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Developmental pathways to social anxiety and irritability: The role of the ERN

Courtney A. Filippi[1], **Anni R. Subar**[1], **Jessica F. Sachs**[1], **Katharina Kircanski**[1], **George Buzzell**[2], **David Pagliaccio**[3], **Rany Abend**[1], **Nathan A. Fox**[2], **Ellen Leibenluft**[1], **Daniel S Pine**[1]

[1]Section on Development and Affective Neuroscience, National Institute of Mental Health, Bethesda, Maryland, 20892

[2]Department of Human Development and Quantitative Methodology, University of Maryland, College Park, Maryland, 20742

[3]Division of Child & Adolescent Psychiatry, New York State Psychiatric Institute, Columbia University, New York, NY, 10032

Abstract

Early behaviors that differentiate later biomarkers for psychopathology can guide preventive efforts while also facilitating pathophysiological research. We test whether the error-related negativity (ERN) moderates the link between early behavior and later psychopathology in two early childhood phenotypes: behavioral inhibition and irritability. From ages 2 to 7 years, children (n=291) were assessed longitudinally for behavioral inhibition (BI) and irritability. BI was assessed via maternal report and behavioral responses to novelty. Childhood irritability was assessed using the Child Behavior Checklist. At age 12, electroencephalogram (EEG) was recorded while children performed a flanker task to measure the ERN, a neural indicator of error monitoring. Clinical assessments of anxiety and irritability were conducted using questionnaires (i.e., Screen for Child Anxiety Related Disorders and Affective Reactivity Index) and clinical interviews. Error monitoring interacted with early BI and early irritability, to predict later psychopathology. Among children with high BI, an enhanced ERN predicted greater social anxiety at age 12. In contrast, children with high childhood irritability and a blunted ERN predicted greater irritability at age 12. This converges with previous work and provides novel insight into the specificity of pathways associated with psychopathology.

Keywords

ERN; behavioral inhibition; irritability; psychopathology; developmental pathways

INTRODUCTION

Error-related negativity (ERN), an electrophysiological marker of error monitoring is a potential psychopathology biomarker (Hanna et al, 2012; Ladouceur et al, 2006; Meyer, Weinberg, Klein, Hajcak, 2012). Data clearly show that the ERN longitudinally links early

*Correspondence to: Courtney Filippi, 9000 Rockville Pike, Bethesda, MD, 20892, 301-402-6955; courtney.filippi@nih.gov.

behavioral inhibition (BI) to later social anxiety (Buzzell et al, 2017; Lahat et al, 2014a; McDermott et al, 2009). However, few studies connect the ERN to other developmental pathways. Thus, it remains unclear if ERN relates uniquely to specific pathways, particularly those involving aberrant, negative-valence, high-arousal responses to threat. To answer such questions on specificity, we compare the associations among BI, ERN, and social anxiety to associations in another developmental pathway involving irritability, an early-life phenotype sharing the aberrant threat-related enhanced response found in BI. In 291 children followed longitudinally from infancy, we test whether early-life phenotyping, combined with preadolescent ERN, predicts social anxiety vs. irritability in pre-adolescence.

The ERN is thought to index error monitoring, a component of cognitive control that is central to adjusting one's behavior in the face of conflict. Larger ERNs have been associated with negative affect (Tucker et al, 1999), and greater response control (Pailing et al, 2002). Studies investigating associations between ERN and *broad classifications of psychopathology* find that larger ERNs map onto internalizing symptoms, whereas smaller ERNs map onto externalizing symptoms; such associations have been found in both children (Hanna et al, 2012; Ladouceur et al, 2006; Meyer, Weinberg, Klein, Hajcak, 2012) and adults (Franken, van Strien, Franzek, van de Wetering, 2007; Hajcak & Simons, 2002; Holmes & Pizzagalli, 2008). However, few studies demonstrate *specific* relations among early childhood phenotypes, the ERN, and clinical outcomes. Evaluating how early childhood phenotypes predict both later biomarker status (such as the ERN) and specific clinical outcomes is important. This can define unique pathways with corresponding profiles in the biological correlates of psychiatric outcomes. Thus, our primary aim was to investigate whether the ERN correlates uniquely with particular clinical correlates of early childhood phenotypes. We focus on two childhood phenotypes that share several common features: behavioral inhibition (BI; an early temperamental phenotype associated with increased risk for social anxiety disorder) and irritability (a phenotype that increases risk for affective disorders particularly among those with elevated irritability sustained over development).

The two phenotypes are similar in measures of attention, affect, and arousal. Both BI and irritability are characterized by aberrant, negative-valence, high-arousal responses to perceived social threat (Henderson, Pine Fox, 2015; Leibenluft & Stoddard, 2013; Perez-Edgar et al, 2011; Salum et al, 2017) and by heightened attention allocation to threat (Hommer et al, 2014; Leibenluft & Stoddard, 2013; Perez-Edgar et al, 2011). However, irritability and BI differ in their *behavioral response* to perceived threat i.e., behaviorally inhibited children tend to *avoid* threat (for review: Fox & Pine, 2012), while irritable children tend to execute an *approach* response to threat (Brotman et al, 2017; Leibenluft, 2017). Since the ERN is thought to index aspects of response control (Pailing et al, 2002), we hypothesized that the ERN manifest unique associations with clinical profiles as a function of these two early-childhood phenotypes. Thus, the ERN could differentially moderate associations between phenotype and psychopathology, a pattern that might arise from the unique role of response control in connecting each early phenotype to specific, later clinical outcomes.

The current study extends the literature by examining specific clinical outcomes in two childhood phenotypes. These outcomes are assessed via careful diagnostic assessments, rather than broad classifications of more general forms of psychopathology. Specifically, we test whether the ERN interacts with early behavior to predict levels of psychopathology concurrent with the ERN assessment, associated with early BI vs early irritability. Previous studies, including similar reports in the current sample (Buzzell et al, 2017; Lahat et al, 2014a; McDermott et al, 2009), found that a ***larger*** ERN influences the strength of the association between BI in toddlerhood and anxiety. Thus, we hypothesize that behaviorally inhibited children who exhibit *larger* ERNs will show greater social anxiety symptoms at age 12. In contrast, previous work in different samples suggests that irritable children who exhibit approach-oriented behavior show relatively diminished error monitoring (Kessler et al, 2016). Therefore, we hypothesize that children with high irritability and a ***blunted*** ERN will show greater irritability symptoms at age 12. This would suggest that variations in a common cognitive process relates to distinct developmental pathways.

