samples having a higher level of maternal education than the larger sample. In response to these sample differences, hierarchical

regression analyses were replicated with imputed data to compare results with non-imputed data, in order to build confidence in current sample results. The imputed regression analyses followed similar trends to the non-imputed regression analyses, suggesting that the missing data may not have influenced the gene-environment interaction results.

Another major limitation of this study was that certain serotonin and dopamine genes linked to emotion regulation were not genotyped for the current sample, likely because of buccal cell degradation (Livy et al., 2012). Specifically, the serotonin transporter gene (5-HTTLPR) was not investigated as a genetic moderator of maternal history of maltreatment to predict emotion regulation. The literature suggests that serotonin production and regulation is a major factor in adaptive emotion regulation skills, in infancy (Auerbach et al., 1999) and childhood (Kochanska et al., 2009). In addition, dopamine receptor D4 (DRD4) was not investigated as a genetic moderator, again limiting a thorough investigation of crucial genetic variants of infant self-regulation. Similar to the serotonin transporter gene, DRD4 has been identified in several studies as an important gene in the development of emotion regulation (Propper et al., 2008). Also, MAOA was not included in the current study as a result of barriers to completion of genotyping the full sample (i.e., a large portion of the sample did not amplify), another gene that has been linked to outcomes related to emotion regulation (i.e., ADHD; Kim-Cohen et al., 2006). For future research, in keeping with hypothesis-driven investigations of gene-environment research in emotion regulation, 5-HTTLPR, DRD4, and MAOA should be investigated as genetic moderators and determination of GXE interaction models should be explored through Roisman et al. (2012) statistical tests.

An important avenue for future research directions will be to identify other environmental factors that explain the link between genetic variants and emotion regulation. This may be

particularly important in understanding the role of oxytocin-related genes in predicting emotion regulation. That is, it is possible that OXTR SNPS combined with different environmental factors other than maternal history of maltreatment, such as maternal depression (Thompson et al., 2011) or infant attachment classification (i.e., Carter, 1998), might prove more powerful in predicting emotion regulation in infants. Several other environmental factors should also be investigated, which might include, but are not limited to, socio-economic status, maternal attention, maternal executive functioning, maternal posttraumatic stress symptoms and unresolved trauma, trauma experienced by the infant, changes in family composition, separation from parents, and maternal stress/support, which are factors that might underlie the influence of maternal history of maltreatment on infant emotion regulation. Evaluating several other environmental factors would allow for specificity of environmental influence within GXE models (Roisman et al., 2012). Furthermore, future research may involve investigating alternative statistical methods in exploring the link between maternal depression, maternal history of maltreatment, and infant emotion regulation. Specifically, exploring maternal depressive symptoms as a mediator of maternal history of maltreatment in predicting emotion regulation may explain an important mechanism of this relationship. Another important area for future research would be investigating GXE interactions through the life span to better understand the changing influence of genetic and environmental factors on emotion regulation over time.

Conclusions

In summary, DRD2 and COMT interacted with maternal history of maltreatment in vantage sensitivity models. The A1+ allele of DRD2 and the Met allele of COMT, combined with low levels of maternal history of maltreatment, predicted higher levels of infant emotion regulation

than the A1- allele of DRD2 and Val allele of COMT, respectively. DAT1 interacted with maternal history of maltreatment, following a diathesis-stress model. The 9-repeat allele for DAT1, combined with high levels of maternal history of maltreatment, predicted lower levels of infant emotion regulation, than with the homozygous 10-repeat genotype. In addition, the cumulative vantage sensitivity score (i.e., derived for the "vantage alleles" of the DRD2 and COMT) followed a vantage sensitivity effect for increased number of vantage alleles, based on Roisman et al. (2012) statistics, to predict regulation.

Differences in genetic-environment interaction models suggest that an adaptive *variation* in genetic vulnerability and vantage sensitivity, across an infant's genome, can cumulatively increase the possibility for optimal self-regulation outcomes, whether the environment is favourable or less favourable (i.e., lower versus higher history of maternal maltreatment, respectively). The culmination of GXE differences, in effect, may overall depict "differential susceptibility." *Differential susceptibility* refers to a plasticity of genes, increasing an individual's susceptibility to environmental influence, in a *'for-better-and-for-worse'* manner. Susceptibility to positive and negative environmental factors influences psychological outcomes positively and negatively, respectively. This effect may occur in concordance with multiple genetic polymorphisms, as opposed to previous discussion on differential susceptibility effect within one genetic polymorphism (Brüne, 2012). That is, some genes will act in vantage sensitivity models (e.g., DRD2 COMT), representing susceptibility to the environment for "better," and others as diathesis-stress models (i.e., DAT1), indicating susceptibility to the environment for "worse."

Table 1

Candidate Genes and Comparison Groups

Candidate gene	Polymorphism-based comparison groups
DRD2	A1+ (A1/A1 and A1/A2); A1- (A2/A2)
DAT1 (40 BP VNTR)	9-repeat present; 9-repeat absent
COMT (val1158met) rs4680*	A/G, A/A (Met/Val or Met/Met); G/G (Val/Val)
OXTR rs53576*	G/G; A/A or A/G
OXTR rs2254298*	G/G; A/A or A/G

Note. Putative plasticity/vantage sensitivity/risk allele(s) listed first.
* indicates exploratory investigations of genetic plasticity variants.

