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Relations between early maternal sensitivity and toddler self-regulation: Exploring variation by oxytocin and dopamine D2 receptor genes

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Abstract

Gene-by-environment interactions between maternal sensitivity during infancy and child oxytocin receptor gene (*OXTR* rs53576) and D2 dopamine receptor gene (*DRD2* TaqIA, rs1822497) genotypes were explored as predictors of toddlers' well-regulated behavioral and physiological responses to maternal compliance demands. Maternal sensitivity was assessed across a range of mother-child interactions when children were 6 months and 1 year of age ($N = 186$), and toddler self-regulatory responses were assessed through compliance and vagal withdrawal during a toy clean-up task when children were 2 years of age. Sensitivity-by-*OXTR* interactions suggested two diathesis-stress patterns, predicting compliance for the GG genotype group, and predicting physiological regulation for the AA/AG genotype group. A main effect for *DRD2* genotype indicated that children with an A1 allele displayed less-compliant behavior in toddlerhood. These results suggest that genetic differences may contribute to variation both in risk for self-regulatory difficulties, and in relations between maternal sensitivity and children's responses to compliance demands at different levels of analysis.

Keywords

maternal sensitivity; self-regulation; GxE; RSA; infancy

Children's self-regulation is a relatively broad construct represented by the ability to modulate emotions and behaviors to meet external demands across different contexts (see Calkins, Perry, & Dollar, 2016). Failures of self-regulation underlie many social and behavioral problems in childhood (e.g., Calkins & Fox, 2002; Kochanska & Knaack, 2003; Eisenberg, Smith, & Spinrad, 2011), so understanding its early developmental underpinnings is a key task for researchers. One common method of assessing children's early regulatory skills is through their compliance responses, that is, their ability to modulate affect and behavior responses in order to comply with external, typically maternal, demands (e.g.,

Kochanska & Askan, 1995). A great deal of past research demonstrates the important role of maternal sensitivity to infant cues in infants' socioemotional development, including the development of self-regulation and related compliance responses (Fox & Calkins, 2003; Kopp, 1982). However, genetic differences have been proposed as a moderating influence in the connection between early experiences and developmental outcomes (e.g., Caspi et al., 2003). In this study we examined variations in the relationship between early maternal sensitivity and later behavioral and physiological responses to maternal compliance demands based on children's genotype for Single Nucleotide Polymorphisms (SNPs) in the oxytocin receptor and D2 dopamine receptor genes.

Maternal Sensitivity and Gene-by-Environment Interactions

Maternal sensitivity reflects the mother's tendency to readily perceive and accurately interpret infant signals and to contingently and appropriately respond to them (Ainsworth, Blehar, Waters, & Wall, 1978). Infants rely on external input to manage distress and other responses, and mothers' tendency to respond sensitively to these cues helps enact the co-regulation of emotional, behavioral, cognitive, and psychophysiological processes that over time support the child's ability to independently modulate and control responses (e.g., Calkins, 2011; Leerkes, Blankson, & O'Brien, 2009; Sameroff & Fiese, 1990). Accordingly, infants whose mothers display high levels of sensitivity to their cues tend to evidence better performance on self-regulatory outcomes relevant to compliance tasks, including competent displays of emotion and behavior, control of cognitive processes, and more adaptive physiological reactivity and regulation (Leerkes et al., 2009; Bernier, Carlson, & Whipple, 2010; Propper & Moore, 2006).

Importantly, individual differences in self-regulatory development are not expected to emerge solely from differences in early caregiving, but also from biologically-based individual differences in reactivity and self-regulation (Bell & Deater-Deckard, 2007). Among many genetic markers explored in previous research (e.g., polymorphisms, variable number/short tandem repeats), SNPs in a number of candidate genes have been highlighted as potential sources of risk or plasticity in development. If individuals with different genotypes demonstrate differing relations between developmental experiences and outcomes, this pattern falls in the realm of gene-by-environment interaction (GxE) (Caspi et al., 2003).

Studies examining GxE effects tend to highlight two distinct perspectives regarding how individual differences interact with early environmental conditions to predict outcomes typically viewed as "better" or "poorer," or to predict conventionally "poorer" outcomes that reflect protective adaptation to one's early environment (Belsky & Pluess, 2009; Roisman et al., 2012). According to the diathesis-stress or dual-risk model, certain characteristics convey greater risk for conventionally poor outcomes when individuals are exposed to less-optimal developmental conditions, but differences will be less apparent in more-optimal conditions (Monroe & Simons, 1991; Zuckerman, 1999). In this perspective, genetic risk is conferred by the presence of a putative "risk" allele on a candidate gene. The diathesis-stress model has been challenged by researchers who instead adopt a differential susceptibility perspective (Belsky & Pluess, 2009; 2013). In this perspective, individual characteristics do

not confer risk so much as plasticity or susceptibility to environmental conditions. This susceptibility is hypothesized to lead to relatively poorer outcomes in less-optimal conditions but relatively *better* outcomes in more-optimal conditions, i.e., a “for better and for worse” pattern. Thus, genetic susceptibility is conferred by the presence of a putative “plasticity” or “susceptibility” allele on a candidate gene.

A number of existing studies have found significant GxE patterns based on parenting quality in relation to children’s socioemotional development and psychopathology (Calkins, Propper, & Mills-Koonce, 2013; Cox, Mills-Koonce, Propper, & Gariépy, 2010; Kim-Cohen & Turkewitz, 2012). Nonetheless, the results of developmental GxE research with respect to maternal sensitivity are mixed and have received criticism due to issues with power and replicability (Belsky et al., 2015; Duncan & Keller, 2011; Leerkes et al., 2017; Luijk et al., 2011). Thus, to further contribute to the growing body of GxE research in developmental psychopathology, the current study focused on SNPs in two candidate genes that have been relatively understudied in infants and children: one related to the oxytocin receptor system (*OXTR* rs53576) and one related to the dopaminergic system (*DRD2* TaqIA, rs1822497). Past research provides a compelling basis for the idea that genotypic variation in each of these SNPs could underlie patterns of social interaction and reward processing that may contribute meaningfully to early self-regulatory outcomes, as well as moderate the manner in which sensitive parenting facilitates the development of children’s regulatory abilities.

Oxytocin Receptor Gene (*OXTR* rs53576)

The oxytocin system has been variously implicated in human relationships and well-being, with the release of oxytocin found to coincide with the development of social attachments, reductions in stress and fear reactivity, prosocial and positive social interactions, and salience and memory for social interactions in adult samples (Campbell, 2010; IsHak, Calhoun, & Fakhry, 2011; Uvnäs-Moberg, 1998). Genetic researchers have identified a SNP rs53576, a G (guanine) to A (adenine) change in the third intron (non-coding region) of the oxytocin receptor (*OXTR*) gene (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011) that may underlie individual differences in receptivity to social stimuli. Both the A and G alleles have been identified as influencing social interactions. Importantly, research on these genotype differences is limited primarily to adult samples, thus the implications of *OXTR* genotype in infancy less clear. However, the literature on older samples may inform hypotheses regarding genetic predispositions relevant to infant developmental processes. The presence of an “A” allele (AA or AG genotypes) is thought to confer risk for social and regulatory difficulties, as it has been linked to greater dispositional and physiological reactivity to stressors and lower levels of empathy and psychological resource variables (Kumsta & Heinrichs, 2012; Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011; Rodrigues, Saslow, Garcia, John, & Keltner, 2009). From a diathesis-stress perspective, A-carriers may be at relatively greater risk for poor regulatory outcomes in less-optimal caregiving environments. Maternal sensitivity may counteract this risk by helping these infants to more consistently and successfully manage their comparatively heightened stress reactivity and related distress and negative reactivity, and in turn increasing the likelihood they will develop regulatory skills necessary for compliance to external demands.