Methods

Participants

In early infancy, 779 typically developing four-month-old infants were recruited from the Washington DC metro area via mailings describing a longitudinal study of early temperament. Exclusion criterion included prematurity, low birth weight, developmental disorder, and/or birth complications. At four months infants were invited to participate in a reactivity assessment. A subset of infants (n=291) were selected to participate in further longitudinal visits. Those families that participated in the longitudinal study consisted of a selected sample that exhibited higher negative reactivity and positive reactivity than would be expected from random sampling (see Supplement for additional information on sampling and relation to the phenotypes reported here). Participating families were invited to the lab four times over the first two years of life and then annually until the age of 5 years—at which point the invited visits occurred every 2 years until the age of 12 years. Visits during early childhood consisted of behavioral, questionnaire, and EEG data collection. Children who participated in ERN visits and clinical assessment visits did not differ from those who chose not to participate in these visits on any measure of interest or in terms of sex or maternal education (ps>.627). Table 1 summarizes sample demographics and attrition rates for each of the assessments of interest. Overall, permanent attrition for this sample was very low i.e., < 10%.

Measures

Early Phenotypes.—This sample was originally identified as high risk for developing anxiety and as such there is considerable phenotyping data available to assess BI. In contrast, there is relatively limited work on phenotyping early irritability, which was not a focus of the early-life assessments. In the current study, we aim to balance our phenotypes by relying on methods of assessing irritability that have shown predictive power (Pagliaccio et al, 2018; Wiggins et al, 2014).

To evaluate irritability and behavioral inhibition we utilize maternal report and in-lab measures from age 2 to 7 years. Of note, the approach to phenotyping behavioral inhibition and irritability is based on prior research with these two constructs. With this approach, the analyses attempt to balance a study strength and a study weakness. A strength follows from the fact that we used construct definitions that were consistent with prior work with minor modifications on each construct. A weakness follows from the fact that this prior research used different sources of information across the two constructs.

Behavioral inhibition (BI).: In the current study, as in Buzzell et al. 2017, we assessed BI at ages 2 and 3 by measuring infants' reactions to novel objects and people (for full description, see Fox et al, 2001; White et al, 2011). We then augmented these measures by adding data obtained at ages 4, 5 and 7, when social reticence was assessed by measuring hesitation to engage with a peer in a free-play session (Chronis-Tuscano et al, 2009). In addition, these data on in-lab behavior were supplemented by parental report on temperament questionnaires at each visit i.e., at ages 2 and 3 parents filled out the Toddler Behavior Assessment Questionnaire (TBAQ; social fear subscale at age 2 and 3- ICC= .577, p<.001, 95% CI [.448 .674]); at ages 4, 5, and 7 parents filled out the Child Behavior Questionnaire (CBQ; shyness subscale at age 4, 5 and 7- ICC= .645, p<.001, 95% CI [.586 .699]). The social fear composite of the TBAQ, the shyness subscale of the CBQ, and behavioral measures were standardized at each age and averaged to create a 2- to 7-year BI composite score. This composite score captures both individual variability in a standardized in-lab assessment and parent report, providing a comprehensive assessment of children's behavioral inhibition across several settings.

Early childhood irritability.: Early childhood irritability was assessed using three items from the Child Behavior Checklist (CBCL), a validated parent report of child behavior problems and social competencies. The CBCL is comprised of 120 items, in which the parent rates the child's behavior over the past 6 months on a scale from 0 (not true) to 2 (often true or very true). Parents filled out the CBCL at each lab visit from age 2 to 7 (CBCL irritability scores at age 2, 3, 4, 5 and 7- ICC=.356, p<.001, 95% CI [.276 .442]). For all analyses to follow, we focused on three items that index irritability ("temper tantrums or hot temper", "stubborn, sullen or irritable", "sudden changes in mood or feelings"). Previous reports have identified these items as loading well onto an irritability factor (e.g., Stringaris et al, 2012), and reports using this composite have indicated strong internal consistency and reasonable stability across time (Wiggins et al, 2014). We chose to use the same three items across all ages for measurement consistency across time. Notably, Wiggins et al (2014) also added a fourth item ("easily frustrated") to her three year irritability composite.We computed the sum scores on these items to index irritability such that higher scores indicate greater irritable symptoms at each assessment.

To phenotype early childhood irritability, we modeled irritability over development because this approach has been shown to be predictive of later outcomes (Paglaccio et al, 2018). To model sustained irritability over development, we utilized latent class growth analysis (implemented in Mplus 8.0 statistical software; Muthén and Muthén, Los Angeles, CA) to identify which children showed high stable childhood irritability (as indexed by the CBCL)

from ages 2 to 7. This method is used to identify groups of individuals who exhibited similar developmental trajectories and has been used previously to identify children with high and stable childhood irritability (Pagliaccio et al, 2018; Wiggins et al, 2014). We estimated models with two to six classes and chose the best-fitting model based on multiple fit indicators (Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC], sample size-adjusted BIC [SSABIC], entropy, Lo-Mendell-Rubin Adjusted Likelihood Ratio Test [LMR-LRT], Vuong-Lo-Mendell-Rubin Likelihood Ratio Test [VLMR], Bootstrapped Likelihood Ratio Test [BLRT], minimum class size of 1%) and interpretability. The analysis used the MLR estimator in which all available data are utilized to estimate model parameters. Intercepts and slopes were constrained to be invariant within each class because we were not interested in within-group variance. We extracted the probability that a child was in the *high stable irritability* class as our early childhood irritability phenotype of interest

Specifically, fit indices demonstrated that the four-class model was the best-fitting model (see Supplement for model fit indicators)[1]. The AIC, BIC, SSBIC were all smaller in the four-class model than the two- and three-class models. The four-class model also showed relatively high entropy, a significant BLRT, and the smallest class was 10.50% of the sample. The VLMR and LMR indicated that the five-class model may be preferable, but the smallest class for the five-class model was <1%. Thus, we selected the four-class model as the best fit.

Overall, 16% of children were assigned to the high stable irritability class. Nevertheless, using this approach we were able to extract (for all subjects) probability scores indicative of the likelihood that any child was classified in the high stable irritable class. Our analyses focus on the probability that a child was assigned to the high stable irritability class because we expected that these children would be the most at risk for developing irritability at age 12. These scores were mean-centered prior to testing interaction effects. Supplement Figure S2 depicts all classes and percentage of sample in each class. See Supplemental Information Table S3 for evidence that, in our sample, other irritability classifications failed to show significant positive associations with increased irritability at age 12.

ERN.

Flanker Task.: At the 12-year visit, children completed a flanker task while continuous EEG data were acquired using a 128-channel HydroCel Geodesic Sensor Net and EGI software (Electrical Geodesic, Inc., Eugene, OR). The task, data, and processing pipeline have been reported previously in Buzzell et al (2017). On each trial, five horizontally aligned arrowheads were presented. The central arrow was “flanked” (or surrounded by) arrows that were either facing the same direction (i.e., congruent; < < < < <) or the opposite direction (i.e., incongruent; < < > < <). The arrows, which were preceded by a fixation cross (~300-600 ms), were presented for 200 ms and followed by a blank screen (~1860 ms). Children were to indicate the direction of the central arrow as quickly as possible.

