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Responsive Parenting, Gene-Environment Interactions, and Heterogeneous Social Development in Autism Spectrum Disorder

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Responsive Parenting, Gene-Environment Interactions, and Heterogeneous Social Development in Autism Spectrum Disorder

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Doctor of Philosophy in Psychology

by

Barbara Jean Caplan

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ABSTACT OF THE DISSERTATION

Responsive Parenting, Gene-Environment Interactions, and

Heterogeneous Social Development in Autism Spectrum Disorder

by

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Doctor of Philosophy in Psychology

University of California, Los Angeles, 2019

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Although autism spectrum disorder (ASD) is defined by core deficits in social communication and social interaction, there is considerable heterogeneity in social functioning among individuals with ASD. Relatively little is known about the origins and development of these individual differences. Emerging research suggests that family environments and genetic variants independently contribute to social functioning in youth with ASD, yet a better understanding of how these factors interact is necessary to: (1) parse apart factors that contribute to social heterogeneity in ASD and (2) develop and select optimal treatments based on individual characteristics. The present studies took an interdisciplinary approach to examine how early parenting quality and child genetics interact to predict trajectories of social functioning in youth with ASD. Participants were 176 families of children aged 4-7 years with ASD selected from a

longitudinal study of developmental processes in ASD. Responsive parenting was rated within the context of free play parent-child interactions. Social development was assessed through multi-rater (parent, teacher) report of child social skills across three time points spanning 1.5 years. Study 1 examined the role of responsive parenting in predicting variation in child social development. Study 2 assessed biologically plausible candidate genes [serotonin transport gene (5-HTTLPR); oxytocin receptor gene (OXTR); dopamine receptor gene (DRD4)] as markers of susceptibility to environmental influence and mechanisms of genetically-informed environmental sensitivity. Specifically, Study 2 evaluated: (a) the additive and interactive effects of 5-HTTLPR, OXTR, DRD4 and responsive parenting in predicting social development in ASD, and (b) whether child emotion regulation mediates observed responsive parenting x child genotype interactions on social development. Initial levels of responsive parenting positively predicted prospective change in social skills by teacher report, and in parent-report models controlling for OXTR genotypes. 5-HTTLPR and DRD4, but not OXTR were found to interact with responsive parenting to predict growth in child social skills; interactions were not mediated by emotion regulation. Findings illuminate pathways of biopsychosocial models of development in ASD and stand to inform targeted, parent-mediated interventions.

The dissertation of Barbara Jean Caplan is approved.

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Dedication Page

I dedicate this dissertation to my family whose unyielding support led me to pursue my passions and persist through every obstacle. I thank my mother for instilling in me a deep compassion for caring for children with developmental disabilities. Her thirty-year career in special education inspired me to pursue this line of clinical research. I thank my father for always being my voice of reason, for modeling how to use logic and fairness to help others and for his unending faith in me. And yes, even for his two cents. Not least of all, I thank my husband for the countless sacrifices he has made to support my career over the years, and for understanding that my passion for research and academia could never overshadow the importance of our family. The work presented in this dissertation would not have been possible without my advisors, Drs. Bruce Baker and Jan Blacher. Their intentional and thoughtful mentorship has shaped my transition from a passionate but green undergraduate into an independent scholar. Thank you for sharing your enthusiasm for understanding children and families at risk, while also demonstrating that a fulfilling academic career and a fulfilling personal life are not mutually exclusive. Finally, I want to dedicate this work to children with developmental disabilities and their families. It is my deepest hope that the research presented here and throughout my career will serve as a mirror for the real-world challenges and successes experienced by families and will help to shape meaningful change.

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Study 2 of the dissertation is in preparation for publication. The first author (BC) conceived of the study, coordinated all coding efforts, coordinated collection and analysis of genetic samples, designed and conducted statistical analyses and drafted the manuscript; co-authors (JB and AE) are the P.I and co-P.I., respectively, of the primary project and provided feedback regarding recruitment and study design; co-authors (BLB and SSL) provided constructive feedback regarding the study methods, analyses and interpretation of the results. All authors reviewed and helped to revise the written product. See citation below.

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SELECT PRESENTATIONS

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Caplan, B., Berkovits, L., Blacher, J., & Eisenhower, A. (2013). Implications of teaching strategies for the student-teacher relationship in young children with ASD. Paper presented in a research symposium, *American Psychological Association Annual Convention*, Honolulu, Hawaii. August 2013.

Introduction.

With increasing recognition and diagnostic acuity, autism spectrum disorders (ASDs) are diagnosed in 1 in 59 children (Baio et al., 2018; *Center for Disease Control*); rates of diagnosis have steadily increased since autism's conception in 1943. On average, it's estimated that the lifetime direct and indirect costs of an individual with autism range between $1.4 and $2.4 million (Buescher, Cidav, Knapp, & Mandell, 2014), a figure that could be considerably reduced with the implementation of early and targeted intervention. The enormous cost of ASD in terms of individual, family and societal wellbeing has motivated substantial research into the pathogenesis of autism. However, complicating matters is the heterogeneity that is characteristic of ASD. While ASD is characterized by impairments in social communication and restricted or repetitive behaviors and interests (DSM-5; American Psychiatric Association, 2013) there is great variability in how children express these phenotypes. Relatively little is known about the origins and development of these individual differences.

This gap in knowledge has hindered progress, particularly with respect to genetic influences. Despite moderate heritability (Hallmayer et al., 2011) there are relatively few replicated genetic variants for ASD, which is often attributed to phenotypic heterogeneity in functioning, including social functioning (Jeste & Geschwind, 2014). The proposed set of studies will take an interdisciplinary approach to explaining sources of this phenotypic heterogeneity, using a large, well-characterized sample of children with ASD. The first study will examine psychosocial factors contributing to social development, namely, responsive and interfering parenting. The second will integrate biological and psychosocial methods to examine how children with specific genotypes may respond differently to responsive and interfering parenting.

Developmental theory posits that responsive parenting, or that which follows a child's lead, supports a child's autonomy and, thereby his/her adaptive cognitive and social development (Landry, Smith, & Swank, 2006). Intrusive parenting, however predicts maladjustment in these domains (e.g. Hubbs-Tait, Culp, Culp, & Miller, 2002). Studies of children with or without developmental delays (DD) suggest that children at developmental risk may be particularly susceptible to individual differences in positive and negative parenting quality (e.g. Baker, Fenning, Crnic, Baker, & Blacher, 2007; Green, Caplan, & Baker, 2014). Although examinations in ASD are relatively limited, there is replicated evidence that responsive parenting is associated with social and language development (Siller & Sigman, 2002; Siller & Sigman, 2008) for children with ASD. These parenting dimensions likely hold implications for heterogeneous social development in ASD, and longitudinal investigations are needed to characterize these patterns of influence over time.

Yet, refined understanding of complex social phenotypes in ASD has been hindered by the lack of interdisciplinary approaches. In human and non-human animal models, parenting behavior *biologically* interacts with specific genes to produce social phenotypes (Meaney, 2010). Rigorous evaluation of gene-environment interactions (GxEs) will help to define boundaries of genetic and environmental influence, and identify those most susceptible to environmental risk or enrichment. Polymorphisms from the serotonin transporter (5-HTTLPR), the oxytocin receptor (OXTR) and dopamine receptor (DRD4) genes, are *biologically plausible* candidates to evaluate GxEs in ASD, given their established relationships with neural networks of "social salience" (Canli & Lesch, 2007; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Camara et al., 2010). Variants of these genes interact with the caregiving environment to predict social

phenotypes in non-ASD samples (Canli & Lesch, 2007; Wade, Hoffmann, & Jenkins, 2015), and may explain variability in social functioning within ASD.

Developmental theorists posit different models for understanding the nature of GxE. One longstanding model, the *diathesis-stress* (aka *dual risk*) model (Monroe & Simons, 1991; Zuckerman, 1999), posits that certain biological-driven characteristics (e.g. genotype, temperament) predispose individuals to be more vulnerable in the context of negative or harsh environments. For example, in one study by Kochanska and colleagues (2009), children with the S-allele of 5-HTTLPR (but not those with the LL genotype) were found to develop poor emotion regulation capacities in the context of insecure attachment. An alternative perspective is represented by the *differential susceptibility* hypothesis. Taking an evolutionary perspective, Belsky and colleagues (Belsky, 2016; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011) posited that developmental processes would select for children to vary in their susceptibility to environmental exposures, particularly parenting. Thus, the differential susceptibility hypothesis posits that the same biologically-driven characteristics may confer susceptibility to positive *and* negative environments, rather than vulnerability to risk alone. Study 2 assessed these competing models of gene-environment interact as they stand to explain heterogeneity in ASD functioning.

Moreover, translational applications of GxE findings require elucidation of the mechanisms underlying GxE effects. Given the functional role of 5-HTTLPR and OXTR in regulatory neurobiology (Canli & Lesch, 2007; Meyer-Lindenberg et al., 2011), and the potential of the parenting environment to influence gene expression (Meaney, 2010), it is plausible that emotion regulation mediates these proposed GxE effects on social functioning. Investigations of gene-environment interplay in ASD stand to inform models of development in ASD and targeted

biological and psychosocial interventions, thus improving identification and promoting resilience for this at-risk population.

The present pair of studies illuminated sources of social heterogeneity in ASD by integrating psychosocial and genetic methods. We addressed the following aims:

Study 1. *Aim 1:* To assess child and family level predictors of responsive parenting in families of young children with ASD.

Aim 2: To determine the role of responsive parenting in predicting concurrent and prospective social skill development in young children with ASD.

Hypotheses. Child clinical characteristics and family demographics will be associated with observed responsive parenting. Responsive parenting will exhibit a modest and positive relationship with concurrent social skills and prospective child social development across 1.5 years.

Study 2. *Aim 1***.** To examine the additive or interactive effects of functional polymorphisms from candidate genes (OXTR, 5-HTTLPR, DRD4) and parenting quality in predicting trajectories of social skills for young children with ASD.

Aim 2. To evaluate child emotion regulation as a mediator of the interactive effect of child genotype and parenting in predicting trajectories of social skills over time.

Hypotheses. Genetic variation of the 5-HTTLPR and OXTR genes will be modestly associated with concurrent and prospective child social skills. Though, 5-HTTLPR, OXTR and DRD4 will interact with observed parenting in a *differential susceptibility* manner, such that children with the low-expressing variants will be more strongly influenced by parenting quality, for better or worse. Child emotion regulation will partially mediate the interactive effects of parenting with 5-HTTLPR and OXTR only.

Study 1. Responsive parenting and prospective social skills development in early school-aged children with autism spectrum disorder

Although autism spectrum disorder (ASD) is defined by core deficits in social communication and restricted or repetitive behaviors and interests, the tremendous phenotypic and etiological heterogeneity characteristic of ASD (e.g., see Jeste & Geschwind, 2014) has complicated efforts for early identification and intervention. Variability in social functioning within ASD is an especially pertinent consideration, as social impairments in ASD are a key predictor of long-term outcomes regardless of intellectual and language functioning (Carter, Davis, Klin, & Volkmar, 2005). Indeed, the degree of social impairment in ASD has been linked to the quality of peer relationships, peer rejection and loneliness (Bauminger & Kasari, 2000; Locke, Ishijima, Kasari, & London, 2010), student-teacher relationship quality (Caplan, Feldman, Eisenhower, & Blacher, 2016), long-term academic and occupational functioning (Howlin, 2000) and risk for mental health problems (e.g., White & Roberson-Nay, 2009).

Responsive Parenting

One contributing factor to the social development of children with ASD is the social environment. While previous, ill-informed and widely refuted theories of autism had given undue blame to parents for causing the development of ASD (Fombonne, 2003), it is now clear that parenting behavior *does not cause* ASD. However, parenting is a primary source of socialization for all young children, and the style and quality of parenting behavior influences social development within the context of ASD. Specifically, responsive parenting has demonstrated causal relationships with positive developmental outcomes across diverse domains including cognitive functioning, language and social skills through randomized control designs (e.g., Eshel, Daelmans, Mello, & Martines, 2006), for both typically developing children and

those with developmental risk (Mahoney & Nam, 2011). The key feature of responsive parenting is that the parent's behaviors follow the child's current focus of attention, or "plan of the moment" (Girolametto, Weitzman, Wiigs, & Pearce, 1999, p.365). Responsive parenting is also characterized by behavior that is immediate, contingent, and an attuned reaction to a child's communication or behavior (Landry et al., 2006). Although parent responsiveness is often characterized as non-directive and contrasted with directiveness (i.e., parents' attempts to direct or guide the child's actions; Marfo, 1992), certain subdomains of responsiveness may allow for or even require parent direction (i.e., 'responsive direction'). Responsive direction includes: *maintaining*, defined as parents' use of questions, suggestions or comments to maintain a child's interest or focus of attention (Mahoney & Nam, 2011), and *"follow-in" directives*, which are directives that coincide with ongoing child activity and interest (McCathren, Yoder, & Warren, 1995). For example, if the child is attending to a cooking play set and pretending to make soup, examples of responsive direction would include asking the child what he or she is going to add to the soup next, or modeling how to stir the soup for the child. The defining feature of responsive direction, then, is that the parent is directing the child's behavior for the purpose of building on the child's current focus of attention, rather than diverting the child's attention in a parent-centered manner (i.e., redirection).

Several developmental theories and research frameworks elaborate on the role of responsive parenting in promoting positive social, cognitive and language development. Attachment theory suggests that a responsive parenting style facilitates child learning of self-regulation, as a parent's attunement to child activity and interests encourages a child's ability to actively explore and engage with the environment and continue to signal to the caregiver (Cassidy & Shaver, 2016; Bornstein & Tamis-LeMonda, 1989; Bowlby, 1963). While related

parenting behaviors linked to the attachment framework such as parent sensitivity may similarly emphasize the immediacy and contingency of parent responses to child cues, the distinction lies in the nature of the child cue and the parent response. Sensitivity is a broader parenting construct that emphasizes the parent's attunement to all child *affective* signals and provision of contingent affective responses (Mesman & Emmen, 2013), while parent responsivity specifically characterizes a parent's ability to attune to the child's interests and focus of attention, and respond in ways that align with ongoing child activity (Mahoney & Nam, 2011). Models of child development suggest that parent use of responsive direction may promote language and social skills in that it directs action on the referent with which the child is already attending (McCathren et al., 1995). That is, by focusing on the child's interests, a parent is likely to sustain the child's joint attention, and provide the child with increased verbal input in the context of joint attention (McCathren et al., 1995), which in turn, provides the child with increased opportunity for social communication and facilitates social cognitive development (Tomasello, 1995).

Responsive Parenting in Typical Development

For children with typical development, responsive parenting is consistently associated with positive developmental outcomes across domains, including social, language, and cognitive development (Bornstein, Tamis-LeMonda, & Haynes, 1999; Tamis-LeMonda, Bornstein, & Baumwell, 2001; Bornstein & Tamis-LeMonda, 1989). In contrast, parenting that disrupts or interferes with a child's focus of attention (i.e., intrusive direction) is predictive of negative developmental and social outcomes (e.g. Masur, Flynn, & Eichorst, 2005; Hubbs-Tait, Culp, Culp, & Miller, 2002). While most examinations focus on the role of responsive parenting in infancy and toddlerhood, evidence supports that responsive parenting predicts the most positive

developmental outcomes when it is maintained across early to middle childhood (Landry, Smith, Swank, Assel, & Vellet, 2001; Smith, Landry, & Swank, 2006).

Responsive Parenting and Autim Spectrum Disorder

Children with ASD exhibit core deficits in social communication behavior and may thus provide fewer opportunities for parents to follow their child's lead. These social communication difficulties may include: low rates of social initiation, limited response to others' initiations, reduced requesting, atypical or limited eye contact, social inhibition, perseveration, sensory sensitivities and poor speech intelligibility (Warren & Brady, 2007). Thus, children with ASD may be at risk for less exposure to responsive parenting and, in line with the transactional model of development (Sameroff, 2009), maladaptive transactions between parenting styles and child social-communication functioning (Rice & Warren, 2004). However, extant findings are mixed in regard to comparing parents' use of responsive parenting with children with or without ASD. Some studies find that parents of infants at risk for ASD implement less responsive and more directive parenting behavior than parents of infants at low risk for ASD (e.g. Wan et al., 2012; Harker, Ibañez, Nguyen, Messinger, & Stone, 2016). In contrast, other studies find no differences in responsive parenting across families of children with or without ASD (Siller & Sigman, 2002; Walton & Ingersoll, 2015).

Evidence from studies of developmental disabilities other than ASD suggest that parents' responsiveness to children's cues and attunement to children's focus of attention may promote an adaptive developmental course. Children who are at developmental risk due to low birth weight demonstrate relations between greater parental maintaining behaviors (an aspect of responsive direction) and gains in cognitive and language abilities over time (Landry, Smith, Swank, & Miller-Loncar, 2000; Landry, Smith, Miller-Loncar, & Swank, 1998). Responsive parenting

likewise positively predicts subsequent communication and social skills for children with various developmental disabilities, including intellectual disability, developmental delays and Fragile X (Green, Caplan, & Baker, 2014; see Warren & Brady, 2007 for review), while intrusive direction is associated with poorer social and adaptive functioning for this group (e.g., Green et al., 2014).

Children with ASD also appear to benefit from parenting that is responsive to their cues and focus of attention. Several studies find a link between maternal responsive verbalizations (both directive and non-directive) and language development in samples of toddlers and young children with ASD (McDuffie & Yoder, 2010; Haebig, McDuffie, & Weismer, 2013a; Haebig, McDuffie, & Weismer, 2013b). Similarly, in a seminal set of studies Siller & Sigman (2002; 2008) found that caregiver responsive verbalizations implemented with preschool-aged children with ASD predicted language gains 3 1/2, 10 and 16 years later. Responsive parenting has also been linked to growth in social smiling for infants at-risk for ASD (Harker et al., 2016), and joint engagement between toddlers with ASD and their parents (Patterson, Elder, Gulsrud, & Kasari, 2014). Taken together, the existing research supports a link between responsive parenting, language development and early social engagement for children with ASD. Though underexamined, responsive parenting may continue to demonstrate an association with social development into the early school years for children with ASD, as it does for children with typical development (Landry et al., 2001; Smith et al., 2006). This is because responsive parenting is not a specific parenting behavior in itself, but a state of following and building on the child's lead and focus of attention (Mahoney & Nam, 2011). Thus, responsive parenting may look somewhat different as children age and engage in more sophisticated play and interactional styles, but likely continues to set the stage for joint engagement, and thus language and social development into the school years.

