HHS Public Access

Author manuscript

Child Dev. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Child Dev. 2023 ; 94(4): e231–e245. doi:10.1111/cdev.13924.

Developmental trajectories of behavioral inhibition from infancy to age seven: The role of genetic and environmental risk for psychopathology

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Abstract

The present study leveraged data from a longitudinal adoption study of 361 families recruited between 2003 and 2010 in the United States. We investigated how psychopathology symptoms in birth parents (BP; M_{age} = 24.1 years; 50.5% – 62.9% completed high school) and adoptive parents (AP; M_{age} = 37.8 years; 80.9% completed college; 94% mother-father couples) influenced children's Behavioral Inhibition (BI) trajectories. We used latent growth models of observed BI at 18 and 27 months, and 4.5 and 7 years in a sample of adopted children (Female = 42%, White = 57%, Black = 11%, Multi-racial = 21%, Latinx = 9%). BI generally decreased over time, yet there was substantial variability in these trajectories. Neither BP nor AP psychopathology symptoms independently predicted systematic differences in BI trajectories. Instead, we found that AP internalizing symptoms moderated the effects of BP psychopathology on trajectories of BI, indicating a gene by environment interaction.

Behavioral Inhibition (BI) is a temperament profile first used by Kagan (1999) to describe a group of 21-month-old infants who were overly cautious of, and withdrew from, unfamiliar stimuli (Garcia Coll et al., 1984). The BI profile is characterized by shy and reticent behaviors, including clinging to the caregiver, vigilance, and avoidance of novel social situations, even in non-threatening contexts. In follow-up investigations, Kagan et al. (1984) reported that childhood BI was preceded by a profile of high reactivity earlier in infancy, characterized by greater limb movements, distress, and back arching in response to novel stimuli. Indeed, longitudinal studies indicate that high negative reactivity at four months predicts increased levels of BI across late infancy and early childhood (Fox et al., 2001), more social reticence and avoidance through adolescence (Kagan et al., 2007), and increased

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risk for social anxiety (Chronis-Tuscano et al., 2009). Together, these studies indicate that at high initial levels of BI there is modest stability and continuity in the BI phenotype from toddlerhood through adolescence. Thus, charting trajectories of behaviorally inhibited tendencies during this period can help better understand long-term developmental and clinical outcomes.

Behavioral Inhibition and Risk for Anxiety

Decades of research suggest that childhood BI is one of the single, most reliable predictors of anxiety symptoms and disorders (Clauss & Blackford, 2012). Specifically, stability of high BI throughout childhood and continuity of the inhibited phenotype from infancy to childhood and into adolescence is associated with an increased anxiety risk. For example, children who retain their high inhibited tendencies through childhood (i.e., stability) show a marked increased risk for social anxiety during adolescence (Chronis-Tuscano et al., 2009). In a meta-analysis, Clauss and Blackford (2012) reported that behaviorally inhibited children were three to four times more likely to develop Social Anxiety Disorder (SAD) by age 15, with a significant odds ratio of 7.59. Similarly, toddlers who show continuity of BI into middle childhood and adolescence are also at a greater risk for social anxiety (Degnan et al., 2014).

Therefore, understanding the factors that contribute to the stability and continuity of BI will help identify and target specific processes for the prevention and treatment of anxiety. The current study used a genetically-informed design to examine trajectories of child BI from 18 months to 7 years, specifically testing how a genetically influenced propensity for psychopathology and environmental exposure to caregiver psychopathology symptoms may contribute to continuity and change in BI over time.

Despite strong links between high levels of BI and anxiety, roughly 60% of behaviorally inhibited children do not grow up to develop clinical levels of anxiety (Fox et al., 2021), attesting to the heterogeneity of BI trajectories. This heterogeneity also suggests the potential for endogenous and exogenous factors that may canalize trajectories towards risk or resilience. Indeed, Henderson et al. (2018) characterizes the development of BI ‘in-context’ through a transactional model of development, emphasizing the role of within-child and contextual factors in shaping developmental trajectories from BI to psychopathology. In line with Bronfenbrenner’s Bioecological theory (Bronfenbrenner & Ceci, 1994), Henderson et al. (2018) highlighted that behaviorally inhibited tendencies contribute to and color children’s social experiences given their sensitivity to novel and unpredictable environmental inputs. In addition, individuals in the proximal environment (e.g., parents, peers, siblings, teachers) may respond to inhibited tendencies in systematic ways, shaping the behaviorally inhibited child’s idiosyncratic experience of the social world (Reck et al., 2013). For example, parents may respond with increased over-solicitous behaviors (Coplan et al., 2009), teachers’ biases about shyness may influence their evaluation of inhibited children (Nadiv & Ricon, 2020), and peers may respond with greater disengagement and rejection (Walker et al., 2015). The cumulative effect of parental, teacher, and peer responses may potentiate children’s inhibited tendencies over time (Henderson et al., 2018). Together, these transactional processes become the developmental engines that canalize unique

trajectories for inhibited children, be it towards stability and amplification of inhibited tendencies or towards reduction in BI over time.

Many studies have investigated endogenous, or within-child, factors that exacerbate the risk for anxiety in behaviorally inhibited children (Buss & Qu, 2018; Sylvester & Pine, 2018). These studies suggest that individual differences in reactive cognitive control (Valadez et al., 2021), attention (Pérez-Edgar et al., 2010), and neural correlates of overcontrol (Poole et al., 2020) may all contribute to an underlying neurobiological profile of BI that predicts continuity of inhibited tendencies and increased risk for social reticence and anxiety (Sylvester & Pine, 2018). While these findings have strengthened our understanding of subgroups of behaviorally inhibited children at greater risk for maladaptive outcomes, the role of children's genetic propensity for psychopathology in shaping trajectories of BI remains understudied. Furthermore, there is a paucity of research examining how early environmental factors may moderate change or continuity of inhibited trajectories (Anaya & Pérez-Edgar, 2019; Liu & Pérez-Edgar, 2019), while also incorporating child-driven effects on the rearing environment (Liu et al., 2020).

Parent Internalizing Symptoms and Child Behavioral Inhibition

Links between parent psychopathology symptoms and child BI seem to be domain specific to internalizing and not externalizing tendencies (Essex et al., 2010), despite the two being modestly correlated in childhood (Willner et al., 2016). Children of parents with higher levels of depressive and anxiety symptoms show higher rates of BI (Rosenbaum et al., 2000) and increased inhibition in novel contexts (Reck et al., 2013). Parents with higher internalizing symptom levels may show lower sensitivity and be less effective when emotionally scaffolding their children (Seymour et al., 2015; Shaw et al., 2006), which may contribute to the stability of child BI (Grady & Karraker, 2014). While these studies capture the influence of the rearing environment on BI, the active role of the behaviorally inhibited child must also be considered.