Table 2

Study Samples compared to Larger Sample on Relevant Variables

Sample		*M*	*SD*	*t*	*df*	*p*
DRD2 (N = 157)	Maternal BDI					
	Included	7.86	6.82	.29	267	.77
	Excluded	7.62	6.88			
	Maternal CTQ					
	Included	35.32	12.95	-1.06	305	.29
	Excluded	36.97	14.36			
	Maternal education					
	Included	3.91	.85	2.04	309	.04*
	Excluded	3.70	.92			
	Mother's salary					
	Included	2.65	1.47	1.49	226	.14
	Excluded	2.35	1.53			

	Spouse's salary					
	Included	3.64	1.64	.23	230	.82
	Excluded	3.59	1.81			
	Sex of baby					
	Included	1.54	.50	2.08	311	.04*
	Excluded	1.42	.50			
	Age of baby					
	Included	1.38	.56	-13.78	208	<.001*
	Excluded	2.96	1.31			
	Ethnicity					
	Included	1.27	.45	.72	304	.47
	Excluded	1.23	.43			
	Emotion Regulation					
	Included	97.72	71.16	.01	181	.99
	Excluded	97.54	58.64			
	DRD2					
	Included	.40	.49	.55	300	.58
	Excluded	.37	.49			
	DAT1					
	Included	.60	.49	.03	279	.98
	Excluded	.60	.49			
	COMT					
	Included	.65	.48	-1.03	300	.30
	Excluded	.71	.46			
	OXTR rs53576					
	Included	.37	.49	-.96	301	.34
	Excluded	.43	.50			
	OXTR rs2254298					
	Included	.72	.45	-.54	301	.59
	Excluded	.75	.44			
DAT1 (N = 147)	Maternal BDI					
	Included	7.70	6.80	-.15	267	.88
	Excluded	7.82	6.90			

Maternal CTQ					
Included	35.56	13.06	-.70	305	.48
Excluded	36.65	14.22			
Maternal education					
Included	3.91	.89	1.92	310	.06
Excluded	3.72	.91			
Mother's salary					
Included	2.63	1.49	1.04	226	.30
Excluded	2.42	1.50			
Spouse's salary					
Included	3.62	1.58	.01	230	.99
Excluded	3.62	1.86			
Sex of baby					
Included	1.54	.50	2.04	311	.04*
Excluded	1.42	.50			
Age of Baby					
Included	1.37	.57	-13.23	227	<.001*
Excluded	2.87	1.32			
Ethnicity					
Included	1.27	.44	.60	304	.55
Excluded	1.24	.43			
Emotion Regulation					
Included	100.97	72.52	1.46	79	.15
Excluded	85.58	54.21			
DRD2					
Included	.42	.50	1.18	293	.24
Excluded	.36	.48			
DAT1					
Included	.60	.49	.22	279	.83
Excluded	.59	.49			
COMT					
Included	.69	.46	.40	300	.69
Excluded	.67	.47			

	OXTR rs53576					
	Included	.38	.49	-.73	301	.47
	Excluded	.42	.50			
	OXTR rs2254298					
	Included	.72	.45	-.65	301	.52
	Excluded	.75	.44			
COMT (N = 157)	Maternal BDI					
	Included	7.80	6.86	.11	267	.91
	Excluded	7.70	6.83			
	Maternal CTQ					
	Included	35.30	12.94	-1.80	305	.28
	Excluded	36.98	14.37			
	Maternal education					
	Included	3.91	.85	2.03	310	.04*
	Excluded	3.70	.92			
	Mother's salary					
	Included	2.64	1.49	1.30	226	.19
	Excluded	2.37	1.49			
	Spouse's salary					
	Included	3.65	1.63	.31	230	.76
	Excluded	3.58	1.82			
	Sex of baby					
	Included	1.53	.50	1.85	311	.07
	Excluded	1.43	.50			
	Age of baby					
	Included	1.38	.56	-13.78	208	<.001*
	Excluded	2.96	1.31			
	Ethnicity					
	Included	1.26	.44	.46	304	.65
	Excluded	1.24	.43			
	Emotion Regulation					
	Included	98.22	71.47	.28	47	.78
	Excluded	94.92	56.43			

	DRD2					
	Included	.40	.49	.50	300	.62
	Excluded	.37	.49			
	DAT1					
	Included	.60	.49	.03	279	.98
	Excluded	.60	.49			
	COMT					
	Included	.65	.48	-1.12	300	.26
	Excluded	.71	.46			
	OXTR rs53576					
	Included	.37	.49	-.96	301	.34
	Excluded	.43	.50			
	OXTR rs2254298					
	Included	.72	.45	-.54	301	.59
	Excluded	.75	.44			
OXTR rs53576 (N = 158)	Maternal BDI					
	Included	7.78	6.85	.06	267	.95
	Excluded	7.73	6.85			
	Maternal CTQ					
	Included	35.30	12.91	-1.09	305	.28
	Excluded	37.00	14.41			
	Maternal education					
	Included	3.90	.85	1.93	310	.06
	Excluded	3.71	.92			
	Mother’s salary					
	Included	2.65	1.49	1.44	226	.15
	Excluded	2.35	1.48			
	Spouse’s salary					
	Included	3.62	1.61	-.06	230	.95
	Excluded	3.63	1.86			
	Sex of baby					
	Included	1.53	.50	1.97	311	.05*
	Excluded	1.42	.50			

	Age of baby					
	Included	1.51	.50	-1.38	246	.17
	Excluded	1.43	.50			
	Ethnicity					
	Included	1.27	.44	.66	304	.51
	Excluded	1.24	.43			
	Emotion Regulation					
	Included	98.55	70.90	.39	181	.69
	Excluded	92.95	59.65			
	DRD2					
	Included	.41	.49	.64	300	.52
	Excluded	.37	.48			
	DAT1					
	Included	.60	.49	.12	279	.90
	Excluded	.59	.49			
	COMT					
	Included	.65	.48	-.95	300	.34
	Excluded	.70	.46			
	OXTR rs53576					
	Included	.37	.49	-.91	301	.36
	Excluded	.43	.50			
	OXTR rs2254298					
	Included	.72	.45	-.41	301	.69
	Excluded	.74	.44			
OXTR rs2254298 (N = 159)	Maternal BDI					
	Included	7.73	6.85	-.08	267	.94
	Excluded	7.80	6.84			
	Maternal CTQ					
	Included	35.27	12.87	-1.13	305	.26
	Excluded	37.04	14.45			
	Maternal education					
	Included	2.28	.31	1.42	233	.16
	Excluded	2.22	.31			

