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Error-Related Brain Activity Is Related to Aversive Potentiation of the Startle Response in Children, but Only the ERN Is Associated With Anxiety Disorders

Alexandria Meyer
Florida State University

Greg Hajcak
Stony Brook University

Catherine R. Glenn
University of Rochester

Autumn J. Kujawa
University of Illinois at Chicago

Daniel N. Klein
Stony Brook University

Identifying biomarkers that characterize developmental trajectories leading to anxiety disorders will likely improve early intervention strategies as well as increase our understanding of the etiopathogenesis of these disorders. The error-related negativity (ERN), an event-related potential that occurs during error commission, is increased in anxious adults and children—and has been shown to predict the onset of anxiety disorders across childhood. The ERN has therefore been suggested as a biomarker of anxiety. However, it remains unclear what specific processes a potentiated ERN may reflect. We have recently proposed that the ERN may reflect trait-like differences in threat sensitivity; however, very few studies have examined the ERN in relation to other indices of this construct. In the current study, the authors measured the ERN, as well as affective modulation of the startle reflex, in a large sample (N = 155) of children. Children characterized by a large ERN also exhibited greater potentiation of the startle response in the context of unpleasant images, but not in the context of neutral or pleasant images. In addition, the ERN, but not startle response, related to child anxiety disorder status. These results suggest a relationship between error-related brain activity and aversive potentiation of the startle reflex during picture viewing—consistent with the notion that both measures may reflect individual differences in threat sensitivity. However, results suggest the ERN may be a superior biomarker of anxiety in children.

Keywords: error-related negativity, startle response, anxiety, children, biomarker

Anxiety disorders are often chronically impairing and typically begin during childhood and adolescence (Beesdo, Knappe, & Pine, 2009; Kessler et al., 2005; Last, Perrin, Hersen, & Kazdin, 1996). However, understanding of the specific pathways that relate to the development of anxiety disorders is limited. Identifying early biomarkers that characterize these developmental trajectories may improve early intervention strategies as well as increase our understanding of the etiopathogenesis of these disorders (Pine, 2007).

One promising biomarker of clinical anxiety is the error-related negativity (ERN). The ERN is a negative deflection in the event-related potential (ERP) waveform that occurs during error commission (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) and is thought to be generated in the anterior cingulate cortex (ACC)—a region of the brain that integrates information related to pain, punishment, and threat (Debener, Ullsperger, et al., 2005; Dehaene, Posner, & Don, 1994; Shackman, Salomons, et al., 2011). Over 40 studies have found an increased ERN in anxious adults (for a meta-analysis, see Moser, Moran, Schroder, Donnellan, & Yeung, 2013). In addition, the ERN is increased in clinically anxious children early in the course of development (i.e., 6 years old; Meyer, Hajcak, et al., 2013), and we recently found that variation in ERN magnitude can predict the onset of new anxiety disorders in children, even after controlling for baseline anxiety symptoms and maternal history of anxiety (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015). In addition, the ERN has been shown to be relatively stable across development (r = .63 across 2 years in children; Meyer, Bress, & Proudfit, 2014) and moderately heritable (between 40–60%; Anokhin, Golosheykin, & Heath, 2008). Taken together, the ERN may be considered a promising bio-

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Alexandria Meyer, Department of Psychology, Florida State University; Greg Hajcak, Department of Psychology, Stony Brook University; Catherine R. Glenn, Department of Psychology, University of Rochester; Autumn J. Kujawa, Department of Psychiatry, University of Illinois at Chicago; Daniel N. Klein, Department of Psychology, Stony Brook University.

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Correspondence concerning this article should be addressed to Alexandria Meyer, Department of Psychology, Florida State University. 1107 West Call Street, Tallahassee, FL 32304. E-mail: meyer@psy.fsu.edu

marker that may be useful in understanding developmental trajectories of anxiety.

Although the ERN has been shown to be reliably increased in anxious individuals, there remains considerable discussion as to what specific processes a potentiated ERN may reflect. We have argued that errors are unpredictable threatening events that provoke an acute defensive response. Indeed, errors prompt a cascade of psychophysiological responses that resemble defensive mobilization: skin conductance and heart rate deceleration (Hajcak, McDonald, & Simons, 2003; Hajcak, McDonald, & Simons, 2004), potentiated startle reflex (Hajcak & Foti, 2008; Riesel, Weinberg, Moran, & Hajcak, 2013), amygdala activation (Pourtois et al., 2010), corrugator "frowning" muscle contraction (Lindström, Mattsson-Mårn, Golkar, & Olsson, 2013), pupil dilation (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005), as well as the subjective feeling of distress (Spunt, Lieberman, Cohen, & Eisenberger, 2012). Although both errors and other aversive stimuli activate a common region of the ACC (Shackman, Salomons, et al., 2011), errors are differentiated from other aversive stimuli insofar as they are self-generated (Weinberg, Meyer, et al., 2016).

