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Multilevel Dynamics of Risk and Resilience in the Development and Plasticity of Youth Externalizing Behavior

A dissertation submitted in partial satisfaction of the requirements

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by

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ABSTRACT OF THE DISSERTATION

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Professor Steve Sung-Yul Lee, Chair

Although growing evidence suggests that biologically-based factors, such as variations in dopaminergic genes and early reactive temperament, may explain 'differential susceptibility' to both social stress and support, little is known about whether patterns of environmental sensitivity change across development. Thus, this dissertation employed a developmental psychopathology framework to test differential susceptibility theory in three longitudinal studies of youth at risk for externalizing behaviors (EB; e.g., aggression, substance use), while directly considering the developmental impact of previous adversity.

Study 1 was based on a longitudinal study of children adopted from foster care. Generalized estimating equations examined whether reactive temperament heightened sensitivity to both pre-adoption maltreatment and later adoptive family support. Children with reactive temperament did not show heightened vulnerability to pre-adoption maltreatment; instead,

maltreatment directly predicted more substance use by late-adolescence. Reactive temperament did heighten sensitivity to the protective effects of family cohesion in early adoption, although effects were not maintained in late-adolescence.

Study 2 used latent growth curve analysis to model EB trajectories in a longitudinal sample of adolescents transitioning into adulthood. Employing a polygenic dopaminergic risk score (DRD4, DRD2, DAT1) previously linked to EB, we compared patterns of gene-environment interactions (GxE) between adolescents with and without histories of maltreatment. Polygenic risk moderated the association between parental closeness and concurrent adolescent EB, but these GxE effects did not predict EB changes over time. Furthermore, adolescents with maltreatment histories showed an overall blunted sensitivity to both parental closeness and friendship involvement, and these effects were largely unaffected by dopaminergic genes.

Study 3 employed a longitudinal sample of children oversampled for ADHD, an early EB risk factor. Based on prenatal programming theory, a moderated mediation model tested how birth weight (a proxy for global prenatal stress) and dopaminergic genes independently and interactively influence formation of early reactive temperament. Dopaminergic genes interacted with birth weight to predict negative emotionality in a pattern consistent with differential susceptibility. Negative emotionality, in turn, directly predicted adolescent EB, beyond the direct and interactive effects of positive and negative parenting behavior.

Overall, results partially support that genetic and temperamental variations influence sensitivity to the environment, although sensitivity was primarily limited to early developmental periods (prenatal period, childhood). We discuss these results in the context of prevailing developmental theories of EB and emphasize the importance of considering the dynamic nature of the environment when investigating individual differences in sensitivity to stress and support.

The dissertation of Irene Tung is approved.

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Introduction

Youth externalizing behavior (EB), including antisocial behaviors (e.g., aggression, delinquency) and substance use, is one of the most common and costly mental health problems in North America (Foster & Jones, 2005; Welsh et al., 2008). Although EB generally decreases after adolescence, some youth exhibit chronic EB that persists into adulthood (Evans, Simons, & Simons, 2014; Moffitt, 1993). Persistent EB is a potent risk factor for serious adult outcomes, including chronic criminal behavior and violence (Boden, Fergusson, & Horwood, 2010; Farrington, 1989; Lynam, 1996), antisocial personality disorder (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004), alcohol and substance use disorders (Fergusson, Horwood, & Ridder, 2007), and low economic stability (Moffitt & Caspi, 2001). Given its clinical and public health significance, identifying early predictors of EB is necessary to prevent these poor adult outcomes and to thwart the intergenerational cycle of violence and related negative outcomes (Widom & Wilson, 2015).

Across development, multiple forms of environmental adversity robustly predict EB. Ranging from prenatal stress (Rice et al., 2010; Zohsel et al., 2014) and disrupted early attachment (Newton, Litrownik, & Landsverk, 2000; Tottenham, 2012) to early maltreatment (Jaffee, Caspi, Moffitt, & Taylor, 2004; Kerig & Becker, 2015) and negative parenting behaviors more generally (e.g., harsh punishment, low warmth, poor monitoring) (Hoeve et al., 2009), these factors are highly consequential. At the same time, there is tremendous variation in short- and long-term outcomes for children exposed to environmental adversity, which catalyzed efforts to identify risk and resilience factors. Developmental psychopathology has focused on identifying *biologically*-based "vulnerability factors" that differentiate children most sensitive to adversity versus children who are resilient to adversity. Guided by a diathesis-stress framework,

early temperament traits and genetic factors acutely increased children's vulnerability to negative environments through gene-environment interactions (GxE) (Caspi et al., 2002; Jaffee et al., 2005) and temperament-environment interactions (TxE) (Kochanska & Kim, 2013).

However, GxE and TxE infrequently replicate across important behavioral and socio-emotional phenotypes, including EB. Unlike the traditional diathesis-stress model, an evolutionary-influenced reinterpretation of GxE and TxE proposed that the same youth more susceptible to negative (i.e., risk-promoting) environments may also be more responsive to positive (i.e., development-enhancing) environments (Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), such as maternal warmth and positive parent-child relationship factors. That is, genetic factors may actually confer heightened sensitivity, or "differential susceptibility," to environmental context, for better *and* for worse. Importantly, this theory shifted the narrow focus on vulnerability to adversity to a broader question about developmental *plasticity.* Although tests of differential susceptibility are relatively new, there is promising preliminary evidence that these interactions are plausible for youth EB. Several biologically-based individual differences in relation to EB have been implicated in differential susceptibility, including the same temperament and genetic factors from early GxE and TxE studies of EB (Belsky, Bakermans-Kranenburg, & IJzendoorn, 2007; Ellis et al., 2011). This dissertation focuses on two factors specifically linked to EB across the lifespan: "reactive" or "difficult temperament" (e.g., negative emotionality) (Pluess & Belsky, 2010) and dopamine-related genes, including polymorphisms in the dopamine receptor D4 (DRD4), the dopamine receptor D2 (DRD2), and the dopamine active transporter 1 (DAT1) (Bakermans-Kranenburg & van Ijzendoorn, 2011; Beaver & Belsky, 2011; Chester et al., 2015; Yu et al., 2014). Emerging studies measuring negative *and* positive environments suggest that

these temperament and genetic factors not only increase risk for children exposed to adversity but may simultaneously confer sensitivity to positive environmental factors that predict better outcomes.

Differential susceptibility has important implications for interventions for children already at risk for EB due to adversity (e.g., disrupted attachment, maltreatment) given that the youth *most* genetically- and temperamentally-vulnerable may simultaneously benefit the most from interventions that enrich the environment, and perhaps even fare better than youth who appear non-responsive to early adversity. However, in reality, many children who are most at risk for EB have already experienced adversity when interventions are implemented, and thus they already exhibit severe EB. This is a key consideration, because initial EB predicts treatment resistance (Masi et al., 2011), calling into question whether differential susceptibility theory applies to children *already* with severe EB due to their vulnerability to early adversity. Furthermore, decades of resilience research converge around one consistent finding: "competence begets competence" and, likewise, "maladaptation begets maladaptation" (Masten, 2014). Starting as early as prenatal stress and early disrupted attachment, these disadvantaged starting points lead to increasingly negative behavioral outcomes across time through complex and multilevel developmental cascades (Cicchetti, 2013; Masten & Cicchetti, 2010).

Thus, there are at least two plausible, competing ideas: that (1) early environment (e.g., adversity) initiates a chain of events to influence future development and perpetuate EB trajectories, and yet (2) children most vulnerable to adversity also may be most sensitive to environmental enrichment. This tension becomes particularly apparent across development, highlighting a crucial limitation of the differential susceptibility theory: namely, *development* is not adequately integrated into GxE and TxE. Framing differential susceptibility in the context of

development raises crucial questions such as: How do changes in the environment (e.g., early adversity vs. later environmental support) influence plasticity of EB? Does early plasticity to the environment extend developmentally into adolescence and adulthood, or are there "sensitive periods" that maximize plasticity? And across development, does environmental sensitivity generalize across different domains of environment, such as to peer environments as children progress into adolescence? These developmentally-sensitive questions remain largely unanswered in current research on developmental plasticity of EB – yet they are critical to understanding the multilevel processes underlying EB development.

Proposed Studies

Thus, despite the promising implications of differential susceptibility for EB prevention and intervention, existing studies of developmental plasticity are restricted by: (1) infrequent longitudinal tests of GxE effects on the *development* of EB over time, (2) limited consideration of developmental changes in the *environment*, including the timing of adversity (e.g., prenatal vs. childhood vs. adolescence) as well as the influence of previous adversity on later environmental influences, and (3) limited exploration of multiple environments (e.g., parenting vs. peers) which may change in their relevance across development. Employing three unique yet complementary longitudinal samples and study designs, these dissertation studies collectively investigated how previous adversity (ranging from prenatal stress to childhood maltreatment), genotypes, as well as individual differences in temperament influence later sensitivity to positive and negative social contexts to predict the development of EB. Study I employed a quasi-experimental design to examine how reactive temperament influences sensitivity to early maltreatment in a high-risk sample of children transitioning from foster-care to adoption. Next, for these same youth, temperament was examined as a plasticity factor to later family context *after* adoption (i.e.,

supportive family context in adoptive family), and short-term (1-5 years) and long-term (11-15 years) EB outcomes were assessed into young adulthood to examine the developmental patterns of these TxE effects. The goal of Study I was to test differential susceptibility, quasi-experimentally, to examine whether children with a previously identified plasticity trait were at once most sensitive to early adversity as well as more sensitive to later environmental enrichment.

Study II built on this aim by including a control group (non-maltreated youth) and examining in more detail how these effects extend into *adolescent* development by using a large population-based longitudinal sample of adolescents transitioning to young adulthood. Study II first investigated how sensitivity to parenting and peer factors may differ for adolescents previously exposed vs. not exposed to childhood maltreatment (e.g., physical/sexual abuse, neglect). Furthermore, this study included examination of polymorphisms from dopaminergic genes linked to plasticity (DRD4, DRD2, and DAT1) to test if these patterns of sensitivity were further accentuated for individuals with "plasticity genotypes" with respect to concurrent and developmental changes in EB to adulthood.

Finally, Study III employed a 6-year longitudinal sample of pre-adolescent children with and without ADHD to integrate GxE and TxE hypotheses in an exploratory, multilevel mechanistic model of differential susceptibility. Specifically, based on emerging evidence of "prenatal programming" GxE effects (Pluess & Belsky, 2011), Study III investigated how prenatal stress and dopaminergic genes independently and interactively influenced formation of early temperaments linked to plasticity (i.e., negative emotionality). I then tested how these temperamental characteristics interacted with postnatal environment (i.e., observational measures of positive and negative parenting behavior) to predict later EB in early adolescence. Thus, using

a developmentally-sensitive moderated mediation model, Study III aimed to elucidate how plasticity is *shaped* by modeling the biobehavioral mechanisms underlying the developmental plasticity of EB. Collectively, these studies represent a rigorous approach to testing differential susceptibility through a developmental lens. By testing how measured genetic and temperamental differences influence sensitivity to social context while explicitly modeling environmental changes and EB development across time, these studies aimed to help elucidate the dynamic processes underlying the developmental plasticity of youth EB.

Study I: Temperamental Sensitivity to Early Maltreatment and Later Family Support for Children Adopted from Foster Care[1]

Abstract

Children in foster care frequently have histories of physical/sexual abuse and neglect, increasing their risk for EB. According to the differential susceptibility theory, children with reactive temperaments may be particularly vulnerable to maladjustment following early maltreatment, but they may also benefit the most from positive family factors such as family cohesion. In a high-risk longitudinal sample of 82 children adopted from foster care, we examined predictions of EB from childhood to adolescence/young adulthood from temperament, maltreatment, and family cohesion. Controlling for age, gender, race-ethnicity, and maltreatment history, reactive temperament predicted higher EB at initial placement into adoptive homes, increasing EB across childhood, and higher likelihood of being arrested or sent to juvenile hall by young adulthood (11-15 years later). Maltreatment history did not predict baseline EB nor change in childhood EB, but maltreated youth used significantly more substances in young adulthood. Finally, children with reactive temperaments benefited the *most* from improved family cohesion across the first five years post-adoption, whereas family cohesion was unrelated to EB change for youth with easy or average temperaments. These interactive effects did not predict arrest history nor substance use 11-15 years later, however. Overall, these results provide partial support that reactive temperament heightens sensitivity to adoptive family enrichment in childhood, but also highlight early reactive temperament and maltreatment as potent risk factors for EB across multiple stages of development. We discuss these findings in the context of the differential susceptibility/biological sensitivity to context theory.

[1] This is an earlier version of Tung, I., Noroña, A. N., Lee, S. S., Langley, A. K., & Waterman, J. M. (2018). Temperamental sensitivity to early maltreatment and later family cohesion for externalizing behaviors in youth adopted from foster care. *Child Abuse & Neglect, 76*, 149-159.

Temperamental Sensitivity to Early Maltreatment and Later Family Support for Children Adopted from Foster Care

Children placed in foster care are at heightened risk for numerous socio-emotional and behavioral difficulties, especially youth externalizing behavior (EB) (e.g., aggression, delinquency, substance use) (Courtney, Piliavin, Grogan-Kaylor, & Nesmith, 2001; Simmel, Brooks, Barth, & Hinshaw, 2001; Vaughn, Ollie, McMillen, Scott Jr., & Munson, 2007). Compared to the general population, male and female former foster youth are 4 and 10 times more likely, respectively, to be arrested for EB (Cusick & Courtney, 2007), an alarming pattern given that EB itself predicts chronic criminality, substance use disorders, academic failure, job/economic instability, and recurrent homelessness (Fergusson et al., 2007; McQuistion, Gorroochurn, Hsu, & Caton, 2014; Moffitt & Caspi, 2001). As a result, EB also contributes to substantial annual societal costs through law enforcement and juvenile justice systems, prisons, rehabilitation programs, and hospitalizations (Welsh et al., 2008).

Children adopted from foster care often have maltreatment histories, including physical and sexual abuse and/or neglect. There are relatively few longitudinal studies of foster care youth, but maltreatment is a key predictor of sustained EB over time (Simmel, 2007). Because maltreatment diverges sharply from the average expected environment, it is conceptualized as one of the most toxic and severe environmental conditions for development (Egeland, Yates, Appleyard, & Dulmen, 2002a; Rogosch, Oshri, & Cicchetti, 2010). Childhood maltreatment initiates cascades of atypical development of neurobiological and physiological processes, emotion regulation, and the formation of attachment and healthy relationships (Cicchetti & Banny, 2014; Rogosch et al., 2010). Together, childhood maltreatment and EB exert substantial individual, family, and societal consequences, and they critically contribute to the

intergenerational continuity of psychopathology (Berlin, Appleyard, & Dodge, 2011; Tzoumakis, Lussier, & Corrado, 2012).

Despite evidence that maltreatment disrupts development across multiple levels of functioning, not all children with maltreatment histories exhibit EB, highlighting the need to identify individual and environmental factors that promote resilience (Haskett, Nears, Ward, & McPherson, 2006; Toth, Gravener-Davis, Guild, & Cicchetti, 2013). Although rarely examined in the foster care population per se, developmental psychopathology studies more broadly have identified several biologically-based "vulnerability factors," including temperament traits, that may differentiate children most sensitive versus "resistant" to adversity. Following a diathesis-stress conceptualization of psychopathology, children exposed to maltreatment or early harsh parenting who *also* had "difficult" or reactive temperaments (e.g., high negative emotionality, high sensitivity, low frustration tolerance, low inhibition) were particularly at risk for developing EB and other psychopathology (Blackson, Tarter, & Mezzich, 1996; Kiff, Lengua, & Zalewski, 2011). That is, temperament acutely increased children's vulnerability to negative environments through Temperament x Environment interactions (Belsky, Hsieh, & Crnic, 1998).

Most early Temperament x Environment studies focused exclusively on negative environmental conditions (e.g., maltreatment, harsh parenting), an important limitation given that caregiving behavior ranges significantly from severe adversity (e.g., maltreatment, disrupted attachment) to positive and development-enhancing factors (e.g., parental support, family cohesion). Emerging studies measuring a *full range* of negative and positive environments have found that compared to children with easy temperaments, children with reactive early temperaments were more likely to manifest EB when exposed to early maltreatment and negative parenting, but they also benefitted more from positive parenting practices (Kochanska & Kim,

2013). That is, according to differential susceptibility theory, children with reactive temperaments may be more sensitive to the environment, for better *and* for worse (Ellis et al., 2011). A growing literature consisting of cross-sectional, longitudinal, and emerging experimental studies support the plausibility that reactive temperament may confer general heightened sensitivity to the social environment (Belsky & Pluess, 2009; Gallagher, 2002). For example, a randomized controlled trial of infant-mother dyads found that highly irritable/reactive infants, who are traditionally considered at risk for later EB, benefited more from a brief intervention designed to increase secure attachments compared to less irritable infants (Cassidy, Woodhouse, Sherman, Stupica, & Lejuez, 2011).

Because early development represents a sensitive period for brain and behavior plasticity (Knudsen, 2004), most differential susceptibility studies have focused on children in infancy and toddlerhood (Hentges, Davies, & Cicchetti, 2015; Leerkes, Nayena Blankson, & O'Brien, 2009; van Zeijl et al., 2007). However, some studies suggest that these plasticity effects may extend at least to school-age (Gallitto, 2015; Nikitopoulos et al., 2014). For example, when exposed to low quality care, children with difficult temperaments exhibited more EB in toddlerhood as well as in late childhood (age 11-12), but these reactive children exhibited *less* EB when exposed to high quality care compared to children with easy temperaments (Pluess & Belsky, 2009, 2010). These studies suggest that compared to children with easy temperaments, children with temperamental risk for EB may continue to show heightened environmental sensitivity later in development, including in response to socially-based interventions.

The implications of this hypothesis for children in foster care are significant: there are over 400,000 children in foster care in the US alone (US Dept. of Health and Human Services, 2011). Children with complex histories including maltreatment, who may present with more

severe EB at initial placement, are particularly stigmatized and less likely to be adopted into nurturing permanent homes (Barth et al., 2007; Chamberlain et al., 2006; Leathers, Spielfogel, Gleeson, & Rolock, 2012). However, differential susceptibility theory suggests that these same children more biologically vulnerable to maltreatment may also be the most sensitive to social enrichment. This theory is particularly relevant for foster-adoptive youth because their environment changes drastically from pre-placement adversity (e.g., maltreatment) to more enriching adoptive family environments (van IJzendoorn & Juffer, 2006). Indeed, adoption is conceptualized as a critical environmental intervention for children in foster care, with meta-analytic evidence that adopted children display significant plasticity in their behavioral outcomes and "catch up" to the general population, even when exposed to early risk (van IJzendoorn & Juffer, 2006), although parenting quality varies across adoptive homes, and there are individual differences in youth responsiveness to this environmental change (Palacios & Brodzinsky, 2010). In the context of these findings, differential susceptibility suggests that the children *most* sensitive to early risk factors such as maltreatment, who have the most severe pre-placement presentations, may also benefit the most from placement in a nurturing adoptive home, and perhaps even fare better than youth who appeared resilient to early adversity.

Despite offering important implications, the assertion that the children most sensitive to early maltreatment may also benefit the most from intervention (even surpassing their counterparts in post-placement behavioral outcomes) may oversimplify the complex developmental processes that influence behavior. To understand whether the differential susceptibility hypothesis extends to high-risk samples with complex histories (e.g., foster-adoptive youth), the role of *development* must be considered. First, because most differential susceptibility research has focused on infants and toddlers, it is unclear if temperamental

sensitivity to negative *and* positive environments extends beyond early childhood to adolescence and adulthood. For example, infant negative emotionality moderated the association between child-care quality and later *adolescent* EB, but the pattern of interaction was consistent with diathesis stress rather than differential susceptibility (Belsky & Pluess, 2012), suggesting that the effects of positive environments on temperamentally sensitive individuals may fade across development. In contrast, temperamental sensitivity to early maltreatment may continue to negatively influence EB in adolescence (Rioux, Castellanos-Ryan, Parent, Vitaro, et al., 2016).