Conversely, being homozygous for the G allele (GG genotype) is linked to greater sociability, trust, other-oriented empathy, and receptiveness to social feedback and support (Feldman, Monakhov, Pratt, & Ebstein, 2016; Li et al., 2015; Rodrigues et al., 2009). As such, individuals with the GG genotype may be more susceptible to the effects of sensitivity consistent with a pattern of differential susceptibility due to their greater sensitivity to social relationships and openness to social support. Early maternal sensitivity could be particularly important in the process of co-regulation and eventual tendency to regulate responses according to maternal demands for these GG infants, but they may also especially struggle to develop these regulatory skills in the context of low maternal sensitivity.

To our knowledge, there is no existing research examining the interaction of maternal sensitivity and *OXTR* rs53576 in relation to self-regulatory development in infancy or early childhood, but several studies have examined GxE patterns with respect to parenting quality and *OXTR* in relation to other child outcomes or in relation to adult coping/regulation. For example, a prospective study of infants at risk for autism spectrum disorder found that the emotional quality of parent-infant interactions related to the child's later empathy toward the parent only for children with a GG genotype (McDonald, Baker, and Messinger, 2016). Evidence also suggests that risks associated with parental maltreatment may be particularly pronounced in carriers of the G allele (GG and AG genotype). In studies comparing individuals with a history of maltreatment to genotype-matched controls, children and adolescents with the GG genotype had the greatest deficit in socioemotional resilience (Cicchetti & Rogosch, 2014) and lower perceived social support (Hostinar, Cicchetti, & Rogosch, 2014). In an adult African-American sample, G-carriers who reported multiple types of childhood maltreatment experiences had significantly higher levels of emotion dysregulation than other genotype and/or maltreatment groups (Bradley et al., 2011). Finally, the quality of one's childhood family environment related to resilient coping and positive affect only for G-carriers after controlling for early child maltreatment/trauma (Bradley, Davis, Wingo, Mercer, & Ressler, 2012). Thus, across studies, there is some evidence for both a "for better" and "for worse" pattern that characterizes the differential susceptibility perspective with respect to *OXTR* rs53576 and parenting. However, because little of this work focuses on outcomes of parenting measured early in life and/or in a community sample, it is unclear if the same pattern would be found for relations between maternal sensitivity and early regulatory responses in the context of maternal compliance demands.

D2 Dopamine Receptor Gene (*DRD2* TaqIA rs1822497)

Elevations in brain dopamine and dopamine receptor availability contribute to reinforcement, learning, and memory consolidation processes related to the experience and pursuit of rewarding stimuli (Wise, 2004; 2005). A number of studies in both the adult and child literature have focused on associations with a SNP in the dopamine D2 receptor gene (*DRD2*). The *DRD2* gene has a TaqI restriction endonuclease site, rs1800497 10 kilobases downstream of the coding region in the 3' untranslated region (Noble, 2003). This site is designated TaqIA to distinguish it from another TaqI restriction site (TaqIB) located elsewhere in the gene. The TaqIA site has a point mutation, C to T, rs1800497. Historically, the T allele, which was not cleaved by TaqI, was termed A1 and the cleaved C allele was

termed A2. Since the majority of literature citations use the A1/A2 designation, we use that terminology here. Neville, Johnstone, and Walton (2004) reported that rs1800497 occurred in exon 8 of the ANKK1 gene on the opposite strand, resulting in a Glu-to-Lys (E713K) substitution within the eleventh ankyrin repeat of ANKK1. There is the possibility that at least some of the associations given to rs1800497 may be the result of changes in ANKK1 and not solely to the DRD2 receptor. For consistency with previous literature, we will refer to rs1800497 as DRD2 TaqIA, realizing that any association found may be due all or in part to ANKK1.

The *DRD2* A1 allele has been conceptualized to confer risk for poorer self-regulatory outcomes. For example, adults with at least one A1 allele (A1/A1 or A1/A2 genotypes), are more likely to display “impulsive-addictive-compulsive” behaviors and outcomes such as sensation-seeking, substance use/dependence, and obesity compared to those with the A2/A2 genotype (Blum et al., 1995; Noble, 2003). Further research on brain functioning found that adults with an A1 allele evidenced a lower density of D2 dopamine receptors, which the authors speculated may have implications for reward processing, perhaps leading to a need for greater levels of limbic dopamine (Pohjalainen et al., 1998; Thompson et al., 1997). Researchers have thus proposed that individuals who carry an A1 allele are predisposed to a “reward deficiency syndrome” in which impulsive-addictive-compulsive behaviors reflect an attempt to stimulate a less-active dopaminergic system (Blum & Braverman, 2000; Noble, 2003).

DRD2 has been highlighted in relatively fewer developmental studies of infants and children compared to, for example, the D4 receptor gene *DRD4* (Belsky et al., 2015). However, the D2 receptor has been found to play a somewhat specialized role in processes of learning and memory in response to reward not found for *DRD4* (Wise, 2004). Genetically-based differences in reward processing could thus potentially contribute to relations between maternal sensitivity and developing self-regulation. If infants who carry an A1 allele tend to require high levels of reward to stimulate the dopaminergic system, then a history of maternal care that is highly sensitive may be necessary to reinforce well-regulated responses, rendering sensitivity a stronger predictor of regulatory responses to maternal demands in these infants. Similarly, the coregulatory effects of maternal sensitivity may be particularly strong for these infants, given evidence that individuals who carry an A1 allele may also pursue reward as a means of negative reinforcement (Berman, Ozkaragoz, Young, & Noble, 2002). Existing findings tentatively support these expectations with respect to other regulatory measures. In one cross-sectional study, maternal sensitivity at 12 months buffered genotype group differences, such that infants with an A1/A1 or A1/A2 genotype who received low levels of maternal sensitivity showed less physiological regulation during a maternal separation than comparison A2/A2 genotype infants, but those who received high levels of maternal sensitivity showed similar levels to the A2/A2 infants (Propper et al., 2008). In the same sample, maternal sensitivity in infancy related to lower affective problems at 36 months only in infants with an A1/A1 or A1/A2 genotype (Mills-Koonce et al., 2007). Further, Belsky and colleagues (2015) found weak evidence for a diathesis-stress pattern for the infants with an A1/A1 or A1/A2 genotype predicting mother-rated social competence and behavior problems. Collectively, one might expect that potential risk for

poorer self-regulatory outcomes in infants with an A1 allele could be attenuated by experiencing higher maternal sensitivity in early life, in a diathesis-stress pattern.