Within this context, we view variability in the ERN as reflecting the degree to which errors are processed as aversive and salient. For instance, in within-subjects experiments, the ERN is potentiated when errors are punished, more valuable, or evaluated by others (Hajcak, Moser, Yeung, & Simons, 2005; Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012). In addition, harsh and critical parenting, which may sensitize children to their mistakes, predicts a greater ERN (Brooker & Buss, 2014; Meyer, Proudfit, et al., 2015). From an individual differences perspective then, an increased ERN is hypothesized to reflect trait-like differences in threat sensitivity (Proudfit, Inzlicht, & Mennin, 2013; Weinberg, Riesel, & Hajcak, 2012).

To date, however, very few studies have examined the ERN in relation to other indices of threat sensitivity. The human startle response is a well-validated measure of defensive activation (Lang, 1994; Lang, Bradley, & Cuthbert, 1990) indexed in humans by the magnitude of eye muscle contraction in response to a loud acoustic probe (Lang, Bradley, et al., 1990). Startle magnitude is modulated by emotional valence or motivational state, such that it is potentiated when participants are viewing threatening stimuli and inhibited when participants are viewing appetitive stimuli (Bradley, Codispoti, & Lang, 2006; Lang, Davis, & Öhman, 2000). Although findings are mixed, the startle reflex appears to relate to individual differences in threat sensitivity insofar as adults and children with fear-based disorders are characterized by a potentiated startle response (Bakker, Tijssen, van der Meer, Koelman, & Boer, 2009; Grillon & Baas, 2003; Vaidyanathan, Patrick, & Cuthbert, 2009; Waters, Lipp, & Spence, 2005), as well as individuals characterized by traits such as high fearfulness (Cook, Davis, Hawk, Spence, & Gautier, 1992; Cook, Hawk, Davis, & Stevenson, 1991), high state anxiety (Grillon, Ameli, Foot, & Davis, 1993), high harm avoidance (Corr, Kumari, Wilson, Checkley, & Gray, 1997), and high behavioral inhibition (Barker, Reeb-Sutherland, et al., 2015; Barker, Reeb-Sutherland, & Fox, 2014). Furthermore, an increased startle response is found in children with a parental history of anxiety disorders (Grillon, Dierker, & Merikangas, 1997, 1998; Kujawa, Glenn, Hajcak, & Klein, 2015; Merikangas, Avenevoli, Dierker, & Grillon, 1999), and a large startle response during safe conditions prospectively predicts the onset of anxiety disorders in adolescents (Craske et al., 2012).

Two previous studies have examined whether the magnitude of the startle response relates to the magnitude of the ERN (Hajcak & Foti, 2008; Riesel, Weinberg, et al., 2013). In both of these studies, the startle response was measured after correct and erroneous responses in a flankers task. Results suggested that the startle response was larger following errors than following correct responses. Hajcak and Foti (2008) found that the degree to which errors potentiated the startle response related to individual variation in the ERN; however, Riesel et al. (2013) failed to replicate this effect. Given the fact that they both utilized relatively small samples (Hajcak & Foti: $N = 31$ and Riesel et al.: $N = 32$), they may have been underpowered. Moreover, these studies did not examine whether ERN related to defensive mobilization using tasks that are more commonly employed to index affective modulation of the startle reflex.

To address these limitations, we recorded eyeblink startle responses while a large sample of individuals viewed pleasant, neutral, and unpleasant images. Participants also completed the flankers task to measure the ERN. In addition, we conducted the current study among a large sample of children, given the potential utility of identifying early biomarkers that characterize developmental trajectories that result in anxiety disorders. We hypothesized that children characterized by a large ERN would also exhibit greater potentiation of the startle response in the context of unpleasant images, but that ERN magnitude would not relate to modulation of the startle response in the context of pleasant and neutral images, thereby supporting the notion that the ERN relates to individual differences in sensitivity to threat. In light of the link between anxiety disorders and both ERN and modulation of the startle reflex, we also examined the relationship between the ERN and affective modulation of the startle reflex in relation to child anxiety disorder status. We hypothesized that children with a lifetime history of an anxiety disorder would be characterized by both a larger ERN and increased startle potentiation in the context of unpleasant images, and that these measures of threat sensitivity may have additive or interactive effects in relation to child anxiety.

