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Child-evoked maternal negativity from 9 to 27 months: evidence of gene-environment correlation and its moderation by marital distress

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Abstract

Past research has documented pervasive genetic influences on emotional and behavioral disturbance across the lifespan and on liability to adult psychiatric disorder. Increasingly, interest is turning to mechanisms of gene-environment interplay in attempting to understand the earliest manifestations of genetic risk. We report findings from a prospective adoption study, which aimed to test the role of evocative gene-environment correlation in early development. 561 infants adopted at birth were studied between 9 and 27 months with their adoptive parents and birth mothers. Birth mother psychiatric diagnoses and symptoms scales were used as indicators of genetic influence, and multiple self-report measures were used to index adoptive mother parental negativity. We hypothesized that birth parent psychopathology would be associated with greater adoptive parent negativity, and that such evocative effects would be amplified under conditions of high family adversity. The findings suggested that genetic factors linked to birth mother externalizing psychopathology may evoke negative reactions in adoptive mothers in the first year of life, but primarily when the adoptive family environment was characterized by marital problems. The observed maternal negativity mediated the effects of genetic risk on child

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adjustment at 27 months. The results underline the importance of genetically-influenced evocative processes in early development.

Keywords

Parenting; genes; gene-environment correlation; marital problems; adoption

There is widespread recognition of the potentially critical role of gene-environment interplay in the evolution of psychiatric disturbance in children and adults (Rutter & Silberg, 2002), beginning in early childhood (Harold et al., 2013; Leve et al., 2010). Attention has increasingly focused on gene-environment correlation as an etiologically important mechanism in the development of psychopathology. Gene-environment correlation refers to a range of processes in which an individual's social environment is associated with their genotype. Studies of gene-environment correlation may help uncover some of the potentially modifiable environmental processes by which genetic effects have their impact on risk for maladjustment. Yet, the majority of existing research on gene-environment correlation has not examined how these processes unfold in very early development, or on their role in directly mediating genetic effects related to psychopathology. In the current study, we therefore investigated the role of gene-environment correlation in the first two years of life, using a prospective cohort of children adopted at birth and their adoptive mothers who were assessed at 9, 18 and 27 months. To examine early appearing, psychiatrically-relevant gene-environment correlations, measurements of proximal factors in young children's family environment and child outcomes were then related to indicators of disorder-linked genes, in the form of detailed diagnostic and symptom-level measurements of birth mother psychopathology.

Gene environment correlation (*r*GE) refers to three distinct processes (Plomin, DeFries, Knopik, & Neiderhiser, 2013). *Passive* gene-environment correlation occurs when the same set of genes that influence parental care also, when passed from parent to child, influence child behavior. This form of *r*GE represents a confounding of putative environmental effects by genes, and as such must be taken into account when investigating the environment). *Active r*GE refers to the tendency for genetically-influenced traits to affect the kinds of environments that individuals select and choose, such as a peer group or romantic partner. *Active r*GE may be increasingly important during development, and the consequences of these choices could affect subsequent risk for psychopathology (Reiss & Leve, 2007). *Evocative r*GE correlation occurs when genetically-influenced traits or behaviors evoke systematic responses from the environment. For example, if a child is genetically predisposed to be irritable or aggressive, a parent may respond to these characteristics with anger, criticism or rejection. Such changes in the quality of parental care, could directly impact on subsequent maladaptive development and therefore mediate the effects of genes; or these environmental responses might amplify or compound genetic effects on a risk-related trait, and thereby, in turn, increase risk for child maladjustment. There is good reason to believe that evocative *r*GE, the focus of the current inquiry, may be the most important form of *r*GE in early development, when opportunities for the active selection of

environments is quite limited and child effects on parental well-being and parenting have been well established. (Bell, 1968; Shaw & Bell, 1993)

When considering what aspects of children's early environments might be most important in the development of psychopathology, and in *r*GE in particular, parental behavior and emotions are key starting points. Several aspects of parenting have been the focus of past developmental research, including distinct parenting dimensions such as warmth, over-reactivity, hostile/rejecting parenting and inconsistent discipline (e.g. O'Leary, Slep, & Reid, 1999), as well as perceived stresses and negative emotions related to parenting (Crnic & Greenberg, 1990; Teti & Gelfand, 1991). The negative facets of parental behavior and experience have often been found to correlate, and may reflect global negative schemas that parents develop regarding their child and their own efficacy as parents (Jones & Prinz, 2005). For example, lab studies suggest that this cluster of parenting behaviors and feelings (which we refer to collectively hereafter as 'parental negativity') aggregate in large part because negative parental perceptions of the child underlie over-reactive parenting and feelings of anger/frustration and helplessness (see O'Leary et al., 1999; O'Leary & Vidair, 2005). A number of studies have suggested that parental negativity correlated with, and precede the emergence of, children's emotional and behavioral problems (O'Leary et al., 1999; Snyder, Cramer, Afrank, & Patterson, 2005; Weaver, Shaw, Dishion, & Wilson, 2008).

A critical question, however, is whether the child's genetic predispositions play a role in the emergence of parental negativity. In view of the role played by parental perceptions of the child in these processes, it is plausible that the parents' responses are partly driven by characteristics of the child, or that they represent the reciprocal interplay between parent and child (Bell, 1968; Del Vecchio & Rhoades, 2010; Verhoeven, Junger, van Aken, Dekovic, & van Aken, 2010). Only genetically-informative studies can directly test whether heritable traits in the child evoke negative responses in the parent. Behavioral genetic studies of parenting have indeed produced quite consistent evidence of *r*GE, particularly in relation to the affective aspects of parenting, such as warmth and negativity/hostility (Kendler & Baker, 2007; Rowe, 1981). For example, a study using a parent-offspring adoption design similar to current report, found that children aged 12–18 years whose birth mothers evidenced multiple indicators of externalizing problems received more negative and harsh parenting from their adoptive parents than those children whose birth mothers did not (Ge et al., 1996). Recent work using extended twin designs has been able to clarify that evocative *r*GE, but not passive *r*GE, is a particularly prominent influence on mothers' negativity and emotional overinvolvement (Narusyte et al., 2011; Neiderhiser, Reiss, Lichtenstein, Spotts, & Ganiban, 2007). Although fewer studies have been conducted in early childhood, Deater-Deckard (2000) found evidence of evocative *r*GE for mothers' reports of child-focused negative and positive affect, as well as directly observed responsiveness in a sample of 3.5 year-old twins (for similar findings with a large twin sample see Larsson et al., 2008). Less still is known about the extent of *r*GE in the first three years of life. Twin studies employing direct observations of global dimensions of parenting, such as sensitivity, have tended not to detect *r*GE during in the first two years of life (DiLalla & Bishop, 1996; Fearon et al., 2006; Roisman & Fraley, 2008). However, in a large population-based twin study, Boivin and

colleagues found evidence of genetic influences on self-reports of parental negativity (particularly over-reactive parenting) as early as 5 months of age (Boivin et al., 2005), which, in keeping with studies of older age groups, suggests that *r*GE may be particularly important in the emergence of parental negativity in early development.

