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ORIGINAL ARTICLE

A Diagnostic Biomarker for Pediatric Generalized Anxiety Disorder Using the Error-Related Negativity

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Abstract
The error-related negativity (ERN) is a negative deflection in the event-related potential following a mistake that is a putative biomarker of anxiety. The study assessed the ERN as a diagnostic biomarker using receiver operating characteristic (ROC) analyses in 96 cases with anxiety disorders (AD) and 96 matched healthy controls (HC) ages 8 to 18 years. Forty-one cases had generalized anxiety disorder (GAD); 55 cases had other anxiety disorders (OAD) without GAD. ERN amplitude was significantly increased in AD cases compared to HC. The area under the curve (AUC) in the ROC analysis was 0.64, indicating the ERN is an inadequate diagnostic test for AD altogether. The ERN was significantly increased in cases with either GAD or OAD compared to HC. The AUC in ROC analyses with GAD and OAD was 0.75 and 0.56, respectively, suggesting the ERN provides an adequate diagnostic test for GAD but not for OAD.

Keywords Anxiety · Biomarker · Diagnosis · Error-related negativity · Pediatric · Receiver operating characteristic analysis

Introduction

Anxiety disorders (AD) are the most common form of psychopathology in youth, with prevalence estimates ranging from 15 to 30% [1–3]. Youth with AD have an increased risk for subsequent anxiety and depressive disorders, illicit drug dependence, suicidal behavior, and educational underachievement as young adults [2, 4, 5]. The identification of mechanistic biomarkers that precede or develop concurrently with the onset of AD may advance our understanding of their pathogenesis, improve diagnostic and preventive strategies, and provide targets for cognitive, behavioral, and pharmacological treatments [6–8].

The error-related negativity (ERN or Ne)—a response-locked negative deflection in the event-related potential (ERP) that peaks within 80 ms after error commission—has been hypothesized to be a biomarker of pediatric AD [6, 7, 9–11]. Psychometric studies have demonstrated the ERN is stable across time and reliable across tasks [12]. The ERN has a heritability of 47% in youth, suggesting it may serve as an endophenotype in genetic studies of childhood psychopathology [13]. The ERN increases in magnitude throughout childhood and adolescence, indicating a prolonged maturation of the system underlying action monitoring [14]. The ERN has been described as a neural marker of error-monitoring processes [9–11], reinforcement learning [15], error-related distress [16], and the motivational significance of errors [17]. Consistent with this functional diversity, the ERN is a unit of analysis in three domains of the Research Domain Criteria (RDoC) project: cognitive system (cognitive control: performance monitoring), negative valence systems (sustained threat), and positive valence systems (reward learning) [18]. Moreover, the ERN has been associated with non-clinical anxiety symptoms in studies of both children [7, 14, 19, 20] and adults [6, 18, 21].

Source localization studies have implicated either the dorsal anterior or posterior cingulate cortex as the generator of the ERN [11, 14, 18, 22–25]. The ERN appears to emerge from a phase-resetting and phase-locking of ongoing theta-band activity, in the context of a general increase in theta power following errors [24, 25]. This sequence of events has

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been proposed to indicate a theta-based signaling of the need for enhanced cognitive control [26]. Similar to the ERN, greater frontal midline theta power has been associated with heightened trait anxiety [27].

Most studies examining the ERN as a biomarker of AD have been done with adults rather than with children and have focused more often on obsessive–compulsive disorder (OCD) than on generalized anxiety disorder (GAD) or other anxiety disorders (OAD: separation anxiety disorder, social anxiety disorder, panic disorder, specific phobia, and agoraphobia) [6, 7, 18, 28, 29]. Four studies found increased ERN amplitudes in heterogeneous samples of youth with AD, in which it was difficult to examine the diagnostic specificity of the ERN findings due to the small number of children with any one anxiety disorder [30–33]. A treatment study noted an enlarged ERN in youth with social anxiety disorder both before and after treatment with either sertraline or cognitive-behavior therapy (CBT); however, a comparable increase in the ERN was not observed in youth with GAD [34]. Another treatment study found an enhanced ERN in youth with AD that did not change regardless of their response to psychotherapy [35]. Three longitudinal studies determined that an enlarged ERN early in life may be associated later in childhood or adolescence with an increased risk for AD [36, 37] or GAD [38].

Studies suggest the ERN may vary in individuals with AD depending upon their type of symptoms or disorder [7, 28]. Extensive research also indicates that as children age their anxiety tends to transition from fears of specific external threats to more abstract concerns about internal threats including worries about behavioral competence or social evaluation [7, 39]. Thus, variation in the ERN may reflect the extent to which an internally generated threat, such as a mistake, is experienced as important and aversive to an individual [18]. A meta-analysis concluded that worry involving cognitive symptoms of anxiety is more strongly associated with an enhanced ERN than symptoms associated with anxious arousal or acute fear, with GAD and OCD being considered as disorders characterized by worry and rumination in that analysis [28]. A study using receiver operating characteristic (ROC) analysis found the ERN discriminated between adults with GAD and HC, with an area under the curve (AUC) of 0.69 [40]. Beyond the prospective study of GAD [38], there have been no large controlled studies assessing the accuracy of the ERN as a diagnostic biomarker for pediatric AD, GAD, or OAD using ROC analyses.

The following study was conducted in 96 older children and adolescents with a lifetime diagnosis of an anxiety disorder without comorbid OCD and 96 age- and sex-matched healthy controls (HC) using a flanker task [31]. The first aim was to compare ERN amplitudes in AD cases and HC. The second aim was to compare the ERN in GAD cases and HC as well as in OAD cases and HC. Consistent with the meta-analysis of the ERN noted above [28], GAD was considered the anxiety disorder characterized primarily by worry and rumination, whereas separation anxiety disorder, social anxiety disorder, panic disorder, specific phobia, and agoraphobia were considered as OAD characterized primarily by anxious arousal or acute fear. The third aim was to critically assess the ERN as a diagnostic biomarker for pediatric AD, GAD, and OAD using ROC analyses [41]. It was hypothesized that compared to HC, ERN amplitude would be increased in GAD cases and OAD cases as well as in AD cases altogether. However, it was also hypothesized that the ERN may provide an adequate diagnostic test for GAD but not for OAD or AD altogether, because the ERN is more strongly associated with worry than with panic or phobic symptoms [7, 28].