Predictors of Responsive Parenting

Characterizing parent and child characteristics that predict naturally occurring levels of responsive parenting will help to inform targeted intervention efforts for at-risk families. In families of children with typical development, several parent- and family-level factors, including family income and parent education predict concurrent responsive parenting behavior (Warren & Brady, 2007; Bornstein & Bradley, 2012), yet it is less clear the extent to which these same relations are at play for families of children with ASD. Moreover, in line with the transactional model of development (Sameroff, 2009), it is likely that child characteristics are linked in a reciprocal manner with responsive parenting. Of special consideration to children with developmental disabilities is the child's level of functioning. Parents of children with developmental delays have been found to demonstrate more intrusive direction with their children than parents of typically development children (Green et al., 2014), suggesting a potential relation between responsive parenting and child developmental functioning (e.g., IQ, language ability). Further, given the link between early social communication behaviors and responsive parenting in families of infants that later receive an ASD diagnosis (Wan et al., 2012), it is plausible that autism symptoms may likewise relate to responsive parenting in childhood. For children with typical development, child sex has also been linked, with boys being exposed to less responsive and more directive parenting than girls (Tamis-LeMonda, Briggs, McClowry, & Snow, 2009). The role of child age is less clear, as some related parenting behaviors (e.g., sensitivity) demonstrate consistency across early child development, while aspects of unresponsive parenting (e.g. detachment, control) show developmental changes (Dallaire & Weinraub, 2005), which may be specific to development risk group (Fenning, Baker, Baker, &

Crnic, 2014). Yet, there is little examination of these predictors of responsive parenting in families of children with ASD.

The Current Study

The present study seeks to assess the role of responsive parenting in predicting prospective changes in child social skills across the early school years. Improving upon prior methodologies, the current study utilizes a large, well-characterized sample of children with ASD, multi-method assessment of child social functioning, and a prospective, longitudinal design. The study builds on previous research by examining child and parent characteristics that predict responsive parenting for this group. We will examine the following questions: (1) Which parent and family characteristics (education level, income) and child characteristics (age, sex, autism severity, IQ, language ability) are associated with responsive parenting in parents of children with ASD? (2) Is responsive parenting (including responsive direction, non-directive responsivity, and lack of intrusive direction) associated with child social engagement within the parent-child interaction? (3) Does responsive parenting predict initial status and prospective growth in child social skills across times? We anticipate child level of functioning (IQ, language) and family income to be positively, and child autism severity to be negatively, associated with responsive parenting. We also predict that parents with higher levels of education, and parents of females will demonstrate greater levels of responsive parenting. Finally, responsive parenting will be positively associated with child social behavior within the interaction, as well as social skills development over time.

Method

Participants

Participants were 176 children with ASD, their parents, and their teachers, all of whom

were involved in the *(blinded for review)*, a longitudinal study of the social, academic and behavioral development of a child with ASD during the early school years. Families were recruited through a variety of methods, including in-print and online advertisements that were distributed to local service agencies for individuals with developmental disabilities (e.g., regional centers), intervention service centers, clinicians, local school districts, and ASD-specific parent support groups and websites. Families were recruited from the Greater Boston area of Massachusetts (n = 58) as well as the Los Angeles and Riverside/San Bernardino county regions (n = 118). This multisite approach was aimed at ensuring a community-based sample that was diverse in terms of geographic location, school setting, child race/ethnicity and individual child functioning.

Child demographic data are reported in Table 1.1. Eligible children were between the ages of 4 and 7 years and enrolled in school (grades Pre-K to 2nd grade) at the initial visit. Eligibility criteria also included an IQ of 50 or higher, and a confirmed diagnosis of ASD (see assessment procedures below). The majority of our participants were male (81.7%) in line with the established sex differences in ASD. Child race was based on an open-ended parent-report item later aggregated into categories: the majority of children were White (56.3%), while others were identified as Latino(a)/Hispanic (8.5%), Asian-American (6.3%), Black or African-American (3.4%), bi- or multi-racial (19.9%), or 'other' (4.0%); 3 individuals (1.7%) did not provide race information. In addition, most participating parents had obtained a bachelor's degree or further education, had an annual gross household income above $50,000 (70.1%), and had a second parent/caregiver living in the home. Most children were enrolled in a public preschool or elementary school, with roughly half of children placed in a special education

setting. Most children were cognitively high functioning, though 17.2% had IQs that fell in the broader range of intellectual disability (< 70).

According to parent report, the majority of children in the sample (88.6%) had received at least one form of early intervention service (e.g., ABA, occupational, or speech therapy, early intervention preschool), with 50.0% of children reported to receive behavior-based intervention for ASD [e.g., ABA, Pivotal Response Training (PRT), Discrete Trial Training (DTT)]. The average number of services reported per child was 2.20 (range: 0 to 6 services). The vast majority of children attended public school, with about half of the sample placed in a special education classroom setting. The majority of the sample remained in the same school setting (i.e., public, private school) and in the same classroom type (i.e., special education. general education) over the course of the study (85.1% and 77.2%, respectively). Of the original 208 participants enrolled in the study, families were included in the present study if they participated in the parent-child interaction at Time 1 (N = 180), and if they had available parent- and teacher-report of social skills at at least one time point (Time 1, 2, or 3; final N = 176).

[See Table 1.1]

Procedures

Data were obtained through laboratory observations and assessments, parent-completed questionnaires, and teacher-completed questionnaires. All procedures were reviewed and approved by the Institutional Review Boards of the universities involved. Prior to participating, parents received a project description, provided informed consent, and completed a brief phone screening with project staff. Child eligibility criteria were confirmed using the ADOS and *Wechsler Preschool and Primary Scale of Intelligence* (WPPSI-III; Wechsler, 2002). Research

reliable staff members administered and scored the ADOS (Lord et al., 2000) using the revised research algorithms (Gotham et al., 2008). Those who did not have a prior ASD diagnosis, or who received a diagnosis of ASD through the school system only, were also administered the ADI-R (Rutter, LeCouteur, & Lord, 2003) to confirm the diagnosis. In addition, all children were administered a short form of the WPPSI-III to estimate IQ. Children with ADOS scores (and ADI-R scores when applicable) in the autism or autism spectrum ranges and WPPSI-III IQs of 50 or higher were eligible for the study. This IQ criterion was selected to ensure valid administration of all study procedures and assessments within the broader longitudinal study (which included academic assessments and protocols that required children to understand and follow verbal directions, as well as to provide simple verbal responses). Data collection was initiated before the later-released versions of these assessments (ADOS-2, WPPSI-IV; released in 2012). At eligibility visits, parents also completed a demographic questionnaire regarding family ethnic and socioeconomic background, school history and intervention services (i.e., presence of any intervention services, receipt of behavior-based interventions, and number of services).

Eligible families were seen in the lab three more times: once in the fall (Time 1) approximately one to two months after the initial screening visit, once in the spring of the same school year (Time 2), approximately six months after Time 1, and once in the winter of the following school year (Time 3), approximately nine months after Time 2. During these visits, parents completed questionnaires while children participated in assessments of language and academic functioning. At the Time 1 visit, parents and their children also participated in a 10-minute free-play interaction. During this interaction, parents and children were provided with a standardized set of age-appropriate toys (e.g. books, food play set, coloring books, building

games) and asked to play with their child as they normally would at home. No other instructions were provided to the families. Interactions were recorded and later rated from video recordings.

The Institutional Review Boards of the participating universities approved all procedures. At each visit, parents provided consent to have the child's teacher complete questionnaires regarding the child's functioning. Teacher participation was voluntary, and all participating teachers also provided informed consent. At each time point, both participating families and teachers received a modest honorarium.

Measures.

Autism Diagnostic Observation Schedule (ADOS, Lord et al., 2000). The ADOS is a clinician administered assessment of autism symptomology and is considered the gold standard diagnostic instrument for autism spectrum disorders in both research and clinical settings (Hurwitz & Yirmiya, 2014). The goal of the ADOS is to elicit spontaneous examples of social interaction and restricted or repetitive behaviors in a semi-structured environment (Lord et al., 2000). The ADOS demonstrates strong specificity and sensitivity and incorporates age- and language-specific modules (Lord et al., 2000). Ratings were determined using the revised ADOS algorithms (Gotham et al., 2008) that generate scores for Social Affect and Restrictive/Repetitive Behavior, consistent with the later-released DSM 5 criteria for ASD. These revised algorithms outperform the original ADOS algorithms, providing improved predictive validity and comparability across modules (Gotham et al., 2008).

Wechsler Preschool and Primary Scale of Intelligence- Third Edition (WPPSI-III; Wechsler, 2002). The WPPSI-III is a widely used assessment instrument of cognitive abilities in children ages 2 years 6 months to 7 years 3 months. The instrument yields IQ scores with a normative mean of 100 and a standard deviation of 15. The WPPSI-III demonstrates strong

psychometric properties, including excellent internal consistency (.86-.97) and test-retest reliability (.84-.92; Wechsler, 2002). Three subtests were administered (Vocabulary, Matrix Reasoning, Picture Completion), from which a full-scale IQ score was estimated using Sattler's conversion tables (Sattler, 2008). Abbreviated versions of the WPPSI have demonstrated high reliability and convergent validity (LoBello, 1991). The composite score from these subtests correlates strongly (r = .90) with the full-scale IQ in the normative sample (Sattler, 2008).

Parent Directiveness and Interference-Revised (PDI-R). Responsive parenting was assessed using a version of the PDI coding system (Green et al., 2014), that was amended for the present study by the current research team, including the original co-developer of the PDI. Developed to rate parent behavior in the context of interactions between parents and their young (3 year-old) children with or without developmental delays, the PDI and PDI-R coding systems distinguish between parent directives that coincides with the child's interest or focus of attention ('Supportive Directiveness'*;* i.e., responsive direction) and that which redirects the child's ongoing behavior or focus of attention in a parent-centered manner ('Interference'; i.e., intrusive redirection). No substantive changes were made to the coding methods for Supportive Directiveness and Interference for the PDI-R. Supportive Directiveness captures parenting behavior, both verbal (e.g. comments, questions) and nonverbal (e,g., orientating toys, demonstrations of play, giving of objects) that is used to supportively direct, shape or influence child behavior in a manner *consistent with* ongoing child activity or interests. This code includes the parent's attempts to build on the child's play (e.g. pointing out specific details of a toy, enacting the next sequence in play) and/or helping the child to articulate his/her goals through the use of questions (e.g., " Who is that?" or "What should the doll do next?"). The key feature of Supportive Directiveness is that the parent is directing or shaping the child's play in line with

ongoing child interests and focus of attention. In contrast, Interference captures the parents' actions or statements that redirect the child *away from* ongoing interests and focus of attention (e.g., the parent suggests that a child play with a different toy, the parent insists that a child play with a toy in a particular way). See the Appendix for further examples of each PDI-R parenting domain. The PDI system demonstrated adequate interrater reliability and predictive validity to child social functioning (Green et al., 2014).

The PDI was amended to account for other, non-directive aspects of responsive parenting that may influence the child's behavior within the session as well as broader child developmental outcomes (see Mahoney & Nam, 2011; Landry et al., 2006). Specifically, a code for parent Supportive Engagement was added as a means of capturing non-directive responsive parenting behavior, including parent positive and contingent responses to the child's ongoing activity (e.g. narrating the child's play, repeating child statements) or parenting behaviors to support social engagement within the context of the child's ongoing interests (e.g. facial expressions or interjections in response to the child's play, making character voices or sound effects, labeling the child's feelings). Parent Supportive Directiveness, Interference and Supportive Engagement are rated on a 1 to 5 Likert scale (1: minimal, 2: low, 3: moderate, 4: moderately high, 5: high). These global ratings take into account the frequency, consistency, perceived quality and appropriateness of parenting behavior (e.g., appropriateness of pacing, complexity of statements or behaviors relative to the child's developmental level, etc.).

In addition, the PDI-R system rates the global level of Child Engagement with the parent. Child Engagement is rated on the basis of the duration of time the child spends attending to, responding to, sharing attention with and interacting (responding, initiating) with the parent. Thus, the Child Engagement code includes child behavior ranging from watching the parent's

actions, to verbally or nonverbally responding to a parents' bid, to initiating discrete social interactions. The code rates the global quality of these behaviors on a 5-point Likert scale: 1- child rarely pays attention to, or engages with the parent; 2- child does not respond or look when the parent engages the child; 3- child is moderately engaged with the parent; 4- child shares toys or interacts socially at least half of the time, but also interested in toys or objects to the exclusion of the parent for half the time; 5- child is very engaged with the parent, as evidenced by sharing attention and interacting with the parent the majority of the time. Lastly, the PDI/PDI-R systems also rate the frequency of the child's Social Initiations, including those that are verbal (e.g., asking questions, making a spontaneous comment) or non-verbal (e.g., pointing, showing, initiating eye contact). For this code, children may initiate a discrete interaction, or may provide a response that elaborates beyond a direct answer to provide added detail for the parent's benefit (e.g., the parent asks a yes/no question, and the child elaborates why the answer is yes or no). Child Social Initiations are rated with a frequency count method.

Five teams of two coders each worked with a 'master coder' (the author and co-developer of the PDI and PDI-R) to learn the coding system. Teams were considered sufficiently reliable to code independently when they reached a reliability of 70% exact agreement with the master coder, and 95% agreement within one code (for the global quality codes, only). For the frequency code, raters needed to fall within 80% agreement of a master code to be considered reliable. Reliability checks were administered for 20% of the videos thereafter to ensure ongoing reliability. Raters demonstrated good to excellent levels of interrater reliability (Hallgren, 2012), with the following intraclass correlations (ICCs) observed: Supportive Directiveness (0.73), Interference (0.82), Supportive Engagement (0.63), Child Engagement (0.68), Social Initiations (0.87).

Social Skills Improvement System (SSiS; Gresham & Elliott, 2008). The SSiS is a standardized, norm-referenced assessment of social skills for children ages 3-18 years. The SSiS utilizes parent (SSiS-P) and teacher (SSiS-T) ratings of the frequency of a variety of child social behaviors on a 3-point scale from 0 (*never)* to 2 (*very often,* always). Both versions of the SSiS yield a Social Skills Total standard score with a mean of 100 and a standard deviation of 15. The SSiS Total score demonstrates high internal consistency (α = .96 to .97), test-retest reliability (*r* = .82 to .84), and convergent validity with the Vineland Adaptive Behavior Scale, 2nd edition and the Behavioral Assessment System, 2nd edition (see Gresham & Elliott, 2008; Gresham, Elliott, Cook, Vance, & Kettler, 2010). Further, the SSiS has been widely used to assess social skills in children with ASD (e.g. Kasari et al., 2016) and in the current sample, demonstrates adequate convergent validity with the Social Responsiveness Scale (*r* = -.58; Constantino et al., 2003).

Comprehensive Assessment of Spoken Language (CASL; Carrow-Woolfolk, 1999). The CASL is a standardized assessment of spoken language in youth between the ages of 3 and 21 years. For the purposes of the current study, two subtests were selected as a representative selection of syntactic (Syntax Construction) and pragmatic language (Pragmatic Judgment) skills. For both subtests, an age-based standard score is derived with a mean of 100 and a standard deviation of 15. In the normative sample, internal consistency coefficients ranged from .85 to .96 and test-retest reliability correlations coefficients ranged from .65 to .96 (Carrow-Woolfolk, 1999). For the purposes of data reduction, the two subtests were averaged to create a composite spoken language score. The correlation among the subscales was .80, suggesting strong interdependence.

Data Analytic Plan

The first study aim was to assess parent and child characteristics associated with parent responsivity. To address this aim, continuous child variables (age, autism severity, IQ, and language) were correlated with concurrent responsive parenting (Supportive Directiveness, Supportive Engagement, Interference), as was family income. T-tests were then used to determine the relationship between these aspects of responsive parenting and dichotomous variables (parent education, child sex). Parent education was dichotomized to assess group differences in parenting between individuals with a bachelor's degree or further education, and those with some college or fewer years of education. Pearson's correlations were likewise utilized to address the second aim, determining the association between parent responsivity and child social behavior within the parent-child interaction.

Structural equation modeling (SEM) was implemented to evaluate the role of responsive parenting in predicting prospective changes in parent- and teacher-reported child social skills across three time points. SEM allows for the examination of simultaneous links between observed variables and (unobserved) latent constructs. Responsive parenting was assessed as a latent variable, with three measured indicators (Supportive Directiveness, Supportive Engagement, Interference). A latent growth curve model (LGCM) was then utilized to assess the relationship of this latent "responsive parenting" variable and change in parent-reported (but not teacher-reported) social skills over time. LGCM allows for the examination of individual differences in growth of variables over time, as well as predictors of growth (Krull & Arruda, 2015). Using a SEM framework, LGCM assesses repeated measures of an outcome as indicators of latent growth factors (i.e., intercept, slope). Estimates of latent intercept and slope were derived from parent-reported social skills (SSiS) across Times 1, 2 and 3. For the model of teacher-reported social skills, a multiple regression model was utilized, assessing the relationship

between the responsive parenting factor and later (Time 2, Time 3) teacher-reported social skills, controlling for concurrent (Time 1) social skills. A regression model was utilized in place of a LGCM for the teacher model, as there was a change in reporters from Time 2 to Time 3. Both the parent and teacher models were modeled using Mplus version 8 (L. K. Muthén & Muthén, 2017).

For SEM models, full information maximum likelihood estimation was used to estimate missing data, which is superior to listwise and pairwise deletion methods with respect to parameter estimate bias, estimate efficiency, and model goodness of fit (Enders & Bandalos, 2001). Additionally, three indices of good model fit were examined: a Chi-square test of fit (non-significant Chi-square values generally reflect good to excellent fit), a comparative fit index (CFI; values above 0.90 indicate good fit), and the root mean square error of approximation (RMSEA; values at or below 0.05 = excellent fit, 0.05–0.09 = good fit, and over 0.10 = inadequate fit; Hu & Bentler, 1999). Parent education was selected as a covariate to control for the potential confounding effects of family socioeconomic status, as parent education (as opposed to family income and other SES indicators) often accounts for the most variance in parenting behavior (Bornstein & Bradley, 2012). Further, child sex was also covaried to account for differences in the levels of parenting attributable to child sex (e.g. Tamis-LeMonda et al., 2009). Intervention services were considered as covariates for analyses; however, children who were reported to receive any early intervention services did not differ from those who did not with respect to levels of parent Supportive Directiveness ($F = 1.67$, $p = .20$), Supportive Engagement ($F = 0.70$, $p = .41$), and Interference ($F = 0.75$, $p = .39$), nor were differences found based on whether children were reported to have received behavior-based interventions for ASD (e.g., ABA, PRT, DTT; $F = .34$ to $.93$, $p = .34$ to $.56$). Responsive parenting domains were

also not associated with the number of interventions received (r = .00 to .13, all p >.05). Thus, intervention services were not covaried in SEM models. Child level of functioning, including autism severity, IQ and language ability, while theoretically tied to parenting, were not covaried given the strong theoretical and observed overlap between these variables and social skills (e.g., teacher reported social skills: r = -.53 to -.38, all p < .001 in the current sample), such that controlling for these variables might preclude the ability to adequately characterize variability in social skills.