[1]A finding that largely replicates previous samples (see Supplemental Information).

The flanker task consisted of 12 blocks with 32 trials per block. At the end of the block, the computer presented feedback based on the child's performance. If accuracy was 90% or above, the feedback provided was "Respond faster". If accuracy was between 75% and 90%, the feedback provided was "Good job". If accuracy was below 75%, the feedback provided was "Be more accurate." This feedback ensured that children produced a sufficient number of errors to analyze EEG activity surrounding erroneous behavior and ensured that differences in ERN response were not a result of differing error rates (See Amodio et al, 2007, Gehring et al, 1993; Hajcak et al, 2003 for evidence that the ERN is larger when participants make fewer errors). Participants completed the flanker task twice, once under standard flanker conditions and once under a "social" pressure manipulation. These manipulations were counterbalanced across individuals, and there was no evidence that manipulation order impacted the amplitude of the ERN (p>.573), nor was there evidence of any significant phenotype-by-order interaction (ps>.193). Here, we report ERN data from the standard flanker task because extensive work has documented that it interacts with levels of BI to predict BI-associated risk for anxiety (See Lahat et al, 2014; McDermott et al, 2009). Of note, the previous report of these data (Buzzell et al, 2017) focused on the social ERN by regressing the social ERN on the standard flanker ERN—thereby generating residual ERN scores that isolate variance in the ERN associated with the social condition, independent of the standard ERN. Thus, the results presented here draw on analyses that were used in Buzzell et al (2017) to generate these residual ERN scores.

EEG preprocessing and Event-Related Potential (ERP) quantification.: All EEG analyses used custom MATLAB scripts (The MathWorks, Natick, MA) and the EEGLAB toolbox (Delorme & Makeig, 2004). Data were high-pass filtered at 0.3 Hz and low-pass filtered at 45 Hz; FAST tools (Nolan, Whelan, & Reilly, 2010) were used to identify and remove bad channels. Artifactual ICA components were detected and removed through a combination of manual and automated procedures using the ADJUST toolbox (Mognon, Jovicich, Bruzzone, & Buiatti, 2011). Missing channels were interpolated using a spherical spline interpolation and then referenced to the average of all electrodes. Data were epoched to the response markers from −500 to 1000 ms and baseline corrected using the 200 ms period preceding response onset. Given that errors are more likely to occur on incongruent trials, only incongruent trials were analyzed to isolate error-specific effects and avoid any confounds related to congruency. Separate ERPs were calculated for the social and non-social conditions of the task, with only the non-social ERPs being analyzed here.

Mean amplitudes of the error-related negativity (ERN) and correct-related negativity (CRN) were calculated from a cluster of frontocentral electrodes surrounding FCz (EGI electrodes 12, 5, 6, 13, 112, 7, 106) for the first 100 ms following response (Barker, 2016; Barker, Troller-Renfree, Pine, & Fox, 2015). The CRN was then subtracted from the ERN for each participant, in order to compute the delta-ERN, which was used for all subsequent analyses. For simplicity, the delta-ERN is referred to as the "ERN" throughout this manuscript. All participants included in the ERP analyses had a minimum of 6 artifact-free incongruent-error trials, which has been shown to elicit a reliable measurement of the ERN in both children and adults (Pontifex et al., 2010; Steele et al., 2016). For a complete description of the EEG/ERP analysis procedures, see Buzzell and colleagues (2017).

Clinical Assessments at age 12.

Social Anxiety.: To assess social anxiety symptoms at age 12, we collected three measures of anxiety from three sources (clinicians, parents, and children) and created a factor score that combined them into one measure. Clinicians conducted semi-structured diagnostic interviews (i.e., the Kiddie Schedule for Affective Disorder and Schizophrenia (KSADS); see Kaufman et al, 1997). All clinicians were trained, and diagnoses were confirmed by senior psychiatrists. Moreover, as reported elsewhere, interviews were recorded, and a random subset were reviewed throughout the study to maintain adequate reliability (Buzzell et al. 2017). In this longitudinal sample, a total of 131 children received KSADS evaluations at age 12. Nine (6.9%) children received a current diagnosis of social anxiety at age 12. Parents and children also completed the Screen for Child Anxiety Related Disorders (SCARED), a 66-item questionnaire measuring anxiety disorder symptoms over the past three months (SCARED parent and child report ICC=.443, p<.001, 95% CI [.306 .560]). SCARED scores range from 0 to 14 for each anxiety subscale with higher scores indicating more anxious symptoms. Previous studies have demonstrated strong internal consistency for the SCARED subscales (See Muris et al, 2004). Our analyses focused on KSADS-social phobia diagnoses and SCARED scores on the social anxiety subscale.

To combine measures of social anxiety across three reporters (parent, child, and clinician), we conducted a confirmatory factor analysis (CFA) that included all individuals in the longitudinal sample who had either KSADS or SCARED data at age 12 (n=194). We used a one-factor model (implemented in Mplus 8.0 statistical software; Muthén and Muthén, Los Angeles, CA). This approach allowed us to detect variability in symptoms across several informants and to utilize as much data available for each child as possible. This approach was also useful given the few children meeting criteria for social anxiety disorder. Given that the diagnostic variable was categorical, the CFA used the default WLSMV estimator in which missing data are excluded on a pairwise basis. The CFA indicated that data from all three reporters had high loadings ($SCARED_{parent}$=604, $SCARED_{child}$=.762, KSADs =.807, all ps<.001) on the latent social anxiety variable. A standardized factor score was extracted for each participant and used as the social anxiety dependent variable of interest, with higher factor scores indicating more severe social anxiety[2].

Irritability.: We assessed irritability symptoms at age 12 from two unique reporters (parents and children). Parents and children completed the Affective Reactivity Index (ARI; Stringaris et al., 2012), a scale that contains six symptom items and one impairment item designed to assess chronic irritability. Each item is scored on a 3-point scale (0 = not true, 1 = somewhat true, and 2 = certainly true). ARI scores range from 0 to 12, and only the first six items are summed to form the total score (as per guidelines outlined in Stringaris et al., 2012). Previous studies have demonstrated internal consistency for the ARI (Stringaris et al., 2012). By and large, our sample did not meet clinical cutoffs for irritability (n=34 [12%] exceeding clinical cutoff; See Kircanski et al, 2017). We averaged the parent report (M=1.25; SD= 1.633; range= 0-6) and child self-report (M=1.89; SD= 2.258; range= 0-10)

[2]This analytic approach differs from previous reports on this sample. Previous reports on this sample (Buzzell et al, 2017) have focused exclusively on the self- and parent-report data and have not utilized the clinician report data.

ARI scores (ARI parent and child report ICC=.220, p<.015, 95% CI [.022 .404]). See Supplemental Information for evidence that ARI scores at age 12 were associated with CBCL externalizing, but not internalizing, symptoms.