Method

Participants

Patients with AD were recruited from the Department of Psychiatry at the University of Michigan and surrounding community. HC were recruited from the surrounding community and were matched to patients by age and sex. Participants were recruited using flyers, paid advertisements, and UM Health Research Studies (https://www.UMHealthResearch.org). Participants or their parents gave written informed consent in accordance with the Declaration of Helsinki. All tasks and procedures were approved by the University of Michigan Medical School Institutional Review Board. Participants were paid for their interviews and psychophysiological recordings. Participants were excluded if their accuracy during the task was less than 65% (n = 1) or they made fewer than 8 errors (n = 11), leaving a total of 192 participants. The final sample consisted of 56 males and 136 females of age 8–18 years, with an ethnic/racial breakdown that was 91% Caucasian, 5% Latino, 2% Asian, and 2% Native American. The case and control groups each had 28 males and 68 females with close age matching. Tables 1 and 2 summarize the demographic, clinical, behavioral, and ERP data for the participants.

The 96 patients had a lifetime diagnosis of 1 or more AD, consisting of specific phobia (n = 44), GAD (n = 41), social anxiety disorder (n = 35), separation anxiety disorder (n = 29), panic disorder (n = 10), and agoraphobia (n = 3). Forty cases (42%) had a lifetime diagnosis of 2 or more AD. In the GAD cases, 26 had at least one other anxiety disorder and 15 had no other AD. Twenty-eight cases also had a lifetime diagnosis of major depressive disorder (MDD). Patients were excluded if they had a lifetime diagnosis of OCD, autism spectrum disorder, anorexia nervosa, schizophrenia, bipolar disorder, or substance-related

Table 1 Demographic, clinical, behavioral, and brain potential data in patients with AD and healthy controls

Variable	Patients with AD		Healthy controls		Patients with AD vs. healthy controls	
	(n = 96)		(n = 96)			
	Mean	SD	Mean	SD	Test statistic	*P*
Demographic and clinical data						
Age (year)	14.4	3.1	14.4	3.2	$t_{190} = 0.08$	94
Age at onset of anxiety disorder symptoms (year)	7.5	3.5				
Child behavior checklist						
Total score	34.3	21.8	8.3	7.6	$t_{189} = 11.03$	< 0.0001
Internalizing score	14.4	9.9	2.7	2.8	$t_{189} = 11.21$	< 0.0001
Externalizing score	6.8	6.7	2.3	2.9	$t_{189} = 6.06$	< 0.0001
Affective problems scale	5.2	4.3	0.5	1.0	$t_{189} = 10.39$	< 0.0001
Anxiety problems scale	4.2	3.2	0.6	1.0	$t_{189} = 10.82$	< 0.0001
Somatic problems scale	2.5	2.5	0.5	1.1	$t_{189} = 6.93$	< 0.0001
Attention deficit/hyperactivity problems scale	3.1	3.0	1.1	1.7	$t_{189} = 5.72$	< 0.0001
Oppositional defiant problems scale	2.6	2.3	1.1	1.5	$t_{189} = 5.20$	< 0.0001
Conduct problems scale	1.6	2.7	0.5	1.0	$t_{189} = 3.83$	0.0002
Behavioral data						
Total number of trials	476.9	69.7	484.1	55.7	$t_{190} = 0.79$	0.43
Total number of error trials	39.9	20.7	41.2	23.6	$t_{190} = 0.42$	0.68
Accuracy on all trials	0.91	0.05	0.91	0.05	$t_{190} = 0.32$	0.75
Accuracy on congruent trials	0.97	0.03	0.97	0.03	$t_{190} = 0.51$	0.61
Accuracy on incongruent trials	0.84	0.01	0.85	0.01	$t_{190} = 0.61$	0.54
Accuracy after correct trials	0.91	0.05	0.91	0.05	$t_{190} = 0.54$	0.59
Accuracy after incorrect trials	0.93	0.08	0.93	0.08	$t_{190} = 1.09$	0..28
Error reaction time (ms)	436.6	150.5	455.3	189.2	$t_{190} = 0.76$	0.45
Correct reaction time (ms)	487.2	126.0	500.6	147.8	$t_{190} = 0.67$	0.50
Reaction time on congruent trials (ms)	454.3	118.4	468.0	134.1	$t_{190} = 0.75$	0.45
Reaction time on incongruent trials (ms)	526.3	139.6	538.3	164.8	$t_{190} = 0.54$	0.59
Post-error slowing (ms)	50.7	58.9	44.5	62.2	$t_{190} = 0.71$	0.48
Event-related brain potential data						
Error-related negativity, FCz (μV)	−4.70	5.31	−2.35	5.48	$F_{1,187} = 9.37$	0.002
Correct response negativity, FCz (μV)	2.27	4.24	30.16	3.85	$F_{1,187} = 3.10$	0.08
ERN standardized residual scores, FCz	−1.01	5.11	1.01	5.31	$F_{1,187} = 7.29$	0.008
CRN standardized residual scores, FCz	−0.20	4.08	0.20	3.73	$F_{1,187} = 0.97$	0.32
ΔERN, FCz (μV)	−6.98	5.82	−5.52	5.85	$F_{1,186} = 2.70$	0.10

AD anxiety disorders, *ERN* error-related negativity, *CRN* correct response negativity, *ΔERN* error-related negativity amplitude minus correct response negativity amplitude, *SD* standard deviation

disorder. The 96 HC had no history of a specific axis I disorder. Lifetime and current axis I diagnoses were made independently by two clinicians using all sources of information according to *DSM-5* criteria [42]. Participants were excluded if they had a history of intellectual disability, head injury with a loss of consciousness, or chronic neurological disorder other than tics. Because studies have indicated that treatment with a serotonin reuptake inhibitor (SSRI) has no effect on the ERN, 31 patients were enrolled taking a stable dose of an SSRI but no other medications [31, 34].