Method

Participants

The current study included a subset of participants ($N = 274$) who had startle, ERP, and clinical diagnostic data from the third assessment of a larger longitudinal study (Torpey, Hajcak, et al., 2013). Participants were originally identified through a commercial mailing list. Eligible families had a child without significant medical condition or developmental disability, and at least one English-speaking biological parent. Of families who were eligible, 66.4% entered the study. Families who agreed and declined participation did not differ significantly on child sex, race, ethnicity, parental marital status, education, or employment status. Census data suggest the sample is reasonably representative of the surrounding county (Bufferd, Dougherty, Carlson, & Klein, 2011; Olino, Klein, Dyson, Rose, & Durbin, 2010). From the subsample of 274 participants with psychophysiological data, 10 were excluded because they terminated the startle task early, 67 were excluded due to poor quality physiological recording during the

startle task (e.g., excessive EMG artifacts), and 27 were excluded for failing to exhibit a measurable startle response on 50% or more trials per condition (i.e., nonresponders). Of the remaining participants, five were excluded from analysis due to poor quality EEG recordings and 10 were excluded for achieving an accuracy level of less than 55% during the flankers task. No children were excluded for making too few errors during the flankers task (i.e., less than six; Meyer, Bress, et al., 2014; Meyer, Riesel, & Hajcak Proudfit, 2013; Olvet & Hajcak, 2009). Therefore, the current study included 155 children (72 female) with adequate startle and EEG data.[1] The mean age of the sample was 9.15 years (SD = 0.39), ranging between the ages of 8.75 and 10.92 years old. Overall 91.9% of the children were Caucasian, 2.0% Asian, 5.4% African American, and 0.7% Native American; 12.1% were also Hispanic. After a description of the study to the parents and children, written informed consent and child verbal assent were obtained. All procedures were approved by the University's Institutional Review Board.

Tasks and Procedure

Children completed a variety of tasks during the lab visit; data from other tasks will be reported elsewhere. Relevant to the current study, the affect-modulated startle task used 36 developmentally appropriate images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008); 12 unpleasant images, 12 pleasant images, and 12 neutral images,[2] divided into two blocks of 18 images. Neutral images included pictures of scenes (e.g., desert) and objects (e.g., lamp), pleasant images included child-friendly scenes (e.g., cute animals), and unpleasant images consisted of threatening images (e.g., vicious animals).

All pictures were presented using Presentation software (Neurobehavioral Systems, Inc., Albancy, CA) to control their presentation and timing. Each picture was displayed for 5 s in color and occupied the entire 19-in (48.3 cm) monitor. The acoustic startle probe was a 50-ms burst of white noise that was set to a volume of approximately 95 dB and was delivered binaurally through headphones. The experiment began with a startle habituation phase (i.e., four startle probes presented). During the task, startle probes were distributed randomly and evenly, occurring on half of all trial types (i.e., unpleasant, pleasant, neutral), and were administered randomly between 3, 4, or 5 s after picture presentation or during the intertrial interval (intertribal interval [ITI]) to increase unpredictability of the startle probes and produce maximal affective modulation of the startle reflex (Bradley, Cuthbert, & Lang, 1993). The duration of the ITI ranged from 6 to 8 s for trials in which no startle probe was presented during the ITI, and from 11 to 15 s on trials in which startle probes were presented during the ITI. No more than two pictures of any type were presented in a row. Stimuli and psychophysiological responses were presented and recorded using PSYLAB hardware and PSYLAB 8 software (Contact Precision Instruments, Cambridge, MA).

Children also completed a flankers task while EEG was recorded. For the EEG task, children were seated approximately 24 in (61 cm) from the computer screen, while they performed an arrow version of the flankers task (Eriksen & Eriksen, 1974) that was administered using Presentation software (Neurobehavioral Systems, Inc., Albancy, CA) to control the presentation and timing of all stimuli. Each stimulus was displayed on a 19-in (48.3 cm) monitor. On each trial, five horizontally aligned arrowheads were presented for 200 ms, followed by an ITI that varied randomly between 2,300 to 2,800 ms. Half of the trials were compatible ("<<<<<" or ">>>>>") and half were incompatible ("<<><<" or ">><>>"); the order of trials was randomly determined. Participants were told to press the right mouse button if the center arrow was facing to the right and to press the left mouse button if the center arrow was facing to the left. After a practice block of 30 trials, participants completed 11 blocks of 30 trials (330 trials total) with each block initiated by the participant. Participants received feedback based on their performance at the end of each block. If performance was 75% correct or lower, the message "Please try to be more accurate" was displayed; if performance was above 90% correct, the message "Please try to respond faster" was displayed; otherwise the message "You're doing a great job" was displayed.