Predicting Regulation at Different Levels of Analysis

Researchers can observe self-regulatory processes at multiple levels of analysis in humans, each of which reflects a related but distinct form of functioning (Calkins & Fox, 2002). Thus, it is also possible that the proposed GxE effects for *OXTR* and *DRD2* emerge differently with different types of regulatory outcomes. This study focused on outcome measures observed at two different levels of analysis during a maternal compliance task in toddlerhood. One outcome was measured at the behavioral level, assessed through outwardly observable compliance responses to maternal requests including compliance with maternal expectations and lower negative affect and defiance (e.g., Calkins & Fox, 2002; Kochanska & Aksan, 1995; Kochanska & Knaack, 2003). The other outcome in this study was measured at the physiological level, assessed through change in respiratory sinus arrhythmia (RSA) from a resting state in response to a task or challenge. Basal RSA is used as a measure of vagal tone, thought to be an index of parasympathetic input to the heart and other organs that reflects a readiness to react to environmental stimuli and engage with one's environment (Porges, 1991). Porges's (1995) Polyvagal Theory suggests that when challenged, there is a withdrawal of parasympathetic influence to the heart, indexed by a decrease in RSA, that allows humans to manage arousal in response to the challenge (Fox & Calkins, 2003; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). The tendency to respond to environmental challenge, such as maternal requests to stop playing and pick up toys, with greater vagal withdrawal may reflect a greater capacity for self-regulation at the physiological level (Calkins & Fox, 2002; Porges et al., 1996).

With respect to *DRD2*, existing research suggests that *DRD2*TaqIA genotype moderates relations between maternal sensitivity in infancy and infant/toddler functioning at both observable and physiological levels of analysis, indicating general benefits of sensitivity for the A1/A1 or A1/A2 genotypes (e.g., Mills-Koonce et al., 2007; Propper et al., 2008). This pattern of effects could be further tested, though, by predicting simultaneous observed and physiological responses to a self-regulatory challenge such as a maternal compliance task.

As mentioned, evidence for *OXTR* rs53576 as a moderator of maternal sensitivity effects on children's self-regulation is lacking, but it is possible that different patterns could be expected for different outcome measures. For example, because infants with an *OXTR* GG genotype display greater levels of sociability and receptivity to relational input (Feldman et al., 2016; Li et al., 2015), maternal sensitivity could have stronger relations with observable, interpersonal indicators of compliance for these infants. That is, the benefits of sensitive caregiving may be expressed more strongly through GG-genotype infants' tendency to sustain competent social interactions with parents and other authority figures during a regulatory challenge, by displaying more compliance to their requests and a lesser tendency to express distress or defiance. Conversely, having an *OXTR* AA or AG (A-carrier) genotype is linked to lower social support-seeking and greater physiological/stress reactivity, so maternal sensitivity may better assist A-carrier infants in the development of regulatory processes at the physiological level. Because of this, the effect of sensitive maternal

caregiving on A-carrier infants' ability to manage distress and build psychological resources may be more apparent in their physiological functioning in response to environmental challenge than in their ability to display compliant social behaviors. Taken together, there is need for greater clarity in *OXTR* and *DRD2* genotypic comparisons in the study of maternal sensitivity and distinct levels of self-regulatory outcomes in children.

Current Study

Highly sensitive and responsive caregiving is thought to support early self-regulatory skills in all children, but genetic differences with respect to relational and reward stimuli may moderate the processes through which sensitivity's benefits are enacted in the context of maternal compliance demands. The current study used a candidate gene design to examine interactions between maternal sensitivity in infancy (6 months and 1 year) and infants' *OXTR* and *DRD2* genotypes in predicting self-regulatory responses during a clean-up compliance task in toddlerhood (2 years). Maternal sensitivity in infancy was assessed during a wide range of tasks designed to elicit infant distress, and reflected the appropriateness of the mother's behavior to the type of affect the infant displayed. Toddler responses during the compliance task were assessed via behavioral compliance and physiological regulation measured by vagal withdrawal.

For moderation by *OXTR*, it was hypothesized that maternal sensitivity would relate more strongly to behavioral compliance in infants with a GG genotype in a differential susceptibility pattern due to their hypothesized susceptibility to social input, and the potential relevance of maternal sensitivity for supporting competent social interactions. It was hypothesized that maternal sensitivity would relate more strongly to physiological regulation in infants with an AA or AG genotype, in a diathesis-stress pattern, due to their predisposition toward stress reactivity and lower reliance on social support, and the potential relevance of maternal sensitivity for managing physiological arousal. For moderation by *DRD2*, it was hypothesized that relations between maternal sensitivity and both self-regulatory outcomes would be stronger for infants with an A1/A1 or A1/A2 genotype relative to those with an A2/A2 genotype, in a diathesis-stress pattern, given the broad risk for regulatory problems associated with the A1 allele.

Mothers were involved in managing the toy clean-up task in which regulatory outcomes were assessed, so maternal sensitivity during that task was treated as a covariate to rule out the possibility that observed associations between early sensitivity and compliance and/or physiological regulation are a function of concurrent sensitivity. Finally, race was examined as a covariate because: (a) genetic researchers recognize that race could underlie systematic differences both in allele frequencies and in associations between genotype and phenotypic outcomes (Cardon & Palmer, 2003) and (b) self-regulatory development may be impacted by sociocultural factors (e.g., Raver, 2004). Confounding of GxE effects by race was also tested following Keller's (2014) recommendations by running the models with additional gene-by-race and sensitivity-by-race interactions. However, based on similar gene-by-sensitivity studies focused on other socioemotional outcomes, different GxE patterns for White and non-White participants were not anticipated in this study (Leerkes et al., 2017; Roisman et al., 2013).

Method

Participants

Participants were 186 primiparous mothers and their children who took part in a longitudinal study in the southeastern United States. Mothers were recruited via flyers and/or presentations in birth education classes, breastfeeding classes, local obstetric practices, clinics, or by referral from other participants. Inclusion criteria for the study included being 18 or older, African-American or European American, fluent in English, and expecting their first child. The original sample ($N = 259$) consisted of mothers who consented to the study and completed an interview and self-report measures prior to the child's birth.

The current study includes data from laboratory observations of the mother and child within two weeks before/after the child turned 6 months of age ($M = 6.39$ months, $SD = .72$), and when the child was approximately 1 year of age ($M = 13.9$ months, $SD = .98$), and 2 years of age ($M = 27.32$ months, $SD = 2.52$ months). DNA data were collected from the infants at the 2-year assessment point. Accordingly, the study sample is limited to individuals who took part in observations at 6 and 12 months and provided DNA data at 2 years. This study sample included 93 European American mothers, 84 African American mothers, and 9 who self-identified as more than one race. They ranged from 18–44 years of age at the start of the study, $M = 25$. The majority (76%) had at least some college level schooling, and self-reported annual family income ranged from under \$2000 to over \$100,000, Median = \$35,000. The majority (60%) of mothers were married or living with a partner, 23% were in a relationship but not living a partner, and 17% were single or divorced. All infants were full term and healthy; 90 (48%) were male and 96 (52%) were female; 89 were European American/White and 97 were non-White (88 African American, 9 multi-racial) based on maternal report.

Participants who left the study prior to the 2-year time point did so primarily because they could not be reached, had moved from the area, or did not have time available to participate. Attrition analyses suggested that those who participated in the 2-year observation and DNA collection did not differ from those who did not on race, marital status, or income-to-needs; however, mothers who participated were significantly older (years at child's birth $M = 25.54$, $SD = 5.49$ compared to $M = 23.48$, $SD = 4.87$, $t(256) = 2.63$, $p < .01$) and reported somewhat higher levels of education ($M = 3.92$, $SD = 1.80$ compared to $M = 3.43$, $SD = 1.72$ on a scale in which 3 = *some college* and 4 = *2-year college degree*, $t(255) = 1.90$, $p = .06$).