Diagnostic Instruments

All participants were interviewed with the Schedule for Schizophrenia and Affective Disorders for School-Aged Children-Present and Lifetime Version [43] and Schedule for Obsessive–Compulsive and Other Behavioral Syndromes [44]. Parents completed the Child Behavior Checklist/6-18 about their children (CBCL/6-18) [45].

Table 2 Demographic, clinical, behavioral, and brain potential data in GAD patients, OAD patients, and healthy controls

Variable	Patients with GAD (n = 41)		Patients with OAD (n = 55)		Healthy Controls (n = 96)		Patients with GAD vs. Patients with OAD vs. Healthy Controls	
	Mean	SD	Mean	SD	Mean	SD	Test Statistic	*P*
Demographic and clinical data								
Age (year)	15.4	2.6††	13.6	3.2	14.4	$3.2_{2,189} = 3.91$	0.02	
Sex (M/F)	9/32		19/36		28/68			0.40
Onset age of anxiety symptoms (year)	7.7	3.4	7.4	3.6	$t_{94} = 0.43$	0.66	$\chi^2_2 = 1.84$	
SSRI (treatment/no treatment)	16/25		15/40				$\chi^2_1 = 1.48$	0.22
Child behavior checklist								
Total score	2.9	23.2****††††	28.1	18.4****	8.3	7.6	$F_{2,189} = 79.3$	< 0.0001
Internalizing score	18.5	10.4****††††	11.6	9.3****	2.8	2.8	$F_{2,189} = 83.5$	< 0.0001
Externalizing score	8.4	8.4*****††	5.6	4.8***	2.3	2.9	$F_{2,189} = 22.7$	< 0.0001
Affective problems	7.2	4.4****††††	3.8	3.7****	0.5	1.0	$F_{2,189} = 79.8$	< 0.0001
Anxiety problems	5.2	3.0*****††	3.7	3.3****	0.6	1.0	$F_{2,189} = 66.2$	< 0.0001
Somatic problems	3.3	2.7*****†††	1.8	2.2****	0.5	1.1	$F_{2,189} = 32.8$	< 0.0001
Attention deficit/hyperactivity problems	3.6	3.0****	2.8	2.9****	1.1	1.7	$F_{2,189} = 17.8$	< 0.0001
Oppositional defiant problems	2.9	2.7****	2.2	2.0***	1.1	1.5	$F_{2,189} = 15.0$	< 0.0001
Conduct problems	2.2	3.7*****††	1.1	1.5	0.5	1.0	$F_{2,189} = 11.0$	< 0.0001
Behavioral data								
Total number of trials	494.6	53.8†	463.7	77.4	484.1	55.7	$F_{2,189} = 3.2$	0.04
Total number of error trials	39.0	19.6	40.5	21.6	41.2	23.6	$F_{2,189} = .15$	0.86
Accuracy on all trials	0.92	0.04	0.90	0.06	0.91	0.05	$F_{2,189} = 1.4$	0.26
Accuracy on congruent trials	0.98	0.02	0.97	0.04	0.97	0.03	$F_{2,189} = 1.2$	0.30
Accuracy on incongruent trials	0.86	0.07	0.83	0.09	0.85	0.07	$F_{2,189} = 1.3$	0.27
Accuracy after correct trials	0.92	0.04††	0.90	0.06	0.91	0.05	$F_{2,189} = 1.2$	0.32
Accuracy after incorrect trials	0.95	0.06*†	0.91	0.08	0.91	0.08	$F_{2,189} = 3.4$	0.04
Error reaction time (ms)	405.6	89.5	459.8	180.7	455.3	189.2	$F_{2,189} = 1.5$	0.23
Correct reaction time (ms)	457.7	66.3	509.2	153.4	500.6	147.8	$F_{2,189} = 1.9$	0.15
Reaction time on congruent trials (ms)	428.9	60.1	473.9	145.2	468.0	134.1	$F_{2,189} = 1.8$	0.16
Reaction time on incongruent trials (ms)	492.3	77.0	551.6	168.4	538.3	164.8	$F_{2,189} = 1.9$	0.15
Post-error slowing (ms)	54.2	45.6	48.1	67.5	44.5	62.2	$F_{2,189} = 0.4$	0.69
Event-related brain potential data								
Error-related negativity, FCz (μV)	−5.53	5.10**	−4.09	5.43*	−2.35	5.48	$F_{2,186} = 4.78$	0.01
Correct response negativity, FCz (μV)	2.60	4.44	2.03	4.11	3.16	3.85	$F_{2,186} = 1.65$	0.20
ERN standardized residual scores, FCz	−1.96	4.76*	−0.30	5.29	1.01	5.31	$F_{2,86} = 3.84$	0.02
CRN standardized residual scores, FCz	0.29	4.18	−0.57	4.00	0.20	3.73	$F_{2,186} = 0.68$	0.51
ΔERN, FCz (μV)	−8.13	5.43	−6.12	6.01	−5.52	5.85	$F_{2,185} = 1.66$	0.19

GAD generalized anxiety disorder, *OADs* other anxiety disorders (i.e., separation anxiety disorder, specific phobia, social anxiety disorder, panic disorder, agoraphobia); SSRI, selective serotonin reuptake inhibitor, *SD* standard deviation, *ERN* error-related negativity, *CRN* correct response negativity, *ΔERN* error-related negativity amplitude minus correct response negativity amplitude, *SD* standard deviation

*Compared to healthy controls, $P < 0.05$; ** compared to healthy controls, $P < 0.01$; *** compared to healthy controls, $P < .001$; **** compared to healthy controls, $P < 0.0001$

†compared to patients with OAD, $P < 0.05$; †† compared to patients with OAD, $P < 0.01$; ††† compared to patients with OAD, $P < 0.001$; †††† compared to patients with OAD, $P < 0.0001$

Stimulus Material and Task Procedures

Participants performed a modified Eriksen flanker task in which arrows appeared on a computer display with congruent (e.g., → → → → →) and incongruent (e.g., → → ← → →) conditions [46]. They were instructed to respond by pressing one of two buttons indicating the direction of the central arrow (i.e., right versus left), while

ignoring the adjacent arrows, and to respond as quickly and accurately as possible, placing equal emphasis on speed and accuracy (Fig. 1). The flanker task is a test of selective attention and response inhibition that activates the anterior cingulate cortex and provides a more efficient and reliable measure of ERN amplitude than either the Stroop or Go/NoGo task [12, 18]. The stimuli remained on the screen for 250 ms, with an interval of 1,500 ms between consecutive trials. Each participant was seated 0.65 m directly in front of the computer monitor. Following 40 practice trials, each subject completed 8 blocks of 64 trials with the number of completed trials ranging from 256 to 512. Performance feedback was provided after every block to yield an error rate of approximately 10%, with encouragement to focus on speed if there were fewer than four errors or to focus on accuracy if there were more than 10 errors [47].