Indeed, because most differential susceptibility studies are cross-sectional, it is unclear how early Temperament x Environment interactions may influence later sensitivity to environmental changes. This is important, because many children at highest risk for EB have already been exposed to maltreatment by the time interventions are implemented, and thus they also exhibit the most severe initial EB. Severe initial EB is linked to treatment resistance (Masi et al., 2011), which suggests that children most sensitive to early maltreatment (and thus with most severe initial EB) may not benefit the most from later intervention. When development is adequately considered, it is unclear whether differential susceptibility applies to children *already* exhibiting severe EB due to their vulnerability to early adversity. Furthermore, due to the naturalistic design of most EB studies, the source of maltreatment (i.e., caregivers) often continues to be present in the child's environment, making it difficult to distinguish between long-term effects from early adversity versus effects from concurrent adversity. Thus, studies employing experimental or quasi-experimental designs that explicitly measure changes in environmental experiences are poised to clarify developmentally-sensitive aspects of differential susceptibility (Belsky & Hartman, 2014; van IJzendoorn & Bakermans-Kranenburg, 2012).

Study Aims

In a high-risk sample of children detained from their biological parents and adopted from foster care, the present study will explore the following research questions: (1) Does reactive temperament represent a vulnerability factor for pre-placement risk (history of abuse or neglect) on EB levels at initial adoptive placement? (2) Do these same temperament traits pose as sensitivity factors for post-placement adoptive family support to predict decreases in later EB across the first five years of placement? And (3) beyond childhood outcomes, how might these Temperament x Environment patterns change across time with respect to long-term EB outcomes such as arrest history and substance use? By employing a study design that manipulates the environment through adoption as an intervention, this study aims to determine whether, as proposed by the differential susceptibility theory, youth with reactive temperaments are at once more vulnerable to early maltreatment as well as benefit the most from measurable differences in adoptive family enrichment.

Methods

Participants

Between 1996 and 2001, families of 82 children were recruited from the UCLA TIES for Adoption program (now TIES for Families) to participate in a longitudinal study. TIES for Adoption aimed to facilitate successful adoption of high-risk children transitioning from foster care to adoption. Based on requirements from the Adoptions Division of the Los Angeles County Department of Child and Family Services (DCFS), prospective adoptive parents attended a series of educational seminars prior to being matched with a child. Approximately 85% of these seminars included announcements about the adoption program, which offered three additional educational meetings. Prospective parents who attended the three education meetings learned

about available services including pre-placement consultation, counseling services, and medical, educational, and psychiatric consultation. Families who subsequently had children placed with them and requested services from TIES for Adoption were asked if they would like to participate in our longitudinal research study. Children were eligible for the study if they were under 9 years of age at baseline and were placed in the adoptive placement within the past 2 months.

Eligible participants completed seven separate assessments (baseline, 1-, 2-, 3-, 4-, and 5-years post-placement, and in a long-term follow-up 11-15 years post-placement). Table 1.1 shows participants' demographic characteristics along with correlations among demographic and study variables. At baseline, children were 4 months to 8 years of age (average = 4 years) and ethnically diverse: most children were Latino/a (35.4%), Black (25.6%), or Biracial (15.9%), whereas 69% of adoptive parents were Caucasian. About 44% of youth had documented maltreatment history. Given the high-risk nature of this sample, there was notable attrition across time, with 52% of families remaining at the 5-year follow-up and 56% at the long-term follow-up. Although there were no demographic differences between participants and non-participants in the follow-up study, we implemented procedures to combat missing data (described below).

Procedures

After determining eligibility, we obtained parental consent and mailed standardized rating scales to parents about their child's temperament and behavioral and social-emotional functioning. When the child lived with two adoptive parents, the primary adoptive parent (i.e., parent spending the most time with the child) completed the rating scales. Families then came in for in-person interviews and testing, including cognitive and academic testing and taped interactions that are beyond the scope of this paper. In addition, the Department of Children and Family Services (DCFS) granted permission to review the child's adoption records, which

yielded additional data about the child's pre-placement history (e.g., abuse/neglect). After the baseline assessment, families returned each year for the next five years and completed highly parallel batteries including assessment of the child's behavior and family functioning. Finally, a long-term follow-up was conducted after 11-15 years to assess the child's outcomes in late adolescence. After obtaining parent and adolescent consent, parents and adolescents completed separate online rating scales assessing emotional and behavioral functioning and related outcomes. All research procedures were approved by the Institutional Review Board.

Measures

Temperament. At baseline, the primary adoptive parent completed the Cameron-Rice Temperament scales (Cameron & Rice, 1989), adapted from previous youth temperament rating scales (Carey & McDevitt, 1978; Fullard, McDevitt, & Carey, 1984; Mcdevitt & Carey, 1978). Developmentally parallel versions of the scales were administered based on the child's age at baseline: Infant Temperament Questionnaire for infants less than 1 years old (n = 4), Toddler Temperament Scale for toddlers 1-3 years old (n = 14), and the Preschool/Child Temperament Questionnaire for children older than 3 (n = 55). Parents rated items about their child's behavior on a 1-6 Likert scale (1 = *almost never*, 2 = *rarely*, 3 = *usually does not*, 4= *usually does*, 5= *frequently*, 6= *almost always*). The items formed seven subscales: sensitivity, activity level, reactivity/intensity, frustration tolerance, adaptability, regularity, and soothability (infants only) or distractibility (toddlers and children only). Three dimensions were unrelated with other temperament dimensions (i.e., frustration tolerance) or were age-specific and only administered to a subset of participants (i.e., soothability and distractability). Excluding these three dimensions, a principal component analysis (PCA) identified six subscales (low adaptability, negative mood, high sensitivity, high intensity, high activity, low approach) that loaded onto a

single dimension (loadings > .35) that was conceptually consistent with difficult or reactive temperament. This composite measure consisted of the mean of these six subscales, with higher scores representing more reactive temperament.

Pre-placement maltreatment. The child's history of maltreatment, including any history of abuse or neglect, was gathered from the child's adoption records, including court and medical records and reports by social workers. Excluding neglect based on prenatal substance exposure, 44% of the sample had documented abuse or neglect, either in their birth homes or in foster care. Types of maltreatment reported included physical abuse, sexual abuse, and neglect of basic needs (adequate supervision, food, clothing, shelter). Maltreatment was coded dichotomously.

Post-placement family support. At each of the five follow-up time points in childhood, family support was assessed using an adapted version of the Family Environment Scale (FES) (Moos & Moos, 1994). The adapted FES is a rating scale that includes 36 of the original 90 items and assesses the interpersonal relationships and overall social environment of the family. The primary adoptive parent rated each item as True or False, and items sum up (after reverse-scoring appropriate items) to form four subscales: Cohesion, Conflict, Expressiveness, and Control. To represent post-placement family support, we used the Cohesion subscale (9 items, e.g., "Family members really help and support one another," "There is plenty of time and attention for everyone in our family") at each time point. Previous studies have found predicted validity for this subscale, such that family cohesion attenuated risk for delinquency and drug and alcohol use among adolescents witnessing community violence (Barr et al., 2012; Kliewer et al., 2006).

Childhood EB. At baseline and at each of the five follow-up time points in childhood, the primary adoptive parent completed the Child Behavior Checklist (CBCL), a standardized rating scale based on a normative sample of girls and boys that yields several broadband scales

of child symptomatology, including items related to EB such as aggressive behaviors (e.g., "gets in many fights," "destroys things belonging to his/her family or others") and delinquency (e.g., "lying or cheating," "runs away from home") (Achenbach, 1991; Achenbach & Rescorla, 2001). Parents rated each behavior based on the preceding 6 months as Not True (0), Somewhat or Sometimes True (1), or Very True or Often True (2). We used T-scores from the Externalizing Behavior broadband scale at baseline and each follow-up time point to model initial and prospective change in EB across time.

Long-term adolescent EB outcomes. At the long-term follow-up, parents and children (now late adolescents/young adults) separately answered questions about the adolescent's behavior through parallel online questionnaires, adapted from items from the National Longitudinal Study of Adolescent Health (Harris et al., 2008). Two long-term EB outcomes were assessed: arrest history and substance use. Arrest history was coded dichotomously with 1= ever been arrested or sent to juvenile hall (as reported by parent *or* child) and 0 = never arrested or sent to juvenile hall according to both parent and child. Substance use ranged from 0-4 that represented the lifetime history of the number of different substances the child used including cigarettes/tobacco, alcohol, marijuana, and "other drugs". A substance was considered positively endorsed if self-reported by the adolescent or by the parent.

Data Analytic Plan

Three sets of analyses were conducted to predict (1) baseline EB, (2) time-varying childhood EB across the five follow-up time points, and (3) long-term adolescent EB outcomes, respectively. All analyses were conducted in Stata 13.

EB at initial placement. First, to examine whether difficult temperament moderated the association between previous maltreatment and baseline EB, we conducted a linear regression to

predict baseline EB from maltreatment, difficult temperament, and their interaction. Child's age at adoptive placement, gender, and race-ethnicity were controlled as covariates. To increase power and address missing data issues due to attrition, we employed multiple imputation using 50 iterations of multivariate imputation by chained equations (MICE) (Schafer & Graham, 2002). MICE employs an iterative multivariable regression technique that treats each variable with missing data as an outcome variable and then imputes the missing values based on the remaining variables in the model (in addition to relevant auxiliary variables). MICE has several advantages to other missing data methods, including yielding more accurate standard errors by incorporating a random element to account for uncertainty in the imputations, as well as appropriately accommodating non-normal data (e.g., count distributions) (Sterne et al., 2009).

Change in childhood EB. Next, to examine temperament and post-placement family cohesion as predictors of change in childhood EB *after* adoptive placement, we employed Generalized Estimating Equations (GEE) to model change in EB and family cohesion across the five childhood follow-up time points. GEE is an extension of the general linear model that uses robust variance estimation in a repeated measures design (Hanley, Negassa, Edwardes, & Forrester, 2003). A significant advantage of GEE to general linear models is that it minimizes Type 1 error and increases statistical power by adjusting for correlated observations across time points. Thus, family cohesion was treated as a *time-varying* predictor (Hardin & Hilbe, 2007) to test its independent effects and interaction with early temperament on time-varying change in EB across the first five years post-placement. We specified an exchangeable working correlation matrix; all tests were based on the *z*-statistic and *ß* parameters are in logits. GEE addresses missing data using the "all available pairs" method, such that all non-missing pairs of data are used in estimating the working correlation parameters. Thus, only the observation for that subject

is missing rather than all variables for that subject. We further employed Little's Test of Missing Completely at Random (Little, 1988) to evaluate whether individual missing observations were missing completely at random (MCAR) and thus appropriate for listwise deletion. Little's test showed that data were MCAR conditional on differences in race-ethnicity (i.e., covariate-dependent missingness; (Li, 2013): $\chi 2$ (289) = 80.33, p = .87. Thus, we controlled for race-ethnicity in the GEE as a covariate. To further enhance specificity of the family cohesion effects, we also controlled for maltreatment history, age of adoption, and gender as covariates. Significant interactions were deconstructed by probing interactions at +1 SD, grand mean, and -1 SD (West & Aiken, 1991) to analyze the time-varying effect of family cohesion on externalizing problems for youth with "easy," "average," and "reactive" temperaments, respectively.

Long-term EB outcomes. Finally, to examine whether Temperament x Family Cohesion effects extended long-term into adolescence, we conducted two complementary generalized linear models (GLMs) to separately predict arrest/juvenile-hall history and substance use. Controlling for adolescent age, sex, race-ethnicity, and maltreatment history, each model consisted of reactive temperament, mean family cohesion in childhood, and their interaction. Specifically, we employed logistic regression to predict adolescent arrest history and fit a generalized linear model to predict the number of substances used, specifying negative binomial distributions to account for its skewed distribution. To account for missing data due to attrition, we employed multiple imputation using 50 iterations of multivariate imputation by chained equations (MICE) for these models to increase power, accommodate the non-normal distributions, and attain more accurate standard errors (Schafer & Graham, 2002).

Results

EB at Initial Placement

Results from the linear regression model predicting baseline EB are presented in Table 1.2. Controlling for child's age of adoption, gender, race-ethnicity, and maltreatment history, reactive temperament was significantly and positively associated with baseline EB. However, maltreatment history and its interaction with reactive temperament did not predict EB.

Change in Childhood EB.

Next, GEE modeled *changes* in EB and family cohesion across the childhood follow-up time points (Table 1.2). Reactive temperament predicted increasing EB across time, whereas family cohesion predicted lower EB across time. Furthermore, temperament moderated the time-varying association of family cohesion with EB, above and beyond age at adoptive placement, gender, race-ethnicity, and maltreatment history. Specifically, increasing adoptive family cohesion predicted decreasing EB over time for children with reactive temperaments ($ß$ = -.02, SE < .01, p < .01), but not for those with average or easy temperaments ($ß$ = -.01, SE =.01, p =.24 and $ß$ = .01, SE =.20, p =.84, respectively).

Long-term EB Outcomes

Finally, temperament had a significant and positive main effect on arrest/juvenile hall history in the long-term follow-up, controlling for demographic characteristics (age, gender, race-ethnicity) and environmental variables (maltreatment, family cohesion) (Table 1.3). Neither maltreatment nor adoptive family cohesion (average across 5 years) had a main effect on arrest/juvenile hall history, and the interaction between family cohesion and temperament was also non-significant. When predicting the number of substances used at the long-term follow-up, youth with a history of maltreatment used significantly more substances at the follow-up than youth without a maltreatment history. However, temperament, family cohesion, and their interaction did not predict substance use.

Discussion

In a high-risk longitudinal sample of children adopted from foster care, we examined prospective predictions of EB across development from baseline reactive temperament; we also explored whether temperament moderated predictions of EB from early maltreatment and later family support. Controlling for age, gender, race-ethnicity, and maltreatment history, reactive temperament predicted higher EB at initial placement into adoptive homes. Reactive temperament also predicted increasing EB across the first five years of adoption and a higher likelihood of being arrested or sent to juvenile hall by adolescence/young adulthood 11-15 years later. Maltreatment history did not predict baseline EB nor change in childhood EB, but maltreated youth used significantly more substances in adolescence/young adulthood. Finally, children with reactive temperaments benefited the *most* from increasing family cohesion across the first five years post-adoption, whereas family cohesion was unrelated to EB change for youth with average or easy temperaments. These results partially implicate reactive temperament as an environmental sensitivity factor, at least in the first five years of adoptive placement. Despite these benefits in childhood, however, family cohesion was unrelated to arrest history and substance use at the 11-15 year young adult follow-up for youth with reactive temperaments. Overall, these results provide partial support that reactive temperament confers heightened sensitivity to family enrichment in childhood, but also highlight early reactive temperament and maltreatment as potent risk factors for EB across multiple stages of development.

First, as expected, children with reactive temperaments had much higher levels of baseline EB. Surprisingly, abuse/neglect did not predict baseline EB, and children with reactive temperaments were not more sensitive to maltreatment. These results diverge from previous studies where temperament moderated predictions of child outcome from negative parenting

(Belsky et al., 1998; Kiff et al., 2011; Kim-Spoon, Haskett, Longo, & Nice, 2012; Lengua, 2008). One potential reason for this difference is that this study focused on maltreatment (i.e., physical and sexual abuse, neglect). However, children in foster care are liable to experience stressors beyond maltreatment that can influence EB, including home instability, harsh or inconsistent parenting, caregiver losses, and exposure to community violence (Greeson et al., 2011; Leve et al., 2012; Simmel, 2007). Because this study employed a clinical sample without a normative comparison group, the "non-maltreated" youth detained from their biological parents may have experienced these other significant stressors in addition to prenatal forms of maltreatment such as prenatal exposure to teratogens. Future studies that use a more global measure of life stress along with a normative comparison group are needed to further evaluate potential differences in sensitivity to stress based on temperament.

Although youth with reactive temperaments had higher baseline EB, their EB across time was also more sensitive to family cohesion: specifically, increasing family cohesion in the first five years post-placement predicted decreases in EB across time, beyond age, gender, race-ethnicity, and maltreatment history. These results suggest that children with temperamental risk for EB may also be the most sensitive to fluctuations in environmental enrichment, at least in childhood. These findings converge with studies that reactive temperament is not purely a risk or vulnerability factor, but represents heightened sensitivity to the positive social environment as well (Bradley & Corwyn, 2008; Gallitto, 2015). However, because few studies have tested the *same* children exposed to both maltreatment and later environmental enrichment, it is unclear if these beneficial effects would be evident in children already exhibiting heightened EB due to early maltreatment. By investigating temperamental sensitivity in a sample that manipulated the environment through adoption, we found that, indeed, the same children with high reactive

temperament who exhibited the most severe EB at baseline were the most sensitive to changes in adoptive family cohesion. Given that foster children with reactive temperaments and high EB may experience more stigma during the adoption process, these preliminary results highlight the critical impact that a supportive family environment can have on changes in EB. Just as increasing patterns of EB can initiate cascades of negative developmental outcomes (Cicchetti & Banny, 2014; Rogosch et al., 2010), decreasing patterns of EB can initiate trajectories of resilience consisting of improved academic, social, and global functioning (Masten, 2015).

Beyond examining temperament and environmental effects on EB in childhood, the final aim of our study was to explore how temperament and positive changes in the family environment related to poor long-term outcomes for foster children: criminality and substance use. Despite its promising role in childhood, heightened temperamental sensitivity to family cohesion did not extend to late-adolescence/young adulthood 10-15 years later. Youth with reactive temperaments were more likely to be arrested or sent to juvenile hall, highlighting the enduring negative effects of early temperament on later EB (Krieger & Stringaris, 2015). By late adolescence, family cohesion did not moderate predictions from reactive temperament, nor did it decrease risk for arrest history. Although this study did not directly test sensitive periods, these results are consistent with evidence that there may be a sensitive period for susceptibility to environmental enrichment over time (Rioux, Castellanos-Ryan, Parent, & Séguin, 2016), and suggests that the positive effects of decreased EB may not extend into adolescence and adulthood. It is important to acknowledge, however, that this study did not include a subgroup of foster children who did not experience adoption, and thus, results cannot speak to predictions of criminality and substance use for non-adopted foster children.

Nonetheless, these preliminary findings suggest that research is needed to investigate potential changes in temperamental sensitivity in adolescence. The transition from adolescence to adulthood includes many biological changes (e.g., hormonal fluctuations, brain development) as well as social changes, such as adolescents spending more time away from the family context (Casey, Jones, & Hare, 2008; Spear, 2000; Steinberg, 2008). In this study, adoptive family cohesion in childhood did not predict arrest history or substance use in adolescence/young adulthood, which is consistent with evidence of the decreasing influence of the parental context in adolescence, when youth spend much more time with peers, romantic partners, and other members of the community (Arnett, 2000; Brown & Bakken, 2011; Laird, Jordan, Dodge, Pettit, & Bates, 2001; Markiewicz, Lawford, Doyle, & Haggart, 2006).

Early maltreatment did not predict arrest history, but youth with maltreatment history did use more substances in adolescence/early adulthood than youth adopted from foster care who were not exposed to maltreatment. These results are consistent with evidence that early maltreatment predicts later substance use (Afifi, Henriksen, Asmundson, & Sareen, 2012; Lansford, Dodge, Pettit, & Bates, 2010). Moreover, our study found enduring effects of maltreatment across 10-15 years, even in the context of children who were physically removed from their previous environment and placed into permanent adoptive homes. Maltreatment increases risk for many factors associated with later substance use problems, including precocious initiation of substance use in early adolescence (Lansford et al., 2010), posttraumatic stress disorder (PTSD) symptoms, and stressful life events (Kilpatrick et al., 2003; White & Widom, 2015). The association between maltreatment and substance use may also reflect shared genetic effects, such that biological parents who engaged in maltreatment may have also experienced substance use problems that predicted the intergenerational continuity of these

problems (Appleyard, Berlin, Rosanbalm, & Dodge, 2011), in addition to directly increasing risk for neglect due to parental substance use. Future genetically-informed studies that directly measure potential mediating factors (e.g., trauma symptoms, coping patterns) are needed to elucidate the causal mechanisms underlying the enduring association between maltreatment and substance use.