Mother's salary					
Included	2.65	1.49	1.49	226	.14
Excluded	2.34	1.49			
Spouse's salary					
Included	3.62	1.60	-.11	230	.91
Excluded	3.64	1.87			
Sex of baby					
Included	1.53	.50	1.86	311	.06
Excluded	1.42	.50			
Age of baby					
Included	1.37	.56	-14.10	205	<.001*
Excluded	2.99	1.30			
Ethnicity					
Included	1.27	.44	.59	304	.56
Excluded	1.24	.43			
Emotion Regulation					
Included	98.24	70.78	.26	181	.80
Excluded	94.54	60.17			
DRD2					
Included	.41	.49	.64	300	.52
Excluded	.37	.48			
DAT1					
Included	.60	.49	.22	279	.83
Excluded	.59	.49			
COMT					
Included	.65	.48	-.95	300	.34
Excluded	.70	.46			
OXTR rs53576					
Included	.37	.49	-.91	301	.36
Excluded	.43	.50			
OXTR rs2254298					
Included	.72	.45	.50	301	.74
Excluded	.74	.44			

* = $p < .05$

Table 3

Infant Emotion Regulation Strategies during the Toy Frustration Task

Emotion Regulation Strategy	Definition
Withdrawal	The infant stops making attempts to obtain the toy from the box. Withdrawal behaviour may include the infant sitting or lying down, while no longer engaging in the task.
Wandering away	The infant walks or crawls away from the task.
Distraction	The infant shifts attention away from the task. Distraction behaviour does not include placing attention on the mother or research assistant. This behaviour must have been present for at least one second; otherwise, it was coded as scanning behaviour.
Orienting to an object	The infant placed attention on an object other than the primary toy of interest in the task.
Scanning	The infant was not focused on one specific object or person, but rather was engaging in visual exploration of the environment.

Table 4

SNPs Genotyped in Current Study

SNP rs number	SNP assays and alleles
COMT_rs4680	C__25746809_50; 1=G=Val; 2=A=Met (positive)
DRD2_rs1800497	TaqIA. C___7486676_10 1=A (A1); 2=G (A2) (positive)
OXTR_rs2254298	C__15981334_10. 1=G; 2=A (positive)
OXTR_rs53576	C___3290335_10. 1=G, 2=A (positive)

Table 5

Frequency of Genotypes and Hardy-Weinberg Equilibrium

Gene	Genotype Frequencies	Chi-squared	*p*-value	Hardy-Weinberg equilibrium?
DRD2	A1/A1 = 10 A1/A2 = 55 A2/A2 = 92	0.21	0.65	Yes
DAT1	10/10 = 88 9/10 = 49 9/9 = 10	0.76	0.38	Yes
COMT	Val/Val = 56 Val/Met = 72 Met/Met = 29	0.47	0.49	Yes
OXTR rs53576	A/A = 25 A/G = 73 G/G = 60	0.13	0.72	Yes
OXTR rs2254298	A/A = 7 A/G = 37 G/G = 115	2.94	0.09	Yes

Note. Chi-squared calculations that were $p < .05$ indicated that genes were in Hardy-Weinberg equilibrium

Table 6

Mean Comparisons of Emotion Regulation on Allelic Expressions by Gene

Gene	Larger samples (N = 147 to 159)
DRD2	F (1, 155) = 0.79, p = .38
A1+	102.43 (65.34), n = 65
A1-	92.29 (74.25), n = 92
DAT1	F (1, 145) = 13.79, p < .001
9 repeat present (9/10, 9/9)	73.75 (57.16), n = 59
9 repeat absent (10/10)	116.91 (75.97), n = 88
COMT	F (1, 155) = 2.69, p = .10
A/G, A/A	103.86 (74.74), n = 101
G/G	84.55 (62.34), n = 56
OXTR rs53576	F (1, 156) = 0.43, p = .51
G/G	102.03 (61.77), n = 60
A/A, A/G	94.42 (75.39), n = 98
OXTR rs2254298	F (1, 157) = 0.24, p = .63
G/G	95.33 (71.93), n = 115
A/A, A/G	101.41 (66.43), n = 44

Table 7

Correlation Matrix with Means and Standard Deviations of larger sample for DRD2 (N = 157)

	1	2	3	4	5	6	7	8	9	10	11	12	M	SD
1. DRD2	-												0.41	0.49
2. DAT1	-.16	-											0.41	0.49
3. COMT	.07	-.07	-										0.65	0.48
4. Regulation	.07	-.30**	.12	-									96.49	70.66
5. CTQ	-.03	-.07	.10	.21*	-								35.55	13.07
6. BDI	-.15	-.12	.08	.20*	.21*	-							7.77	6.77
7. Infant sex	.13	-.21*	.13	.11	.12	-.08	-						1.53	0.50
8. Ethnicity	.32***	-.08	-.02	.11	.02	.11	-.04	-					1.27	0.45
9. Mother salary	.04	-.04	-.10	-.02	-.28***	-.25**	.09	.04	-				2.67	1.47
10. Spouse salary	-.04	.07	.06	-.06	-.10	-.15	-.01	-.28***	.13	-			3.68	1.66
11. Maternal education	.10	.03	-.04	-.04	-.30***	-.15	-.14	-.02	.33***	.15	-		3.91	0.85
12. Maternal sensitivity	.08	-.14	.05	.05	-.03	-.03	.04	-.10	.17*	.15	.29***	-	.50	.27

Correlations means, and standard deviations for CTQ and BDI are non-centred in this table
* = p < .05, ** = p < .01, *** = p < .001

Table 8

Correlation Matrix with Means and Standard Deviations of larger sample for DAT1 (N =147)

	1	2	3	4	5	6	7	8	9	10	11	12	M	SD
1. DRD2	-												.43	.50
2. DAT1	-.16	-											.40	.49
3. COMT	.05	-.07	-										.68	.47
4. Regulation	.07	-.30***	.09	-									99.59	72.03
5. CTQ	-.04	-.07	-.01	.20*	-								35.80	13.18
6. BDI	-.15	-.11	.08	.22*	.24**	-							7.61	6.74
7. Infant sex	.16*	-.21*	.14	.11	.11	-.06	-						1.53	.50
8. Ethnicity	.30***	-.22*	-.001	.12	.04	.13	-.02	-					1.27	.45
9. Mother salary	.04	-.03	-.10	-.04	-.26***	-.23*	.06	.03	-				2.65	1.49
10. Spouse salary	-.03	.08	.06	-.05	-.15	-.16	-.05	-.25**	.17*	-			3.66	1.62
11. Maternal education	.09	.04	-.06	-.04	-.29***	-.17*	-.11	-.04	.35***	.19*	-		3.91	.85
12. Maternal sensitivity	.08	-.10	.05	.08	-.01	-.04	.05	-.12	.19*	.16	.32***	-	.50	.26