Electrophysiological Recording and Data Reduction

The electroencephalogram was recorded from DC-104 Hz with 64 Ag/AgCl scalp electrodes, two mastoid electrodes, and two vertical and two horizontal electro-oculogram electrodes, using the BioSemi ActiveTwo system (Amsterdam, the Netherlands). Data were digitized at 512 Hz, referenced to a ground formed from a common mode sense active electrode and driven right leg passive electrode (see https://www.biosemi.com/faq/cms&drl.htm), and rereferenced offline to the average of the two mastoid electrodes. Data were bandpass filtered 0.1–30 Hz using zero-phase shift filters. EEG data were screened using automated algorithms that rejected epochs in which absolute voltage exceeded 500 μV and epochs containing peak to peak activity > 500 μV within 200 ms, with a 100 ms moving window, for midline channels (Fz, FCz, Cz, CPz, Pz). Ocular movement artifacts were then corrected using a regression-based algorithm [48]. After ocular correction, individual trials were rejected if they contained absolute amplitudes > 100 μV, a change > 50 μV measured from one data point to the next point, or a maximum voltage difference < 0.5 μV within a trial in any of the midline electrodes.

The ERN was quantified using mean amplitude measures relative to a pre-response baseline (− 200 to − 50 ms). The mean amplitude of the ERN was computed on incorrect response trials in a window from 0 to 80 ms following the incorrect response. The correct response negativity (CRN) consisted of the same measure computed on correct response trials. The primary ERP data analyses were done with the ERN and CRN. The ΔERN was calculated by subtracting the CRN from the ERN, which has been thought to isolate neural activity specific to error processing [11]. However, the ΔERN is correlated both with the ERN and CRN, but in opposite directions, and is not therefore a measure independent of the CRN [49]. As an alternative, ERN and CRN standardized residual scores (ERN_{resid} and CRN_{resid}) were

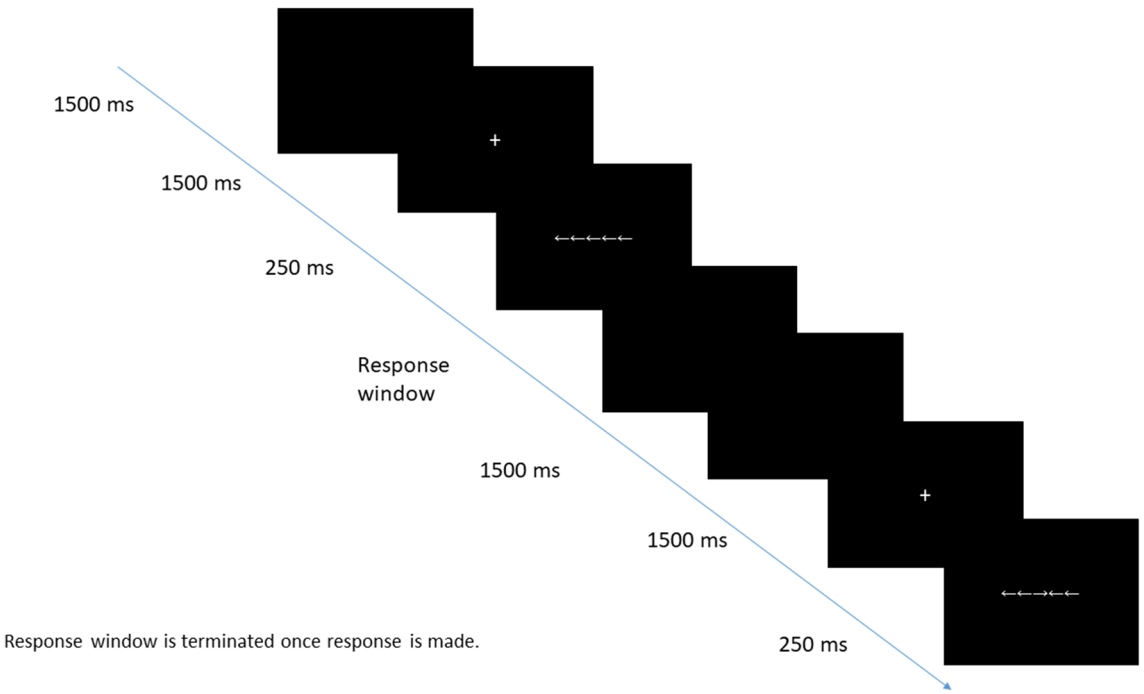

Fig. 1 Schematic depiction of the flanker task. Participants were instructed to respond by pressing one of two buttons indicating the direction of the central arrow (i.e., right versus left), while ignoring the adjacent arrows, and to respond as quickly and accurately as possible, placing equal emphasis on speed and accuracy

calculated based on measuring the variance leftover in a regression equation in which one score (e.g., CRN) is modeled as a predictor of another score (e.g., ERN; i.e., regression residuals or residualized scores), because they may be preferable to subtraction-based difference scores in separating error processing from response monitoring [49]. Secondary data analyses were done with the ΔERN, ERN_{resid} and CRN_{resid} to compare the two methods. Amplitudes were calculated for electrodes FCz and Cz, with the focus of the present study on the ERN at FCz. Correlational analyses with these measures indicate that numerically greater negative values represent higher ERP amplitudes.

