A genetic variant brain-dervied neurotrophic factor (*BDNF*) polymorphism interacts with hostile parenting to predict error-related brain activity and thereby risk for internalizing disorders in children

ALEXANDRIA MEYER, GREG HAJCAK, ELIZABETH HAYDEN, HAROON I. SHEIKH, SHIVA M. SINGH, AND DANIEL N. KLEIN
Florida State University

Abstract

The error-related negativity (ERN) is a negative deflection in the event-related potential occurring when individuals make mistakes, and is increased in children with internalizing psychopathology. We recently found that harsh parenting predicts a larger ERN in children, and recent work has suggested that variation in the brain-derived neurotrophic factor (*BDNF*) gene may moderate the impact of early life adversity. Parents and children completed measures of parenting when children were 3 years old (*N* = 201); 3 years later, the ERN was measured and diagnostic interviews as well as dimensional symptom measures were completed. We found that harsh parenting predicted an increased ERN only among children with a methionine allele of the *BDNF* genotype, and evidence of moderated mediation: the ERN mediated the relationship between parenting and internalizing diagnoses *and* dimensional symptoms only if children had a methionine allele. We tested this model with externalizing disorders, and found that harsh parenting predicted externalizing outcomes, but the ERN did not mediate this association. These findings suggest that harsh parenting predicts both externalizing and internalizing outcomes in children; however, this occurs through different pathways that uniquely implicate error-related brain activity in the development of internalizing disorders.

Psychopathology often begins in childhood and can result in chronic, life-long impairment (Beesdo, Knappe, & Pine, 2009; Kessler et al., 2005; Last, Perrin, Hersen, & Kazdin, 1996; Rutter, Kim-Cohen, & Maughan, 2006). Elucidating developmental trajectories may pave the way for earlier intervention strategies as well as an increased understanding of the etiopathogenesis of internalizing and externalizing disorders (Pine, 2007). While approaches that examine the biological and environmental bases of psychopathology *separately* have gained some traction in understanding developmental trajectories of psychopathology, approaches that *integrate* biological and environmental vulnerabilities across development are likely to be more effective (Beauchaine & McNulty, 2013; Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). Previous work suggests that psychopathology is rooted in complex Gene × Environment correlations and interactions that unfold across multiple domains of analysis and change over the course of development (Beauchaine & Gatzke-Kopp, 2012; Bergen, Gardner, & Kendler, 2007). Most of the work in this area has focused on Gene × Environment interactions; there is much less research on interactions of other biological variables with the environment or with

specific genetic polymorphisms. Identifying early neural markers that relate to the development of psychopathology, along with environmental and genetic vulnerabilities that interact with and modify these biomarkers, is likely to lead to an increased understanding of these complex developmental trajectories.

Along these lines, we previously found that harsh parenting (i.e., an environmental vulnerability) is related to increases in error-related brain activity (i.e., the error-related negativity [ERN]), and that this neural measure mediated the relationship between parenting and anxiety disorder status (Meyer, Proudfit, et al., 2014). We hypothesized that harsh parenting may, like aversive conditioning, potentiate neural sensitivity to errors and thereby increase risk for anxiety. In the current investigation, we examined whether a genetic polymorphism that has been linked to fear learning may moderate these relationships.

The ERN is a promising biomarker that has been related to both internalizing and externalizing psychopathology (Olvet & Hajcak, 2008). The ERN is a negative deflection in the event-related potential (ERP) waveform elicited by error commission at frontocentral electrode sites (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) and is thought to be generated in the anterior cingulate cortex (Debener et al., 2005; Dehaene, Posner, & Don, 1994; Hoffmann & Falkenstein,

Address correspondence and reprint requests to: Alexandria Meyer, Department of Psychology, Florida State University, 1107 West Call Street, Tallahassee, FL 32304; E-mail: meyer@psy.fsu.edu.

2010), a region of the medial prefrontal cortex where information about threat, pain, and punishment is integrated (Shackman et al., 2011). Individual variation in ERN magnitude is thought to index differences in sensitivity to error commission and defensive reactivity following mistakes (Hajcak, 2012; Weinberg, Riesel, & Hajcak, 2012). In keeping with the view that individuals with internalizing and externalizing tendencies have increased and decreased sensitivity to potential threat, respectively, studies have consistently found an increased ERN among internalizing individuals and a decreased ERN among externalizing individuals For example, work in adults and children suggests that the ERN magnitude is increased in individuals characterized by internalizing disorders or traits, such as obsessive–compulsive disorder (OCD; Carrasco et al., 2013; Endrass, Klawohn, Schuster, & Kathmann, 2008; Endrass et al., 2010; Gehring, Himle, & Nisenson, 2000; Hajcak, Franklin, Foa, & Simons, 2008; Riesel, Endrass, Kaufmann, & Kathmann, 2011; Ruchsow, Grön, et al., 2005), depression (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008, 2010; however, see Olvet, Klein, & Hajcak, 2010; Weinberg, Klein, & Hajcak, 2012), generalized anxiety disorder (Weinberg, Olvet, & Hajcak, 2010; Xiao et al., 2011), heterogeneous anxiety disorders (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Meyer et al., 2013), OCD traits (Gründler, Cavanagh, Figueroa, Frank, & Allen, 2009; Hajcak & Simons, 2002; Santesso, Segalowitz, & Schmidt, 2006), trait anxiety (Meyer, Weinberg, Klein, & Hajcak, 2012; Pourtois et al., 2010), negative affect (Bush, Luu, & Posner, 2000; Hajcak, McDonald, & Simons, 2004), and behavioral inhibition (Amodio, Master, Yee, & Taylor, 2008; Boksem, Tops, Wester, Meijman, & Lorist, 2006; McDermott et al., 2009). In contrast, the ERN tends to be diminished in individuals characterized by externalizing disorders or traits, such as substance abuse (Franken, van Strien, Franzek, & van de Wetering, 2007; Luijten et al., 2014; Marhe, van de Wetering, & Franken, 2013), attention-deficit/hyperactivity disorder (ADHD; Albrecht et al., 2008; Groen et al., 2008; Hermann, Ziegler, Birbaumer, & Flor, 2002), psychopathy (Munro et al., 2007; Von Borries et al., 2010), trait impulsivity (Potts, George, Martin, & Barratt, 2006; Ruchsow, Spitzer, Grön, Grothe, & Kiefer, 2005), disinhibitory personality traits (Dikman & Allen, 2000), and externalizing traits (Hall, Bernat, & Patrick, 2007).

Given evidence suggesting that ERN magnitude is relatively stable within children and adults across time (Meyer, Bress, & Proudfit, 2014; Weinberg & Hajcak, 2011) and moderately heritable (Anokhin, Golosheykin, & Heath, 2008), this neurobehavioral trait may be useful in understanding developmental risk trajectories (Hajcak, 2012). We recently found that the ERN predicts the onset of anxiety disorders in young children, even when controlling for baseline anxiety symptoms and maternal history of anxiety (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, in press). Although there is evidence that the ERN is stable and heritable, a large portion of the variance is unaccounted for by genetic influences (between 40% and 60%; Anokhin et al., 2008),

suggesting that environmental factors may play an important role in the development of the ERN. Consistent with this view, we found that punishing errors results in an increase in the ERN (Meyer, Gawlowska, & Hajcak, 2017; Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012); moreover, this effect persists following punishment, suggesting that learning experiences surrounding error commission can have a lasting impact on the ERN. During child development, one of the most important aspects of the learning environment is parenting style. Harsh parents punish their children's mistakes more intensely and frequently (Robinson, Mandleco, Olsen, & Hart, 2001), often resulting in children's excessive concern over making mistakes (Kawamura, Frost, & Harmatz, 2002). This led us to hypothesize that one mechanism that may contribute to an altered ERN in childhood is chronic exposure to a punitive learning environment via harsh parenting.

We recently explored this possibility in a sample of young children, finding that both observational and self-report measures of hostile parenting at age 3 prospectively predicted an enhanced ERN in children 3 years later (Meyer, Proudfit, et al., 2014). The same pattern of results was found in a group of preschool-aged children (Brooker & Buss, 2014): greater fearfulness and harsher parenting at 2 years of age predicted larger ERN amplitudes at age 4, suggesting that early learning-related experiences that relate to increased sensitivity to errors may lead to an increased ERN. Furthermore, in our study, a mediation analysis indicated that the ERN mediated the relationship between harsh parenting and child anxiety disorders, suggesting that an increased ERN may be one mechanism through which parenting influences child psychopathology (Meyer, Proudfit, et al., 2014).

In light of evidence that early learning experiences relate to the ERN magnitude, we were interested in exploring whether the effects of these early experiences are modulated by genetic factors in the current study. We focused on a polymorphism involved in regulating brain-derived neurotrophic factor (BDNF), a growth factor that plays an important role in learning through its influence on neuronal survival, growth, and synaptic plasticity in the central nervous system. The human genome contains a common single nucleotide polymorphism that codes for a valine to methionine substitution at codon 66 (*val*66*met*), which leads to reduced levels of BDNF (Egan et al., 2003). Expression of the *BDNF* methionine allele has been associated with impairments in certain forms of learning and memory (Casey et al., 2009; Egan et al., 2003), as well as susceptibility to psychopathology (Neves-Pereira et al., 2002; Sen et al., 2003; Sklar et al., 2002). Using fear-learning paradigms, researchers have demonstrated in both mouse models and humans that carriers of the methionine allele are characterized by a deficit in extinction learning (Johnson & Casey, 2014; Peters, Dieppa-Perea, Melendez, & Quirk, 2010; Soliman et al., 2010), which they hypothesized may relate to an increased risk for psychopathology. Moreover, these deficits can be reversed through infusion of BDNF, further supporting the notion that this

growth hormone plays an important role in extinction learning (Peters et al., 2010). If we conceptualize harsh parenting as a form of fear-learning wherein children learn to associate making mistakes with punishment, we might expect children with the methionine allele to be less able to extinguish this association, despite experiencing other situations wherein their mistakes are not punished. Furthermore, previous studies have found that parenting behaviors have a greater impact on children's psychological outcomes among youth carrying a methionine allele (Ibarra et al., 2014; Park et al., 2014; Suzuki et al., 2012; Willoughby, Mills-Koonce, Propper, & Waschbusch, 2013). Given these findings, we hypothesized that young children with the *BDNF* methionine allele may be differentially impacted by harsh parenting (i.e., a more punishing learning environment) compared to children without the methionine allele.

In addition, we wished to explore whether the potential *BDNF* genotype and harsh parenting interaction may more closely adhere to a diathesis–stress or a differential susceptibility model. More specifically, the diathesis–stress model posits that negative developmental experiences (e.g., harsh parenting) are more likely to impact individuals with risk factors (e.g., *BDNF* methionine allele), which are a latent "diatheses" that can become activated (Heim & Nemeroff, 1999; Monroe & Simons, 1991). Alternatively, the differential susceptibility model suggests that the "risk" factor (e.g., *BDNF* methionine allele) is actually a plasticity factor. For example, the *BDNF* methionine allele may not only amplify risk for maladaptation in the context of harsh parenting but also increase the possibility of positive adaptation in the context of supportive parenting (Belsky & Pluess, 2009).