Children are not passive recipients of caregiving (Bell, 1979; Belsky, 1984), thus children's behaviorally inhibited tendencies can also influence the rearing environment (Ryan & Ollendick, 2018). Furthermore, many genetically-informed studies show that children's genetically-influenced characteristics can elicit distinct parenting behaviors (Avinun & Knafo, 2013), and parent psychopathology symptoms (Ahmadzadeh et al., 2019) to influence the rearing environment. Therefore, to better capture the role of parent internalizing symptoms in reinforcing BI, we need to model children's own inherited propensity for internalizing symptoms as one child characteristic that may evoke internalizing symptoms in their rearing environment.

Parents with higher levels of internalizing symptoms may be more likely to avoid social interactions, hindering children's access to a more diverse range of contexts and limiting most of their interactions to the home environment. Concomitantly, children's genetic propensity for psychopathology may also lead to a profile of behaviors (e.g., dysregulated fear in non-threatening contexts, frequent negative affect in social settings, and difficulty soothing) that increases parent's own reticence in social interactions (Buss et al., 2013). As

a result of limited social stimulation, children may struggle to habituate to novel interactions and situations, which may reinforce BI over time. For example, behaviorally inhibited children who receive home care are more likely to retain an inhibited profile compared to behaviorally inhibited children who attend daycare (Fox et al., 2001). Daycare settings may provide more diverse social opportunities for behaviorally inhibited children to experience and solve social problems with peers.

An early environment characterized by limited social interactions may be particularly detrimental to behaviorally inhibited children. Indeed, children of mothers with higher avoidant behaviors, specifically, seem to show higher distress to novelty (Reck et al., 2013). Parents with higher levels of internalizing symptoms may themselves be affected by novel situations and by their own child's genetic predispositions for inhibition, hindering parents' ability to scaffold their child when navigating settings that elicit reticent and avoidant tendencies. Furthermore, these parents may also directly model avoidant and inhibited strategies to their children as normative coping mechanisms. For example, Lester et al. (2009) reported that more anxious parents seem to extend their own threat interpretive biases onto their children's environment, suggesting that these parents may socialize their children to interpret ambiguous situations as threatening. The incidence of BI is higher in children of parents who report higher levels of anxiety, panic disorder, and comorbidity with major depression (Rosenbaum et al., 2000; Warren et al., 2003). Although correlational, these studies support Henderson et al.'s (2018) transactional model, suggesting that repeated exposure to parent internalizing symptoms may amplify BI over time.

In contrast, parents with low levels of internalizing symptoms may provide emotional scaffolding to their inhibited child more efficiently, modeling how to engage in novel situations and socializing their child to pursue more social interactions. For example, toddlers characterized as shy and inhibited display less social wariness when their mothers verbally encourage them to play and interact with unfamiliar peers (Grady & Karraker, 2014). Furthermore, parents with low levels of internalizing symptoms may have better self-regulation skills (Paulus, 2015), which may provide them with greater behavioral and emotional flexibility to parent an inhibited child, and to foster the child's own development of self-regulation (Sun et al., 2020). In turn, better self-regulation in behaviorally inhibited children may reduce risk for anxiety (White et al., 2011).

In summary, the current literature suggests that parent internalizing symptoms may be a critical factor that exacerbates child BI over time through environmental exposure to parental modeling and over-solicitous behaviors. Studies of bidirectional relations between BI and parenting also suggest that inhibited tendencies influence the very parenting behaviors that may contribute to amplification of BI over time (Ryan & Ollendick, 2018). However, most of these findings have come from studies examining parents rearing their own biological children. Genetically related families share both their genes and their rearing environment, making it impossible to disentangle characteristics of the rearing environment from genetic factors that may contribute to the amplification of BI. Furthermore, previous studies have documented significant genetic contributions to variability and continuity of BI (Saudino & Cherny, 2001; Smith et al., 2012), suggesting the need to disentangle genetic from environmental effects.

A Behavioral-Genetics Framework

Twin studies report moderate to high heritability of BI (Saudino & Cherny, 2001) and genetic influences on the relation between temperamental inhibition and psychopathology (Goldsmith et al., 2007), suggesting that links between parent psychopathology and child BI may be explained by shared genetic variance. The MacArthur Longitudinal Twin Study (Plomin et al., 1993) collected repeated measures of temperament (including BI) in a twin sample between 14 and 36 months. Change in BI trajectories, whether toward amplification or reduction in inhibited tendencies, may also be explained by genetic factors. For example, Saudino and Cherny (2001) used longitudinal ACE models to compute covariation among twin siblings to estimate additive genetic effects (*A*), the common shared environment (*C*), and the unique environment (*E*). They reported that continuity of BI from 14 to 20 months and across 20, 34, and 36 months was explained, in part, by genetic influences. However, Saudino and Cherny (2001) also reported that genetic and environmental influences also accounted for change in BI over time, which was evident from new genetic and nonshared environmental effects emerging at later ages.

Together, these findings suggest that continuity and change in children's BI can be accounted for by both environmental and genetic influences. To test possible mechanisms of environmental and genetic transmission, both independently and transactionally, we will examine trajectories of child BI using a parent-offspring adoption design.

Adoption designs are ideal for clarifying rearing environmental influences on children's BI because birth parents (BPs) do not provide the rearing environment but do provide genes (and birth mothers provide the prenatal environment). Thus, associations between adoptive parent (AP) psychopathology symptoms and child BI are not confounded by genes shared by parents and children. This genetically-sensitive design can help us understand the extent to which rearing parents' psychopathology symptoms directly – via the rearing environment – exacerbate or reduce child BI over time. We can also test associations between BP psychopathology symptoms and their biological children's BI to estimate the role of genetic factors in this association. It should be noted that twin studies, rather than adoption studies, are better suited to estimate genetic influences on children's behavior. However, adoption studies uniquely provide sensitive tests of gene by environment interactions by modeling potential interactions between AP and BP psychopathology symptoms in relation to the developmental trajectory of child BI.

Using the same adoption sample presented here, Brooker et al. (2011) reported that higher birth mother's social phobia was associated with higher inhibited behaviors in their 9-month-old infants, but only for infants with better attention control (i.e., greater sustained attention on a toy) and in the context of higher AP self-reported anxiety symptoms. Brooker et al. (2014) then examined child internalizing symptoms at 18 and 27 months and found a direct effect of AP anxiety symptoms on children's internalizing symptoms. Additionally, they found that higher infant attention control predicted lower internalizing symptoms only for infants of BPs with higher anxiety symptoms in the context of low AP anxiety symptoms.

These results suggest that when measured concurrently, the impact of internalizing manifestations in the early environment may be dormant (Brooker et al., 2011), and only emerge over time as infants become more active agents in their own environment. However, these studies only measured BI concurrently or across two occasions during infancy, underscoring the need to examine repeated measures of child BI and investigate longer-term genetic and environmental influences. Additionally, these prior studies tested genetic effects on child BI through specific associations with BP anxiety levels. While manifestations of AP internalizing and externalizing symptoms may distinctly and specifically shape infants' rearing environment, prior work (Caspi et al., 2014) has proposed that a general genetic liability for psychopathology may better capture how genetic vulnerability unfolds throughout development into manifestations of psychopathology. Indeed, empirical studies indicate that a general genetic psychopathology factor is more parsimonious and stable over time compared to a bifactor model of internalizing/externalizing dimensions (Murray et al., 2016), and has a significant single nucleotide polymorphism heritability of 38% (Neumann et al., 2016). When the general genetic psychopathology factor is included in the bifactor model, domain-specific genetic effects of internalizing and externalizing significantly decrease (Caspi et al., 2014), suggesting that using this general psychopathology factor may increase sensitivity to capture genetic vulnerability for child BI transmitted from birth parents to children.

