

Error-related brain activity in pediatric anxiety disorders remains elevated following individual therapy: a randomized clinical trial

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Background: Anxiety disorders are associated with an overactive action monitoring system as indexed by a larger error-related negativity (ERN). This study tests whether ERN magnitude changes following treatment, predicts response to treatment, and varies by treatment type. **Methods:** The sample included 130 youth (9–14 years): youth with an anxiety disorder (ANX; $n = 100$) and healthy control (HC; $n = 30$) youth with no lifetime DSM-IV disorders. ANX youth were randomized to either a manualized cognitive-behavior therapy (CBT) or a comparison child-centered therapy (CCT). The ERN was assessed before and after 16 sessions of treatment and within a comparable interval for HC. Subjective ratings about making errors on the task were obtained following each testing session. The ClinicalTrials.gov identifier is NCT00774150. **Results:** The ERN was larger in ANX than HC youth but ERN magnitude did not significantly change following treatment in the ANX youth, regardless of treatment type, and baseline ERN did not predict treatment response. Post-task ratings revealed that ANX youth worried more about task performance feedback than HC. Like the ERN, mean ratings did not significantly change following treatment. However, these ratings were not correlated with ERN amplitude. **Conclusions:** Findings of greater ERN in pediatric anxiety disorders are replicated in a larger sample. More importantly, findings from this randomized control trial show that a larger ERN and feeling worried about performance feedback remain unchanged following treatment and are unrelated to treatment response. Such findings suggest that action monitoring systems remain overactive in anxious youth treated with psychotherapy, suggesting the need for future investigation of whether novel complimentary cognitive and emotional training programs can modify these systems would be warranted. **Keywords:** Error-related negativity; pediatric anxiety disorders; cognitive-behavioral therapy; child-centered therapy; electroencephalography.

Introduction

Pediatric anxiety disorders have their onset in childhood or early adolescence and frequently lead to other psychiatric disorders in adulthood, including anxiety disorders and depression (Copeland, Wolke, Shanahan, & Costello, 2015). A growing number of studies have reported that anxiety disorders are associated with an overactive action monitoring system as indexed by elevated error-related brain activity in anxiety disorders (Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006; Weinberg, Olvet, & Hajcak, 2010) and obsessive-compulsive disorders (OCD) (Carrasco, Harbin et al., 2013; Hajcak, Franklin, Foa, & Simons, 2008). Such findings were also reported in individuals with nonclinical symptoms of OCD (Santesso, Segalowitz, & Schmidt, 2006) and anxiety (Meyer, Weinberg, Klein, & Hajcak, 2012) as well as in children before the onset of anxiety disorders (Meyer, Proudfit, Torpey-Newman, Kujawa, & Klein, 2015). Such findings have led

researchers to propose that elevated error-related brain activity could represent a potential biomarker for anxiety disorders (Meyer, 2016; Weinberg et al., 2016). Yet, few studies have investigated whether such brain activity could change with treatment or predict treatment response.

Error-related brain activity has been assessed using the error-related negativity (ERN), a negative deflection in the event-related potential (ERP) that occurs within 100 ms following the onset of a commission error. Studies using neuroimaging and dipole source localization suggest the ERN appears to be generated within a network of brain regions, including the anterior cingulate cortex (ACC) as well the supplementary motor area, dorsomedial prefrontal cortex, and anterior insula (Bastin et al., 2017; Gehring, Liu, Orr, & Carp, 2012). It is thought to serve as a neural index of response monitoring and error detection processes (Gehring, Goss, Coles, Meyer, & Donchin, 1993) and has been shown to be stable across time and reliable across tasks (Meyer, Riesel, & Proudfit, 2013; Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013). While the ERN has been documented

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in younger children (Torpey, Hajcak, & Klein, 2009), ERN amplitude seems to increase with age (Grammer, Carrasco, Gehring, & Morrison, 2014) to reach adult levels by mid- to late adolescence (Davies, Segalowitz, & Gavin, 2004; Ladouceur, Dahl, & Carter, 2007). Such age-related changes are thought to reflect maturational changes in the ACC and its connection with other action monitoring (Tamnes, Walhovd, Torstveit, Sells, & Fjell, 2013) and fronto-striatal-limbic regions (Holroyd & Coles, 2002).

The functional role of the ERN remains a matter of intense debate. Some posit that the ERN reflects evaluative cognitive control subprocesses (Yeung, Botvinick, & Cohen, 2004), while others consider it to reflect dopamine learning signals in the ACC (Holroyd & Coles, 2002). However, relevant to anxiety, studies have shown that affective and motivational variables (e.g. losing points when making an error) influence the magnitude of the ERN (Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012), which has led to the proposal that a larger ERN could index greater sensitivity to endogenous threat based on the perception of errors as catastrophic (Weinberg et al., 2016). Findings suggest that ERN amplitude does not seem to be affected by state-related changes in anxiety symptoms in clinical samples (Ladouceur et al., 2006; Moser, Hajcak, & Simons, 2005) and that more negative ERN in temperamentally inhibited children predicts adolescent onset of an anxiety disorder (McDermott et al., 2009). Taken together, these data suggest that greater ERN amplitude could represent a trait marker of anxiety disorders but it remains unclear whether the ERN changes with treatment.