Analytic Strategy.

Preliminary Analyses.

Relation between behavioral inhibition and childhood irritability.: To begin, we tested whether our behavioral phenotypes (i.e., behavioral inhibition and childhood irritability) were correlated with one another. We also tested whether our phenotypes differ in terms of demographics. In particular, some studies suggest that there are sex differences as a function of chronic irritability (Leibenluft et al, 2006) and others report that SES may be related to risk for psychopathology (Velez et al, 1989). We used Mann-Whitney and Kruskal-Wallis tests to evaluate whether there were any sex or maternal education differences associated with either childhood phenotype.

Focal Analysis Strategy.: First, we evaluated the relations between each of the two early phenotypes of interest (BI and chronic high irritability) and clinical outcome (social anxiety composite score and mean ARI) using Pearson correlation. Second, we tested whether the ERN interacts with early phenotype to predict clinical outcome using the PROCESS macro in SPSS (Hayes, 2018). To supplement this analysis, we evaluated whether any combination of phenotype and level of ERN magnitude resulted in increased risk for psychopathology. To do so, we computed tertiles for ERN data. Tertiles allowed us to compare groups with equal sample sizes and resulted in the following cut-points for the ERN (High ERN reflects scores less than −2.84 n=43), Moderate ERN reflect scores between −2.84 and −1.11 (n=42), Low ERN reflects scores greater than −1.11 (n=42); See histogram in supplemental information). We chose to use tertiles rather than splitting the groups based on mean and +/− 1 standard deviation because the latter split resulted in some groups having far fewer subjects than others (See supplemental information for details and results of a parallel analysis using this method of splitting). Using these ERN groupings, we replotted our data to compute the correlation between early phenotype and clinical outcome. If individuals are at increased risk for developing psychopathology, we would expect the correlation between phenotype and outcome to be significantly greater than 0. If there is no significant link between phenotype and clinical outcome, the correlation between phenotype and outcome will not differ from 0. Supplemental Information demonstrates that splitting the data in tertiles, generally aligns with a split defined by mean +/− 1 standard deviation (compare main text figures to Figures S3 & S4) with some exceptions in terms of the irritability model.

Results

Preliminary Analyses.

Relation between childhood behavioral phenotypes.—There was no significant association between childhood behavioral inhibition and childhood irritability (p>.29), suggesting that these behavioral phenotypes are not related (See Table 2). Results also indicated that irritability and BI did not differ as a function of sex and maternal education (ps> .37). As such, we did not include these variables in further analyses.

Focal Analyses.

Early phenotypes predict clinical outcome.—First, we tested whether our early behavioral phenotypes predicted our clinical outcomes of interest. Results indicated that behavioral inhibition predicted social anxiety at age 12 (r=.34, p<.001). Results further indicated that high stable childhood irritability predicted irritability at age 12 (r=.35, p<.001; See Figure 1). Both relations remained significant when controlling for the other phenotype (BI-social anxiety: r=.33, p<.001; childhood irritability-12-year irritability: r=.35, p<.001). Furthermore, BI did not predict irritability at age 12 and irritability in childhood did not predict social anxiety at age 12 (ps>.76).

ERN as a domain-specific correlate.—Next, we tested whether the correlation between early-childhood phenotypes and clinical outcomes differed as a function of ERN.

Behavioral inhibition to social anxiety.: Results indicate distinct correlations between ERN and social anxiety in children with and without BI (β=−.121, ΔR^2=.035, F(1,122) = 5.360, p<.022; see Figure 2); and that these results remained significant when controlling for irritability (see Table 3). Specifically, children with high BI who have larger (more negative) ERNs have greater social anxiety.

To supplement these continuous analyses, we next examined whether association between phenotype and clinical outcome differed as a function of ERN magnitude. To assess whether this was the case, we examined the correlation between phenotype and clinical outcome for individuals in each ERN group using a tertile split (described above). Results indicated that the association between BI and social anxiety was significant for the high ERN (r(41)=.559, p<.001) and the moderate ERN groups (r(41)=.463, p< .002) but not the ERN-low group (p>.572). This suggests that the association between BI and social anxiety found in the two higher ERN groups fails to manifest among individuals who exhibit a low ERN. These correlations held when controlling for childhood irritability (high ERN- r(35)=.535, p<.001; moderate ERN- r(41)=.437,p<.003; low ERN-p<.633).

Childhood irritability to irritability at age 12.: The association between childhood irritability and age-12 irritability differed as a function of ERN magnitude (β=.892, ΔR^2 =.111, F(1,59) = 8.571,p<.005; see Figure 3 and Table 4). These results remained significant when controlling for BI (see Table 4). Specifically, highly irritable children who have smaller (more positive) ERNs exhibit high irritability in early adolescence.

To further evaluate whether risk for psychopathology increased in individuals who exhibited different ERN magnitude, we examined whether the correlation between childhood irritability and ARI at age 12 differed as a function of ERN groups (i.e., tertile splits described above). Results indicated that the correlation between childhood and age-12 irritability did manifest in the low ERN group (r(24)=.651, p<.001) but in neither the high or moderate ERN groups (ps>.123). These results held when controlling for BI (low ERN- r(22)=.650, p<.001; moderate and high ERN- ps<.207). Together, these results suggest that the association between high stable childhood irritability and 12-year irritability manifests only in individuals with a low ERN but not among individuals who exhibit a high or moderate ERN. Nevertheless, caution is warranted when interpreting the absence of

correlations in these relatively small groups, as small samples of the individuals with ARI data reduced power to detect effects.

Discussion

The goal of the current study was to examine whether the ERN manifested unique correlations with two specific clinical outcomes: social anxiety and irritability. Our results suggest that the ERN correlates with concurrent psychopathology in unique ways, based on early temperament: children who exhibit elevated behavioral inhibition during childhood and demonstrate an increased ERN show elevated social anxiety at age 12. In contrast, children who exhibit elevated irritability symptoms in early childhood and later show a more blunted ERN exhibit higher irritability symptoms at age 12. Together, this work suggests that the ERN, when considered in combination with early behavior, may act as a biomarker that can identify distinct developmental pathways to anxiety and irritability.