Results

Descriptive statistics

Descriptive statistics and correlations between key study variables are reported in Table 1.2. No site differences were found for any of the 14 key study variables, with the exception of Time 2 social skills (parent report only; Boston > Southern California). On average, parents of children with ASD demonstrated moderate to moderately high levels of directive (Supportive Directiveness) and non-directive (Supportive Engagement) forms of responsive parenting, and low levels of Interference. Parent Supportive Directiveness and Supportive Engagement were positively associated with one another; both were negatively associated with Interference. Parent Supportive Directiveness was positively associated with teacher-reported social skills at Time 2 and Time 3, while Interference was negatively associated with social skills at Time 3. No significant associations were found between parent-reported social skills and observed parenting. Teacher-reported social skills were modestly correlated with parent-reported social skills at concurrent time points (r = .26 to .33).

[See Table 1.2]

Concurrent predictors of responsive parenting

Table 1.3 depicts correlations between responsive parenting domains and concurrent child behavior and characteristics. Supportive Directiveness was positively associated, and Interference negatively associated, with concurrent child IQ and language ability, but not child autism severity. However, child IQ, language and autism severity were not significantly associated with parent Supportive Engagement. Child age was positively associated with Supportive Engagement only. Child sex differences were found for Supportive Directiveness and Interference, such that parents of female children with ASD demonstrated more Supportive Directiveness (Cohen's $d = 0.36$) and less Interference (Cohen's $d = .0.42$) than parents of males with ASD (see Figure 2.1). Post-hoc analyses revealed no significant differences in child IQ ($t = - 0.35$, $p = .73$) or language ($t = - 1.14$, $p = .27$) by child sex, suggesting that these characteristics were unlikely to explain the differences found by child sex. In terms of family and parent characteristics, family income was not associated with responsive parenting domains ($r = -.06$ to .08, ns), nor did parents differ in responsive parenting by educational status (i.e., whether the parent obtained a bachelor's degree; $t = - 0.67$ to 1.53, ns).

[See Table 1.3 and Figure 2.1]

Table 1.4 also depicts the correlations between parent and child behavior within the free play interaction at Time 1. Parent Supportive Directiveness was moderately and positively associated with the frequency of child social initiations, as well as global ratings of the child's social engagement with the parent. In contrast, Interference was found to be negatively associated with child initiations and engagement with the parent. Supportive Engagement was positively associated with child social engagement, but not child initiations.

[See Table 1.4]

Responsive parenting and prospective growth in child social skills

Structural equation modeling (SEM) was utilized to assess whether responsive parenting (measured as a latent factor) predicted growth in child social skills over time, as reported by both teachers and parents. All three indicators of the latent parenting factor were significant at $p < .001$ in both models, with Supportive Directiveness and Supportive Engagement positively, and Interference negatively, loading onto the factor. The SEM for the teacher-report model (multiple regression with a latent factor; see Figure 2) demonstrated excellent model fit (χ^2 (14) = 14.86, p = .39; CFI = 1.00; RMSEA = .02). Results indicated that the latent factor of responsive parenting did not concurrently relate to Time 1 social skills; however, after controlling for concurrent (Time 1) social skills, it did positively predict social skills at Times 2 and 3. Thus, greater responsive parenting was associated with positive growth in teacher-reported social skills across the three time points, spanning 1.5 years. With regard to parent-reported social skills, a LGCM was utilized to determine the association between responsive parenting and concurrent social skills (i.e., intercept) as well as linear growth in social skills over time (i.e., slope). The parent-report model (see Figure 3) also demonstrated excellent model fit ($\chi^2(18) = 19.94$, $p = .34$; CFI = 1.00; RMSEA = .03). Responsive parenting positively predicting initial social skills at a trend level, but not growth in social skills over time.

[See Figures 2 and 3]

Discussion

The present study sought to characterize responsive parenting in the context of social development for early school-aged children with autism. Specifically, the study aimed to determine child- and family-level predictors of responsive parenting, as well as the association between responsive parenting with concurrent and prospective growth in child social skills.

Responsive Parenting and Child Characteristics

Findings revealed that child characteristics, but not parent education or family income, predicted responsive parenting. Of note, higher child level of functioning (IQ, language ability) was positively associated with responsive direction (i.e., Supportive Directiveness) and negatively associated with intrusive direction (i.e., Interference). This finding is consistent with prior research demonstrating that parents tend to be more interfering with children with developmental delays than those with typical development (Green et al., 2014; Spiker, Boyce, & Boyce, 2002), that responsive parenting is positively associated with nonverbal IQ and mental age for children with ASD (Siller & Sigman, 2008), and that parents tend to be more directive with infants at high risk for ASD than those with low risk (Harker et al., 2016). Interestingly, some studies of children with ASD found no associations between responsive parenting and child characteristics (e.g., developmental level, adaptive behavior; Ruble, McDuffie, King, & Lorenz, 2008), which may be attributable to varied parenting assessment methods and sample characteristics (i.e., size, specialized recruitment settings versus community samples).

One potential explanation for the link between responsive parenting and child developmental level may relate to the parents' perceptions of the child's needs. Parents of children with lower IQs or language abilities may perceive their children as requiring more parental direction in play. Indeed, children with developmental delays are more likely to engage in less functional play and exhibit fewer social communication bids than those without delays (Warren & Brady, 2007), which may leave parents with fewer opportunities for responsiveness, and more perceived need for parent-centered direction. Moreover, low verbal cognitive abilities are associated with poorer social communication for children with ASD (Joseph, Tager-Flusberg, & Lord, 2002). Thus, parents of children with ASD and lower cognitive and language skills may

provide more interfering direction in response to their child's relatively less frequent and less sophisticated communication bids.

Differences in responsive parenting were also found by child sex, with females exposed to more responsive direction and less interfering direction than males. One potential explanation for this may be the different diagnostic profiles of males and females with ASD. In the current study, child IQ and language were not found to differ by sex, and therefore are unlikely to explain the difference. However, females with ASD often show varied patterns of social communication, and their relative social communication strengths in certain domains (e.g., gestures) may serve to "camouflage" other areas of impairments (Rynkiewicz et al., 2016), though some studies find no sex differences in social communication (e.g., Rubenstein, Wiggins, & Lee, 2015). Moreover, females with ASD tend to display less restricted and repetitive patterns of behavior than males (Rubenstein et al., 2015), which may facilitate more responsiveness from parents. Further research is necessary to determine explanatory models of potential sex differences in responsive parenting. Importantly, all parents studied, regardless of child gender, exhibited relatively high levels of responsive direction and low levels of intrusive direction. Yet, the small to medium differences noted by child sex may indeed reflect a meaningful difference, given the prolonged exposure to parenting behavior across development.

Taken together, the present findings have implications for identifying families who are at risk for sub-optimal parent-child interactions, thus providing a more targeted approach to intervention. That parents of children with lower IQs and lower language abilities demonstrate less responsive parenting behavior suggests that these families may experience unique barriers to or challenges in providing this style of parenting. Coaching these families to identify and address potential barriers, for example, by pausing and waiting for a child cue and identifying and

responding to subtle signs of child engagement, may enhance parent-mediated interventions. Further, interventions may be enhanced by including psychoeducation regarding child characteristics associated with responsive parenting (IQ, language, sex).

Responsive Parenting and Social Skills

Within the context of parent-child free play, responsive parenting was also associated with child social behavior. Specifically, responsive direction was positively associated, and intrusive direction negatively associated, with child social initiations and engagement. These findings coincide with research suggesting that directive forms of responsive parenting (e.g., 'maintaining', 'follow-in directives'), in which the parent is guiding the child's behavior in line with the child's interest and focus of attention, can promote child engagement and opportunities for communication (Flynn & Masur, 2007; McCathren et al., 1995). Likewise, intrusive direction was associated with less child engagement, consistent with prior research for children with developmental risk (Mahoney & Nam, 2011). These findings may help to clarify the conflicting literature on parent directiveness and child development in ASD. While some studies find negative relationships between parent directiveness on child engagement (Patterson et al., 2014), others find positive associations with child development (Haebig, McDuffie, & Weismer, 2013). The present findings suggest that the degree of responsivity (child-versus parent-centered) within parent directives may determine the level of child engagement within the interaction. Indeed, researchers acknowledge that directiveness and responsivity are not mutually exclusive (e.g., Harker et al., 2016), and parents may effectively use these strategies in combination to interact with their children. However, given that parent and child behavior were measured within the same interaction, it is possible the opposite direction of effect holds, such that parents' responsivity is in response to their child's ability to make social bids and engage socially. Thus, a

primary goal of this present study was to assess the role of responsive parenting in predicting prospective changes in child social behavior.

When looking longitudinally, responsive parenting positively predicted changes in social skills over time by teacher report, but not parent report. Responsive parenting predicted change in teacher-reported social skills through one school year (Time 2), and even into the winter of the following school year (Time 3), as rated by a different teacher. These findings suggest that responsive parenting may positively influence child social development in a way that extends to contexts outside of the parent-child interaction, carrying over into the school setting. The same association did not hold when looking at parent-reported social skills over time. While responsive parenting was concurrently associated with parent-reported social skills at a trend level, responsive parenting did not predict growth in social skills. Therefore, responsive parenting in the early school years may help to promote social skills as witnessed by teachers in the school context (e.g., social interactions with peers and teachers), rather than those social skills observed by the parent in the home (e.g., interactions with siblings and parents).

Differences in teacher- and parent- report are not entirely surprising, as agreement between parents and teachers on child social skills tends to be modest across child populations with typical development (Winsler & Wallace, 2002; Verhulst & Akkerhuis, 1989) or with ASD (e.g., Jepsen, Gray, & Taffe, 2012). Examinations of cross-informant ratings of social skills for children with ASD suggest that parents tend to endorse initiation behaviors at a higher rate, while teachers tend to endorse more social response and maintenance behaviors (Murray, Ruble, Willis, & Molloy, 2009). It is possible, then, that responsive parenting may serve to *model* to children how to respond to, and maintain interactions with others, which is better captured by teacher than parent observation. Alternatively, the same types of social skills (initiations,

responses) may serve different purposes across home and school contexts. While skills employed with parents and siblings at home may reflect more cooperative or compiant behavior, teachers may be more likely to observe skills employed to form and maintain friendships with peers, and the latter may be more likely to be influenced by responsive parenting. That levels of responsive parenting associated with teacher- but not parent-reported social skills hold implications for intervention, as parents' motivation to build responsivity skills may be negatively impacted if parents themselves do not see a corresponding change in child social skills. This present findings may then reinforce the utility of multi-method assessment of child progress in the context of clinical practice. It will be important for both parents and clinicians to collect teacher ratings in addition to parent and clinician ratings to accurately assess child progress in the setting in which the change occurs.

The present findings, in conjunction with the prevailing research on parent responsivity, have implications for parent-mediated interventions. Several developmental interventions utilized with very young children including Pivotal Response Training, Project ImPACT, and Early Start Denver Model (ESDM) have begun to integrate elements of responsivity with behavioral approaches in therapist-, teacher- and parent-mediated interventions with notable positive developmental gains (see Schreibman et al., 2015 for review). Though, some such interventions find variable outcomes across children (e.g., Carter et al., 2011). The present study suggests that these integrative approaches may continue to be beneficial for social development beyond toddlerhood and into the early school years for children with ASD.

Study Limitations and Conclusions

The present study should be interpreted within the context of the study's limitations. Due to the lack of experimental design, no causal claims can be made about the direct effects of

responsive parenting on social development for children with ASD. It will be important for future studies to employ rigorous designs (i.e., randomized control trials, cross-lagged longitudinal studies) to assess or approximate the causal role of responsive parenting on child social development in ASD. Further, the present study examined responsive parenting within the context of an in-laboratory, free play parent-child interaction. Future studies may enhance our understanding of the generalizability or specificity of these findings by examining the same parenting constructs across settings (e.g., naturalistic/in-home) and tasks (e.g., structured tasks), as reported on previously with different coding schemes (Blacher, Baker, & Kaladjian, 2012; Spiker et al., 2002). The present study also did not benefit from the use of observational measures of child social skills in growth models.

Further, children with IQs lower than 50 were not represented in the present sample. It will be essential for future studies of responsive parenting to include individuals representing the full range of the IQ spectrum, including those with very low IQs, to establish generalizability of findings. Likewise, our understanding of responsive parenting in ASD may be aided by future research that independently assesses its relationship to receptive and expressive language. Finally, family-level predictors of responsive parenting were limited to demographic variables (education, income). Future research should include other important aspects of family functioning (e.g., parenting stress) that have been linked to child functioning and parent behavior in ASD (Davis & Carter, 2008).

The present study exhibited many methodological strengths, including a large, well-characterized sample of children with ASD, their parents and their teachers. The project rigorously assessed parenting behavior using a well-defined, observation based coding scheme, holding strict criteria for reliability. This allowed for rigorous assessment of observed parenting

behavior. Multi-method, multi-rater assessments of the primary developmental outcome (child social functioning) were employed over time, thus reducing measurement error and shared method variance. Moreover, multi-rater assessment yielded different results, which may help to refine our understanding of the specificity of the effect of responsive parenting on child social development. Overall, the present study suggests that parent responsivity continues to play an important role in the social development of children with ASD during the early school years and should be considered as a tool for developmentally-focused interventions for this at-risk group.

Table 1.1

Child, family and school demographics (N= 176)

	Mean or %	SD
Child		
Child age at intake (years)	5.5	1.0
Child sex (% Male)	81.7%	--
Child race (% White)	56.3%	--
IQ (WPPSI-III)	87.6	17.8
ADOS (% autism vs. spectrum classification)	89.8%	--
CASL (Time 1)	81.7	17.5
Parent/Family		
Parent age (years)	38.1	5.4
Parent sex (% Female)	88.9%	
Parent race (% White)	65.0%	
Parent education (% BA or above)	64.4%	
Parent employment status (% Working a paid full-time job)	32.8%	
Second parent or parenting partner in home (%)	86.0%	
Family household income (Median range)	$65,000-$80,000	
Teacher/School and Intervention		
Teacher: Current Grade(s) Teaching		
Preschool/Pre-Kindergarten	34.8%	
Kindergarten	19.9%	
1st Grade	13.5%	
2nd Grade	5.6%	
Combination	26.2%	
Teacher: Highest Level of Education		
Associate's degree or below	6.7%	
Bachelor's degree	26.4%	
Master's degree or above	66.9%	
School setting (% Public school)	91.7%	
Classroom setting (% Special education)	51.4%	

Note. CASL: scores reported reflect the average between the standard scores of two scales (Syntax Construction, Pragmatic Judgment) assessed at Time 1; each scale has a normative mean of 100, and standard deviation of 15. BA: Bachelor's degree. Teacher data is reported for the teacher of the student at Times 1 and 2. Combination: teacher teaches multiple grades between pre-k and 2nd grade.

Table 1.2

Descriptive statistics and correlations between responsive parenting domains and child social skills across three time points

	Mean (SD)	**1. Supp. Dir. T1**	**2. Supp. Eng. T1**	**3. Inter. T1**	**4. SSiS-P T1**	**5. SSiS-P T2**	**6. SSiS-P T3**	**7. SSiS-T T1**	**8. SSiS-T T2**	**9. SSiS-T T3**
1	3.53 (1.0)	1								
2	2.97 (0.9)	.53***	1							
3	2.02 (0.9)	-.62***	-.33**	1						
4	76.6 (15.0)	.10	-.02	-.06	1					
5	77.3 (16.1)	.11	.06	-.04	.76***	1				
6	77.8 (15.6)	.10	.06	-.06	.61***	.65***	1			
7	83.1 (15.7)	.05	.13	-.07	.27**	.34***	.28**	1		
8	85.4 (15.3)	.18*	.12	-.11	.33***	.33***	.44***	.79***	1	
9	86.6 (14.5)	.22*	.12	-.20*	.25**	.26**	.26**	.40***	.47***	1

Note. Supp. Dir.: Supportive Directiveness. Supp. Eng.: Supportive Engagement. Inter.: Interference. Responsive parenting domains are reported on a 1-5 (high) Likert scale. SSiS-P: Social Skills Improvement System, Social Skills Total T-Score, Parent report. SSiS-T:
Social Skills Improvement System, Social Skills Total T-Score, Teacher report. T1: Time 1, T2: Time 2, T3: Time 3. *p<.05,** p<.01, ***p<.001

Table 1.3

Correlations demonstrating relationships between responsive parenting and concurrent child behavior and characteristics

	1. Supp. Dir.	**2. Supp. Engage.**	**3. Inter.**	**4. Child Init.**	**5. Child Engage.**	**6. Child Age**	**7. ADOS Total**	**8. WPPSI-III IQ**	**9. CASL T1**
1	1								
2	.53***	1							
3	-.62***	-.33**	1						
4	.34***	.11	-.27**	1					
5	.41***	.27***	-.34***	.46***	1				
6	-.01	.17*	-.05	.06	.01	1			
7	-.12	-.08	.11	-.21**	-.27***	-.07	1		
8	.28***	.10	-.25**	.39***	.39***	.03	-.55***	1	
9	.25**	.00	-.21**	.42***	.38***	-.21**	-.41***	.72***	1

Note. Supp. Dir.: Supportive Direction. Supp. Eng. Supportive Engagement. Inter.: Interference. Child Init.: Child Social Initiations. Child Engage.: Child Engagement with Parent. Child age: age reported in months at Time 1 visit. T1: Time 1. *p<.05,** p<.01, ***p<.001

Table 1.4

Correlations between responsive parenting and concurrent child behavior within the parent-child interaction

	1. Supportive Directiveness	2. Supportive Engagement	3. Interference	4. Child Initiations	5. Child Engagement
1	1				
2	.53***	1			
3	-.62***	-.33**	1		
4	.34***	.11	-.27**	1	
5	.41***	.27***	-.34***	.46***	1