The etiological significance of heritable evocative effects for the development of psychopathology is suggested by several lines of inquiry. First, in Ge et al.'s (1996) adoption work, birth parent antisocial behaviors (drug/alcohol use, antisocial personality disorder) were used to characterize children's genetic risk for externalizing problems, in effect restricting the scope of genetic effects to those specifically linked to adult externalizing disorder. Second, twin findings have shown that genetic influences on negative parenting overlap with genetic influences on child externalizing symptoms during adolescence (Narusyte et al., 2008; Neiderhiser, Marceau, & Reiss, 2013; Pike, McGuire, Hetherington, Reiss, & Plomin, 1996) and childhood (Jaffee et al., 2004). In addition, genetic influences on parenting predict the child's later behavioral problems, after accounting for variance in children's earlier behavioral problems (Burt, McGue, Krueger, & Iacono, 2005; Larsson, Viding, Rijsdijk, & Plomin, 2008; Neiderhiser, Reiss, Hetherington, & Plomin, 1999). However, thus far no genetically-informative studies have tested the independent contribution of *r*GE on child development in the first three years of life.

Almost exclusively, studies of rGE have focused on main effects of genes on the social environment. However, recent work has drawn attention to the potentially important role of environmental moderation of *r*GE (*r*GE x E, see Horwitz & Neiderhiser, 2011; Reiss & Leve, 2007). Moderated *r*GE could arise in two ways. First, *r*GE may appear in response to child traits that are themselves under the control of G x E mechanisms. In other words, *r*GE may be most pronounced when certain genotypes and environments co-occur because these circumstances give rise to evocative traits in the child. A number of social-environmental variables have been found to modulate genetic effects on child behavior and adjustment, including marital disharmony and family conflict (Button, Scourfield, Martin, Purcell, & McGuffin, 2005; Cadoret, Yates, Woodworth, & Stewart, 1995; Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007; O'Connor, Caspi, DeFries, & Plomin, 2003; Rhoades et al., 2011; Rice, Harold, Shelton, & Thapar, 2006), parental depression (Tully, Iacono, & McGue, 2008) and economic adversity (Cloninger, Sigvardsson, Bohman, & von Knorring, 1982; South & Krueger, 2011; Tuvblad, Grann, & Lichtenstein, 2006). To the extent that such child traits lead to associated responses in the social environment one would expect to observe moderated rGE. Second, moderated *r*GE could occur as a result of environmental conditions directly altering how susceptible a parent is to becoming evoked by a genetically influenced child trait. Accordingly, it is notable that data suggest that early negative parental reactions may be more pronounced under conditions of marital conflict (O'Leary & Vidair, 2005), economic distress (Mills-Koonce et al., 2007) or parental depressed or anxious mood (Lorber & Slep, 2005). Thus, via either of these pathways we would hypothesize that *r*GE may be moderated by the presence or extent of marital problems, economic distress, and parental affective symptoms. Direct evidence in support of this has been reported by Ulbricht and colleagues (Ulbricht et al., 2013), who found greater

genetic influences on maternal parenting negativity (i.e., greater *r*GE) under conditions of poorer marital adjustment in a sample of adolescent twins and siblings and their parents.

In the current report, using data from a prospective adoption study (the Early Growth and Development Study, EGDS, see Leve et al., 2013), we aimed to test the role of *r*GE in relation to parental negativity in the first two years of life. We sought to focus specifically on *r*GE mechanisms linked to psychopathology in two ways, by a) restricting the scope of genetic effects to those related to birth mother psychopathology, and b) by examining the longitudinal association between *r*GE and child emotional and behavioral problems. In so doing, we directly tested the role of rearing parent negativity in mediating the effects of disorder-linked genes on child maladjustment. Finally, we examined the extent to which these *r*GE effects were moderated by family context, with a particular focus on adoptive family characteristics that are likely to play a moderating role as we have just reviewed: marital problems, economic distress and adoptive parent affective disturbance. The use of a prospective adoption design allowed us to test these key questions concerning gene-environment interplay in early development whilst ruling out any effects of passive gene-environment correlation.

Methods

Participants

The participants were 561 families recruited as part of the Early Growth and Development Study (EGDS), an ongoing, multi-site longitudinal, adoption study (Leve et al., 2013). Participants were recruited from adoption agencies across the United States if they met the following criteria: 1) adoption was domestic, 2) the baby was placed within 3 months post-partum, 3) the baby was placed with a non-relative adoptive family, 4) the baby had no known medical conditions and 5) the adoptive and birth parents were able to read or understand English at an eighth-grade level, and 6) the adoption was a domestic placement. The mean child age at adoption placement was 6.2 days (*SD* = 12.4 days). The adoptive parents were typically college educated, middle- to upper-class families. The adoptive mothers' mean age was 37 years (SD=5.64). Ninety-one percent of the adoptive mothers were Caucasian. Birth mothers typically had less than a college education and had household annual incomes less than $25,000. Birth mother mean age was 24.8 (SD = 8.51). Seventy percent of the birth mothers were Caucasian. Detailed information regarding the composition and representativeness of the sample is presented in Leve et al (Leve et al., 2013). The adoptive parents contributed questionnaire data regarding parenting during home visits conducted when the children were 9, 18, and 27 months of age. In this report, we focus exclusively on adoptive mothers' reports for assessing parenting negativity, and use adoptive fathers' reports to obtain independent information regarding the child's temperament. We chose this strategy for two reasons. First, in order to maximize power we sought to conduct the smallest possible number of statistical tests, focused on the strongest hypothesized effects. Second, doing so allowed us to independently measure temperament in a way that limited potential bias associated with the effects of shared method variance. Data on birth mother psychopathology was obtained through diagnostic interview and via repeated assessments of symptom scores when the infant was 18 and 27 months of age. A

subset (n = 25, 4.4 %) of adoptive families included divorced single fathers or two adoptive fathers. In these families, the father deemed the primary caregiver completed the measures labeled as "adoptive mother." Space precluded repeatedly qualifying the use of the label "adoptive mothers."

Measures

Adoptive Mother Parenting Negativity—At all three times of assessment (9, 18, and 27 months), we collated data from adoptive mothers using three well-validated scales (from three different questionnaires) relating to negative parenting behavior and feelings: 1) *The Parenting Scale (*Arnold, O'Leary, Wolf, & Acker, 1993). This widely used and well-validated instrument asks parents to endorse the extent to which they use a range of ineffective parenting strategies on a 7-point scale. The Overreactive parenting subscale includes negatively and positively worded items related to parents' tendencies to endorse becoming angry, irritable and harsh when their child misbehaves or is otherwise challenging. Negative examples include "I raise my voice or yell", or "I get so frustrated that my child can see I'm upset". Positive examples include "I handle it without getting upset", "things don't get out of hand". Internal consistencies of the scales (Cronbach's alpha) at 9, 18 and 27 months were .70, .78 and .79 respectively; 2) *Parenting Self-Efficacy Scale* (Teti & Gelfand, 1991) is a 10-item questionnaire measuring feelings of competence as a parent in relation to several caregiving areas, such as knowing what a child wants or needs and how to manage their distress. Each item is rated on a 4-point scale reflecting their degree of confidence in each area, from "not good at all" to "very good". Scale scores are composed of the sum of these 10 items. Internal consistencies across waves 9 through 27 months were . 73, .72 and 74 respectively; 3) *Parenting Daily Hassles Scale* (PDHS, Crnic & Greenberg, 1990) is a 20-item questionnaire measuring the extent to which parents feel hassled and stressed in the parenting role and in their daily dealings with their children. Parents rate the frequency of individual items (5-point scale) and whether it represents a problem for the parent (yes or no). In the current study, we focused solely on the frequency of hassles. In terms of content, the instrument has been used as two inter-correlated scales comprising 8 items reflecting hassles and stress associated with daily duties and chores associated with parenting and 7 items reflecting hassles specifically associated with the child's challenging behavior. As the PDHS was originally devised for toddler and preschool-age children, it was not surprising to find that 5 of the 15 items were rated as "not applicable" by more than 15% of the sample when administered to parents at 9 months, including such items such as "being nagged, whined, or complained to", "child doesn't listen without being nagged" or "referee needed for sibling fights" (this last item being deemed not applicable in many cases across all ages). Thus, to ensure consistency of scaling across ages (which is necessary for the growth curve analyses used in this report see Stoel, van den Wittenboer, & Hox, 2004), these items were excluded. The remaining 10 items were combined into a single scale, which had acceptable levels of internal consistency at each wave of testing (9 months alpha = .81, 18 months alpha = .76, 27 months alpha = .76).