Procedures

6-month and 1-year laboratory visits.—Mothers and children took part in several tasks at the 6-month and 1-year laboratory visit for the purposes of assessing maternal sensitivity. During the 6-month visit, following a free play task, interactions were observed during an arm restraint, a novel toy introduction, and a still face procedure; all took place while the infant was seated in a baby seat. The arm restraint was designed to elicit frustration; an experimenter gently held the infants' arms down for 4 minutes. The novel toy introduction was designed to elicit fear; a toy truck moved back and forth toward the infant

and made noise for 4 minutes. In each task, the mother was asked to remain neutral for one minute, then could interact with the infant for the remaining 3 minutes however she liked except for removing the infant from the seat or touching the novel toy. During the Face-to-Face Still Face procedure (Tronick, Als, Adamson, Wise & Brazelton, 1978), the mother sat facing the infant at eye level. The mother was asked to play with the infant as she normally would using voice and hands for 2 minutes, then look away briefly and look back at their infant with a still face for 2 minutes, then look away briefly and return to playing with the infant for 2 minutes.

During the 1-year visit, following the Strange Situation and a free-play task, interactions were observed during a toy removal and a novel person approach. The toy removal was intended to elicit frustration; the experimenter allowed the child to play with a toy phone for 1 minute, removed the toy and placed it in a clear plastic jar the infant was unable to open, then repeatedly prompted the child to get the phone for 4 minutes. The novel person approach was intended to elicit fear; an experimenter wearing a green ogre costume entered the laboratory and repeatedly approached and withdrew from within 2 feet of the infant while restating a standard script (“Hi, [Child]. What are you doing? I’m an ogre. Do you know what an ogre is?...”) for 4 minutes, as described in Leerkes and Wong (2012). In each task, the mother was asked to remain neutral for 1 minute, then could interact with the infant for 3 minutes however she liked except for taking the phone out of the jar or speaking to or touching the ogre. At each time point, infants who were distressed by a task were soothed by the mother and/or experimenter before beginning the next task. As such, relatively few infants failed to engage in the tasks included in this report (2 did not complete the still-face re-engagement episode at 6 months because they were inconsolable; 2 did not complete the toy removal task at age 1 because they were uninterested; 2 did not complete the novel person approach at age 1 because they were inconsolable).

2 year laboratory visit.—Self-regulatory responses to maternal compliance demands were assessed during a clean-up task during the laboratory visit at 2 years. Toddlers wore three disposable electrodes throughout the laboratory visit, one placed on each ribcage and one on the collarbone, connected to a Biolog (UFI, Morro Bay, CA) for R-wave detection (i.e., heart rate collection). As a baseline, mothers were asked to play with their child as they normally would for 7 minutes using toys set up in the laboratory. Next, the experimenter brought in 2 containers and instructed the mother to get the child to clean up all the toys. Mothers could behave however they wanted, but had to involve the child in the clean-up. The task ended after 5 minutes or when all the toys were in the containers. An experimenter pressed an event marker on a key fob to signal the start and stop time of each portion (free play, clean-up) with the Biolog. Following the clean-up, dyads engaged during a fear-inducing spider approach and frustration-inducing goal blockage task (i.e., attractive toy in a locked box) not included in this report.

At the end of the visit, DNA was collected via buccal samples using the Oragene™ (DNAgenotek, Ottawa, Ontario, Canada) swab format (#OG-575). An experimenter used a small sponge-tipped swab to soak up saliva from the child’s mouth and deposited the saliva into a collection tube using an attached funnel. After a 2ml saliva sample was collected, the

tube was capped to release a stabilizing lysis buffer and then stored at 15–30°C prior to DNA extraction.

Measures

Behavioral coding.—The mother-child interaction tasks were continuously coded from digital media files using INTERACT 9 (Mangold, Arnstorf, Germany). Event based coding was used, meaning once a code was activated, it remained active until another code was selected. For all behavioral coding, coders were blind to other data, reliability cases were selected at random, and disagreements were resolved via consensus.

Maternal sensitivity (6 months and 1 year).—Maternal sensitivity was rated in the mother-involved portions of the distress-eliciting tasks at 6 months and 1 year based on infant affect and mother behavior. The process for determining maternal sensitivity scores was described in detail in Leerkes (2010). First, infant affect in each task was continuously rated on a 7-point scale from 1 = *high positive affect* to 7 = *high negative affect* based on vocalizations, facial expressions, and body tension (adapted from Braungart-Rieker & Stifter, 1996). Interrater reliability was assessed on 16% of cases at 6 months, weighted kappa = .76, and 15% of cases at 1 year, weighted kappa = .75. At 6 months 96% of infants became distressed during the tasks (i.e., displayed negative affect, defined as an affect level 5, at any point during the distress tasks), and at 1 year 91% of infants became distressed. Mother behavior was coded in each task using 12 mutually exclusive categories (engagement, routine care, supportive, negative, intrusive, mismatch affect, withdraw, distracted, persistent ineffective, monitor, calming). Interrater reliability was assessed on 14% of cases at 6 months, kappa = .77, and 13% of cases at 1 year, kappa = .80. Next, the infant affect and maternal behavior code files were merged and the appropriateness and quality of maternal behavior at each moment was assigned a sensitivity rating based on whether concurrent infant was negative, neutral, or positive on an established 3 point scale, 1 = *insensitive*, 2 = *moderately sensitive*, and 3 = *sensitive*. The specific sensitivity rating assigned to each maternal behavior code given the infant's current affect was consistent with the detailed rating scheme described in Leerkes (2010) and reported in online supplemental information Table S.1. For example, calming behavior (soothing the child physically or vocally) while the child displays negative affect is assigned a score of 3 (sensitive) because the mother is responding to a clear distress cue from the infant and appropriately attempting to help the infant reduce this distress. Conversely, distracted behavior (uninvolved or minimally involved with child) while the child displays negative affect is assigned a score of 1 (insensitive).

The mean level of sensitivity across all distress-eliciting tasks was calculated at each time point based on the sum of time spent at each sensitivity level divided by the total time (6 month $M = 2.69$, $SD = .18$; 1 year $M = 2.36$, $SD = .28$), and these correlated positively ($r = .38$, $p < .001$). Thus, a single early maternal sensitivity score was calculated by averaging the 6 month and 1 year scores; higher scores indicate higher sensitivity.

Maternal sensitivity (2 years).—Given its potential influence on concurrent child responses, a global rating of maternal sensitivity was made during the clean-up task. The micro-coding approach described above was not used to code this task because it was developed

specifically for use in the distress-eliciting tasks described above and did not adequately capture maternal responses unique to a cleanup task (e.g., playful attempts to engage child in clean up, firm directives, etc). Accordingly, sensitivity was rated on a scale from 1 = *highly insensitive* to 9 = *highly sensitive*, following Ainsworth, Bell, and Stayton (1974). Interrater reliability was assessed on 15% of cases, ICC = .95. This was used as a control variable in all analyses ($M = 6.46$, $SD = 1.90$). Notably, global sensitivity scores such as this have been found to correlate with micro-coded sensitivity scores in infancy (Leerkes, 2010).