** $p<.01$, *** $p<.001$

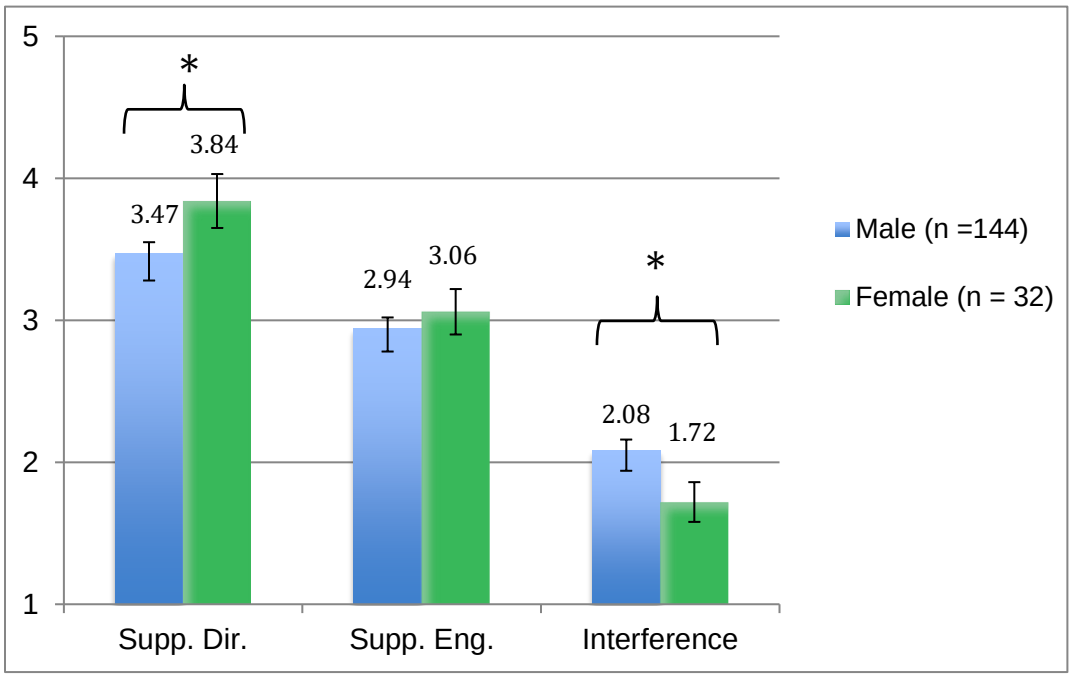

Figure 1.1. Group differences in responsive parenting for children with ASD by child sex. Supp. Dir.: Supportive Directiveness. Supp. Eng. Supportive Engagement.*p<.05

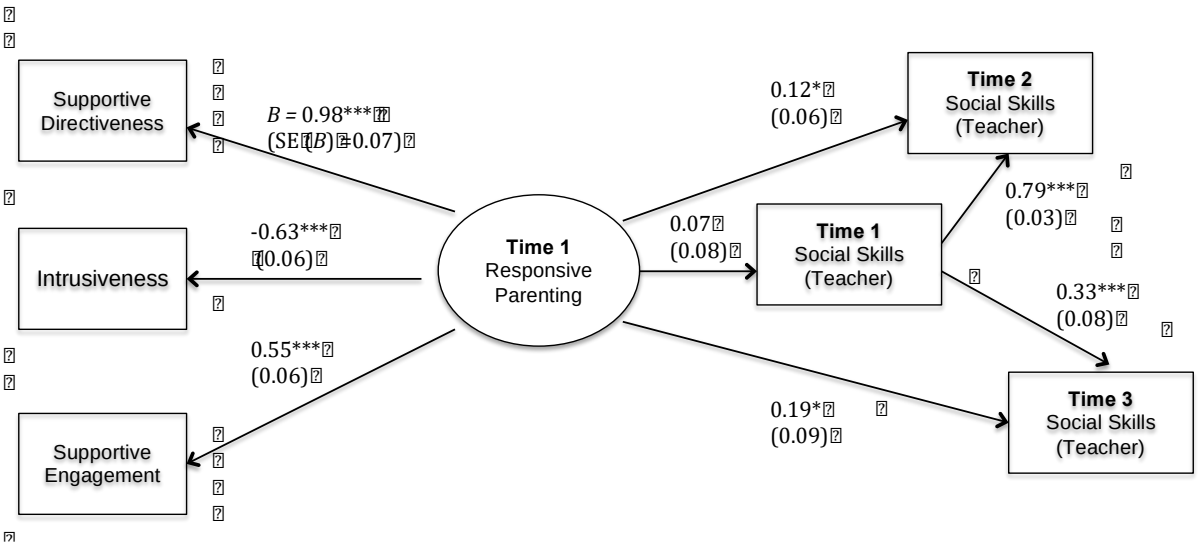

Figure 1.2. Structural equation model of latent responsive parenting predicting Time 2 and Time 3 teacher-reported social skills, controlling for Time 1 social skills. Because Time 1 and 2 social skills were reported by a different teacher than Time 3, a regression model (shown here) was conducted rather than a latent growth curve model. Covariates included*:* Child sex, parent education. Residual variances not listed for simplicity of presentation. Model fit: χ^2 (14) = 14.86, p = .39.

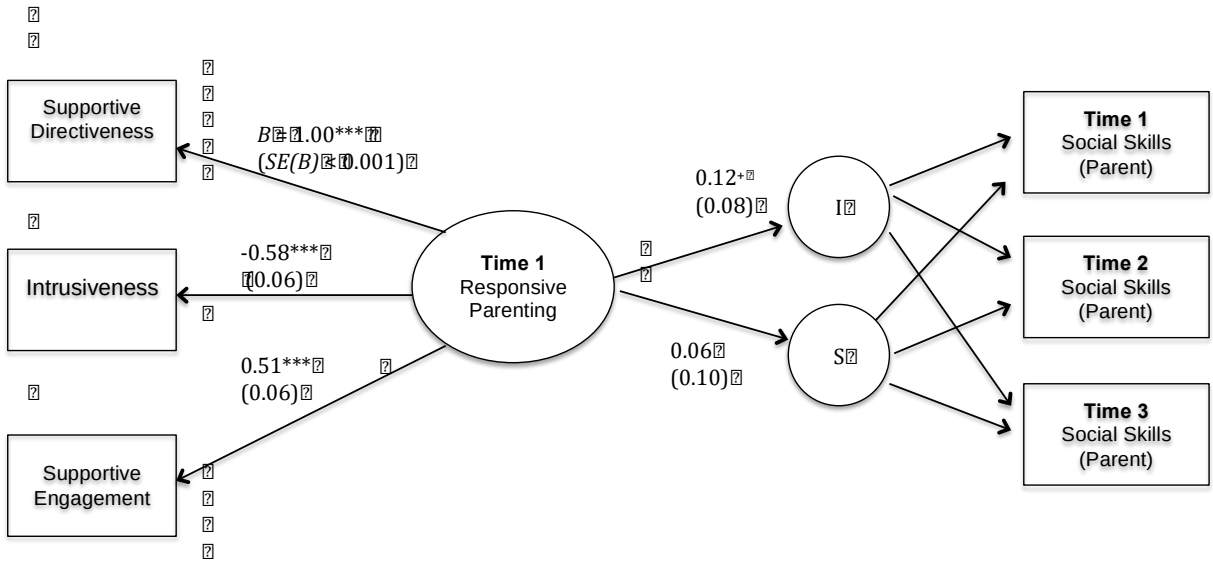

Figure 1.3. Latent growth curve model of responsive parenting predicting changes in parent-reported social skills. Covariates: Child sex; parent education. Residual variances not listed for simplicity of presentation. Model fit: χ^2 (18) = 19.94, p=.34. $^{+}$p<.10.

Study 2. Gene-parenting interaction and heterogeneous social development in autism: the mediating role of emotion regulation.

As noted in Study 1, while autism spectrum disorder (ASD) is defined by core deficits in social communication and social interaction, there is considerable heterogeneity with respect to the etiology, phenomenology, and long-term outcomes of ASD. Emerging research suggests that genetic variation and family environments independently contribute to social functioning in youth with ASD, yet progress has been hindered by a lack of integration of genetic and social methods to explain heterogeneity in social development. In other realms of developmental psychopathology, gene-environment interactions (GxEs) have been shown to contribute to symptomatology for a variety of childhood disorders, including Attention Deficit/Hyperactivity Disorder (ADHD) and other externalizing disorders (e.g. Kim-Cohen et al., 2006; Stevens et al., 2009; Salvatore et al., 2014). Such gene-environment interplay is nearly unexplored in autism, and stands to inform future genetics and behavioral research, as well as biological and psychosocial interventions. Implementing rigorous methodology, the proposed study will leverage the same large, well-characterized ASD sample, multi-method assessment and repeated-measures design as described in Study 1 to ascertain the independent and interactive contributions of responsive caregiving and child genetics.

Gene-environment contributions to social functioning

Theoretical models of developmental psychopathology have increasingly recognized that development results from the complex interplay of internal and external processes (Calkins et al., 2013; National Research Council, 2015). In the context of autism, heritability rates are estimated to be moderate (Hallmayer et al., 2011), leaving substantial variance attributable to environmental factors and gene-environment interplay. Moreover, genetic influences on autism

are likely diverse, spanning common disease/common variant modes as well as rare variants. Next generation genome wide approaches, while promising, still have largely failed to identify replicated variants. Previous genetics studies are limited by their frequent reliance on dichotomous phenotyping, despite the continuous nature of clinical phenotypes, as well as the lack of examination of GxEs which may serve to explain inconsistent genetic findings (Manuck & McCaffery, 2014). Rigorous phenotyping (e.g. continuous, repeated measurement) will serve to improve power and increase sensitivity to known developmental influences, including GxEs.

Developmental theorists posit different models for understanding the nature of GxE. As noted in the Introduction, two of these competing models are the *diathesis-stress* and *differential susceptibility* models. The longstanding *diathesis-stress (aka dual risk) model* (Monroe & Simons, 1991; Zuckerman, 1999a), posits that certain biological-driven characteristics (e.g. genotype, temperament) predispose individuals to be more vulnerable in the context of negative or harsh environments. In contrast, the *differential susceptibility hypothesis* (Belsky, 2016; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011) takes an evolutionary perspective, theorizing that the same biologically determined characteristics might actually confer susceptibility to positive *and* negative environments, rather than vulnerability to risk alone. The present study will assess these competing models of gene-environment interaction for three biologically plausible candidate genes: the serotonin transporter (5-HTTLPR), oxytocin receptor gene (OXTR) and dopamine receptor (DRD4) genes. These specific genes were selected given: (1) their role in neural networks related to "social salience", (2) their involvement in epigenetic processes (which may serve to mediate GxEs), and (3) relationship to ASD-related phenotypes.

5-HTTLPR

The functional polymorphism of the serotonin transporter (5-HTTLPR) is a key regulator of serotonin, a neurotransmitter widely implicated in neuropsychological processes (e.g. attention, emotion, arousal) as well as hypothalamic-pituatary-adrenal (HPA) system function (Brummelte, Mc Glanaghy, Bonnin, & Oberlander, 2016). 5-HTTLPR is a variable number tandem repeat in the 5' region of the promoter region (Canli & Lesch, 2007). 5-HTTLPR is comprised of short (*S*) or long (*L*) alleles, which contain fourteen and sixteen repeat units, respectively. The short and long alleles differentially modulate the expression and function of the serotonin transporter, with the short form associated with decreased availability of serotonin at the synaptic cleft (Lesch et al., 1996).

This low-expressing short ('S') allele of the serotonin transporter gene (5-HTTLPR; rs4795541 and rs25531), is not only associated with autism, but also with psychopathology more generally and changes in social functioning over time (Kinast, Peeters, Kolk, Schubert, & Homberg, 2013). These diverse phenotypes may arise from the pleiotropic effects of the serotonergic system on neurobiological and behavioral development (Canli & Lesch, 2007). However, small effect sizes and heterogeneous phenotypes may be attributed to GxEs involving 5-HTTLPR (Homberg & van den Hove, 2012). For example, 5-HTTLPR has been found to moderate the influence of caregiving quality *on relevant social phenotypes* in humans (Caplan et al., in preparation) as well as non-human species (Watson, Ghodasra, & Platt, 2009; Canli & Lesch, 2007; Homberg & van den Hove, 2012).

The interactions between 5-HTTLPR and psychosocial environments are likely mediated through neural pathways. Specifically, 5-HTTLPR variation is associated with cortico-limbic structures and function (e.g. decreased amygdala activation and functional coupling between the prefrontal cortex (PFC) and amygdala for carriers of the 'S' allele; Homberg & van den Hove,

2012). Further, experimental and correlational designs reveal that neural systems relevant for social cognition, emotional salience, and the regulation of attention to emotional cues are engaged *differentially* in an individual with the 'SS' genotype (Drabant et al., 2012; Canli & Lesch, 2007). Thus, it can be inferred that individuals with different 5-HTTLPR genotypes are processing their social environments in varied ways, and this may lead to differing pathways of development.

OXTR

Single nucleotide polymorphisms (SNPs) of the oxytocin receptor gene (OXTR; rs53576A, rs2254298, rs237887, rs7632287) also stand to reveal novel mechanisms of social heterogeneity in autism. The neuropeptide oxytocin (OXT) plays a key role in encoding social information, and is associated with complex social behavior and autism (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011). Further, the administration of intranasal oxytocin is associated with increases in social behavior (Meyer-Lindenberg et al., 2011), suggesting a causal relationship. Low expressing variants in OXTR SNPs are likewise associated with social phenotypes and overly transmitted in autism (Meyer-Lindenberg & Tost, 2012). These social phenotypes are mediated through neural endophenotypes involved in social-affective functioning, including a limbic circuit involving the amygdala, cingulate gyrus, and hypothalamus (Tost et al., 2010; Meyer-Lindenberg & Tost, 2012).

However, direct effects of OXTR of neural and behavioral phenotype are small, highlighting the need to take into account other factors that influence gene expression, including GxE. OXTR is a biologically plausible candidate for GxE, given its role in neurobiology regulating social information processing (e.g. hypothalamus, anterior cingulate cortex, amygdala; Meyer-Lindenberg & Tost, 2012). Further, OXTR variation has been proposed as a marker of

"social salience" to positive *and* negative environmental stimuli (Tabak, 2013), suggesting that OXTR GxE may follow a model of differential susceptibility. These GxE processes, in turn, are likely mediated through epigenetic processes. Indeed, psychosocial stress may regulate OXTR expression (Shalev & Ebstein, 2015).

Though studies of OXTR-caregiving interactions are in their infancy, preliminary evidence suggests that OXTR moderates the influence of psychosocial environments on social phenotypes. On the positive end of the spectrum, Wade and colleagues (2015) found that OXTR moderated the influence of maternal cognitive sensitivity on one aspect of social functioning (i.e., theory of mind), while Bradley et al. (2013) demonstrated the moderating role of OXTR in the relationship between positive parenting and positive coping and resilience in adulthood. Others (Bradley et al., 2011; McQuaid, McInnis, Stead, Matheson, & Anisman, 2013) found that early childhood maltreatment moderated the association between OXTR genotype and emotion-related phenotypes. Further, evidence that DNA methylation moderates the relationship between childhood maltreatment and affective outcomes supports the role of epigenetics in mediating OXTR-environment interactions (Smearman et al., 2016). Thus, while OXTR is likely to relate to differences in social functioning within autism, parenting quality may further affect how these social phenotypes develop over time.

DRD4

The dopamine D4 receptor (DRD4) is located on 11p15.5 and contains a 48 base pair variable number tandem repeat polymorphism in exon 3. This locus consists of 2 to 11 repeats, although 4 and 7 repeats are the most common. Variation in DRD4 may reveal sources of heterogeneity in ASD. While not be directly linked to ASD symptomatology (Grady et al., 2005), DRD4 has been associated with heterogeneous phenotypes within ASD (Gadow,

DeVincent, Olvet, Pisarevskaya, & Hatchwell, 2010). Beyond direct effects on behavioral phenotypes, DRD4 is often studied in the context of GxE due to its functional role in the regulation of dopamine in the brain. The 7-repeat (7R) allele of DRD4, in comparison to other repeats (e.g. 2, 4, 6, 8), is associated with less efficient dopamine binding and function of neural circuits implicated in reward salience, including social rewards (e.g. ventral striatum, ACC, inferior parietal cortex; Camara et al., 2010; Asghari et al., 1995). DRD4 has been well-studied as a marker of GxE in non-ASD populations (e.g. Knafo, Israel, & Ebstein, 2011; Bakermans-Kranenburg & van IJzendoorn, 2006). In these studies, the 7R allele interacts with caregiving environments, as assessed through both observational and experimental designs, to predict relevant behavioral phenotypes (Knafo et al., 2011; Bakermans-Kranenburg & van IJzendoorn, 2006; Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008).

Emotion regulation as a mechanism for GxE in ASD

In order to inform targeted intervention efforts, it is essential to understand the mechanisms through which GxEs exert their influence on social development. Emotion regulation is a suitable phenotypic candidate for investigating mediation of the proposed GxE effects. This proposition reflects extensive evidence that emotion regulation is fundamental to positive social functioning (Gross, 2011), and associated with core features and behavioral phenotypes in ASD, potentially due to shared underlying neurobiology (Bachevalier & Loveland, 2006). Although definitions of emotion regulation vary, most emphasize the dynamic interplay of *internal and external* processes involved in initiating, maintaining, and modulating the occurrence, intensity, and expression of emotions (Morris, Silk, Steinberg, Myers, & Robinson, 2007). Thus, whereas the family context is central to regulatory development (Morris et al., 2007; Gross, 2013), this influence will interface with child biology to affect child

regulation. Recently, regulatory processes have been studied from a developmental systems perspective (Thompson, 2011), which seeks to identify the key components of emotion regulation (e.g. attention, cognition, neurobiology, social influence) that mutually influence one another. This perspective highlights the role of early environmental influence on developing regulatory neurobiology. Through this lens, caregiver influences on regulatory development can be understood through the environmental shaping of both "top down" (prefrontal cortex-amygdala) and "bottom-up" (limbic-cortex) neurobiological systems (Gross, 2013), as well as epigenetic processes responsible for GxEs (e.g. DNA methylation; Weaver et al., 2004; van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011).

Indeed, gene-parenting interactions may contribute to heterogeneity in autism via influence on emotion regulation abilities. Specifically, 5-HTTLPR and OXTR are known to influence neurobiological functioning essential to the regulation of emotions. Variation in 5-HTTLPR is associated with corticolimbic circuitry (e.g., amygdala-prefrontal cortex coupling) and HPA-function, both of which play a functional role in emotion regulation (Canli & Lesch, 2007; Homberg & Lesch, 2011). Likewise, OXTR is associated with regulatory neurobiology involving the amygdala and hypothalamus (Tost et al., 2010; Meyer-Lindenberg & Tost, 2012). Further, the S allele of 5-HTTLPR has been proposed as a marker of susceptibility to the environment. Indeed, preliminary evidence suggests that 5-HTTLPR variation interacts with caregiving to predict child regulatory abilities (Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2015; Kochanska, Philibert, & Barry, 2009; Noroña et al., 2017).