Correlations means, and standard deviations for CTQ and BDI are non-centred in this table
* = $p < .05$, ** = $p < .01$, *** = $p < .001$

Table 9

Correlation Matrix with Means and Standard Deviations of larger sample for COMT (N = 157)

	1	2	3	4	5	6	7	8	9	10	11	12	M	SD
1. DRD2	-												.41	.49
2. DAT1	-.15	-											.41	.49
3. COMT	.07	-.07	-										.64	.48
4. Regulation	.07	-.30***	.13	-									96.97	70.97
5. CTQ	-.03	-.07	.03	.21*	-								35.54	13.06
6. BDI	-.15	-.12	.09	.19*	.22*	-							7.71	6.81
7. Infant sex	.13	-.21*	.15	.12	.13	-.08	-						1.53	.50
8. Ethnicity	.31***	-.22*	-.01	.11	.21	.12	-.04	-					1.26	.44
9. Mother salary	.04	-.02	.12	-.04	-.28**	-.24**	.06	.03	-				2.66	1.49
10. Spouse salary	-.03	.07	.06	-.07	-.10	-.15	-.01	-.27**	.14	-			3.68	1.66
11. Maternal education	.10	.04	-.05	-.06	-.30***	-.15	-.15	-.02	.34***	.15	-		3.91	.85
12. Maternal sensitivity	.10	-.13	.06	.07	-.02	-.02	.05	-.09	.19*	.16	.32***	-	.50	.27

Correlations means, and standard deviations for CTQ and BDI are non-centred in this table
* = $p < .05$, ** = $p < .01$, *** = $p < .001$

Table 10

Multiple Regression Terms for each Gene

Gene	Model	B	Std. Error	*t*	Sig.
DRD2	Constant	90.42	7.10	12.73	.000*
(N = 157)	BDI	1.68	.84	2.01	.046*
	CTQ	1.47	.51	2.93	.004*
	DRD2	13.84	11.12	1.25	.22
	DRD2XCTQ	-1.84	.94	-1.96	.05*
DAT1	Constant	115.01	7.08	16.26	.000*
(N = 147)	BDI	1.27	.85	1.49	.14
	CTQ	1.56	.52	2.98	.003*
	DAT1	-40.98	11.23	-3.65	.000*
	DAT1XCTQ	-2.35	.91	-2.58	.01*
COMT	Constant	86.56	9.01	9.61	.000*
(N = 157)	BDI	1.90	.82	2.31	.02
	CTQ	2.30	.63	3.64	.000*
	COMT	16.49	11.24	1.47	.14
	COMTXCTQ	-2.43	.85	-2.87	.005*
OXTR	Constant	91.76	6.93	13.23	.000*
rs53576	BDI	1.70	.82	2.06	.04*
(N = 158)	CTQ	1.31	.98	2.66	.009*
	OXTR	11.66	11.39	1.02	.31
	OXTRXCTQ	-1.35	.98	-1.38	.17
OXTR	Constant	99.17	10.46	9.48	.000*
rs2254298	BDI	1.62	.82	1.97	.05*
(N = 159)	CTQ	1.17	.75	1.55	.12
	OXTR	-3.24	12.27	-.26	.79
	OXTRXCTQ	-.37	.90	-.41	.68
CVS	Constant	96.45	5.33	18.10	.000*
(N = 155)	BDI	1.91	.81	2.36	.02*
	CTQ	.53	.44	1.22	.23
	CVS	14.21	7.5	1.89	.06
	CVSXCTQ	-1.92	.58	-3.32	.001*

