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The moderating role of externalizing problems on the association between anxiety and the error-related negativity in youth

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Abstract

The error-related negativity (ERN) is an event-related potential that reflects error monitoring. Enhanced ERN indicates sensitivity to performance errors and is a correlate of anxiety disorders. In contrast, youth with externalizing problems exhibit a reduced ERN, suggesting decreased error monitoring. Anxiety and externalizing problems commonly co-occur in youth, but no studies have tested how comorbidity might modulate the ERN. In a sample of youth ($N = 46$, ages 7–19) with and without anxiety disorders, this preliminary study examined the interactive effect of anxiety and externalizing problems on ERN. Results suggest that externalizing problems moderate the relation between anxiety symptoms and ERN in youth. Anxious youth with less externalizing problems exhibited enhanced ERN response to errors. Conversely, anxious youth with greater externalizing problems demonstrated diminished ERN in response to errors. The regions of significance and proportion affected tests indicated that the moderating the effect of externalizing problems was only significant for youth with anxiety disorders. Findings suggest that enhanced neural error sensitivity could be a specific neurophysiological marker for anxiety disorders, whereas anxious individuals with comorbid externalizing problems demonstrate reduced error monitoring, similar to those with primary externalizing pathology. Results underscore the utility of examining neural correlates of pediatric anxiety comorbidity subtypes.

KEYWORDS

anxiety, error-related negativity, externalizing behaviors

1 | INTRODUCTION

Anxiety disorders are some of the most common forms of childhood psychopathology (e.g., Copeland, Angold, Shanahan, & Costello, 2014), which typically emerge in late childhood and early adolescence (e.g., Beesdo, Knappe, & Pine 2009). Epidemiological studies of community samples of adolescents have shown the prevalence estimate of having any type of anxiety disorder is 25% within a 12-month period, and 15% in a 30-day period (e.g., Kessler et al., 2012). Longitudinal representative population-based research has also estimated that 16% of youth has an anxiety disorder at some point during their childhood and adolescence, and 30% of these anxious youth also meet criteria for an anxiety disorder at subsequent assessments (e.g., Bittner, Egger, Costello, Foley, & Angold, 2007). Notably, many youth with anxiety disorders also have other comorbid psychiatric diagnoses, including externalizing pathology. Among clinical and general population samples, research has indicated that

anywhere from 15% to 23% of anxious youth meet criteria for attention-deficit hyperactivity disorder (ADHD; Angold, Costello, & Erkanli, 1999; Kendall, Brady, & Verduin, 2001), and about 9% of anxious youth meet criteria for oppositional defiant disorder (ODD; Kendall et al., 2001). It is well established that childhood comorbidity is associated with significantly worse short- and long-term psychosocial impairments (Fraire & Ollendick, 2013; Franco, Saavedra, & Silverman, 2007). Despite moderate rates of anxiety and externalizing psychopathology comorbidity, their neurobiological origins are not well understood, which is significant given increasing clinical research emphasis on understanding the underlying pathophysiology of common psychiatric disorders and syndromes, and identifying the extent to which disorders and subtypes are associated with similar or unique neurophysiological characteristics (Insel et al., 2010; Shankman & Gorka, 2015).

Psychophysiological tools, such as scalp-recorded electroencephalogram (EEG) recordings in response to environmental cues of threat and error monitoring, have proven to be useful in identifying neural correlates of different forms of psychopathology across the life span (e.g., Shankman & Gorka, 2015). Over 50 studies have focused on the error-related negativity (ERN), an event-related potential (ERP) component typically measured at frontocentral electrodes 50–100 ms following commission of an error (Olvet & Hajcak, 2008; Weinberg, Riesel, & Hajcak, 2012). Source localization studies and investigations employing EEG and functional magnetic resonance imaging (fMRI; Debener et al., 2005; Fitzgerald et al., 2005; Mathalon, Whitfield, & Ford, 2003) have identified the anterior cingulate cortex (ACC) as the region of the brain that generates the ERN. The ACC is the primary brain mechanism involved in online monitoring for conflict between simultaneously active but incompatible streams of information (Shiels & Hawk, 2010). Greater ERN amplitudes are theorized to reflect processes of heightened conflict monitoring (Yeung, Botvinick, & Cohen, 2004), and sensitivity to threat (Weinberg et al., 2016) and punishment (Shackman et al., 2011; Zambrano-Vazquez, & Allen, 2014). Research has indicated that the ERN represents a trait-like neural response to errors, as it demonstrates strong test-retest reliability and rank-order stability. Furthermore, ERN amplitudes appear to be multiply determined by genetic and environmental influences (Weinberg, Klein, & Hajcak et al., 2012).