In summary, genetically-informed studies of BI converge on one key finding: neither higher genetic propensity for internalizing nor higher internalizing symptoms in the child's environment are strongly predictive of child BI during infancy or early childhood anxiety risk. Instead, higher genetic propensity for psychopathology may condition how infants respond to, and are influenced by, their environment, an effect that may change across development. However, to our knowledge, no study has tested how trajectories of observed BI may vary as a function of the interaction between general genetic propensity for psychopathology and environmental exposure to internalizing symptoms.

The Present Study

To address these research gaps, the present study used data from 361 children adopted at or near birth, their BPs, and their APs, and examined the influences of BP psychopathology and AP internalizing symptoms on the developmental trajectories of child BI, observed at 18 months, 27 months, 4.5 years, and 7 years of age. Additionally, we examined the influence of AP internalizing symptoms, along with AP externalizing symptoms, to statistically test domain specificity in the relation between environmental exposure to internalizing symptoms and the development of child BI. Genetic risk is indicated by BP psychopathology (e.g., internalizing problems, externalizing problems, and substance use), whereas environmental risk is indicated by AP self-reported internalizing (i.e., anxiety and depression) and externalizing (i.e., substance use and antisocial behaviors) symptoms, averaged across mother and father to create an AP index of internalizing and externalizing symptoms.

We hypothesized that: (a) across the sample, BI trajectories would decrease from 18 months to 7 years in line with noted declines in BI as regulation strategies become more effective

(Fox et al., 2021), (b) higher genetic risk for psychopathology and higher environmental risk for internalizing, but not externalizing, symptoms would independently predict higher initial levels of BI and stable or increasing BI trajectories over time, and (c) higher genetic risk coupled with higher AP internalizing symptoms would lead to increasing BI trajectories, suggesting a dual risk model of gene by environment (GxE) interaction on the stability and continuity of BI.

Method

Participants

Data was collected from the Early Growth and Development Study (EGDS), a longitudinal sample of 561 adopted children and their birth and adoptive parents recruited in two cohorts (Leve et al., 2019). Recruitment details are described in the Supplement (S1) and study procedures are described in Leve et al. (2019). We include Cohort I, a set of 361 triads of adopted children, APs (357 mothers; 362 fathers), and BPs (359 mothers; 119 fathers), who provided behavioral data.

Children (58% male) were 57% White, 11% Black/African American, 21% Multi-racial, 9% Hispanic/Latinx, and 2% other. Birth mothers were 71.7% White, 11.1% Black/African American, 2.9% American Indian/Alaska Native, 1.7% Asian-American, 0.3% Native Hawaiian/Pacific Islander, 4.6% reported more than 1 race, and 0.9% did not report race. Birth fathers were 72.4% White, 8.7% Black/African American, 0.8% American Indian/Alaska Native, 4.7% reported more than 1 race, and 4.7% did not report race. A small number of birth mothers (6.9%) and birth fathers (8.7%) identified as Hispanic.

Most BPs (50.5% of birth mothers and 62.9% of birth fathers) reported high school as their highest completed level of education. Mean age of BPs was 24.1 years (SD = 5.9) at the time of their child's birth. Most participating BPs (96.6%) reported their annual household income, with 43.7% of birth mothers and 42.1% of birth fathers reporting earnings of less than $15,000 per year. Most APs were white (> 90%) and married (> 98%) at study enrollment. APs (80.9%) most frequently reported education levels of a 4-year college degree or higher. Mean age of APs was 37.8 years (SD = 5.5) at the adopted child's birth. Median annual household income ranged between $70,000 and $100,000.

Measures

Observed Behavioral Inhibition at 18 and 27 Months—Children's inhibited behaviors were observed during the Stranger Task, a standardized assessment derived from the Laboratory Temperament Assessment Battery (Lab TAB) that measures infants' and toddlers' responses to unfamiliar social encounters (Goldsmith & Rothbart, 1999; Planalp et al., 2017). Video recordings of the Stranger Task were coded by trained coders using a coding system adapted from Kochanska (1991). Child's proximity and inhibition to stranger, proximity to caregiver, inhibition to exploration, and active exploration were rated on a 4-point scale ranging from 1 (*not inhibited/fearless/explorative*) to 4 (*very inhibited/fearful/not explorative*) during each 30s interval. Global ratings of the child's fearlessness with the toys and inhibition towards toys were also collected. Inter-rater reliability based

on double-coding 15% of videos ranged from ICC = 0.791 to 0.941 at 18 and 27 months. Details of task implementation, coding, and reliability are provided in Supplement S2.

Observed Behavioral Inhibition at 4.5 Years—Inhibited behaviors were observed at age 4.5 during the Scary Mask episode of the Preschool Lab TAB (Goldsmith et al., 1993; Buss et al., 2013). In the Scary Mask episode, an experimenter first engages the child while wearing a scary mask, then later takes it off to reveal that it is just a mask. This encounter is designed to elicit novelty and mild threat in the child's environment. Child fear, distress, approach, avoidance, and gaze aversion were coded by trained staff on a scale from 0 (*behavior is absent*) to 3 (*behavior is frequently present*), and fidgeting behaviors were rated as present or absent. Based on double-coding 15% of videos, inter-rater reliability or kappas when applicable ranged between 0.770 and 0.986. Task implementation and coding details are fully described in Supplement S3.

Observed Behavioral Inhibition at 7 Years—Children's inhibited tendencies were observed at age 7 using the Speech task, a revised version of the *Storytelling* episode from the middle childhood Lab TAB (Goldsmith et al., 2010). In this task, children give a speech while facing a camera that will record their performance, creating a stressful but non-threatening situation (Almas et al., 2015). The interviewer rated their global impressions of children's nervousness, excitement, fidgeting, whispered speech, and comfort on a scale from 1 (*Very true*) to 4 (*Not true*). Task details and interviewers' ratings are fully described in Supplement S4.