Birth Mother Psychiatric Diagnosis: Composite International Diagnostic Interview (CIDI, see Andrews & Peters, 1998)—The CIDI is a comprehensive, fully standardized diagnostic interview based on the DSM-IV criteria, devised to be used by non-

clinical staff. The test-retest reliabilities reported in the literature for each disorder range from kappa= .45 to .63. Birth mothers were interviewed in person by trained research staff when the study infants were 18 months of age. In the current sample, 13.7% of birth mothers received a lifetime diagnosis of Social Phobia, 22.2% Specific Phobia, 28.6% Major Depression, (7.9%), 1% Panic Disorder, 7.3% Generalized Anxiety Disorder, 3.7% Agoraphobia, 6.7% Antisocial Personality Disorder, 26.3% Drug Abuse and 30.5% Alcohol abuse.

Birth Mother Psychiatric Symptom Inventories—To create a robust multi-method operationalization of birth mother liability to externalizing and internalizing psychopathology, the above diagnostic data were supplemented with diagnostically relevant self-report data, all except one of which (novelty seeking) were obtained on two separate occasions (4 and 18 months postpartum), standardized and then averaged. These self-report instruments were: The *Beck Anxiety (BAI) and Depression (BDI) Inventories*. The BAI is a widely used 21-item self-report measure of anxiety with acceptable reliability and validity. Respondents are asked to indicate the degree to which they are bothered by specific symptoms of anxiety (i.e. terrified or afraid, numbness, sweating) in the past week on a 4-point scale ranging from *not at all* to *severely*. The internal consistency of the BAI was .91 and .92 at the two assessment points. The BDI is a well-established and widely used measure of depressive symptoms with acceptable reliability and validity. Participants are asked to choose one of four statements that range from positive to depressed feelings about life in the past week. Internal consistencies were .92 and .91 at the two assessment points. Because the BAI and BDI scales were highly correlated (r = .70) they were standardized and averaged to create an overall index of affective symptomatology. The *Elliot Social Behavior Scale* (Elliott, Huizinga & Ageton, 1985) is a 38-item self-report questionnaire examining the extent to which adults engage in a range of delinquent or antisocial behavior (e.g., stealing, damaging property, carrying a weapon, αs = .75 and .68, respectively). Finally, we chose the Novelty Seeking scale of the Temperament Character Inventory (Cloninger et al., 1993) as a continuous trait linked to substance abuse. This scale assesses adults' tendencies to seek highly exhilarating sources of stimulation, as well as impulsiveness and excitability. The scale's internal consistency was satisfactory (α = .72). It is important to note that while birth father data was collected in this study, we chose not to use it for this paper *a priori* because of the high rates of missing data (<50% of cases had data from birth fathers).

Family Context Moderators—*W*e measured three areas of the adoptive family's context that previous research indicated may moderate genetic effects on caregiving or child development: 1) Economic Distress, 2) Parent Affective Symptoms, and 3) Marital Problems. *Economic Distress* was computed as the standardized average of three scales obtained over the three assessment periods (9 months, 18 months and 27 months) of a questionnaire regarding family satisfaction with their financial situation (Conger, Ge, Elder, & Simons, 1994). The items concerned whether or not (on a 5-point scale) families experienced difficulties buying essential family items (e.g., clothes, food), making ends meet (e.g., paying bills), or making financial cutbacks in the last year. The internal consistency of the combined scale was satisfactory (α = .82). *Parent Affective Symptoms* were computed as the average of adoptive mother and father's standardized scores for

anxiety and depression (using the aforementioned Beck questionnaires) over the three assessment periods (alpha = .86). *Marital Problems* was computed as the average across three waves and across adoptive mothers' and fathers' reports of marital harmony using the Marital Relationship Questionnaire (Booth, Johnson, & Edwards, 1983). The internal consistency of the combined scales was alpha = .91.

The Child Behavior Checklist 1.5 – 5 Years (CBCL, Achenbach & Rescorla, 2000)—The CBCL is a widely used and well-validated instrument for the assessment of children's emotional and behavioral problems. Adoptive mothers and fathers completed the CBCL when the child was 27 months. The scale consists of 99 items, each scored from 0–2, indicating whether a problem behavior is "Not true"," Sometimes True" or "Very True" with respect to the target child. Items are summed and age-normed scaled to create two overall factors reflecting Internalizing Problems (e.g., "too fearful and anxious") and Externalizing Problems (e.g., "hits others", "disobedient at school", "argues a lot"). In the current study, internal consistencies were good for the Internalizing (mother α = .73; father α= .77) and Externalizing (motherα = .87; father α=.88) scales.

Covariates: Temperament—Adoptive fathers completed two questionnaires regarding infants' temperament when the infants were 9 months, the *Infant Behavior Questionnaire* (Rothbart, 1981) and the *Infant Characteristics Questionnaire* (Bates, Freeland, & Lounsbury, 1979). The Infant Behavior Questionnaire yields 6 scales reflecting 1) activity level (α = .81), 2) distress to limitations (α = .85), 3) Distress to novel stimuli (α = .71), 4) Duration of orienting (α = .77), 5) Smiling and laughter (α = .86), and 6) Soothability (α = . 78). The Infant Characteristics Questionnaire was used to obtain an overall index of infant difficulty (irritable, prone to negative emotions, α = .87). Both instruments are well validated and the scales demonstrate good internal consistency. Given the focus of this paper on evoked negativity in adoptive parents, we focused on the two distress scales from the IBQ (distress to novel stimuli and distress to limitations) and the overall difficultness score from the ICQ. We chose adoptive father's assessments of the child's temperament to avoid the problem of bias that might be caused by relying on the same informant when examining temperament and parental negativity.

Adoption Openness—To account for the possibility that contact between adoptive and biological families could confound any apparent genetic effects we assessed the degree of openness in the adoption arrangements using a composite measure of perceived adoption openness averaged across the three waves (9, 18 and 27 months) from biological mothers and adoptive mothers and fathers (see Ge et al., 2008). Interrater agreement was high (*r* range = .72 – .85, *p* values all < .001).