Research has shown that the ERN is a neural correlate of psychopathology, particularly anxiety disorders. Specifically, enhanced (i.e., more negative) ERN in anxious individuals is frequently observed, and has been consistently replicated in both adult (Hajcak, Klawohn, & Meyer, 2019; Weinberg, Dieterich, & Riesel, 2015) and pediatric samples (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Meyer, 2017). Enhanced ERN has been shown to prospectively predict the onset of anxiety psychopathology in school-age children (Meyer, Proudfit, Torpey-Newman, Kujawa, & Klein, 2015), adolescents (Meyer, Nelson, Perlman, Klein, & Kotov, 2018), and adults (Tang et al., 2020), to identify individuals with a family history of anxiety (Riesel et al., 2019), and to associate with fear-based anxiety symptoms in adults (Gorka, Burkhouse, Afshar, & Phan, 2017).

Although studies have been more limited, differences in ERN have also been documented in individuals with externalizing symptomatology (Pasion & Barbosa, 2019). Externalizing symptoms and disorders have been linked with error-related hypoactivity or a blunted ERN, which means more positive rather than negative ERN amplitudes, the latter being observed in anxiety disorders (Hall, Bernat, & Patrick, 2007; Pasion & Barbosa, 2019; Shiels & Hawk, 2010). Blunted ERNs have been documented in youth with ADHD and disruptive behavior disorders (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013; Meyer & Klein, 2018; Vilà-Balló, Hdez-Lafuente, Rostan, Cunillera, & Rodriguez-Fornells, 2014). This suggests that externalizing symptoms and psychopathology are characterized by deficient error responding and impaired error evaluation.

It is important to note that ERN findings in the anxiety and externalizing literatures have not been entirely consistent, such that symptom/disorder and ERN patterns do not always demonstrate the expected directional relationships, particularly when there is comorbid psychopathology. For example, some adult studies have found that ERN and anxiety disorder associations differ when individuals have comorbid depression (Weinberg, Klein, et al., 2012; Weinberg, Kotov, & Proudfit, 2015). In addition, Stieben et al. (2007) found that the association between externalizing problems and a blunted ERN was less apparent among children with comorbid internalizing problems.

Despite the high prevalence of anxiety disorders (Beesdo et al., 2009; Copeland et al., 2014) and frequent co-occurrence of externalizing problems in childhood (Angold, Costello, & Erkanli, 1999; Kendall et al., 2010; Verduin & Kendall, 2003), how anxiety and externalizing comorbidity patterns relate to ERN profiles has yet to be tested. Research that examines these relations could have the potential to resolve some of the inconsistencies observed in the ERN pediatric literature, increase precision in our understanding of neural correlates of anxiety comorbidity subtypes, and elucidate primary sources of impairment that could have translational implications. Accordingly, the primary aim of this preliminary study was to be one of the first to investigate how ERN responses could differentiate anxious subtypes as defined by those with and without comorbid externalizing problems in a pediatric sample. Healthy youth, defined as those without lifetime histories of psychiatric disorders, were also included in order to examine psychiatric symptom and ERN relations dimensionally. The overall sample consisted of anxious youth and healthy controls (ages 7–19 years old) who were recruited for a study of the treatment of pediatric anxiety disorders. Based on prior work on ERN in anxiety disorders (Meyer, 2017; Meyer et al., 2013), we hypothesized that youth with greater anxiety symptoms who did not have co-occurring externalizing problems would demonstrate enhanced ERN (i.e., greater sensitivity to errors). Drawing on preliminary studies suggesting anxiety and ERN relations could be qualified by psychiatric comorbidity (Stieben et al., 2007), we predicted that youth with co-occurring anxiety symptoms and externalizing

problems would exhibit a blunted ERN, indicating reduced error monitoring.

2 | METHODS

2.1 | Procedures and participants

The current sample was drawn from a multisite study of pediatric anxiety disorders at the University of Michigan (UM) and the University of Illinois at Chicago (UIC) that recruited youth with and without anxiety disorders. At each site youth were recruited from outpatient psychiatric clinics and from the surrounding communities via Internet postings and flyers. Participants and their parents completed a battery of diagnostic interviews and symptom assessments. Youth completed a flanker task while EEG was recorded. Participants included 46 youth (anxious participants, $n = 27$; healthy controls, $n = 19$) who were between the ages of 7 and 19 ($M = 13.11$, $SD = 3.21$) and had usable EEG and complete questionnaire data. Psychiatric diagnoses were obtained through the semi-structured Schedule of Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997), which was administered by trained master's- and doctoral-level clinicians. Anxious participants ($n = 27$) had primary diagnoses of generalized anxiety disorder ($n = 18$), social anxiety disorder ($n = 7$), or separation anxiety disorder ($n = 2$). Some anxious participants also met criteria for panic disorder ($n = 1$) and specific phobia ($n = 1$), and 37.0% met criteria for more than one anxiety disorder. Anxious youth also had a comorbid depressive disorder ($n = 2$), obsessive-compulsive disorder ($n = 1$), and ADHD ($n = 2$). Healthy controls ($n = 19$) had no lifetime psychiatric histories. Exclusionary criteria included the history of bipolar or schizophrenia disorders, intellectual disability, pervasive developmental disorders, current substance abuse, and current suicidal ideation.