Index of Birth Parent Psychopathology—BP psychopathology was assessed by creating composite "genetic risk" scores given genetic overlap across different internalizing disorders, and for internalizing and externalizing symptoms (Marceau & Neiderhiser, 2020). We modeled BP's global risk for psychopathology to more comprehensively capture the genetic profile shared between BPs and children (Allegrini et al., 2020) that could contribute to amplification of BI over time. BP scores were computed via Principal Component Analyses (PCAs) using the following indicators: (a) psychopathology symptom count, (b) diagnosis count, (c) earliest age of onset of disorder from the Composite International Diagnostic Interview (CIDI; Kessler & Üstün, 2004) collected at the 18-month assessment, and (d) proportion of first-degree relatives experiencing psychopathology symptoms (reported at the 4-month assessment) using the Family History-Research Diagnostic Criteria (Andreasen et al., 1977). PCA analyses first yielded three independent components: Internalizing, Externalizing, and Substance Use risk. These components were then shown to load onto a single higher-order component reflecting general psychopathology risk. These genetic risk scores are proxies for the genetic propensity of psychopathology inherited by the child. Birth fathers were difficult to locate, resulting in missing data for their psychopathology risk (64% – 70% missing depending on the PCA indicator). However, birth fathers provide 50% of the offspring's genes and thus are important informants in modeling genetic psychopathology risk. Therefore, birth father reports were included in the PCA analysis, and missing data imputed. Full details of PCA analyses are reported in Marceau et al. (2019) and supporting details and justification for the imputation method are provided in Supplement S6.

Adoptive Parent Internalizing Symptoms—AP internalizing symptoms were indexed by composite scores of depression and anxiety symptoms measured via the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), respectively, when children were 18 months (Steer & Beck, 1997). Cronbach's α indicated good reliability for both AP reports on the BDI (α's range from 0.79 to 0.81) and BAI (α's range from 0.79 to 0.80). These measures were z-scored and averaged to create a parent internalizing composite.

Adoptive Parent Externalizing Symptoms—Externalizing symptoms were indexed by composite scores of substance use and antisocial traits assessed at the 18-month assessment. Substance use was measured via the Composite International Diagnostic Interview - Short Form (CIDI-SF, Kessler et al., 1998), where parents reported their lifetime use of a list of drugs. Endorsement of any drug was coded as a binary variable, such that a score of 0 indicated no drug use, and a score of 1 or greater indicated serious use of at least one drug. Antisocial traits were measured via self-reports on the Antisocial Action questionnaire (Levenson et al., 1995) with good reliability (α = .82).

Control Variables—We included AP reports of openness of adoption, AP divorce, AP household income, BP obstetric complications, child race, and child sex as covariates. Openness of adoption indicated the degree to which APs were open to, had contact with, and knowledge of the BPs. Adoptive children may be more likely to resemble their BPs if they have more contact with them, threatening the assumption of estimates capturing *independent* associations between BPs, APs, and the adoptive child. Most families in the sample reported semi-open (15.7% – 25.4%) and open contact (26.5% – 40%) across the duration of the study, and there was strong agreement between AP and BP reported levels of openness (r = .71 – .84). Thus, we used mean AP openness across the waves that child BI was measured. Correlations between openness and birth and adoptive family measures in this sample are approximately what would be expected by chance (Leve et al., 2010). Divorce occurred in 14% of families during participation in the study and was included to account for the possibility that changes in BI would be influenced by this family event. Obstetric complications were measured through self-report and coding of medical records (88.6% reported ≥ 1 complications; see Marceau et al., 2016 for details). All other covariates were assessed at time of enrollment. The questionnaires and scales used in the current analysis are fully described in Supplement Table S1.

Data Analysis Approach

Data analysis proceeded in five stages. Behavioral tasks intentionally differed across age to capture developmentally sensitive progressions in BI with multiple behavioral codes of BI during each task. We first used a series of cross-sectional Confirmatory Factor Analysis (CFA) to estimate a BI factor at each wave. This approach served as 1) a data reduction technique to create BI composites and 2) a way to standardize BI factor scores across waves for use as indicators in latent growth curve models. CFA results are presented in the Supplement (Table S2). Second, descriptive and correlational statistics were examined among all study variables and relevant covariates.

Third, we used latent growth curve analyses to examine the structure of BI trajectories at the four assessments, 18 months, 27 months, 4.5 years, and 7 years. A latent intercept variable was estimated by setting indicator paths from the 18-month to 7-year BI factors equal to 1. A latent slope variable representing linear change in BI was estimated by setting indicator paths from the 18-month to 7-year BI factors equal to 0, 0.5, 2, and 3.65, modeling the unequal time intervals. A latent slope variable representing quadratic change was also estimated, setting the indicator paths equal to 0, 0.25, 4, and 13.32, respectively. We used a chi-squared difference test to assess significant differences in model fit between the linear and quadratic models. In a fourth step, we added all relevant covariates as predictors of the latent intercept and slope variables. Covariates were trimmed when not significant.

In the final step, we conducted two conditional latent growth models to address the main objective of the study, examining whether BI latent trajectories varied as a function of genetic and environmental risk for psychopathology. In the first conditional model we added BP psychopathology, AP internalizing, and AP externalizing variables as direct and independent predictors of the BI latent intercept and slope parameters. In the second model, we tested GxE interaction effects by further adding the product terms between the BP psychopathology variable and the AP internalizing and externalizing variables, respectively. This step resulted in two product terms: BP psychopathology by AP externalizing symptoms and BP psychopathology by AP internalizing symptoms.

Statistical analyses were conducted in R (R Core Team, 2021). CFAs and growth models were fitted in *lavaan* (Rosseel, 2012), using Full Information Maximum Likelihood (FIML) estimation (Enders & Bandalos, 2001). Significant interaction effects were probed using the *interactions* package (Long, 2019). Specifically, we probed the relation between BI and *time* (i.e., BI trajectories) at 1SD below the mean (lower risk), mean, and 1SD above (higher risk) the mean of BP and AP psychopathology symptom variables.

Results

Cross-sectional CFAs and Correlational Data

Cross-sectional CFAs yielded a 1-factor solution at the 18-month (N=338), 27-month (N=317), 4.5-year (N=272), and 7-year (N=287) assessments. The standardized factor scores were extracted from each CFA. The factor scores from the 18- and 27-month assessments were reverse coded so that positive values indicated high levels of BI. We also tested longitudinal measurement invariance across BI factors to establish partial invariance, indicating that our BI factors reflected the same underlying construct over time. Details of measurement invariance analyses are reported in the Supplement (S5). As indicated in Table 1, BI scores were significantly correlated from 18 to 27 months (r = 0.30, p = .001), the two assessments that employed the same task, and were earliest and closest in time. No other associations between BI factor scores across time were significant (ps > .22). AP internalizing and externalizing symptoms were positively correlated (r = 0.19, p = .001). Only BI scores at the 4.5-year assessment were positively associated with BP psychopathology (r = 0.16, p = .01, all others rs < 0.03, ps > .15). These BI scores were based on the Scary Mask task, which was qualitatively different from the other tasks in that it introduces a degree of fantasy into the social context by presenting a wolf mask to

4-year-old children. Thus, it is possible that this task may capture more extreme inhibited behaviors or a degree of inhibition that may be more heritable, resulting in the differential association noted with BP psychopathology relative to the earlier BI tasks.