Behavioral measures included the number of erroneous and correct trials for each subject, as well as accuracy expressed as a percentage of valid trials. Mean reaction times on error and correct trials were calculated separately, and trials were excluded if their reaction times were > 3 standard deviations from the mean. Reaction time and accuracy after errors were evaluated to determine whether there were group differences in post-error behavioral adjustments [11]. Reaction times were analyzed with group as a between-subject factor and response type as a within-subject factor. The mean number of errors per subject contributing to the analysis was 40.5 (SD = 22.1; range = 8–131).

Statistical Analyses

Student *t*-tests or χ^2 tests were used to evaluate group differences in demographic, clinical, and behavioral data. Pearson correlation coefficients were used to examine associations of response-related amplitudes with age, behavioral measures, and clinical measures. The ERN, CRN, ERN_{resid}, CRN_{resid}, and ΔERN was analyzed separately using a repeated-measure analysis of covariance with group (cases with AD and HC) as a between-subject factor and age, accuracy, and reaction time on incorrect or correct trials as covariates [11]. Similar analyses were conducted to examine performance monitoring in GAD cases, OAD cases, and HC. Cohen's effect size conventions were used to describe the magnitude of effects (small: $d \geq 0.20$; medium: $d \geq 0.50$; large: $d \geq 0.80$) [50].

ROC analyses were done to assess the sensitivity and specificity of the ERN as a diagnostic biomarker for AD, GAD, and OAD. The ROC analysis uses the association between sensitivity and specificity to derive an AUC, which indicates the extent to which a measure distinguishes between case positive (i.e., AD, GAD, or OAD) and case negative (i.e., HC) in a given sample irrespective of the base rate. In general, an AUC of 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding [41]. The Youden index, *J*, was used to select cut-scores for the ERN that give equal weight to sensitivity and specificity [51, 52]. Analyses were performed with JMP Pro Version 14 software. All tests were two-tailed with $\alpha = 0.05$.

Results

Behavioral Data in Youth with AD and HC

Participants were significantly more accurate on congruent than incongruent trials (paired $t\,(191) = 26.61$, $P < 0.0001$). There were no significant differences between AD cases and HC in accuracy, reaction time during correct or incorrect trials, or post-error slowing (Table 1). Correct responses were significantly slower than incorrect responses (paired $t\,(191) = 9.85$, $P < 0.0001$). Age in all participants had significant positive correlations with accuracy ($r = 0.33$, $P < 0.0001$), posterror accuracy ($r = 0.43$, $P < 0.0001$), and postcorrect accuracy ($r = 0.28$, $P < 0.0001$). Age in all participants had significant negative correlations with reaction time on correct ($r = -0.63$, $P < 0.0001$) and incorrect trials ($r = -0.48$, $P < 0.0001$), but had no significant correlation with posterror slowing ($P = 0.51$). There were no significant group or sex differences in accuracy, postcorrect accuracy, posterror accuracy, or posterror slowing (all *P* values > 0.18).

Event-Related Potential Data in Youth with AD and HC

Age in all participants had significant correlations with the ERN ($r = -0.27$, $P = 0.0002$), ERN_{resid} ($r = -0.32$, $P = 0.0009$), CRN_{resid} ($r = 0.21$, $P = 0.004$), and ΔERN ($r = -0.34$, $P < 0.0001$) but not with the CRN ($P = 0.08$). Accuracy in all participants had significant correlations with the ERN ($r = -0.17$, $P = 0.02$) and ERN_{resid} ($r = -0.14$, $P = 0.05$), but not with the CRN, CRN_{resid}, or ΔERN (all *P* values > 0.1). Reaction time on incorrect trials had significant correlations with the ERN ($r = 0.22$, $P = 0.002$), ERN_{resid} ($r = 0.29$, $P < 0.0001$), and ΔERN ($r = 0.34$, $P < 0.0001$). Reaction time on correct trials had significant correlations with the CRN ($r = -0.19$, $P = 0.007$), CRN_{resid} ($r = -0.27$, $P < 0.0001$), and ΔERN ($r = 0.37$, $P < 0.0001$). Post-error slowing had no significant correlations with the ERN, ERN_{resid}, CRN, CRN_{resid}, or ΔERN (all *P* values > 0.06). There were no significant sex differences in any brain potentials (all *P* values > 0.2).

ERN amplitude was significantly increased in AD cases compared to HC ($F_{1, 187} = 9.37$, $P = 0.002$, Cohen's $d = 0.44$), with a significant effect for age ($F_{1, 187} = 5.25$, $P = 0.04$) but not for accuracy or reaction time on incorrect trials (both *P* values > 0.16) (Table 1; Fig. 2). The ERN_{resid} was significantly enhanced in AD cases compared to HC ($F_{1, 187} = 7.29$, $P = 0.008$, Cohen's $d = 0.39$), with significant effects for