The Present Study

The present study sought to address inconsistencies in the autism literature by explaining novel sources of heterogeneous social development. Specifically, we tested competing models of

GxE (diathesis stress vs. differential susceptibility) with biologically plausible candidate genes for environmental sensitivity and psychosocial functioning, 5-HTTLPR, OXTR and DRD4. We addressed the following aims:

Aim 1. To examine the additive or interactive effects of functional polymorphisms from candidate genes (5-HTTLPR, DRD4, OXTR) and parenting quality in predicting trajectories of social skills for young children with ASD. We hypothesized that genetic variation of the 5-HTTLPR and OXTR genes (but not DRD4) would modestly associated with concurrent and prospective child social skills. We also anticipated that the proposed genes (5-HTTLPR, DRD4, OXTR) will interact with observed parenting in a *differential susceptibility* manner, such that children with the low-expressing variants will be more strongly influenced by parenting quality, for better or worse.

Aim 2. To evaluate child emotion regulation as a mediator of the interactive effect of child genotype and parenting in predicting trajectories of social skills over time. We hypothesized that child emotion regulation would partially mediate the interactive effects of parenting with 5-HTTLPR and OXTR only.

Methods

Participants

Participants were sampled from the pool of families who originally participated in the *Smooth Sailing Autism Research Project*, a longitudinal study of children with ASD and their families (see Llanes, Blacher, Stavropoulos, & Eisenhower, 2018). Families were recruited through in-print and online advertisements that were distributed to local service agencies for individuals with developmental disabilities (e.g., regional centers), intervention service centers, clinicians, local school districts, and ASD-specific parent support groups and websites.. Families

were recruited from the Greater Boston area of Massachusetts (n = 31) as well as the Los Angeles and Riverside/San Bernardino county regions (n = 81). The participating child and primary participating parent (87.5% mothers) were asked to participate in a total of four study visits: an eligibility visit (EV), a Time 1 visit (in the fall), a Time 2 visit (in the spring; approximately 6 months after Time 1) and a Time 3 visit (in the following winter; approximately 6 months after Time 2). At the Time 1 visit, the participating parent and their child also participated in a 10-minutes free-play interaction. For the present study, families who participated in the Time 1 assessment, including the observed parent-child interaction (N = 176), and provided written consent to be contacted in the future were invited to participate in a follow-up DNA collection procedure. For the follow-up procedure, families were offered the opportunity to provide DNA saliva samples for the participating child and parent using Oragene DNA Collection Kits (OGR-500). Families were given the option to participate via mail or in person, with the vast majority participating via mail. Research staff obtained verbal consent over the phone and families were also mailed consent forms to supply written consent. Families were provided with collection kits and (when applicable) prepaid envelopes to mail their samples back to the research laboratory. Research staff followed-up with phone calls to clarify consent and participation procedures as appropriate. A small number of families expressed having trouble with their child depositing saliva using the tradition kits (OG-500). In these instances, a swab method was utilized (OG-575; ORAcollect for Pediatrics; n = 6), or families withdrew from participation (n = 3). Unlike buccal cell collection, the swab method provides a stable liquid sample and provides comparable DNA quality and genotyping success rates as whole-saliva procedures (Koni et al., 2011). All procedures were reviewed and approved by the Institutional Review Board (IRB) of the sponsor institution. Families were provided a modest ($30)

honorarium for participation in the DNA procedures.

The final sample included 112 parent-child dyads. Children who participated in the follow-up DNA were more likely to have higher IQs (mean IQ: 90.2 vs. 83.6; t= -2.50, $p < .05$), and a greater proportion were female (25% versus 8.3%; χ^2 (1) = 7.94), compared to those that participated in the Time 1 visit but did not complete the DNA follow-up study (n = 64). No significant differences between the two groups were found by child race, family income, and parent education. Table 2.1 reports demographic information for the present sample by 5-HTTLPR, DRD4 and OXTR genotypes. No significant differences in demographic variables (child IQ, family income, parent education, child race) were found by child genotype, with the exception of child age [DRD4: children with 7 repeat (7+) were significantly older than those without (7-)], and ADOS-2 autism severity [OXTR: more 'A' alleles associated with higher autism severity]. Parent genotype was associated with child genotype across all genes (all $p <$ .001). The vast majority of participating parents were biological mothers (82.1%), followed by biological fathers (11.6%). One participating caregiver was a biological grandmother (0.9%). Six families were adoptive families (5.4%); these families did not provide a DNA sample for the participating parent. Families with non-biological parents were retained in the sample, child genotype, but not parenting genotype was a primary variable of interest, and missing parent genetic data could be estimated using full information maximum likelihood.

[See Table 2.1]

Measures

Autism Diagnostic Observation Schedule (ADOS, Lord et al., 2000). The ADOS is a clinician administered assessment of autism symptomology and is considered the gold standard diagnostic instrument for autism spectrum disorders (Hurwitz & Yirmiya, 2014). The ADOS

demonstrates strong specificity and sensitivity and incorporates age- and language-specific modules (Lord et al., 2000). Ratings were determined using the revised ADOS algorithms (Gotham et al., 2008) that generate scores for Social Affect and Restrictive/Repetitive Behavior, consistent with the later-released DSM 5 criteria for ASD. These revised algorithms outperform the original ADOS algorithms, providing improved predictive validity and comparability across modules (Gotham et al., 2008).

Wechsler Preschool and Primary Scale of Intelligence- Third Edition (WPPSI-III; Wechsler, 2002). The WPPSI-III is a widely used assessment instrument of cognitive abilities in children ages 2 years 6 months to 7 years 3 months. The instrument yields IQ scores with a normative mean of 100 and a standard deviation of 15. The WPPSI-III demonstrates strong psychometric properties, including excellent internal consistency (.86-.97) and test-retest reliability (.84-.92; Wechsler, 2002). Three subtests were administered (Vocabulary, Matrix Reasoning, Picture Completion), from which a full-scale IQ score was estimated using Sattler's conversion tables (Sattler, 2008). Abbreviated versions of the WPPSI have demonstrated high reliability and convergent validity (LoBello, 1991). The composite score from these subtests correlates strongly (r = .90) with the full-scale IQ in the normative sample (Sattler, 2008).

Parent Directiveness and Interference-Revised (PDI-R). Maternal responsive and interfering direction was assessed using a revised version of the PDI coding system (Green, Caplan, & Baker, 2014; Caplan, Blacher & Eisenhower, in press). The PDI-R coding system distinguishes between a parent directive that is responsive to a child's needs or focus of attention ('*Supportive Directiveness')* and that which redirects the child's ongoing behavior or focus of attention ('*Interference*'). Supportive Directiveness captures parenting behavior, both verbal (e.g. comments, questions) and nonverbal (e,g., orientating toys, demonstrations of play, giving of

objects) that is used to supportively direct, shape or influence child behavior in a manner *consistent with* ongoing child activity or interests. The PDI was amended to account for other, non-directive aspects of responsive parenting that may influence the child's behavior within the session as well as broader child developmental outcomes (see Mahoney & Nam, 2011; Landry et al., 2006). Specifically, a code for parent Supportive Engagement was added as a means of capturing non-directive responsive parenting behavior, including parent positive and contingent responses to the child's ongoing activity (e.g. narrating the child's play, repeating child statements) or parenting behaviors to support social engagement within the context of the child's ongoing interests (e.g. facial expressions or interjections in response to the child's play, making character voices or sound effects, labeling the child's feelings). Parent Supportive Directiveness, Interference and Supportive Engagement are rated on a 1 to 5 Likert scale (1: minimal, 2: low, 3: moderate, 4: moderately high, 5: high). These global ratings take into account the frequency, consistency, perceived quality and appropriateness of parenting behavior (e.g., appropriateness of pacing, complexity of statements or behaviors relative to the child's developmental level, etc.). See Study 1 for further description of the coding system, including evidence of reliability and validity.

Social Skills Improvement System (SSiS; Gresham & Elliott, 2008). The SSiS is a standardized, norm-referenced assessment of social skills for children ages 3-18 years. The SSiS utilizes parent (SSiS-P) and teacher (SSiS-T) ratings of the frequency of a variety of child social behaviors on a 3-point scale from 0 (*never)* to 2 (*very often,* always). Both versions of the SSiS yield a Social Skills Total standard score with a mean of 100 and a standard deviation of 15. The SSiS Total score demonstrates high internal consistency (α = .96 to .97), test-retest reliability (r = .82 to .84), and convergent validity with the Vineland Adaptive Behavior Scale, 2nd edition and

the Behavioral Assessment System, 2nd edition (see Gresham & Elliott, 2008; Gresham, Elliott, Cook, Vance, & Kettler, 2010). Further, the SSiS has been widely used to assess social skills in children with ASD (e.g. Kasari et al., 2016) and in the current sample, demonstrates adequate convergent validity with the Social Responsiveness Scale (r = -.58; Constantino et al., 2003).

Emotion Regulation Checklist (ERC; Shields & Cicchetti, 1997). The ERC is a parent report measure of a child's methods for managing emotional reactions. Though originally developed with children ages 6–12 years, it has also been used in children as young as 5 years of age (Graziano, Reavis, Keane, & Calkins, 2007). The 24-items of the ERC yields scores for two subscales: Negativity/Lability and Emotion Regulation. The Negativity/Lability scale assesses a child's lack of flexibility, rapid changes in mood states, and dyregulation of affect, while the Emotion Regulation scale measures a child's overall mood, ability to label and express appropriate levels of positive and negative emotion in social contexts. The ERC has been successfully used with children with ASD, demonstrating high reliability (α=.84) and predictive validity with this population (Berkovits, Eisenhower, & Blacher, 2017; Weiss, Thomson, & Chan, 2014; Jahromi, Bryce, & Swanson, 2013). For the present study, the Emotion Regulation and Negatively/Lability scales of the ERC at both Times 2 and 3 were assessed as indicators of one latent 'emotion regulation' variable. Emotion regulation was not assessed at Time 1 in order to assess temporal precedence from X to M (MacKinnon, Fairchild, & Fritz, 2007).

Genotyping. DNA saliva samples were extracted using Oragene DNA collection kits or ORAcollect for Pediatric kits (Ottawa, ON, Canada). All SNP genotyping (OXTR), and repeat length sequencing (DRD4, 5-HTTLPR) were performed by Laragen, Inc. (Culver City, CA). Samples were then transferred and securely stored at the UC Riverside Genomics Core. OXTR SNPs (rs53576A, rs2254298, rs237887, rs7632287) were selected due to their established

relationships with social phenotypes and implicated neurobiology (Kumsta & Heinrichs, 2013; LoParo & Waldman, 2015), including through meta-analyses (Li et al., 2015), and/or preliminary implication in GxE (e.g., Bradley et al., 2011; Flasbeck, Moser, Kumsta, & Brüne, 2018). SNPs were genotyped using predesigned assays from Applied Biosystems (ABI, Foster City, CA, USA, *Assay-on-Demand by Applied Biosystems*®) following manufacturer protocols. These markers were genotyped with the ABI 7900-HT Sequence Detection System® using the TaqMan 5' nuclease assay for allelic discrimination. OXTR genes were assessed as an additive model, resulting in a quantitative variable reflecting the number of minor (A) alleles across SNPs.

5-HTTLPR short and long alleles (43-base pair deletion/insertion) were determined by the ABI 3730 Sequencer with Genemapper Mode using standard primers (Hu et al., 2006; 5′-GGCGTTGCCGCTCTGAATGC-3′ forward, and 5′-GAGGGACTGAGCTGGACAACCAC-3′ reverse), including the downstream SNP rs25531 that influences 5-HTTLPR functionality, such that the G allele, when paired with the L allele, results in a low expressing variant (L_G). In concordance with previous studies (Cervilla et al., 2007; Noroña et al., 2017), we compared individuals with two-low expressing alleles (i.e., SS, SL_G, L_GL_G; for simplicity, annotated as 'SS') with all others (SL/LL). The *DRD4* exon 3 VNTR was amplified with primer sets (5′- FAM-CGCGACTACGTGGTCTACTCG -3′ and 5′- AGGACCCTCATGGCCTTG -3′. Polymerase chain reactions (PCRs) were conducted in 20 μl volumes using Thermo Start PCR master mix. The size of PCR products were then determined with ABI 3730 Sequencer with GeneMapper mode. Consistent with prior research (Lee & Humphreys, 2014; Berry, McCartney, Petrill, Deater-Deckard, & Blair, 2014), individuals with one or more 7-repeat sequences (7+), were compared to those without a 7-repeat sequence (7-).

We observed the following allele frequencies: 5-HTTLPR (S: .56, L: .44), OXTR

rs53576 (A: .34, G: .66), OXTR rs2254298 (A: .19, G: .81), OXTR rs237887 (A: .52, G: .48), OXTR rs7632287 (A: .21, G: .79). Child DRD4 genotypes were as follows: 2/2 (n = 2), 2/3 (n=3), 2/4 (n= 16), 2/7 (n= 1), 3/4 (n=5), 3/5 (n=2), 3/10 (n= 1), 4/4 (n=47), 4/7 (n =25), 4/8 (n=1), 4/9 (n=1), 6/7 (n=1), 7/7 (n= 7). The observed allele frequencies, along with analytic methods employed (i.e., the aggregate assessment of OXTR SNPs), readily allowed for the assessment of moderation effects. All genotypes were in Hardy-Weinberg equilibrium (p =.08 to .77). Population stratification may be a threat to the internal validity of gene-association studies. However, race-ethnicity was unrelated to genotype in the current sample (see Table 2.1), a necessary condition for population stratification (Hutchison, Stallings, McGeary, & Bryan, 2004). Still, race-ethnicity was controlled in all analyses to ease potential concerns regarding population stratification.

Data Analytic Plan

The first aim of the study was to test the additive or interactive effects of functional polymorphisms from candidate genes (5-HTTLPR, OXTR, DRD4) and parenting quality in predicting trajectories of social skills for young children with ASD. To address this aim, structural equation modeling (SEM) was implemented in MPlus Version 8 (Muthén & Muthén, 2017) to evaluate the role of responsive parenting and specified genotypes in predicting prospective changes in parent- and teacher-reported child social skills across three time points. In SEM, the proportion of variance common to multiple indicators of a given construct is estimated, and the latent construct is then modeled, disattenuated from measurement error (Little et al., 2007). In all models, responsive parenting was assessed as a latent variable, with Supportive Directiveness and Supportive Engagement positively, and Interference negatively, loading onto the factor. Models were run separately by genotype (5-HTTLPR, OXTR, DRD4), and by parent

and teacher report, resulting in six models. Gene-environment interactions were modeled using a latent variable interaction approach. As latent variable interactions in MPlus do not yield traditional fit indicators, guidelines for testing progressive fit indices as recommended by Muthén and Asparouhov (2015) were followed. Models were run in the following order to ensure model fit of both iterations: (1) latent parenting variable with child genotype and covariates, (2) latent interaction term (responsive parenting x genotype). As noted by Muthén and others, the addition of the latent interaction term should not affect model fit, as the interaction term does not yield a mean, variance, or covariances with other parameters (Muthén, 2012; Maslowsky, Jager, & Hemken, 2015).

When GxE estimates did not reach significance ($p < .05$), models reported results for the main effects model. For SEM models, full information maximum likelihood (FIML) was used to estimate missing data, which is superior to listwise and pairwise deletion methods with respect to parameter estimate bias, estimate efficiency, and model goodness of fit (Enders & Bandalos, 2001). Additionally, three indices of good model fit were examined: a Chi-square test of fit (non-significant Chi-square values generally reflect good to excellent fit), a comparative fit index (CFI; values above 0.90 indicate good fit), and the root mean square error of approximation (RMSEA; values at or below 0.05 = excellent fit, 0.05–0.09 = good fit, and over 0.10 = inadequate fit; Hu & Bentler, 1999). Model fit indices for the final models are reported in Table 2.2. Continuous variables were all mean centered prior to being entered into the model.

Parent-report models utilized latent growth curve models (LGCMs) to assess the relationship of latent GxE, and where appropriate, main effect of responsive parenting and child genotype, in predicting change in parent-reported social skills over time. As teachers changed between Time 2 and Time 3, an auto-regressive model was utilized in lieu of a LGCM, assessing

prediction to Time 2 and Time 3 social skills, controlling for the prior time point (Time 1 and Time 2 social skills, respectively). Covariates were assessed as in Study 1 (i.e., child sex, parent education). In addition, child race/ethnicity was dummy coded and added as a covariate to all GxE models. Parent genotype was covaried to control for undue influence of passive gene-environment correlation (Knafo & Jaffee, 2013). For DRD4, genotype differences were also found by child age. Thus, for DRD4 models only, child age was also covaried to control for potential confounding effects. Significant GxEs were probed using region of significant procedures (i.e. Johnson-Neyman procedure; Preacher, Curran, & Bauer, 2006); simple slopes were also calculated by genotype and plotted using tools developed by Jeremy Dawson (Dawson, 2014; http://www.jeremydawson.co.uk/slopes.htm). Slope difference tests were calculated for LCGMs.

Study aim 2 involves assessing the mechanism underlying the proposed GxEs (i.e., mediated moderation). Here, I plan to test whether the interaction between the specified genes (5-HTTLPR, OXTR, DRD4) and parenting in predicting social skills development is explained by child emotion regulation. Given that causal steps approaches to mediation have been shown to be lowest in power relative to more modern approaches (Hayes, 2009), I will employ an estimation procedure in which I will first estimate the indirect effect of parenting-gene interactions on social skills through the mediating effect of emotion regulation, and then conduct an inferential test (e.g. bootstrap confidence interval) for the indirect effect (Fairchild & MacKinnon, 2008; Little et al., 2007) utilizing Mplus code from Stride and colleagues (Stride, Gardner, Catley, & Thomas, 2015). This approach will sufficiently test whether the mediated moderation effect and direct effect significantly differ from 0.

Results

Preliminary Analyses

Table 2.1 reports the descriptive statistics and correlations for key study variables in the overall sample (N = 112). On average, parents were rated as demonstrating parenting levels that corresponded to 'moderate' to 'moderately high' levels of responsive directive (Supportive Directiveness), 'moderate' levels of non-directive responsivity (Supportive Engagement) and 'some' Interference. Parent Supportive Directiveness was positively associated with teacher-reported social skills at Time 2 (at a trend level) and Time 3, as well as parent-reported social skills at Time 3. Supportive Engagement was positively associated with teacher-reported social skills (Time 2 and 3) at a trend level, while Interference was negatively associated with teacher-reported social skills at Time 1 (at a trend level) and at Time 3. Supportive Engagement and Interference were not significantly associated with parent-reported social skills.