In the current study, we examined the potential Gene × Environment interaction between the *BDNF* genotype and parenting in relation to the ERN in a longitudinal study including 201 parent and child dyads. Because we were interested in the relationship of *BDNF* to early learning experiences, we assessed parenting when the children were young (∼3 years old) using both observational and self-report measures. During a second assessment, when children were approximately 6 years old, ERPs were recorded while children completed a go-no/go task to measure the ERN, and diagnostic interviews and questionnaires were completed with the parent to assess child psychopathology. We previously reported that both observational and self-reported harsh parenting was related to an increased ERN magnitude in these children (Meyer, Proudfit, et al., 2014); here, we examined the novel question of whether this relationship is moderated by children's *BDNF* genotype, such that children with the methionine allele would be more impacted by harsh parenting. We also planned to explore whether this interaction was more consistent with a diathesis–stress or differential susceptibility model. Furthermore, we extend previous findings by characterizing developmental trajectories that lead to *both* internalizing and externalizing outcomes in children. To do this, we explored two separate moderated mediation models wherein we tested whether the interaction between parenting

and the *BDNF* genotype predicting ERN magnitude would mediate the relationship of harsh parenting to internalizing (Model 1) and externalizing disorders and symptoms (Model 2) in children. Based on previous work, we hypothesized that the full moderated mediation model predicting internalizing disorders would be significant. However, given that externalizing disorders have not previously been characterized by an enhanced ERN, we predicted that this full moderated mediation model would not reach significance. Instead, based on previous work linking harsh parenting to externalizing outcomes in children (e.g., McKee, Colletti, Rakow, Jones, & Forehand, 2008), we hypothesized there would be a direct relationship between parenting and externalizing disorders.

Method

Participants

The sample for the current study consisted of 201 (118 male) children identified through a commercial mailing list (see Olino, Klein, Dyson, Rose, & Durbin, 2010 for details). An initial assessment was completed when children were approximately 3 years of age, wherein a primary caretaker brought the child into the laboratory to complete a series of tasks. At this assessment, the primary parent completed self-reports regarding parenting style and both the child and parent participated in a series of parent–child interaction tasks that provided an observational measure of hostile and supportive parenting behavior. Buccal cells were also collected from the inside of each child's cheek for genetic analysis. Three years later, when children were approximately 6 years of age, they returned to the laboratory for an EEG assessment and clinical interview and questionnaires with the parent (among a series of other tasks). As previously reported (Torpey, Hajcak, Kim, Kujawa, & Klein, 2012), EEG data from 87 out of 413 children were not included in the analyses (69 due to committing 5 or fewer errors, 16 due to having 5 or fewer artifact-free error trials, 1 due to technical error, and 1 due to having an ERP value more than 3 *SD* from the overall mean).[1] Of the 326 children with adequate EEG data from the age 6 assessment, 280 mothers completed questionnaires regarding their parenting style and the Teaching Tasks battery.[2] Of these 280 mothers and children, 201 children had adequate DNA for genetic analysis.[3] In the final sample of 201 children,[4] the mean age at the first assessment was 3.56 (*SD* = 0.27) and 6.04 (*SD* = 0.38) at the second assessment. Eighty-seven percent of the children were Caucasian, 1% Asian, 5% Hispanic, 1% African American, and

---

1. These 87 children did not differ from the rest of the sample in age, race, or any of the study variables (all $ps > .20$).
2. These 46 children did not differ from the rest of the sample in age, race, or any of the study variables (all $ps > .10$).
3. These 79 children did not differ from the rest of the sample in age, race, or any of the study variables (all $ps > .10$).
4. The final sample of children did not differ from the full sample in age, race, or any of the study variables (all $ps > .10$).

6 % identified as other. The study was approved by the Stony Brook Institutional Review Board and completed with consent of the participants.

Procedures and measures

Observed parental hostility. At the first assessment, the parent who accompanied the child to the laboratory (93% mothers) and the child participated in a session that included a modified version of the Teaching Tasks Battery (Egeland et al., 1995). This battery included six standardized tasks (e.g., block building and book reading) that were designed to elicit various parent and child behaviors. Parental hostility was defined as a parent's expression of anger, frustration, and/or criticism toward her child. Behavioral examples include blames child for mistakes or emphasizes child's failures, frequent use of harsh or negative tone, parroting, or hurtful mimicking of child. Coders rated parents' hostile behavior on a 5-point scale for each task, and these ratings were averaged across tasks ($M = 1.18$, $SD = 0.31$, range = 1.0–3.00). Coders were unaware of self-reported parenting style. Interrater reliability (based on 55 assessments) and internal consistency (intraclass correlation = 0.83, $\alpha = 0.76$) was acceptable.

Each task took between 3 and 5 min. In the first task, the parent and child read and discussed a short book. In the second task, the parent encouraged her child to name as many things with wheels as possible during a 4-min period. In the third task, the parent and child were required to build large square blocks from a set of smaller blocks. In the fourth task, the parent helped the child match game pieces based on color and shape. In the fifth task, the parent assisted the child in completing a maze by turning knobs on an Etch A Sketch. In the sixth task, the parent presented the child with a small gift, and then the parent and the child played with the toy together.

Self-reported parenting style. The primary parent also completed the Parenting Styles and Dimensions Questionnaire (PSDQ; Robinson et al., 2001) at the first assessment. The PSDQ contains 37 items. Parents rate each item on a scale from 1 (*never*) to 5 (*always*), measuring three parenting styles: authoritative (high control, high warmth), authoritarian (high control, low warmth), and permissive (low control, high warmth). The factors' internal consistencies (authoritative: $\alpha = 0.82$, authoritarian: $\alpha = 0.75$, permissive: $\alpha = 0.74$) were acceptable. Observed parental hostility and the PSDQ authoritarian factor ($M = 20.26$, $SD = 4.87$) were significantly, albeit modestly, correlated ($r = .19$, $p < .001$). As aggregate measures of parenting from multiple sources have been shown to be more consistent and generalizable than single measures (Bögels & van Melick, 2004), we z-scored and combined the PSDQ authoritarian factor and observed hostile parenting score to derive an index reflecting both self-reported and observed parenting (i.e., harsh parenting; $M = 0.05$, $SD = 1.52$, range = –2.22 to 5.95).

Diagnostic interviews. As previously reported (Meyer et al., 2013), the Preschool Age Psychiatric Assessment (Egger, Ascher, & Angold, 1999) was used to assess a range of disorders from the DSM-IV (American Psychiatric Association, 2000) in children at the second assessment when they were 6 years old. The Preschool Age Psychiatric Assessment is a semistructured parent-report interview with good psychometric properties (see Egger et al., 2006). The interview focuses on the previous 3 months to maximize recall. For this report, we aggregated internalizing disorders ($N = 73$; specific phobia, separation anxiety disorder, social phobia, generalized anxiety disorder, OCD, agoraphobia, major depressive disorder, and dysthymia) and externalizing disorders ($N = 25$; ADHD and oppositional defiant disorder). Fourteen children had comorbid internalizing and externalizing disorders. Interviews were conducted face-to-face with parents by master's-level psychologists. A second diagnostician rated audiotapes of 35 interviews for reliability, oversampling for psychopathology. Kappas ranged from acceptable to excellent: any anxiety disorder (0.89), separation anxiety (1.00), specific phobia (0.79), agoraphobia (1.00), any depressive disorder (0.64), ADHD (0.64), and oppositional defiant disorder (0.87). In the statistical models, children were dichotomously coded as either meeting or not meeting criteria for having an internalizing disorder (Model 1) or an externalizing disorder (Model 2).

Children's internalizing and externalizing symptoms. Parents completed the Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1981) as a measure of their children's internalizing and externalizing symptoms. The CBCL is a 113-iten parent-report checklist assessing emotional and behavioral problems in children over the past 6 months, which are rated on a scale from 0 (*not true*) to 2 (*very or often true*). In the current study, we focused on composite internalizing and externalizing symptom scores.

Genotyping. Buccal cells were collected from the inside of each child's cheek for genetic analysis during the first laboratory visit. The Qiagen DNA Micro-Kit (Qiagen Valencia, CA) was used to isolate genomic DNA (gDNA) from individual buccal cells according to manufacturer instructions (see Hayden et al., 2010, for details). Individual gDNA isolates were used to genotype the *val66met* polymorphism in the *BDNF* gene using the amplified refractory polymerase chain reaction–restriction fragment length polymorphism method described by Sheikh, Hayden, Kryski, Smith, and Singh (2010). In the current sample, 94 children (47%) were homozygous for the val/val genotype, 97 (48%) were heterozygous, and 10 (5%) were homozygous for the met/met genotype. Because of the relative infrequency of the met/met genotype in Caucasian samples (and the associated lower power), analyses compared children with the val/val genotype with those with at least one methionine allele (Hayden et al., 2010).

EEG task and materials. As previously described (Meyer et al., 2013; Torpey et al., 2012), a go/no-go task was administered using Presentation software (Neurobehavioral Systems, Inc.). The stimuli were green equilateral triangles presented in one of four different orientations for 1200 ms in the middle of the monitor. On 60% of the trials, triangles were vertically aligned and pointed up, 20% were vertically aligned and pointed down, 10% were tilted slightly to the left, and 10% were tilted slightly to the right. Children were told to respond to upward-pointing triangles by pressing a button, and to withhold a response to all other triangles. Following the presentation of the triangle, a small gray fixation cross was displayed in the middle of the monitor for between 300 and 800 ms before the next trial began. Children completed four blocks of 60 trials each.

Psychophysiological recording. The Active Two system (Biosemi, Amsterdam) was used to acquire EEG data, and 32 Ag/AgCl-tipped electrodes were used with a small amount of electrolyte gel (Signa Gel; Bio-Medical Instruments Inc., Warren, MI) at each electrode position. All data were sampled at 512 Hz. The ground electrode during acquisition was formed by the common mode sense active electrode and the driven right leg passive electrode.

Data were processed offline with a Brain Vision Analyzer (Brain Products, Gilching, Germany). EEG data were rereferenced to the nose and high- and low-pass filtered at 1.0

Table 1. *Means, standard deviations, and ranges for main study variables*

|	Mean	*SD*	Range
Observed parental hostility	1.18	0.31	1.00–3.00
PSDQ authoritarian factor	20.26	4.87	12.00–40.00
CBCL internalizing symptoms	3.45		0.00–56.00
CBCL externalizing symptoms	5.16	5.96	0.00–59.00
ΔERN	−4.75	8.38	−30.90 to 32.66

Note: PSDQ, Parenting Styles and Dimensions Questionnaire; CBCL, Child Behavior Checklist; ΔERN, change in error-related negativity.

and 30 Hz, respectively. EEG segments of 1500 ms were extracted from the continuous EEG, beginning 500 ms prior to responses. Data were then corrected for eye movements and blinks (Gratton, Coles, & Donchin, 1983), and artifacts were rejected if any of the following criteria were met: a voltage step of $>50 \mu V$ between data points, a voltage difference of 300 μV within a single trial, or a voltage difference of $<0.5 \mu V$ within 100-ms intervals. After this, data were visually inspected for remaining artifacts. ERP averages were created for error and correct trials, and a baseline of the average activity from –500 to –300 ms prior to the response was subtracted from each data point.