The present findings should be interpreted in the context of several important study limitations. First, although our study is rare in its longitudinal study of high-risk foster youth across 10-15 years, the modest sample size (N = 82) may have limited power to detect potential interactions; future studies with larger sample sizes are needed to further assess temperament-based sensitivity to maltreatment and family support across time. Second, shared method variance may have influenced the observed associations between parent-reported temperament, family-cohesion, and externalizing problems in childhood, although we integrated multiple informants by combining youth and parent-report whenever possible (i.e., at the young-adult follow-up). Finally, similar to other studies of maltreatment (Appleyard et al., 2011; Jonson-Reid et al., 2010), our study relied on official records of abuse and neglect to identify children with and without a history of maltreatment, which may be subject to report bias and investigation bias (Brown, Cohen, Johnson, & Salzinger, 1998).

Overall, our study highlights the importance of considering temperament when predicting EB development for children in foster care, who are already at significant risk for EB across multiple stages of development. Compared to children in foster care with an easy temperament, children with reactive temperaments had substantially higher EB at baseline and a higher chance of being arrested or sent to juvenile hall in adolescence/early adulthood, even with control of demographic variables (age of adoptive placement, sex, race-ethnicity), maltreatment history,

and adoptive family cohesion in childhood. Temperament did not operate purely as a risk factor across all developmental stages, however, because youth with reactive temperaments also appeared more sensitive to family cohesion in the first five years of adoption. Overall, these results highlight the importance of taking a developmental approach to prevention and intervention. Findings suggest that a preventative rather than reactive approach to ameliorating EB may have the largest impact given the enduring effects of reactive temperament and maltreatment on adolescent/adult EB outcomes. Reducing EB may require early interventions directly targeted at temperamental factors underlying EB, such as negative emotionality or effortful control (DeLisi & Vaughn, 2014). For youth who already exhibit highly reactive temperaments and present with elevated initial EB in their placements, it may be particularly important to take advantage of their heightened behavioral malleability in early childhood by enhancing family cohesion to maximize resilient pathways of development.

Table 1.1. Descriptive statistics and correlations among demographic and study variables in Study 1

Variable	M (SD) or %	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. T1 age in years	3.92 (2.20)	--																	
2. Gender [a]	53.7%	.09	--																
3. Race-ethnicity [b]	18.3%	-.12	<.01	--															
4. Reactive temperament	3.44 (.46)	.54**	-.11	-.14	--														
5. Maltreatment	43.8%	.47**	-.01	.12	.35**	--													
6. T2 Family cohesion	7.95 (1.27)	-.15	-.21	-.08	-.39*	<.01	--												
7. T3 Family cohesion	8.03 (.94)	-.25	-.03	.06	-.54**	-.48**	.55**	--											
8. T4 Family cohesion	7.96 (1.09)	.08	-.04	-.47*	-.26	-.24	-.03	.13	--										
9. T5 Family cohesion	8.19 (.90)	-.40*	.03	-.22	-.35	-.36*	.15	.47*	-.05	--									
10. T6 Family cohesion	8.15 (.93)	<.01	.17	-.08	-.18	-.20	-.21	.25	.45	.30	--								
11. T1 Externalizing	58.63 (10.40)	.43**	<.01	-.05	.65**	.39**	-.14	-.42*	-.21	<.01	-.14	--							
12. T2 Externalizing	56.48 (12.80)	.29*	.14	.23	.52**	.33*	-.30	-.54**	-.41*	-.24	-.41*	.75**	--						
13. T3 Externalizing	55.65 (11.24)	.33*	.26	.07	.46**	.21	-.07	-.40*	-.18	-.17	.10	.74**	.77**	--					
14. T4 Externalizing	55.33 (11.43)	.35*	-.06	.24	.47**	.23	-.04	-.25	-.39	-.04	-.30	.65**	.64**	.70**	--				
15. T5Externalizing	59.44 (11.03)	.19	.10	.18	.33	.05	-.01	-.26	-.52*	-.04	<.01	.72**	.70**	.76**	.85**	--			
16. T6 Externalizing	56.15 (11.58)	-.01	.22	.29	-.02	-.09	.15	-.04	-.53*	.03	-.01	.35	.46**	.66**	.66**	.85**	--		
17. Arrest History	24.1%	.08	<.01	.04	.42**	.03	-.74**	-.37	.13	-.07	.08	.37*	.33*	.13	-.05	.24	.14	--	
18. Substance use	2.19 (1.52)	.48**	.04	-.06	.39**	.41**	-.24	-.16	.17	-.35	-.12	.32*	.22	.14	.17	.31	.26	.36**	--

Note. * $p < .05$ ** $p < .01$. T1, T2, etc. = timepoint 1, timepoint 2, etc. [a] % boys (1 = boys, 0 = girls). [b] % Caucasian (1 = Caucasian, 0 = non-Caucasian).

Table 1.2. Linear regression predicting baseline EB and generalized estimating equations predicting changes in EB across first five years of adoptive placement

	Main Effects		Adding Interaction	
	β (*SE*)	*p*	*β* (*SE*)	*p*
Baseline EB (Linear Regression)				
Age at Adoptive Placement	1.07 (.66)	.11	1.03 (.67)	.13
Gender [a]	.86 (2.24)	.70	.90 (2.26)	.69
Race-Ethnicity[b]				
African-American	-2.59 (2.89)	.37	-2.44 (2.90)	.40
Hispanic or Latino	-3.04 (2.62)	.25	-2.99 (2.61)	.26
Mixed or Other	1.39 (3.17)	.66	1.38 (3.18)	.67
Reactive Temperament	12.72 (2.73)	**< .01**	11.85 (18.52)	.53
Maltreatment History	3.28 (2.27)	.15	13.39 (3.34)	< .01
Temperament x Maltreatment			-2.42 (5.32)	.65
Changes in EB Post-Adoption (GEE)[c]				
Time	<.01 (.01)	.77	<.01 (.01)	.62
Age at Adoptive Placement	.01 (.01)	.32	.01 (.01)	.38
Gender [a]	.03 (.05)	.65	.03 (.05)	.57
Race-Ethnicity [b]				
African-American	**-.15 (.07)**	**.03**	-.16 (.07)	.02
Hispanic or Latino	-.11 (.06)	.08	-.10 (.06)	.08
Mixed or Other	-.08 (.07)	.22	-.06 (.06)	.31
Maltreatment History	.01 (.05)	.87	.04 (.05)	.48
Reactive Temperament	**.13 (.06)**	**.03**	.37 (.11)	< .01
Family Cohesion	**-.02 (.01)**	**.02**	.10 (.05)	.04
Temperament x Family			**-.03 (.01)**	**.01**

Note. [a] 1 = boys, 0 = girls. [b] Compared to Caucasian children. [c] *β* parameters for GEE models are in logs. Significant effects boded for emphasis.

Table 1.3. Logistic and linear regression predicting long-term EB outcomes from temperament and family cohesion

	Arrest History				Substance use			
	Main Effects		Adding Interaction		Main Effects		Adding Interaction	
	β (*SE*)	*p*	*β* (*SE*)	*p*	*β* (*SE*)	*p*	*β* (*SE*)	*p*
Age at Adoptive Placement	-.31 (.32)	.33	-.32 (.33)	.33	.09 (.05)	.06	.10 (.05)	.03
Gender [a]	.91 (1.00)	.37	.94 (1.01)	.35	-.01 (.15)	.93	-.01 (.16)	.93
Race-Ethnicity [b]								
African-American	-.14 (1.41)	.92	-.08 (1.53)	.96	-.04 (.30)	.90	-.01 (.32)	.97
Hispanic or Latino	-.21 (1.44)	.89	-.17 (1.45)	.90	.28 (.28)	.32	.24 (.28)	.40
Mixed or Other	.02 (1.31)	.99	.05 (1.33)	.97	.37 (.27)	.17	.35 (.28)	.21
Maltreatment History	-1.14 (1.02)	.27	-1.20 (1.06)	.26	**.35 (.16)**	**.03**	.28 (.15)	.07
Reactive Temperament	**3.30 (1.66)**	**.04**	3.42 (11.89)	.77	.17 (.22)	.44	-.12 (2.03)	.95
Family Cohesion	-1.25 (.85)	.14	-1.30 (5.46)	.81	-.06 (.14)	.68	-.19 (.98)	.85
Temperament x Family Cohesion			-.01 (1.55)	.99			.04 (.26)	.88

Note. [a] 1 = boys, 0 = girls. [b] Compared to Caucasian children. Significant main effects bolded for emphasis.

Study II: Childhood Maltreatment Affects Adolescent Sensitivity to Parenting and Close Friendships in Predicting Trajectories of Externalizing Behavior[2]

Abstract

Childhood maltreatment robustly predicts adolescent EB (e.g., antisocial behavior, substance use), and may crystalize patterns of EB by influencing sensitivity to the social environment (e.g., parental closeness, friendships). In a nationally-representative sample of 9,421 adolescents followed into adulthood, latent trajectories of EB from age 13 to 32 years were modeled, including predictions from maltreatment; we then explored whether maltreated youth differed from non-maltreated youth in their sensitivity to perceived parental closeness, friendship involvement, and polymorphisms from dopamine genes linked to EB (DRD4, DRD2, and DAT1). Overall, adolescents with childhood histories of maltreatment had significantly higher levels of EB across adolescence and young adulthood, although both maltreated and non-maltreated youth showed a quadratic pattern of EB change over time. Maltreatment reduced sensitivity to parental closeness and friendship involvement on initial EB and its change over time, although patterns varied between antisocial behavior versus substance use outcomes. Finally, maltreatment status did not significantly affect predictions of EB from a dopamine polygenic risk score. Although a dopaminergic risk x parental closeness interaction predicted baseline antisocial behavior (but not substance use), it was unrelated to change in EB over time. These findings underline the enduring effects of maltreatment on EB trajectories and implicate that maltreatment contributes to long-term risk for EB by influencing children's sensitivity to social relationship factors in adolescence.

[2] This is an earlier version of Tung, I., Noroña, A. N., & Lee, S. S. (in press). Childhood maltreatment affects adolescent sensitivity to parenting and close friendships in predicting growth in externalizing behavior. *Development and Psychopathology*.

Childhood Maltreatment Affects Adolescent Sensitivity to Parenting and Close Friendships in Predicting Trajectories of Externalizing Behavior

Externalizing behavior (EB), including violence, delinquency, and substance abuse, is one of the costliest public health problems in North America (Foster & Jones, 2005; Welsh et al., 2008). Individual differences in EB are highly sensitive to development, including a precipitous increase during adolescence (Moffitt, 1993). Ranging from daily social experiences with parents and friends (Sentse & Laird, 2010) to severe stressors such as maltreatment (Jaffee et al., 2004; Oshri, Rogosch, Burnette, & Cicchetti, 2011), social experiences affect EB trajectories, which are further influenced by genetic variation (Bakermans-Kranenburg & van Ijzendoorn, 2011). Transient and mild EB may be normative in adolescence, reflecting identity formation and pursuit of social status (Brezina & Piquero, 2007; Englund et al., 2013; Roisman, Monahan, Campbell, Steinberg, & Cauffman, 2010). However, EB persists for a sizable minority of youth (Evans et al., 2014; Moffitt, 1993), predicting antisocial personality disorder, alcohol/substance use disorders, and economic instability (Brown et al., 2008; Maughan et al., 2004; Moffitt & Caspi, 2001). Even individuals whose EB decreases in adulthood often continue to commit low-level crimes and struggle with psychopathology compared to non-offending youth (Nagin, Farrington, & Moffitt, 1995; Odgers et al., 2008; Roisman, Aguilar, & Egeland, 2004). Given EB's clinical and public health significance, identifying modifiable predictors of EB trajectories from adolescence to adulthood, including resilience, is necessary to design effective prevention programs.

Maltreatment and EB

One of the most consistent and robust predictors of EB is childhood maltreatment (Jaffee et al., 2004; Kerig & Becker, 2015), including physical abuse, sexual abuse, and neglect. Youth

with maltreatment histories are at elevated risk for adolescent aggression, delinquency, and substance use (Oshri et al., 2011), particularly in combination with other family-level stressors such as domestic violence (Moylan et al., 2010). Additionally, early maltreatment has long-term sequelae: among 574 youth followed prospectively, youth with abuse histories were almost twice as likely than non-abused youth to be arrested 17 years later (Lansford et al., 2007).

Maltreatment likely has enduring effects on EB by influencing the biological processes involved in responding to the social environment (Bender, 2010; Egeland, Yates, Appleyard, & Dulmen, 2002; Rogosch, Oshri, & Cicchetti, 2010). Drawing from evolutionary theories, exposure to stressful and chaotic early environments may shift organisms toward heightened biological sensitivity to the environment, which may calibrate their biological systems (e.g., activation thresholds, stress reactivity) to better match their ecological environment (Del Giudice, Ellis, & Shirtcliff, 2011; Ellis & Boyce, 2008). For example, early exposure to significant stress (e.g., physical abuse) may heighten vigilance to threat and increase aggressive behaviors to thwart salient threats from the environment (Boyce, 2007; Lee & Hoaken, 2007). In line with this theoretical model, some studies of infants and young children found that maltreatment *heightened* sensitivity to environmental stimuli, including amplified neural activity in response to angry faces (Curtis & Cicchetti, 2011, 2013).

At the same time, maltreatment also interferes with adaptive symptoms such as attachment and responsiveness to social relationships (Cicchetti & Banny, 2014; Rogosch et al., 2010), and thus may also blunt sensitivity to *positive* social relationships or effective socially-based interventions for EB. For example, a longitudinal study of high-risk families found that maltreated children developed less close relationships with their parents, which subsequently predicted EB in elementary school as well as later adolescent conduct problems (Egeland, Yates,

Appleyard, & Dulmen, 2002b). Thus, maltreatment may contribute to adolescent EB by compromising children's interpersonal relationships. This is particularly relevant for maltreated youth at risk for EB, given that most interventions for EB assume that changes in the social environment, including at home (e.g., parent training) and school (e.g., bullying), are sufficient to reduce EB. Clarifying which maltreated youth may be differentially influenced by their environments in adolescence is necessary to design appropriate interventions for maltreated adolescents at-risk for persistent EB.

Sensitivity to Parenting and Peer Relationships

A parent-child relationship characterized by emotional closeness, warmth/support, and communication is a potent protective factor in the development of severe EB (Chassin et al., 2005; Shaw, Hyde, & Brennan, 2012), including promoting resilient outcomes among maltreated youth (Afifi & Macmillan, 2011). Thus, parent training is commonly integrated into EB prevention and intervention programs, particularly in childhood. However, not all youth benefit equally from parenting interventions. Compared to non-maltreated youth, adolescents with a history of maltreatment have substantially higher risk for exhibiting severe EB, which is linked with treatment resistance (Masi et al., 2011). Although interventions targeting the early parent-child relationship (e.g., attachment) are effective for children with maltreatment histories (Moss et al., 2011), these effects may not be sustained over time (Stronach, Toth, Rogosch, & Cicchetti, 2013). Moreover, because early childhood is a 'sensitive period' for healthy attachment formation, most studies have focused on infants and young children. However, it is unclear if and how sensitivity to parenting factors changes across development, a critical limitation given that many youth at risk for developing EB do not receive services until later childhood or adolescence. Given that maltreatment may disrupt important socioemotional developmental

milestones such as attachment formation with caregivers (Lowell, Renk, & Adgate, 2014), childhood maltreatment may affect sensitivity to parental support in adolescence and adulthood.

Beyond relationships in the home, peer relationships (e.g., friendships) assume increasing relevance during adolescence and the transition to adulthood (Laible, Carlo, & Raffaelli, 2000). Multiple peer factors are linked to EB, including deviant peer affiliation (Hou et al., 2013; Wang & Dishion, 2012), peer acceptance and social status (Menting, van Lier, & Koot, 2011), and dyadic friendship support and conflict (Sentse & Laird, 2010). Peers play a critical socialization role during the malleable adolescence period. For example, having friendships characterized by frequent hostility or unresolved conflict can limit learning of prosocial skills and promote heightened sensitivity to rejection (Patterson, Reid, & Dishion, 1992; Zimmer-Gembeck, 2016) that lead to increased EB, whereas high friendship closeness and warmth predicts lower EB (Sentse & Laird, 2010; You & Bellmore, 2012). Although maltreatment contributes to rejection sensitivity (Luterek, Harb, Heimberg, & Marx, 2004) and hostile attribution bias (Kay & Green, 2016), which positively predict aggression in response to negative peer environments (Ayduk, Gyurak, & Luerssen, 2008; Dodge et al., 2015; Romero-Canyas, Downey, Berenson, Ayduk, & Kang, 2010), few studies have tested whether friendship effects on EB differ based on maltreatment history. In contrast, one study reported that maltreated children exhibited *decreased* neural responses to social rejection cues (Puetz et al., 2016), and thus may show a blunted sensitivity to peer socialization effects. Peers play a central role in adolescent development, and it is important to improve understanding of how these processes influencing adolescent EB may differ between maltreated and non-maltreated youth.

Genetic Influences on EB

Finally, genetic variation can also influence sensitivity to parenting and peer environments, although few studies have explored how these patterns may differ between maltreated and non-maltreated youth. Whereas early gene-environment interaction (GxE) studies assumed a dual-risk model whereby genotypes increased vulnerability to early adversity (e.g., abuse, neglect, harsh parenting) (Bakermans-Kranenburg & van IJzendoorn, 2006; Caspi et al., 2002), the differential susceptibility or biological sensitivity to context theory proposed that genetic "risk" may actually confer heightened susceptibility to the social environment, for better *and* for worse (Ellis et al., 2011). That is, genotypes once thought to singularly increase vulnerability to early adversity may also increase sensitivity to environmental enrichment (Belsky et al., 2007). Dopaminergic genes associated with EB have been implicated in differential susceptibility, including polymorphisms in the dopamine receptor D4 (DRD4), the dopamine receptor D2 (DRD2), and the dopamine active transporter 1 (DAT1) (Bakermans-Kranenburg & van Ijzendoorn, 2011; Belsky & Beaver, 2011; Brody, Yu, & Beach, 2015; Chester et al., 2015; Yu et al., 2014). Youth carrying "plasticity alleles," including the 7R allele of DRD4, the 10R allele of DAT1, and the A1 allele of DRD2, were more vulnerable to early stress (e.g., maltreatment), but also more sensitive to social enrichment (Boardman et al., 2014; Brody et al., 2015), such as positive parenting or peer relationships. Meta-analyses of cross-sectional and intervention studies suggest that differential sensitivity to the environment based on genetic variation is not only plausible, but may improve the precision of interventions (Bakermans-Kranenburg & van Ijzendoorn, 2011; Bakermans-Kranenburg & van IJzendoorn, 2015).

Although theorized to lead to enduring developmental changes (Ellis et al., 2011), most studies have examined differential susceptibility in young children. Thus, it is unclear how these

effects may change over time in adolescence. Studies of adolescent differential susceptibility are more inconsistent compared to studies of early development: some evidence suggests that differential susceptibility to positive and negative parenting extends to adolescence and even young adulthood (Chhangur et al., 2015; Nikitopoulos et al., 2014), whereas other studies have observed differential susceptibility in childhood and preadolescence, but not in later adolescence (Zhang et al., 2015). Examining differential susceptibility in adolescence is more complicated than in early childhood, because models must consider salient environmental experiences over time, including the potential impact of previous adversity. Given that maltreatment itself may already influence sensitivity to parenting and peer influences through early stress x later environment interactions, it is unclear if patterns of genetic sensitivity to parenting and peer factors would be similar for maltreated versus non-maltreated youth. One study of young children found that genetic variation in DRD4 and the serotonin transporter (5-HTTLPR) predicted attachment disorganization for non-maltreated children, whereas it had minimal effect on attachment organization for maltreated children (Cicchetti, Rogosch, & Toth, 2011). Although this study did not examine whether these effects influenced later outcomes in childhood or adolescence, it suggests that the impact of genetic variation on relational processes may differ based on early exposure to maltreatment.