Clinical interviews were also completed at this assessment. The Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL: Kaufman, Birmaher, et al., 1997) was completed separately with the parent and child, regarding the child's lifetime diagnostic status. Interviews were administered by a master's level interviewer with extensive clinical experience and clinical psychology graduate students in video-recorded, face-to-face interviews. The K-SADS is designed to assess a range of psychopathology in children and adolescents. Lifetime *DSM-IV* diagnoses were derived from a combination of the parent and child reports and if discrepancies arose, the interviewer attempted to reconcile them with the parent and child at the end of the interview. All diagnoses were reviewed in case conferences led by an experienced child psychiatrist and a clinical psychologist. Reliability ratings were performed by the interviewers based on 74 randomly selected videotaped interviews; the k for any anxiety disorder was .67. Of the children included in the current study, 25 met criteria for at least one lifetime anxiety disorder (some children had more than one lifetime anxiety disorder): six for separation anxiety, seven for social phobia, seven for specific phobia, four for generalized anxiety disorder, one for obsessive–compulsive disorder, and six for anxiety disorder not otherwise specified.

Data Recording, Reduction, and Analysis

Startle responses were recorded from EMG activity using PSYLAB Stand Alone Monitor Unit (SAM) and BioAmplifier (Contact Precision Instruments, Cambridge, MA) in accordance with current guidelines (Blumenthal, Cuthbert, et al., 2005). Two 4-mm Ag-AgCl electrodes were placed approximately 25 mm apart over the orbicularis oculi muscle beneath the left eye, and an isolated ground was placed in the middle of the forehead. EMG activity was sampled at 1,000 Hz, and band-pass filtered between 30 and 500 Hz. Startle EMG was rectified in a 200-ms window beginning 50 ms before the startle probe and smoothed using a 6-point

[1] Children included in the current study did not differ from the larger sample in age, gender, race, ethnicity, parent education status, all $ps > .10$.

[2] The numbers of the IAPS pictures used were the following: pleasant (1463, 1710, 1750, 1811, 2091, 2070, 2224, 7325, 2340, 2345, 7330, 8496), unpleasant (1304, 1052, 1205, 1050, 1300, 2458, 2811, 3022, 6190, 6231, 6510, 6571), and neutral (5390, 5500, 5731, 5740, 7002, 7010, 7026, 7090, 7100, 7175, 7002, 5900).

running average. Raw startle magnitude was expressed as the difference between the average of the EMG in the 50 ms window prior to the startle probe and the maximum in the 150 ms post-probe window. Each participant's data were examined on a trial-by-trial basis. Trials with no perceptible eyeblink response were scored as zero and included in the overall averages; trials with excessive baseline artifacts or magnitudes that were outliers for each subject according to Grubbs test (Grubbs, 1969) were excluded from analysis. Children with three or fewer trials (50%) with a visible startle response per condition were excluded from subsequent analyses. To control for interindividual variability in startle magnitude, all startle analyses focused on ITI-corrected (i.e., average of startle magnitudes during each emotion condition minus startle magnitude during ITI) startle magnitudes (Kujawa, Glenn, et al., 2015).

Continuous EEG recordings were collected using an elastic cap and the Active Two system (Biosemi, Amsterdam, Netherlands). Thirty-four electrode sites were used, based on the 10/20 system, in addition to two electrodes on the right and left mastoids. Electrooculogram generated from eye movements and eyeblinks was recorded with four facial electrodes; horizontal eye movements were measured by two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Vertical eye movements and blinks were measured by two electrodes placed approximately 1 cm above and below the right eye. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of one by a BioSemi Active Two system (BioSemi, Amsterdam, The Netherlands). The data were digitized at 24-bit resolution with a sampling rate of 1,024 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 204.8 Hz. Active electrodes were measured online with respect to a common mode sense (CMS) active electrode producing a monoploar (i.e., nondifferential) channel. Offline, all data were referenced to the average of the left and right mastoids, and band-pass filtered between 0.1 and 30 Hz; eyeblink and ocular corrections were then conducted (Gratton, Coles, & Donchin, 1983).

To reject artifacts, a semiautomatic procedure was employed. The criteria applied were a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than .50 μV within 100-ms intervals. These intervals were rejected from individual channels in each trial. Visual inspection of the data was then conducted to detect and reject any remaining artifacts.

The EEG was segmented for each trial beginning 500 ms before response onset and continuing for 800 ms after the response; a 200 ms window from −500 to −300 ms before the response onset served as the baseline. Correct and error trials were averaged separately. The ERN was quantified as the average activity from 0 to 100 after error commission at FCz, where error-related neural activity was maximal. In addition, the correct response negativity (CRN) was evaluated in the same time window at FCz following correct responses, and the ΔERN was calculated as the ERN minus the CRN. Behavioral measures included both the number of error trials for each subject and average reaction times (RTs) on both error and correct trials.