Approximately 47.8% of the participants were female ($n = 22$). Participants identified as Caucasian (60.9%), Latinx (10.9%), African American (21.7%), and Asian or Pacific Islander (6.5%). About 23.9% of the sample identified as Hispanic. Study procedures were approved by the UM and UIC Institutional Review Boards prior to data collection. Informed consent and assent were obtained from youth and their legal guardians prior to the administration of study measures.

2.2 | Assessment of anxiety symptoms and externalizing behavior problems

To measure anxiety symptom severity, youth were administered the Pediatric Anxiety Rating Scale (PARS), which is an interviewer-rated measure of anxiety symptom severity across seven dimensions of anxiety (e.g., frequency and number of symptoms, overall symptom severity, physical symptom severity, avoidance, and interference at home and outside of the home; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002). Parents completed the Child Behavior Checklist for Ages 6–18 (CBCL; Achenbach & Rescorla, 2001), which is a parent report measure of a broad range of problems experienced by youth. Parents indicate whether their child experiences a particular behavior problem on a 0–2 rating scale (0 = Not true, 1 = Somewhat or Sometimes True, 2 = Very true or Often True). The CBCL includes eight empirically derived syndrome scales. The aggressive behavior ($\alpha = 0.89$), rule-breaking behavior ($\alpha = 0.69$), and social problems ($\alpha = 0.83$) subscales were used as the indicators of externalizing behavior problems, and demonstrated adequate internal consistency. We also chose to use the social problems subscale, as prior research has demonstrated that it assesses specific social behavior problems of externalizing behaviors that are not captured by the aggressive behavior and rule-breaking scales (e.g., Bunford et al., 2017). We observed variability in scores across the different CBCL subscales. On the social problems subscale, 52.2% of the sample had scores above the normative mean, with 13% of scores ≥1 standard deviation (*SD*) above the normative mean. For the aggressive behavior subscale, 28.2% of the sample had scores above the normative mean, with 17.4% of scores falling ≥1 *SD* above the normative mean. For rule-breaking behavior, 47.8% of the sample had scores above the normative mean, with 13% of participants with scores ≥1 *SD* above the normative mean. The subscales were positively and significantly correlated with each other (*r*s ranged from 0.58 to 0.70, *p*s < .01). Principal component analysis with varimax rotation was performed on the three subscales. Inspection of the eigenvalues (>1) and scree plot supported a single-factor solution. The solution accounted for 75.06% of the variance, yielding positive loadings for aggressive behavior ($r = 89$), rule breaking ($r = .88$), and social problems ($r = .83$). Subscales were aggregated to create an internally consistent composite of youth externalizing behavior problems ($\alpha = 0.75$). Anxiety symptoms and the externalizing problems composite were significantly correlated, $r = .61$, $p < .01$. Anxiety symptoms and externalizing problems were normally distributed (absolute skewness <2; absolute kurtosis <4; George & Mallery, 2010; Hair, Black, Babin, & Anderson, 2010).

2.3 | Error monitoring task

Participants completed a modified flanker task (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991), which measures performance monitoring in response to errors. A large body of evidence has shown that the Flanker task reliably elicits the ERN across development and evinces excellent test–retest reliability (e.g., Olvet & Hajcak, 2009; Weinberg & Hajcak, 2011). The flanker task consists of 11 blocks of 30 trials (330 trials total). On each trial horizontally aligned arrowheads are presented on a computer screen for 200 ms, which is then followed by an intertrial interval between 2,300 and 2,800 ms. On half the trials, the arrows are aligned in the same direction (»»> or ««<), and on the other half, the center arrowhead is in an opposing, incompatible direction to the other arrowheads (« > « or» < »). Participants were instructed to press the left or right mouse button to indicate the direction of the center arrow. Participants