Action monitoring requires both the ability to detect when an error has occurred (i.e., error monitoring) and the ability to adjust performance in response to these errors (i.e., control instantiation; Botvinick, Braver, Barch, Carter, Cohen, 2001). While BI and irritability share several common features (including negative affect), they differ in their behavioral response to threat. BI children tend to respond to threat with increased control (i.e., avoidance); whereas irritable children tend to exhibit decreased control (i.e., approach the threat; Salum et al, 2017). Error detection and control instantiation are thought to be linked (Debener, 2005; Gehring et al, 1993). Indeed, anxious individuals tend to show *both* a larger ERN (i.e., increased error detection) and increased reaction times (i.e., which may reflect increased control instantiation) following an error (or “post-error slowing”; Meyer, Weinberg, Klein, Hajcak, 2012; Buzzell et al, 2017). Thus, larger ERNs are thought to facilitate greater post-error slowing and thus the avoidance of subsequent errors (although see Buzzell et al, 2017 for an alternative explanation). The link between the ERN and subsequent control instantiation fits with the patterns observed in our data. We found that individuals at risk for anxiety show both BI and enhanced error monitoring (as indexed by a larger ERN). Speculatively, this enhanced error monitoring may relate to children’s tendency to avoid situations where errors and other threatening events occur. Furthermore, the opposite might be true among individuals who are irritable. That is, children who are irritable and, compared to other irritable children, less capable of robust error monitoring (i.e., blunted ERN) may fail to implement strategies that support avoidance of errors. Such failure could lead these irritable children to exhibit less avoidance (or greater approach behavior) than irritable children more capable of effective error monitoring. Future work should examine relations among the ERN and post-error slowing in irritable patients.

Critically, these results also highlight the variability in error monitoring processes for individuals who experience BI or irritability in childhood—not all children who show BI or irritability also experience enhanced/reduced error monitoring. Thus, these findings may suggest that those individuals whose error monitoring processes map onto their approach and avoidance tendencies in childhood are most at risk for developing psychopathology. Further research is needed to understand what facilitates this link between the error monitoring response and childhood behavioral tendencies.

Our results replicate past studies demonstrating that BI predicts social anxiety (Clauss et al, 2012) and examining the moderating effect of BI on the development of anxiety (Lahat et al, 2014; McDermott et al, 2009). Additionally, our findings extend previous studies (including those in this sample) by demonstrating that the link between BI and social anxiety persists when measures of social reticence across early childhood are integrated into the early phenotype measure and when clinician report is integrated into the social anxiety metric. This analytic approach is unique from previous reports in that it uses all the phenotyping data (rather than focusing solely on behavioral assessments in toddlerhood) and clinical data collected (rather than focusing solely on self-report measures). Previous reports in this sample have also focused on the ERN in a social context (See Buzzell et al, 2017), whereas the current study reports data from the standard flanker (what Buzzell et al, 2017 refer to as the "non-social context"). The current study focuses on the ERN in a nonsocial as opposed to social context because more previous work utilizes this standard version of the flanker task and allows our results to be generalized to the broader conflict monitoring literature. Furthermore, we know from previous studies that the standard flanker moderates the link between BI in toddlerhood and anxiety in later childhood (See Buzzell et al, 2017; Lahat et al, 2014a; McDermott et al, 2009) so these findings replicate previous reports in the literature. Nevertheless, future work could examine the role of social context to test whether error monitoring under social conditions better moderates the link between early phenotypes of social threat and later clinical outcomes. We further demonstrate that the association between BI and anxiety is not present in children with blunted ERNs.

The effect that we found for irritability is opposite to the one we observed in BI; i.e., children exhibiting a relatively large or even moderate-amplitude ERN show no association between early irritability and ARI at age 12, whereas children with a small, blunted ERN showed an association between early irritability and 12-year irritability. Broadly speaking, longitudinal studies find relatively *low* levels of cognitive control to typically predict negative outcomes including, but not limited to, most forms of psychopathology (e.g., Moffitt et al, 2011; Snyder Miyake, Hankin, 2015). Interestingly, we see this pattern in irritability but not in BI. In contrast, in BI, enhanced error monitoring is associated with worse outcomes. This pattern could suggest that individuals with highly active fear circuits could have a naturally heightened behavior monitoring system which results in inflexibility of attention that, in turn, contributes to increased anxious symptoms.

To date, limited work examines childhood irritability and the ERN. Kessler and colleagues (2016) provide some of the first evidence that children with irritability show distinct symptom patterns as a function of the ERN: children who were irritable at age 3 and exhibited a large ERN (at age 6) showed greater internalizing symptoms at age 9 whereas irritable children with blunted ERNs showed greater externalizing symptoms. Thus, the current study differed from Kessler et al (2016) both in the ages that irritability and outcomes were assessed and the outcome-assessment tools. In particular, Kessler et al (2016) provided data on early childhood irritability (i.e., age 3) which may not map onto irritability trajectories from age 2-7 years. Previous work suggests that normative irritability tends to decline after the preschool years (Dougherty et al, 2013). Thus, Kessler et al (2016) may have failed to quantify levels of stable childhood irritability, but rather captured heightened irritability at one cross-sectional time point. Whether irritability at age 3 is

longitudinally predictive of irritability at later ages is an open question that could inform how these results map onto those of the current study. Furthermore, in contrast to Kessler et al (2016) who measured clinical outcomes using CBCL, our study assessed irritability at age 12 using a clinical assessment tool—the ARI. While the CBCL broadly characterizes externalizing behaviors, the ARI more narrowly indexes irritability associated with temper tantrums or other displays of anger and frustration (Stringaris et al, 2012). Indeed, data in the supplemental information demonstrate that the ARI significantly predicts the externalizing but not the internalizing subscale of the CBCL at age 12. This further supports the idea that our results are more narrowly indexing irritability associated with externalizing behaviors. When considered together with the results of Kessler et al (2016), our results replicate the finding that irritability and a blunted ERN predict a developmental trajectory related to outward expressions of anger.

Multiple studies show cross-sectional (Stoddard et al, 2013), longitudinal (Vidal-Ribas et al, 2016), and genetic (Savage et al, 2015; Stringaris et al, 2012) associations between irritability in childhood and internalizing symptoms (i.e., anxiety and depression) in adolescence and adulthood. However, our study did not find a significant correlation between *social* anxiety and irritability at age 12. This could indicate that while irritability and general anxiety are related, irritability and *social* anxiety may not be related. This study is also the first to examine associations between BI and irritability, and we did not find a significant correlation. Further work is needed to replicate this finding and examine whether these childhood risk phenotypes co-occur or are distinct—particularly because irritability and anxiety regularly co-occur. Additionally, future research might examine whether our ERN findings generalize to children who show persistently high levels of both irritability and internalizing symptoms from an early age.