ERP and behavioral results in the full sample have been previously reported (Torpey et al., 2012). The ERN and cor-
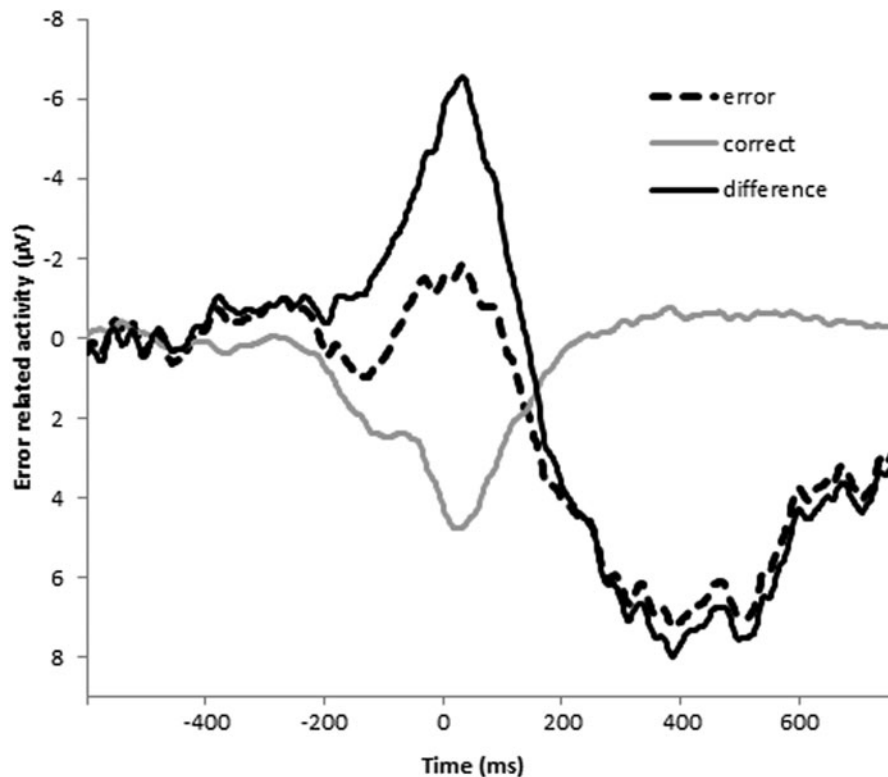
Figure 1. Response-locked event-related potential waveforms for correct (light) and error (dashed) trials, as well as the difference waveform (i.e., error minus correct, dark) for the entire sample at Fz. Negative is plotted up, and response onset occurred at 0 ms.
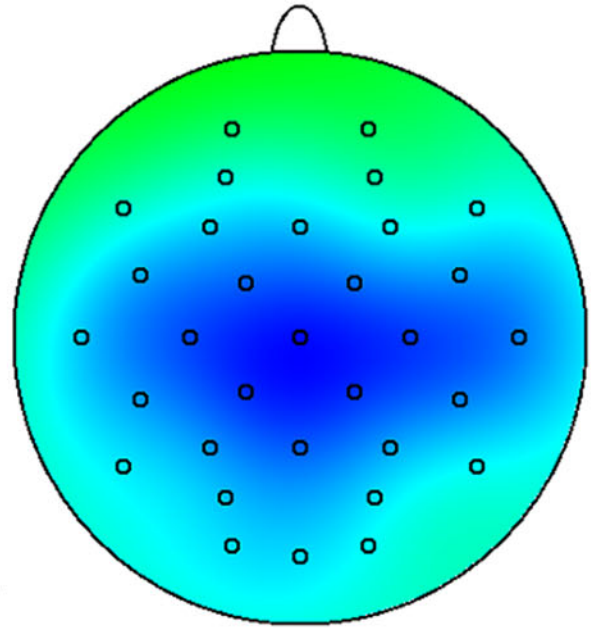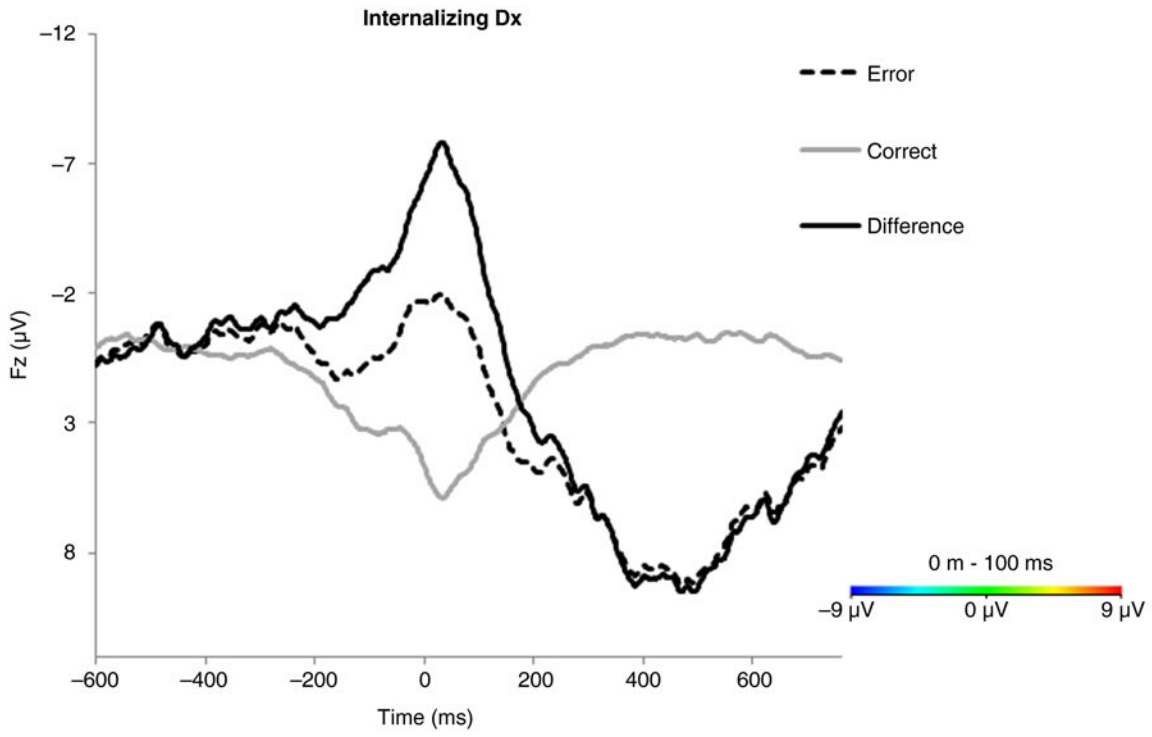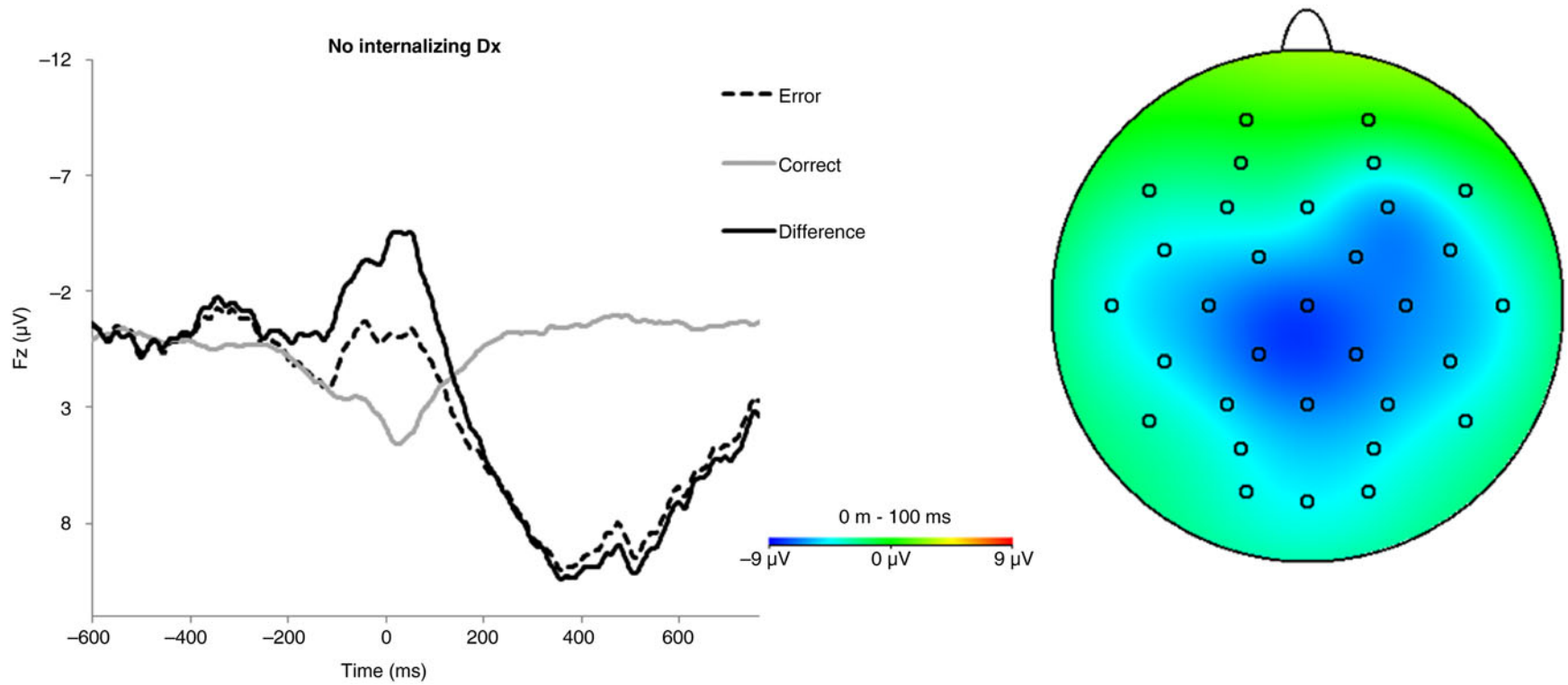
Internalizing Dx

Figure 2. (Color online) Response-locked event-related potential waveforms for correct (light) and error (dashed) trials, as well as the difference waveform (i.e., error minus correct, dark) for children with internalizing disorders (top) and children without internalizing disorder (bottom). On the right, topographical headmaps are depicted for both groups, error minus correct, from 0 to 100 ms after the response.

rect-related negativity (CRN) were scored as the average voltage in the window between 0 ms and 100 ms after response commission on error and correct trials, respectively; the CRN and ERN were quantified at Fz, where error-related brain activity was maximal. The change in ERN (ΔERN), thought to reflect error-specific activity, was calculated by subtracting the CRN from the ERN.