Structure of Behavioral Inhibition Trajectories

An unconditional latent growth curve model with a linear trend fit the data well (CFI: 0.934; TLI: 0.869; RMSEA: 0.04; SRMR: 0.04). Based on modification indices, the covariance between the 18-month and the 4.5-year BI scores was freed. The chi-squared difference test comparing model fit between this linear growth model and a quadratic model was not significant $\Delta\chi^2(1) = 3.937$, $p = .139$, suggesting that a quadratic trend did not improve the model fit. Therefore, we retained the linear model as more parsimonious. In this unconditional linear growth model, there was significant variance in the latent intercept (0.259, $p = .001$) but not the slope (0.021, $p = .115$). The mean linear slope (−0.082, $p = .019$) was significant, indicating a linear decrease in BI over time. Raw developmental trajectories of BI scores are shown in Figure 1 as a function of intercept levels (i.e., 18-month BI scores). To this unconditional model we added child sex, child race, adoption openness, obstetric complications, AP income, and AP divorce as covariates. Covariates were trimmed from the model as their addition significantly worsened the model fit, $\Delta\chi^2(14) = 33.05$, $p = .003$, and they did not significantly predict the latent intercept or slope variables ($ps > .213$).

Direct Effects of Birth Parent and Adoptive Parent Psychopathology

Based on the modification indices, we freed the covariance between the 18-month and 4.5-year BI assessments and the intercept of the 7-year assessment. The final model fit the data well (CFI: 0.887; TLI: 0.745; RMSEA: 0.03; SRMR: 0.04) based on RMSEA and SRMR indices. Based on previous reports that CFI and TLI are downwardly biased when sample size is < 500 (Shi et al., 2019) and that RMSEA and SRMR in our model showed excellent fit, we retained this model. There was significant variance in the latent intercept (0.269, $p = .001$), but not slope (0.019, $p = .157$). The mean intercept and linear slope were not different from zero ($M_I = -0.141$, $M_S = 0.023$, ps > .792). The BI latent slope was significantly predicted by BP psychopathology, indicating that higher BP psychopathology scores predicted lesser decreases or flatter slopes in BI trajectories ($\beta = 0.033$, $p = .044$).

Gene x Environment Interaction

The final model with paths from the product terms to the latent intercept and slope fit the data well (CFI: 0.982; TLI: 0.964; RMSEA: 0.01; SRMR: 0.04; unstandardized path coefficients in Figure 2). BP psychopathology and AP internalizing symptoms were positively associated with the BI latent intercept at trend level ($\beta = 0.258$ and 0.270, $ps < .065$, respectively), and AP internalizing symptoms were significantly and negatively associated with the BI latent slope ($\beta = -0.142$, $p < .029$). Additionally, the product term of BP psychopathology by AP internalizing symptoms significantly predicted the BI latent intercept and slope ($\beta_I = -0.129$ and $\beta_S = 0.059$, $ps < .024$). We used simple-slopes and regions of significance analysis to probe this interaction.

Figure 3 shows the simple slopes of low (−1SD), mean, and high (+1SD) levels of BP psychopathology and AP internalizing symptoms (Panel A), and the regions of significance for these slopes (Panel B). These analyses suggested that at low and mean levels of AP internalizing symptoms, BI trajectories were stable over time and did not systematically vary as a function of BP psychopathology. Interestingly, differences in BI trajectories across levels of BP psychopathology only emerged in the context of higher levels of AP internalizing symptoms. For these children, lower BP psychopathology symptoms (< −0.79) were associated with BI trajectories that significantly decreased from 18 months to 7 years (β = −0.09, SE = .04). In contrast, higher BP psychopathology symptoms (> 1.36) were associated with BI trajectories that significantly increased over time (β = 0.10, SE = .04), although it should be noted that the size of this latter subgroup of children was rather small (n = 20).

Discussion

We sought to understand how BI may change over time as a function of the child's genetic and environmental risk for psychopathology, and their interaction. We examined data from a longitudinal adoption study to model trajectories of child BI from 18 months to 7 years as a function of BP and AP psychopathology symptoms. While BI generally decreased over time, there were notable individual differences in trajectories. Our results did not support any direct genetic or environmental effects on BI trajectories. Rather, we noted a GxE interaction effect on the continued high stability of inhibited tendencies over time that was specific to a higher genetic propensity for psychopathology and higher internalizing levels in the adoptive family.

Consistent with our initial hypothesis, BI trajectories across the sample significantly decreased from 18 months to 7 years. It is worth noting that the effect size of this decreasing prototypical trajectory was small (i.e., ECR = .017), and at least one previous study found no change in BI across similar ages (Pérez-Edgar et al., 2010). However, based on the small effect size, it is possible that the smaller sample (n = 80) in Pérez-Edgar et al. (2010) may have limited their ability to detect change over time. One study examining group-based trajectories of BI and social reticence with a similar sample size and age groups to the current report identified a high-decreasing trajectory for the largest percent of the sample (~ 43%) and predicted the lowest risk for behavioral outcomes at age five (Degnan et al., 2014). While Degnan and colleagues used a person-centered approach, making direct comparisons with the present study difficult, the significant negative slope we report here may map onto the high-decreasing group trajectory they reported, and suggest that a decrease over time may reflect the prototypical development of inhibited tendencies from infancy to middle childhood when describing the whole sample.

Indeed, studies that support moderate levels of stability in BI have focused on samples selected for extreme levels of inhibition and grouping of participants based on their stable or changing levels of inhibition over time (Chronis-Tuscano et al., 2009; Fox et al., 2001). In this study, we focused on mapping raw trajectories of inhibited tendencies in an unselected sample of economically well-resourced adopted children from infancy to early school age. In doing so, we show that at the level of the sample, there is substantial variability in the

developmental patterns of inhibited tendencies, indicating that infants exhibit varying levels of inhibition and varying decreasing patterns of inhibition. This decrease over time is in line with the transition to school, a period when peer interactions gain influence. Reinforcement from peers may disfavor inhibited tendencies and reward social engagement, leading to decreases in normative levels of inhibition. This pattern of feedback from peers and adults also reflects Western cultural norms that view shyness as a negative trait (Rubin et al., 2006).

BP, but not AP, psychopathology symptoms independently predicted change in BI, partially in line with our hypotheses. Maternal psychopathology (e.g., anxiety and depression) is associated with higher levels of BI and with greater stability of BI trajectories in genetically-related families (Rosenbaum et al., 2000). Parental modeling and socialization may contribute to these patterns, as parents' beliefs and behavioral transactions with their children may mediate the link between parents' psychopathology and child BI beyond heritable influences on early child temperament (Henderson et al., 2018). However, our results did not fully support this environmental effect, as we did not find a significant independent association between AP internalizing and BI slope that would support a direct role of parental socialization. Additionally, most of these previous studies have almost entirely focused on maternal effects. A major strength of the current analysis is that internalizing symptoms were assessed in both adoptive mothers and adoptive fathers, providing a more comprehensive measure of psychopathology levels in the child's proximate environment.