completed a practice block of 30 trials before starting the task to ensure their understanding of the rules of the task. Participants received feedback on their performance at the end of each block in order to obtain an adequate number of error trials. The message "Please try to be more accurate" was displayed on the screen if their accuracy was below 75%, and "Please try to respond faster" was displayed if their accuracy was above 90%. Otherwise, the message "You're doing a great job" appeared on the screen. To reduce the potential impact of study site effects, procedures for the flanker task were identical across the two study sites (e.g., administered in a quiet room with one observer present, same version of the task and software). To be consistent with exclusionary criteria from published studies with this dataset (Kujawa et al., 2016; Peters et al., 2019), all of the participants had permissible error rates (>6 errors after artifact rejection) and percent accuracy (>60% correct on trials with responses) on the task. On average, youth committed 32.80 errors (SD = 24.74, Range = 3–98), which corresponds with an overall percent accuracy rate of 90% (SD = 0.08, Range = 0.70–0.99). Average response time across the trials was 445.99 ms (SD = 137.26, Range = 152.65–975.46). Anxious youth and healthy youth did not differ in total errors (F (1, 41) = 0.24, p = .63), percent accuracy (F (1, 41) = 0.24, p = .63), or average reaction time (F (1, 41) = 0.50, p = .48) on the task.

2.4 | EEG data acquisition and preprocessing

The EEG data acquisition and preprocessing steps were identical across the study sites. Continuous EEG recordings were collected while participants completed the flanker task using the BioSemi 34-channel cap (32 channels plus FCz and Iz). Data acquisition and processing procedures for the study have been detailed in previous publications (Kujawa et al., 2016; Peters et al., 2019). Electrodes were placed on the right and left mastoids. To account for ocular artifacts that result from eye blinks and other eye movements, electrooculargram (EOG) signals were recorded from two electrodes placed 1 cm above and below the right eye to measure vertical eye blinks and movements and two electrodes placed 1 cm beyond the outer edge of each eye to measure horizontal eye blinks and movements. Data were digitized at a 24-bit resolution with least significant bit (LSB) value of 31.25 nV and sampling rate of 1,024 Hz. Processing of EEG data was performed offline using Brain Vision Analyzer software (Brain Products, Gilching). Data were converted to a linked mastoid reference, filtered with high-pass and low-pass filters of 0.1 and 30 Hz, and segmented 500 ms before the response through 1,000 ms after the response. Eye blinks were corrected using standard methods (Gratton, Coles, & Dochin, 1983), and semi-automated artifact rejection procedures were used to detect and eliminate artifacts with a voltage step of >50 μV between sample points, with a maximum voltage difference of 175 μV within 400 ms intervals, and additional artifacts were removed using visual inspection. ERPs to errors and correct responses were averaged separately and baseline corrected to the window 500–300 ms before the response. The ERN was scored by pooling frontocentral sites (Fz, FCz, Cz) as mean activity 0 to 100 ms after the response (Figure 1; prior to adjusting for other study variables of interest). As expected, the ERP was more negative to error versus correct responses (t (45) = −6.14, p < .001). As employed in prior work (Meyer, Lerner, De Los Reyes, Laird, & Hajcak, 2017), a residual scoring approach was used to operationalize ERN. This was accomplished by regressing the error values on to the correct values in order to obtain unstandardized residual scores, which were then saved in the dataset and used in the study analyses. The unstandardized residual ERN score allows for isolation of the variance in the ERP wave related to performance monitoring (Luck, 2005). More negative residual ERN amplitudes indicate enhanced response to errors relative to correct responses (i.e., increased error monitoring).

2.5 | Data analytic plan

Statistical analyses were conducted with SPSS Version 25 (IBM Corp.). Multiple linear regression analyses were performed to examine main and interactive effects between anxiety symptoms and externalizing problems in relation to ERN amplitudes in youth and in association with youths' behavioral performance on the flanker task (e.g., reaction time, total errors, percent accuracy). For the interaction analysis we employed a residual centering approach (Little,

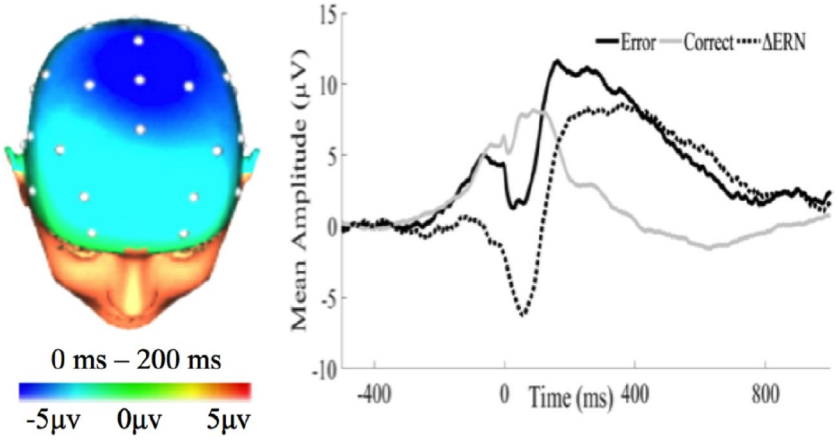

FIGURE 1 The topographic map of neural activity (error minus correct) and response-locked event-related potential (ERP) waveforms at an average of Fz, FCz, and Cz across the entire sample. The raw waveforms for correct and error responses and the error-correct difference (dotted line) are shown in the graph. Negative voltages are plotted down, and represent increases in ΔERN