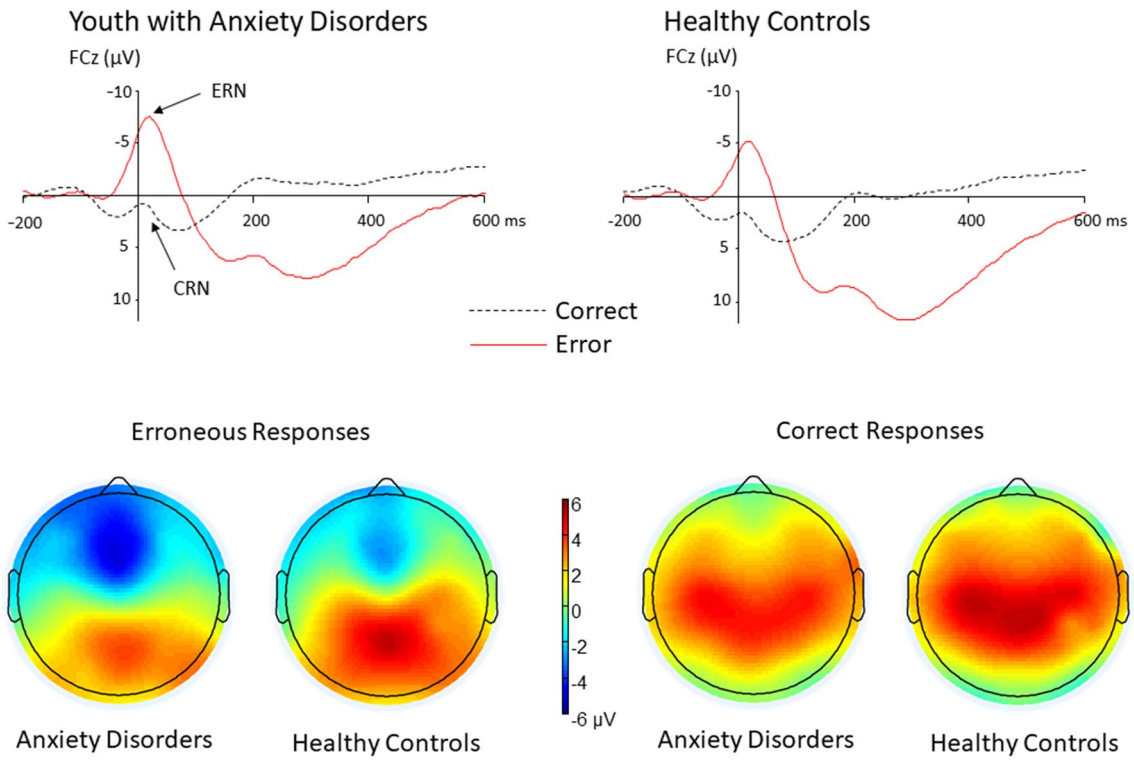

Fig. 2 Grand averages of electroencephalogram (EEG) recordings in 96 patients with anxiety disorders (AD) and 96 healthy controls (HC). Note: The top images depict response-locked grand average waveforms recorded at the central (FCz) electrode for correct and incorrect responses. Responses occurred at 0 ms. The mean amplitude of the error-related negativity (ERN) was computed in a window 0 to 80 ms after incorrect response trials. The mean amplitude of the correct response negativity (CRN) consisted of the same measure computed on correct response trials. The bottom images depict the topography of mean amplitudes of erroneous and correct waveforms measured between 0 and 80 ms

age ($F_{1, 187} = 7.84$, $P = 0.006$) and reaction time on incorrect trials ($F_{1, 187} = 4.44$, $P = 0.04$) but not for accuracy ($P = 0.52$). There were no significant differences between the AD cases and HC in the CRN, CRN_{resid}, or ΔERN (all P values > 0.08).

Event-Related Potential Data in GAD Cases, OAD Cases, and HC

In a comparison of the ERN in GAD cases, OAD cases, and HC, there were significant effects for group ($F_{2, 186} = 4.78$, $P = 0.01$) and age ($F_{1, 186} = 4.25$, $P = 0.03$) but not for accuracy or reaction time on incorrect trials (both P values > 0.16) (Table 2; Fig. 3). The ERN was significantly increased in GAD cases compared to HC ($F_{1, 132} = 6.93$, $P = 0.01$, Cohen's $d = 0.60$), with a significant effect for age ($F_{1, 132} = 4.69$, $P = 0.03$) but not for accuracy or reaction time on incorrect trials (both P values > 0.34). The ERN was significantly enlarged in OAD cases compared to HC ($F_{1, 146} = 5.12$, $P = 0.025$, Cohen's $d = 0.32$), with a significant effect for age ($F_{1, 146} = 3.97$, $P = 0.048$) but not for accuracy or reaction time on incorrect trials (both P values > 0.26). Results for the ERN_{resid}, CRN, CRN_{resid}, and ΔERN in the three groups are summarized in Table 2. There were no significant differences between GAD and OAD cases in the ERN, CRN, ERN_{resid}, CRN_{resid}, and ΔERN (all P values > 0.54).

ROC Analyses with AD Cases, GAD Cases, OAD Cases, and HC

In a comparison of AD cases and HC, the optimal ERN cut-score was − 0.52 μV (sensitivity = 0.83, specificity = 0.51, accuracy = 0.67, Youden $J = 0.34$) with an AUC of 0.64, resulting in the correct classification of 80/96 AD cases and 47/96 HC (Fig. 4). In a comparison of GAD cases and paired HC, the cut-score was − 1.24 μV (sensitivity = 0.88, specificity = 0.63, accuracy = 0.64, Youden $J = 0.51$) with an AUC of 0.75, resulting in the correct classification of 36/41 GAD cases and 26/41 HC. In a comparison of OAD cases and paired HC, the cut-score was − 0.52 μV (sensitivity = 0.80, specificity = 0.42, accuracy = 0.62, Youden $J = 0.22$) with an AUC of 0.56, resulting in the correct classification of 44/55 OAD cases and 23/55 HC.