* = $p < .05$

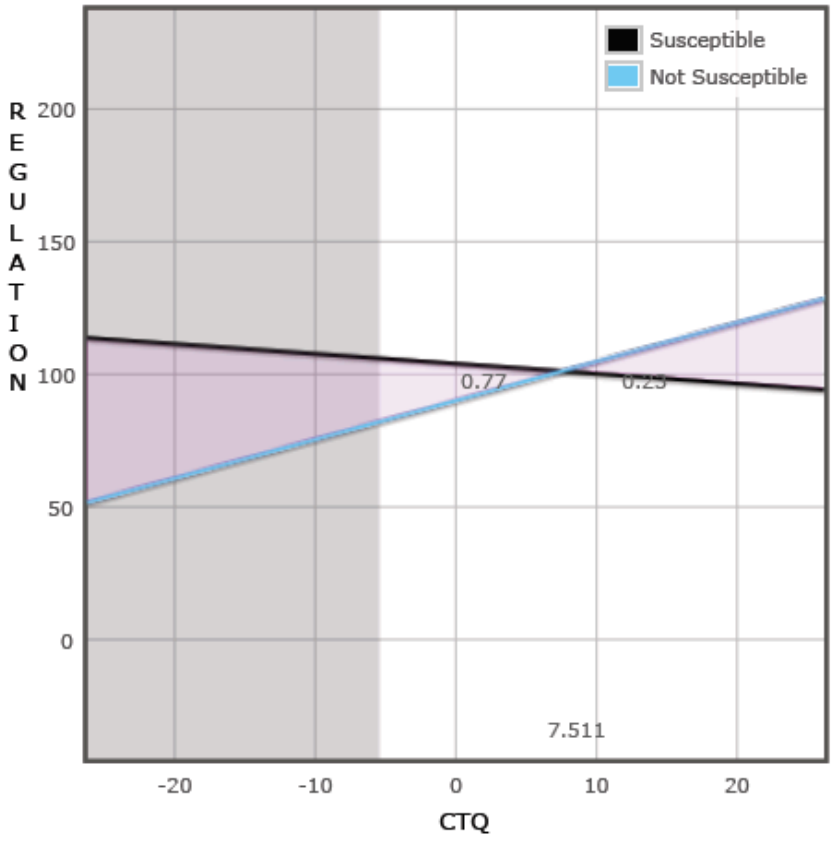
Table 11

Regression Terms and Roisman et al. (2012) Indices

	Regression Estimates					*ROS Z*		*ROS X*					
Gene	b_0	b_1	b_2	b_3	Adjusted R^2	Lower Bound	Upper Bound	Lower Bound	Upper Bound	PoI	PA	Crossover	X^2 or ZX^2?
DRD2	90.42	1.47	13.84	-1.84	.08	-82.74	.34	-1272.95	-5.42	.77	.86	7.51	No
DAT1	115.01	1.56	-40.98	-2.35	.16	.30	1.97	-75.70	-6.89	.04	0	-17.45	No
COMT	86.56	2.30	16.49	-2.43	.10	.60	1.99	-2.48	28.73	.74	.85	6.79	No
CVS	96.45	.53	14.21	-1.92	.13	-.15	1.25	-.32	1.25	.76	.86	7.40	No

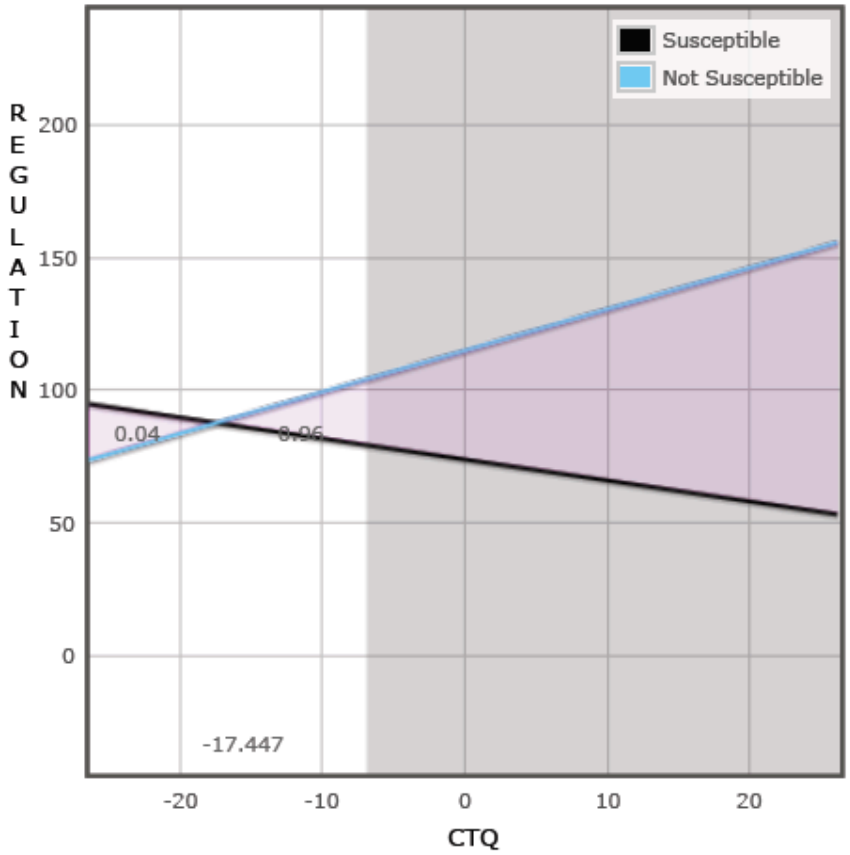
CVS = Cumulative Vantage Sensitivity Index

Figure 1. DRD2 by CTQ Interaction to predict Emotion Regulation (N = 157)



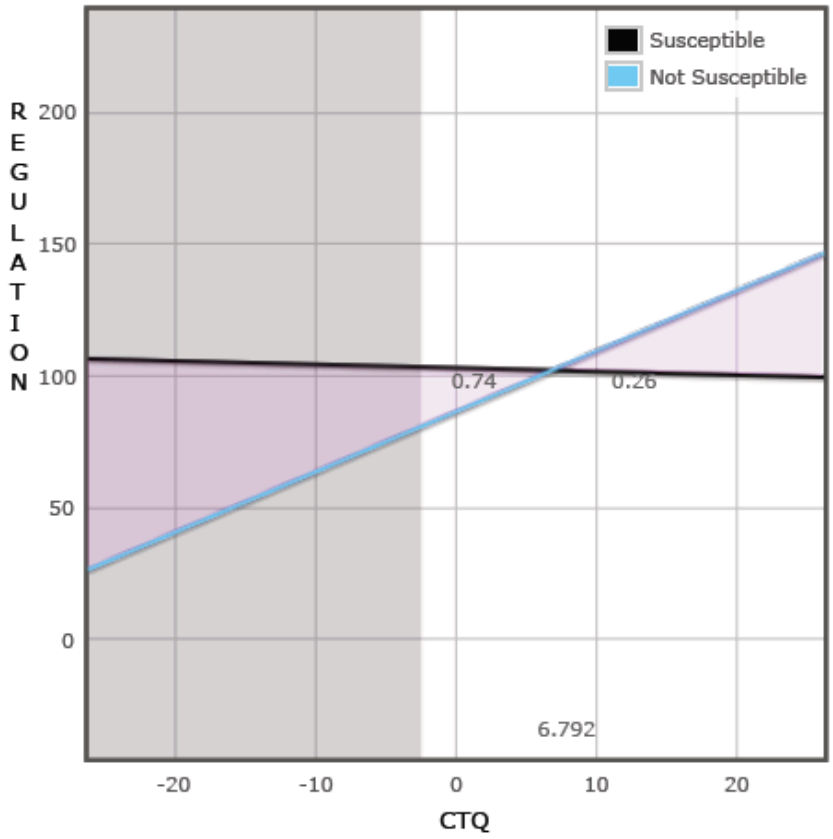
Note. The "Susceptible" allele is A1+ and the "Not Susceptible" allele is A1-

Figure 2. DAT1 by CTQ Interaction to predict Emotion Regulation (N = 147)