Differences in key study variables (responsive parenting indices, teacher- and parent-reported social skills) were also assessed by child genotype. No differences in responsive parenting indices were found by 5-HTTLPR genotype (SS vs. SL/LL; t = -1.21 to 0.85, p = .23 to .98) or DRD4 genotype (7+ vs. 7-; t = .53 to 1.59, p = .13 to .60). Moreover, the additive OXTR genotype (i.e., number of A alleles across SNPs) was not associated with responsive parenting (r = .04 to .07, p = .42 to .71), limiting our concern regarding passive gene-environment correlation. Further, no differences in teacher- or parent-reported social skills were found for 5-HTTLPR (t = -0.85 to 1.49, p = .13 to .93) or DRD4 (t = - 0.13 to 1.32, p = .19 to .91). The number of A alleles (OXTR) was negatively associated with teacher-reported social skills at Time 1 only (r = -.23, p = .03). Thus, with the exception of OXTR and social skills at Time 1, child genotype was not directly associated with parenting or child social skills.

Gene-Environment Interactions

Teacher-Reported Social Skills

The first aim of the study was to assess the additive and interactive role of responsive parenting and child genotype in predicting prospective changes in child social skills by teacher-report and parent report, respectively. Autoregressive SEM models were run in MPlus to assess the presence of child genotype (5-HTTLPR, OXTR and DRD4) by latent responsive parenting interactions in predicting teacher-reported social skills. The first model examined GxE with 5-HTTLPR (see Table 2.4). Though the GxE term did not reach significance in predicting Time 2 social skills, examination of simple effects revealed that responsive parenting positively predicted changes in social skills from Time 1 to Time 2 for children with the SS genotype (β = 0.24, p = .04), but not those with the SL/LL genotypes (β = 0.12, p = .16). Results did yield a significant GxE effect for predicting change to Time 3 child social skills, such that children with the 5-HTTLPR SS genotype demonstrated a positive predictive association between responsive parenting and Time 3 social skills (controlling for prior social skills; β = 0.43, p < .01), while those with the SL/LL genotypes did not (β = 0.02, p = .90; see Figure 1). Tests of regions of significance revealed a *disordinal interaction*, such that slopes between the two groups (SS and SL/LL) significantly differed at lower levels of responsive parenting (2.83 SD below the mean and below) and higher levels of responsive parenting (0.11 SD above the mean and above).

[See Figure 2.1]

Models of GxE were also assessed for OXTR (see Table 2.5). Results regarding OXTR did not reveal a significant GxE in predicting change in child social skills to Time 2 or Time 3. Significant main effects were found for responsive parenting, with higher responsive parenting predicting positive growth in social skills to Time 2 (but not Time 3). Significant main effects

were also found for child race and parent genotype, with child bi-racial/multi-racial status being associated with more positive social skills growth to Time 2 and Time 3, and a greater number of parent A alleles associated with negative growth in child social skills to Time 2 (but not Time 3).

Table 2.6 depicts models assessing the role of DRD4 and DRD4 x responsive parenting interactions in predicting teacher-reported social skills. Models revealed a significant GxE predicting change in child social skill to Time 2 (but not Time 3), such that children with the 7 repeat allele (7+) demonstrated a positive relationship between responsive parenting and change in child social skills (β = 0.40, p < .01), while those without the 7 repeat allele (7-) did not (β = 0.09, p = .25; see Figure 2.2). The DRD4 x responsive parenting interaction predicting change in social skills to Time 3 was not significant; rather, a main effect of responsive parenting was found such that greater responsive parenting was associated with greater change in social skills over time. Tests of regions of significance revealed an *ordinal interaction*, such that slopes between the two groups (7+ and 7-) significantly differed at low levels (0.49 SD below the mean and below) of responsive parenting only.

[See Figure 2.2]

Parent-Reported Social Skills

Child genotype x responsive parenting interactions were also assessed via LGCM models of parent-reported social skills across Times 1, 2 and 3. First, we tested models of 5-HTTLPR x responsive parenting interactions (see Table 2.7). No significant 5-HTTLPR x responsive parenting interactions were found in predicting the intercept or slope of child social skills; these GxE terms were dropped from the model and main effects were assessed. Results for the intercept model revealed a significant relationship between child sex and initial parent-reported social skills, such that females were rated to have significantly lower social skills at baseline

relative to males. In assessing predictors of linear change in social skills, results indicated a trend-level positive effect of responsive parenting such that higher levels of responsive parenting were associated with more positive growth in social skills. In contrast, a trend-level association was found for child genotype, with the SS genotype associated with relatively poorer growth in social skills over time.

No significant OXTR x responsive parenting interactions were found in predicting the intercept or slope of parent-reported social skills (see Table 2.8). Child sex again emerged as a significant predictor of initial social skills (male > females). Only responsive parenting significantly predicted growth in child social skills, controlling for child and parent OXTR genotype and other covariates. Models of DRD4 x responsive parenting interactions revealed a significant GxE in predicting linear slope in social skills (see Table 2.9). The results revealed an unexpected direction of effect, such that responsive parenting positively predicted growth in parent-reported social skills for children with the 7- allele (β = 0.74, p<.01), but not the 7+ allele (β = - 0.11, p = .62; see Figure 2.3). Regions of significance (ROS) for LGCM models calculate the range of responsive parenting scores in which slopes are significantly different from zero for each genotype. ROS terms were not provided for the 7+ group, as responsive parenting did not predict growth in social skills at high (e.g., 2 SD above the mean) nor low (e.g., 2 SD above the mean) levels of responsive parenting. For the 7- group, regions of significance analyses revealed that the slopes of responsive parenting were significantly different from zero at high (1.67 above the mean or above) and low (2.28 SD below the mean or below) levels of responsive parenting. Slope difference tests yielded significant differences in slopes by genotype and high levels of responsive parenting (2 SD above the mean; t = -2.69, p < .01) and low levels of responsive parenting (2 SD below the mean; t = -2.68, p < .01), suggesting a *disordinal interaction* such that

significant slope differences by genotype are seen at low *and* high levels of the predictor (i.e., responsive parenting).

[See Figure 2.3]

In summary, responsive parenting interacted with 5-HTTLPR and DRD4, but not OXTR, in predicting changes in teacher-reported social skills. In the 5-HTTLPR and DRD4 models, the low expressing variants (SS of 5-HTTLPR and 7R of DRD4) demonstrated stronger relationships with social skills growth, consistent with study hypotheses. However, in the models of parent-reported social skills, only DRD4 significant interacted with responsive parenting to predict social skills growth. Here, only the higher expressing variant (7-) demonstrated relationships between responsive parenting and social skills growth.

Mediation by Emotion Regulation

The second aim of the study was to assess child emotion regulation as a potential mediator of GxE effects. Thus, mediated moderation models were assessed for the significant GxEs found: 5-HTTLPR and DRD4 (teacher report models) and DRD4 (parent-report model). First assessed were the indirect effects of 5-HTTLPR x responsive parenting interactions on change in child social skills (Time 2 to Time 3) via emotion regulation. Emotion regulation was assessed as a latent variable of the Lability/Negativity and Emotion Regulation scales of the ERC at Times 2 and Times 3. Results indicated no significant mediated moderation effect of emotion regulation (B = -1.02, p = .34; 95% CI: - 3.14 to 1.09). The indirect effect of responsive parenting on social skills via emotion regulation was not significant for the SS group (B = -0.63, p = .42), nor the SL/LL group (B = 0.38, p = .49). The direct effect of responsive parenting on social skills remained significant for the SS group (B = 7.90, p =.03; total effect: B = 7.26, p= .04). The direct effect (B = 0.69, p= .78) and total effect (B = 1.07, p = .67) were not significant

for the SL/LL group.

Next, we assessed emotion regulation as a mediator of DRD4 x responsive parenting interactions on change in child social skills (Time 1 to Time 2). Results indicated no significant mediated moderation effect of emotion regulation (*B* = -1.02, *p* = .34; 95% CI: -1.92 to 2.59). The indirect effect of responsive parenting on social skills via emotion regulation was not significant for children with the 7-repeat allele (7+; *B* = 0.35, *p* = .50), nor those without the allele (7-; *B* = - 0.03, *p* = .91). The direct effect remained significant for the 7+ group (*B* = 6.61, p = .02; total effect: *B* = 6.93, p = .02). The direct effect (*B* = 2.21, *p* = .19) and total effect (*B* = 2.09, *p* = .20) were not significant for the 7 – group. Finally, emotion regulation was assessed as a mediator of DRD4 x responsive parenting interactions for the linear slope in parent-reported social skills from Time 1 to Time 3. Results indicated no significant mediated moderation effect of emotion regulation (*B* = -0.07, *p* = .88; 95% CI: -1.02 to 0.88). The indirect effect of responsive parenting on linear slope of social skills via emotion regulation was not significant for the 7+ group (B = 0.78, *p* = .72), nor the 7- group (B = .24, p = .73). The direct effect (*B* = 3.06, *p* < .001) and total effect (*B* = 3.29, *p* = .002) of responsive parenting on social skills were significant for the 7- group, but not the 7+ group (direct effect: *B* = -0.36, *p* = .74; total effect: *B* = 0.41, *p* = .77).

No significant GxEs were found for OXTR. For OXTR models (teacher, parent), emotion regulation was assessed as a mediator of the relationship between responsive parenting and growth in social skills. The indirect effect of responsive parenting on change in social skills via emotion regulation was not significant in the model of teacher-reported social skills (Time 1 to Time 2 social skills; *B* = - 0.04, *p* = .82, 95% CI: - 0.39 to 0.25); the direct effect of responsive parenting remained significant (*B* = 2.75, *p* =.03). Emotion regulation was also assessed as a

mediator for the parent-report LGCM. However, the addition of emotion regulation to the model to test mediation resulted in poor model fit [$\chi^2(98)= 254.27$, $p<.001$] and a covariance matrix that is non-positive definite, precluding our ability to formally assess mediation in an SEM framework. Thus, emotion regulation did not surface as a significant mediator for any of the significant GxEs found.

Discussion

The present study sought to characterize the role of specific candidate genes (5-HTTLPR, DRD4, OXTR) and their interactions with responsive parenting environment in predicting social development in ASD. Importantly, the present study improved upon prior GxE methodologies in child development by assessing prospective changes in the phenotype (i.e., social skills), employing multi-rater assessment, and modeling observed parenting behavior including both positive *and* negative aspects of parenting (i.e., responsive direction and engagement, interference). While previous studies allude to the role of 5-HTTLPR, DRD4 and OXTR in GxE involving developmental outcomes in childhood (e.g., Cicchetti & Rogosch, 2012), no known studies to date have examined previously implicated GxEs in the context of the heterogeneous social phenotype in ASD. Results from present study revealed significant GxEs for 5-HTTLPR and DRD4, while OXTR did not significantly interact with responsive parenting to predict child social skills development. Significant GxEs were found to be in the expected direction of effect for teacher-report models of social skills, such that children with the minor expressing variants (SS genotype of 5-HTTLPR, 7R of DRD4) demonstrated stronger predictive relationships between responsive parenting and growth in social skills over time than those with the alternative genotypes. In the assessment of parent-reported social skills, an unexpected direction of effect was found for the DRD4 x responsive parenting interaction, such that those without the 7-repeat

allele (7-), demonstrated stronger associations between responsive parenting and growth in social skills over time.

5-HTTLPR x Responsive Parenting Interactions

The study first assessed the role of 5-HTTLPR x responsive parenting interactions in predicting child social skills development as reported by teachers. Findings revealed a *disordinal* interaction; consistent with the differential susceptibility model of GxE (Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011), children with the SS genotype were found to have significantly poorer prospective social skills development in the context of lower levels of responsive parenting, and better social skills development in the context of higher levels of responsive parenting relative to children with the SL/LL genotypes. The present findings suggest that the SS genotype of 5-HTTLPR may confer differential susceptibility to environmental influence for youth with ASD, as it has found to do for other clinical and community-based child populations (e.g. Manco, Soares, & Wasterlain, 2018; Noroña et al., 2017), including through meta-analysis (Tielbeek et al., 2016; Van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). While some studies find the L allele to be a marker of differential susceptibility (Davies & Cicchetti, 2014), these differences across studies are likely explained by racial differences across samples. Importantly, the present study controlled for race-ethnicity in analyses of GxE, using Caucasian group as a reference group. It will be important for future studies to assess the generalizability of study findings across ethnic/racial groups to enhance our understanding of the specificity of these GxE effects across ethnic/racial groups within ASD.

Translational research with 5-HTTLPR suggests that the SS genotype is associated with neural networks involved in social cognition and emotion regulation (Turhan Canli & Lesch,

2007; Hariri & Holmes, 2006) and emotional salience (Drabant et al., 2012), and that these same neural networks are sensitive to epigenetic modification of 5-HTTLPR (Nikolova et al., 2014). The present findings suggests the SS genotype may also be a marker of sensitivity to positive and negative social environments in ASD, which importantly may help to elucidate sources of heterogeneity in social functioning in ASD as genetic and parenting effects on social functioning likely depend on one another. In turn, these GxE effects may be explained by differential neural responses (e.g., amygdala activation and habituation) to social stimuli by 5-HTTLPR genotype in individuals with ASD (Wiggins, Swartz, Martin, Lord, & Monk, 2014), which may suggest increased salience to cues in the environment for those with the SS genotype.

Notably, this GxE finding was only present for teacher-report models of social skill development. Latent growth curve models revealed trend-level main effects of responsive parenting positively and SS genotype negatively predicting linear growth in parent-reported social skills over time. These findings are consistent with evidence of positive relationships with responsive parenting and social development in individuals with or without ASD (Landry, Smith, & Swank, 2006; Siller & Sigman, 2002) and negative social phenotypes associated with the SS genotype (Canli & Lesch, 2007). However, these effects only reached significance at a trend-level in the present study and should be interpreted with caution. That GxEs were present for teacher-report but not parent-report models suggests the importance of examining the specificity of GxE effects across contexts. It may be that children with the SS genotype take in information from the caregiving environments (due to differences in vigilance and attention; Canli & Lesch, 2007) in a way that more readily translates to social skills observed in the school setting (e.g., social initiation and response with peers) rather than in the home setting (cooperation with parents and siblings). Understood in the context of social learning theory (O'Connor, Matias,

Futh, Tantam, & Scott, 2013), responsive parenting may serve to model to children how to respond to and maintain interactions with others, skills which may be better captured by teachers than parents of children with ASD (Murray et al., 2009).

OXTR x Responsive Parenting Interactions

Another aim of the study was to assess the role of OXTR in social skills development, independently and interactively with the social environment (i.e., responsive parenting). The neuropeptide oxytocin has gained much attention in the ASD literature due to its connection to social affiliation and motivation (Gordon, Martin, Feldman, & Leckman, 2011), and potential for clinical translation (e.g., through administration of intranasal oxytocin, drug targets; Gordon et al., 2016; Modi & Young, 2012). OXTR has also been implicated in GxE due to associations with phenotypes relevant for 'social saliences' (Tabak, 2013) as well as findings suggesting that epigenetic regulation of OXTR plays a role in social phenotypes (Kumsta, Hummel, Chen, & Heinrichs, 2013). However, results of the present study revealed no significant interactions between OXTR genotypes (assessed as the number of low-expressing a alleles across selected SNPs) and responsive parenting in predicting social skills by teacher- and parent-report. Assessments of GxE by OXTR are in their relative infancy, and further research will be necessary to determine if and when OXTR plays a role in GxE in ASD. Though several studies have emerged implicating OXTR in GxE, these studies often find different SNPs playing a role in environmental susceptibility (e.g., rs11131149: Wade, Hoffmann, & Jenkins, 2015, rs2254298: Brüne, 2012; rs53576: Flasbeck, Moser, Kumsta, & Brüne, 2018).

One possibility is that different SNPs may play a role in GxE dependent on the environmental agent and the social phenotype of interest. While certain SNPs have been implicated in GxE of social cognitive phenotypes (e.g. theory of mind; Wade et al., 2015), others

have been connected to social ability and risk for ASD (Brüne, 2012). Future studies may choose to compare GxEs across SNPs and social outcomes to elucidate the specificity of OXTR x environment interactions in ASD, when present. For example, McDonald and colleagues (McDonald, Baker, & Messinger, 2016) found that the OXTR rs53576, but not rs2254298, moderated the association between one aspect of positive parenting (affective mutuality) and empathy in toddlers at high or low biological risk for developing ASD. The current study did not find OXTR x responsive parenting interactions, nor OXTR main effects to predict change in child social skills. It may be the case that OXTR may play a role in GxE, but that these effects may differ by SNP, developmental timing, child social phenotype and/or parenting style. Given the preliminary nature of GxE research in ASD, future studies assessing these nuances of OXTR x parenting interactions in ASD is warranted. In terms of OXTR main effects on social development, it is possible that certain OXTR SNPs may have a direct association with ASD (see LoParo & Waldman, 2015 for meta-analysis) in case-control designs, but play less of role in social variability or GxE with ASD. Finally, OXTR effects on social phenotypes may be very small, such that the current study was underpowered to detect the signal. Future studies of OXTR in ASD (in behavioral genetic and GxE designs) should choose to incorporate very large samples to adequately detect the effects of OXTR on child social development.

DRD4 x Responsive Parenting Interactions

Regarding DRD4, significant DRD4 x responsive parenting interactions were found for both teacher- and parent-report models of social skill development. However, models yielded opposite directions of effect, such that individuals with the 7+ allele demonstrated stronger relationships between responsive parenting and social skills development in the teacher-report model, but those with the 7- allele demonstrated stronger relationships in the parent-report

model. Results regarding DRD4 x responsive parenting interactions in teacher-report models are consistent prior research with young children (e.g., Bakermans-Kranenburg et al., 2008) in that 7+ is often found to be the marker of susceptibility. The 7+ allele of DRD4 is thought to be a marker of sensitivity to both positive and negative environments as it is associated with increased reward sensitivity and activation of neural networks involved in reward processing (Camara et al., 2010). However, in the present study, the interaction between DRD4 and responsive caregiving in the teacher-report model was *ordinal,* with individuals with the 7+ allele only demonstrating disadvantage in the context of lower levels of responsive parenting, but not advantage at higher levels of responsive parenting. These results suggest a diathesis stress model (Monroe & Simons, 1991) rather than differential susceptibility model of influence. That individuals with the 7+ would be more susceptible to less responsive parenting environments may relate to 7+-linked phenotypes. Individuals with the 7+ allele are more likely to demonstrate inattention and novelty seeking (e.g., Roussos, Giakoumaki, & Bitsios, 2009; Nikolac Perković et al., 2013) which are risk factors for poor behavioral and social development, particularly in the context of negative parenting environments (e.g., Tung et al., in press).