In addition to several strengths, our results are also limited in several respects. First, despite our selected sample being at increased risk for psychopathology (particularly BI; Fox et al, 2015), clinical assessments identified few individuals meeting criteria for social anxiety disorder (< 10% of the sample) or irritability at age 12 (12% of the sample) However, it is important to note that psychopathology was measured when children were quite young and thus, more can be expected to develop symptoms later. urther work in samples with a greater prevalence of psychopathology is needed to better assess the clinical validity of these developmental relations and the generalizability of these data. Second, our measurement of the ERN and our clinical assessments were both taken at age 12. Thus, the current findings should be extended through studies examining both the ERN and clinical data at multiple time points. Third, we examined early childhood phenotypes using two different assessment metrics. Childhood irritability was assessed using questionnaire measures and via a latent class growth analysis, whereas BI was assessed using both behavioral and questionnaire measures via a standardized composite score. We chose to use these metrics because they represent the standard method of assessment in each subfield and also allowed us to use the most longitudinal data available in creating our early phenotypes. Indeed, the longitudinal cohort reported here was more extensively assessed for levels of BI than for levels of irritability. Interest in evaluating irritability increased when subjects had reached age 12, thereby resulting in less data available for characterizing irritability. Thus, we aimed to maximize the amount of data used for characterizing each phenotype and the analytic

approach used to assess variability. This led us to use different methods to capture stable phenotypes in each domain and thus leaves open questions about whether one metric captures stability of early behavior better than another and the associated effect on our findings. Even so, our results demonstrate that these early phenotypes are roughly equal in sensitivity because both map onto previously-reported patterns from community samples in the literature (Fox et al, 2001; Wiggins et al, 2014). Nevertheless, it is possible that the irritability metric is less sensitive because it relied exclusively on parent-report measures. Further, this approach complicates attempts to determine the extent to which differences between the phenotypes are related to differences in information sources. Future work should aim to establish age-appropriate behavioral assessments of irritability to be incorporated in longitudinal study designs. This approach would allow for a more direct comparison of childhood irritability and BI. Further replication of these results in community and clinical samples could evaluate the specificity of the proposed risk pathways.

Identifying specific biomarkers that can identify which individuals are most at risk for developing specific clinical outcomes is foundational to understanding the pathophysiology of childhood mental illness. The ERN has received considerable interest as a potential biomarker (Olvet & Hajcak, 2008). Together the findings presented here demonstrate that the ERN interacts with phenotype to predict distinct pathways to psychopathology. Our results replicate previous findings on BI and provide novel data about how error monitoring may be linked to persistent irritability beyond early childhood. In sum, our results show that risk for psychopathology is related to both early behavioral phenotypes and error monitoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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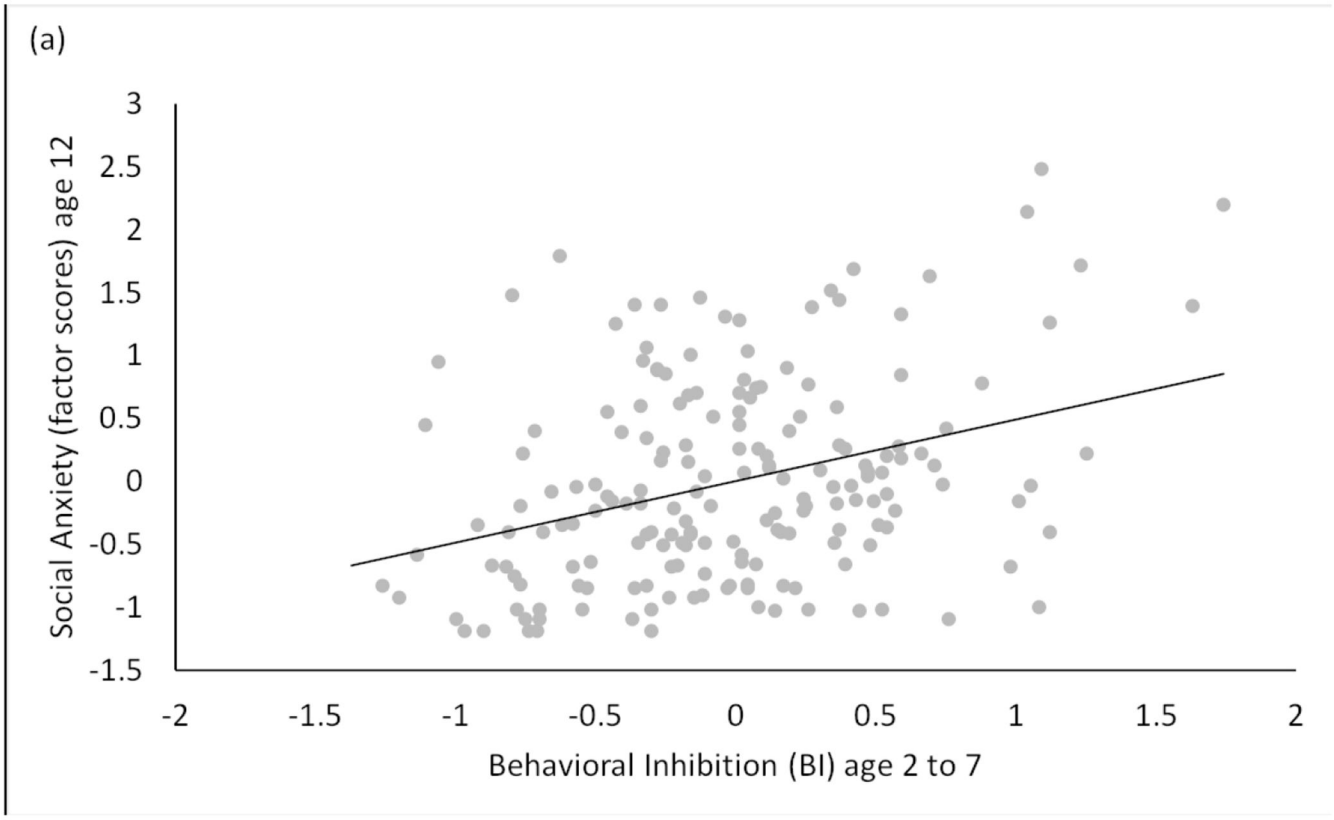