A within-subjects repeated-measures analysis of variance (ANOVA) was conducted to evaluate affective modulation (i.e., pleasant vs. neutral vs. unpleasant) of the startle response. Next, another within-subjects repeated-measures ANOVA was conducted to evaluate modulation of neural activity by response type (i.e., error vs. correct). Pearson correlations were used to investigate the relationship between the ERN, CRN, and ΔERN and startle magnitude elicited during pleasant, neutral, and unpleasant picture presentations. To examine unique predictors of the ΔERN, a simultaneous multiple regression was performed wherein startle during the pleasant, neutral, and unpleasant condition were all entered predicting ΔERN.

To examine relationships with child anxiety, two repeated-measures ANOVAs were conducted with startle response (i.e., pleasant vs. neutral vs. unpleasant) and neural activity (i.e., errors vs. correct), with child lifetime anxiety status entered as a between subject variable. After this, a simultaneous binary, logistic regression was conducted wherein startle during unpleasant picture viewing, the ΔERN, as well as their interaction were entered predicting childhood anxiety status.

Results

Startle Response

A repeated-measures ANOVA confirmed affective modulation of the startle reflex, $F(2, 308) = 4.49$, $p < .05$, $\eta_p^2 = .03$. Follow-up paired samples t tests indicated that the startle response was potentiated during unpleasant images compared to both pleasant images, $t(154) = 3.17$, $p < .01$, and neutral images, $t(154) = 1.87$, $p = .06$, at a trend level. Startle magnitude during neutral and pleasant images did not differ from one another, $t(154) = 1.03$, $p = .30$. Means and standard deviations for startle magnitude during all three conditions can be found in Table 1. In addition, neither child age nor gender related to affective modulation of the

Table 1
Means and Standard Deviations for ERPs and Startle Magnitude During All Three Conditions, as Well as Pearson Correlation Coefficients Between All Variables

Study variables	1	2	3	4	5	*M*	*SD*
1. ΔERN						−5.53	5.99
2. ERN	.56**					2.36	7.60
3. CRN	−.25**	.66**				7.89	6.61
4. Startle during pleasant	−.08	−.03	.10			3.73	12.37
5. Startle during unpleasant	−.18*	−.09	.06	.57**		6.66	12.39
6. Startle during neutral	−.03	.05	.09	.45**	.51**	4.81	12.48

Note. ERPs = event-related potentials; ERN = error-related negativity; CRN = correct response negativity.
* $p < .05$. ** $p < .01$.

startle response or startle magnitude during neutral, pleasant, or unpleasant picture viewing, all *p*s > .10.

Behavioral Data

Overall, children made an average of 57.47 errors, *SD* = 23.45, and obtained an average accuracy level of 82%, *SD* = 7.4 during the flankers task. Reaction times varied as a function of trial type, $F(1, 154) = 449.26$, $p < .001$, $\eta_p^2 = .75$, such that children were faster on error trials, *M* = 425.49, *SD* = 69.04, than correct trials, *M* = 576.63, *SD* = 112.16. Overall, children were slower on trials that occurred after an error trial, *M* = 563.27, *SD* = 119.15, compared to trials that occurred after a correct trial, *M* = 547.97, *SD* = 104.84, $F(1, 154) = 15.09$, $p < .001$, $\eta_p^2 = .09$. Behavioral data (i.e., accuracy, RTs, and posterror slowing) did not relate to startle magnitude during any condition or the ERN, CRN, or ΔERN, all *p*s > .20 and were therefore excluded from any subsequent analyses.

Error-Related Brain Activity

A repeated-measures ANOVA confirmed that the ERP response was more negative following errors than correct responses, $F(1, 154) = 131.77$, $p < .001$, $\eta_p^2 = .46$. Pearson correlations between the ERPs and startle magnitude during all three conditions can be found in Table 1. The ΔERN related to startle magnitude, but only during unpleasant pictures, such that children who were characterized by a large ΔERN were also characterized by a large startle response during unpleasant pictures, $r(154) = -.18$, $p < .05$ (see Figure 1).[3] In addition, neither age nor gender related to the ERN, CRN, or ΔERN, all *p*s > .10.

Next we entered the startle response during all three picture conditions to predict ΔERN in a simultaneous multiple regression (see Table 2). The startle response elicited during unpleasant picture viewing uniquely predicted the ΔERN when accounting for the impact of the startle magnitude elicited during neutral and pleasant trials.