In contrast, results from the parent-report model suggest that the *7-* allele is a marker of susceptibility to both low and high levels of responsive parenting (i.e., a disordinal interaction), consistent with a model of differential susceptibility for the 7- genotype. It is not entirely clear why GxE models differed across teacher and parent models of social development. Agreement between parent and teacher reports of social skills tend to be modest in ASD (Jepsen, Gray, & Taffe, 2012; Zeedyk, Cohen, Eisenhower, & Blacher, 2015), with parents rating social initiation behaviors at a higher rate and teachers more likely to endorse social response/maintenance behaviors for children with ASD (Murray et al., 2009). Moreover, parents and teachers observe

social behaviors in different settings. One possibility is that parents may be more likely to endorse social skills that are linked to behavior problems. This would be supported by findings that young children with shorter variants (less than 7 repeats) of DRD4 demonstrate a negative association between warm-responsive caregiving and externalizing problems for very young children (Propper, Willoughby, Halpern, Carbone, & Cox, 2007). Further research is needed to interpret differences in GxEs found for social phenotypes in ASD as observed across home and school settings. Our understanding will be further enhanced by assessment of alternative mediators of GxE (e.g., behavior problems), as well as observation-based assessment of the phenotype.

Mediation by Emotion Regulation

Another key aim of the present study was to assess whether child emotion regulation mediates the GxEs identified. Results revealed no significant mediated moderation effect of GxEs by child emotion regulation as assessed through parent report. This lack of association suggests two possible implications: (1) child emotion regulation does not explain the link between 5-HTTLPR and DRD4 interactions with responsive parenting in predicting change in child social skills, or (2) the specific methods of assessment of emotion regulation did not allow for the detection of meditational effects, if present. First, if emotion regulation is not a mechanism of the identified GxEs, questions are left as to what other processes might be at play. It may be that gene x parenting interactions in ASD may be more influential for basic cognitive or attentional processes including theory of mind, attention and effortful control (e.g., Wade et al., 2015; Berry, McCartney, Petrill, Deater-Deckard, & Blair, 2014; Smith et al., 2012) moreso than emotion regulation, and these processes in turn impact social functioning. Alternatively, it may be that the behavioral (parent-report) assessment of emotion regulation may not be best

suited to identify meditational effects. Neural endophenotypes are proposed to be closer to the mechanisms of gene action, and therefore presumed to have larger, more readily detectable genetic effects (Caspi & Moffitt, 2006). Future studies may enrich our understanding of GxE by assessing activation of neural systems involved in emotion processing (e.g., corticolimbic systems) as potential mechanisms of GxE. Alternatively, task-based assessment of emotion regulation may better assess the construct of emotion regulation free from rater bias (e.g., Baker, Fenning, Crnic, Baker, & Blacher, 2007; Harrison & Gibb, 2015), and allow for the detection of mediation effects, if present.

Implications for Intervention

Taken together, the present findings hold important implications for scientific understanding of complex social phenotypes in ASD, as well as efforts for targeted and person-centered interventions. Autism spectrum disorder is understood to be a heterogeneous disorder with multiple complex genetic and environmental etiologies (see Jeste & Geschwind, 2014). Evidence of GxE in ASD will be an important consideration for genetics and neurobiological sciences. Refining genetic etiologies through behavioral phenotypic subgroups has proven difficult (see Müller & Fishman, 2018) likely due to issues of equifinality and multifinality informed by GxEs amongst other complex processes. Genetics studies in ASD may thus be enhanced by: (a) considering important environmental agents in analyses, and/or (b) examining neural endophenotypes which are presumed to be closer to the level of gene action (Geschwind, 2011).

Further, the present findings have implication for tailored ASD interventions based on individual differences in child biology. While mounting evidence supports the efficacy of responsivity-based interventions on social and developmental outcomes in ASD (see Schreibman

et al., 2015), substantial heterogeneity remains in regards to response to intervention. The present GxE findings may help to resolve differential findings across intervention trials as well as discrepant responses across individuals. Investigations of GxEs in ASD are in their infancy and require replication before translational efforts are justified. If substantiated with future research, evidence of the GxEs found may provide important information regarding which individuals are most likely to benefit from parent-mediated interventions (i.e., individuals with low-expressing variants of 5-HTTLPR and DRD4), while also suggesting that alternative or adjunctive interventions (e.g. pharmacological interventions, perhaps targeting serotonergic or dopaminergic systems) may be required for individuals with genetic markers of low susceptibility to environmental influence.

Limitations

The present findings should be interpreted in the context of several limiting factors. While the study exhibited strength in its use of a community-based sample enrolled in a larger longitudinal study, we discovered a few key differences between children that participated in the genetics procedures and those that did not. These differences include a higher percentage of females participating at follow-up and higher mean IQs represented in the sample that participated at follow-up than those that did not. This issue of generalizability is pervasive in genetic and neuroscience research in ASD, and future studies should work to overselect individuals with ASD and low IQs and include procedures that are likely to be tolerable to this population (e.g. swab method, in person assessments). Anecdotally, families of children with low IQs were observed to be more likely to request the swab method, or to not send back a sample after agreeing to participate. The present study was limited to measures of observational parenting; multi-method assessment including subjective reports of responsive parenting will enhance our understanding of

the specificity of GxE effects on social development in ASD. Our confidence in the GxE relationships found will also be improved through the implementation of experimental designs (i.e., randomized control trials of responsive parenting interventions). The present study should also be considered within the context of common criticisms of the field of candidate GxE research (Duncan & Keller, 2011), including the potential for type I error and replication failure. The present sample size was modest for candidate gene research, and findings should be interpreted as exploratory in nature until sustained with replication in large samples. Indeed, candidate GxE research remains a controversial field, with some criticizing the use of sample sized below 1,000 due to possible very small effect sizes (Dick et al., 2015). However, the majority of large-scale GxE studies lack rigorous assessment of the social environment and child phenotypes (i.e., observational and repeated measures assessment), and can be difficult to achieve in clinical populations. The science of GxE in ASD will advance with a balance of large-scale designs with more modestly-sized, yet rigorously assessed samples.

Strengths

The present study exhibited several methodological strengths rarely utilized in GxE research, including prospective longitudinal design, use of observational measurement of the parenting environment, and use of advanced structural equation modeling, all of which serve to increase power by reducing measurement error. Further, the longitudinal design aids our understanding of the developmental nature of GxE in the context of a crucial time for social development in ASD, the early school years. The current study also enhanced our understanding the specificity of GxE effects by employing multi-rater assessment of child social functioning. Results suggest that parenting and GxE relationships may differ in their impact on social skills exhibited in home and school settings. Finally, the study assessed and controlled for parent

genotype in analyses of GxE, which improves internal validity by controlling for the potential confounding effects of gene-environment correlation (see Knafo & Jaffee, 2013).

Future Directions

One key future direction for the present line of research is to replicate these findings assessing the same environment agents and child phenotypes across larger samples of children with ASD. Once validated in larger samples, it will be important to assess or approximate causality of effects through experimental or cross-lagged panel design. Further, it will be informative for future research designs to test the specificity of the GxE effects found by testing GxEs across different environmental settings (home, school) and across different parenting practices known to impact child development in youth with or without ASD (e.g., sensitivity, scaffolding, harsh or inconsistent discipline, neglect; NICHD, 2002). Finally, as noted above, further consideration is warranted regarding the mechanisms of the GxEs found including examination of neural endophenotypes and multi-method assessment of emotion regulation. In particular, it will be informative to test competing models of mediation by social neural networks versus networks involved in the regulation and modulation of emotional responses (e.g. corticolimbic systems) through neurogenetics designs.

Table 2.1

Demographics for overall sample and by child genotype (N = 112)

	Overall Sample	5-HTTLPR			DRD4			OXTR A alleles [a]
	Mean (SD) or %	SS (n = 36)	SL/LL (n = 74)	t-test *or* c^2	7- (n = 77)	7+ (n = 35)	t-test *or* c^2	r or F (N = 111)
Child Age	5.63 (1.0)	5.61 (0.9)	5.64 (1.1)	t = 0.15	5.49 (1.1)	5.93 (0.9)	t = -2.11*	r = .00
Child IQ	90.2 (18.2)	91.0 (18.9)	90.4 (17.8)	t = - 0.17	90.1 (18.8)	90.3 (17.1)	t = -0.05	r = -.13
ADOS-2 Severity Score	7.4 (1.7)	7.5 (1.8)	7.0 (1.5)	t = 1.62	7.4 (1.7)	7.4 (1.7)	t = 0.07	r = .26**
Child sex (% male)	75.5%	75.0%	75.7%	c^2 = 0.06	77.9%	71.4%	c^2 = 0.55	F = 1.13
Chile Race/Ethnicity	--	--	--	c^2 = 7.81$^+$	--	--	c^2 = 5.73	F = 0.22
Caucasian (%)	52.7%	38.9%	59.5%	--	55. 8%	45.7%	--	--
Latino (%)	11.6%	11.1%	12.2%	--	10.4%	14.3%	--	--
Af. American (%)	5.4%	5.6%	5.4%	--	2.6%	11.4%	--	--
Asian (%)	7.1%	2.7%	13.9%	--	9.1%	2.9%	--	--
Mixed Race/Ethnicity (%)	23.2%	30.6%	20.3%	--	22.1%	25.7%	--	--
Family income (% above $65,000)	57.1%	55.6%	56.8%	c^2 = 0.01	58.4%	54.3%	c^2 = 0.17	F = 3.05$^+$
Parent education[b] (% BA or above)	60.7%	63.9%	58.1%	c^2 = 0.34	89.6%	88.6%	c^2 = 0.03	F = 0.22
Parent Genotype[c]	--	50.0% (SS)	14.5% (SS)	c^2 = 14.85***	16.9 % (7+)	79.4% (7+)	c^2 = 38.48***	r = .39***
School setting (% public school)	85.6%	83.9%	89.3%	c^2 = 0.46	81.3%	96.4%	c^2 = 3.70$^+$	F = 1.42
Classroom setting (% special education)	39.6%	34.4%	50.0%	c^2 = 1.95	36.5%	46.4%	c^2 = 0.80	F = 1.61

Note. [a:] A alleles represent the additive number of A alleles observed across OXTR SNPs rs53576, rs2254298, rs237887, rs7632287 (mean = 2.51, standard deviation = 1.06). [b] Parent education: Assessed as percentage of parents with a Bachelor's degree or more education. [c]Parent genotype: Assessed within each genotype as: 5-HTTLPR (% SS), DRD4 (% with one or more 7 repeats), OXTR (number of a alleles across four SNPs reported above). 7+: Presence of one or more 7 repeat alleles. 7-: no presence of 7 repeat allele. ***p<.001, **p.>01, *p<.05, $^+$p<.10.

Table 2.2

Indicators of model fit for structural equation models predicting growth in teacher- and parent-reported social skills (SSiS-Total) by responsive parenting and child genotype.

	Main Effects Model					*Latent Interaction (GxE) Model*	
	χ^2 (39, 41)	*p*-value	RMSEA	AIC	BIC	AIC	BIC
Teacher Models							
5-HTTLPR	51.37	0.088	.056	2571	2665	2571	2670
OXTR	51.53	0.105	.053	2588	2679	2593	2692
DRD4	53.25	0.064	.060	2598	2693	2598	2697
Parent Models							
5-HTTLPR	54.43	0.078	.056	3043	3133	3048	3146
OXTR	53.85	0.086	.055	3073	3163	3078	3175
DRD4	59.85	0.068	.057	3073	3168	3074	3176

Note. Teacher models: Autoregressive models of teacher reported social skills. Parent model: Latent growth curve models of parent-reported social skills across three time points. RMSEA: Root Mean Square Error of Approximation.

Table 2.3

Descriptive statistics and correlations for key study variables

Variable	Mean (SD)	1	2	3	4	5	6	7	8	9
1. Supp. Dir.	3.6 (0.9)	1								
2. Supp. Eng.	2.9 (0.9)	.58***	1							
3. Interference	2.0 (0.9)	-.54***	-.28**	1						
4. SSiS-T (Time 1)	83.5 (16.6)	.10	.14	-.19+	1					
5. SSiS-T (Time 2)	86.1 (16.4)	.20+	.20+	-.14	.79***	1				
6. SSiS-T (Time 3)	87.5 (14.3)	.30**	.21+	-.23*	.31*	.38**	1			
7. SSiS-P (Time 1)	76.3 (15.3)	.03	-.03	.01	.25*	.31**	.28*	1		
8. SSiS-P (Time 2)	74.9 (16.5)	.15	-.02	-.04	.31**	.32**	.36**	.81***	1	
9. SSiS-P (Time 3)	77.5 (16.9)	.21*	.16	-.15	.30+	.43***	.30**	.60***	.62***	1

Note. Supp. Dir.: Supportive Direction. Supp. Eng. Supportive Engagement. Responsive parenting domains are reported on a 1-5 (high) Likert scale. SSiS-P: Social Skills Improvement System, Social Skills Total Standard Score, Parent report. SSiS-T: Social Skills Improvement System, Social Skills Total Standard Score, Teacher report. ***p<.001, **p.>01,*p<.05.

Table 2.4

Structural equation model (SEM) predicting changes in teacher-reported social skills to Time 2 and Time 3 by 5-HTTLPR, responsive parenting and their interaction

	B	SE (*B*)	Beta	*p-value*
A. SSiS-T – Time 2				
SSiS-T – Time 1	**0.78*** **	**0.08**	**0.76**	**<.001**
Race 1[a]	0.00	9.07	0.00	1.00
Race 2[a]	-0.88	4.16	-0.01	0.83
Race 3[a]	0.94	4.14	0.02	0.82
Race 4 [a]	4.93	3.10	0.13	0.11
Parent Education[b]	-0.82	3.69	-0.02	0.82
Sex: Female	3.63	2.99	0.09	0.23
Parent Genotype	-2.72	2.61	-0.07	0.30
Res. Parenting	2.10	1.55	0.12	0.16
5-HTTLPR	4.37	2.79	0.13	0.30
GxE	2.28	2.48	0.06	0.36
B. SSiS-T – Time 3				
SSiS-T – Time 2	**0.26**	**0.11**	**0.29**	**0.02**
Race 1[a]	2.73	9.70	0.04	0.78
Race 2[a]	-5.64	5.76	-0.09	0.33
Race 3[a]	1.75	3.64	0.04	0.63
Race 4 [a]	-6.94	5.12	-0.21	0.18
Parent Education[b]	1.20	4.17	0.03	0.77
Sex: Female	-3.45	3.51	-0.10	0.33
Parent Genotype	1.69	3.22	0.10	0.60
Res. Parenting	0.25	2.10	0.02	0.90
5-HTTLPR	3.44	3.01	0.10	0.25
GxE	**6.60**	**2.32**	**0.20**	**0.004**

Note. Statistically significant results are bolded for emphasis. Italics reflect non-significant GxE terms (p <.10) that were were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed. [a]Race is effect coded. [b]Mother education is assessed as the highest grade completed per mother report. [c]Genotype for 5-HTTLPR was coded SS =1, SL/LL =0. GxE: Gene-environment interaction. *B* = unstandardized coefficient. *SE(B)* = standard error of unstandardized coefficient. *ß* = standardized coefficient. †p<.10, *p<.05, **, p<.01, ***p<.001.

Table 2.5

Structural equation model (SEM) predicting changes in teacher-reported social skills to Time 2 and Time 3 by OXTR, responsive parenting and their interaction

	SE(*B*)	Beta	*p-value*	*B*
A. SSiS-T – Time 2				
SSiS-T – Time 1	**0.80*** **	**0.08**	**0.77**	**<.001**
Race 1[a]	3.64	6.16	0.05	0.55
Race 2[a]	1.02	4.95	0.01	0.84
Race 3[a]	2.60	3.65	0.05	0.48
Race 4 [a]	**5.64***	**2.62**	**0.15**	**0.03**
Parent Education[b]	0.43	4.28	0.01	0.92
Sex: Female	2.54	2.57	0.07	0.32
Parent Genotype	**-2.70***	**1.22**	**-0.16**	**0.03**
Res. Parenting	**2.85***	**1.28**	**0.16**	**0.03**
OXTR	1.30	1.12	0.08	0.25
GxE	*-1.11*	*1.40*	*-0.07*	*0.43*
B. SSiS-T – Time 3				
SSiS-T – Time 2	**0.32****	**0.10**	**0.36**	**0.002**
Race 1[a]	3.43	7.06	0.05	0.63
Race 2[a]	-10.09	8.70	-0.15	0.35
Race 3[a]	1.95	5.92	0.04	0.74
Race 4 [a]	**-8.60***	**4.30**	**0.25**	**0.04**
Parent Education[b]	0.26	5.24	0.01	0.96
Sex: Female	-4.06	3.69	-0.12	0.27
Parent Genotype	2.32	1.96	0.16	0.24
Res. Parenting	1.21	2.08	0.08	0.56
OXTR	0.49	1.53	0.04	0.75
GxE	*-0.22*	*1.15*	*-0.02*	*0.85*

Note. Statistically significant results are bolded for emphasis. Italics reflect non-significant GxE terms (p <.10) that were were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed. [a]Race is effect coded. [b]Mother education is assessed as the highest grade completed per mother report. [c]Genotype for OXTR coded as the number of 'a' alleles across identified SNPs. GxE: Gene-environment interaction. *B* = unstandardized coefficient. *SE(B)* = standard error of unstandardized coefficient. *ß* = standardized coefficient. †p<.10, *p<.05, **, p<.01, ***p<.001.

Table 2.6

Structural equation model (SEM) predicting changes in teacher-reported social skills to Time 2 and Time 3 by DRD4, responsive parenting and their interaction

	B	SE(*B*)	Beta	*p-value*
A. SSiS-T – Time 2				
SSiS-T – Time 1	**0.75*** **	**0.09**	**0.74**	**<.001**
Race 1[a]	2.11	7.33	0.03	0.77
Race 2[a]	7.03	4.79	0.08	0.14
Race 3[a]	2.16	3.72	0.04	0.56
Race 4 [a]	**5.31***	**2.48**	**0.14**	**0.03**
Parent Education[b]	0.61	3.48	0.01	0.86
Sex: Female	4.39	2.88	0.11	0.13
Parent Genotype	2.68	2.77	0.01	0.33
Res. Parenting	1.66	1.45	0.09	0.25
DRD4	-3.97	3.12	-0.12	0.20
GxE	**5.51***	**2.68**	**0.15**	**0.03**
B. SSiS-T – Time 3				
SSiS-T – Time 2	**0.33****	**0.11**	**0.37**	**0.004**
Race 1[a]	0.01	7.15	0.00	0.99
Race 2[a]	**-14.09+**	**8.09**	**-0.19**	**0.08**
Race 3[a]	2.31	3.77	0.05	0.54
Race 4 [a]	-6.73	5.30	-0.20	0.20
Parent Education[b]	0.13	4.00	0.00	0.97
Sex: Female	-5.22	3.82	-0.15	0.17
Parent Genotype	-3.67	3.48	-0.12	0.29
Res. Parenting	**4.05***	**1.86**	**0.26**	**0.03**
DRD4	5.23	4.59	0.17	0.26
GxE	-6.22	4.57	0.13	0.17

Note. Statistically significant results are bolded for emphasis. Italics reflect non-significant GxE terms (p <.10) that were were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed. [a]Race is effect coded. [b]Mother education is assessed as the highest grade completed per mother report. [c]Genotype for DRD4 was coded based on the presence of a 7 repeat allele [1= 7 repeat present (7+); 0 = 7-repeat not present (7-)]. GxE: Gene-environment interaction. *B* = unstandardized coefficient. *SE(B)* = standard error of unstandardized coefficient. *ß* = standardized coefficient. †p<.10, *p<.05, **, p<.01, ***p<.001.