Perinatal Risk—A further threat to the validity of detected genetic effects in the adoption design are perinatal factors; thus we conducted detailed assessments of perinatal obstetric complications using birth mothers reports of: 1) Maternal/Pregnancy Complications (e.g., illness, exposure to drugs), 2) Labor and Delivery Complications (e.g., prolonged labor, cord complications) and 3) Neonatal Complications (e.g., prematurity, low birth weight) using a pregnancy screener and a pregnancy calendar method developed for the study (derived from

Caspi, Moffitt, Thornton, & Freedman, 1996). A comprehensive coding system for perinatal risk was devised for scoring the data based on the McNeil-Sjostrom Scale for Obstetric Complications (McNeil & Sjostrom, 1995) (see Marceau et al., 2013 for more detail). The original Obstetric Complications scale has established reliability and validity (McNeil et al., 1994).

Missing Data

Because not all participants provided complete data, and because excluding such cases can undermine statistical power and bias parameter estimates (Allison, 2003) we employed the Full Information Maximum Likelihood (FIML) method, which uses all the available data to estimate the parameter estimates of a model (by calculating the log-likelihood of the data for each observational unit separately). This approach is clearly superior to mean substitution and listwise deletion, and of comparable performance to multiple imputation (Allison, 2003; Schafer & Graham, 2002). The primary source of missing data was missing psychiatric information concerning the birth mothers. All analyses were conducted using Mplus version 7 (Muthen & Muthen, 2012).

Data Analysis

Latent growth curve (LGC) analysis is a structural equation modeling approach to longitudinal data, which estimates parameters representing the initial level (or intercept, usually the first time point) of a measure and its linear or non-linear growth over time. These overall effects are modeled as latent variables whose means represent the grand average at time 1 (the intercept) and the average growth (slopes) over time, respectively. LGC models also allow estimation of each individual's intercept and trajectory, which are captured by individual-level variance in the latent variables representing the intercept and slopes. Once estimated, the variances—or individual differences—in the intercepts and slopes may then be related to a range of other constructs (e.g., correlated with other measured or latent variables). In the current paper, we employed three separate indicators of parental negativity, and so *multivariate* latent growth curve modeling was used. This extension of LGC analysis simultaneously estimates a latent growth curve for each measurement and then models the inter-relations between their respective intercepts and slopes. These inter-relations are assumed to reflect two underlying factors related to a) common variance in their intercepts and b) common variance in their slopes. The two factors therefore represent the extent to which the intercepts of each measure correlate with each other, and the extent to which the slopes of each measure correlate with each other, and could be assumed to reflect the growth of a general tendency or common factor (i.e., manifesting across multiple measures/ domains) unfolding over time. In so doing, the model minimizes measurement error in both the estimate of the intercept and slope of the common factor, and efficiently summarizes the shared properties of several measurements taken repeatedly over time. These error-free latent variables can then be related to other constructs of interest. In the current paper, we regressed these latent intercept and slope variables on our key indices of genetic influence, environmental moderators, and their interaction. A schematic diagram describing the statistical model is shown in Figure 1.

After checking model fit using standard indices (Comparative Fit Index [CFI] and Root Mean Square Error of Approximation [RMSEA]), our main hypotheses were tested by comparing models where the key regression paths were estimated freely with a nested submodel in which they were constrained to zero. The difference in the likelihood ratio statistic between the two models was used to derive significance tests. Individual model regression/path coefficients are also reported.

In this study our primary hypotheses concerned *r*GE and moderated *r*GE, which translates analytically into genetic main effects and gene-environment interactions on environmental outcomes (the parenting negativity latent intercept and slope). To minimize the type I error rate, we tested all hypotheses using a joint test (2 *df*) of association between genetic indices or variables representing GxE interaction in relation to the latent intercept and slope of parental negativity. Follow-up analyses were only conducted when the joint test was significant. In all, we tested 8 such joint tests; 2 tests of genetic main effects for internalizing and externalizing adult psychopathology respectively and 6 tests of gene-environment interaction (birth mother internalizing and externalizing liability against each of three environmental moderators). As the terms representing these effects were correlated (in some cases quite strongly), we employed a bonferonni adjustment corrected for the level of correlation amongst the tests (the average correlation across all 8 predictor variables was $r = .43$). Using this correction, overall family-wise error rate is maintained at <.05 if the per-test alpha level is set to .016 (see Perneger, 1998).

Results

Overview

Before performing our primary analyses, we took a number of steps to develop our indices of genetic risk, check for genetic effects on our main environmental moderators (economic distress, marital problems, adoptive parent affective symptoms), and establish our model for describing the growth of parental negativity from 9 to 27 months of age. These sections are presented first, before turning to the main analyses, where we tested the effects of genetic effects and gene-by-environment interactions on the growth of parenting negativity over time.

Genetic Risk: Birth Mother Psychiatric Diagnoses and Symptom Scales—The lifetime psychiatric diagnoses (social anxiety disorder, specific phobia, panic disorder, GAD, major depression, agoraphobia, antisocial personality disorder, alcohol abuse and drug abuse) and current symptoms measures (Beck Anxiety/Depression, antisocial behavior, novelty seeking) were used to create overall indices of birth mother psychiatric liabilities for internalizing and externalizing behaviors (Kendler et al., 2003). A two-factor structural equation model, with diagnoses specified as dichotomous indicators of two continuous factors, fit the data fairly well ($\chi^2(53) = 95.72$, $p < .001$, RMSEA = .038; CFI = .94). Allowing residual correlation between two of the symptom measures (Beck Anxiety/Depression and antisocial behavior) further improved model fit ($\chi^2(52) = 76.45$, $p = .015$; RMSEA = .029, CFI = .97). The two birth mother psychopathology latent variables were estimated to correlate with each other at $r = .45$ ($SE = .071$, $p < .001$). Estimated individual

factor scores derived from this latter model for each participant were then used in subsequent analyses as indicators of genetic effects related to birth mother internalizing and externalizing psychopathology.

Genetic Associations With Environmental Moderators

To establish that the putative environmental moderator variables were not directly influenced by the children's genetic predispositions, we ran a series of correlations between our genetic risk variables and our proposed family-context environmental moderators (i.e., adoptive family marital problems, economic distress, and affective symptoms). The correlations were all non-significant and numerically small. For the marker of externalizing genetic influences, the correlations with adoptive family marital problems, economic stress and affective symptoms were, respectively, $r = -.042$, *ns* ($N = 542$); $r = .018$, *ns* ($N = 545$); and $r = -.036$, *ns* ($N = 548$). For the marker of internalizing genetic influences, the corresponding respective correlations were $r = .020$, *ns* ($N = 542$), $r = .018$, *ns* ($N = 545$); and $r = -.036$, *ns* ($N = 545$).

Modeling the growth in parental negativity

The means, standard deviations, correlations and covariances of the indicators of mothers' parental negativity at each time point are shown in Table 1. Fitting the multivariate latent growth curve model initially with no exogenous predictors showed that the model had acceptable fit ($\chi^2(30) = 66.14$, p <.001; CFI = .98, RMSEA = .047). Results from this analysis indicated that there was significant inter-individual variance in the common factors representing the initial level (intercept variance = .75, *se* =.11, $p < .001$) and slope (slope variance =.12, *se* = .02, $p < .001$) in parental negativity and that overall parental negativity increased from 9 to 27 months (linear slope mean =.47, *se* = .03, $p < .001$). The latent growth curve model with standardized parameter estimates is shown in Figure 1.