Compliance (2 years).: Child affect was continuously coded throughout the clean-up task based on the 7-point scale described above. Toddler mean affect during the task was calculated such that higher scores indicate more negative affect ($M = 4.10$, $SD = .30$). Interrater reliability was assessed on 17% of cases, weighted kappa = .81. Children's behavioral compliance to their mother's clean-up request was continuously coded into five mutually exclusive and exhaustive categories used in previous studies (Crockenberg & Litman, 1990; Kochanska & Aksan, 1995). In this report we include three of these behaviors, two of which most clearly map onto well-regulated, compliant behavior and one which clearly maps onto dysregulated, defiant behavior. Compliant behavior is the proportion of time children engaged in committed compliance, defined by immediate and sustained clean-up behavior upon initial request, or situational compliance, defined by clean-up behavior with repeated maternal prompts (i.e., the two were summed; $M = .47$, $SD = .27$). Defiance is the proportion of time children engaged in any behavior that was resistant, confrontational, or rebellious ($M = .07$, $SD = .17$). Interrater reliability was assessed on 15% of cases, kappa = .75. Observed affect reversed, compliance, and defiance reversed were significantly positively correlated ($r_s .56-.96$, $p_s < .001$). Thus, a composite compliance score was calculated as the mean of standardized scores for each measure. Higher scores represent well-regulated behavior characterized by more compliance and less defiance and negative affect.

Physiological regulation (2 years).—Toddlers' electrocardiogram was recorded at a sampling rate of 1 kHz. A data file containing the interbeat intervals (time between R-waves) during the 2-year tasks was transferred from the Biolog to a laptop computer for artifact editing (resulting from movement). Standard editing procedures (i.e., scanned for outlier points and these points were edited by dividing or summing them to be consistent with adjacent data) were used by a staff member who was trained by and demonstrated reliability with staff from the Brain-Body Center, University of Illinois at Chicago. Task data requiring artifact editing for >10% of data was removed from the raw data file; task data with artifact editing for <10% of data were retained. Analyses to derive heart period variance were completed using CardioEdit software (Brain-Body Center, University of Illinois at Chicago). Measures of RSA, reflecting vagal tone, were calculated in ms^2 using Porges' (1985) method in 15-s epochs for each task. A band pass filter extracted heart period variance within the frequency band of spontaneous respiration (.24–1.04 Hz) in young children. Epoch scores were averaged within task. Vagal withdrawal scores were calculated for the clean-up task by subtracting average RSA during the clean-up from average RSA during the baseline free play. Higher scores indicated greater vagal withdrawal from baseline to clean-up and indicated better physiological regulation. A single imputation of the raw data

was then performed to generate complete RSA data for 43 participant tasks (23% of the final analytic sample) with >10% artifact editing (34 cases during the clean-up among the final analytic sample) or missing due to equipment failure (9 cases during the clean-up among the final analytic sample) using SPSS Version 22 (IBM Corp, Armonk, NY). RSA and heart rate variables were correlated across all other 2-year tasks, so these variables and participant race were entered into the imputation model as predictors. Ten toddlers had no RSA data for any 2-year task due to equipment failure.

DNA extraction.—As detailed in Leerkes et al. (2017), DNA was prepared at the Molecular/Cellular Biology Core Laboratory at the University of North Carolina at Greensboro using methods described by Oragene. Then, DNA was quantified by spectrophotometry (Nanodrop Spectrophotometer) and standardized to a working concentration of 20 ng/μl. Genotyping was performed at the Institute for Behavioral Genetics at the University of Colorado under the supervision of Dr. Andrew Smolen. Two individuals scored genotypes independently, and inconsistencies were reviewed and rerun when necessary.

The *OXTR* (rs53576) assay was completed using a fluorogenic 5' nuclease (Taqman®, Life Technologies, Grand Island, NY) method with primer-probe reagents obtained from the company (assay number C__3290335_10_M) using company protocols. Genotypes considered in this study were AA, AG, and GG. The AG genotype was more prevalent among non-White children than White children ($\chi^2(1) = 6.82, p < .05$). Genotype frequencies were in Hardy-Weinberg Equilibrium (HWE) for non-White children ($p = .14$) but not for White children ($p = .003$). Deviation from HWE is likely due to small sample size, possible mixed-race of the children reported to be White by the mother, or the existence of multiple isolated genomic populations with shared skin color. *OXTR* rs53576 genotypes were also found to deviate from HWE in a White sample in one of the few published studies examining this SNP in infants (Luijk et al., 2011), suggesting possible genetic diversity of this SNP in White populations. Nonetheless, we acknowledge this violation of HWE differs from the norms of adult research on rs53576. Given the literature suggesting potential regulatory deficits in A-carrier genotypes, in addition to susceptibility to social information associated with G allele and more specifically the GG genotype, children were placed into two genotype groups for the purpose of analyses, an AA or AG (A-carrier) genotype group ($N = 103$) and a GG genotype group ($N = 83$).

The *DRD2* TaqIA (rs1800497) SNP was assayed using a Taqman® method as described by Haberstick and Smolen (2004). Genotypes considered in this study were A1/A1, A1/A2, A2/A2. The A1 allele was more prevalent among non-White children than White children ($\chi^2(1) = 12.53, p < .01$), but genotype frequencies were in the Hardy-Weinberg Equilibrium ($p = .18$ for White and $p = .17$ for non-White). Based on previous research identifying risk associated with the A1 allele, children were placed into two genotype groups for the purpose of analyses, with $N = 73$ in a group of those carrying an A1 allele (A1/A1 or A1/A2 genotype) and $N = 113$ in the A2/A2 genotype group.

Statistical Analyses

The hypotheses were tested using two hierarchical multiple regression models, one predicting the compliance score and one predicting the physiological regulation score. These models controlled for infant race and mother sensitivity during the compliance task. The predictors for each model included the two control variables (Step 1), the early maternal sensitivity score, *OXTR* genotype (AA or AG vs. GG), and *DRD2* genotype (A2/A2 vs. A1/A1 or A1/A2) (added in Step 2), and the interaction of maternal sensitivity and *OXTR* genotype and interaction of maternal sensitivity and *DRD2* genotype (added in Step 3). Regressions were run simultaneously for each step in Mplus 7.3 (Muthén & Muthén, Los Angeles, CA) using full information maximum likelihood estimation to account for any missing data in the outcome variables. However, because maternal sensitivity during the compliance task was specified as a predictor variable in the model, the final sample size for analyses was 186.

Significant gene-by-sensitivity interaction terms were probed in two ways. First, the simple slope of maternal sensitivity for each genotype group of the relevant gene was tested. Additionally, diathesis-stress compared to differential susceptibility patterns were tested based on Roisman et al.'s (2012) recommendations using a supplemental online utility (available at <http://www.yourpersonality.net/interaction>). We used this utility to calculate the region(s) of significance for the interaction, which indicate any range of maternal sensitivity scores at which the genotype groups differed significantly on the outcome. To aid in interpretation, we also tested whether the genotype groups differed significantly on the outcome at ± 1 *SD* and ± 2 *SD* on maternal sensitivity. The utility also calculated the crossover point for the interaction, and the proportion of the interaction graph at each side of the crossover. In this study, the crossover point is the maternal sensitivity score at which the genotype group simple slopes cross. The proportion of interaction indicates the proportion of the observed range of maternal sensitivity scores to the left and to the right of the crossover point. The results may indicate a differential susceptibility pattern with a crossover point toward the mean of maternal sensitivity, with a roughly equal (.50) proportion of interaction to the left and right, a significant simple slope for only one genotype group, and regions of significance present to the left and right of the crossover (i.e., one genotype group is lower than the other on the outcome at low levels of maternal sensitivity and higher on the outcome at higher levels of maternal sensitivity). The results may indicate a diathesis-stress pattern with a crossover point at a relatively higher level of maternal sensitivity, a greater proportion of interaction to the left, a significant simple slope for only one genotype group, and a region of significance present only to the left of the crossover (i.e., genotype groups differ only at lower levels of maternal sensitivity).