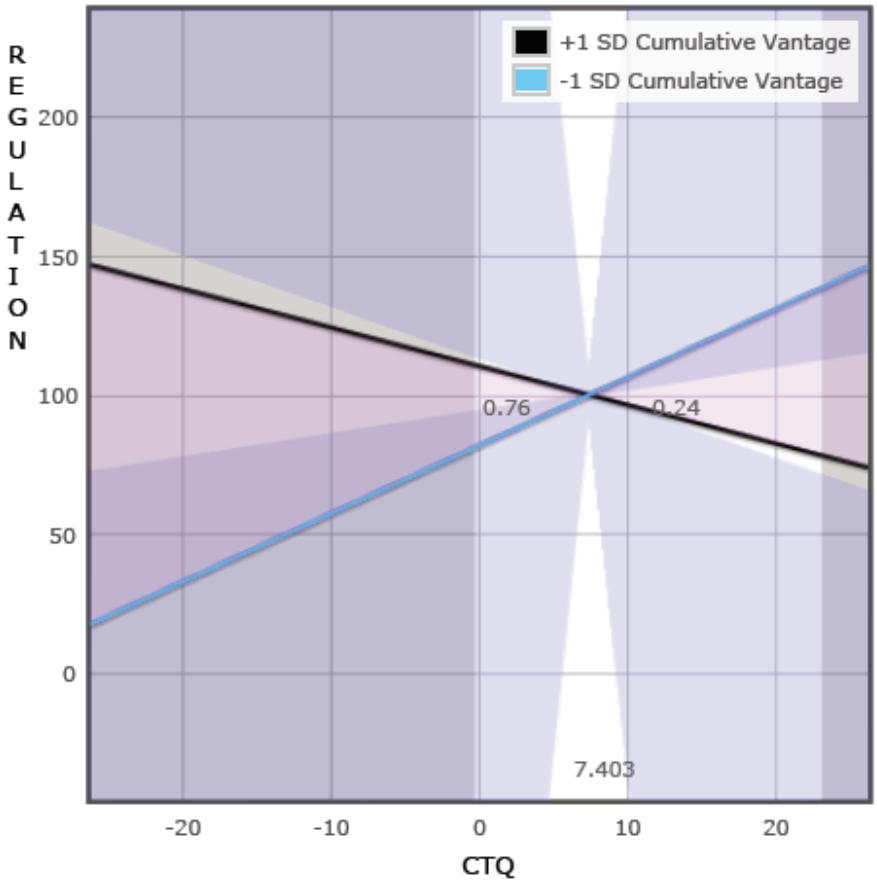
Note. The "Susceptible" allele is when 9-repeat allele is present and the "Not Susceptible" genotype is when 9-repeat allele is absent

Figure 3. COMT by CTQ Interaction to predict Emotion Regulation (N = 157)



Note. The "Susceptible" allele is when Met is present and the "Not Susceptible" allele is when Val is present

Figure 4. CVS Index by CTQ Interaction to predict Emotion Regulation (N = 155)



Appendix A: Complete Sample Results, Tables, and Figures

For the *complete sample* (N = 144), CTQ total scores ranged from 25 to 98 (M = 35.87, SD = 13.31). BDI total scores ranged from 0 to 36 (M = 7.72, SD = 6.75). The majority of mothers (95%) did not meet the clinical cut-off score for depression.

Correlation matrix with means and standard deviations on all study variables for the complete sample (N = 144)

	1	2	3	4	5	6	7	8	9	10	11	12	M	SD
1. DRD2	-												.43	.50
2. DAT1	.15	-											.41	.49
3. COMT	.05	-.07	-										.68	.47
4. Regulation	.07	-.30***	.07	-									99.41	72.36
5. CTQ	-.04	-.07	-.01	.20*	-								35.87	13.31
6. BDI	.17*	-.12	.08	.22**	.23**	-							7.72	6.75
7. Infant sex	.16	-.21*	.13	.10	.11	-.06	-						1.53	.50
8. Ethnicity	.29**	-.22**	.001	.13	.03	.08	-.03	-					1.27	.44
9. Mother salary	.04	-.03	-.10	-.03	-.27**	-.24**	.07	.01	-				2.66	1.48
10. Spouse salary	-.02	.07	.06	-.05	-.15	-.17	-.04	-.25**	.18*	-			3.68	1.63
11. Maternal education	.08	.03	-.05	-.03	-.30***	-.18*	-.11	-.05	.34***	.19*	-		3.92	.86
12. Maternal sensitivity	.08	-.14	.05	.08	-.01	-.04	.05	-.11	.20*	.16	.32***	-	.50	.27

Correlations means, and standard deviations for CTQ and BDI are non-centred in this table
* = $p < .05$, ** = $p < .01$, *** = $p < .001$

Multiple regression terms for all genes in complete sample (N = 144)

Gene	Model	B	Std. Error	t	Sig.
DRD2	Constant	92.44	7.69	12.02	.000*
	BDI	2.01	.90	2.24	.03*
	CTQ	1.43	.53	2.70	.008*
	DRD2	15.02	11.82	1.27	.21
	DRD2XCTQ	-1.97	.97	-2.03	.04*
DAT1	Constant	115.06	7.23	15.92	.000*
	BDI	1.31	.86	1.52	.13
	CTQ	1.56	.53	2.97	.003*
	DAT1	-40.91	11.37	-3.60	.000*
	DAT1XCTQ	-2.35	.91	-2.57	.01*
COMT	Constant	92.16	10.12	9.10	.000
	BDI	2.37	.89	2.67	.008*
	CTQ	2.35	.68	3.45	.001*
	COMT	10.55	12.29	.86	.39
	COMTXCTQ	-2.56	.89	-2.87	.005*
OXTR rs53576	Constant	95.67	7.43	12.88	.000*
	BDI	2.05	.89	2.29	.02*

	CTQ	1.22	.52	2.32	.02*
	OXTR	7.18	12.26	.59	.56
	OXTRXCTQ	-1.31	1.02	-1.28	.20
OXTR rs2254298	Constant	102.31	10.92	9.37	.000*
	BDI	1.98	.90	2.20	.03*
	CTQ	1.22	.80	1.52	.13
	OXTR	-4.33	12.96	-.33	.74
	OXTRXCTQ	-.55	.96	-.58	.57