Study Aims

To investigate how childhood maltreatment (i.e., physical/sexual abuse, neglect) influences adolescent sensitivity to peer and parenting factors, the present study tested the following questions in a nationally-representative longitudinal sample of adolescents: (1) Compared to non-maltreated youth, do youth with a history of maltreatment have more persistent developmental trajectories of ASB and substance use from adolescence to adulthood? (2) Does

childhood maltreatment influence later sensitivity to parenting (ranging from low to high closeness) and friendship (ranging from low to high involvement with a close friend) on adolescent EB? If so, does early maltreatment blunt or heighten later sensitivity to the social environment? (3) Finally, if maltreatment affects sensitivity to later parenting and peer factors, are these patterns of sensitivity particularly pronounced for youth carrying a greater number of dopaminergic "plasticity genotypes" identified in previous studies (Bakermans-Kranenburg & van Ijzendoorn, 2011; Belsky & Beaver, 2011; Brody et al., 2015)?

Methods

Participants

This study used data from the National Longitudinal Study of Adolescent Health (Add Health), an ongoing nationally-representative study of U.S. adolescents (Harris et al., 2008). Details of the study design are available at http://www.cpc.unc.edu/projects/addhealth. In 1994, 80 high schools and 52 middle schools were selected using a stratified cluster design. A subsample of individuals participated in in-home interviews at Wave 1 in 1994-1995 (n = 20,745, grades 7-12, ages 11 to 19 years). These participants were interviewed again a year later at Wave 2 in 1996 (n = 14,738, aged 13-20), another 6-7 years later at Wave 3 in 2001-2002 (n = 15,197, aged 18-28), and another 7 years later at Wave 4 in 2008 (n = 15,701, aged 25-34). Saliva samples were obtained at Wave 4 for genotyping. The present study included participants with available weight data in all four waves (n = 9,421). Approximately 54.6% of adolescents included in analyses were female, and participants were racially and ethnically diverse (64.9% identifying as White, 21.5% Black, 3.6% Native-American, 7.1% Asian, 8.5% "other" race, and 15.4% Hispanic ethnicity).

Measures

Antisocial behavior. Violence and delinquency were assessed during a structured home interview with the youth at Waves 1, 2, 3, and 4. Items asked about the frequency or presence of ASB in the past 12 months, including items assessing violence (e.g., "In the past 12 months, how often did you hurt someone badly enough to need bandages or care from a doctor or nurse?", "During the past 12 months, how often did this happen: you shot or stabbed someone?") and delinquent behaviors (e.g., "In the past 12 months, how often did you steal something worth more than $50?", "In the past 12 months, how often did you go into a house or building to steal something?"). Given inconsistent scaling (e.g., dichotomous vs. frequency counts) and inclusion of some items (but not others) across time, we focused on the 10 items that were administered at all four waves and dichotomized them (0 = absence of behavior, 1 = presence of behavior) for eventual summing for a total ASB scale at waves 1-4 ($\alpha = .73$, $\alpha = .73$, $\alpha = .66$, $\alpha = .64$, respectively). Previous Add Health studies created similar composite scores of ASB and demonstrated predictive validity with key outcomes including gang membership, substance use, and neighborhood disadvantage (Barnes, Beaver, & Miller, 2010; Barnes & Jacobs, 2013; Marcus & Jamison, 2013). The present study used the sum of ASB at each wave to model change in ASB across adolescence and early adulthood.

Substance use. The structured adolescent home-interview at Waves 1, 2, 3, and 4 also included questions about the frequency of using various substances in the past 30 days, including tobacco, marijuana, and other illicit drugs (e.g., cocaine, LSD, PCP, ecstasy, mushrooms, inhalants, heroin). In addition, participants were asked about binge drinking in the past year (i.e., "Over the past 12 months, on how many days did you drink 5 or more drinks in a row?"), and responded based on the following options: "Never, 1-2 days, Once a month or less (3-12 times), 2-3 days a month, 1-2 days a month, 3-5 days/month, or Every day/almost every day." Tobacco,

marijuana, and other illicit drugs were recoded dichotomously (0 = not used in past month, 1 = used once or more in past month). To be consistent with the 30-day scale, binge drinking was recoded dichotomously such that 0 = "once a month or less (3-12 times)" or less and 1 = "2-3 days/month" or more. These four dichotomous substance variables (i.e., binge drinking, tobacco, marijuana, other illicit drugs) were then summed at each wave to model change in the number of substances used in the past month across adolescence and adulthood. Similar polysubstance variables in Add Health demonstrated significant and directionally consistent associations with related constructs (e.g., deviant peer affiliation, alcohol problems) (Vaughn, Beaver, DeLisi, Perron, & Schelbe, 2009).

Maltreatment. Childhood maltreatment was retrospectively assessed at Waves 3 and 4. During the in-home interview at Wave 3, participants reported the frequency of exposure to maltreatment from a parent or adult caregiver prior to age 12, including physical abuse (e.g., "how often had your parents or other adult care-givers slapped, hit, or kicked you?"), sexual abuse (e.g,, "how often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?"), and neglect (e.g., "how often had your parents or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing?"). During the in-home interview at Wave 4, maltreatment prior to age 18 was retrospectively assessed, including physical abuse ("before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or down stairs?") and sexual abuse ("how often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?"). Items were recoded to create an overall maltreatment variable, in which participants were scored positive in history of

maltreatment if physical abuse, sexual abuse, or neglect were endorsed as occurring more than once in either the Wave 3 or Wave 4 interview (Haberstick et al., 2005). Among participants included the present study, 64.3% of youth reported no maltreatment history and 35.7% reported more than one episode. Previous studies showed the maltreatment variable from Add Health to demonstrate predictive validity with a range of expected outcomes such as youth violence, young adult intimate partner violence, poor health, depression, binge drinking, and substance use (Fang & Corso, 2007; Hussey, Chang, & Kotch, 2006).

Perceived parental support. An in-home structured interview at Wave 1 asked youth to report on various dimensions of parenting behavior. For youth living in a two-parent household, responses regarding maternal support were prioritized to facilitate comparisons with the majority of previous studies on parenting and differential susceptibility. The parental support index (7 items; $\alpha = .85$) measures perceived emotional warmth, closeness, and communication between parent and child (e.g., "How close do you feel to your parent?", "How much do you think your parent cares about you?", "Most of the time, your mother is warm and loving toward you"). Items were measured on a 5-point Likert scale (1 = not at all, 5 = very much) and summed to form a total perceived parental support score. This scale demonstrated predictive validity with multiple offspring outcomes including self-regulation, self-esteem, depression, and juvenile delinquency (Belsky & Beaver, 2011; Bynum & Kotchick, 2006; J. J. Li, Berk, & Lee, 2013).

Friend involvement. The structured home-interview at Wave 1 asked participants to name their closest female and male friend. Participants then answered whether they did (yes = 1) or did not (no = 0) engage in the following activities with their friend in the past seven days: "went to friend's house," "met the friend after school to hang out or go somewhere," "spent time with the friend during the past weekend," "talked with the friend about a problem," and "talked

to the friend on the telephone." Each friendship activity was scored as positively endorsed if the participant reported engaging in the activity with either their closest male or female friend. Items were then summed to form a total friend involvement scale (5 items; $\alpha = .64$), with higher scores indicating more interaction with close friends.

Dopamine gene index. Saliva samples were collected from participants in Wave 4, and genomic DNA was isolated from buccal cells using standard methods to genotype for several candidate polymorphisms. The present study used three functional polymorphisms related to the dopaminergic system that have previously been linked to developmental plasticity (Bakermans-Kranenburg & van Ijzendoorn, 2011; Belsky et al., 2009; Belsky & Beaver, 2011). First, the 48 bp VNTR polymorphism located on chromosome 11p15.5 in exon 3 of the dopamine D4 gene (DRD4) was genotyped, which yields loci of 2 to 11 repeats. DRD4 genotypes including the most common polymorphisms (4-repeat and 7-repeat) include 7/7, 7/4, and 4/4. Second, the 40-bp VNTR polymorphism in the 3'untranslated region of exon 15 of the dopamine transporter (DAT1) was genotyped, yielding 9-repeat (440 bp) and 10-repeat (480 bp) polymorphisms to form the following genotypes: 9/9, 9/10, and 10/10. Third, the TaqIA (rs1800497) polymorphism located on chromosome 11q22.3 of the dopamine receptor D2 (DRD2) was genotyped, yielding A1and A2 alleles with the following genotypes: A1/A1, A1/A2, A2/A2. Hardy-Weinberg equilibrium (HWE) was tested for each allele genotype in race/ethnicity specific strata; deviations from HWE (at $\alpha \sim 0.05$) were identified among blacks for DRD4, but no deviations were observed for DRD2 or DAT1 (Smolen et al., 2013). Thus, race-ethnicity was controlled as a covariate in all models. Following previous strategies (Belsky & Beaver, 2011), we recoded each polymorphism such that the 7R/7R and 7R/4R (vs. 4R/4R) genotypes of DRD4, the 10/10R (vs. 9/10 or 9/9) genotype of DAT1, and the A1/A1 or A1/A2 (vs. A2/A2) genotypes of DRD2

were identified as “plasticity genotypes.” Each polymorphism was assigned a point if the participant had a plasticity genotype. These values were summed to form a cumulative index of dopamine genotypes ranging from 0-3, with higher scores representing more genetic plasticity.

Data Analytic Plan

All analyses were conducted using Mplus version 6.12. Appropriate survey weights and design effects were included to account for potential sample and population differences, selection probabilities, and differential rates of non-response and attrition. This also helps compensate for potential chance fluctuations of the sample from the broader population, which increases generalizability of the results to the general U.S. population.

Unconditional latent growth model. Latent growth modeling (LGM) (also called latent growth curve analysis) was used to model change in ASB and substance use across ages 13-32. LGM is a longitudinal estimate of growth over time based on a structural equation modeling (SEM) framework. LGM estimates the mean parameter level at a given point in time (i.e., intercept), the rate of increase/decrease over time (i.e., linear slope), and the rate of change of the increase/decrease (i.e., latent quadratic trend). Given that each wave of assessment in Add Health contained significant variability in chronological age (e.g., ranging from 11-19 in Wave 1), an accelerated longitudinal design was employed, in which age (vs. wave) represented the unit of time (Bollen & Curran, 2006; Duncan, Duncan, & Hops, 1996). Thus, LGM modeled continuous change in ASB and substance use from age 13 (youngest participant at Wave 1 with sufficient data) to age 32 (oldest participant at Wave 3 with sufficient data). This approach results in substantial missing data that are “missing by design” (Muthen & Muthen, 2007), which is considered data “missing completely at random” (Little & Rubin, 1987). Mplus uses a maximum likelihood approach to appropriately account for this pattern of missingness (Duncan, Duncan,

Stycker, & Chaumeton, 2007). Modern missing data approaches such as ML are significantly advantageous to older methods such as listwise deletion or imputation.

First, to determine if changes in ASB and substance use are best captured by linear or quadratic growth, a series of unconditional models (i.e., without predictors) modeled ASB and substance use from age 13-32. Zero-inflated Poisson (ZIP) modeling was employed given the skewed count data represented by many youth not engaging in any ASB or substance use (Liu, 2007). The Satorra-Bentler chi-square difference test (Satorra & Bentler, 2001) evaluated whether a model including both a linear and quadratic function fit better than the model including only linear slope. Model fit was further evaluated by comparing the Akaike information criterion (AIC), Bayesian information criterion (BIC), and the sample-adjusted BIC (lower values indicate better fit for all three indices).

Conditional LGMs. After establishing the latent growth components (intercept, linear slope, quadratic function) appropriate for modeling change in ASB and substance use, these outcomes were regressed on perceived parental support and friendship, controlling for sex and race-ethnicity (dichotomous variables simultaneously entered into the model: White, Black, Native American, Asian, Other, and Hispanic). Next, the main effect of dopaminergic gene index and its 2-way interaction terms with parental support and friendship were added to the model. Separate models were conducted to predict ASB and substance use outcomes.

Multiple-group comparisons. For all unconditional and conditional models, a multi-group framework was employed to compare adolescents with versus without a history of maltreatment. Multiple-group LGMs simultaneously evaluate developmental hypotheses in multiple groups (e.g., maltreated vs. non-maltreated adolescents) (Duncan, Duncan, & Strycker, 2013). Specifically, group differences were tested on (1) the intercept, slope, and quadratic

function of ASB and substance use, (2) independent associations of parental closeness and friendship involvement, and (3) interactive associations between dopaminergic genes and the environmental variables (parental closeness, friendship) on ASB and substance use. Significance of group differences was determined by testing for equality of parameters between maltreated and non-maltreated youth using the Wald chi-square test.

Results

Preliminary analyses

Table 2.1 shows bivariate correlations among the primary study variables. As expected, maltreatment history was significantly correlated with higher ASB and substance use at all waves. Parental closeness was inversely correlated with maltreatment and showed some weak negative correlations with ASB and substance use. Parental closeness was *inversely* associated with friendship involvement, which was *positively* correlated with ASB at the first two waves and with substance use across all waves. These different patterns of correlations between parental closeness and friendship involvement highlight the need to consider critical differences between parenting and friendship effects during this developmental period. Finally, polygenic dopaminergic risk was not correlated with the environmental variables (i.e., maltreatment, parental closeness, friendship involvement; all p's > .05), reducing concerns about evocative gene-environment correlations.

Latent growth of ASB

Modeling growth in ASB from age 13-32, all fit indices (AIC, BIC, and sample-adjusted BIC) and the Satorra-Bentler chi-square test indicated that the nonlinear (quadratic) unconditional model fit better than the linear (slope) unconditional model ($\Delta\chi^2(2) = 25.27$, $p <$ .01). Overall, ASB started low at age 13 (intercept $b = -.473$, $SE = .052$, $p < .001$); change from

age 13-32 did not change linearly with age (slope b = -.001, SE = .013, p = .951), but showed a quadratic trend characterized by increasing ASB in early adolescence that quickly decreased in late adolescence and adulthood (quadratic b = -.003, SE = .001, p < .001). Multigroup models comparing maltreated to non-maltreated youth found that maltreated youth had significantly higher initial ASB at age 13 (intercept) compared to non-maltreated youth, although their patterns of linear and quadratic change across time did not significantly differ (Figure 2.1).

Parenting and Friendship. Controlling for sex and race-ethnicity, parental closeness and friendship involvement on age 13 ASB (intercept) significantly differed for maltreated vs. non-maltreated youth (Table 2.2). Parental closeness predicted lower age 13 ASB for both maltreated and non-maltreated youth, but this effect was significantly smaller for maltreated youth. In contrast, friendship involvement predicted higher age 13 ASB for both maltreated and non-maltreated youth; this effect was also significantly reduced for maltreated youth.

Given that change in ASB was best characterized by quadratic change, we next examined whether parental closeness and friendship involvement may differentially influence quadratic change in ASB based on maltreatment history (Table 2.2). There was a significant difference between maltreated and non-maltreated youth on the effects of both perceived closeness and friendship involvement. Controlling for sex and race-ethnicity, perceived parental closeness significantly predicted negative quadratic change for non-maltreated youth, but did not predict change in ASB for maltreated youth. In contrast, friendship involvement predicted a positive quadratic effect for non-maltreated youth, but did not have this effect on maltreated youth. Thus, parental closeness and friendship involvement had opposite effects on the direction of ASB growth, and these environmental effects were only evident for non-maltreated youth; parental closeness and friendship were unrelated to ASB change for maltreated youth.

Genetic Susceptibility. To explore if group differences (maltreated vs. non-maltreated) in sensitivity to parental closeness and friendship involvement were additionally heightened by genetic susceptibility, the main effect of dopaminergic risk and its interaction with parental closeness and friendship involvement were added to the model (Table 2.2). Predicting age 13 ASB (intercept), the direct effect of dopaminergic risk and its two-way interactions with parental closeness and friendship involvement did not significantly differ between maltreated and nontreated youth. In the full sample (combining maltreated and non-maltreated youth), dopaminergic risk was not directly related to age 13 ASB, but it moderated the effect of parental closeness. Post-hoc analyses showed that parental closeness predicted lower age 13 ASB at all levels of dopaminergic risk; however, contrary to hypothesis, these effects were larger for adolescents with no risk genotypes (b = -.116, SE = .014, p < .001) compared to adolescents with three risk genotypes (b = -.050, SE = .017, p = .004). Neither the main effect of dopaminergic risk nor its interaction with parental closeness predicted *change* in ASB, however, regardless of maltreatment history. Furthermore, dopaminergic risk did not moderate the effects of friendship involvement on age 13 ASB nor on ASB change from age 13-32.

Latent growth of substance use

Similar to the pattern of ASB growth, all fit indices and the Satorra-Bentler chi-square test indicated that the nonlinear (quadratic) model of substance use fit better than the linear (slope) unconditional model ($\Delta\chi^2(2) = 377.94$, $p < .01$). Overall, substance use started low at age 13 (intercept b = -.925, SE = .049, p < .001), increased during adolescence (slope b = .114, SE = .009, p < .001), and then significantly decreased in rate of change in adulthood (quadratic b = -.005, SE < .001, p < .001). A multigroup model revealed that compared to non-maltreated youth,

maltreated youth used significantly more substances at age 13 (intercept), and they also showed a slower rate of decline (quadratic) in substance use in adulthood (Figure 2.2).

Parenting and Friendship. Next, we examined whether the effects of parental closeness and friendship involvement on substance use differed for youth with and without a history of maltreatment. Controlling for sex and race-ethnicity, higher parental closeness was associated with lower age 13 substance use, but this effect was significantly smaller for maltreated versus non-maltreated youth (Table 2.3). In contrast, friendship involvement was positively associated with substance use at age 13, and this effect did not differ based on maltreatment history.

When predicting *change* in substance use from age 13-32 (Table 2.3), higher parental closeness predicted increasing substance use, whereas friendship involvement predicted decreasing substance use over time. These differential effects of parental closeness and friendship involvement on changes in substance use did not differ between maltreated and non-maltreated youth.

Genetic Susceptibility. The direct effect of dopaminergic risk and its two-way interactions with parental closeness did not significantly predict substance use at age 13 (intercept), and it also did not predict linear or quadratic change in substance use from age 13-32 (Table 2.3). These GxE effects did not differ based on maltreatment history. Similarly, dopaminergic risk did not moderate friendship involvement in predicting age 13 substance use or its change over time, regardless of maltreatment history.

Discussion

In a nationally-representative sample of adolescents followed into adulthood, we modeled latent trajectories of EB (ASB and substance use separately) from age 13 to 32 years and explored their sensitivity to childhood maltreatment; we additionally tested whether

maltreatment status affected sensitivity to perceived parental closeness and friendship involvement, including whether these effects were differentially affected by dopamine genes associated with environmental sensitivity. Overall, youth with childhood histories of maltreatment had consistently higher levels of ASB and substance use from adolescence to young adulthood; however, their *patterns* of EB change did not differ from non-maltreated youth, such that ASB and substance use followed a quadratic trend of increasing in adolescence and then decreasing in adulthood. Maltreatment appeared to reduce sensitivity to parental closeness *and* friendship involvement on initial ASB and change in ASB over time. Parental closeness effects on early adolescent substance use were also attenuated for maltreated youth, but the effect of parental closeness on change in substance use did not differ based on maltreatment history. Furthermore, predictions of substance use from friendship involvement were comparable for maltreated versus non-maltreated youth. Finally, there were no maltreatment group differences with respect to the effects of dopaminergic genetic risk on ASB or substance use, although dopaminergic risk did interact with parental closeness to predict baseline ASB when examining the full sample. We discuss each of these findings below in the context of previous literature and emphasize key considerations when interpreting these results.