Bovaird, & Widaman, 2006), which ensures orthogonality between the interaction variable and the first-order main effects. This technique began with centering the main effect variables and then multiplying them to create the product term. In the next step, the product term was regressed on the centered main effect predictor variables to remove main effect information contained in the interaction term. The residual score was saved as a new variable in the dataset and utilized in the analysis. Significant interactions were followed up with simple slopes analysis (Fraley, 2012; http://www.yourpersonality.net/interaction/ros.pl). Anxiety symptoms and externalizing problems were plotted at ±1 *SD*s from their centered means.

3 | RESULTS

3.1 | Descriptive statistics

Demographic and clinical characteristics of the sample are presented in Table 1. Age and gender distributions were similar across healthy and anxious youth participants, as were proportions of youth who identified as Caucasian, African American, Asian, and Hispanic. There were marginally more anxious participants who identified as Latinx ($n = 5$) relative to the healthy youth ($n = 0$; χ^2 (1) = 3.95, $p = .05$). Mean levels of anxiety symptoms (F (1, 46) = 41.73, $p < .01$) and externalizing behaviors (F (1, 46) = 29.17, $p < .001$) were significantly greater among anxious youth compared to healthy youth.

3.2 | Primary analysis

To examine the relation between anxiety and externalizing symptoms and the ERN, the main effects of anxiety symptoms and externalizing problems, and their two-way interaction were entered into a multiple linear regression model with ERN set as the dependent variable. The overall model accounted for significant variance in youth ERN (F (3, 45) = 4.13, $p = .01$, $R^2 = .23$). The main effect of anxiety symptoms on ERN was not significant ($\beta = -0.19$, $t = -1.10$, $p = .28$, 95% CI = −0.22, 0.06). The main effect of externalizing

TABLE 1 Demographic and clinical characteristics of anxious and healthy youth

	Healthy youth ($n = 19$)		Anxious youth ($n = 27$)					
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p* value
Age	14	2.92	12.48	2.92	13.11	3.21	2.59	.12
PARS total score	1.16	2.29	23.96	4.23	14.54	11.89	41.73	<.01
Externalizing problems	1.89	2.08	12.33	9.94	8.02	9.27	29.17	<.01
Accuracy (% correct)	0.91	0.07	0.90	0.08	0.90	0.07	0.24	.63
Total errors	30.62	23.09	34.43	26.13	32.8	24.74	0.24	.53
Response time	428.54	131.97	459.09	142.46	445.99	137.26	0.50	.48
	N	%	*N*	%	*N*	%	χ^2	*p* value
Sex (% female)	8	42.1	14	51.9	22	47.8	0.43	.52
Ethnicity								
Hispanic	3	15.8	8	29.6	11	23.9	1.17	.28
Race								
Caucasian	13	68.4	15	55.6	28	60.9	0.78	.38
African American	6	31.6	4	14.8	10	21.7	1.84	.18
Asian or Pacific Isl.	0	0.0	3	11.1	3	6.5	2.26	.13
Latinx	0	0.0	5	18.5	5	21.7	3.95	.05
Primary diagnoses								
Generalized anxiety	—	—	18	39.1				
Separation anxiety	—	—	2	4.3				
Social anxiety	—	—	7	15.2				
Comorbid diagnoses								
ADHD	—	—	2	4.3				
Depressive disorders	—	—	2	4.3				
Obsessive-compulsive	—	—	1	2.2				
Panic	—	—	3	6.5				
Specific phobia	—	—	1	2.2				

Abbreviations: ADHD, attention-deficit hyperactivity disorder; Isl., Islander; PARS, pediatric anxiety rating scale; *SD*, standard deviation.

problems on ERN was significant (β = 0.37, t = 2.14, p = .04, 95% CI = 0.01, 0.38), specifically greater externalizing problems were associated with reduced ERN amplitudes (i.e., blunted error response). There was a significant two-way interaction effect between anxiety symptoms and externalizing problems on ERN (β = 0.38, t = 2.78, p = .01, 95% CI = 0.011, 0.068; see Table 2). We reanalyzed the regression model adjusting for the potential influence of age and gender on ERN. The two-way interaction effects remained significant (β = 0.31, t = 2.215, p = .03, 95% CI = 0.003, 0.06). The main effects of age (β = −0.22, t = 0.47, p = .15, 95% CI = −0.80, 0.13) and gender (β = −0.07, t = 0.49, p = .63, 95% CI = −3.64, 2.21) on ERN were not significant.