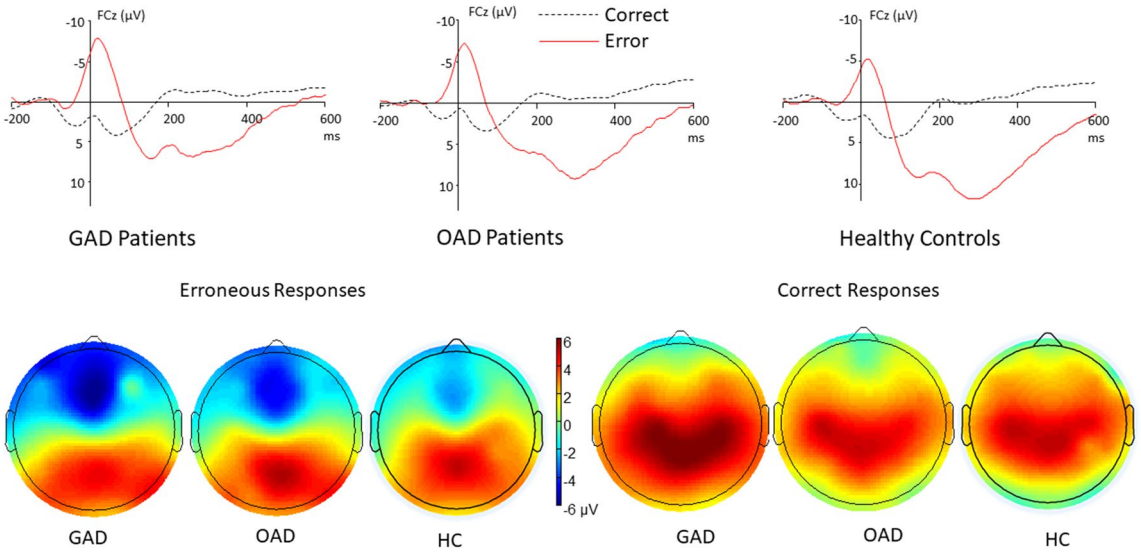

Fig. 3 Grand averages of electroencephalogram (EEG) recordings in 41 patients with generalized anxiety disorder (GAD), 45 patients with other anxiety disorders (OAD), and 96 healthy controls (HC). Note: The top images depict response-locked grand average waveforms recorded at the central (FCz) electrode for correct and incorrect responses. Responses occurred at 0 ms. The mean amplitude of the error-related negativity (ERN) was computed in a window 0 to 80 ms after incorrect response trials. The mean amplitude of the correct response negativity (CRN) consisted of the same measure computed on correct response trials. The bottom images depict the topography of mean amplitudes of erroneous and correct waveforms measured between 0 and 80 ms

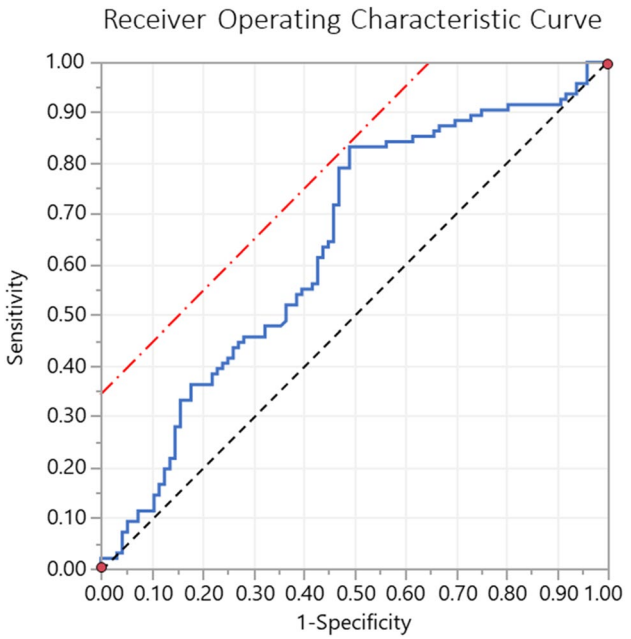

Fig. 4 Receiver operating characteristic (ROC) curve illustrating performance of the error-related negativity (ERN) in classifying patients with anxiety disorders and healthy controls (solid blue line). Sensitivity is plotted as a function of the false positive rate (i.e., 1- sensitivity). The area under the curve (AUC) is 0.67. Chance classification (0.50 AUC) is plotted for comparison (black dashed line). The red dashed line intersects the ROC curve at the optimal cut-off score (Color figure online)

Clinical and Event-Related Potential Data in Cases with AD and HC

The ERN had a significant correlation with CBCL/6–18 Anxiety Problems scores in the total sample ($r = -0.17$, $P = 0.02$), but not in cases or HC considered separately (both P values > 0.3). The ERN had a significant correlation with CBCL/6-18 Affective Problems scores in the total sample ($r = -0.22$, $P = 0.002$), but not in the two groups considered separately (both P values > 0.15). Similar correlations were also found with the ERN_{resid} and ΔERN (Table 3). There was no significant difference in the ERN between the 28 cases with a history of MDD and the 68 cases without that history ($P = 0.81$).

Discussion

Consistent with previous reports of increased performance monitoring in pediatric AD cases during a task eliciting response conflict, we found an increased ERN and ERN_{resid} in a large sample of older children and adolescents with a history of separation anxiety disorder, social anxiety disorder, panic disorder, specific phobia, agoraphobia, or GAD [6, 7, 30–35]. The small effect size for the enlarged ERN in pediatric AD is similar to that noted in a previous study of the ERN in OCD cases in the same age range (Cohen's $d = 0.44$ versus 0.41, respectively) [53]. In contrast to the findings with the ERN and ERN_{resid}, an increased ΔERN

Table 3 Correlation matrix for Child Behavior Checklist *DSM*-Oriented Scales, error-related negativity (ERN), correct response negativity (CRN), ERN minus CRN (ΔERN), ERN residualized scores, and CRN residualized scores at electrode FCz in patients with AD and healthy controls

	Affective problems	Anxiety problems	Somatic problems	Attention deficit/hyperactivity problems	Oppositional defiant problems	Conduct problems
Affective problems	–	0.64****	0.60****	0.45****	0.53****	0.48****
Anxiety problems	0.64****	–	0.57****	0.41****	0.38****	0.24****
Somatic problems	0.60****	0.57****	–	0.29****	0.38****	0.38****
Attention deficit/hyperactivity	0.45****	0.42****	0.38****	–	0.59****	0.54****
Oppositional defiant problems	0.53****	0.38****	0.38****	0.59****	–	0.67****
Conduct problems	0.48****	0.24****	0.38****	0.54****	0.67****	–
ERN, FCz	− 0.22**	− 0.17*	− 0.10	− 0.01	0.02	0.006
CRN, FCz	0.05	− 0.03	0.03	− 0.07	0.05	0.03
ERN residualized scores, FCz	− 0.24***	− 0.17*	− 0.11	0.01	0.004	− 0.004
CRN residualized scores, FCz	0.12	0.02	0.05	− 0.07	0.05	0.03
ΔERN, FCz	− 0.24***	− 0.14	− 0.11	0.04	− 0.02	− 0.02

AD anxiety disorders, *SD* standard deviation, *ERN* error-related negativity, *CRN* correct response negativity, *ΔERN* error-related negativity amplitude minus correct response negativity amplitude

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$

was not detected in AD cases, suggesting the ERN_{resid} may be superior to the ΔERN in separating error processing from response monitoring [27]. Consistent with that interpretation is the observation that accuracy had a significant correlation with the ERN_{resid} but not with the ΔERN. An earlier study found, however, both an increased ERN_{resid} and ΔERN in pediatric AD [35]. The AUC in the ROC analysis of the ERN in AD cases and HC was 0.64, indicating the ERN does *not* provide an adequate diagnostic test for the common pediatric AD taken together [41].