All statistical analyses were conducted using SPSS (Version 17.0) general linear model software, with Greenhouse–Geisser correction applied to p values with multiple degrees of freedom, repeated-measures comparisons when necessitated by violation of the assumption of sphericity. The Pearson correlation coefficient (r), one-way analyses of variance, and chi-squares (χ^2) were used to examine associations between all study variables.

We used a nonparametric bootstrapping method (MacKinnon, Lockwood, & Williams, 2004) to examine whether the *BDNF* polymorphism moderated the relationship between harsh parenting and error-related brain activity. After this, we used a bootstrapping test to explore the extent to which the *BDNF* polymorphism moderated the mediation of error-related brain activity on the relationship between parenting and child psychopathology. This approach has been shown to be more statistically powerful than other tests of moderated mediation (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). To test for moderated mediation, we used an SPSS macro (Process: Preacher & Hayes, 2004), which provided a bootstrap estimate of the indirect effect between the independent and dependent variable, an estimated standard error, and 95% confidence intervals for the population value of the indirect effect. When confidence intervals for the indirect effect do not include zero, this indicates a significant indirect effect at the $p < .05$ level. Direct and indirect effects were tested using 5,000 bootstrap samples. Process uses ordinary least squares methods for estimating two-way interactions in moderation models and estimates regions of significance using the Johnson–Neyman technique. In addition, we calculated proportion of the interaction (PoI) and proportion affected (PA) values with the web-based application (Roisman et al., 2012; http://www.yourpersonality.net/interaction/). All variables were z-scored before being included in analyses.

Results

Means, standard deviations, and ranges are provided in Table 1 for all main study variables. Consistent with previous reports from the larger sample (Meyer et al., 2013; Torpey et al., 2012), the ERP response was more negative following errors than correct responses, $F (1, 200) = 64.61, p < .001$ (see Figure 1).[5] The ΔERN was larger among children with inter-

nalizing disorders ($M = –6.51$ μV, $SD = 8.06$) compared to children without internalizing disorders ($M = –3.75$ μV, $SD = 8.42$), $F (1, 200) = 5.17, p < .05$ (see Figure 2), but did not differ between children with and without externalizing disorders, $F (1, 200) = 0.71, p = .40$. Continuous variation in CBCL internalizing and externalizing symptoms did not correlate with the ΔERN, $r (199) = –.10, p = .18$ and $r (199) = .02, p = .79$, respectively. The ΔERN also did not differ between the two *BDNF* genotype groups, $F (1, 200) = 0.05, p = .83$. As previously reported (Meyer, Proudfit, et al., 2014), an enhanced ΔERN in children was related to harsh parenting, $r (199) = –.12, p = .08$, albeit at a trend level in this smaller sample.

In addition, harsh parenting did not differ by *BDNF* genotype group, $F (1, 200) = 0.15, p = .70$. While parenting did not differ between children with and without internalizing disorders, $F (1, 200) = 0.04, p = .84$, parents of children with externalizing disorders were characterized by a harsher parenting style, $F (1, 200) = 5.98, p < .05$. This was consistent with findings from CBCL symptom scores: harsh parenting did not relate to internalizing symptoms, $r (199) = .04, p = .58$, but did relate to increased externalizing symptoms, $r (199) = .15, p < .05$. In addition, rates of both internalizing and externalizing disorders were comparable between the two *BDNF* genotype groups, $\chi^2 (1, N = 201) = 2.04, p = .15$, and $\chi^2 (1, N = 201) = 1.33, p = .25$, respectively.

Moderation of the BDNF genotype on the relationship between parenting and child error-related brain activity

We used a nonparametric bootstrapping method (MacKinnon et al., 2004) to examine whether the *BDNF* polymorphism moderated the relationship between harsh parenting and error-related brain activity. Results suggested that while the main effects of neither the *BDNF* gene nor harsh parenting were significantly related to the ΔERN in this model, both ps $> .8$, the interaction between the *BDNF* genotype and harsh parenting explained a significant amount of variance in ΔERN magnitude in children, $\Delta R^2 = .02, F (1, 197) = 3.67, p = .05$.[6] As depicted in Figure 3, among children with a methionine allele, harsh parenting was associated with an increased ΔERN, $t = –2.56, p < .01$, 95% confidence interval (CI) $[−0.45, –0.06]$. However, among children with the val/val *BDNF* genotype, harsh parenting was not associated with the ΔERN magnitude in children, $t = 0.21, p = .84$, 95%

---

5. Behavioral data for the sample has been previously reported (Meyer et al., 2013; Torpey et al., 2012). In the current sample, children were faster on error trials ($M = 503.14$ ms, $SD = 87.73$) compared to correct trials ($M = $

622.82 ms, $SD = 72.19$), $F (1, 194) = 691.34, p < .001$. Children committed an average of 25.97 ($SD = 14.07$) errors and 212.33 ($SD = 15.14$) correct responses. Neither reaction times nor accuracy related to any of the study variables (all ps $> .05$).

6. To examine whether the interaction remained significant in the full sample (including children with missing data on one of the variables of interest), we completed this same analysis in AMOS, using the estimation of means and intercepts. In the full sample ($N = 651$), the interaction of the *BDNF* genotype and harsh parenting predicting ERN magnitude remained significant (estimate = 1.78, $SE = 0.047$, capability ratio = 37.89, $p < .001$), even when including children with missing data.
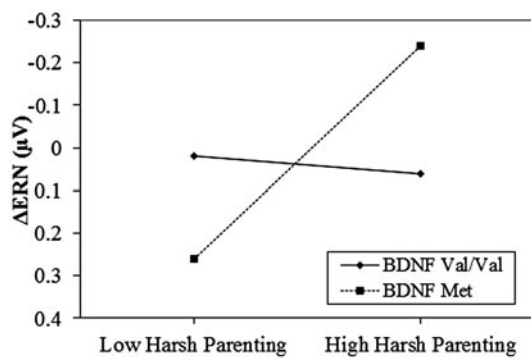
Figure 3. Depiction of the interaction between harsh parenting and the *BDNF* genotype in predicting the error-related negativity in children.

CI [−0.18, 0.23]. Probing regions of significance in the interaction indicated that differences in ΔERN magnitude between the *BDNF* groups were only apparent at high levels of harsh parenting (above 5.13, $p < .05$), with no differences evident at lower levels of harsh parenting (harsh parenting values between –2.22 and 2.26, all $ps > .10$). Trend-level differences were observed when harsh parenting values were between 2.27 and 5.13 ($ps = .06–.10$). Waveforms and topographical headmaps are depicted in Figure 4 for children with high levels of harsh parenting (median split), grouped by *BDNF* genotype (val/val vs. met).

To help distinguish differential susceptibility from diathesis–stress, Roisman et al. (2012) suggest that researchers utilize the PoI and PA index to help distinguish differential susceptibility from diathesis–stress, in addition to probing regions of significance. The PoI value provides an expression of the proportion of the total interaction that is represented on the left and right sides of the crossover point. The results suggested the PoI value was equal to 0.54. According to Roisman et al., PoI values close to 0.50 suggest strong evidence for differential susceptibility. Values closer to 0.00 suggest strong evidence for diathesis–stress. The PA index represents the proportion of the people differentially affected by the crossover interaction. Results suggested the PA value was equal to 0.53. According to Roisman et al., PA values close to 0.50 indicate strong evidence of differential susceptibility.

Moderated mediation model: Predicting internalizing disorders

We previously reported a mediation model wherein the ΔERN mediated the relationship between harsh parenting and child anxiety disorder status (Meyer, Proudfit, et al., 2014). In the current study, we examined a moderated mediation model wherein the interaction between the *BDNF* genotype and harsh parenting predicting the ΔERN mediated the relationship between parenting and internalizing disorders in children (see Figure 5). In this model, the interaction between the *BDNF* genotype and harsh parenting predicted ΔERN magnitude in children ($t = 1.92$, coefficient = 2.30,

$p = .05$). In addition, as can be seen in Table 2, the ΔERN predicted internalizing disorders, $z = –2.21$, coefficient = –0.04, $p < .05$, 95% CI [−0.67, –0.04]. While the direct path between parenting and internalizing disorders was not significant, $z = –0.08$, coefficient = –0.01, $p = .93$, 95% CI [−0.20, 0.18], the results supported a moderated mediation model, index of moderated mediation = 0.10, $SE = 0.07$, 95% CI [0.01, 0.26].[7] The pattern of the moderated mediation was consistent with the original mediation model: among children with a methionine *BDNF* genotype, the relationship between harsh parenting and internalizing disorders was mediated by ΔERN magnitude, effect = 0.09, $SE = 0.06$, 95% CI [0.01, 0.23], but this relationship was not significant among children with the val/val *BDNF* genotype, effect = –0.01, $SE = 0.04$, 95% CI [–0.10, 0.06]. In other words, the mediation of parenting to child psychopathology via error-related brain activity was contingent on the *BDNF* genotype, only occurring among children with at least one methionine allele.

In a second version of this model, we entered CBCL internalizing symptoms as the outcome, instead of disorder status. The pattern of results was consistent with the findings reported above: the interaction between the *BDNF* genotype and harsh parenting predicted ΔERN magnitude ($t = 1.81$, coefficient = –2.25, $SE = 1.24$, $p = .07$) at a trend level. In addition, the ERN predicted internalizing symptoms, $z = –2.15$, coefficient = –0.08, $SE = 0.03$, $p < .05$, 95% CI [–0.144, –0.006]. In addition, while the direct path between parenting and internalizing symptoms was not significant, $z = –1.23$, coefficient = –0.37, $SE = 0.30$, $p = .22$, 95% CI [–0.965, 0.222], the results supported a moderated mediation model, index of moderated mediation = 0.17, $SE = 0.12$, 95% CI [0.015, 0.562].