To parse the significant two-way interaction, we performed a simple slopes analysis. Youth anxiety and externalizing problems were plotted at ±1 *SD*s from their respective centered means, and externalizing problems was set as the moderator. For youth with less externalizing problems (−1 *SD* from the mean), greater anxiety symptom severity was associated with an enhanced ERN response (greater error monitoring, b = −0.44, t = 2.96, p = .01; Figure 2). For youth with greater externalizing problems (+1 *SD* from the mean), greater anxiety symptom severity was associated with a trend for a diminished ERN (i.e., reduced error monitoring, b = 0.28, t = 1.91, p = .06; Figure 2). However, the regions of significance showed that this relation became significant for values of externalizing problems that were greater than 10.41, which represents 1.12 *SD* from the centered mean and was represented in the dataset. Regions of significance test for anxiety symptoms showed that low and high externalizing youth did not differ in ERN responses when anxiety symptoms were at the low end of the distribution (b = −0.27, t = 1.40, p = .17). However, youth with high and low externalizing problems demonstrated significantly different and opposing ERN amplitudes when anxiety symptoms were at the high end of the distribution (b = 0.66, t = 3.47, p = .001).

We also examined the proportion affected (PA) index, which quantifies the number of participants who are differentially affected by the interaction effect. The PA index is computed by finding the value on anxiety symptoms where the regression lines intersect, which corresponded with a total score of 18 on the PARS (sample range = 0–30). We accomplished this by creating a new variable in the dataset where 1 was coded for all the participants whose anxiety symptoms were above the cross-over point. When we examined how many cases in the dataset that fell above the cutoff we found it directly corresponded with the number of youth in the sample that had anxiety disorders (n = 27). Given that low and high externalizing youth only differed in ERN responses when anxiety symptoms were high, this suggests youth with anxiety disorders were the participants driving the interaction effect.

Lastly, we performed multiple linear regression to examine the main effects of anxiety symptoms and externalizing problems and their two-way interaction with total errors, percent accuracy, and average reaction time. There were no main effects of anxiety symptoms on total errors (β = 0.16, t = 0.81, p = .43, 95% CI = −0.50, 1.16), percent accuracy (β = −0.16, t = 0.81, p = .43, 95% CI = −0.004, 0.002), or average reaction time (β = −0.10, t = −0.48, p = .63, 95% CI = −5.83, 3.58). There were also no main effects of externalizing problems on total errors (β = 0.02, t = 0.09, p = .93, 95% CI = −0.99, 1.09), percent accuracy (β = −0.02, t = −0.09, p = .93, 95% CI = −0.003, 0.003), or average reaction time (β = 0.32, t = 1.59, p = .12, 95% CI = −1.27, 10.57). There were no significant two-way interaction effects between externalizing problems and anxiety symptoms on total errors (β = 0.29, t = 1.90, p = .07, 95% CI = −0.01, 0.30), percent accuracy (β = −0.29, t = −1.90, p = .07, 95% CI = −0.001, 0.000), or average reaction time (β = 0.02, t = 0.13, p = .90, 95% CI = −0.83, 0.95). Effects were unchanged when adjusting for age and gender in the models. However, there were significant main effects of age on total errors (β = −0.80, t = −6.97, p < .001, 95% CI = −8.55, −4.70) and percent accuracy (β = 0.80, t = 6.97, p < .001, 95% CI = 0.01, 0.03), which indicated that older children were more accurate in their responses and committed fewer errors. Lastly, there were no significant main effects of gender on total errors (β = 0.09, t = 0.84, p = .40, 95% CI = −6.39, 15.48), percent accuracy (β = −0.09, t = −0.84, p = .40, 95% CI = −0.05, 0.02), or average reaction time (β = 0.03, t = 1.17, p = .87, 95% CI = −87.30, 103.08).

TABLE 2 Multiple linear regression analysis examining the interaction effect between anxiety symptoms and externalizing problems on ERN

Independent variable	*b*	*SE*	*β*	*t*	*p* value
Anxiety symptoms	−0.078	0.07	−0.19	−1.10	.28
Ext. problems	0.197	0.09	0.37	2.14	.04
Anxiety symptoms × Ext. problems	0.039	1.56	0.38	2.78	.01

Abbreviations: Ext., externalizing; *SE*, standard error.