Given that the ERN and CRN are highly correlated, and the ΔERN is correlated in the opposite direction with both the ERN and CRN, we wished to follow-up our preliminary analyses to explore whether it was neural activity during error or correct trials (or both) that was

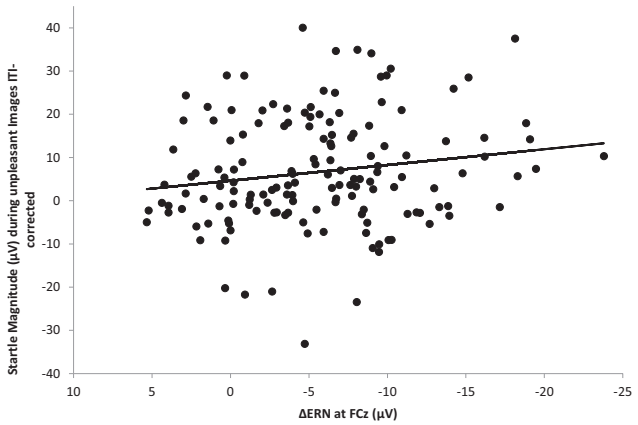

Figure 1. Scatter plot illustrating the relationship between the ΔERN and startle magnitude during unpleasant pictures.

Table 2
Results From a Simultaneous Multiple Regression Wherein Startle Magnitude During All Three Conditions Were Entered predicting the ΔERN at Electrode FCz

Variables entered	ΔERN (*N* = 155)		
	b	*SE*	*t*
Startle during neutral	.07	.05	.78
Startle during pleasant	.02	.05	.15
Startle during unpleasant	−.23	.05	−2.18*
Overall model: total *R*-squared		.04	

Note. ERN = error-related negativity.
* $p < .05$.

contributing to the relationship observed between startle magnitude during unpleasant picture viewing and the ΔERN. We have recently proposed using a regression-based approach as a way of addressing this problem (Meyer et al., in press). In the current study, we entered both the ERN and CRN, as well as interaction term (ERN × CRN), simultaneously into a regression equation predicting the startle response during unpleasant picture trials. Results suggested that although startle magnitude during unpleasant picture viewing was related to the ERN, $t = -2.12$, $p < .05$, neither the CRN nor the interaction (ERN × CRN) reached significance, both *p*s > .10, indicating that it was neural activity unique to error trials that related to aversive potentiation of the startle reflex.

Child Anxiety

A repeated-measures ANOVA suggested affective modulation of the startle reflex did not differ by child anxiety status, $F(2, 304) = 1.35$, $p = .26$. In addition, follow-up one-way ANOVAs suggested that startle magnitude did not differ in any condition by child anxiety status: startle during neutral picture viewing, $F(1, 153) = .15$, $p = .70$, startle during pleasant picture viewing, $F(1, 153) = .17$, $p = .68$, startle during unpleasant picture viewing, $F(1, 153) = 1.52$, $p = .22$.

A repeated-measures ANOVA suggested a significant interaction between response type (i.e., error vs. correct) and child anxiety disorder status, $F(1, 152) = 3.95$, $p < .05$, $\eta_p^2 = .03$, such that the ΔERN was larger in children with a lifetime anxiety disorder, *M* = −7.66, *SD* = 5.58, compared to those without an anxiety disorder, *M* = −5.08, *SD* = 6.01 (see Figure 2). Follow-up one-way ANOVAs suggested that neither the ERN nor CRN differed between children with and without an anxiety disorder, $F(1. 153) = .26$, $p = .61$, and $F(1, 153) = 1.47$, $p = .23$, respectively. Results of a logistic regression predicting child anxiety, wherein startle magnitude during unpleasant picture viewing, the ΔERN, as well as their interaction suggest that only the ΔERN significantly predicts child anxiety, *B* = −.10, odds ratio = .91, Wald = 4.77, $p < .05$, all other *p*s > .5.

Discussion

Consistent with our hypotheses, children characterized by a large ΔERN also exhibited greater potentiation of the startle re-

[3] This relationship remained significant when children with a lifetime history of anxiety disorder were excluded from the analysis, $r(129) = -.21$, $p < .05$.