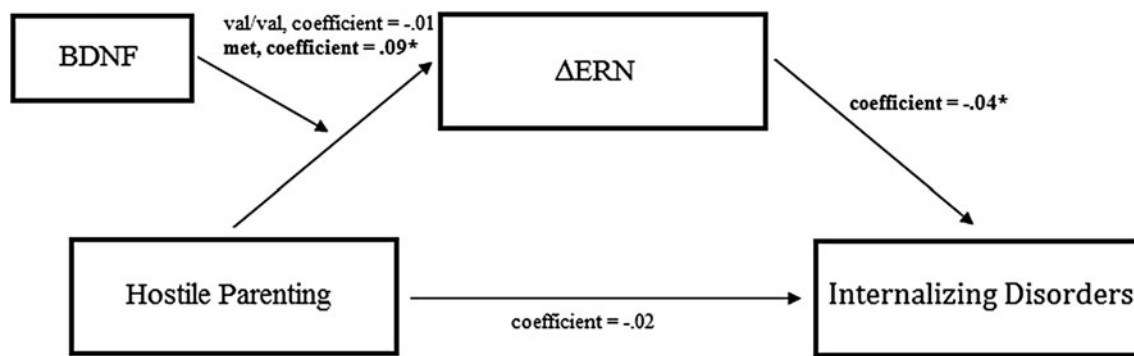### Moderated mediation model: Predicting externalizing disorders

To examine specificity, we ran a second model, using the same moderated mediation pattern described above, this time predicting externalizing disorders instead of internalizing disorders (see Figure 6 and Table 3). Again, in this model, the interaction between the *BDNF* genotype and harsh parenting predicted ΔERN magnitude ($t = 1.92$, coefficient = 2.30, $SE = 1.20$, $p = .05$). However, ΔERN magnitude did not predict externalizing disorders in children, $z = 1.19$, coefficient = 0.49, $SE = 0.19$, $p = .23$, 95% CI [−0.16, 0.66]. Although the results did not support a moderated mediation model, index of moderated mediation = −0.04, $SE = 0.09$, 95% CI

---

7. When children with comorbid internalizing and externalizing disorders were excluded from the analysis ($N = 14$), the pattern of results was consistent, that is, results suggested a significant moderated mediation model predicting internalizing disorders, index of moderated mediation = 0.14, 95% CI [0.018, 0.361]. In addition, when all children with externalizing disorders were excluded from the analysis, the pattern of results also supported a significant moderated mediation model predicting internalizing disorders, index of moderated mediation = 0.09, 95% CI [0.001, 0.305].

High Harsh Parenting:
BDNF Met

11
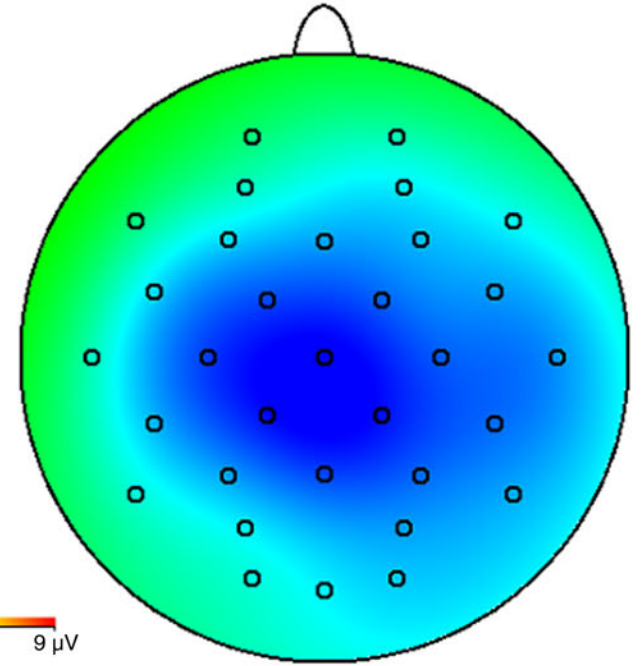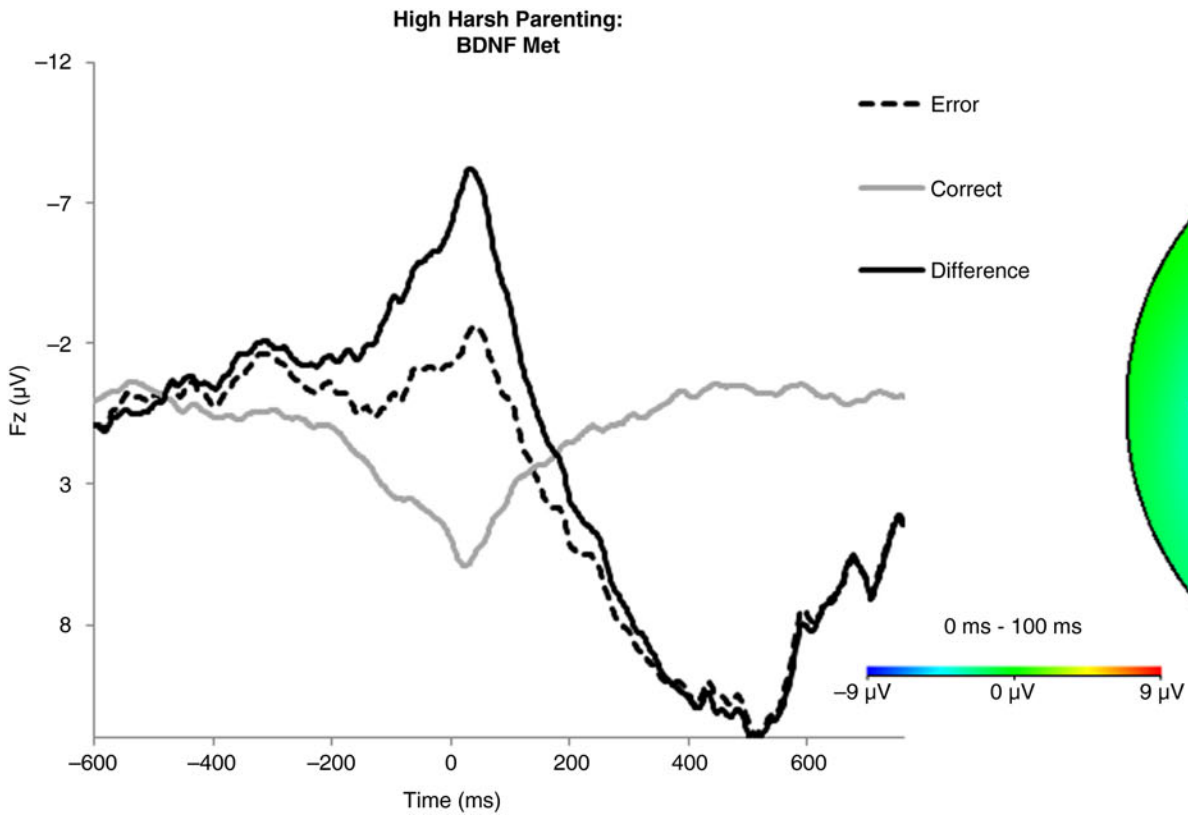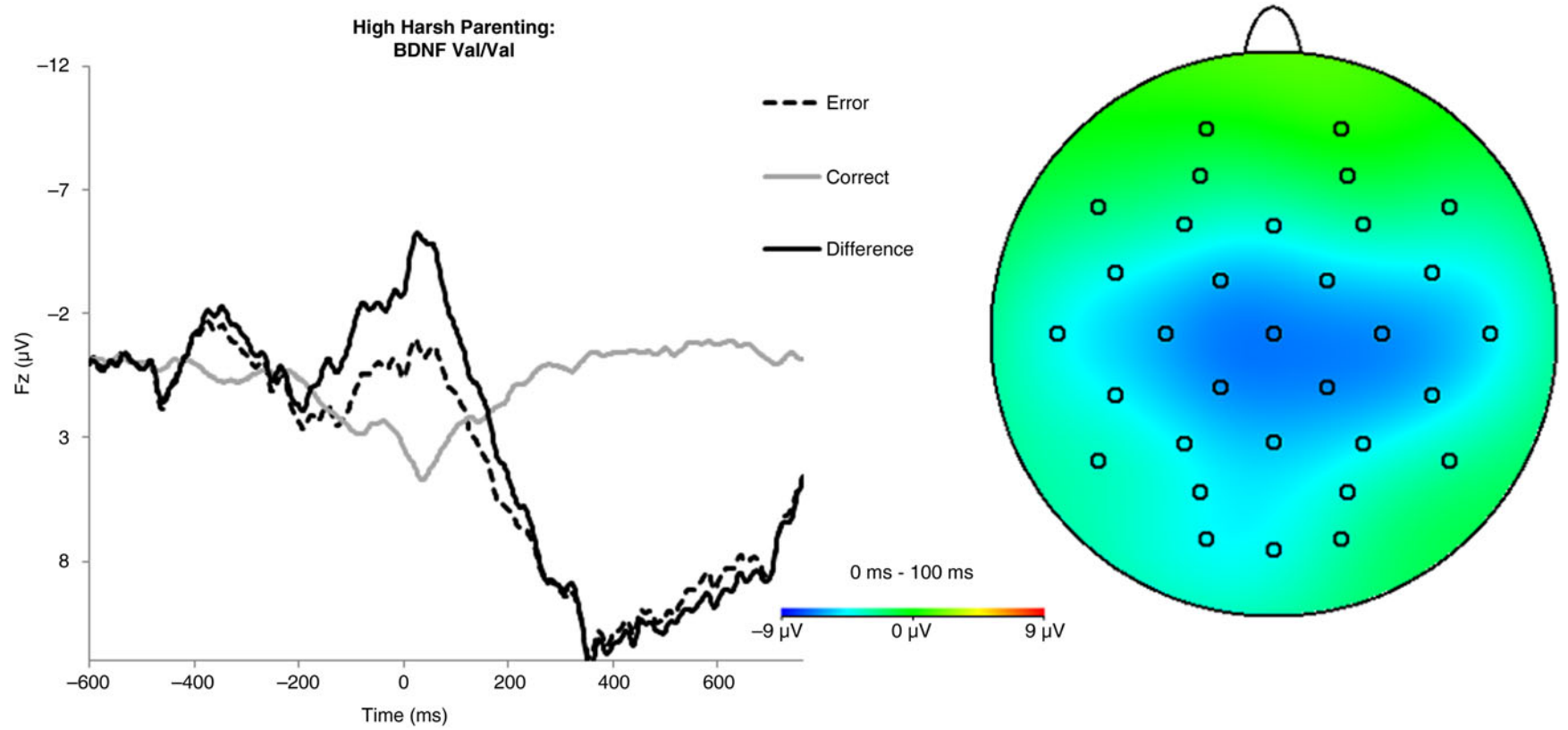
Figure 4. (Color online) Response-locked event-related potential waveforms for correct (light) and error (dashed) trials, as well as the difference waveform (i.e., error minus correct, dark) for children with the *BDNF* met genotype (top) and children with the *BDNF* val/val genotype (bottom). On the right, topographical headmaps are depicted for both groups, error minus correct, from 0 to 100 ms after the response.

Figure 5. A moderation mediation model with harsh parenting predicting internalizing disorders, wherein this relationship is mediated by the interaction between the *BDFN* genotype and harsh parenting predicting the magnitude of change in children's event-related negativity. *$p < .05$.

Table 2. *Moderated mediation model: Predicting internalizing disorders*

	Coeff.	SE	z	p	LLCI	ULCI
Direct effect						
ΔERN on internalizing	−0.04	0.02	−2.21	<.05	**−0.67***	**−0.04***
Hostile parenting on internalizing	−0.02	0.15	−0.08	.93	−0.20	0.18
Conditional indirect effects of hostile parenting on internalizing by *BDNF* group						
Val/val	−0.01	0.04	—	—	−0.10	0.06
Met	0.09	0.05	—	—	**0.01***	**0.23***
Full model: index of moderated mediation	0.10	0.07	—	—	**0.01***	**0.26***

Note: ΔERN, change in error-related negativity; *BDNF*, brain-derived neurotrophic factor gene; Val, valine; Met, methionine; LLCI, lower level confidence interval; ULCI, upper level confidence interval.
*$p < .05$.