Two sets of follow-up analyses were performed. First, as previously mentioned, we confirmed that the results were not confounded by child race by re-running each model with additional 2-way interactions between race and early maternal sensitivity, *OXTR* genotype group, and *DRD2* genotype group. Second, we confirmed the longitudinal nature of these hypothesized GxE patterns by testing effects of concurrent (2 year) maternal sensitivity in the place of early (6 month/1 year) maternal sensitivity. As such, the models were re-run to

include concurrent maternal sensitivity and interactions between genotype group and concurrent sensitivity, controlling for earlier sensitivity.

Results

Correlations between control and primary study variables are reported in Table 1. Child race was significantly correlated with maternal sensitivity such that mothers of White infants displayed greater sensitivity than those of non-White infants. Infant sex was not correlated with any variables. Maternal sensitivity during the clean-up at 2 years was significantly correlated with *DRD2* genotype group (lower sensitivity with infants who had an A1 allele), as well as less-compliant behavioral responses, justifying its use as a control variable in analyses, along with child race. Early maternal sensitivity was related to more-compliant behavioral responses at 2 years, but was not significantly correlated with *OXTR* or *DRD2* genotype group nor physiological regulation. *DRD2* genotype group was correlated with compliance at 2 years, indicating less compliant behavior in infants who had an A1 allele. Observed compliance was not significantly correlated with physiological regulation during the clean-up task.

Compliance

Results from the regression model predicting observed compliance are presented in Table 2. Among the control variables, higher maternal sensitivity during clean-up predicted more compliant behavioral responses. Early maternal sensitivity and *OXTR* genotype group were not significant predictors, but *DRD2* genotype group had a significant main effect. Infants with an A1/A1 or A1/A2 genotype displayed less compliant responses than infants with an A2/A2 genotype. There was also a significant interaction of early maternal sensitivity and *OXTR* (see Figure 1; raw data plots are also reported in online supplemental information Figures S1-S2). Simple slopes tests indicated that early maternal sensitivity was positively associated with compliance for infants with the GG genotype ($B = .68, p = .12$) and negatively associated compliance for infants with the AA or AG genotype ($B = -.50, p = .35$), but neither simple slope was significant.

However, the regions of significance indicated that the GG genotype group displayed significantly less compliance than the AA/AG genotype group at or below a value of 2.28 on maternal sensitivity ($N = 30$ participants in the current sample fell below this value), whereas the GG group was not significantly more compliant than the AA/AG group at any observed level of maternal sensitivity. Tests of the difference between *OXTR* genotype groups at ± 1 *SD* and ± 2 *SD* of early maternal sensitivity indicated that at lower levels of maternal sensitivity the GG group displayed less compliance than the AA/AG group (-1 *SD*: $B = -.33, p = .05$; -2 *SD*: $B = -.57, p = .03$), but the groups did not differ at higher levels of sensitivity ($+1$ *SD*: $B = .16, p = .36$; $+2$ *SD*: $B = .40, p = .14$). Approximately 17% of the sample fell below the -1 SD maternal sensitivity score and 12% fell above the $+1$ SD score. This suggests that neither genotype displayed both “for worse” and “for better” effects based on early maternal sensitivity. The genotype group lines crossed at a maternal sensitivity value of 2.59 and the proportion of interaction was .81 to the left of the crossover point, suggesting the right side of the crossover interaction affected a small proportion of

individuals in the sample. Taken together, these results lend tentative support for *OXTR* genotype differences in relations between early maternal sensitivity and later compliance to maternal demands, with a potential diathesis-stress pattern for the GG genotype.

Physiological Response

Results from the regression model predicting physiological regulation are presented in Table 3. Among the control variables, child race predicted physiological regulation such that non-White infants displayed greater regulation than White infants. Neither *DRD2* genotype group nor the interaction of *DRD2* genotype group and maternal sensitivity were significant predictors. Early maternal sensitivity predicted physiological regulation such that greater sensitivity was related to greater regulation. However, this main effect was qualified by a significant interaction of early maternal sensitivity and *OXTR* genotype group (see Figure 2). Simple slopes tests for maternal sensitivity indicated that maternal sensitivity was related to greater physiological regulation for the AA/AG genotype group ($B = .84, p = .02$), but not the GG genotype group ($B = -.02, p = .95$).

The regions of significance indicated that the AA/AG genotype group had significantly lower physiological regulation than the GG genotype at or below a value of 2.43 on maternal sensitivity ($N = 67$ participants in the current sample fell below this value), but the AA/AG group was not significantly higher than the GG group at any observed level of maternal sensitivity. Tests of the difference between *OXTR* genotype groups at ± 1 *SD* and ± 2 *SD* of early maternal sensitivity indicated that at lower levels of maternal sensitivity the AA/AG group displayed lower levels of physiological regulation than the GG group (-1 *SD*: $B = .28, p = .02$; -2 *SD*: $B = .46, p = .01$), but the groups did not differ at higher levels of sensitivity ($+1$ *SD*: $B = -.07, p = .54$; $+2$ *SD*: $B = -.25, p = .17$). This suggests the AA/AG genotype displayed “for worse” but not “for better” effects based on early maternal sensitivity. The genotype group lines crossed at a maternal sensitivity value of 2.64 and the proportion of interaction was .86 to the left of the crossover point, suggesting the right side of the crossover interaction affected a small proportion of individuals in the sample. Taken together, these tests provide support for a diathesis-stress pattern for the *OXTR* AA/AG genotype group in the relations between early maternal sensitivity and later physiological regulation in response to maternal compliance demands.

Follow-up Interactions with Race and Concurrent Maternal Sensitivity

None of the interactions between race and early maternal sensitivity or genotype group were statistically significant (β s = $|.001-.12|$, p s = $.28-.99$). The addition of these terms to the models also did not change the pattern of main effects or interaction effects reported above, thus these are discussed no further. Likewise, concurrent maternal sensitivity (2 year) did not interact significantly with either genotype group variable in relation to either regulation outcome (β s = $|.04-.10|$, p s = $.35-.74$).

Discussion

This study used a GxE approach to explore previously unaddressed questions about the relation between maternal sensitivity and infant self-regulatory outcomes based on child

OXTR rs53576 and *DRD2* TaqIA genotype. It was predicted that maternal sensitivity would interact with *OXTR* such that its relation to outwardly observable compliance responses would be stronger for infants with the GG genotype, potentially in a differential-susceptibility pattern, and its relation to physiological regulation would be stronger for infants with an AA or AG genotype in a diathesis-stress pattern. Secondly, it was predicted that maternal sensitivity would interact with *DRD2* such that its relations to either outcome would be stronger for infants with an A1/A1 or A1/A2 genotype compared to those with an A2/A2 genotype, in a diathesis-stress pattern.

The results for *OXTR* offered partial support for these predictions. Specifically, the relations between maternal sensitivity and physiological regulation evidenced a diathesis-stress pattern for the AA/AG genotype group such that they displayed lower physiological regulation than the GG genotype group at lower levels of maternal sensitivity, but the groups displayed similar physiological regulation at higher levels of maternal sensitivity. It was anticipated that A-carriers (AA or AG genotype) could be at risk for regulatory difficulties due to greater stress reactivity (Kumsta & Heinrichs, 2013; Rodrigues et al., 2009), thus the coregulatory influences of early maternal sensitivity may buffer this risk at the physiological level. The present results are consistent with this prediction. This finding is particularly important to consider given that, although past studies found that early parenting and family influences appeared to be stronger for G-carrier genotypes (Cicchetti & Rogosch, 2014; Hostinar et al., 2014; McDonald et al., 2016; Bradley et al., 2011; 2012) none examined physiological functioning as an outcome. Early caregiving that encourages better physiological regulation in response to maternal compliance demands may support children's competence in responding to regulatory challenges over time.