We found a significant independent association between BP psychopathology symptoms and the BI slope, supporting direct genetic influences on trajectories of inhibition. This effect was no longer significant when GxE interaction effects were incorporated in the model. There are significant genetic influences on average levels of BI, the stability and change of inhibited tendences (Smith et al., 2012), and on the overlap between BI and psychopathology (Goldsmith et al., 2007). The latter finding is consistent with the direct, genetic effect that conventional conceptualizations of temperament usually imply when they describe temperamental tendencies as largely constitutional and biologically-based. However, our results join at least one older study (Eley, 1997) and a more recent body of literature (Brooker et al., 2011; Field et al., 2020) in which direct heritable influences on inhibition and social fear have been absent when GxE interactions are also considered. It is possible that the larger genetic effects previously reported are an artifact of study design, because adoption studies are optimized for detecting specific rearing effects but less sensitive for detecting genetic effects, since the latter are modeled across generations. It is also possible that our BP psychopathology scores, which were estimated using imputations of a large number of missing values, may underestimate direct genetic associations. While our approach was complementary (Malti & Cheah, 2021) by testing commonality in genetic variation for psychopathology in tandem with specificity of internalizing manifestations in the rearing environment, narrowing the specificity of genetic and environmental propensity for internalizing disorders is an important future direction to advance our understanding of risk for high BI. For example, parsing specificity in genetic propensity for anxiety and depression disorders and their influence on BI over time when these symptoms are also present in the rearing environment would be informative for both basic research and prevention and intervention efforts.

The interaction between genetic influence and environmental internalizing and externalizing levels were generally consistent with our hypotheses. We noted a significant interaction between BP psychopathology and AP internalizing, but not externalizing, levels. The specific effect of internalizing symptoms in the rearing environment may be surprising in the context of comorbidity between internalizing and externalizing symptoms (Wright et al. 2013). However, it should be noted that we examined AP internalizing and externalizing symptoms in the same model, controlling for their overlap. The specificity of this effect is in line with BI studies linking inhibited and shy tendencies to increased risk for internalizing problems (Chronis-Tuscano et al., 2009) and a three- to four-fold increase in risk for social anxiety (Clauss & Blackford, 2012). When we probed this interaction, we found that BI trajectories systematically varied as a function of genetic influences but only in the context of higher internalizing levels in the child's rearing environment. Two patterns emerged.

First, children of BPs with lower levels of psychopathology showed BI trajectories that decreased at a faster rate than the decreasing trajectory seen on average for the full sample. A low genetic propensity to psychopathology was associated with an accelerated decrease in BI over time within a rearing environment that may have otherwise reinforced inhibited and shy behavioral expressions. As a result, these children showed a decrease in BI over time that was greater or more drastic than that of children reared by APs with low and average internalizing levels. Although taken at face value these results may suggest a protective genetic effect, a few caveats are worth discussing. In the additive model, BP psychopathology levels significantly predicted the BI slope ($\beta = 0.033$, $p = .044$), indicating that lower BP psychopathology symptoms were associated with lower, or more negative, slopes regardless of AP environment. Although this direct effect did not emerge in the additive growth model, and we prefer not to interpret lower-order interactions when higher-order interactions are significant, it is possible that children with a lower genetic propensity to psychopathology may simply fit a developmental profile of inhibition that will generally decrease over time regardless of rearing environment.

This interpretation would be in line with twin studies reporting significant heritable influences on observed BI (Smith et al., 2012) and heritable contributions to the overlap between BI and psychopathology outcomes (Goldsmith et al., 2007). However, this interpretation is not fully supported by our simple-slopes analysis, which shows that at low and average levels of AP internalizing symptoms, BI trajectories of children with the same lower genetic propensity were not significantly different from the rest of the sample. Instead, our findings suggest that this pattern of accelerated decrease in inhibition was specific to a rearing environment characterized by relatively higher levels of internalizing symptoms. Potentiated decreases in BI may still seem counterintuitive in this context because higher caregivers' internalizing levels are usually interpreted as risk factors and low inhibition and shyness are usually seen as positive (Coplan et al., 2011). However, some research suggests the latter need not always be true.

For example, some studies have reported that very low-inhibited or exuberant children are at risk for conduct disorder and ADHD (Forbes et al., 2017), as well as internalizing problems during the school years (Stifter et al., 2008). We did not test how increases or decreases in BI were associated with later child outcomes. Therefore, the extent of our interpretation

is that children with a lower genetic propensity for psychopathology were specifically and significantly influenced by the higher internalizing levels in their environment. Whether the link between higher rearing internalizing levels and an accelerated decrease in BI over time represents resilience or risk for maladaptation remains a question for future research.

The second pattern that emerged from our simple-slope analysis was in line with our hypothesis, showing that within the context of higher levels of internalizing symptoms in the APs, children of BPs with higher psychopathology symptoms exhibited significant increases in inhibition from 18 months to 7 years compared to the overall sample's decreasing trajectory. These results seem to be in line with a diathesis-stress model (Rende & Plomin, 1992), where higher genetic propensity for psychopathology seems to be compounded by higher levels of internalizing in the rearing environment, leading these children to diverge from the prototypical decreasing trajectory of the sample. These children exhibit trajectories of inhibition and shyness that are reinforced over time, a pattern that is consistently associated with greater risk for anxiety (Clauss & Blackford, 2012). We report this effect with caution, as the size of this subgroup of children in our sample was rather small ($n = 20$), and thus future replication is warranted.

Some limitations of the present study should be noted. First, while our sample's demographic characteristics are comparable to other adoption studies in the U.S. (Plomin et al., 1993), the generalizability of our findings is limited because APs were predominantly white, highly educated, and of medium to high SES status. All these characteristics are more likely to afford these families a privileged extended environment of high support and access to resources in their community that research shows are less readily available to families from underrepresented background, with limited education, and/or low SES (Hoff & Laursen, 2019). The raw BI trajectories we present here are, however, more generalizable because adopted children were more racially diverse than APs. Second, our four observations of BI were not equally spaced over a 7-year period, and it is possible that we may have missed substantial developmental changes taking place in between some of our longer intervals (e.g., 27 months to 4.5 years, to 7 years). A third limitation is that, as mentioned above, the subgroup of children with higher genetic propensity living in homes with APs with higher levels of internalizing symptoms is too small to make strong inferences and should be replicated in the future.

Fourth, we only included AP internalizing symptoms at 18 months in order to focus on early genetic and environmental influences. However, future studies should examine repeated measures of AP internalizing symptoms, perhaps probing whether stable and fluctuating levels of internalizing in the child's proximal environment may lead to distinct BI trajectories. Finally, although our primary goal was to test the interaction between genetic and environmental influences on BI trajectories, understanding how these factors influence the link between BI and anxiety development is equally important, and should be examined in future studies.