Testing genetic influences on parental negativity

Having established our model describing the initial level and growth of adoptive mother parental negativity, we next tested for the presence of *r*GE and *r*GE x E by examining genetic main effects and gene-by-family-context interactions on adoptive mother parental negativity. To test for *r*GE main effects, we regressed the initial level and slope factors of parental negativity on the two birth mother psychopathology indices, controlling for adoption openness, obstetric risk and child sex. A likelihood ratio test of the significance of the genetic effects was computed by comparing model fit when the effects of interest were free to be estimated, with when they were forced to be zero. Genetic effects on the intercept and slope of adoptive mother parental negativity were non-significant for the birth mother externalizing factor (joint test: $\Delta\chi^2(2) = 1.76$, *ns*; genetic effect on intercept: $B = -.073$, se = .119, $\beta = -.034$; genetic effect on slope: $B = -.042$, se = .054, $\beta = -.049$) and for the birth mother internalizing factor (joint test: $\Delta\chi^2(2) = .85$, *ns*; genetic effect on intercept: $B = .091$, se = .102, $\beta = .050$; genetic effect on slope: $B = -.029$, se = .047, $\beta = -.039$).

We then tested the full *r*GE x E model, in which genetic, environmental and gene x environmental-context interaction effects were included in the prediction of adoptive mother parental negativity, again controlling for obstetric risk, adoption openness and infant gender.

This model was run separately for each combination of genetic indicator (externalizing and internalizing) and environmental-context variable. Considering externalizing genetic effects first, the model including interactions between genes and adoptive family marital problems revealed evidence of significant interactive effects ($\Delta\chi^2(2) = 15.84$, $p < .001$). The model parameter estimates are summarized in Table 2. The interaction term showed a significant effect on the intercept ($B = .423$, se = .134, $p = 002$; $\beta = .150$) but not the slope ($B = .095$, se = .073, *ns;* $\beta = .083$) of adoptive mothers' parental negativity. To examine the form of the interaction, the predicted values for adoptive mother's parental negativity were plotted for high and low scores on the birth mother externalizing psychopathology factor (+- 1 SD from the mean) and for high and low marital problems (also +- 1 SD). This plot is shown in Figure 2. As can be seen in the plot, even at the earliest age, the association between marital problems and adoptive mothers' parental negativity was larger for infants whose birth mothers scored high on externalizing psychopathology and this effect persisted over time. Interestingly, when we examined these effects on the intercept (i.e., just at 9 months) we found no significant effect of marital problems on adoptive mother parental negativity when birth mother externalizing liability was low ($B = .095$, $SE = .086$, $\beta = .083$, *ns*); but when the externalizing genetic liability score was high, the effect of marital problems on parental negativity was substantial ($B = .442$, $SE = .092$, $\beta = .39$, $p < .001$). To further understand the nature of this interaction, we examined the interaction between birth mother externalizing psychopathology and adoptive family marital problems at the 9-month time point, and examined regions of significance of the genetic effect at varying levels of adoptive family marital problems. This plot is shown in Figure 3, with the regions of significance of the genetic effect (at $p < .05$) shown in gray. The Figure illustrates that infants whose birth mothers had high levels of externalizing psychopathology also experienced higher levels of maternal negativity in the context of high marital problems, but *less* parental negativity when marital problems were low.

The models including the other two interaction terms (externalizing genetic effects x adoptive family economic distress and adoptive family affective symptoms) yielded no evidence of interaction (Economic distress: $\Delta\chi^2(2) = 1.28$, *ns*; Affective symptoms: $\Delta\chi^2(2) = 0.65$, *ns*).

Turning to internalizing genetic effects, none of the joint tests of interaction were significant (Internalizing genetic effects x Marital problems: $\Delta\chi^2(2) = 5.12$, $p = .078$; Internalizing genetic effects x Economic distress: $\Delta\chi^2(2) = 1.35$, *ns*; Internalizing genetic effects x affective symptoms: $\Delta\chi^2(2) = 1.08$, *ns*).

It is important to note that the findings reported above were quite robust to variations in analytic approach. In standard regression analyses, findings were essentially the same as those reported above when a DV was computed as the standardized sum of the three indicators of parental negativity at 9 months (*r*G x E interaction $p = .007$) or as a standardized sum of these indicators across all three time points (*r*G x E interaction $p < .001$).

Does infant temperament account for children's evocative effects?

A series of analyses were conducted with the aim of identifying the evocative characteristic in the child that was associated the effects we observed on adoptive mother parental negativity. However, in no case could we find evidence that the moderated *r*GE effect could be explained by father reports of infant temperament (difficultness, distress to novel stimuli or distress to limitations).

Parental negativity as a mediator of genetic risk on child behavior problems at 27 months

Finally, we investigated the extent to which adoptive mothers' parental negativity might mediate the effect of the gene-by-environment interaction on adoptive children's behavioral problems at age 27 months. To do this, we estimated two final models in which a latent variable representing mothers' and fathers' reports of externalizing and internalizing symptoms were included as dependent variables, respectively. The latent variable representing child outcome was regressed on the maternal negativity intercept, which in turn was regressed on the genetic and environmental main effects and interaction (see Figure 4). From this model we then tested mediation by estimating the indirect effect of the gene-by-environment interaction on child behavioral problems via the maternal negativity intercept using bootstrapped standard errors and confidence intervals (1000 bootstrapped samples were taken). For both child externalizing and internalizing problems, the indirect effects were small but significant (Externalizing indirect effect $B = 1.98$, $SE = .69$, $\beta = .070$, $p = .004$; Internalizing indirect effect $B = 1.28$, $SE = .49$, $\beta = .050$, $p = .009$). The path estimates for both models are shown in Figure 4.

Discussion

This study yielded evidence that genes involved in the development of psychopathology may manifest themselves very early in life by evoking maladaptive responses in mothers. The finding adds to a number of emerging, broadly convergent, results that also attest to the potential significance of gene-environment correlation in early development and in risk for psychopathology (e.g., Boivin et al., 2005; Harold et al., 2013). A wealth of past studies, using quantitative genetic methods, had already highlighted the potential significance of gene-environment correlations in human development, but until quite recently few studies had been specifically designed to observe their emergence in very early childhood; fewer still had used an adoption design, which can rule out complicating effects of passive gene-environment correlation, or used a broad and robust multi-method approach to characterizing birth parent psychopathology, so that inferences regarding the psychopathological relevance of any observed genetic effects are relatively secure. In this paper, we also examined a novel but potentially important manifestation of gene-environment correlation referred to as moderated *r*GE (Horwitz & Neiderhiser, 2011; Leve et al., 2007).