First, as expected, adolescents with maltreatment histories had significantly higher levels of ASB and substance use in early adolescence compared to non-maltreated youth, and they continued to show higher EB across early adulthood. However, the developmental pattern of EB change across time was similar regardless of maltreatment history, such that both ASB and substance use followed a quadratic trend of increasing in adolescence and then decreasing in adulthood. The overall quadratic pattern of development for EB is consistent with prevailing developmentally-informative models of EB (Moffitt, 1993). Maltreated youth exhibited higher

ASB and substance use from age 13 to 32 compared to non-maltreated youth. These group differences are consistent with literature showing that maltreatment not only predicts EB in adolescence (Egeland et al., 2002b; Oshri et al., 2011), but also has enduring effects on EB in adulthood (Lansford et al., 2007). Because few studies have compared developmental trajectories of EB for maltreated versus non-maltreated youth, it has been unclear if maltreatment affects the way EB develops into adulthood. Multi-group latent growth modeling showed that group differences in EB based on maltreatment were specific to a higher intercept rather than linear or quadratic change. These results suggest that the enduring effects of maltreatment operate by elevating initial levels of EB that are maintained over time, rather than changing the *pattern* of EB development in adolescence or adulthood. Because we did not model development prior to early adolescence, however, it is unclear when this severity gap emerges. Studies that model these developmental patterns in preadolescence and childhood are needed to further elucidate how and when maltreatment begins to predict significant differences in EB, which will clarify key developmental periods to target through prevention programs for maltreated youth.

Beyond the developmental patterns of EB, our study also examined how childhood maltreatment affected later sensitivity to parental closeness. Overall, perceived parental closeness in early adolescence inversely predicted initial ASB and a negative quadratic pattern of ASB across development, even after controlling for sex, race-ethnicity, and friendship effects. These results are consistent with a large body of literature supporting the protective effects of perceived support and emotional closeness with a parent (Chassin et al., 2005); not only does parental closeness affect EB in early adolescence, but also its developmental pattern over time (Branstetter, Low, & Furman, 2011). However, these effects were significantly smaller in magnitude for maltreated versus non-maltreated youth, and parental closeness did not predict

changes in EB for maltreated youth (whereas it did for non-maltreated youth). Thus, one potential way maltreatment may lead to enduring EB over time is by blunting children's receptivity to later protective factors such as parental closeness and warmth. This is consistent with previous evidence that maltreatment impairs relational processes (e.g., attachment) involved in facilitating positive parent-child relationships (Cicchetti & Banny, 2014; Lowell et al., 2014).

In considering these results, however, it is important to note that parents who engage in child abuse or neglect may also show lower parental warmth and closeness in early adolescence. Indeed, maltreatment was weakly but significantly correlated with parental closeness in this sample. Thus, it is possible that the attenuated association between parental closeness and EB for maltreated youth reflects that adolescents feel less close to the parent who maltreated them. Alternatively, youth who exhibit higher EB may evoke negative parenting behaviors through evocative gene-environment correlations (rGE). Compared to adopted children without genetic risk (i.e., parental history of EB), children with genetic risk for EB were more likely to receive negative parenting from adoptive parents, supporting an evocative rGE (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). However, much of the association between negative parenting and child EB was *not* explained by the evocative rGE, suggesting that parenting also has an environmentally mediated effect on EB (O'Connor et al., 1998). These findings support the plausibility that parental closeness plays a causal protective role in reducing EB change over time, and our results suggest that youth exposed to childhood abuse or neglect may show reduced sensitivity to these effects in adolescence. Studies that experimentally change parenting behavior (e.g., intervention studies) and separate maltreatment from later parenting behavior (e.g., adoption studies of previously maltreated youth) are needed to substantiate these differential

patterns of sensitivity for maltreated and non-maltreated youth, as well as to test potential mediating mechanisms underlying these differences in sensitivity.

In contrast to the overall protective effects of parental closeness, friendship involvement predicted higher initial ASB and substance use. These results highlight the differential influences of dyadic parenting from dyadic friendship effects in adolescence. Whereas previous studies reported that friendship closeness decreased EB (Sentse & Laird, 2010), these findings highlight the need to more closely examine what close friendship entails. For example, this study used a broad measure of friendship involvement (e.g., how much time spent with a friend, how often they communicate or talk about problems), which can reflect several separable aspects of friendship, ranging from emotional closeness to number of hours spent in each other's presence. One study of adolescents found that friendship support and negative interpersonal interactions with friends largely did not predict nor protect against substance use, whereas friend's substance-using behavior was consistently related to use of different substances and changes in substance use over time (Branstetter et al., 2011). Indeed, peer deviance and substance use predicts adolescent EB, and adolescents may tend to choose friends that engage in similar levels of EB (Hou et al., 2013; Poulin, Kiesner, Pedersen, & Dishion, 2011). Thus, interpreting main effects of "friendship involvement" on EB require further assessment of what adolescents are doing with their closest friend when they are together, particularly in relation to ASB and substance use.

Similar to its effect on sensitivity to parental closeness, maltreatment also attenuated sensitivity to friendship involvement on initial ASB and change in ASB over time. The fact that maltreated youth also showed a blunted sensitivity to friendship effects, social relationships outside of the context of the home, suggest that childhood maltreatment may attenuate later sensitivity to social relationships overall and not just to the same parents who potentially

maltreated the adolescents in childhood. Interestingly, whereas maltreatment attenuated friendship effects on both initial ASB and change in ASB across development, maltreatment did not influence the effect of friendship involvement on substance use. Friendship involvement predicted more substance use in early adolescence and a positive quadratic trend of substance use across development, regardless of maltreatment history.

Finally, we explored whether group differences in sensitivity to parenting and friendship effects may be influenced by dopamine genes previously linked to environmental sensitivity (Bakermans-Kranenburg & van Ijzendoorn, 2011; Belsky & Beaver, 2011). After accounting for sex, race-ethnicity, and the main effects of parental closeness and friendship involvement, almost no direct genetic effects and gene-environment interactions (GxE) were observed in predictions of ASB and substance use, and these patterns did not differ based on maltreatment history. Only one significant GxE was observed, such that dopaminergic risk interacted with parental closeness in predicting age 13 ASB in the full sample. Surprisingly, parental closeness predicted lower ASB across all levels of genetic risk, but carrying more "plasticity alleles" *decreased* sensitivity to parental closeness, which is inconsistent with previous studies of dopaminergic risk in younger children. We emphasize several considerations when interpreting these findings in our sample of adolescents. First, these preliminary results emphasize the need for well-powered replication studies of GxE that investigate multiple stages of development. Most differential susceptibility studies focus on young children, despite adolescence also representing a 'sensitive period' of neuroplasticity and behavioral development (Steinberg, 2005). Inconsistencies across GxE studies may partially reflect genuine heterogeneity in how the environment influences gene expression across development (Munafò & Flint, 2009). For example, our results are consistent with previous reports of unexpected genotypic "flipping" based on the type of EB outcome

(Glenn, 2011), demographic characteristics (Long et al., 2013), and type of environmental variable (Kretschmer, Dijkstra, Ormel, Verhulst, & Veenstra, 2013), suggesting that genotype flipping may actually reflect meaningful differences in the nature of GxE across development. However, we emphasize that these GxE effects did not influence change in ASB over time, and they also did not predict adolescent substance use or change in substance use over time. Furthermore, the effects were much smaller than the direct effects of parental closeness and friendship involvement on EB. In fact, parental closeness had a significant protective effect on age 13 ASB for youth with all levels of dopaminergic plasticity. Well-powered longitudinal studies are needed to further evaluate whether these and other genetic markers of plasticity contribute to clinically meaningful differences in sensitivity to the social environment across later stages of development, beyond the *direct* effects of these environments on EB.

These results should be interpreted in the context of several important study limitations. First, because adolescents reported on perceived parental support, friendship involvement, maltreatment history, and EB, findings are subject to shared method variance. Future replication studies including additional informants and assessment procedures are needed, although the convenience and efficiency of self-report measures is an important consideration in large-scale survey studies such as Add Health. Furthermore, by including temporal separation between constructs (e.g., parental support and friendship at Wave 1 and EB at Waves 1-4), some reduction of method bias was afforded in this study (Podsakoff, MacKenzie, & Podsakoff, 2012). Second, maltreatment was retrospectively assessed, which may underestimate the frequency of maltreatment compared to prospective longitudinal studies of maltreatment (A. Shaffer, Huston, & Egeland, 2008). Similarly, the present study explored how maltreatment broadly impacts EB development and sensitivity to social factors; however, the timing, type, and severity of

maltreatment may differentially impact these developmental processes as well (Jackson, Gabrielli, Fleming, Tunno, & Makanui, 2014; Manly, Cicchetti, & Barnett, 1994). Although these questions were beyond the scope of this study, we encourage future studies to further elucidate these potential differences in childhood maltreatment that may differentially impact youth's sensitivity to social factors in adolescence.

Overall, our findings underline the enduring effects of childhood maltreatment on EB development from adolescence to young adulthood, and they suggest that one way maltreatment contributes to enduring EB is by influencing children's sensitivity to parenting and peer factors in adolescence. Understanding how and when children are differentially sensitive to the social environment is a central topic in developmental psychopathology and key to tailoring psychosocial interventions for youth at risk for EB. This recognition is evident in the influx of studies in the past decade exploring genetic effects underlying differential susceptibility to the environment. Although G x E studies represent a promising avenue for understanding individual differences in environmental sensitivity, our results highlight the need to re-consider the role of *development* itself and, specifically, the dynamic nature of the environment across time when investigating complex developmental phenotypes such as EB. Given the multiple factors across biological and social domains that likely affect environmental sensitivity, we encourage more studies to actively integrate dynamic models of EB (e.g., including multiple measures of environmental stress and support across time) to further elucidate the developmental mechanisms underlying EB development across the life span.

Table 2.1. Bivariate correlations among primary variables in Study 2

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. Maltreatment	--											
2. Parental closeness	-.14**	--										
3. Friendship involvement	-.01	-.06**	--									
4. Polygenic Risk	.01	-.01	-.01	--								
5. W1 ASB	.14**	-.16**	.08**	.01	--							
6. W2 ASB	.12**	-.10**	.05**	.01	.54**	--						
7. W3 ASB	.14**	-.02	-.01	-.01	.26**	.28**	--					
8. W4 ASB	.12**	-.01	<.01	-.02	.19**	.21**	.31**	--				
9. W1 Substance	.10**	-.20**	.21**	-.01	.44**	.31**	.12**	.11**	--			
10. W2 Substance	.08**	-.16**	.19**	-.02*	.36**	.40**	.16**	.13**	.68**	--		
11. W3 Substance	.10**	-.07**	.09**	-.03*	.23**	.24**	.37**	.20**	.37**	.42**	--	
12. W4 Substance	.09**	-.05**	.07**	-.02	.24**	.23**	.27**	.28**	.33**	.38**	.59**	--

Note. * $p < .05$ ** $p < .01$

Table 2.2. Multi-group LGM parameter estimates of parental closeness, friendship involvement, and dopaminergic risk on ASB intercept, slope, and quadratic trend from age 13-32 for maltreated and non-maltreated youth

Predicting ASB	Full Sample (n = 9,421)			Non-Maltreated (68%)			Maltreated (32%)				
	B (*SE*)	β		B (*SE*)	β		B (*SE*)	β		Wald Test	
Model 1 [a]											
Intercept (age 13)											
Intercept	-.413 (.216)	-.383		-.015 (.264)	-.013		-.521 (.275)	-.519			
Parental closeness	-.086 (.009)	-.333	***	-.105 (.010)	-.365	***	-.056 (.012)	-.263	***	10.645	**
Friendship involvement	.190 (.027)	.259	***	.256 (.032)	.337	***	.117 (.040)	.170	**	7.759	**
Linear Slope (age 13-32)											
Intercept	-.191 (.058)	-1.714	**	-.324 (.085)	-2.211	***	-.071 (.070)	-.836			
Parental closeness	.008 (.003)	.317	**	.017 (.004)	.445	***	.002 (.004)	.100		8.133	**
Friendship involvement	-.027 (.008)	-.357	***	-.046 (.009)	-.464	***	-.008 (.012)	-.138		8.356	**
Quadratic (age 13-32)											
Intercept	.006 (.003)	1.294		.012 (.005)	1.801	*	.001 (.004)	.206			
Parental closeness	<.001 (<.001)	-.277	*	-.001 (<.001)	-.463	***	<.001 (<.001)	.158		11.034	***
Friendship involvement	.001 (<.001)	.426	**	.002 (.001)	.529	***	<.001 (<.001)	.172		6.672	***
Model 2 [b]											
Intercept (age 13)											
Intercept	-.384 (.249)	-.359		.071 (.312)	.065		-.528 (.313)	-.527			
Dopaminergic (DA) Risk	-.055 (.043)	- .049		-.054 (.054)	-.047		-.092 (.072)	- .092		.202	
DA Risk x Parenting	.022 (.008)	.152	**	.030 (.013)	.184	*	.015 (.011)	.015		.736	
DA Risk x Friendship	.034 (.027)	.081		.038 (.030)	.089		.021 (.046)	.021		.095	
Linear Slope (age 13-32)											
Intercept	-.194 (.073)	-1.672	**	-.331 (.100)	-.220	**	-.056 (.081)	-.545			
DA Risk	.008 (.013)	.069		-.002 (.017)	- .014		.030 (.020)	.288		1.605	
DA Risk x Parenting	-.003 (.003)	- .198		-.003 (.004)	- .153		-.003 (.003)	- .025		.023	
DA Risk x Friendship	-.010 (.009)	- .223		-.011 (.011)	- .180		-.007 (.013)	- .071		.037	
Quadratic (age 13-32)											
Intercept	.007 (.004)	1.382		.013 (.006)	1.843	*	<.001 (.004)	.056			
DA Risk	-.001 (.001)	- .111		<.001 (.001)	.007		-.002 (.001)	- .379		1.373	
DA Risk x Parenting	<.001 (<.001)	.178		<.001 (<.001)	.025		<.001 (<.001)	.007		.229	
DA Risk x Friendship	<.001 (.001)	.199		<.001 (.001)	.048		<.001 (.001)	.063		.004	

Note. B = unstandardized parameter estimate; β = standardized parameter estimate. * $p < .05$ ** $p < .01$ *** $p < .001$ (significance based on unstandardized parameter estimates)

[a] Models adjusted for sex and race-ethnicity.

[b] Models adjusted for sex, race-ethnicity, and the main effects of parental closeness and friendship involvement.

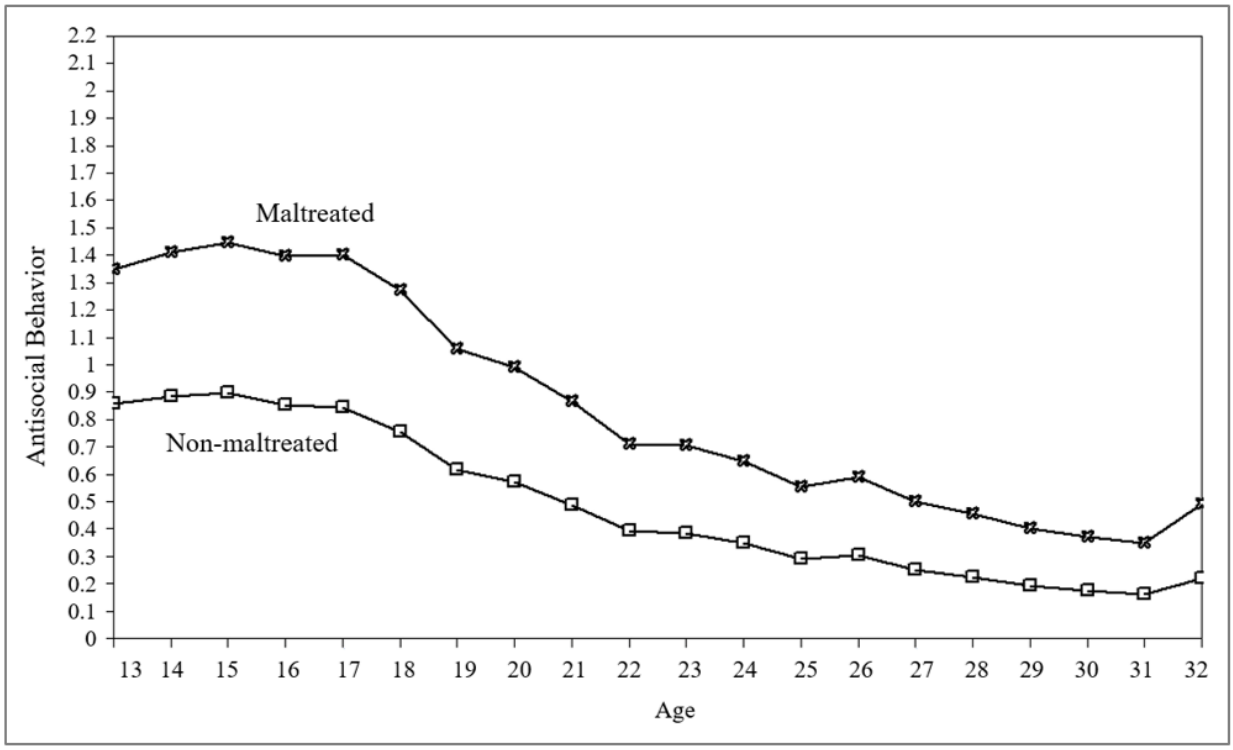
Table 2.3. Multi-group LGM parameter estimates of parental closeness, friendship involvement, and dopaminergic risk on substance use intercept, slope, and quadratic trend from age 13-32 for maltreated and non-maltreated youth

Predicting Substance Use	Full Sample (n = 9,421)			Non-Maltreated (68%)			Maltreated (32%)			
	B (*SE*)	*β*		B (*SE*)	*β*		B (*SE*)	*β*		**Wald Test**
Model 1 [a]										
Intercept (age 13)										
Intercept	-1.045 (.188)	-1.095	***	-.977 (.285)	-.984	**	-1.012 (.254)	-1.107	***	
Parental closeness	-.084 (.007)	-.367	***	-.093 (.009)	- .363	***	-.066 (.010)	- .339	***	3.929 *
Friendship involvement	.283 (.028)	.436	***	.322 (.035)	.476	***	.241 (.049)	.382	***	1.809
Slope										
Intercept (age 13-32)	-.069 (.036)	.790		.056 (.065)	.551		.089 (.046)	1.202		
Parental closeness	.011 (.001)	.537	***	.014 (.002)	.531	***	.008 (.002)	.510	***	3.12
Friendship involvement	-.031 (.006)	- .528	***	-.037 (.007)	- .534	***	-.027 (.010)	- .532	***	.626
Quadratic (age 13-32)										
Intercept	-.003 (.002)	-.851		-.003 (.003)	-.728		-.003 (.002)	-1.015		
Parental closeness	<.001 (<.001)	- .512	***	-.001 (<.001)	- .516	***	<.001 (<.001)	- .421	**	3.099
Friendship involvement	.001 (<.001)	.519	***	.002 (<.001)	.517	***	.001 (<.001)	.528	**	.312
Model 2 [b]										
Intercept (age 13)										
Intercept	-.991 (.200)	-1.039	***	-1.046 (.320)	-1.062	**	-.7762 (.295)	-.840	**	
Dopaminergic (DA) Risk	-.040 (.038)	- .040		-.008 (.046)	-.007		-.103 (.079)	-.107		1.061
DA Risk x Parenting	.007 (.007)	.057		.013 (.010)	.089		-.002 (.012)	-.016		.864
DA Risk x Friendship	.008 (.028)	.021		.016 (.033)	.042		.006 (.044)	.015		.035
Slope (age 13-32)										
Intercept	.051 (.043)	.565		.071 (.075)	.700		.018 (.061)	.211		
DA Risk	.009 (.008)	.091		<.001 (.009)	-.004		.025 (.016)	.273		1.935
DA Risk x Parenting	-.001 (.002)	- .099		-.002 (.002)	-.124		<.001 (.003)	-.042		.178
DA Risk x Friendship	-.002 (.007)	- .061		-.004 (.007)	-.111		.001 (.010)	.033		.250
Quadratic (age 13-32)										
Intercept	-.002 (.002)	-.630		-.004 (.004)	-.825		-.001 (.003)	-.146		
DA Risk	<.001 (<.001)	- .115		<.001 (<.001)	-.026		-.001 (.001)	-.258		1.212
DA Risk x Parenting	<.001 (<.001)	.095		<.001 (<.001)	.097		<.001 (<.001)	.104		.009
DA Risk x Friendship	<.001 (<.001)	.064		<.001 (<.001)	.163		<.001 (<.001)	-.127		.775