In summary, the present study expands the BI literature by modeling for the first time, trajectories of inhibited tendencies in the context of genetically-unrelated families and suggesting that in line with sociocultural perspectives, inhibition seems to, on average,

decrease over time. We also show that BI trajectories systematically differed as a function of genetic influence only in the context of higher internalizing levels in the child's rearing environment. This finding is consistent with the most recent conceptualizations of BI as a developmental phenomenon that is better captured *over time*, through transactional investigations across *multiple levels of analysis*, and which consider individual traits, context, and specific experience (Pérez-Edgar & Fox, 2018). This area of research would further benefit from future studies that investigate associations between trajectories of BI and anxiety risk with genetically informed designs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

The Early Growth and Development Study was supported by grant R01 HD042608 from the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), and the Office of Behavioral and Social Sciences Research (OBSSR), NIH, U.S. PHS (PI Years 1–5: David Reiss, M.D.; PI Years 6–10: Leslie Leve, Ph.D.), grant R01DA020585 from NIDA, the National Institute on Mental Health (NIMH), the OBSSR, NIH, U.S. PHS (PI: Jenae Neiderhiser, Ph.D.), grant R01 MH092118 from NIMH (PIs: Jenae Neiderhiser, Ph.D. and Leslie Leve, Ph.D.), grant R01 DA045108 from NIDA (PI: Jenae Neiderhiser), and grant UH3 OD023389 from the Office of the Director, NIH, U.S., PHS (MPIs: Leslie Leve, Ph.D., Jenae Neiderhiser, Ph.D., and Jody Ganiban, Ph.D.). This research was also supported by grant F99NS120411 from the National Institute of Neurological Disorders and Stroke (NINDS; PI: Berenice Anaya), and grant R01 MH094633 from NIMH (PI: Koraly Pérez-Edgar). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank the birth and adoptive families who participated in this study and adoption agencies who helped with the recruitment of study participants. The data and materials necessary to reproduce the analyses presented here may be shared upon request. The analytic code is available from the first author. Analyses were not pre-registered.

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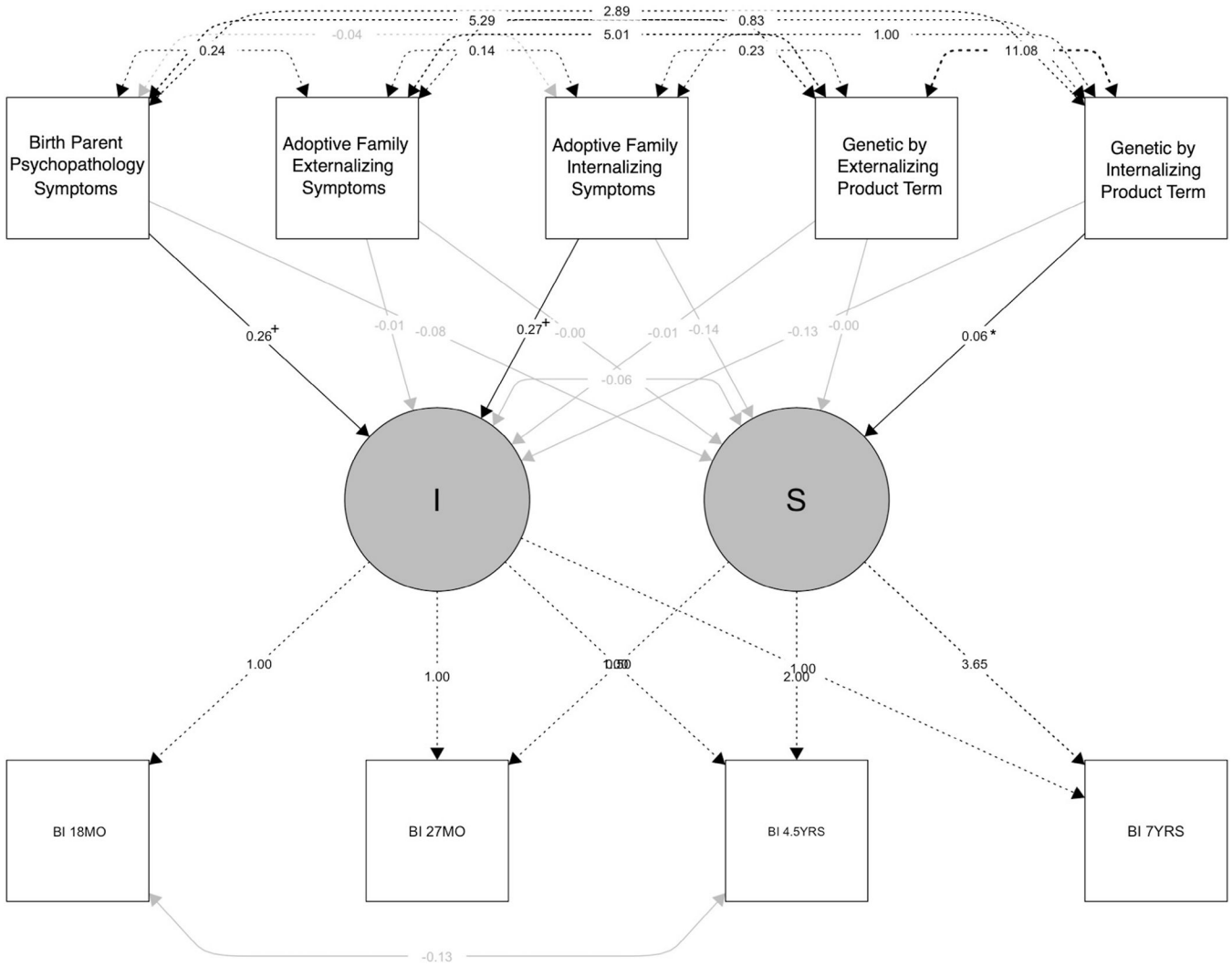

Figure 1:

Raw trajectories of behavioral inhibition (BI) from 18 months to 7 years of age as a function of BI intercept levels. Black slope line indicates the sample's average trajectory.