The findings of the study indicated that genetic factors linked to adult psychopathology, evidenced via birth mother psychiatric diagnoses and symptom measures, may be capable of evoking a series of inter-linked negatively toned reactions in adoptive mothers, characterized jointly by a tendency to over-react to challenging behavior, feelings of

powerless in the parenting role, and perceptions of stress in daily dealings with the child. This outcome, from the point of view of the parent, likely represents the accumulation of numerous 'micro-parenting' events that gradually lead the parent into an exasperated, helpless or antagonistic state of mind with respect to the child. A host of studies indicate that these parenting processes impact negatively on the child's emotional and behavioral development (Johnson, Cohen, Kasen, Smailes, & Brook, 2001; Jones & Prinz, 2005; Miller-Lewis et al., 2006; Teti & Gelfand, 1991; Weaver et al., 2008), and indeed are the target of several intervention programs (Sanders, Markie-Dadds, Tully, & Bor, 2000; Webster-Stratton & Hammond, 1997). Critically, the data from our study suggest that these evoked processes may emerge as early as 9 months of age. Consistent with previous adoption studies (Ge et al., 1996), we found that adoptive mother parental negativity was specifically linked to birth mother externalizing psychopathology, and not internalizing psychopathology. Furthermore, the genes involved in these early appearing *r*GE processes (as indicated by birth mother externalizing psychopathology) appeared linked to the child's subsequent behavioral problems, as reported by adoptive mothers and fathers at 27 months.

It is essential to note, however, that we did not find evidence of direct genetic main effects of birth mother psychiatric status on parental negativity. Instead, the evoked parenting processes were only observed when the adoptive parents' marital relationship was also experiencing stress and difficulty. Seemingly, the results indicate that marital problems may be particularly and selectively important in increasing the sensitivity of mothers to reacting negatively to the child's heritable traits. These moderated *r*GE findings are highly complementary to those reported by Ulbricht and colleagues (Ulbricht et al., 2013) in adolescents, as well as an earlier report from the EGDS sample showing that adoptive family marital problems were more strongly associated with toddler (18-month) anger/frustration when birth mothers scored highly on temperamental frustration (Rhoades et al., 2011).

A final important feature of the results of our study was that genetic effects did not appear to represent simple 'risk factors' for negative parenting. Instead, children whose birth mothers had a history of externalizing disorder appeared most likely to receive negative parenting when the adoptive family experienced higher levels of marital stress, but *least* likely to do so when marital quality was high. Thus, these findings suggest that children from biological parents with externalizing problems may evoke maladaptive care when environmental circumstances are unfavorable, but more optimal care when environmental conditions are supportive. We might refer to this phenomenon as 'parental differential reactivity' (cf. child differential susceptibility, Belsky & Pluess, 2009). One plausible hypothesis is that infants that are highly sensitive to context may, under optimal circumstances, be very engaging, interactive and rewarding for parents, but when circumstances are more difficult these same characteristics are experienced as overwhelming or frustrating. In that regard, it was notable that we were unable to identify dimensions of child temperament involved in evoking more or less negativity among mothers in this sample, using fathers' ratings of infant difficultness or negative affect (distress to novelty and distress to limitations). Future research may therefore benefit from a consideration of other domains of child behavior that are not captured by these indices of infant temperament, such as context-sensitivity, social engagement or attentional control. For example, child exuberance may be a positive and

engaging characteristic when there is little stress within the family, but a strain on parents when there is a high degree of stress.

These results add to a growing body of evidence that testifies to the close interplay between genes and environments in the development of psychopathology. Much work is still needed before a thorough understanding of the specific genetic mechanisms involved is achieved. Nevertheless, it is notable that several studies have replicated an association between the GABRA2 polymorphism and alcohol abuse, drug dependence and antisocial behavior (Agrawal et al., 2006; Covault, Gelernter, Hesselbrock, Nellissery, & Kranzler, 2004; Dick, Bierut, et al., 2006; Fehr et al., 2006), and found these effects to interact with environmental moderators including, notably, marital conflict (Dick, Agrawal, et al., 2006) and parental monitoring (Dick et al., 2009).

Our data suggest that the environmental moderation and mediation of genetic effects associated with adult externalizing psychopathology may begin very early in development and may center on the mothers' perceptions of parenting and of the child, which may in turn partially mediate the effect of risk-related genes on children's behavioral adjustment. These adjustment problems may represent an early-appearing pathway in the etiology of adult externalizing psychopathology (Moffit, Caspi, Dickson, Silva, & Stanton, 1996). The close interplay between genes and environments in these unfolding developmental processes may imply that the observed genetics' effects may be malleable to environmental modification. If the effects observed in this study can be shown to causal, new and important modes of intervention suggest themselves. Our research could indicate that effective early intervention for adult externalizing disorder may be achieved by disrupting processes of gene-environment correlation, either by directly supporting parenting in the early toddler years or by treating the marital relationship, or both. There is quite good evidence that marital interventions can have positive effects on both parenting and child outcomes (Cowan & Cowan, 2002), and we speculate that these treatment effects may work, partially or entirely, by strengthening the capacity of couples to support each other's parenting, thereby dampening the potentially negative effects of evocative child characteristics, some of whose origins lie in the child's genotype.

Despite these positive findings, the current study suffers from several limitations that need to be considered. First, the results rely on parental reports of parenting behavior, which, though well suited for detecting the tendencies and affective experiences associated with parental difficulties in childrearing, are also susceptible to reporter bias. Furthermore, while they index relevant processes in the emergence of child emotional and behavioral problems, they may only indirectly identify the interaction patterns most proximally implicated in them. Further work combining parental reports of negativity with direct observations of parent-child interactions would be invaluable in refining our understanding of the interactive processes involved. However, with this limitation in mind, our use of fathers as a reporter of both the magnitude of moderating factors and child behavior at 27-months avoids, in large measure, common source effects that are typically associated with parental self-reports. Second, the choice of an adoption design brings with it several notable strengths, particularly the clean separation of genetic from environmental influences and the capacity to rule out passive *r*GE, but it also carries with it two inherent limitations. The first is that

the range of adversity in the adoptive family environment is more limited than the general population, and hence the findings of the current study may not apply to more disadvantaged contexts. Second, although the infants in this study were placed in the adoptive family very early in life, we cannot rule out antenatal effects, such as antenatal stress or exposure to toxins or drugs. This is particularly important given the relatively high rates of alcohol and drug abuse that we observed in the birth mothers involved in this study. Efforts were made to collect high quality data from birth mothers regarding alcohol and drug use during pregnancy, as well as a range of other indicators of obstetric risk, so that these could be controlled for in our analyses. However, such measures cannot be assumed to be without their limitations. The findings of the current study need to be replicated and would benefit from replication using alternative designs, such as longitudinal twin designs or even longitudinal cohorts employing genome-wide Complex Trait Analysis or related methods (Yang et al., 2011).

In summary, the current study found evidence that genes involved in the development of externalizing disorder manifest themselves in the first two years of life ‘outside the skin’, as a spectrum of negative maternal behaviors and feelings towards the child. The study suggests that the marital relationship plays a critical gate-keeping role in the family system, by increasing or decreasing mothers’ liability to this genetically-driven reaction.