Note. B = unstandardized parameter estimate; *β* = standardized parameter estimate. * $p < .05$ ** $p < .01$ *** $p < .001$ (significance based on unstandardized parameter estimates)

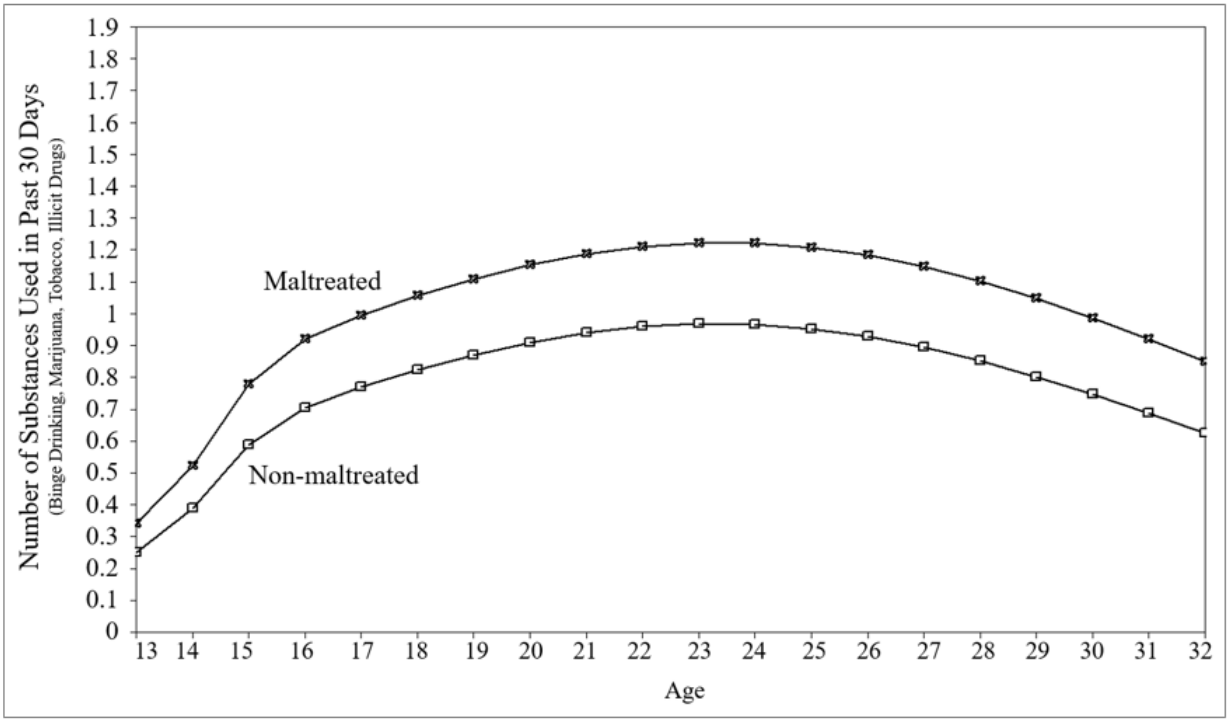
[a] Models adjusted for sex and race-ethnicity.

[b] Models adjusted for sex, race-ethnicity, and the main effects of parental closeness and friendship involvement.



	Non-Maltreated		Maltreated		Wald Test	
	B (SE)	*p*	B (SE)	*p*	Value	*p*
Intercept	-.622 (.032)	<.001	-.148 (.028)	<.001	161.774	<.001
Slope	< .001 (.011)	.978	.005 (.010)	.603	0.170	.680
Quadratic	- .004 (.001)	<.001	-.003 (.001)	<.001	0.740	.390

Figure 2.1. Latent growth curves of ASB for maltreated and non-maltreated youth with parameter estimates for the intercept, linear slope, and quadratic trend.



	Non-Maltreated		Maltreated		Wald Test	
	B (SE)	*p*	B (SE)	*p*	Value	*p*
Intercept	-1.034 (.034)	<.001	-.728 (.030)	<.001	73.292	<.001
Slope	.120 (.008)	<.001	.104 (.007)	<.001	2.986	.084
Quadratic	-.006 (<.001)	<.001	-.005 (<.001)	<.001	5.609	.018

Figure 2.2. Latent growth curves of substance use for maltreated and non-maltreated youth with parameter estimates for the intercept, linear slope, and quadratic trend.

Study III: Prenatal Programming of Postnatal Plasticity: Testing an Integrated Developmental Model of Genetic and Temperamental Sensitivity to the Environment[3]

Abstract

Although both gene-environment and temperament-environment interactions contribute to the development of youth externalizing problems, it is unclear how these factors jointly affect environmental sensitivity over time. In a seven-year longitudinal study of 232 children (aged 5-10) with and without ADHD, we employed moderated mediation to test a developmentally-sensitive mechanistic model of genetic and temperamental sensitivity to prenatal and postnatal environmental factors. Birth weight, a global measure of the prenatal environment, moderated predictions of child negative emotionality from a composite of dopaminergic polymorphisms (i.e., DRD4 and DAT1), such that birth weight inversely predicted negative emotionality only for children with high genetic plasticity. Negative emotionality, in turn, predicted externalizing behavior 4-5 years later, beyond genetic and postnatal parenting effects. Finally, birth weight moderated the indirect effect of dopaminergic genotypes on externalizing problems through negative emotionality, partially supporting a prenatal programming model. We discuss theoretical and empirical implications for models of environmental sensitivity.

[3] This is an earlier version of Tung, I., Morgan, J. E., Noroña, A. N., & Lee, S. S. (2017). Prenatal programming of postnatal plasticity for externalizing behavior: Testing an integrated developmental model of genetic and temperamental sensitivity to the environment. *Developmental Psychobiology, 59*(8), 984-996.

Prenatal Programming of Postnatal Plasticity: Testing an Integrated Developmental Model of Genetic and Temperamental Sensitivity to the Environment

Individual differences in sensitivity to the environment are a central theme of developmental psychopathology. Several complementary theories proposed that biologically-based factors, such as genetic variation, early temperament, and physiology critically affect reactivity or plasticity to the social environment (Boyce, 2016; Pluess, 2015). The diathesis-stress framework contends that risk factors, including specific genotypes or emotionally reactive temperament traits, increase vulnerability to environmental adversity. More recently, vantage sensitivity posits that similar biologically-based characteristics may also heighten reactivity to *positive* environments (Pluess & Belsky, 2013). Finally, guided by evolutionary reasoning and studies including a full range of positive and negative environments, differential susceptibility or biological sensitivity to context theory suggests that children with plasticity factors may be more vulnerable to early environmental stress and, at the same time, benefit the *most* from environmental enrichment (e.g., parental support; Bakermans-Kranenburg & van Ijzendoorn, 2011; Belsky, Bakermans-Kranenburg, & IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011)

Although environmental sensitivity models have been applied to many health and socio-emotional outcomes, there has been particular interest in its role in the development of youth externalizing behavior problems (EB), such as aggression/violence and rule-breaking behaviors (Bakermans-Kranenburg, Van IJzendoorn, A, Mesman, & Juffer, 2008; Bradley & Corwyn, 2008; Caspi et al., 2002; Jaffee et al., 2005; Kochanska & Kim, 2013). Early EB, particularly when accompanied by attention-deficit/hyperactivity disorder (ADHD), robustly predicts academic, interpersonal, familial, and mental health problems (Armstrong, Lycett, Hiscock,

Care, & Sciberras, 2014; Biederman et al., 2008; Faraone et al., 1993; Kuhne, Schachar, & Tannock, 1997). Thus, identifying factors that increase children's risk for EB in the context of adversity, but *also* amplify benefits from supportive environments, including intervention-induced enrichment, will critically innovate prevention programs for children most at risk for EB.

Genetic and Temperamental Sensitivity

Diverse biological systems, including genetic variation, neurotransmitter production, brain circuitry, physiological reactivity, and early temperament have been implicated as conferring environmental sensitivity (Boyce, 2016; Ellis et al., 2011). Early temperament and genetic variation have been most consistently implicated in differential susceptibility for EB, including several dopaminergic "plasticity alleles" [i.e., 7-repeat (7R) allele of the dopamine transporter D4 (DRD4) and the 10-repeat (10R) allele of the dopamine active transporter (DAT1)] (Bakermans-Kranenburg & van Ijzendoorn, 2011). Consistent with differential susceptibility, DRD4 moderated a parenting intervention on toddler EB with stronger effects for 7R carriers (Bakermans-Kranenburg et al., 2008). Similarly, the association between maternal unresponsiveness and childhood EB was moderated by child DAT1 genotype, with children's uninhibited temperament mediating these effects (Davies, Cicchetti, & Hentges, 2015). Further, dopaminergic plasticity genes cumulatively affected motivational sensitivity to environmental stimuli by affecting neural structures mediating reward, motivation, and learning (Feder, Nestler, & Charney, 2009; Wise, 2004). Thus, carriers of multiple plasticity alleles (e.g., 7R of DRD4 *and* two copies of the10R of DAT1) may be particularly sensitive to positive and negative family environments (Belsky & Pluess, 2013a).

In a parallel body of work, the association between early parenting and EB was moderated by early temperament traits in a differential susceptibility pattern (Kochanska & Kim, 2013). Temperament is a relatively stable, biologically-based construct that influences children's self-regulation and reactivity to their environments. Meta-analytic evidence suggests that compared to children with "easy" temperaments, children with more reactive temperaments (e.g., high negative emotionality) were more vulnerable to negative parenting, but they also benefited more from positive parenting behaviors (Slagt, Dubas, Deković, & van Aken, 2016). Although most studies have focused on infant temperament and toddler outcomes (Leerkes et al., 2009; Pluess & Belsky, 2009), these effects may extend to school-age and early adolescence (Gallitto, 2015; Nikitopoulos et al., 2014; Pluess & Belsky, 2010).

Integrating Models of Sensitivity

Despite its expanding evidence base, most environmental sensitivity studies have focused narrowly on one level of measurement (e.g., genotype) rather than integrating multiple plasticity factors *across* levels of analysis (e.g., genotype *and* temperament). This limitation has prevented understanding of *how* these different plasticity factors, together, contribute to the patterns of environmental sensitivity over time (Boyce, 2016; Weeland, Overbeek, Castro, & Matthys, 2015). Given consistent findings across genotype and temperament, these constructs may reflect a single underlying plasticity factor that affects how individuals perceive, experience, approach, and react to the environment. That is, perhaps the "sensitive" individuals separately identified by each trait (e.g., individuals with DRD4 7R allele or high in negative emotionality) are the *same* individuals across multiple markers of susceptibility. Temperamental sensitivity markers such as negative emotionality may mediate phenotypic markers of underlying genetic plasticity. This is supported by evidence that carriers of plasticity alleles for DRD4 and DAT1 exhibit higher

negative emotionality or emotional reactivity (De Luca et al., 2003; Holmboe, Nemoda, Fearon, Sasvari-Szekely, & Johnson, 2011; Ivorra et al., 2011; Oniszczenko & Dragan, 2005). In contrast, in a study of toddlers and school-aged children, Belsky & Pluess (2013b) included both DRD4 x Caregiving and Temperament x Caregiving interactions and found that each interaction *uniquely* predicted EB. These results suggest that negative emotionality is not simply an endophenotype of genetic plasticity, but instead may uniquely interact with the environment beyond genetic variation.

Importantly, beyond genetic effects, early environmental factors also influence the development of negative emotionality (Huizink, 2012; Shiner et al., 2012), highlighting that developmental plasticity *itself* may be influenced by environmental factors. Proposing an archeology of the mechanisms of differential susceptibility, Boyce (2016) suggested that early gene x environment interactions (GxE) shape biological sensitivity to the environment (e.g., negative emotionality temperament) as a means of calibrating an organism to maximize its adaptation to the environment. In turn, temperament may then interact with later environmental factors, through Temperament x Environment interactions (TxE), to affect EB. Thus, different plasticity factors across multiple levels and periods of development provide a certain level of flexibility in adaptive development, enabling the environment to play a continuous role in calibrating plasticity sequentially. In this way, early GxE may affect the most adaptive level of susceptibility to the future environment, and this "programming" of the organism may be particularly active during developmental periods when adaptive systems are still organizing, such as in utero (Boyce, 2007).

Prenatal Programming of Postnatal Plasticity

From an evolutionary biology perspective, the prenatal period represents a critical stage where programming occurs, calibrating the fetus to the expected postnatal environment to maximize adaptation (Glover, O'Connor, & O'Donnell, 2010). To illustrate, prenatal maternal stress may forecast a stressful and inconsistent postnatal environment, for which elevated infant negative emotionality (e.g., vigilance and reactions to threat) may advantage fitness. In this maladaptive postnatal environmental context, negative emotionality then contributes to heightened risk for the development of EB, which may be *adaptive* for survival and reproduction in an unstable setting (Glover, 2011; Pluess & Belsky, 2011; Talge, Neal, & Glover, 2007). This "prenatal programming of postnatal plasticity" is supported by the link between prenatal stress and infant negative emotionality (Blair, Glynn, Sandman, & Davis, 2011; Glover, 2011; Pluess & Belsky, 2011). For example, elevated maternal cortisol during pregnancy predicted elevated infant negative emotion at 7 weeks postpartum (de Weerth, van Hees, & Buitelaar, 2003). Similarly, lower birth weight, a correlate of prenatal stress (Rice et al., 2010), predicted higher temperamental negative emotionality in 5-year old children (Pesonen et al., 2006).

Beyond these main effects, some individuals may be particularly sensitive to prenatal effects due to their genetic makeup (Pluess & Belsky, 2011). That is, negative emotionality as a sensitivity factor may reflect independent and interactive effects of genotype *and* prenatal environment. Although genetic influences on the association between prenatal environment and later development are not well characterized, genetic moderation of these prenatal programming effects may occur. Grizenko et al. (2012) reported that DRD4 moderated the association between prenatal stress and child ADHD; moderate to high prenatal stress (retrospectively reported by mothers) predicted more ADHD symptoms, but only for children homozygous for the 7R allele. Similarly, DRD4 genotype moderated the association of prenatal stress and EB in school age and

adolescence, such that 7R carriers were more likely to be diagnosed with EB such as conduct disorder or oppositional defiant disorder when their mothers reported higher levels of stress during pregnancy, whereas prenatal stress was unrelated to EB outcomes for non-carriers (Zohsel et al., 2014). Thus, there is emerging evidence to support a mechanistic model of differential susceptibility in which genes interact with prenatal environment to predict temperamental measures of plasticity, which then interact with the postnatal environment to predict complex behavioral outcomes such as EB.

Study Aims

Despite its important theoretical implications and the growing number of GxE and TxE studies supporting environmental sensitivity, much less is known about its underlying developmental mechanisms. Testing a developmentally-sensitive and integrated model of genetic and temperamental sensitivity may critically elucidate *how* developmental plasticity of EB forms and changes over time. However, no empirical studies of EB have integrated these multiple levels of analysis by explicitly modeling these interactive associations across prenatal and postnatal development in a single study. The present study employed a longitudinal sample of children to integrate GxE and TxE hypotheses in prediction of EB. Based on emerging evidence of prenatal programming GxE effects (Pluess & Belsky, 2011), our aims were two-fold: (1) to model the independent and interactive effects of prenatal stress and dopaminergic genes on the formation of early temperament traits linked to plasticity (i.e., negative emotionality), and (2) to explore how negative emotionality interacts with postnatal environment (i.e., positive and negative parenting behavior) to predict EB in pre-/early adolescence. See Figure 3.1 for a conceptual model. Thus, using a developmentally-sensitive moderated mediation model, we aimed to elucidate how plasticity is *shaped* by modeling the mechanisms underlying EB

development. If supported, results would suggest that developmental plasticity itself is a function of both nature and nurture and can, thus, be shaped by modifiable developmental experiences (e.g., prenatal stress) to prospectively influence EB outcomes in childhood and adolescence.

Methods

Participants

Participants were 232 children (aged 5-10 at baseline) and their parents (88% mothers) from a prospective longitudinal case-control study of children with and without ADHD. The means, standard deviations, and bivariate correlations among all demographic and study variables appear in Table 3.1. Participants were racial-ethnically diverse (52.5% White Non-Hispanic, 10.8% Hispanic, 8.5% Black, 3.6% Asian, 24.7% Mixed or Other) and mostly male (68%). Families were recruited from a large metropolitan city in the Western United States through presentations to self-help groups, advertisements mailed to local elementary schools, and referrals from pediatric offices and mental health clinics. All children were required to have an IQ of at least 70, live with one biological parent at least half time, and be fluent in English. Participants were excluded if they had a current/previous autism spectrum, seizure, or neurological disorder that prevented full participation in the study. As part of the larger case-control study, ADHD diagnostic status was ascertained at baseline from the Diagnostic Interview Schedule for Children, 4th edition (DISC-IV-P; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), a fully structured parent interview keyed to DSM-IV criteria (e.g., age of onset, symptom persistence, cross-situational). Non-ADHD comparison youth were negative for ADHD according to the DISC but were allowed to meet diagnostic criteria for other mental disorders (e.g., anxiety, ODD).

Procedure

At baseline (timepoint 1 or T1; ages 5-10), study eligibility for interested families was determined through a telephone screening based on the inclusion and exclusion criteria listed above. Eligible families were mailed rating scales and invited to complete a laboratory-based assessment. After obtaining parental consent and child assent, parents completed multi-method measures of child psychopathology and temperament; in a separate room, children were assessed with measures beyond the scope of the present study including cognitive, academic, and social-emotional functioning. Finally, parents and children were videotaped during a parent-child interaction task. Children and parents provided saliva samples for genotyping. The child's diagnostic status was initially masked to all interviewers, although this was difficult to maintain following the completion of the DISC-IV. Approximately 94% of children were assessed in our laboratory without psychotropic medications. If a child was normally medicated (17%), we asked that parents provide ratings based on the child's unmedicated behavior.

Families were invited back to the laboratory for a follow-up assessment approximately four to five years after baseline (time 2; T2) when children were aged 9-15 years of age. Procedures for the follow-up visit were highly parallel to those in the baseline assessment. Approximately 83% of the initial sample (n = 183) participated in the 4-5-year follow-up assessment; participants who dropped-out did not differ significantly from participants included the present study on any baseline demographic (i.e., child age, sex, race-ethnicity), clinical (i.e., child ADHD symptoms), or genetic and temperament variables. We employed Full Information Maximum Likelihood procedures (FIML; described below) so that analyses were conducted on the full sample of 232 youth. The Institutional Review Board approved all study procedures.

Measures

Dopaminergic gene index. During the baseline evaluation, DNA was extracted from saliva samples using DNA Genotek Oragene Self-Collection Kits (DNA Genotek, Inc., Ottawa, CA). The present study created a dopaminergic gene index based on two dopamine-related polymorphisms associated with plasticity (Bakermans-Kranenburg & van Ijzendoorn, 2011; Belsky & Beaver, 2011). First, the 48-base pair (bp) variable number tandem repeat (VNTR) polymorphism located on chromosome band 11p15.5 of the DRD4 gene was genotyped using standard primers. The allele frequencies for the most common genotypes (4/4, 4/7, 2/4, 3/4, 7/7) of DRD4 were in Hardy-Weinberg equilibrium, $\chi 2(4) = .97$, $p = .21$. Following previous strategies (Bakermans-Kranenburg & van Ijzendoorn, 2011), participants with at least one 7R allele (36.2%) were compared to non-carriers (63.8%). Next, the 40-bp VNTR polymorphism in the 3' untranslated region of the DAT1 gene was genotyped, which produced the two most common polymorphisms (9R and 10R) in the following distribution: 10/10 (56.5%), 9/10 (36.4%), and 9/9 (7.0%). These frequencies were in Hardy-Weinberg equilibrium, $\chi 2(1) = 0.25$, $p = .62$. We created an index of dopaminergic genotypes that represented the number of plasticity genotypes for each participant where participants with at least one 7R allele of DRD4 were assigned one plasticity "point," and participants with the 10/10 genotype of DAT1 were assigned one point. Thus, dopaminergic gene index scores ranged from 0-2, with higher scores representing more genetic plasticity.