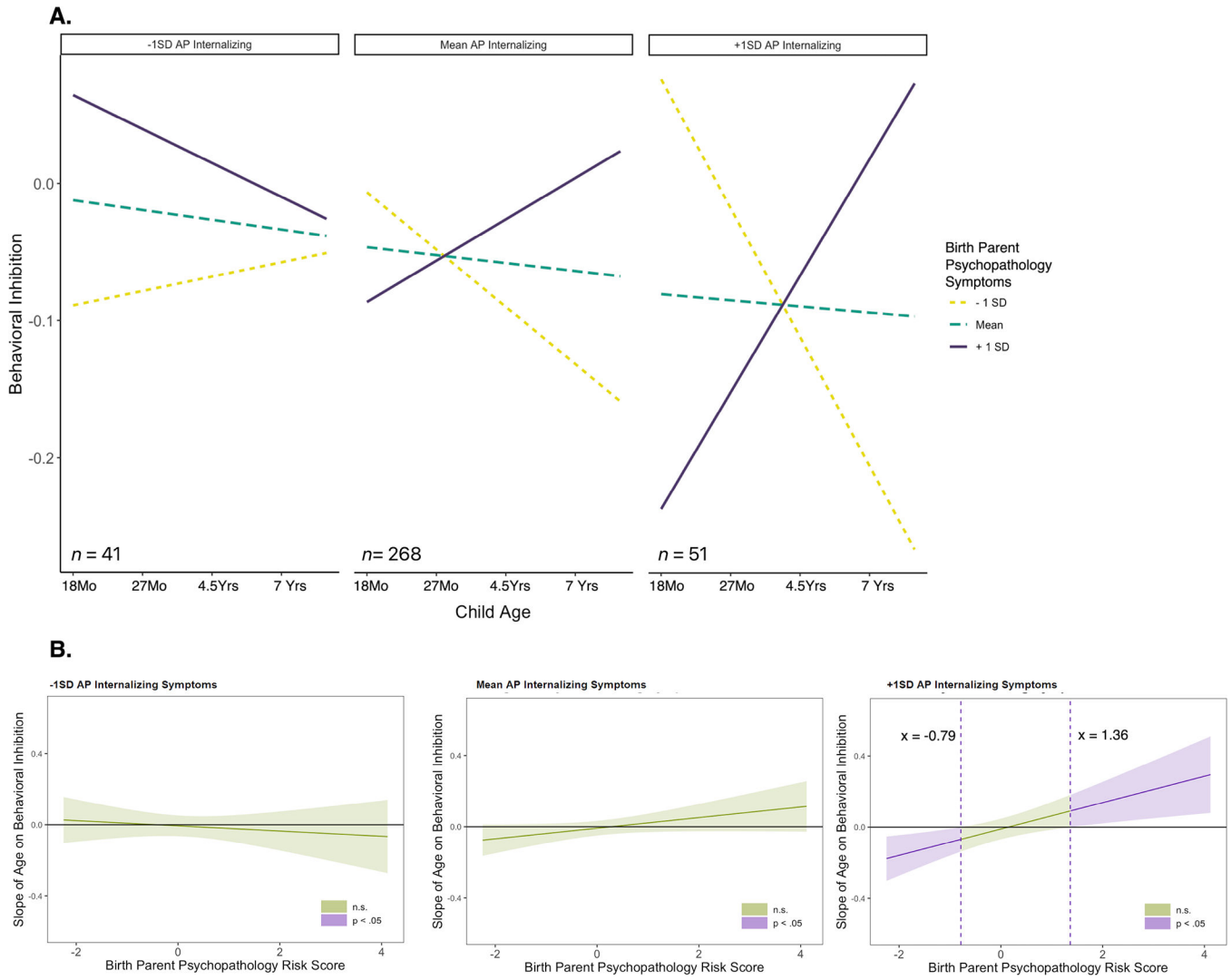

Figure 2:

Model testing the effect of product terms between genetic and environmental risk. Gray paths indicate negative effects. *$p < .05$, +$p < .07$. I, latent intercept; S, latent slope.

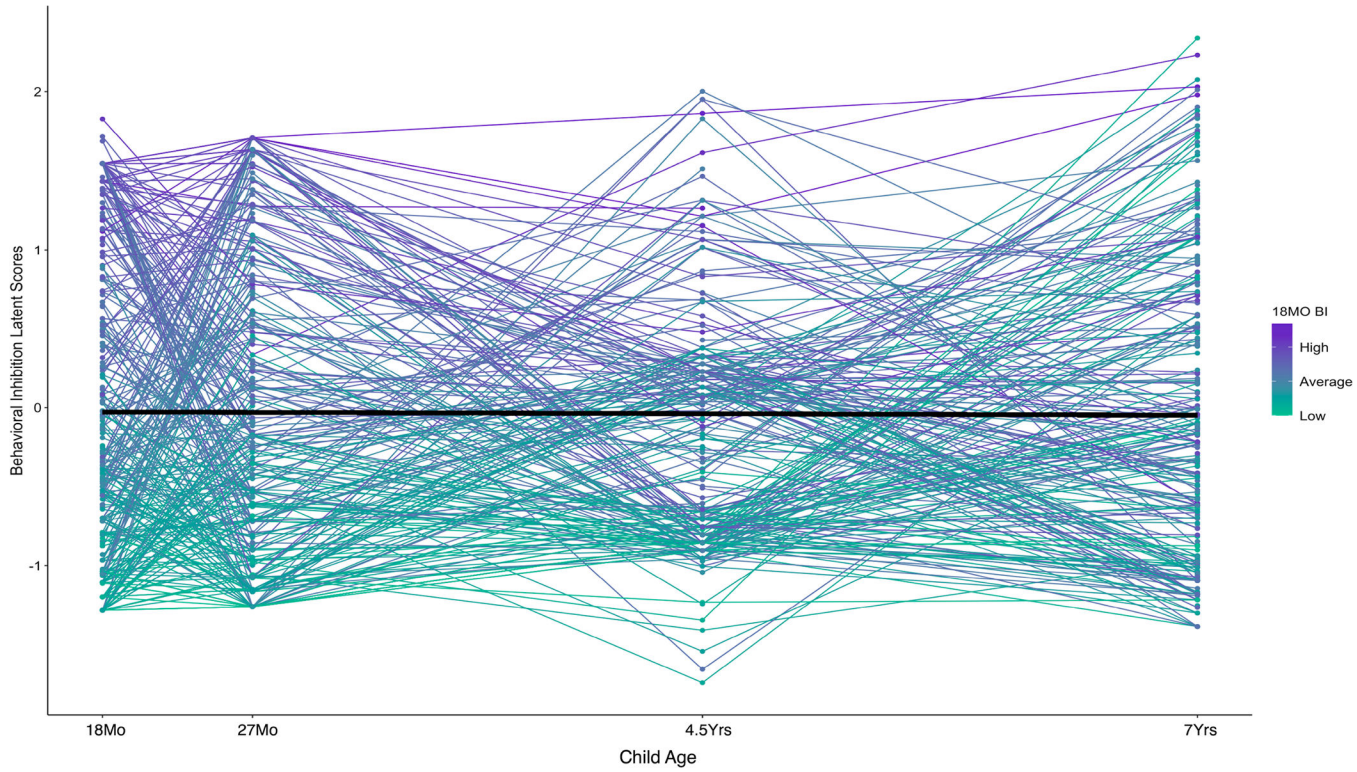

Figure 3:

Simple slopes analysis (Panel a) and regions of significance (Panel b) displaying the relation between BI and child age as a function of BP psychopathology risk scores and low (−1SD), mean, and high (+1SD) levels of AP internalizing symptoms.

Table 1.

Descriptives and Zero-Order Correlations among Study Variables.

	Descriptives		**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**
	M	*SD*							
BI 18 Mo	0.00	0.98	-						
BI 27 Mo	−0.04	0.95	**0.30**	-					
BI 4.5 Yrs	−0.16	0.74	−0.02	0.07	-				
BI 7 Yrs	−0.01	1.00	0.07	0.04	0.08	-			
BP Psychopathology	2.38	1.24	−0.08	0.00	**0.16**	0.03	-		
AP Internalizing	1.97	0.69	−0.01	−0.03	−0.08	−0.02	−0.05	-	
AP Externalizing	2.96	1.18	−0.10	−0.02	0.02	−0.06	**0.16**	**0.19**	-

Note: Significant correlations ($p < 0.05$) are in bold.