* = $p < .05$

Multiple regression terms and Roisman et al. (2012) indices, N = 144

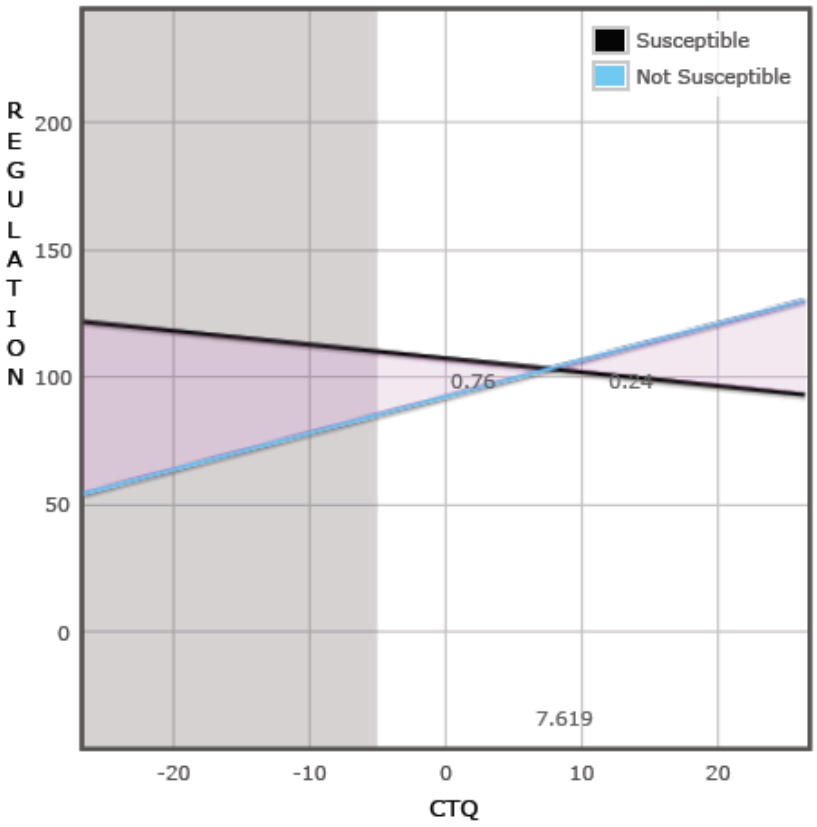
Regression Estimates						*ROS Z*		*ROS X*					
Gene	b_0	b_1	b_2	b_3	Adjusted R^2	Lower Bound	Upper Bound	Lower Bound	Upper Bound	PoI	PA	Crossover	X^2 or ZX^2?
DRD2	92.44	1.43	15.02	-1.97	.09	.28	16.55	-5.02	309.98	.76	.86	7.62	No
DAT1	115.06	1.56	-40.91	-2.35	.16	.30	1.99	-75.86	-6.79	.04	0	-17.39	No
COMT	92.16	2.35	10.55	-2.56	.13	.57	1.86	-6.24	22.20	.65	.77	4.12	No

* = $p < .05$

Mean comparisons of emotion regulation on allelic expressions of each gene

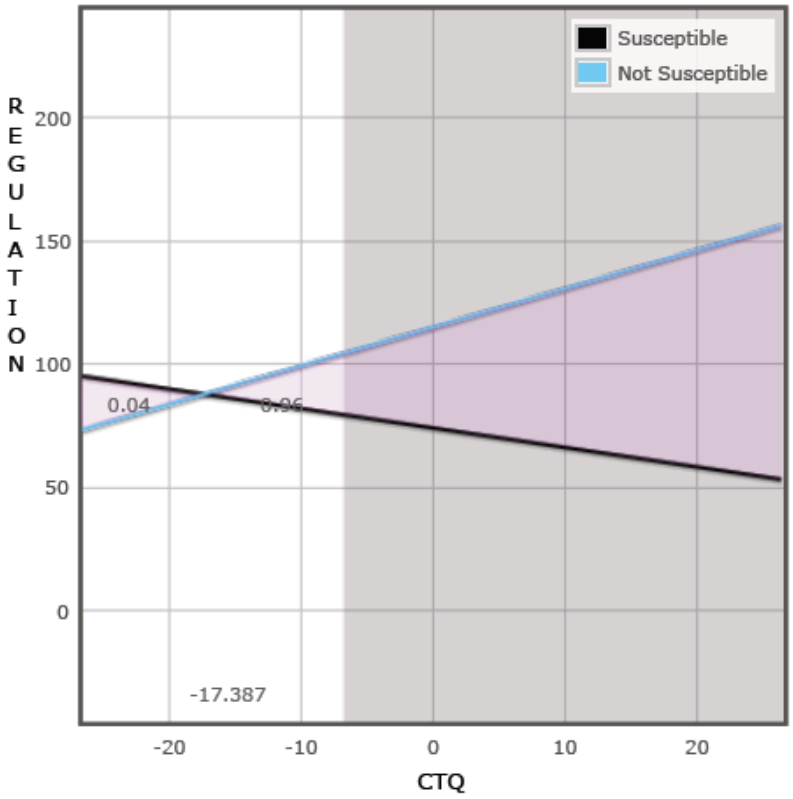
Gene	Larger samples (N = 147 to 159)	Complete sample (N = 144)
DRD2	F (1, 155) = 0.79, p = .38	F (1, 143) = 0.45, p = .50
A1+	102.43 (65.34), n = 65	125.28 (74.37), n = 62
A1-	92.29 (74.25), n = 92	115.61 (93.54), n = 82
DAT1	F (1, 145) = 13.79, $p < .001$	F (1, 143) = 15.98, $p < .001$
10 repeat absent	73.75 (57.16), n = 59	87.19 (58.82), n = 59
10 repeat present	116.91 (75.97), n = 88	142.40 (94.02), n = 85
COMT	F (1, 155) = 2.69, p = .10	F (1, 143) = 0.40, p = .53
A/G, A/A	103.86 (74.74), n = 101	122.87 (88.13), n = 98
G/G	84.55 (62.34), n = 56	113.20 (80.71), n = 46
OXTR rs53576	F (1, 156) = 0.43, p = .51	F (1, 143) = 0.19, p = .66
G/G	102.03 (61.77), n = 60	123.85 (74.08), n = 54
A/A, A/G	94.42 (75.39), n = 98	117.33 (92.23), n = 90
OXTR rs2254298	F (1, 157) = 0.24, p = .63	F (1, 143) = 0.26, p = .61
G/G	95.33 (71.93), n = 115	117.43 (87.73), n = 102
A/A, A/G	101.41 (66.43), n = 44	125.48 (81.17), n = 42