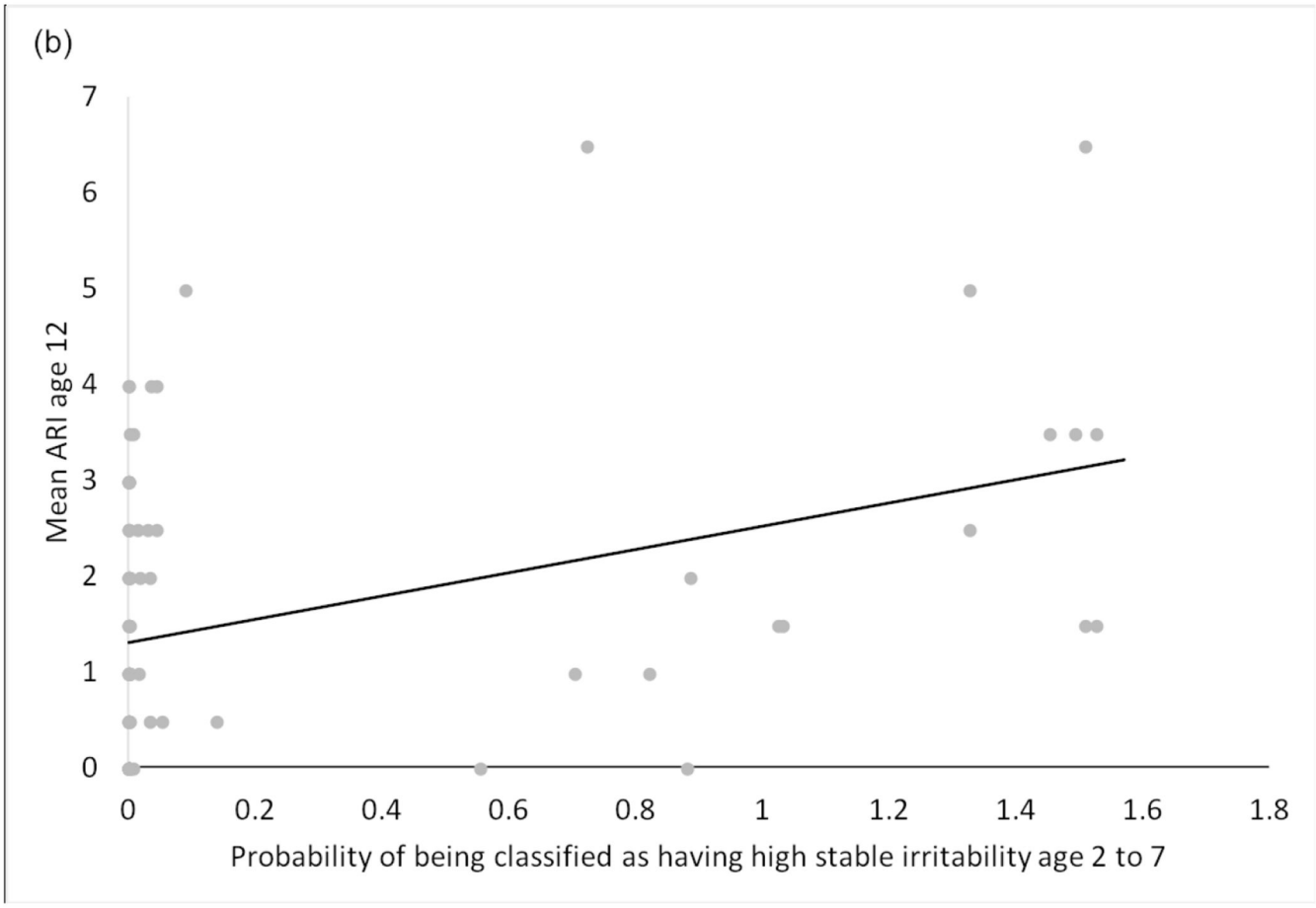

Figure 1.

Relation between early phenotype and 12-year psychopathology symptoms. (a) Demonstrates that behavioral inhibition predicts social anxiety at age 12. (b) Demonstrates that high stable irritability predicts 12-year irritability. Irritability probability scores have been arcsin transformed and jittered for the purposes of better illustrating the distribution of scores.

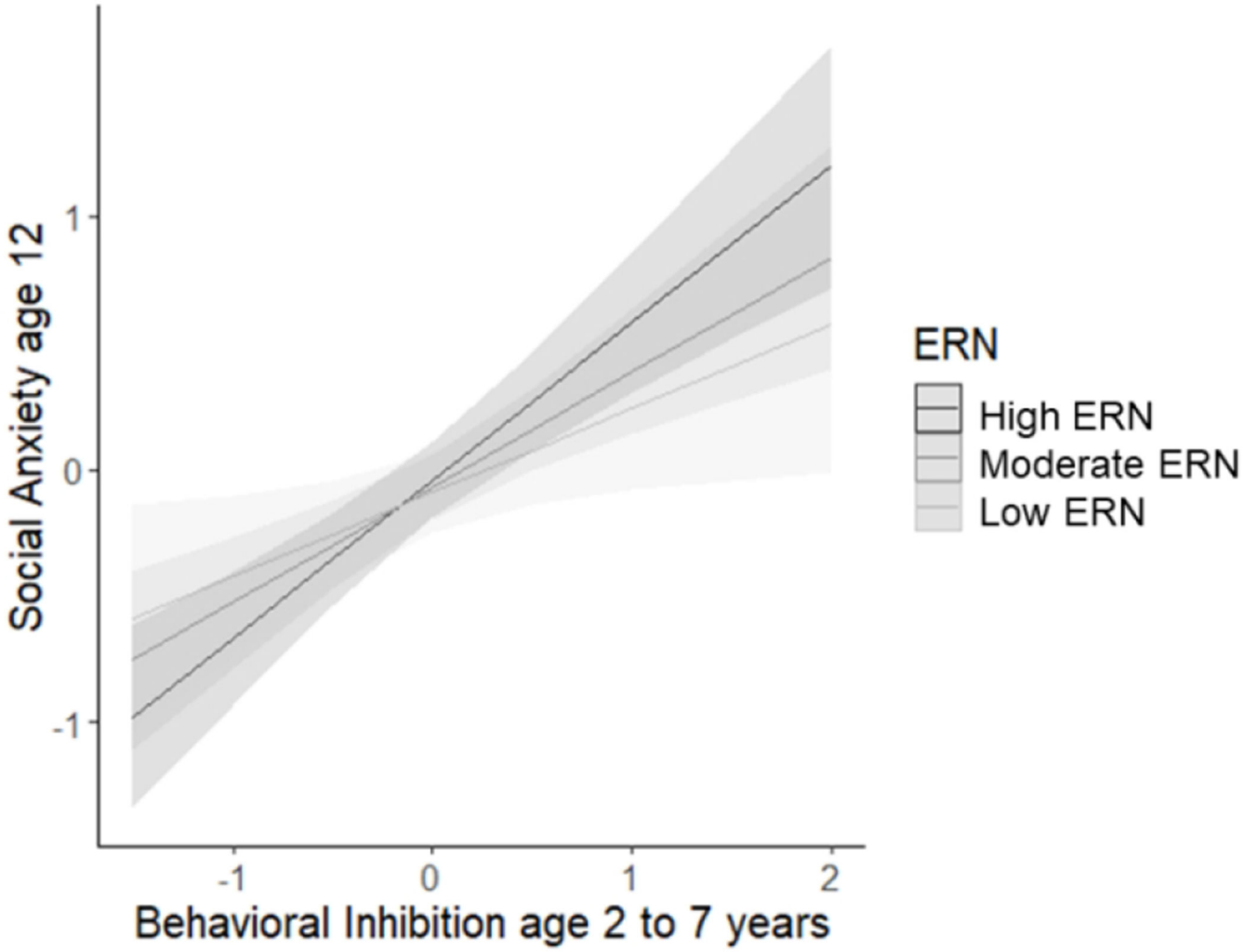

Figure 2.
Depicts the moderating effect of ERN on risk for developing social anxiety. Each line depicts low/moderate/high ERNs as determined by dividing the data into tertiles.