Compared to controls, ERN amplitudes were increased in cases with either GAD or OAD, with GAD having a moderate effect size and OAD having a small effect size (Cohen's $d = 0.60$ versus 0.32, respectively). Although the ERN_{resid} was increased in GAD cases, there was only a trend for an increased ERN_{resid} in OAD cases. The ROC analysis of the ERN in GAD cases and HC found an AUC of 0.75, which is somewhat higher than the AUC of 0.69 found in a previous study of adults with GAD [40]. The ERN results are consistent with the suggestion that the RDoC sustained threat construct may be relevant to understanding the pathophysiology of GAD, in which persistent doubts about actions and excessive worries about potential mistakes may function as endogenous threats that are reflected in the ERN [54]. If these results are replicated in other laboratories using both HC and other psychiatric disorder comparison groups, the ERN may be shown to provide an adequate diagnostic test for pediatric GAD [41]. Furthermore, because studies support the ERN as a biomarker for pediatric GAD that is independent of symptom severity and treatment effects [35, 38], the ERN could be examined as a possible endophenotype in the unaffected relatives of pediatric GAD cases as has been done in studies of OCD [13, 18, 55].

In contrast to the promising results with pediatric GAD, the ROC analysis of the ERN in OAD cases and HC found an AUC of only 0.56, indicating that the ERN does *not* provide an adequate diagnostic test for OAD in older children and adolescents [41]. Hence, the results suggest overall that an enlarged ERN may have a stronger association with GAD than with OAD, consistent with the hypothesis that ERN variation is more strongly correlated with worry involving cognitive symptoms of anxiety than with symptoms associated with anxious arousal or acute fear [7, 21, 28, 29]. Nonetheless, the ERN results also indicate that increased performance monitoring may occur in some AD other than GAD and that studies with larger samples will be necessary to adequately assess performance monitoring in each of the OAD. Consistent with that possible complexity in pediatric AD, one study found an enlarged ERN in youth with social phobia but not with GAD [34].

Because of the limitations of the ERN in discriminating AD, GAD, and OAD cases from HC, it may be useful to consider the ERN as one of several measures in a composite biomarker scale that may have higher sensitivity and specificity than the ERN alone [40, 56]. Preliminary evidence indicates that the ERN and error-related theta power may

uniquely distinguish between adults with GAD and HC, suggesting these error-related neural measures may provide a more sensitive and specific diagnostic biomarker for GAD than the ERN alone [57]. Similarly, a study of preschoolers found that associations between the ERN and parent ratings of social withdrawal and social inhibition were moderated by error-related theta power [58]. Specifically, low theta power and an enlarged ERN predicted more social withdrawal, whereas the ERN and social withdrawal were unrelated when theta power was high, suggesting that the ERN and theta power may jointly contribute to anxiety risk in early childhood.

In contrast to some studies of adults with GAD, we found no evidence that MDD moderated the ERN in AD cases [59, 60]. Instead, more negative ERN amplitudes were associated with both higher CBCL/6-18 Anxiety and Affective Problems scores in the total sample but not in cases or HC considered separately. Furthermore, the ERN did not differentiate between cases with and without a history of MDD. Longitudinal studies may determine whether the ERN in youth with AD is predictive of the subsequent onset of MDD or other disorders. In contrast to some studies of the ERN in children with attention-deficit/hyperactivity disorder, there were no significant correlations between the CBCL/6-18 Attention-Deficit/Hyperactivity Problems scores and any brain potentials (Table 3) [18].

Our study has limitations requiring further consideration. Participants were primarily Caucasian and treatment was not controlled; nonetheless, it is doubtful that ERN amplitudes would be different with a more diverse or untreated sample [34, 35]. With the limited sample sizes for each anxiety disorder and the relatively small effect size in the OAD, only GAD was considered separately from the other AD [28]. It is possible that other studies will find that the ERN is consistently enlarged in one of the pediatric AD other than GAD [34]. The ERN was not compared between cases with a current or past diagnosis of an anxiety disorder because the ERN has been considered in general to be a trait-like diagnostic biomarker for AD; however, that comparison may be useful in a larger sample with more statistical power [6, 34, 35].

Our results provide further evidence of an enlarged ERN in pediatric AD that may serve as a transdiagnostic liability index that is independent of symptom severity and treatment effects [7, 35, 37, 38]. The results overall are consistent with the hypothesis that ERN variation is more strongly correlated with worry involving cognitive symptoms of anxiety than with symptoms associated with anxious arousal or acute fear [7, 21, 28, 29]. The results from our ROC analyses suggest that the ERN is a diagnostic biomarker for pediatric GAD, as has been suggested for adult GAD [40, 57], but not for the common pediatric AD taken together [41]. Studies with larger samples will be necessary to adequately assess the ERN and error-related theta activity as diagnostic biomarkers for pediatric AD.

Summary

The ERN is a negative deflection in the event-related potential following an incorrect response that is a putative mechanistic biomarker of anxiety across the lifespan. The study compared ERN amplitudes in youth with a lifetime diagnosis of one or more AD and HC, and assessed the ERN as a diagnostic biomarker using ROC analyses. The ERN, CRN, and accuracy were measured during a flanker task to assess performance monitoring in 96 patients with AD and 96 matched HC ages 8 to 18 years. Forty-one cases had a history of GAD; 55 cases had a history of OAD without GAD. ERN amplitude was significantly increased in AD cases compared to HC (Cohen's $d = 0.44$). The AUC in the ROC analysis with AD cases and HC was 0.64, indicating the ERN is an inadequate diagnostic test for AD altogether. The ERN was significantly increased in cases with either GAD or OAD compared to HC (Cohen's $d = 0.60$ versus 0.32, respectively). The AUC in ROC analyses with GAD and OAD cases was 0.75 and 0.56, respectively, suggesting the ERN provides an adequate diagnostic test for GAD but not for OAD. The results provide further evidence that an enlarged ERN in pediatric AD represents a transdiagnostic liability index that is more strongly associated with pediatric GAD than other pediatric AD.

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