Additionally, there was evidence for stronger relations between maternal sensitivity and compliance responses for the GG genotype group, such that toddlers in the GG group were significantly less compliant than the AA/AG group at lower levels of maternal sensitivity. This is somewhat consistent with our expectations regarding the GG group's presumed receptivity to social stimuli, such that regulatory difficulties resulting from less-sensitive early caregiving may be expressed most clearly through more-negative emotional and behavioral displays to the parent. However, the results did not indicate any evidence for a differential susceptibility effect. One explanation might be that the clean-up task was still quite challenging for children of this age; thus, maternal sensitivity most closely related to a lack of negative reactivity rather than extending to positive and committed compliance. Alternatively, a pattern of differential susceptibility may not hold for these relations, and the GG's group responsivity to maternal sensitivity may be more a matter of buffering risk. Nonetheless, this interaction effect also appeared to emerge in part due to slightly higher levels of compliance in the AA/AG group at lower levels of maternal sensitivity. This effect was weak in magnitude, but one potential explanation is that lower sensitivity may predict an avoidant response (i.e., less expressed distress) in A-carrier infants. Cassidy (1994) proposed that a caregiver's rejection of infant attachment cues encourages the child to minimize negative emotional displays in order to avoid future rejection. In this study, avoidance could be expressed as less-negative affect and fewer displays of defiance, resulting in a higher compliance composite score. In any case, because the simple slopes of

maternal sensitivity for each genotype group did not reach significance, these findings are certainly in need of replication before stronger inferences can be made.

Together, these findings for *OXTR* rs53576 inform our understanding of genetic differences in the development of self-regulation in two ways. First, to our knowledge this is the first study to examine *OXTR* as a moderator of caregiving influences on self-regulation in the early years. The present results suggest that genetic differences may underlie differential outcomes based on normative variations in sensitive parenting, and not just exposure to adverse experiences (Hane & Fox, 2006). Secondly, these results suggest that patterns of risk may not be apparent at the behavioral level alone. Importantly, if lower maternal sensitivity is associated with less physiological regulation in A-carriers without relations to observable affect/behavior, these children may not be as easily identified as having regulatory difficulties, and may be at risk for more ingrained patterns of stress reactivity and dysregulation, as highlighted in adult samples (e.g. Kumsta & Heinrichs, 2012; Rodrigues et al., 2012).

The current results did not demonstrate the predicted interactions between maternal sensitivity and *DRD2* TaqIA genotype group as found in previous studies (Mills-Koonce et al., 2008; Propper et al., 2008). Instead, there was one main effect of *DRD2* group in which the group including infants with an A1/A1 or A1/A2 genotype displayed less-compliant responses than A2/A2 infants. The clean-up task observed in this study might be described as a request to end an enjoyable, rewarding interaction in order to produce a less desired behavior. This finding may illustrate a difficulty disengaging from reward stimuli in individuals with an A1 allele relatively early in life, consistent with evidence for compulsive or addictive patterns of reward-seeking in this genotype in adulthood (Blum & Braverman, 2000). It is also important to acknowledge a possible gene-environment correlation pattern in the present results, such that concurrent maternal sensitivity during the clean-up task was lower in mothers of infants with an A1 allele relative to A2/A2 infants, and was itself a robust predictor of compliance (see Tables 1–2). This variation points to the possibility of child evocative effects (Bell, 1968; Scarr & McCartney, 1983) such that children with an A1 allele engage in behaviors that evoke less sensitive maternal behavior. Notably, although *DRD2* was associated with observed sensitivity at 2 years during the clean-up task, it was not associated with early sensitivity across a range of distress eliciting tasks. This raises three intriguing possibilities. First, behavioral phenotypes affiliated with *DRD2* TaqIA genotypes carrying an A1 allele may be apparent at birth and gradually undermine mothers' sensitivity over time. Alternatively, this behavioral phenotype may become apparent later in development, hence explaining the non-significant association with sensitivity earlier in infancy. For example, mothers of children with an A1 allele may experience new challenges in sensitively managing child behavior as these children develop skills to more autonomously and assertively pursue reward and display noncompliance. Or, finally, the behavioral phenotype affiliated with genotypes with an A1 allele may be particularly apparent in the context of maternal compliance demands. Toddlers who carry an A1 allele may be especially resistant to the direction to stop a gratifying experience and/or remove reward stimuli from the environment, and these tendencies may tax their mothers' ability to maintain highly sensitive responses in this context. Regardless, the association between the *DRD2* genotype and sensitivity serves as an important reminder that children's genotypes

may influence developmental outcomes in ways beyond GxE effects. Further, although correlations between genotype group and maternal sensitivity were otherwise close to zero in the present study, other unmeasured gene-environment correlation patterns may qualify the GxE effects found here.

There also appeared to be differing relations between early versus concurrent maternal sensitivity and each outcome measure. Mother sensitivity during the clean-up task was assessed using a global rating, thus limiting comparability with the early sensitivity scores. However, these measures were significantly correlated over time, and concurrent sensitivity appeared to be a stronger predictor of children's compliance than earlier maternal sensitivity. This points to the potential precedence of mothers' in-the-moment behavior in predicting toddlers' affective and behavioral responses to regulatory challenge. In contrast, earlier maternal sensitivity was more closely related to infants' physiological regulation, consistent with prior evidence that sensitivity early in life is particularly relevant to the development of vagal regulation (Calkins et al., 2016; Propper & Moore, 2006). However, the fact that this effect emerged only in the regression model, which accounted for other characteristics related to sensitivity like race and *DRD2* genotype, not in the simple correlations, and was qualified by *OXTR* genotype, suggests that the link between early maternal sensitivity and physiological regulation depends on other developmental factors. For example, the strength of association may depend on children's genetic status across multiple SNPs, such that it is stronger for children who carry a risk/susceptibility allele for two or more genes. On the other hand, this link may also depend on variations in social and cultural characteristics of the child's environment, including those typically correlated with child race (e.g., socioeconomic status). It is also possible that children's physiological regulation may be better predicted by trajectories of mothers' sensitivity over the first 2 years of life than by early sensitivity alone. Further, this link may be stronger after accounting for variation due to correlations between genetic and environmental characteristics. These distinctions may be important to keep in mind when exploring longitudinal relations between parenting and children's self-regulatory responses.

This study had a number of strengths, including a longitudinal study design, racially diverse sample, observational measures of parent-child interactions, and self-regulatory measures that spanned multiple levels of analysis. Follow-up analyses also confirmed that the longitudinal effects could be interpreted similarly even in light of child race and concurrent (2-year) levels of maternal sensitivity. In terms of limitations, this study had a relatively small sample size for molecular genetic analyses. Additionally, just two polymorphisms were studied among many that have been highlighted in research on individual regulatory differences, and it is possible that others may have more meaningful predictive power with reference to maternal sensitivity. We also note that although the present results contribute to the small body of research on *OXTR* rs53576 in infants and children, they are limited by a violation of HWE in the White participants. This is not the first study to encounter this problem (Luijk et al., 2011), and heterogeneity in rs53576 could have consequences for interpretation of findings across samples, including findings regarding diversity in emotional characteristics by genotype and specific GxE effects. This heterogeneity should be addressed in future research. Third, although the present analyses focused on potential GxE effects, we acknowledge that gene-environment correlation patterns may also explain some variation in

self-regulatory outcomes. Lastly, although maternal sensitivity was assessed across several tasks and two time points, the regulatory outcomes were assessed in a single compliance task. Children may have enacted other regulatory processes in response to the compliance challenge that were not captured by the present measures (e.g., self soothing, distraction, help-seeking). Additionally, different patterns of compliance and/or self-regulatory responses may emerge in different types of challenging tasks, including those that do not include the mother.