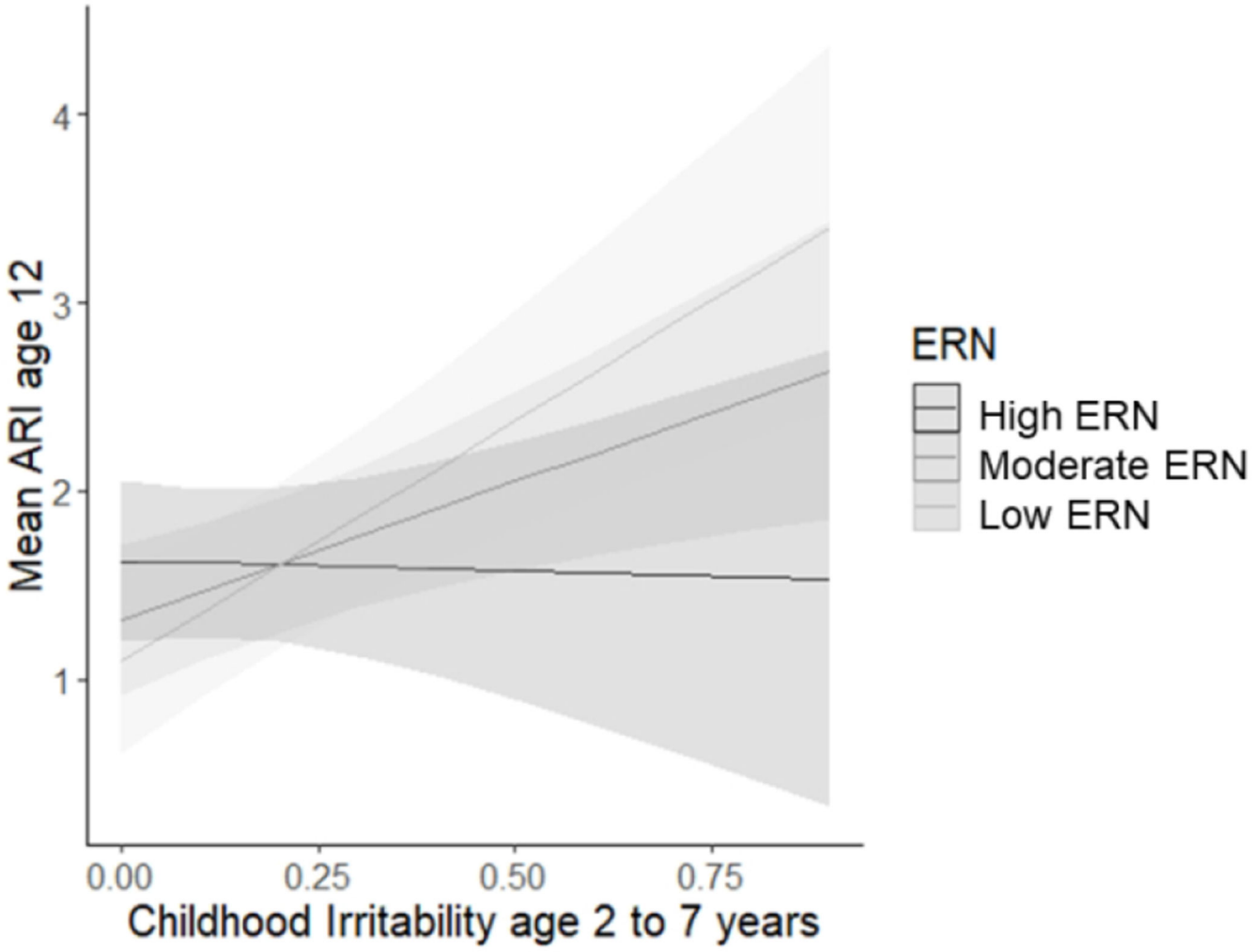

Figure 3.

Depicts the moderating effect of ERN on risk for exhibiting irritability symptoms at age 12. Each line depicts low/moderate/high ERNs as determined by dividing the data into tertiles.

Table 1.

Demographic characteristics and data collected

Characteristic	N (% of original sample)	M
N	291	--
Male	135 (46.4%)	--
Child Ethnicity		
White	186 (41.8%)	--
African American	41 (9.2%)	--
Asian	6 (1.3%)	--
Hispanic	10 (2.2%)	--
Other/ no information	5 (1.1%)	--
Maternal Education		
High school graduate	47 (16.2%)	--
College graduate	122 (41.9%)	--
Graduate/ professional training	104 (35.7%)	--
Other	16 (5.5 %)	--
No information	2 (<1%)	
Behavioral data *available*		
BI (age 2-7)	272 (93.5%)	−.031
Probability of High stable Childhood	234 (80.4%)	.143
Irritability (age 2-7)		
Cognitive Control data *available*		
ERN (age 12)	127 (43.6%)	-2.226
Clinical Data *available*		
Parent ARI	89 (30.6%)	1.247
Child ARI	91 (31.3%)	1.890
Parent SCARED	179 (61.5%)	3.80
Child SCARED	187 (64.3%)	4.92
KSADS	131 (45.0%)	9

Table 2.

Correlations among focal variables of interest

	(1)	(2)	(3)	(4)	(5)
(1) Childhood BI	--	--	--	--	--
(2) High stable irritability childhood	.070	--	--	--	--
(3) ERN	.027	.053	--	--	--
(4) 12-year Social Anxiety	.341**	−.031	.006	--	--
(5) 12-year Irritability (ARI)	−.035	.350**	−.125	.190	--

** $p<.01$

Table 3.

Regression results predicting social anxiety at age 12

Model	Predictor	β	*SE B*	*t*	*p*	*Fit*
1	BI	.251	.179	1.401	.164	R^2=.194,*p*<.001
	ERN	−.017	.028	−.576	.566	
	BI x ERN	−.121	.052	−2.315	.022	
2	BI	.254	.184	1.379	.170	R^2=. 191,*p*<.001
	ERN	−.017	.300	−.582	.562	
	BI x ERN	−.119	.054	−2.217	.029	
	High childhood irritability	−.013	.213	−.063	.950	

Table 4.

Regression results predicting ARI at age 12

Model	Predictor	β	*SE B*	*t*	*p*	*Fit*
1	High childhood irritability	2.95	.699	4.218	.0001	R^2=.239, p<.001
	ERN	−.179	.082	−2.185	.033	
	High childhood irritability x ERN	.892	.305	2.93	.005	
2	High childhood irritability	2.918	.705	4.141	.0001	R^2=.243,p<.003
	ERN	−.184	.083	−2.218	.031	
	High childhood irritability x ERN	.904	.307	2.943	.005	
	BI	.183	.320	.573	.569	