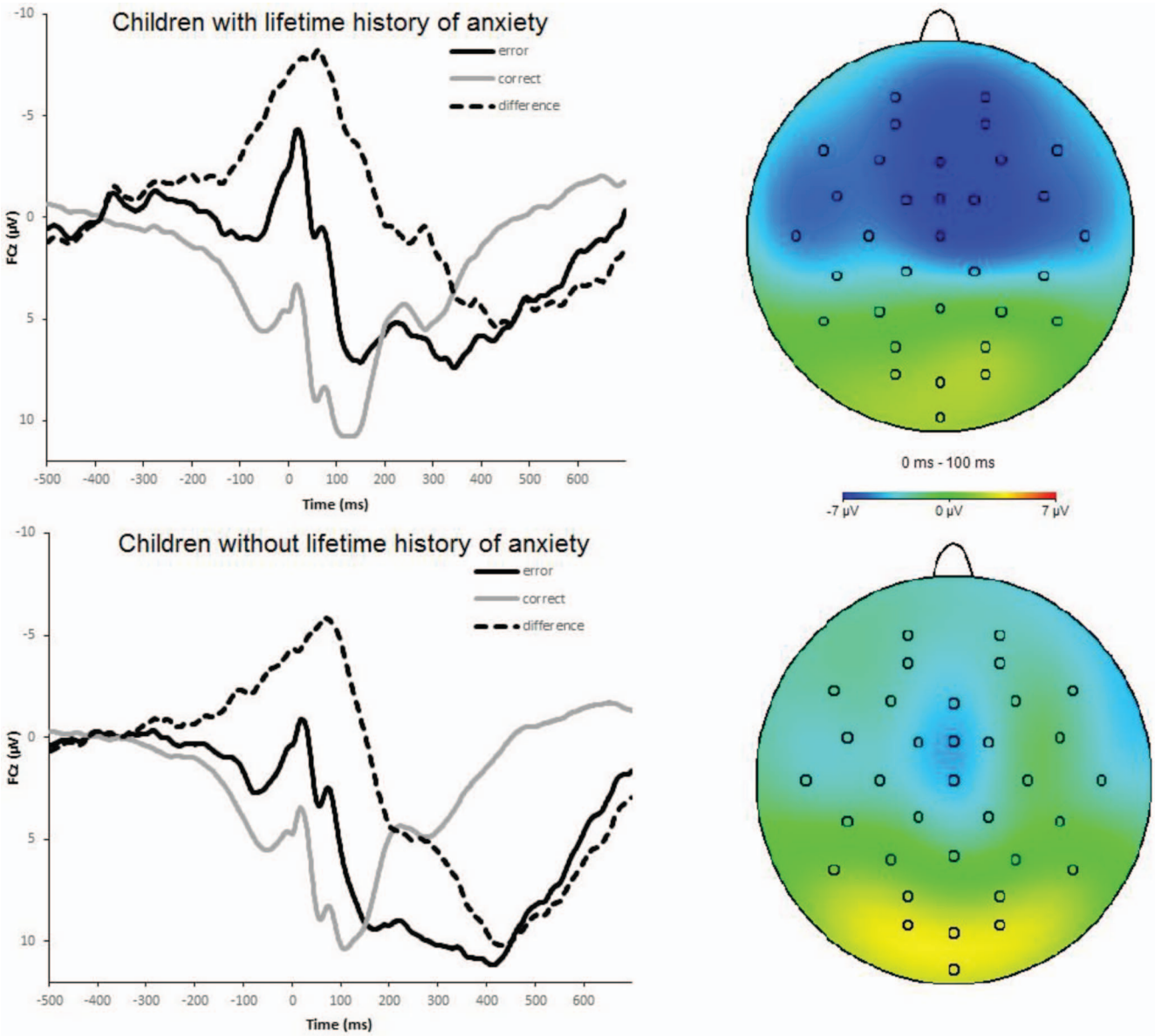

Figure 2. On the left, response-locked event-related potential (ERP) waveforms for correct and error trials, as well as the difference waves (top = children with lifetime anxiety disorder, bottom = children without lifetime history of anxiety disorder). On the right, topographical maps of activity (error minus correct; top = children with lifetime anxiety disorder, bottom = children without lifetime history of anxiety disorder). See the online article for the color version of this figure.

sponse when viewing unpleasant images. However, the ΔERN magnitude did not relate to modulation of the startle response in the context of pleasant and neutral images. These analyses were consistent using both bivariate and regression-based approaches. Additional analyses confirmed that this relationship was driven by neural activity unique to errors. Thus, these results suggest a relationship between error-related brain activity and aversive potentiation of the startle reflex during picture viewing—consistent with the notion that both measures may reflect individual differences in the construct of threat sensitivity.

The current results are consistent with one previous study that found an association between the ERN and startle response across individuals (Hajcak & Foti, 2008). In this study, the startle response was larger after errors compared to correct responses, and the extent to which errors potentiated the startle response related to the magnitude of the ERN. However, Riesel and colleagues (2013) did not replicate this finding. Using a much larger sample and affective modulation of the startle reflex during picture viewing, the current study provides more compelling evidence that individual differences in the ERN relates to a well-validated measure of threat sensitivity (i.e., aversive potentiation of the startle reflex). It is unclear whether the current results differ from Riesel et al. (2013) due to sample size differences, the utilization of affective modulation of startle, or the fact that the current study was com-

pleted in younger participants that may be characterized by increased threat sensitivity and ongoing neural development. Future work could explore this topic by examining startle modulation following errors as well as affective modulation of startle in relationship to the ERN in a large adult sample.