Negative emotionality. At baseline, child negative emotionality was assessed using the Child and Adolescent Dispositions Scale (CADS), a parent interview of temperament that was explicitly designed for studies of psychopathology by excluding synonyms and antonyms of psychiatric symptoms (Lahey et al., 2008). Parents rated 50 items based on how well the item described their child on a 4-point Likert scale, ranging from 1 (*not at all*) to 4 *(very much/very*

often). Previous psychometric studies identified three factors: negative emotionality, prosociality, and daring, which evidenced excellent internal consistency, high re-test reliability, and predictive and concurrent validity in multiple samples (Lahey et al., 2008; Trentacosta, Hyde, Shaw, & Cheong, 2009). The present study used the total score from the negative emotionality factor (11 items, Cronbach's $\alpha = .82$), which includes items such as "does [your child] react intensely when he/she gets upset?" and "does [your child] get upset easily?."

Birth weight. We followed Pluess & Belsky (2011) and treated birth weight as reported by the primary parent as a proxy for global prenatal stress. Birth weight reported through maternal recall is highly correlated with medical record data into offspring adulthood (e.g., intraclass correlation [ICC] = .99 in Yawn, Suman, & Jacobsen, 1998; also see Buka, Goldstein, Spartos, & Tsuang, 2004; Jaspers, de Meer, Verhulst, Ormel, & Reijneveld, 2010; O'Sullivan, Pearce, & Parker, 2000; Rice et al., 2007). Given its sensitivity to multiple forms of prenatal stress, including prenatal exposure to trauma and violence (Hill, Pallitto, McCleary-Sills, & Garcia-Moreno, 2016), chronic stress and poverty (Bolten et al., 2010; Kayode et al., 2014; Strutz et al., 2014), cigarette smoking (Bailey, McCook, Hodge, & McGrady, 2011), and pregnancy-related stress and anxiety (Bussières et al., 2015), we interpreted lower birth weight as suggesting more prenatal stress. Children in the present study represented a full range of birth weights (from 2.6-9.8 lbs).

Parenting behavior. Observed measures of positive and negative parenting behavior were coded from a parent-child interaction task administered at baseline using the Dyadic Parent Child Interaction Coding System (DPICS; Eyberg, Nelson, Duke, & Boggs, 2005). The DPICS is a well-validated system of rating parent-child interaction in children with disruptive behavior disorders. Discrete parent and child behaviors were coded continuously, and then composite

categories of parenting were created (Chronis-Tuscano et al., 2008; Eyberg et al., 2001; J. J. Li & Lee, 2013). Negativity was coded when parents made hostile or critical comments to their child (e.g., "You're so irritating sometimes," "You're doing that wrong"), negative commands (e.g., "Stop doing that!"), or sarcastic and condescending remarks (e.g., "You think you're so clever, don't you?"). Praise was coded when parents made positive appraisals of their children's behavior, attributes, or products that their children created (e.g., "You're a good builder," "That's a really pretty picture of a dog you drew"). All parent-child interactions were digitally recorded. Research assistants completed intensive training on DPICS coding procedures until at least 70% agreement was attained. The present study used the negativity (ICC = .75) and praise composites (ICC = .88) as measures of negative parenting and positive parenting, respectively. Please see Li and Lee (2013) for further details about the DPICS coding system.

EB. Children's EB at the follow-up evaluation was assessed using the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), a widely-used 113-item parent rating scale that yields multiple scales of internalizing and externalizing problems. Parents rated each behavior based on the preceding 6 months as 0 (*Not True*), 1 (*Somewhat or Sometimes True*), or 2 (*Very True or Often True*). Normative data are available for boys and girls ranging from 6-18, and the scales have demonstrated convergent validity with other common measures of behavioral and emotional functioning (Bender et al., 2008). The scales also discriminated between disordered and non-disordered children (Brasil & Bordin, 2010). The present study used T-scores from the Externalizing Behavior broadband scale, which includes aggressive behavior (e.g., "cruelty, bullying, or meanness to others," "gets in many fights") and rule-breaking behaviors (e.g., "breaks rules at home, school, or elsewhere," "steals at home").

Data analysis

Prenatal programming of postnatal sensitivity to the environment was explored using two complementary moderated mediation models (also called conditional indirect effects models; Hayes, 2015) to examine sensitivity to negative and positive parenting (see Figure 3.1 for the conceptual model). Each model simultaneously estimated (1) coefficients for the direct effects between dopaminergic genes, negative emotionality, and EB, (2) the indirect effect of dopaminergic genes on EB through negative emotionality, and (3) the *conditional* indirect effect based on birth weight and parenting behavior (two separate models for positive and negative parenting). That is, we tested whether the indirect effect of dopaminergic genes on EB through negative emotionality was *moderated* by prenatal and/or postnatal environment. Significant moderated mediation was indicated when the Index of Moderated Mediation indicated a significant difference between conditional indirect effects across different levels of birth weight (-1SD, grand mean, +1SD) or parenting behaviors (-1SD, grand mean, +1SD; Hayes, 2015). Given the case-control design of the sample, all models controlled for baseline child ADHD symptoms to improve specificity. We additionally controlled for race-ethnicity in all models; the CBCL Externalizing Problems T-scores accounted for differences in EB based on age and sex.

Both moderated mediation models were conducted in Mplus 6.12 (Muthén & Muthén, 1998-2011). Parameter estimates and 95% bias-corrected (BC) confidence intervals (CIs) for point estimates of the indirect effects, conditional indirect effects, and the difference between these effects were calculated based on 5,000 bootstrap resamples (statistical significance is assumed when the interval excludes zero; Hayes, 2015). Bootstrapping is a powerful nonparametric re-sampling procedure that enables simultaneous evaluation of mediators and moderators with adjustment for potential covariates (Hayes, 2013; Preacher & Hayes, 2008). In addition to these critical advantages, bootstrapping-based mediation is also statistically more

powerful than traditional approaches (i.e., Sobel test; Zhao, Lynch, & Chen, 2010). For all moderated mediation analyses, variables were centered and FIML estimation with robust standard errors was used to address missing data and to increase model power. Modern missing data approaches such as FIML are significantly advantaged over common methods (e.g., listwise deletion, mean imputation) given that they produce less biased parameter and standard error estimates and decrease Type 1 error (Collins, Schafer, & Kam, 2001; R. J. Little & Rubin, 1987).

Results

Prenatal Programming of Sensitivity to Negative Parenting

Conditional direct effects. The first model examined moderation of the direct and indirect effects of dopaminergic genes on EB through negative emotionality by birth weight and negative parenting behaviors, controlling for ADHD symptoms and race-ethnicity (EB T-scores are already adjusted for age and sex). Path coefficients for this full model are presented in Figure 3.2. First, neither dopaminergic genes nor birth weight had a significant direct effect on negative emotionality (Figure 3.2). Instead, they significantly interacted to predict negative emotionality (Figure 3.3). To examine *how* dopaminergic plasticity influenced the association of birth weight (representing prenatal environment) and later temperamental sensitivity, post hoc regression models separately tested the association between birth weight and negative emotionality for children across 0, 1, and 2 dopaminergic plasticity genotypes. For children with high dopaminergic plasticity (i.e., with 7R allele of DRD4 *and* the 10/10 genotype of DAT1), birth weight inversely predicted negative emotionality ($ß$ = -.07, SE = .04, p = .04) such that children with high birth weights were less negatively emotional (i.e., theoretically "less sensitive" temperament) whereas low birth weight children had high negative emotionality. In contrast,

birth weight did not influence negative emotionality for children with moderate or low dopaminergic plasticity (*ß* < .01, *SE* = .03, *p* = .97 and *ß* = .03, *SE* = .04, *p* = .48, respectively).

In addition to prenatal programming effects, this model also tested the direct effects of negative emotionality, negative parenting, and their interaction on later EB. Controlling for ADHD symptoms, race-ethnicity, and dopaminergic genes, negative emotionality had a significant positive direct effect on EB 4-5 years later, and negative parenting had a marginally significant positive direct effect on EB (Figure 3.2). Furthermore, negative parenting marginally moderated the prospective association between negative emotionality and EB (Figure 3.2).

Conditional indirect effects. As expected, neither the total effect of dopaminergic genes on EB nor its indirect effect through negative emotionality were significant, supporting the need to examine potential moderating effects by environmental factors. The moderating effects of birth weight and negative parenting on the *indirect* effects of dopaminergic genes on EB through negative emotionality are presented in Table 3.2. The index of moderated mediation compared the difference in indirect effects at -1 SD, grand mean, +1 SD levels of birth weight and suggested significant moderated mediation effect by birth weight (Table 3.2). For children with high birth weights (representing a stable/enriching prenatal environment), high genetic plasticity predicted *low* negative emotionality, which in turn predicted lower levels of EB 4-5 years later. In contrast, this indirect effect was not significant for children with low or average birth weights. Negative parenting did not significantly moderate the indirect effect of dopaminergic genes on EB through negative emotionality (Table 3.2).

Prenatal Programming of Sensitivity to Positive Parenting

Conditional direct effects. Next, to explore how prenatal programming effects may influence sensitivity to *positive* postnatal parenting behaviors, we examined moderation of the

direct and indirect effects of dopaminergic genes on EB through negative emotionality by birth weight and positive parenting behaviors, controlling for ADHD symptoms and race-ethnicity. Path coefficients for this full model are presented in Figure 3.3. Similar to results from the negative parenting model, neither birth weight nor dopaminergic genes directly predicted negative emotionality, although their interaction did so marginally. Negative emotionality, in turn, had a significant direct effect on EB, but positive parenting behaviors and the interaction between positive parenting and negative emotionality were not significant (Figure 3.3).

Conditional indirect effects. In the positive parenting model, both indices of moderated mediation were non-significant (Table 3.2). Thus, in this model, neither birth weight nor positive parenting behaviors moderated the indirect effect of dopaminergic genes on EB through negative emotionality.

Discussion

In a developmentally-sensitive and multi-method longitudinal study of children and early adolescents, we tested an integrated model of genetic and temperamental sensitivity to the environment to explore prenatal and postnatal mechanisms underlying EB development. Whereas previous studies of environmental sensitivity typically focused on a single plasticity marker (e.g., single genotype), we integrated these biologically-based levels into a single moderated mediation model to explore how plasticity is formed. First, birth weight moderated the association between dopaminergic genes and negative emotionality in childhood, supporting genetic moderation of prenatal programming effects on temperament traits linked to plasticity (Pluess & Belsky, 2011). Childhood negative emotionality, in turn, positively predicted EB 4-5 years later in pre/early adolescence. The association between negative emotionality and EB was marginally moderated by negative parenting, but not by positive parenting. Thus, we observed

partial support for postnatal plasticity, with these marginal effects following a diathesis-stress pattern of environmental sensitivity. Finally, birth weight moderated the indirect effect of dopaminergic genes on EB through negative emotionality, such that the mediating pathway was only significant for children with high birth weights (representing stable, nurturing prenatal environments).

These preliminary findings suggest that individual differences in childhood negative emotionality were sensitive to genetic x prenatal environment interactions. Specifically, birth weight inversely predicted negative emotionality, but only for children with greater genetic plasticity (i.e., with both the 7R allele of DRD4 and the 10/10 genotype of DAT1). These results suggest that temperamental traits linked to plasticity (such as negative emotionality) are not direct phenotypic markers of underlying genetic plasticity. Rather, the prenatal environment likely plays a key adaptive role in guiding the fetus to exhibit either a highly *reactive* postnatal temperament (i.e., high negative emotionality) when the prenatal environment forecasts a chaotic postnatal environment, or a less sensitive and "easy" temperament when exposed to a stable, nurturing prenatal environment (Boyce, 2016; Pluess & Belsky, 2011). Thus, these results implicate genetic moderation of prenatal programming effects on negative emotionality. Considering the moderating role of the prenatal environment helps shed light on why dopaminergic plasticity predicted *higher* negative emotionality in some studies (De Luca et al., 2003; Holmboe et al., 2011; Ivorra et al., 2011; Oniszczenko & Dragan, 2005), but predicted *lower* negative emotionality in other studies (Auerbach et al., 1999; Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Papageorgiou & Ronald, 2013).

Next, this study partially supported temperament-based postnatal plasticity, such that negative emotionality predicted significantly higher EB 4-5 years later, and this effect was

marginally heightened if the postnatal parenting environment was *negative*; negative emotionality did not affect sensitivity to positive parenting behaviors. Furthermore, given that the interaction between negative emotionality and negative parenting was marginal, the more prominent postnatal effect was the *direct* effect of negative emotionality on EB 4-5 years later, beyond dopamine genotypes, parenting behaviors, ADHD symptoms, and demographics (e.g., age, sex, race-ethnicity). The prospective prediction of EB from negative emotionality is consistent with evidence that negative emotionality is an etiological marker for EB (Singh & Waldman, 2010). Thus, understanding the early developmental processes that predict lower negative emotionality may be a critical way to target early prevention of later EB.

Finally, we evaluated a moderated mediation model to examine how prenatal and postnatal environmental factors influence the *mediating* pathway from dopaminergic genes to negative emotionality to EB. Birth weight moderated the indirect effect of dopaminergic genes on EB through negative emotionality, supporting a genetically-moderated prenatal programming model of EB. Surprisingly, post hoc tests revealed that the mediating pathway from dopaminergic genes to EB through negative emotionality was only significant for children with *high* birth weights (representing stable, nurturing prenatal environment). When exposed to a positive prenatal environment, children with high genetic plasticity exhibited less negative emotionality, which directly predicted lower EB in pre/early adolescence, beyond the postnatal environment. In other words, compared to children with moderate or low genetic plasticity, children with high genetic plasticity *benefited more* from a stable, nurturing prenatal environment, which in turn predicted less negative emotionality and lower EB. However, low birth weight did not predict negative emotionality and EB for children with high genetic plasticity. This pattern of prenatal plasticity is consistent with a vantage sensitivity framework

(Pluess & Belsky, 2013), in which genetic markers heightened sensitivity to *positive* prenatal environments, but not negative prenatal environments.

It is important to interpret these preliminary results in the context of this sample characteristics and relevant methods. The sample included primarily middle to middle-upper SES families, which may have limited the amount of severe prenatal stress experienced. We did observe a full range of birth weight (ranging from 2.6 to 9.8 lbs), but low birth weight likely reflects multiple factors beyond prenatal stress (e.g., genetic effects; Lunde, Melve, Gjessing, Skjærven, & Irgens, 2007). Thus, future studies are needed to replicate this model in high-risk samples, such as infants exposed to prenatal maltreatment, chronic poverty, or community violence. Second, due to medical record data being unavailable, birth weight was assessed via maternal recall, which is highly correlated with medical record data (e.g., Yawn et al., 1998) but less accurate. Furthermore, although birth weight meaningfully approximates a global measure of the prenatal environment, future studies that examine separable measured aspects of the prenatal environment are needed to clarify which specific prenatal experiences have the largest influence on later postnatal plasticity. Finally, the results should be interpreted in the context of the relatively modest sample size, which may have been underpowered to detect all moderated mediation effects and/or to sufficiently probe significant interactions. Given that several marginal effects were observed in the current model, larger sample sizes are warranted to clarify the nature of these effects.

The rapidly growing number of GxE and TxE studies in the past decade make clear that biologically-based processes of environmental sensitivity critically underlie EB development. However, environmental sensitivity itself is a dynamic process, fluctuating based on developmental period and influenced by multiple levels of biology (Boyce, 2016; Ellis et al.,

2011). Because most environmental studies have narrowly focused on one biological level or developmental period, the causal mechanisms underlying EB development remain elusive. Studies integrating these multiple levels of analysis are timely and needed to understand not only *who* is most sensitive to the environment, but *how* this environmental sensitivity is shaped across time (Boyce, 2016; Weeland et al., 2015). If replicated, our exploratory findings have clinically meaningful implications for the timing and targets of intervention and prevention programs for EB. We found that for children with plasticity variations of dopaminergic genes (i.e., the 7R allele of DRD4 and 10/10 genotype of DAT1), a stable and positive prenatal environment led to significantly lower childhood negative emotionality, which in turn predicted lower EB 4-5 years later. In contrast, postnatal negative parenting behavior had only a marginal independent and interactive effect on EB above and beyond the direct effects of negative emotionality, and positive parenting did not prospectively predict EB. These preliminary findings speak to a preventative rather than a reactive approach to reducing child and adolescent EB. Reducing EB may require interventions directly targeted at temperamental factors underlying EB, such as negative emotionality, that may need to start as early as the prenatal environment for at-risk mothers. Ultimately, this exploratory study emphasizes that to understand the development of complex behavioral outcomes such as EB, we must consider individual and environmental factors across multiple levels. Future replication studies testing integrated models of genetic and temperamental sensitivity that also consider different sources of environmental stress and support across developmental periods are needed to clarify how plasticity is shaped over time.