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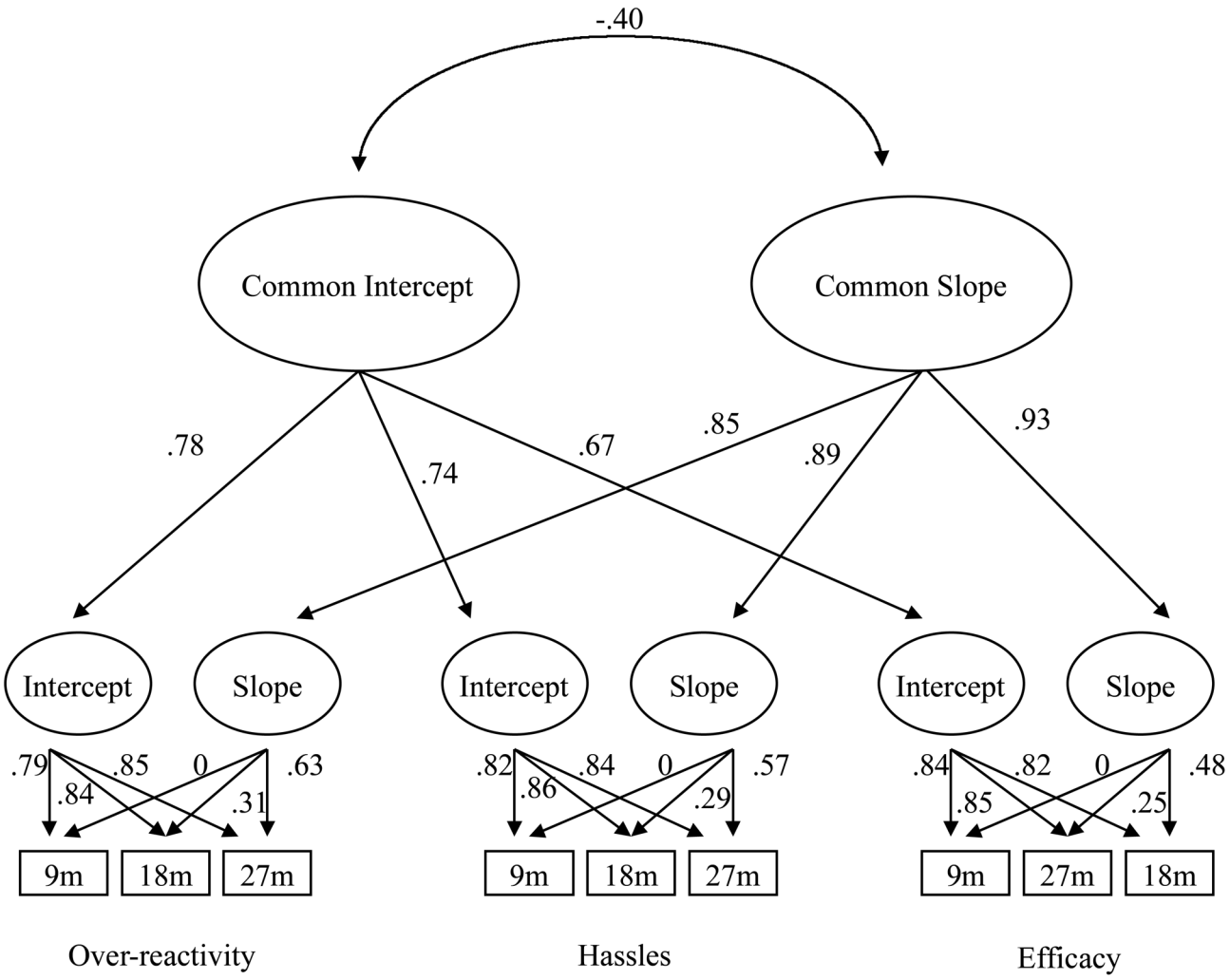

Figure 1.
Multivariate Latent Growth Curve Model of Adoptive Mother Parental Negativity

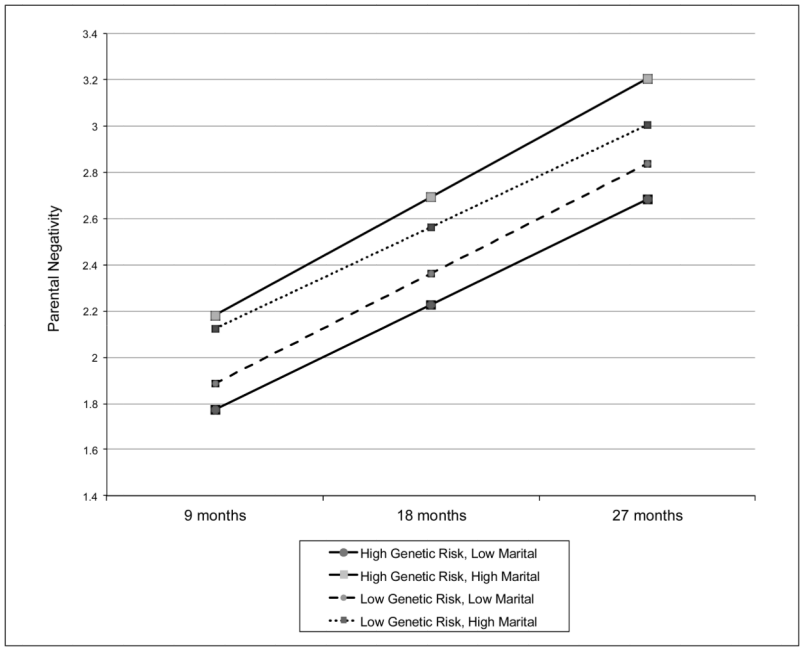

Figure 2.

Latent trajectories of adoptive mother parental negativity by birth mother externalizing disorder liability and adoptive family marital problems

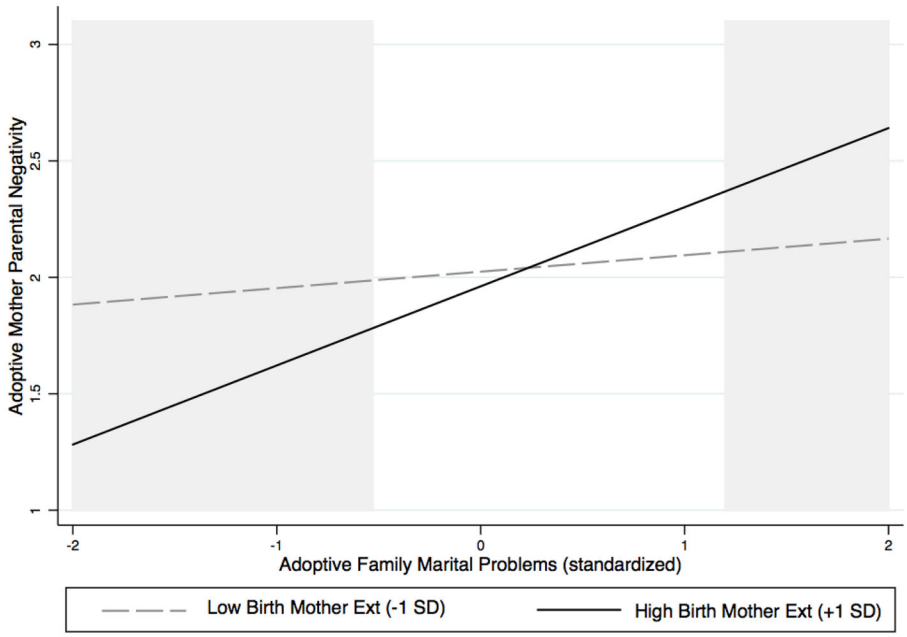

Figure 3.