[–0.18, 0.05], the direct path between harsh parenting and externalizing disorders was significant, $z = 2.48$, coefficient = 0.49, $SE = 0.20$, $p < .01$, 95% CI [0.07, 0.57], such that harsher parenting was associated with an increased rate of externalizing disorders in children.[8]

In a second version of this model, we entered CBCL externalizing *symptoms* as the outcome, instead of disorder status.

---

8. Our sample included 5 Asian children (out of 201). The results from χ^2 analyses suggest that BDNF expression did differ in Asian children: all 5 were methionine dominant ($\chi^2 = 4.12$, $p < .05$). However, BDNF expression did not differ by any other ethnic group (all $ps > .10$). We reexamined a moderation mediation model wherein the interaction between the *BDNF* genotype and harsh parenting predicting the ΔERN mediated the relationship between parenting and internalizing disorders in children, excluding those 5 children who identified as Asian. The pattern of results was the same as reported in the manuscript: among children with a methionine *BDNF* genotype, the relationship between harsh parenting and internalizing disorders was mediated by ΔERN magnitude, index of moderated mediation = 0.08, 95% CI [0.007, 0.252]. When children with comorbid internalizing and externalizing disorders were excluded from the analysis ($N = 14$), the pattern of results was consistent, that is, the moderated mediation model predicting externalizing disorders did not reach significance, index of moderated mediation = –0.13, 95% CI [–0.435, 0.046]. In addition, when all children with internalizing disorders were excluded from the analysis, the moderated mediation model did not reach significance, index of moderated mediation = –0.07, 95% CI [–0.485, 0.055].

The pattern of results was broadly consistent with the findings reported above: the interaction between the *BDNF* genotype and harsh parenting predicted ΔERN magnitude ($t = 1.86$, coefficient = 2.30, $SE = 1.24$, $p = .06$) at a trend level. In this model, however, ΔERN magnitude predicted externalizing symptoms at a trend level, $z = 1.79$, coefficient = 0.07, $SE = 0.04$, $p = .07$, 95% CI [–0.007, 0.147]. Although results did not support a moderated mediation model, index of moderated mediation = –0.16, $SE = 0.15$, 95% CI [–0.592, 0.065], the direct path between harsh parenting externalizing symptoms was significant, $z = 2.35$, coefficient = 0.78, $SE = 0.33$, $p < .01$, 95% CI [0.125, 1.430].

Discussion

Overall, the results were consistent with our hypotheses: the *BDNF* genotype interacted with harsh parenting such that harsh parenting only related to an increased ERN among children carrying at least one methionine allele. Among children with the *BDNF* val/val genotype, parenting did not relate to ERN magnitude. In addition, the mediation of parenting to internalizing disorders in children via error-related brain activity was contingent on the *BDNF* genotype, but this relationship was evident only among children with at least one
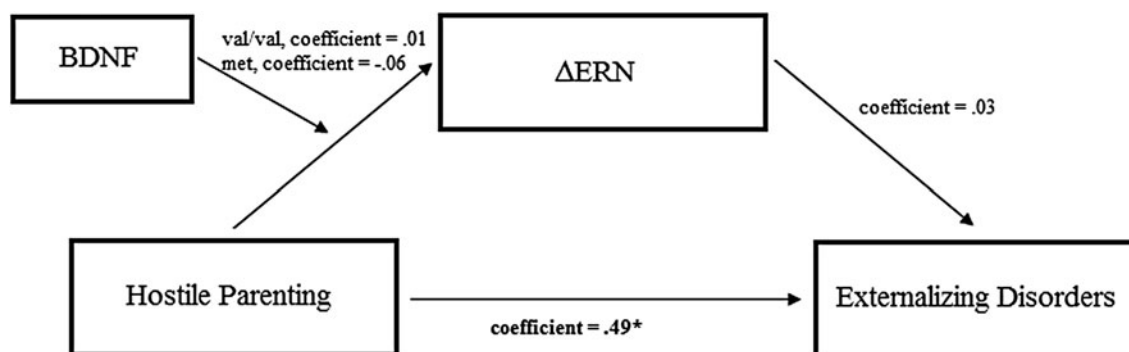
Figure 6. A moderation mediation model with harsh parenting predicting externalizing disorders, wherein this relationship is mediated by the interaction between the *BDFN* genotype and harsh parenting predicting the magnitude of change in children's event-related negativity. *$p < .05$.

Table 3. *Moderated mediation model: Predicting externalizing disorders*

	Coeff.	*SE*	z	*p*	LLCI	ULCI
Direct effect						
ΔERN on externalizing	0.03	0.03	1.19	.23	−0.16	0.66
Hostile parenting on externalizing	0.49	0.20	2.48	<.01	**0.07***	**0.57***
Conditional indirect effects of hostile parenting on externalizing by *BDNF* group						
Val/val	0.01	0.04	—	—	−0.04	0.12
Met	−0.06	0.08	—	—	−0.20	0.11
Full model: index of moderated mediation	−0.04	0.09	—	—	−0.18	0.05

Note: ΔERN, change in error-related negativity; *BDNF*, brain-derived neurotrophic factor gene; Val, valine; Met, methionine; LLCI, lower level confidence interval; ULCI, upper level confidence interval.
*$p < .05$.

methionine allele. Furthermore, while harsh parenting was related to an increased rate of externalizing disorders in children, the mediation via *BDNF* and ERN was not significant, suggesting unique mechanisms whereby parenting is related to internalizing versus externalizing outcomes in children. The pattern of results was the same whether diagnoses from a clinical interview or dimensional symptom measures from a parent report were used as the outcome variable, lending further support to the current findings.

Consistent with previous work suggesting that punishing errors has a lasting impact on the ERN (Meyer et al., 2017; Riesel et al., 2012), harsh parenting was related to an increased ERN magnitude in children (Meyer, Proudfit, et al., 2014). We extended previous findings in this sample by exploring whether the *BDNF* genotype moderated the effects of parenting in predicting the ERN, and found that parenting only related to error processing among children with a methionine allele. Previous work suggests that carriers of the *BDNF* methionine allele are more affected by parenting behavior (Ibarra et al., 2014; Park et al., 2014; Suzuki et al., 2012; Willoughby et al., 2013), display deficits in extinction learning (Johnson & Casey, 2014; Peters et al., 2010; Soliman et al., 2010), and are more susceptible to psychopathology (Neves-Pereira et al., 2002; Sen et al., 2003; Sklar et al.,

2002). Harsh parenting may operate in a similar way as fear-learning paradigms in the lab, wherein children associate making mistakes with punishment (i.e., parental criticism). Perhaps children with a methionine allele are unable to extinguish this learned association, despite experiencing other situations in which their mistakes are not paired with punishment. The possibility that the deficit in extinction learning that characterizes *BDNF* methionine allele carriers underlies the association between harsh parenting and ERN magnitude in children could be explored in future studies that also measure extinction learning in the lab.

In addition, when probing regions of significance in the interaction between parenting and the *BDNF* genotype, results indicated that differences in ΔERN magnitude between the *BDNF* groups were only apparent at high levels of harsh parenting. However, findings from the PoI and PA analysis support a *differential susceptibility model*. This model assumes that sources of vulnerability (i.e., the *BDNF* methionine allele) are actually plasticity factors that not only amplify risk for maladaptation but also increase the probability of positive adaptation (Roisman et al., 2012). This fits with other research indicating that the *BDNF* methionine allele may function as a neuronal plasticity factor (Cheeran et al., 2008). This finding has implications for intervention work insofar as chil-

dren with the methionine allele may be more impacted not only by hostile parenting but also by more positive parenting practices. In other words, these children may be particularly impacted by parenting and thus ideal targets for intervention strategies that include parenting components.

Children with internalizing disorders were also characterized by increased error-related brain activity. As previously discussed, this is consistent with a large body of work suggesting that individuals with internalizing disorders and traits display increased ERNs, which has been hypothesized to reflect an increased sensitivity and defensive response to errors, or perhaps more broadly, increased responding to internal sources of threat (Hajcak, 2012; Weinberg et al., in press). Inconsistent with some previous findings, we did not find a relationship between the magnitude of the ERN and externalizing disorders. One reason for this could be the relatively smaller number of children with externalizing disorders in the sample, leading to insufficient power to detect this relationship. Another reason may be the substantial comorbidity between internalizing and externalizing disorders in this sample. Consistent with this, in a post hoc analysis wherein we removed all children with internalizing disorders from the sample, children with externalizing disorders were characterized by a blunted ERN. Future work should explore the degree to which comorbidity of internalizing and externalizing psychopathology may influence error-related brain activity in children.

Extending our previous work, by examining *both* internalizing and externalizing outcomes, we found evidence for specificity in terms of delineating trajectories from parenting to psychopathology in children. By investigating a genotype (i.e., *BDNF*), an environmental factor (i.e., harsh parenting), and a neural marker (i.e., the ERN), we were able to further characterize pathways leading to divergent psychopathology outcomes (Beauchaine & McNulty, 2013). We found that harsh parenting only related to children's error processing if children carried the *BDNF* methionine allele, and that this pathway explained a significant amount of variance in the relationship between harsh parenting and internalizing disorders. In contrast, this mediated pathway through the ERN did not predict externalizing outcomes, which were instead directly predicted by harsh parenting.

It is important to consider limitations of the current investigation. As previously mentioned, only 25 children in the current sample had an externalizing disorder, and we may have not had sufficient power to detect associations and/or interactions with the ERN. In addition, the amount of variance in the ERN predicted by the parenting/BDNF interaction was small (2%). While we would not expect a single genetic polymorphism to explain a large amount of variance in psychological outcomes, the clinical application of the current findings in isolation would be relatively limited. Future work might identify other interactions between risk factors and genes to be used in conjunction with the current findings.

Previous work in humans and other animals supports the notion that parenting behavior has a substantial impact on brain development and stress reactivity in offspring (Caldji et al., 1998; Francis, Diorio, Liu, & Meaney, 1999; Kertes et al., 2009; Kryski et al., 2013; Teicher et al., 2003). Some work has suggested that parenting may program biological responses to threatening stimuli through epigenetic mechanisms, allowing offspring to thrive under the unique demands of their environment (Francis et al., 1999). The findings from the current study support this notion insofar as harsh parenting may increase the threatening nature of errors and thereby potentiate children's neural response to their own mistakes, especially in children with relatively less available BDNF. It is possible that other measures of threat sensitivity may also be differentially impacted by parenting as a function of *BDNF* genotype (e.g., startle response, amygdala reactivity, and cortisol reactivity), and these processes may then also characterize developmental trajectories leading to psychopathology. Future work should explore these possibilities.

Previous work has suggested that magnitude of the ERN increases across development (Tamnes, Walhovd, Torstveit, Sells, & Fjell, 2013), reaching adultlike levels around age 18. Although we were unable to test this in the current study, it is possible that children with the methionine allele who experienced harsh parenting early in life experienced a greater developmental increase in the ERN than other children. Future work could explore whether the normative increase in the ERN magnitude across development is greater in some subgroups of children (e.g., with the *BDNF* methionine allele, with harsh parents, or with increases in anxiety) than in others.