4 | DISCUSSION

The overarching goal of the study was to examine whether youth error monitoring patterns, as measured by the ERN, were qualified by the extent to which youth had co-occurring anxiety and externalizing problems. Consistent with our hypotheses, we found that externalizing problems moderated the relation between anxiety symptoms and ERN. For youth with low externalizing problems, greater anxiety symptom severity was significantly associated with enhanced ERN amplitudes. In contrast for youth with greater externalizing problems, greater anxiety symptom severity was associated with decreased ERN amplitudes, demonstrating an opposing blunted pattern. Further parsing of the simple slope effect showed that youth with low and high externalizing problems only demonstrated statistically different ERN amplitudes when anxiety symptoms were at the higher, and not at the lower end of the distribution. Furthermore, we found that the proportion of youth who were affected by the

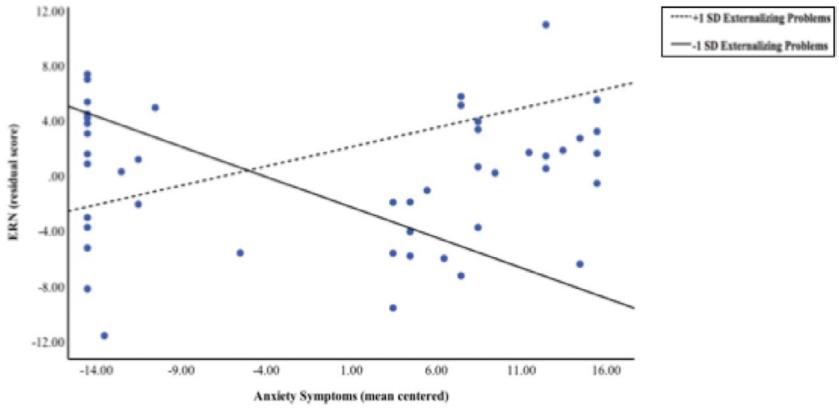

FIGURE 2 Plot of the significant anxiety symptom × externalizing problems interaction on youth's error-related negativity (ERN). Values on the *Y*-axis represent unstandardized residual ERN values, and negative values are plotted down. More negative values indicate enhanced error monitoring. Values on the *X*-axis are centered anxiety symptoms. Higher scores indicate greater anxiety symptom severity. Solid line represents the simple slope for youth with externalizing problems at −1 *SD* from the centered mean. Dashed line represents the simple slope for youth with externalizing problems at +1 *SD* from the centered mean

interaction effect directly corresponded with the 27 youth in the sample with diagnosed anxiety disorders.

It is well documented that many anxious youth have co-occurring issues with externalizing behaviors (Angold, Costello, & Erkanli, 1999; Kendall et al., 2010; Verduin & Kendall, 2003). However, there is a gap in understanding of the neuropsychological patterns that characterize this clinical subpopulation, since anxiety and externalizing symptom comorbidity is generally not accounted for in pediatric ERN studies. To our knowledge, the current study provides initial novel evidence that the direction of the relation between anxiety symptoms and ERN depends on whether youth have co-occurring externalizing problems, and that youth with comorbidity demonstrate diminished error sensitivity patterns that are more characteristic of patients with ADHD (e.g., Geburek, et al., 2013; Meyer & Klein, 2018; Shiels & Hawk, 2010) and ODD (Meyer & Klein, 2018; Vilà-Balló et al., 2014). In other words, in instances of comorbidity, anxiety and ERN relations are driven by the presence of externalizing problems. These findings are also notable in that only two participants in our sample met criteria for an externalizing disorder (e.g., ADHD), which potentially suggests that this neuropsychological profile emerges at subthreshold levels of externalizing pathology. This finding is in line with evidence that subclinical syndromes are associated with psychosocial impairments (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Bubier & Drabick, 2009), and subthreshold clinical conditions represent important areas of focus in prevention and intervention efforts (e.g., Shankman et al., 2009).

Specific conclusions regarding why youth with comorbid anxiety and externalizing problems demonstrate a diminished sensitivity to error responding cannot be derived from the current findings. However, drawing on existing theory one hypothesis for this finding is that for anxious youth with comorbid externalizing problems sustained anxiety may induce the depletion of inhibitory control and other monitoring processes, which then confers challenges with performance monitoring and response inhibition and manifests in acting out or aggressive behaviors (Drabick, Ollendick, & Bubier, 2010; Oh, Greenberg, Willoughby, & Family Life Project Key Investigators, 2020). Although this hypothesis is completely speculative, it could be useful in guiding future studies that can address these questions. For example, longitudinal studies that include youth with primary anxiety and psychiatric externalizing disorders (e.g., ADHD, ODD, conduct disorder) and anxiety-externalizing disorder comorbidities could empirically examine how comorbid anxiety and externalizing psychiatric disorders impact inhibitory control and other monitoring processes in predicting specific social and behavioral challenges.