Table 3.1. Descriptive statistics and correlations among demographic and variables in Study 3

Variable	M (SD) or %	1	2	3	4	5	6	7	8	9	10
1. Age in years (T1)	7.42 (1.14)	--									
2. Sex (% girls) [a]	31.9%	-.04	--								
3. Race-ethnicity (% Caucasian) [b]	52.5%	-.01	.02	--							
4. ADHD symptoms (T1)	7.96 (5.52)	-.11	.18**	-.08	--						
5. Dopaminergic plasticity score	0.91 (0.67)	-.05	-.04	-.06	-.03	--					
6. Negative emotionality (T1)	25.15 (5.64)	<.01	.04	.09	.54**	-.07	--				
7. Birth weight in ounces	117.92 (19.11)	-.07	.18*	<.01	-.04	-.01	-.01	--			
8. Parental Negativity (T1)	9.22 (9.00)	-.09	.04	-.15	.18*	-.03	.08	-.08	--		
9. Parental Praise (T1)	12.49 (10.92)	-.20**	.09	.10	.10	-.02	-.04	.01	-.01	--	
10. Externalizing Problems T-score (T2)	50.77 (10.34)	.06	<.01	-.12	.43**	-.08	.50**	-.01	.20*	-.13	--

Note. T1 = timepoint 1 (baseline); T2 = timepoint 2 (4-5 year follow-up). [a] 1 = boys, 0 = girls. [b] 1 = Caucasian, 0 = non-Caucasian.
* $p < .05$ ** $p < .01$

Table 3.2. Indirect effects of dopaminergic genes on EB through negative emotionality conditioned on birth weight and parenting behavior

	Point Est.	*SE*	*95% BCa Bootstrap CI*	
			Lower	*Upper*
Negative Parenting Model				
Total effect	-1.034	1.194	-3.327	1.255
Indirect effect	-0.349	0.400	-1.237	0.368
Index of Moderated Mediation by Birth Weight	**-0.044**	**0.024**	**-0.099**	**-0.004**
Conditional indirect: Low birth weight	0.495	0.526	-0.508	1.583
Conditional indirect: Moderate birth weight	-0.349	0.400	-1.237	0.367
Conditional indirect: High birth weight	**-1.192**	**0.672**	**-2.829**	**-0.125**
Index of Moderated Mediation by Negative Parenting	-0.016	0.022	-0.080	0.013
Conditional indirect: Low negative parenting	-0.205	0.281	-1.016	0.163
Conditional indirect: Moderate negative parenting	-0.349	0.400	-1.237	0.367
Conditional indirect: High negative parenting	-0.492	0.566	-1.764	0.509
Positive Parenting Model				
Total effect	-1.085	1.208	-3.235	1.388
Indirect effect	-0.286	0.382	-1.120	0.421
Index of Moderated Mediation by Birth Weight	-0.038	0.023	-0.089	0.002
Conditional indirect: Low birth weight	0.438	0.503	-0.546	1.470
Conditional indirect: Moderate birth weight	-0.286	0.382	-1.120	0.421
Conditional indirect: High birth weight	-1.009	0.645	-2.493	0.083
Index of Moderated Mediation by Positive Parenting	0.003	0.013	-0.013	0.043
Conditional indirect: Low positive parenting	-0.321	0.441	-1.459	0.348
Conditional indirect: Moderate positive parenting	-0.286	0.382	-1.120	0.421
Conditional indirect: High positive parenting	-0.250	0.374	-1.160	0.369

Note. Boldface indicates significant conditional indirect effect and/or significant index of moderated mediation; Point est. = point estimate of the indirect effect; BCa Bootstrap CI = bias corrected and accelerated confidence interval

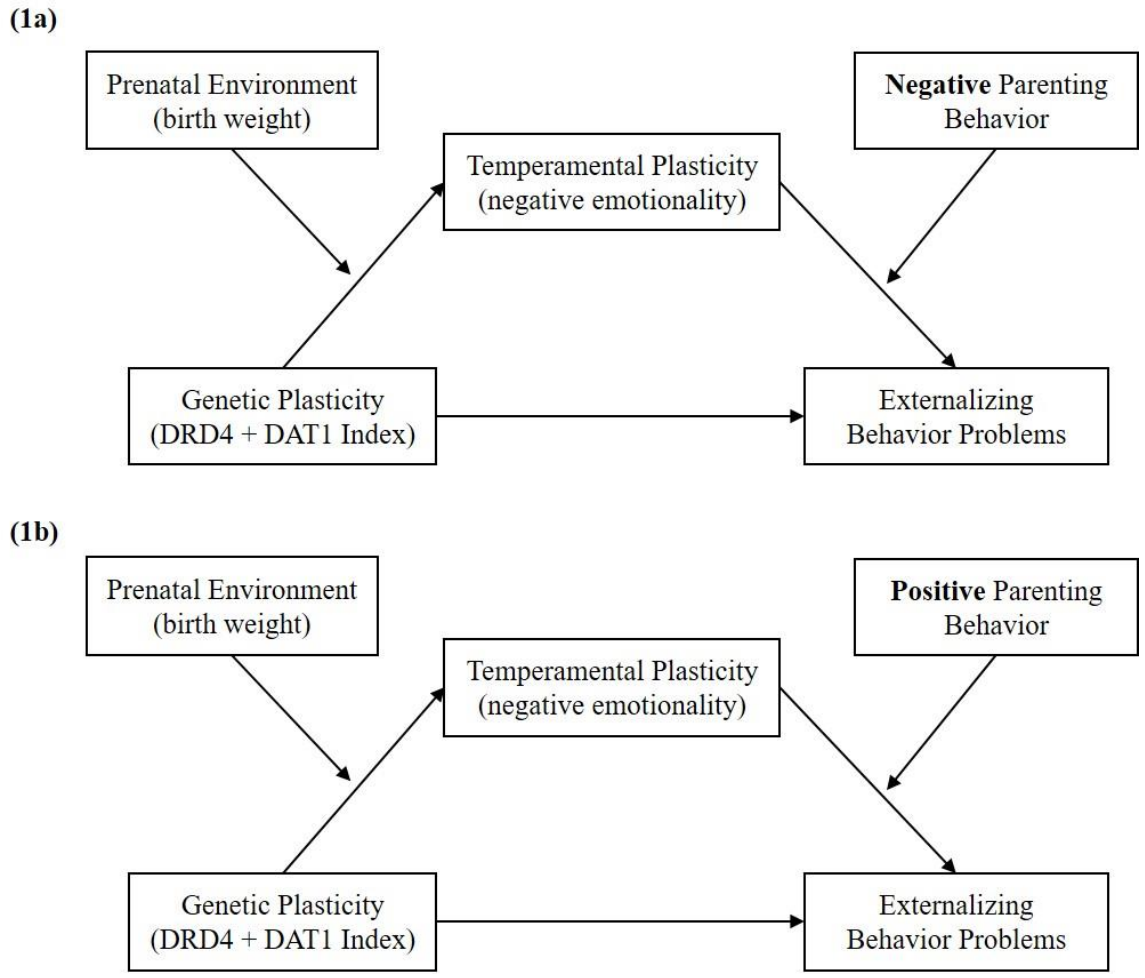


Figure 3.1. Conceptual diagrams of moderated mediation models exploring prenatal programming of postnatal sensitivity to (1a) negative parenting and (1b) positive parenting

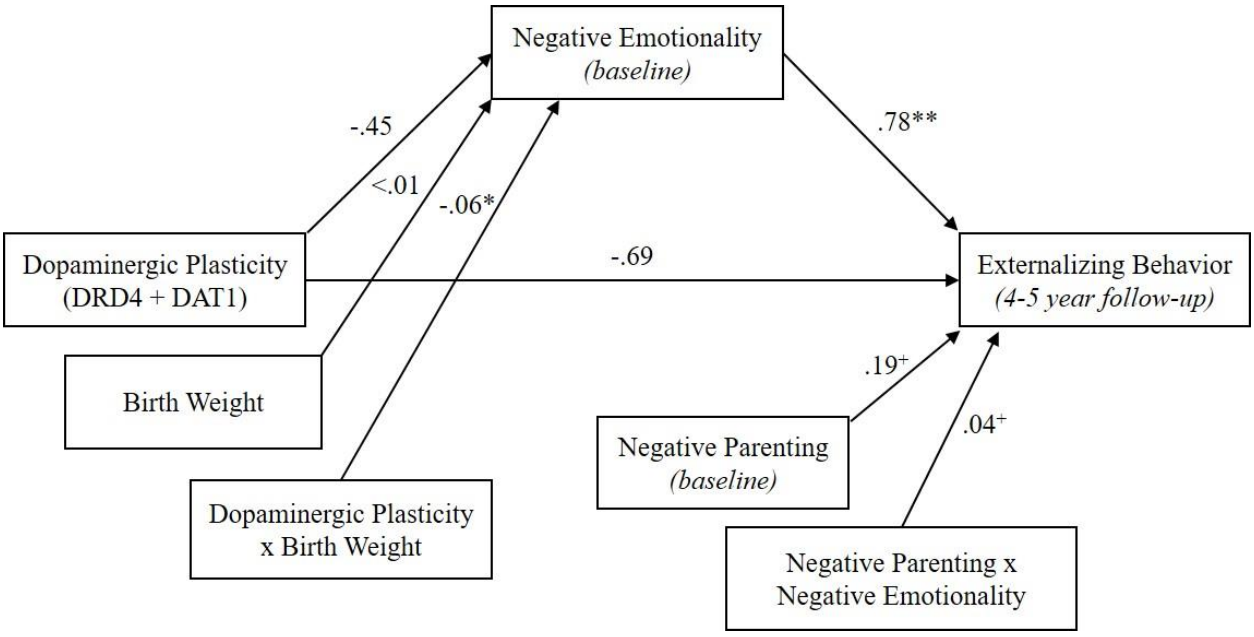


Figure 3.2. Path coefficients from the model estimating moderation by birth weight and negative parenting behavior of the indirect effect of dopaminergic genes on EB through negative emotionality, controlling for child race-ethnicity and ADHD symptoms (EB T-scores also adjusted for age and sex). *Note*. Numbers shown reflect unstandardized beta coefficients; $^{+}p <$ .10 $*p < .05$ $**p < .01$

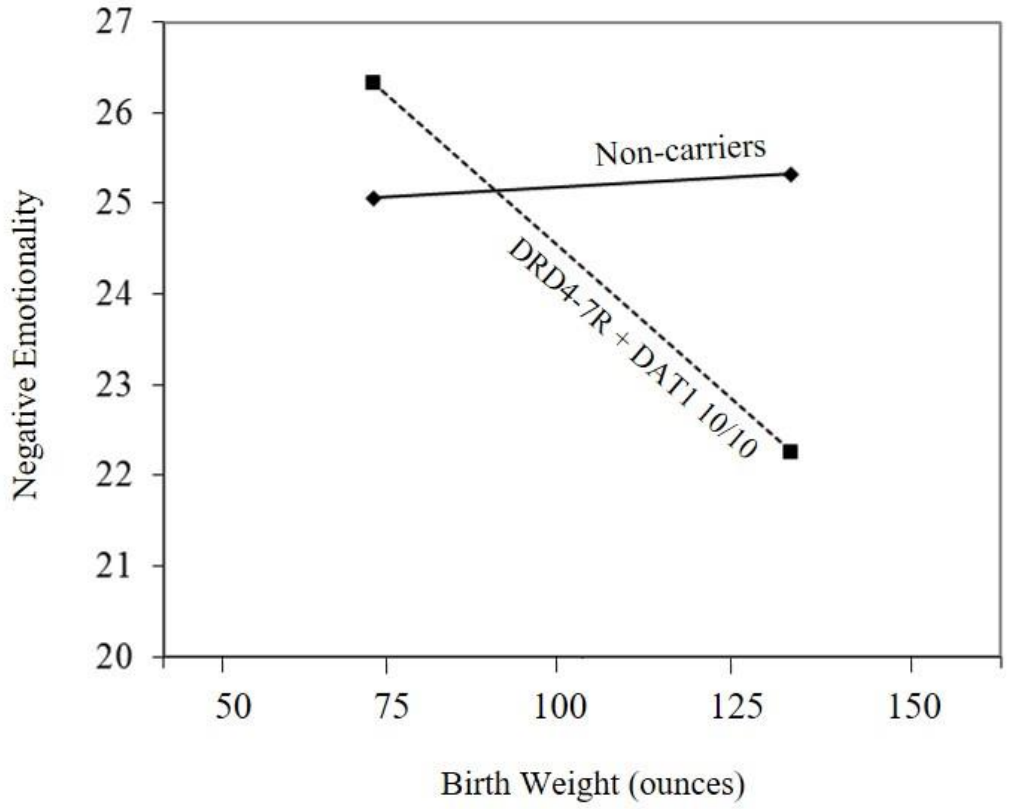


Figure 3.3. Genetic moderation of prenatal effects (measured by birth weight) on child negative emotionality

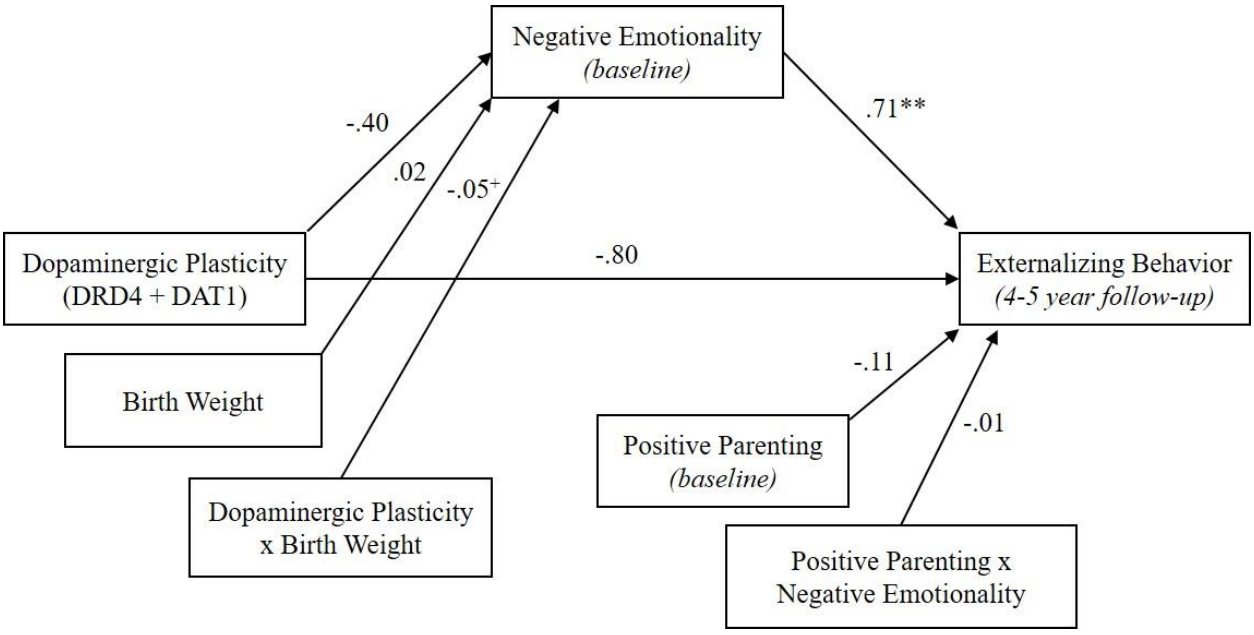


Figure 3.4. Path coefficients from the model estimating moderation by birth weight and positive parenting behavior of the indirect effect of dopaminergic genes on EB through negative emotionality, controlling for child race-ethnicity and ADHD symptoms (EB T-scores also adjusted for age and sex). *Note*. Numbers shown reflect unstandardized beta coefficients; $^{+}p <$ .10 $*p < .05$ $**p < .01$

Conclusions

Despite the promising implications of differential susceptibility for EB prevention and intervention, most studies have been restricted by cross-sectional designs or measured EB at single time-points. Thus, little is known about how environmental sensitivity changes *across development,* a critical limitation given that EB is highly sensitive to developmental period. Furthermore, although many youth at highest risk for EB have already been exposed to early stress and adversity, almost no studies have considered whether these early experiences (e.g., maltreatment) influence later sensitivity to the environment, either in combination with or above and beyond the plasticity genotypes and temperament traits proposed by differential susceptibility theory. Thus, a primary goal of this dissertation was to infuse developmental perspectives into tests of differential susceptibility by employing rigorously designed prospective studies with developmentally-informative analytic methods. Employing three unique yet complementary longitudinal samples, these studies collectively aimed to explore how previous adversity (ranging from prenatal stress to childhood maltreatment) and individual differences in temperament and genotypes collectively influence later sensitivity to positive and negative social contexts to predict the development of EB across childhood through young adulthood.

To review, Study I employed a quasi-experimental design to examine how reactive temperament influences sensitivity to early maltreatment and later family cohesion in a high-risk sample of children transitioning from foster-care to adoption. Extending these questions into later development, Study II used latent growth curve analysis to model change in EB from age 13 to 32 in a large population-based sample of adolescents transitioning into adulthood, and then examined whether adolescent sensitivity to parenting and friendship effects differed based on childhood maltreatment and polymorphisms of dopamine genes related to EB (DRD4, DRD2,

DAT1). Finally, Study III employed a longitudinal sample of pre-adolescent children with and without ADHD to integrate GxE and TxE hypotheses in an exploratory, multilevel mechanistic model of differential susceptibility. Based on emerging evidence of prenatal programming GxE effects, Study III employed a moderated mediation model to investigate how prenatal stress and dopaminergic genes (DAT1 and DRD4) independently and interactively influence formation of early temperaments linked to plasticity (i.e., negative emotionality). I then explored how these temperament traits interacted with postnatal environment (i.e., observational measures of positive and negative parenting behavior) to predict later EB in early adolescence. Several key findings emerged across studies that are reviewed below, and I discuss clinical implications and directions for future research.

Overall, results from these three longitudinal studies partially support that genetic and temperamental variations influence sensitivity to the environment, although patterns of sensitivity were primarily evident early in development (prenatal period, early childhood). In Study I, foster children with early reactive temperament (vs. easy temperament) showed the highest EB at initial placement in their adoptive homes, but they were also more sensitive to positive family cohesion in the first five years of adoption, although these effects were not maintained in late-adolescence/young-adulthood. Similarly, in Study II, a polygenic risk score moderated the effect of parental closeness on concurrent levels of antisocial behavior in early adolescence. However, the directionality of effects was inconsistent with differential susceptibility, and these GxE effects did not predict *changes* in EB from adolescence to adulthood. Finally, Study III found preliminary evidence that dopaminergic genes may interact with the *prenatal* environment to predict childhood negative emotionality in a pattern conceptually consistent with differential susceptibility. Negative emotionality, in turn, directly

predicted EB 4-5 years later; however, children with high negative emotionality were not more sensitive to the postnatal parenting environment (positive and negative parenting behavior). Together, these findings suggest that when environmental sensitivity is considered (e.g., measured, tested quantitatively) developmentally, patterns of genetic and temperamental sensitivity may be more inconsistent and likely vary across developmental period.

One potential reason for apparent inconsistency in environmental sensitivity over time is that early stress itself (e.g., maltreatment) may influence sensitivity to the social environment later in development, which is rarely considered in differential susceptibility studies. Indeed, Studies I and II converged to highlight the enduring effects of early maltreatment on EB in adolescence and young adulthood. In Study I, exposure to early maltreatment was unrelated to childhood EB in the first five years of adoptive placement. However, maltreated youth used significantly more substances by late-adolescence/young adulthood, whereas the protective effect of adoptive family cohesion declined in this later developmental period. These results highlight the enduring effects of early abuse and neglect and the need to better understand how early adversity impacts sensitivity to support in adolescence. Building on these findings, Study II modeled trajectories of antisocial behavior and substance use from age 13-32 for adolescents with and without a history of childhood maltreatment. Consistent with results from Study I, adolescents with maltreatment histories (vs. non-maltreated youth) had consistently higher levels of antisocial behavior and substance use across adolescence and young adulthood. Furthermore, maltreated adolescents showed a *blunted* sensitivity to parental closeness and friendship involvement on initial EB *and* its trajectory into adulthood, and these effects were largely unaffected by variations in polymorphisms of dopamine genes related to differential susceptibility. Overall, these results highlight the need to consider the dynamic nature of the

environment when predicting EB outcomes across time. Although replication studies are clearly required, these findings suggest that for youth who have already been exposed to serious early stressors such as maltreatment, the implications of genetically-based differential susceptibility may not be as clinically meaningful as the impact of maltreatment itself.

Beyond the role of early stress, dispositional factors such as reactive temperament also independently predicted EB in both Studies I and III. Compared to children in foster care with an easy temperament, children with reactive temperaments in Study I had substantially higher EB at baseline and a higher chance of being arrested or sent to juvenile hall in adolescence/early adulthood, even beyond the effects of early maltreatment and adoptive family cohesion in childhood. As noted, temperament did not operate purely as a risk factor across all developmental stages, as children with reactive temperaments also appeared more sensitive to family cohesion in the first five years of adoption; however, these protective effects were not maintained in young-adulthood. Overall, these findings highlight the need to better understand the role of temperament in maintaining EB across time, as well as how early temperament initially forms. Consistent with emerging studies of prenatal programming, Study III found that negative emotionality was shaped by a combination of genetic factors and prenatal environmental factors. Specifically, children with a high dopaminergic polygenic risk score were significantly more likely to develop negative emotionality, but only if born at low birth weights, a global measure of overall stress during pregnancy. Thus, the prenatal environment may interact with our genetic "blue print" to influence early temperament, which, in turn, directly predicted later preadolescent EB even beyond the effects of the postnatal parenting environment.

Together, these findings speak to a preventative rather than a reactive approach to reducing externalizing problems such as aggression, delinquency, and substance abuse. That

early maltreatment demonstrated enduring effects and predicted antisocial behavior and substance use outcomes in young adulthood highlights the need for policymakers and health-care providers (of children *and* adults) to consider the far-reaching effects of child abuse and neglect on long-term EB outcomes. Furthermore, the robust effects of early temperament that emerged across studies suggest that reducing EB may require interventions directly targeted at temperamental factors underlying EB, and they may need to start as early as the prenatal environment for at-risk mothers. Ultimately, the studies in this dissertation emphasize that to understand the development of complex behavioral outcomes such as EB, we must consider individual and environmental factors across multiple levels and time points. Given extensive evidence that EB is highly sensitive to developmental changes over time, it is critical that future studies investigating environmental sensitivity directly consider the developmental nature of EB when trying to understand how genetic and temperamental differences may differentially influence EB. Future studies that consider different sources of environmental stress and support across developmental periods are needed to further elucidate the developmental mechanisms underlying EB development and plasticity across time.

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