It is also important to consider that genetic and environmental influences most likely shift in importance across the life span (Bergen et al., 2007). For example, the region of the brain wherein the ERN is generated, the anterior cingulate cortex, demonstrates more environmental plasticity later in development relative to early childhood (Lenroot et al., 2009). In addition, previous work has suggested that BDNF levels substantially increase across development so that the deficit in BDNF levels found in methionine allele carriers may have a specific impact on learning *earlier* in development (Casey et al., 2009). Parenting may also become less important across development as peer groups increase their influence on behavior (Larson & Richards, 1991). Thus, it will be important for future work to consider both environmental and genetic factors as having a dynamic impact on outcomes across development in order to accurately characterize pathological trajectories and perhaps identify critical risk periods wherein certain factors are particularly related to subsequent outcomes.

Finally, identifying critical periods wherein specific genotypes and/or environmental influences are important may aid us in early intervention strategies (Beauchaine et al., 2008). Previous work has suggested that early parenting interventions may alter the trajectory of psychopathology in at-risk children (e.g., Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2010). In the future, it may be possible to target children,

for example, in a certain age range, with specific genotypes (e.g., *BDNF*), neural risk markers (e.g., an increased ERN), and other risk factors, for early parenting interventions. By

taking a targeted, or personalized, approach, we may be better able to allocate resources toward preventing life-long pathological trajectories (Shoham & Insel, 2011).

References

Achenbach, T. M., & Edelbrock, C. (1981). *Child Behavior Checklist*: Burlington, VT: University of Vermont, Department of Psychiatry.

Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., . . . Banaschewski T. (2008). Action monitoring in boys with attention-deficit/hyperactivity disorder, their nonaffected siblings, and normal control subjects: Evidence for an endophenotype. *Biological Psychiatry*, *64*, 615–625.

Amodio, D. M., Master, S. L., Yee, C. M., & Taylor, S. E. (2008). Neurocognitive components of the behavioral inhibition and activation systems: Implications for theories of self-regulation. *Psychophysiology*, *45*, 11–19.

Anokhin, A. P., Golosheykin, S., & Heath, A. C. (2008). Heritability of frontal brain function related to action monitoring. *Psychophysiology*, *45*, 524–534.

Beauchaine, T. P., & Gatzke-Kopp, L. M. (2012). Instantiating the multiple levels of analysis perspective in a program of study on externalizing behavior. *Development and Psychopathology*, *24*, 1003–1018.

Beauchaine, T. P., & McNulty, T. (2013). Comorbidities and continuities as ontogenic processes: Toward a developmental spectrum model of externalizing psychopathology. *Development and Psychopathology*, *25*, 1505–1528.

Beauchaine, T. P., Neuhaus, E., Brenner, S. L., & Gatzke-Kopp, L. (2008). Ten good reasons to consider biological processes in prevention and intervention research. *Development and Psychopathology*, *20*, 745–774.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *Psychiatric Clinics of North America*, *32*, 483–524.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885.

Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: A meta-analysis. *Twin Research and Human Genetics*, *10*, 423–433.

Bögels, S. M., & van Melick, M. (2004). The relationship between child-report, parent self-report, and partner report of perceived parental rearing behaviors and anxiety in children and parents. *Personality and Individual Differences*, *37*, 1583–1596.

Boksem, M. A. S., Tops, M., Wester, A. E., Meijman, T. F., & Lorist, M. M. (2006). Error-related ERP components and individual differences in punishment and reward sensitivity. *Brain Research*, *1101*, 92–101.

Brooker, R. J., & Buss, K. A. (2014). Harsh parenting and fearfulness in toddlerhood interact to predict amplitudes of preschool error-related negativity. *Developmental Cognitive Neuroscience*, *9*, 148–159.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*, 215–222.

Caldji, C., Tannenbaum, B., Sharma, S., Francis, D., Plotsky, P. M., & Meaney, M. J. (1998). Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proceedings of the National Academy of Sciences*, *95*, 5335–5340.

Carrasco, M., Harbin, S. M., Nienhuis, J. K., Fitzgerald, K. D., Gehring, W. J., & Hanna, G. L. (2013). Increased error-related brain activity in youth with obsessive-compulsive disorder and unaffected siblingseased error-related brain activity in youth with obsessive-compulsive disorder and unaffected siblings. *Depression and Anxiety*, *30*, 39–46.

Casey, B., Glatt, C. E., Tottenham, N., Soliman, F., Bath, K., Amso, D., . . . Levita L. (2009). Brain-derived neurotrophic factor as a model system for examining gene by environment interactions across development. *Neuroscience*, *164*, 108–120.

Cheeran, B., Talelli, P., Mori, F., Koch, G., Suppa, A., Edwards, M., . . . Rothwell J. C. (2008). A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *Journal of Physiology*, *586*, 5717–5725.

Chiu, P., & Deldin, P. (2007). Neural evidence for enhanced error detection in major depressive disorder. *American Journal of Psychiatry*, *164*, 608–616.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., von Cramon, D. Y., & Engel, A. K. (2005). Trial-by-trial coupling of concurrent electroenceph-

alogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *Journal of Neuroscience*, *25*, 11730–11737.

Dehaene, S., Posner, M. I., & Don, M. T. (1994). Localization of a neural system for error detection and compensation. *Psychological Science*, *5*, 303–305.

Dikman, Z. V., & Allen, J. J. (2000). Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology*, *37*, 43–54.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., . . . Dean M. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112*, 257–269.

Egeland, B., Weinfield, N., Hiester, M., Lawrence, C., Pierce, S., Chippendale, K., & Powell, J. (1995). *Teaching tasks administration and scoring manual*. Unpublished manuscript, University of Minnesota.

Egger, H. L., Ascher, B. H., & Angold, A. (1999). *The Preschool Age Psychiatric Assessment: Version 1.1*. Durham, NC: Duke University Medical Center, Department of Psychiatry and Behavioral Sciences, Center for Developmental Epidemiology.

Egger, H. L., Erkanli, A., Keeler, G., Potts, E., Walter, B. K., & Angold, A. (2006). Test-retest reliability of the Preschool Age Psychiatric Assessment (PAPA). *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*, 538–549.

Endrass, T., Klawohn, J., Schuster, F., & Kathmann, N. (2008). Overactive performance monitoring in obsessive-compulsive disorder: ERP evidence from correct and erroneous reactions. *Neuropsychologia*, *46*, 1877–1887.

Endrass, T., Schuermann, B., Kaufmann, C., Spielberg, R., Kniesche, R., & Kathmann, N. (2010). Performance monitoring and error significance in patients with obsessive-compulsive disorder. *Biological Psychology*, *84*, 257–263.

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components: II. *Error processing in choice reaction tasks*. Electroencephalography and Clinical Neurophysiology, *78*, 447–455.

Francis, D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*, *286*, 1155–1158.

Franken, I. H., van Strien, J. W., Franzek, E. J., & van de Wetering, B. J. (2007). Error-processing deficits in patients with cocaine dependence. *Biological Psychology*, *75*, 45–51.

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science*, *4*, 385–390.

Gehring, W. J., Himle, J., & Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, *11*, 1–6.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, *55*, 468–484.

Groen, Y., Wijers, A. A., Mulder, L. J., Waggeveld, B., Minderaa, R. B., & Althaus, M. (2008). Error and feedback processing in children with ADHD and children with autistic spectrum disorder: An EEG event-related potential study. *Clinical Neurophysiology*, *119*, 2476–2493.

Gründler, T. O. J., Cavanagh, J. F., Figueroa, C. M., Frank, M. J., & Allen, J. J. B. (2009). Task-related dissociation in ERN amplitude as a function of obsessive–compulsive symptoms. *Neuropsychologia*, *47*, 1978–1987.

Hajcak, G. (2012). What we've learned from mistakes. *Current Directions in Psychological Science*, *21*, 101–106.

Hajcak, G., Franklin, M. E., Foa, E. B., & Simons, R. F. (2008). Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *American Journal of Psychiatry*, *165*, 116–123.

Hajcak, G., McDonald, N., & Simons, R. F. (2004). Error-related psychophysiology and negative affect. *Brain and Cognition*, *56*, 189–197.

Hajcak, G., & Simons, R. F. (2002). Error-related brain activity in obsessive–compulsive undergraduates. *Psychiatry Research*, *110*, 63–72.

Hall, J. R., Bernat, E. M., & Patrick, C. J. (2007). Externalizing psychopathology and the error-related negativity. *Psychological Science*, *18*, 326–333.

Hayden, E. P., Klein, D. N., Dougherty, L. R., Olino, T. M., Dyson, M. W., Durbin, C. E., . . . Singh S. M. (2010). The role of brain-derived neurotrophic factor genotype, parental depression, and relationship discord in predicting early-emerging negative emotionality. *Psychological Science*, *21*, 1678–1685.

Heim, C., & Nemeroff, C. B. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry*, *46*, 1509–1522.

Hermann, C., Ziegler, S., Birbaumer, N., & Flor, H. (2002). Psychophysiological and subjective indicators of aversive Pavlovian conditioning in generalized social phobia. *Biological Psychiatry*, *52*, 328–337.

Hoffmann, S., & Falkenstein, M. (2010). Independent component analysis of erroneous and correct responses suggests online response control. *Human Brain Mapping*, *31*, 1305–1315.

Holmes, A. J., & Pizzagalli, D. A. (2008). Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Archives of General Psychiatry*, *65*, 179–188.

Holmes, A. J., & Pizzagalli, D. A. (2010). Effects of task-relevant incentives on the electrophysiological correlates of error processing in major depressive disorder. *Cognitive, Affective, & Behavioral Neuroscience*, *10*, 119–128.

Ibarra, P., Alemany, S., Fatjó-Vilas, M., Córdova-Palomera, A., Goldberg, X., Arias, B., . . . Fañanás L. (2014). The BDNF Val66Met polymorphism modulates parental rearing effects on adult psychiatric symptoms: A community twin-based study. *European Psychiatry*. Advance online publication.

Johnson, D., & Casey, B. (2014). Easy to remember, difficult to forget: The development of fear regulation. *Developmental Cognitive Neuroscience*. Advance online publication.

Kawamura, K. Y., Frost, R. O., & Harmatz, M. G. (2002). The relationship of perceived parenting styles to perfectionism. *Personality and Individual Differences*, *32*, 317–327.

Kertes, D. A., Donzella, B., Talge, N. M., Garvin, M. C., Van Ryzin, M. J., & Gunnar, M. R. (2009). Inhibited temperament and parent emotional availability differentially predict young children's cortisol responses to novel social and nonsocial events. *Developmental Psychobiology*, *51*, 521–532.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*, 593–602.

Kryski, K. R., Dougherty, L. R., Dyson, M. W., Olino, T. M., Laptook, R. S., Klein, D. N., & Hayden, E. P. (2013). Effortful control and parenting: Associations with HPA axis reactivity in early childhood. *Developmental Science*, *16*, 531–541.