There were limitations to the current study that warrant attention. First, the current study was preliminary with a relatively small sample size, and replication is needed in a larger study. The majority of anxious youth in the sample had a primary diagnosis of GAD relative to other anxiety disorders. Given this, future studies should examine whether the detected ERN patterns were primarily driven by a specific anxiety disorder and externalizing comorbidity profile. Additionally, we did not detect gender- or age-related effects in our ERN analyses; a larger sample might be required to detect these effects. Although some prior work has documented age-related attenuation in the ERN in anxious populations (e.g., Davies, Segalowitz, & Gavin, 2004), it is important to note that the two-way anxiety symptom x externalizing problems interaction effect on ERN remained significant even when adjusting for age in the model. Furthermore, age did not provide unique variance in ERN above and beyond anxiety symptoms, externalizing problems, and their interaction.

In addition, the current study was cross-sectional. Therefore, it is unclear whether an enhanced or reduced ERN represents a correlate or neural vulnerability that predicts risk for specific anxiety-externalizing comorbidity subtypes, or is a consequence of these disorders, and what this could mean for risk for disorders with adult onset, such as substance and alcohol abuse. For example, adolescent anxiety and externalizing comorbidity is associated with increased risk for alcohol and substance abuse problems (e.g., Egerton et al., 2020), although some research has found protective effects of anxiety (e.g., Colder et al., 2017). With respect to the neuropsychological

literature, some studies have indicated that adults with substance use disorders (SUD) demonstrate a decreased ERN (Franken, Ivan Strien, Franzek, & van de Wetering, 2007; Luijten et al., 2014), a relationship that has been extended to cocaine abuse (Franken et al., 2007; Morie, De Sanctis, Garavan, & Foxe, 2014; Sokhadze, Stewart, Hollifield, & Tasman 2008), smoking (Luijten, van Meel, & Franken, 2011), and current alcohol use and abuse (Bartholow, Henry, Lust, Saults, & Wood, 2012; Gorka et al., 2019; Smith & Mattick, 2013). The extent to which ERN and alcohol and substance abuse patterns are predicted by anxiety and externalizing comorbidities with childhood onset is unknown. Future prospective and longitudinal studies should examine how neural ERN profiles associated with pediatric anxiety-externalizing subtypes predict substance abuse and health risk behaviors (e.g., smoking) in adulthood.

Finally, future studies should also determine the temporal association between ERN and anxiety subtypes to determine which precedes the other and the influence of environmental factors. Meyer, Proudfit, et al. (2015) demonstrated that harsh parenting shapes children's neural error responding, which later predicted increased ERN among anxious youth. A separate study found that youth who remain in institutional-rearing environments demonstrated reduced event-related mediofrontal theta oscillations, a neural mechanism that contributes to ERN and cognitive control, at age 16, which in turn predicted greater transdiagnostic risk for psychopathology (Buzzell et al., 2020). Thus, future studies should consider the potential role of socialization experiences in predicting ERN patterns in commonly occurring anxiety subtypes and psychopathology.

Determining whether anxiety disorders with and without comorbid externalizing symptoms associate with unique neural patterns could have translational implications for increasing precision in psychiatric diagnosis and improving treatment response for anxiety disorder subgroups. Clinical translational neuroscience research approaches could empirically test whether ERN profiles can be used to identify whether the anxiety or externalizing disorder is the primary source of impairment among patients with comorbid presentations. This has particular clinical importance as some treatment studies indicate that anxious youth with comorbid externalizing problems are less responsive to traditional treatments for anxiety, such as cognitive behavioral therapy (CBT), and exhibit worse outcomes over time (Flannery-Schroeder, Suveg, Safford, Kendall, & Webb, 2004; Rapee et al., 2013). Greater understanding of neural correlates of co-occurring anxiety and externalizing problems may provide novel insights into potential treatment moderators and targets for youth with comorbid conditions. Indeed, recent clinical translation studies have shown that neuromarkers (e.g., ERPs) can be used to predict CBT and psychopharmacological treatment (e.g., serotonin uptake inhibitors) responses in youth and adults with heterogeneous anxiety disorders (e.g., Kujawa et al., 2016). Extending this work to pediatric patients with anxiety and externalizing disorder comorbidity could increase understanding of the neurobiological profiles of these diagnostic anxiety subtypes and the extent to which neural traits predict treatment response (medication versus CBT) for this particular clinical population that can be difficult to treat effectively.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data supporting findings are available from the corresponding author upon reasonable request.

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