Interaction between adoptive family marital problems and birth mother externalizing psychopathology in relation to parental negativity at 9-months (regions of significance of genetic effect shaded in gray)

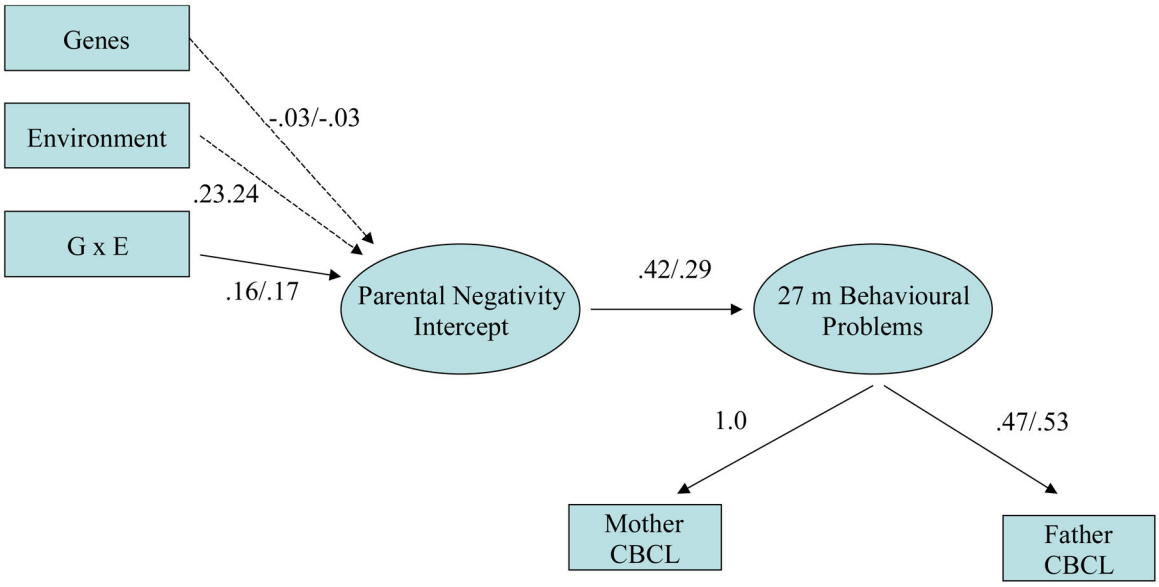

Figure 4.

Longitudinal model testing the role of parental negativity in mediating GxE effects on child adjustment

Note: paths for model testing effects on externalizing problems and internalizing problems respectively shown separated by a '/'

Table 1

Descriptive Statistics and Variance-Covariance Matrix of Indicators of Parental Negativity from 9 to 18 months

	Indicators of Parental Negativity								
	Hassles 9m	**Hassles 18m**	**Hassles 27m**	**Efficacy 9m**	**Efficacy 18m**	**Efficacy 27m**	**Overreactivity 9m**	**Overreactivity 18m**	**Overreactivity 27m**
					Descriptives				
Means	18.52	19.08	19.66	10.05	10.43	10.44	1.99	2.46	2.92
SDs	5.53	5.18	5.25	1.36	1.32	1.37	1.38	1.34	1.30
N	505	520	491	531	515	488	527	513	488
					Covariance/Correlational Matrix[1]				
Hassles 9m	30.55	0.66	0.60	0.36	0.33	0.23	0.38	0.35	0.28
Hassles 18m	18.79	26.87	0.67	0.24	0.25	0.19	0.31	0.35	0.26
Hassles 27m	17.54	18.18	27.59	0.18	0.29	0.32	0.26	0.38	0.39
Efficacy 9m	2.74	1.71	1.28	1.86	0.63	0.55	0.32	0.23	0.20
Efficacy 18m	2.41	1.71	1.99	1.14	1.75	0.69	0.27	0.34	0.34
Efficacy 27m	1.76	1.36	2.30	1.03	1.25	1.86	0.19	0.30	0.38
Over-reactivity 9m	2.93	2.21	1.91	0.59	0.50	0.36	1.90	0.59	0.54
Over-reactivity 18m	2.61	2.46	2.66	0.43	0.60	0.54	1.09	1.79	0.71
Over-reactivity 27m	2.02	1.75	2.70	0.35	0.59	0.67	0.96	1.24	1.70

[1]Note: Correlations are presented in the upper triangle of the correlation/covariance matrix, covariances in the lower triangle. Variances appear along the diagonal.

Table 2

Results of Multivariate Growth Curve Modeling with Genetic and Environmental Predictors of Common Intercept and Slope

	Latent Growth Curve Factors of Parental Negativity							
	Intercept				***Linear Slope***			
Predictors	**B**	**SE**	***Z***	***p***	**B**	**SE**	***Z***	***p***
				Adoptive Family Marital Problems				
Adoptive Family Marital Problems	0.247	0.061	4.039	<0.001	−0.001	0.029	−0.039	0.969
Birth Mother Externalizing Factor	−0.074	0.11	−0.674	0.500	−0.053	0.056	−0.946	0.344
Interaction	0.423	0.134	3.153	0.002	0.095	0.073	1.301	0.193
Adoptive Family Marital Problems	0.245	0.062	3.918	<0.001	0.002	0.029	0.079	0.937
Birth Mother Internalizing Factor	0.051	0.001	0.515	0.607	−0.031	0.047	−0.657	0.511
Interaction	0.228	0.115	1.980	0.048	0.02	0.066	0.301	0.764
				Adoptive Family Economic Distress				
Adoptive Family Economic Stress	0.088	0.033	2.685	0.007	0.013	0.015	0.871	0.384
Birth Mother Externalizing Factor	0.686	0.625	1.097	0.273	−0.164	0.329	−0.498	0.618
Interaction	−0.086	0.07	−1.228	0.219	0.014	0.037	0.364	0.716
Adoptive Family Economic Stress	0.085	0.033	2.61	0.009	0.013	0.015	0.825	0.409
Birth Mother Internalizing Factor	0.663	0.575	1.153	0.249	−0.309	0.323	−0.956	0.339
Interaction	−0.067	0.066	−1.01	0.312	0.033	0.038	0.857	0.392
				Adoptive Family Affective Symptoms				
Adoptive Family Affective Symptoms	0.119	0.022	5.348	<.001	0.004	0.011	0.381	0.703
Birth Mother Externalizing Factor	−0.001	0.179	−0.001	.998	−0.099	0.093	−1.064	0.287
Interaction	−0.013	0.05	−0.256	0.798	0.019	0.025	0.747	0.455
Adoptive Family Affective Symptoms	0.121	0.022	5.604	<0.001	0.005	0.011	0.442	0.658
Birth Mother Internalizing Factor	0.17	0.177	0.962	0.336	−0.021	0.083	−0.258	0.797
Interaction	−0.038	0.051	−0.745	0.456	−0.003	0.024	−0.121	0.903

Note: All parameters are corrected for the effects of child gender, obstetric risk and adoption openness