A number of remaining questions could be addressed by future research. First, the results of this study suggest that early caregiving experiences may have differing outcomes at the behavioral level compared to the physiological level. Approaching the study of person-by-environment interactions with comparisons across multiple levels of analysis may provide beneficial insight to the field of developmental science. Future studies should attempt to replicate the present findings, as well as examine similar patterns utilizing other forms of early environmental exposure or other developmental outcomes. Second, despite the large body of research on the role of oxytocin in early development and parent-child interactions, it appears that little research explores the role of *OXTR* genotype in predicting outcomes of early parenting. Third, it would be valuable to explore toddler self-regulation outcomes across a range of tasks to capture their responses to a range of social and/or reward stimuli. Fourth, there remains the possibility that epigenetic processes may contribute to apparent GxE effects such that environmental influences like maternal sensitivity influence patterns of gene expression and/or phenotypic traits that appear to confer risk or susceptibility. Our data are insufficient to address this question, but future researchers may utilize more sophisticated genetic designs to consider varying genetic and epigenetic contributors to children's self-regulatory outcomes. Similarly, although the present analyses focused on potential GxE effects, with mostly weak associations between genotype group and measures of maternal sensitivity, we acknowledge that gene-environment correlation patterns may also explain some variation in self-regulatory outcomes. Finally, researchers should certainly continue to compile the results of this and similar studies at an integrated or meta-analytic level to make more confident inferences about GxE effects, or to explore GxE patterns based on sets of candidate genes.

In conclusion, our results provide evidence that *OXTR* rs53576 genotype moderates the extent to which early maternal sensitivity predicts later self-regulatory responses to maternal compliance demands at both the behavioral and physiological level. In addition, *DRD2* *TaqIA* rs1822497 genotype is linked with variation in behavioral regulation as a main effect and perhaps indirectly via child evocative effects on maternal sensitivity. Thus, genetic variation remains an importance potential contributor to variation in maternal sensitivity and children's responses to such variation. Molecular genetic research may continue to inform our understanding of the unique needs of different types of children and their parents in the development of self-regulatory skills at the behavioral and physiological levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Relations between maternal sensitivity and toddler compliance (composite of standardized behavior and affect scores) in the clean-up task based on *OXTR* genotype group.

Note: Maternal sensitivity (x-axis) values are centered at the mean (2.52). Region of significance is shaded on graph. Values near the lines refer to the proportion of interaction to the left and right of the crossover point, and .074 refers to the crossover point value.

Figure 2.

Relations between maternal sensitivity and toddler physiological regulation (change from baseline mean to task mean) in the clean-up task based on *OXTR* genotype group.

Note: Maternal sensitivity (x-axis) values are centered at the mean (2.52). Region of significance is shaded on graph. Values near the lines refer to the proportion of interaction to the left and right of the crossover point, and .123 refers to the crossover point value.

Table 1

Correlations among Study Variables

Variable	1	2	3	4	5	6	7	8
1. Child race (non-White = 0, White = 1)	---	<.001	.35**	.23**	.13 ⁺	-.17*	.03	-.12
2. Child sex (male = 0, female = 1)		---	.11	.04	.04	.13 ⁺	.09	.11
3. Maternal sensitivity during clean-up (2 years)			---	.43**	-.02	-.20**	.37**	-.08
4. Early maternal sensitivity (6 months/1 year)				---	-.05	-.02	.23**	.08
5. <i>OXTR</i> group (AA or AG = 0, GG = 1)					---	-.08	-.07	.07
6. <i>DRD2</i> group (A2/A2 = 0, A1/A1 or A1/A2 = 1)						---	-.19*	-.001
7. Compliance (2 years)							---	-.04
8. Physiological regulation (2 years)								---
	<i>M</i>	48%	6.44	2.52	55%	61%	-.01	.46
	<i>SD</i>	52%	1.93	.20	46%	39%	.88	.55

⁺ $p < .10$,* $p < .05$,** $p < .01$ Note: For race, sex, and gene group variables, *M* and *SD* rows include percentage of sample in the group coded 0 and 1, respectively.

Hierarchical Multiple Regression Model Predicting Toddler Compliance from Early Maternal Sensitivity, OXTR Genotype, and DRD2 TaqIA Genotype

Table 2

Variables & Steps	B	SE(B)	β	R ²	F	R ²	F
Step 1				.15	16.15**		
Child race	-.20	.13	-.11				
Maternal sensitivity during clean-up	.19	.03	.41**				
Step 2							
Child race	-.23	.13	-.13 ⁺	.18	7.90**	.03	2.20 ⁺
Maternal sensitivity during clean-up	.16	.04	.34**				
Early maternal sensitivity	.48	.32	.11				
OXTR group (AA or AG vs. GG)	-.10	.12	-.06				
DRD2 group (A2A2 vs. A1/A1 or A1/A2)	-.26	.12	-.14*				
Step 3				.21	6.56*	.03	2.80 ⁺
Child race	-.18	.13	-.10				
Maternal sensitivity during clean-up	.14	.04	.31**				
Early maternal sensitivity	-.50	.51	-.12				
OXTR group (AA or AG vs. GG)	-.09	.12	-.05				
DRD2 group (A2A2 vs. A1/A1 or A1/A2)	-.24	.12	-.13*				
Early maternal sensitivity X OXTR	1.18	.58	.21*				
Early maternal sensitivity X DRD2	.97	.61	.13				

⁺ $p < .10$;* $p < .05$;** $p < .01$

Hierarchical Multiple Regression Model Predicting Toddler Physiological Regulation from Early Maternal Sensitivity, OXTR Genotype, and DRD2 TaqIA Genotype

Table 3

Variables & Steps	B	SE(B)	β	R ²	F	R ²	F
Step 1				.02	1.39		
Child race	-.11	.09	-.10				
Maternal sensitivity during clean-up	-.01	.02	-.04				
Step 2							
Child race	-.15	.09	-.14 ⁺	.05	1.70	.03	1.88
Maternal sensitivity during clean-up	-.03	.03	-.11				
Early maternal sensitivity	.44	.22	.17 [*]				
OXTR group (AA or AG vs. GG)	.10	.08	.09				
DRD2 group (A2A2 vs. A1/A1 or A1/A2)	-.05	.09	-.04				
Step 3				.08	2.12 [*]	.03	3.09 [*]
Child race	-.17	.09	-.16 [*]				
Maternal sensitivity during clean-up	-.03	.03	-.11				
Early maternal sensitivity	.84	.35	.31 [*]				
OXTR group (AA or AG vs. GG)	.11	.08	.10				
DRD2 group (A2A2 vs. A1/A1 or A1/A2)	-.06	.08	-.05				
Early maternal sensitivity X OXTR	-.86	.40	-.25 [*]				
Early maternal sensitivity X DRD2	.35	.42	.07				

⁺ $p < .10$;

^{*} $p < .05$;

^{**} $p < .01$