DRD2 by CTQ Interaction to predict Emotion Regulation (N = 144)



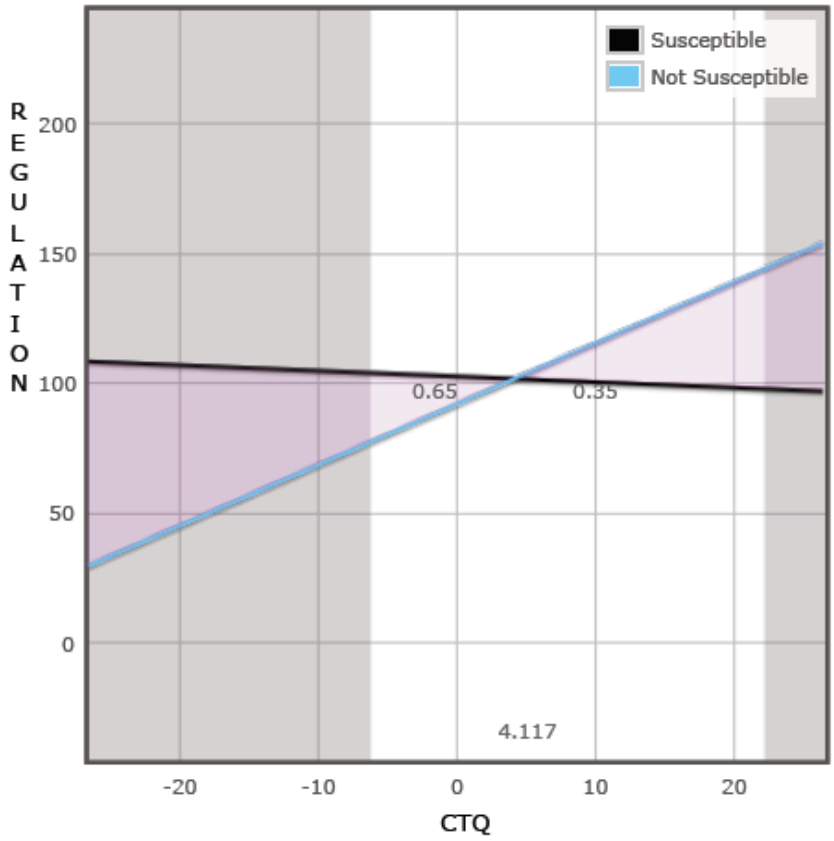
Note. The “Susceptible” allele is A1+ and the “Not Susceptible” allele is A1-

DAT1 by CTQ Interaction to predict Emotion Regulation (N = 144)



Note. The "Susceptible" allele is when 9-repeat allele is present and the "Not Susceptible" genotype is when 9-repeat allele is absent

COMT by CTQ Interaction to predict Emotion Regulation (N = 144)



Note. The "Susceptible" allele is when Met is present and the "Not Susceptible" allele is when Val is present

Appendix B: Multiple Imputation

Since the current sample had missing data for maternal depressive symptoms, maternal history of maltreatment, and infant emotion regulation, multiple imputations were conducted to compare hierarchical multiple regression results. Described below, imputed multiple regression results followed the same trends as regression analyses that were not imputed.

Multiple imputation can address missing data by replacing it with $x > 1$ sets of simulated imputed cells. This process results in x plausible, but unique, versions of the complete dataset. Each of the x datasets is analyzed uniformly and then combined to provide estimates and standard errors, while taking into account sample variation and missing-data uncertainty (Collins, Shafer, & Kam, 2001). In the present study, 20 imputations were conducted (above the recommended number), which is sufficient to yield efficient inferences (Collins, Shafer, & Kam, 2001; Graham, 2009). The average of the 20 imputations for each model's significance and the pooled predictors are reported here.

Before running imputation, Little's missing completely at random (MCAR) test was conducted to determine if the data was suitable for imputation. Based on Little's MCAR test, the data were missing at random, χ^2 (7) = 3.81, p = .80, and thus imputation was appropriate (Collins et al., 2001). For the imputed dataset, imputed correlations followed the same trends of significance as those of the non-imputed samples; that is, out of all covariates aside from genes, only CTQ and BDI significantly correlated with infant emotion regulation. Therefore, BDI was controlled for as a covariate for the imputed multiple regression analyses.

Multiple imputations were performed for the DRD2, DAT1, and COMT GXE models. CTQ and BDI scores were centred after data was imputed, before multiple regressions were run.

The pooled imputed findings are summarized in the table below. All interaction terms were significant, consistent with non-imputed results.

Pooled Imputed Findings

Gene	Model	B	Std. Error	*t*	Sig.
DRD2	Constant	94.19	6.59	14.30	.000*
	BDI	1.50	.83	1,81	.07
	CTQ	1.30	.48	2.72	.007*
	DRD2	7.45	10.25	.73	.47
	DRD2XCTQ	-1.74	.81	-2.14	.03*
DAT1	Constant	113.42	6.54	17.34	.000*
	BDI	1.22	.87	1.40	.16
	CTQ	1.13	.47	2.40	.02*
	DAT1	-35.99	10.45	-3.45	.001*
	DAT1XCTQ	-2.02	.86	-2.35	.02*
COMT	Constant	91.62	8.45	10.84	.000
	BDI	1.68	.84	2.00	.05*
	CTQ	1.67	.58	2.91	.004*
	COMT	9.27	10.60	.88	.38
	COMTXCTQ	-1.78	.78	-2.28	.02*

* = $p < .05$

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