Table 2.7

Latent growth curve models (LCGMs) of 5-HTTLPR x responsive parenting interactions predicting parent-reported social skills from Time 1 to Time 3

	5-HTTLPR			
	B	SE (*B*)	Beta	*p-value*
A. Intercept				
Race 1[a]	-8.75	6.30	-0.14	0.17
Race 2[a]	-5.80	6.49	-0.09	0.37
Race 3[a]	-7.45	4.64	-0.16	0.11
Race 4 [a]	-3.75	3.54	-0.11	0.29
Parent Education[b]	-0.08	4.84	0.00	0.99
Sex: Female	**-13.04*** **	**3.54**	**-0.38**	**<.001**
Parent Genotype	0.24	3.55	0.01	0.95
Res. Parenting	2.08	1.73	0.13	0.23
5-HTTLPR[c]	2.71	3.26	0.09	0.41
GxE	1.99	3.05	0.06	0.51
B. Linear Slope				
Race 1[a]	-0.58	3.02	-0.03	0.85
Race 2[a]	4.14	3.30	0.23	0.21
Race 3[a]	0.31	2.14	0.02	0.89
Race 4 [a]	0.44	1.68	0.04	0.80
Parent Education[b]	0.95	2.27	0.07	0.48
Sex: Female	1.19	1.69	0.12	0.68
Parent Genotype	0.45	1.66	0.05	0.79
Res. Parenting	**1.41+**	**0.79**	**0.32**	**0.07**
5-HTTLPR[c]	**-2.98+**	**1.54**	**-0.33**	**0.05**
GxE	*-0.93*	*1.52*	*-0.10*	*0.54*

Note. Statistically significant results are bolded for emphasis. Italics reflect non-significant GxE terms (p <.10) that were were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed. [a]Race is effect coded. [b]Mother education is assessed as the highest grade completed per mother report. [c]Genotype for 5-HTTLPR was coded SS =1, SL/LL =0. GxE: Gene-environment interaction. *B* = unstandardized coefficient. *SE(B)* = standard error of unstandardized coefficient. *ß* = standardized coefficient.
†p<.10, *p<.05, **, p<.01, ***p<.001.

Table 2.8

Latent growth curve models (LCGMs) of OXTR x responsive parenting interactions predicting parent-reported social skills from Time 1 to Time 3

	OXTR			
	B	SE(*B*)	Beta	*p-value*
A. Intercept				
Race 1[a]	-8.87	6.28	-0.14	0.16
Race 2[a]	-8.14	6.73	-0.13	0.23
Race 3[a]	**-8.59+**	**4.76**	**-0.18**	**0.07**
Race 4 [a]	-4.51	3.51	-0.13	0.20
Parent Education[b]	1.38	4.82	0.03	0.78
Sex: Female	**-13.50*** **	**3.56**	**-0.38**	**<.001**
Parent Genotype	-0.36	1.56	0.02	0.82
Res. Parenting	0.90	1.71	0.06	0.60
OXTR[c]	1.43	1.51	0.10	0.34
GxE	-1.70	1.59	-0.11	0.29
B. Linear Slope				
Race 1[a]	-1.32	3.00	-0.08	0.66
Race 2[a]	3.18	3.38	0.18	0.35
Race 3[a]	-0.57	2.18	-0.04	0.79
Race 4 [a]	-0.03	1.67	-0.00	0.98
Parent Education[b]	-0.42	2.24	-0.03	0.85
Sex: Female	1.19	1.68	0.12	0.48
Parent Genotype	0.58	0.73	0.14	0.43
Res. Parenting	**1.63***	**0.78**	**0.37**	**0.04**
OXTR[c]	0.82	0.71	0.21	0.24
GxE	*-0.31*	*0.97*	*-0.07*	*0.75*

Note. Statistically significant results are bolded for emphasis. Italics reflect non-significant GxE terms (p <.10) that were were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed. [a]Race is effect coded. [b]Mother education is assessed as the highest grade completed per mother report. [c]Genotype for OXTR coded as the number of 'a' alleles across identified SNPs. GxE: Gene-environment interaction. *B* = unstandardized coefficient. *SE(B)* = standard error of unstandardized coefficient. *ß* = standardized coefficient. DRD4 model also included child sex as a covariate. †p<.10, *p<.05, **, p<.01, ***p<.001.
Table 2.9

Latent growth curve models (LCGMs) of DRD4 x responsive parenting interactions predicting parent-reported social skills from Time 1 to Time 3

	DRD4			
	B	SE(*B*)	Beta	*p-value*
A. Intercept				
Race 1[a]	-9.36	6.82	-0.16	0.17
Race 2[a]	**-8.59+**	**4.81**	**-0.11**	**0.08**
Race 3[a]	**-8.59***	**4.00**	**-0.18**	**0.03**
Race 4 [a]	-5.43	3.30	-0.16	0.10
Parent Education[b]	3.00	4.35	0.06	0.49
Sex: Female	**-12.86*****	**3.35**	**-0.37**	**<.001**
Parent Genotype	2.65	3.04	0.09	0.38
Res. Parenting	0.12	2.59	0.01	0.97
DRD4[c]	-0.40	3.46	-0.01	0.91
GxE	1.66	4.02	0.05	0.68
B. Linear Slope				
Race 1[a]	-3.54	2.42	-0.21	0.14
Race 2[a]	**7.56**	**1.43**	**0.35**	**<.001**
Race 3[a]	0.62	2.75	0.05	0.82
Race 4 [a]	1.07	1.51	0.11	0.43
Parent Education[b]	-0.65	2.33	-0.05	0.32
Sex: Female	1.31	1.65	0.14	0.78
Parent Genotype	-0.91	1.38	-0.11	0.51
Res. Parenting	**3.32****	**1.10**	**0.74**	**0.003**
DRD4[c]	-1.79	1.47	0.21	0.22
GxE	**-3.71****	**1.28**	**-0.39**	**0.004**

Note. Statistically significant results are bolded for emphasis. Italics reflect non-significant GxE terms (p <.10) that were were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed. [a]Race is effect coded. [b]Mother education is assessed as the highest grade completed per mother report. [c]Genotype for DRD4 was coded based on the presence of a 7 repeat allele [1= 7 repeat present (7+); 0 = 7-repeat not present (7-)]. GxE: Gene-environment interaction. *B* = unstandardized coefficient. *SE(B)* = standard error of unstandardized coefficient. *ß* = standardized coefficient. Child sex was included as a covariate. †p<.10, *p<.05, **, p<.01, ***p<.001.

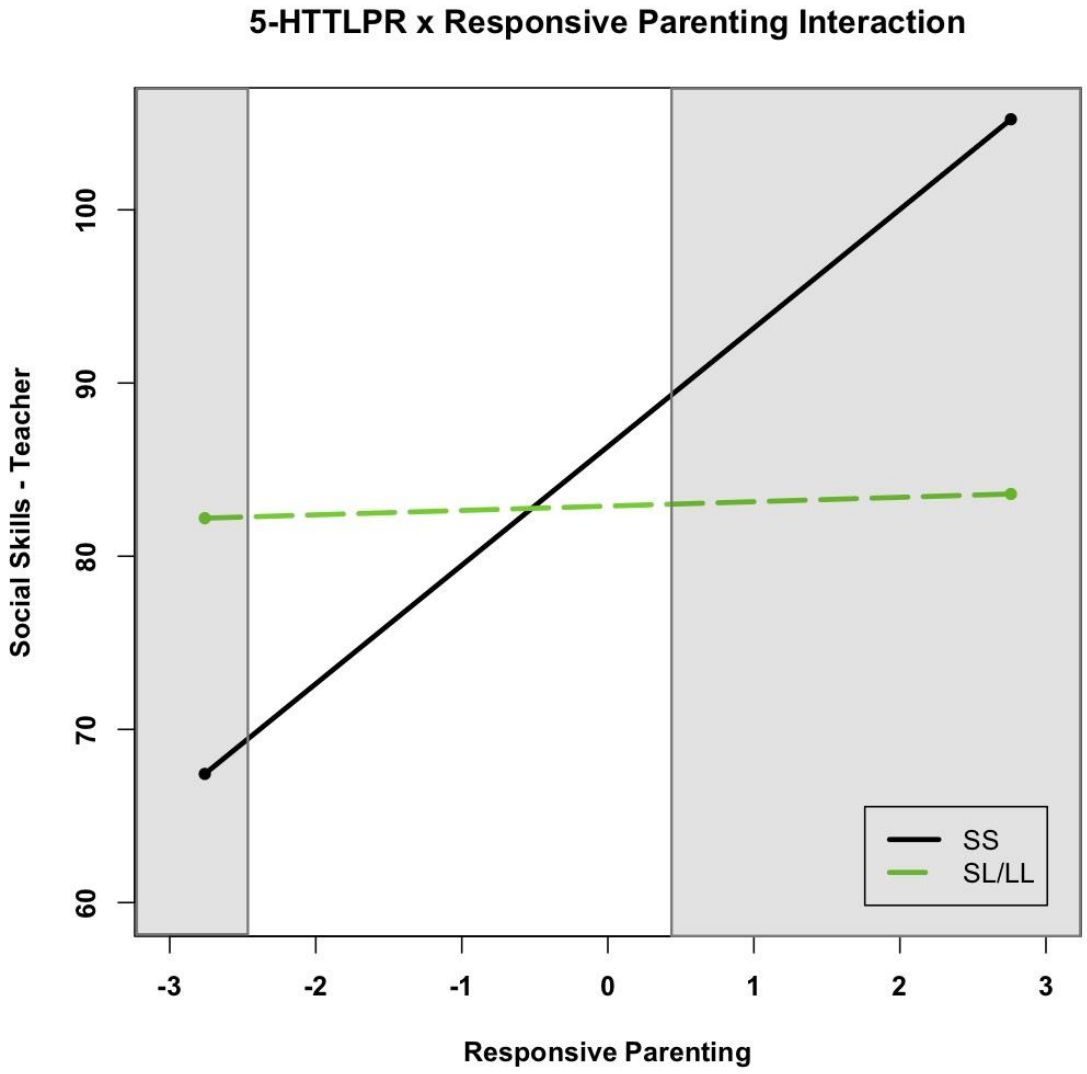

Figure 2.1. Interaction of child 5-HTTLPR genotype and responsive parenting in predicting later teacher-reported social skills at Time 3 (controlling for Time 2 social skills). Responsive parenting depicted in latent variable units (mean = 0, standard deviation = 0.917). Shaded areas depicts regions in which slopes are significantly different by child genotype. SS: 5-HTTLPR SS genotype. SL/LL: 5-HTTLPR SL or LL genotype.

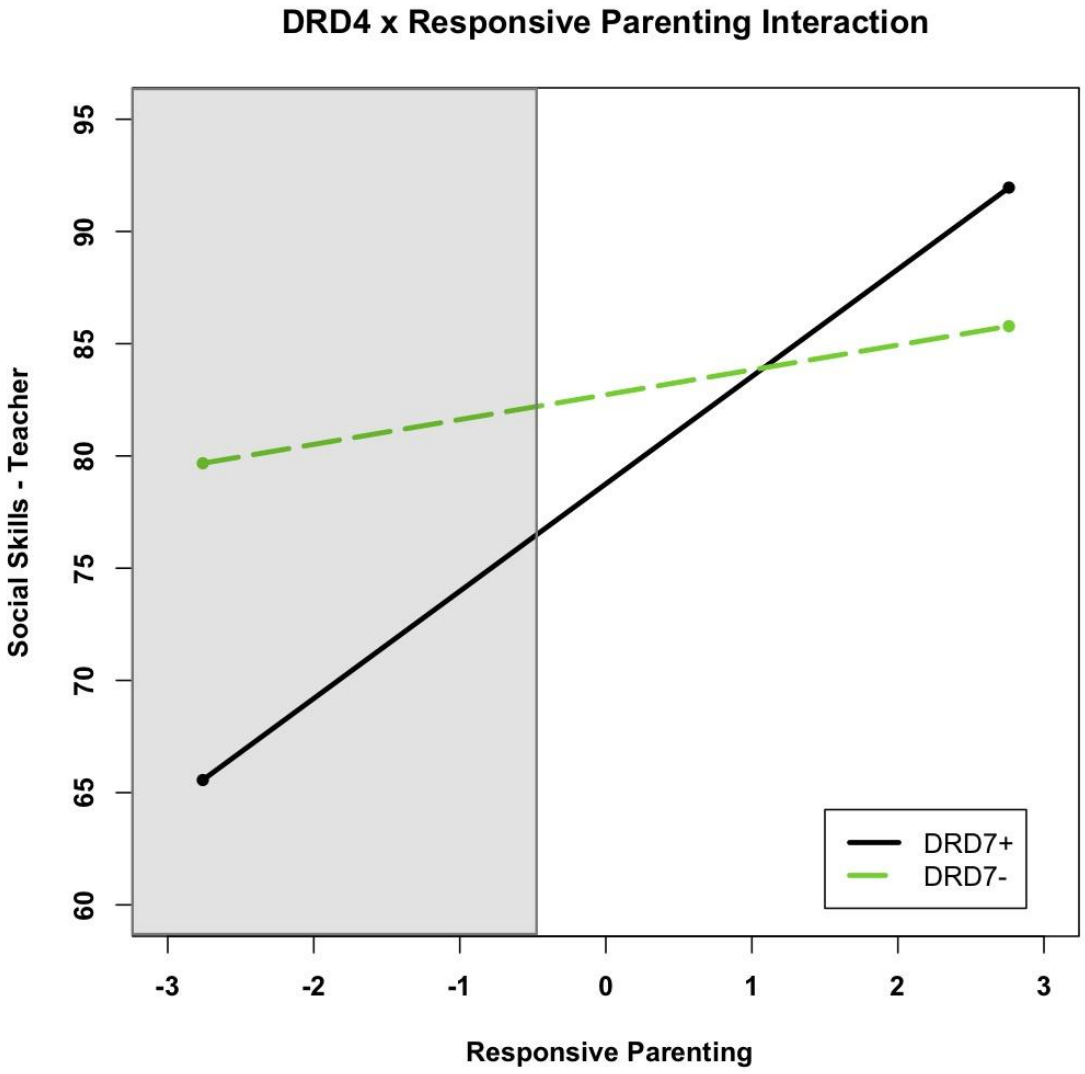

Figure 2.2. Interaction of child DRD4 genotype and responsive parenting in predicting later teacher reported social skills at Time 3 (controlling for Time 2 social skills). Interaction of child DRD4 genotype and responsive parenting in predicting later teacher-reported social skills at Time 3 (controlling for Time 2 social skills). Responsive parenting depicted in latent variable units (mean = 0, standard deviation = 0.917). Shaded area depicts region in which slopes are significantly different by child genotype. DRD4 7+: Individuals with one or more 7 repeat alleles. DRD4 7-: Individuals with no 7 repeat alleles.

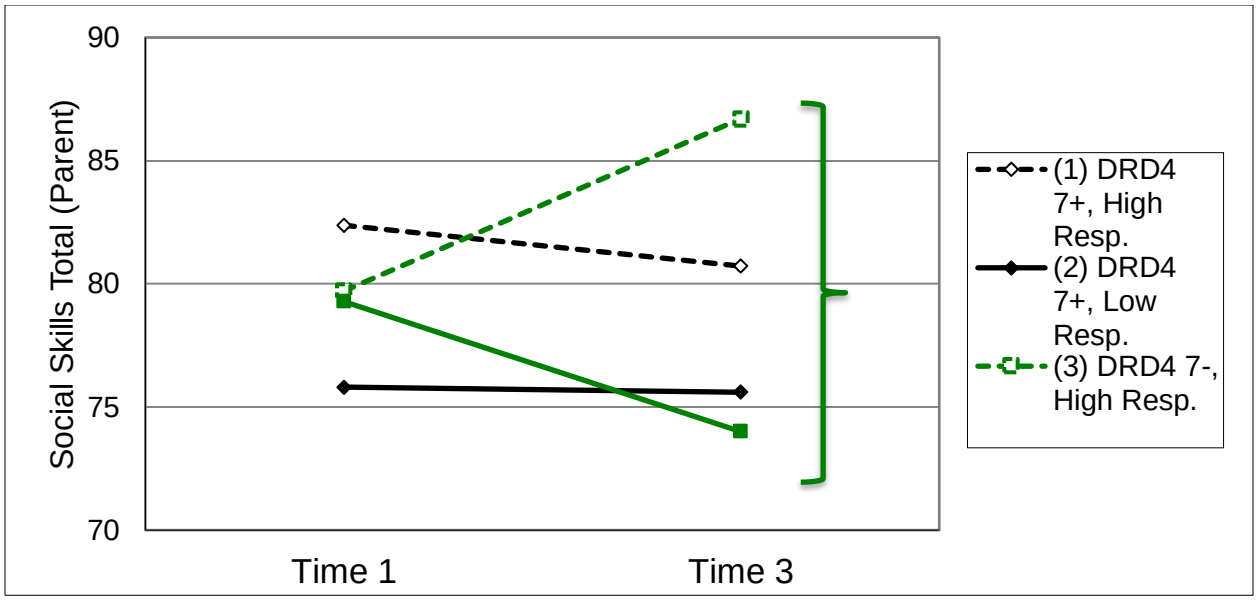

Figure 2.3. Interaction of child DRD4 genotype with responsive parenting predicting linear growth in parent-reported child social skills from Time 1 to Time 3. High Resp. = 1 SD above the mean on the latent variable of responsive parenting. Low Resp. = 1 SD below the mean on the latent variable of responsive parenting. DRD4 7+: Individuals with one or more 7 repeat alleles. DRD4 7-: Individuals with no 7 repeat alleles.

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