Consistent with previous work (Hajcak, Franklin, Foa, & Simons, 2008; Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Meyer, Hajcak, et al., 2013) children with a lifetime history of an anxiety disorder were characterized by an increased ERN. This finding further supports the notion that the ERN tracks trait-like individual differences related to threat sensitivity and may be a useful biomarker. However, affective modulation of the startle response did not differ between children with and without anxiety. This was unexpected given that previous work suggests that startle reactivity is potentiated in both anxious individuals and among individuals at risk for anxiety (Bakker, Tijssen, et al., 2009; Barker, Reeb-Sutherland, et al., 2014; Cook, Davis, et al., 1992; Cook, Hawk, et al., 1991; Grillon & Baas, 2003; Kujawa, Glenn, et al., 2015; Reeb-Sutherland, Helfinstein, et al., 2009; Vaidyanathan, Patrick, et al., 2009; Waters, Lipp, et al., 2005; Waters, Neumann, Henry, Craske, & Ornitz, 2008). However, most of this work has been completed in adults, and findings in developmental populations appear more mixed. For example, some work has only found differences in startle reactivity in anxious children during "safety" conditions (Barker, Reeb-Sutherland, et al., 2014; Craske et al., 2012; Reeb-Sutherland, Helfinstein, et al., 2009), whereas other work has found differences in general startle reactivity during affective modulation tasks, but not during "safety" conditions (Waters, Neumann, et al., 2008). Yet another study found that it was only startle magnitude measured from the "whole-body," and not just the orbicularis oculi (i.e., the blink response) that differentiated anxious from nonanxious children (Bakker, Tijssen, et al., 2009). It is possible that the lack of a "safety" condition in the current task or method of measuring the startle response (i.e., orbicular oculi activity) was not ideal for measuring differences in startle reactivity in anxious children. Future work should explore these possibilities.

Although the current study supports the notion that variability in the ERN may reflect individual differences in threat sensitivity—insofar as the ERN related to startle potentiation during unpleasant picture viewing and to anxiety disorder status, results suggested that these measures share a relatively small amount of variance—and their shared variance did not relate to anxiety disorders in children. Rather, it was only the ERN that differentiated children with anxiety, and this relationship persisted even after controlling for the impact of affective modulation of the startle response. It is possible that both the ERN and startle response index some partially overlapping aspect of the threat sensitivity construct, but that only variability in the former measure relates to anxiety in children. The ERN potentially indexes sensitivity to threat that is related to internal monitoring of one's own actions, which may be more specific to anxiety disorders. It is also possible that startle potentiation after errors might relate to individual differences in anxiety in children, rather than affective modulation of the startle response to picture viewing.

Another possibility is that both the ERN and startle are indexing a similar aspect of threat sensitivity that relates to anxiety, but the psychometric properties of the affectively modulated startle response may be lower and thus have less power to relate to individual differences in anxiety in children. Previous work suggests that both the ERN (Meyer, Riesel, & Hajcak Proudfit, 2013; Olvet & Hajcak, 2009) and startle response (Bradford, Starr, Shackman, & Curtin, 2015; Larson, Ruffalo, Nietert, & Davidson, 2000) have good psychometric properties in adults; however, only the ERN has been established as a reliable indicator in children (Meyer, Bress, et al., 2014). Future work should explore the psychometric properties of the affective modulation of the startle response in children.

Patrick et al. (2013) suggests using a construct-network approach to better link psychological disorders to neural systems. To address the problem of method variance, they outline a method wherein psychometric operationalizations of neurobiological constructs are used to identify relevant neural and psychophysiological measures. In the current study, two measures of threat sensitivity were examined in relation to child history of anxiety. Future work might explore the construct of threat sensitivity using the relationship between three or more measures (e.g., the ERN, affective modulation of the startle response, cortisol reactivity, attention bias, etc.) in relation to self-report and diagnostic assessments to further bridge the gap between psychopathology and neurobiology - thus improving our ability to predict outcomes as well as identify novel targets for treatment. In addition, future studies could expand this work to children even earlier in the course of development to improve future identification and intervention strategies.

The current study had several limitations. Given the relatively narrow age-range of the participants, we may have been unable to detect developmental changes in both the ERN and startle response. In addition, the current sample did not include enough children with any one anxiety disorder to examine specificity (e.g., perhaps ERN and startle modulation relate differentially to specific disorders). Also, given that the current investigation was cross-sectional, we were unable to determine whether the ERN and startle response could predict the onset of disorders longitudinally.

Overall, results from the current study support the notion that the ERN may index threat sensitivity insofar as affective modulation of the startle response related to error-related neural activity. Further, children with current or past anxiety disorders were characterized by an increased ERN but did not differ in startle magnitude, suggesting that the ERN may be a more viable biomarker of anxiety. In addition, the study was conducted in children, further supporting the notion that these measures may be useful in understanding how anxiety disorders emerge early in the course of development. Future work could build on the current findings by examining additional measures of threat sensitivity in relation to each other and emerging anxiety symptoms to increase detection and refine intervention strategies.

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