Ladouceur, C. D., Dahl, R. E., Birmaher, B., Axelson, D. A., & Ryan, N. D. (2006). Increased error-related negativity (ERN) in childhood anxiety disorders: ERP and source localization. *Journal of Child Psychology and Psychiatry*, *47*, 1073–1082.

Larson, R., & Richards, M. H. (1991). Daily companionship in late childhood and early adolescence: Changing developmental contexts. *Child Development*, *62*, 284–300.

Last, C. G., Perrin, S., Hersen, M., & Kazdin, A. E. (1996). A prospective study of childhood anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *35*, 1502–1510.

Lenroot, R. K., Schmitt, J. E., Ordaz, S. J., Wallace, G. L., Neale, M. C., Lerch, J. P., . . . Giedd J. N. (2009). Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Human Brain Mapping*, *30*, 163–174.

Luijten, M., Machielsen, M. W., Veltman, D. J., Hester, R., de Haan, L., & Franken, I. H. (2014). Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *Journal of Psychiatry & Neuroscience*, *39*, 149.

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*, *7*, 83.

MacKinnon, D. P., Lockwood, C. M., & Williams, J. (2004). Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivariate Behavioral Research*, *39*, 99–128.

Marhe, R., van de Wetering, B. J., & Franken, I. H. (2013). Error-related brain activity predicts cocaine use after treatment at 3-month follow-up. *Biological Psychiatry*, *73*, 782–788.

McDermott, J. M., Perez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry*, *65*, 445–448.

McKee, L., Colletti, C., Rakow, A., Jones, D. J., & Forehand, R. (2008). Parenting and child externalizing behaviors: Are the associations specific or diffuse? *Aggression and Violent Behavior*, *13*, 201–215.

Meyer, A., Bress, J., & Proudfit, G. H. (2014). Psychometric properties of the error-related negativity in children and adolescents. *Psychophysiology*. Advance online publication.

Meyer, A., Gawlowska, M., & Hajcak, G. (2017). *Enhanced error-related negativity is specific to punishment condition in high trait anxiety.* Manuscript submitted for publication.

Meyer, A., Hajcak, G., Torpey, D. C., Kujawa, A., Kim, J., Bufferd, S., . . . Klein D. N. (2013). Increased error-related brain activity in six-year-old children with clinical anxiety. *Journal of Abnormal Child Psychology*, *41*, 1257–1266.

Meyer, A., Hajcak, G., Torpey-Newman, D. C., Kujawa, A., & Klein, D. N. (in press). Enhanced error-related brain activity in children predicts the onset of anxiety disorders between the ages of 6 and 9. *Journal of Abnormal Psychology*.

Meyer, A., Proudfit, G. H., Bufferd, S. J., Kujawa, A. J., Laptook, R. S., Torpey, D. C., & Klein, D. N. (2014). Self-reported and observed punitive parenting prospectively predicts increased error-related negativity in six-year-old children. *Journal of Abnormal Child Psychology*. Advance online publication.

Meyer, A., Weinberg, A., Klein, D. N., & Hajcak, G. (2012). The development of the error-related negativity (ERN) and its relationship with anxiety: Evidence from 8- to 13 year-olds. *Developmental Cognitive Neuroscience*, *2*, 152–161.

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, *110*, 406.

Munro, G. E., Dywan, J., Harris, G. T., McKee, S., Unsal, A., & Segalowitz, S. J. (2007). ERN varies with degree of psychopathy in an emotion discrimination task. *Biological Psychology*, *76*, 31–42.

Neves-Pereira, M., Mundo, E., Muglia, P., King, N., Macciardi, F., & Kennedy, J. L. (2002). The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: Evidence from a family-based association study. *American Journal of Human Genetics*, *71*, 651–655.

Olino, T. M., Klein, D. N., Dyson, M. W., Rose, S. A., & Durbin, C. E. (2010). Temperamental emotionality in preschool-aged children and depressive disorders in parents: Associations in a large community sample. *Journal of Abnormal Psychology*, *119*, 468.

Olvet, D. M., & Hajcak, G. (2008). The error-related negativity (ERN) and psychopathology: Toward an endophenotype. *Clinical Psychology Review*, *28*, 1343–1354.

Olvet, D. M., Klein, D. N., & Hajcak, G. (2010). Depression symptom severity and error-related brain activity. *Psychiatry Research*, *179*, 30–37.

Park, S., Kim, B.-N., Kim, J.-W., Jung, Y.-K., Lee, J., Shin, M.-S., . . . Cho S.-C. (2014). The role of the brain-derived neurotrophic factor genotype and parenting in early life in predicting externalizing and internalizing symptoms in children with attention-deficit hyperactivity disorder. *Behavioral and Brain Functions*, *10*, 43.

Peters, J., Dieppa-Perea, L. M., Melendez, L. M., & Quirk, G. J. (2010). Induction of fear extinction with hippocampal-infralimbic BDNF. *Science*, *328*, 1288–1290.

Pine, D. S. (2007). Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology & Psychiatry*, *48*, 631–648.

Potts, G. F., George, M. R. M., Martin, L. E., & Barratt, E. S. (2006). Reduced punishment sensitivity in neural systems of behavior monitoring in impulsive individuals. *Neuroscience Letters*, *397*, 130–134.

Pourtois, G., Vocat, R., N'diaye, K., Spinelli, L., Seeck, M., & Vuilleumier, P. (2010). Errors recruit both cognitive and emotional monitoring systems: Simultaneous intracranial recordings in the dorsal anterior cingulate gyrus and amygdala combined with fMRI. *Neuropsychologia*, *48*, 1144–1159.

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, and Computers*, *36*, 717–731.

Rapee, R. M., Kennedy, S. J., Ingram, M., Edwards, S. L., & Sweeney, L. (2010). Altering the trajectory of anxiety in at-risk young children. *American Journal of Psychiatry*, *167*, 1518–1525.

Riesel, A., Endrass, T., Kaufmann, C., & Kathmann, N. (2011). Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: Evidence from unaffected first-degree relatives. *American Journal of Psychiatry*, *168*, 317–324.

Riesel, A., Weinberg, A., Endrass, T., Kathmann, N., & Hajcak, G. (2012). Punishment has a lasting impact on error-related brain activity. *Psychophysiology*, *49*, 239–247.

Robinson, C., Mandleco, B., Olsen, S. F., & Hart, C. (2001). The Parenting Styles and Dimensions Questionnaire (PSDQ). *Handbook of Family Measurement Techniques*, *3*, 319–321.

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis–stress: Recommendations for evaluating interaction effects. *Development and Psychopathology*, *24*, 389–409.

Ruchsow, M., Grön, G., Reuter, K., Spitzer, M., Hermle, L., & Kiefer, M. (2005). Error-related brain activity in patients with obsessive-compulsive disorder and in healthy controls. *Journal of Psychophysiology*, *19*, 298–304.

Ruchsow, M., Spitzer, M., Grön, G., Grothe, J., & Kiefer, M. (2005). Error processing and impulsiveness in normals: Evidence from event-related potentials. *Cognitive Brain Research*, *24*, 317–325.

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry*, *47*, 276–295.

Santesso, D. L., Segalowitz, S. J., & Schmidt, L. A. (2006). Error-related electrocortical responses are enhanced in children with obsessive-compulsive behaviors. *Developmental Neuropsychology*, *29*, 431–445.

Sen, S., Nesse, R. M., Stoltenberg, S. F., Li, S., Gleiberman, L., Chakravarti, A., . . . Burmeister M. (2003). A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology*, *28*, 397–401.

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience*, *12*, 154–167.

Sheikh, H. I., Hayden, E. P., Kryski, K. R., Smith, H. J., & Singh, S. M. (2010). Genotyping the BDNF rs6265 (val66met) polymorphism by one-step amplified refractory mutation system PCR. *Psychiatric Genetics*, *20*, 109.

Shoham, V., & Insel, T. R. (2011). Rebooting for whom? Portfolios, technology, and personalized intervention. *Perspectives on Psychological Science*, *6*, 478–482.

Sklar, P., Gabriel, S., McInnis, M., Bennett, P., Lim, Y., Tsan, G., . . . Owen M. (2002). Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. *Molecular Psychiatry*, *7*, 579–593.

Soliman, F., Glatt, C. E., Bath, K. G., Levita, L., Jones, R. M., Pattwell, S. S., . . . Somerville L. H. (2010). A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science*, *327*, 863–866.

Suzuki, A., Matsumoto, Y., Shibuya, N., Ryoichi, S., Kamata, M., Enokido, M., . . . Otani K. (2012). Interaction effect between the BDNF Val66Met polymorphism and parental rearing for interpersonal sensitivity in healthy subjects. *Psychiatry Research*, *200*, 945–948.

Tamnes, C. K., Walhovd, K. B., Torstveit, M., Sells, V. T., & Fjell, A. M. (2013). Performance monitoring in children and adolescents: A review of developmental changes in the error-related negativity and brain maturation. *Developmental Cognitive Neuroscience*, *6*, 1–13.

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & Biobehavioral Reviews*, *27*, 33–44.

Torpey, D. C., Hajcak, G., Kim, J., Kujawa, A., & Klein, D. N. (2012). Electrocortical and behavioral measures of response monitoring in young children during a Go/No-Go task. *Developmental Psychobiology*, *54*, 139–150.

Von Borries, A., Brazil, I., Bulten, B., Buitelaar, J., Verkes, R., & De Bruijn, E. (2010). Neural correlates of error-related learning deficits in individuals with psychopathy. *Psychological Medicine*, *40*, 1559–1568.

Weinberg, A., & Hajcak, G. (2011). Longer term test–retest reliability of error-related brain activity. *Psychophysiology*, *48*, 1420–1425.

Weinberg, A., Klein, D. N., & Hajcak, G. (2012). Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *Journal of Abnormal Psychology*, *121*, 885–896.

Weinberg, A., Meyer, A., Hale-Rude, E., Perlman, G., Kotov, R., Klein, D. N., & Hajcak, G. (in press). Errors as endogenous threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology*.

Weinberg, A., Olvet, D. M., & Hajcak, G. (2010). Increased error-related brain activity in generalized anxiety disorder. *Biological Psychology*, *85*, 472–480.

Weinberg, A., Riesel, A., & Hajcak, G. (2012). Integrating multiple perspectives on error-related brain activity: The ERN as a neural indicator of trait defensive reactivity. *Motivation and Emotion*, *36*, 84–100.

Willoughby, M. T., Mills-Koonce, R., Propper, C. B., & Waschbusch, D. A. (2013). Observed parenting behaviors interact with a polymorphism of the brain-derived neurotrophic factor gene to predict the emergence of oppositional defiant and callous–unemotional behaviors at age 3 years. *Development and Psychopathology*, *25*, 903–917.

Xiao, Z., Wang, J., Zhang, M., Li, H., Tang, Y., Wang, Y., . . . Fromson J. A. (2011). Error-related negativity abnormalities in generalized anxiety disorder and obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*, 265–272.