Preliminary evidence suggests that ERN amplitude is not associated with treatment outcome in anxiety disorders (Carrasco, Hong, et al., 2013; Hajcak et al., 2008; Kujawa et al., 2016; Riesel, Endrass, Auerbach, & Kathmann, 2015). For instance, the ERN was measured prior to and following treatment in a subset of 8- to 17-year olds ($n = 23$) diagnosed with OCD ($n = 18$) seeking cognitive-behavioral therapy (CBT) and a healthy comparison group ($n = 18$) (Hajcak et al., 2008). Results from this first study showed that despite changes in OCD symptom severity with treatment, there were no changes in ERN amplitude. However, the small sample size, the wide age range, the lack of randomization to treatment, and the potential confounding effects of medication precluded firm conclusions about the effects of treatment on the ERN. A more recent study also reported no change in ERN amplitude following treatment [i.e. CBT or selective serotonin reuptake (SSRI)] in 28 participants (8–26 years old) with an anxiety disorder and 35 healthy controls (Kujawa et al., 2016). Results showed that greater ERN magnitude seemed to persist with symptom remission in patients with social anxiety disorder (SocAD). ERN amplitude in patients with generalized anxiety disorder (GAD) did not significantly differ from controls before or after treatment. Here too,

interpretations of the findings are limited by the relatively small heterogeneous sample and the combination of CBT and SSRI treatment.

The present study aimed to address these issues by employing a randomized controlled trial (RCT) design comparing CBT for child anxiety and Child-Centered Therapy (CCT) (Cohen, Deblinger, Mannarino, & Steer, 2004) and examining error-related brain activity prior to and following treatment in a large sample of young adolescents diagnosed with an anxiety disorder and a healthy age-matched comparison group. CBT has consistently been shown to be superior to wait-list control (Walkup et al., 2008) and focuses on improving anxious children's ability to self-regulate their emotions and to habituate, through exposure, to the aversiveness of negative events, including making mistakes. In their research on trauma-focused CBT, Cohen and Mannarino developed CCT, an active comparison intervention for children and adolescents that draws on principles from client-centered therapy, an approach that is widely used in the community (Cohen et al., 2004). CCT has previously been implemented as an active comparison condition for two trials testing the efficacy of trauma-focused CBT for youth with post-traumatic stress disorder (PTSD) (Cohen, Mannarino, & Iyengar, 2011; Cohen, Mannarino, & Knudsen, 2005; Cohen et al., 2004). In these studies, children in both CBT and CCT improved from pre- to post-treatment, but CBT showed superiority over CCT in magnitude of treatment gains, rates of clinical remission, and treatment response at 1 year. It emphasizes the use of core nonspecific therapeutic skills such as active listening, reflection, accurate empathy, and encouragement to talk about feelings, but does not include directive problem solving, psychoeducation about anxiety or coping skills, or exposure. In a recent study, we adapted CCT for use in GAD, SocAD, and separation anxiety disorder (SAD) and reported that the majority of youth responded positively to both treatments but that youth treated with CBT were significantly more likely to reach full recovery of all targeted anxiety diagnoses and symptom normalization following acute treatment compared to youth treated with CCT (Silk et al., 2016). Compared to CCT, CBT focuses on self-regulatory processes such as reappraisal and employs exposure to anxiety-provoking situations. As such, we hypothesized that ERN magnitude would significantly reduce following CBT compared to CCT, and that it would predict reduction in symptoms following CBT but not CCT. We also examined subjective ratings regarding task performance and explored the influence of sex and pubertal status on these findings.

Methods

Participants

Participants ($n = 130$; 9–14 years) included anxious (ANX; $n = 100$) and healthy control youth (HC; $n = 30$) with no

lifetime DSM-IV disorders and good quality electroencephalography (EEG) data. They were a subset of participants recruited as part of a randomized clinical trial study examining the neurobehavioral mechanisms of individual treatment in anxious youth (see Silk et al., 2016 for a description of the larger sample, Figure 1 for the CONSORT Flow Diagram and Appendix S1 for CONSORT 2010 Checklist). Anxious youth were required to meet DSM-IV criteria for current GAD, SocAD, and/or SAD (Table 1). Exclusion criteria included: IQ < 70, use of psychoactive medications, presence of neurological impairments, current primary diagnosis of major depressive disorder, and other current (e.g. PTSD) or lifetime (e.g. psychosis) Axis-I diagnoses.

Procedures

Study procedures, including obtaining written consent from the primary caregiver and written assent from the participant, were approved by the University of Pittsburgh Institutional Review Board. Following the intake assessment, participants completed an EEG assessment to assess error-related brain activity using event-related potentials at pre-treatment. EEG assessment was repeated following 16 sessions of individual therapy in the ANX group and within a comparable interval for HC (mean number of weeks following initial EEG assessment: ANX: 22.5 weeks, HC: 21.5 weeks; there were no group differences, $t(92) = 1.17, p = .24$). Participants in the ANX group were randomized to either CBT or CCT treatment using restricted randomization procedures to balance participants across conditions by age and sex. The CBT treatment was delivered using the *Coping Cat* workbooks (Kendall & Hedtke, 2006) and the CCT treatment was delivered using a manualized supportive psychotherapy based on humanistic principles (CCT; Cohen et al., 2004) (see Silk et al., 2016 for more details). Interviews and rating scales were administered to the child and his/her primary caregiver before and after

Table 1 Participant characteristics by group

Variable	Anxious youth (n = 100)	Healthy controls (n = 30)
Age	11.14 (1.46)	11.50 (1.70)
Female, (n)	54	15
Caucasian, (n)	88	22
Current diagnosis ^a , (n)		
Generalized anxiety disorder	71	–
Social anxiety disorder	21	–
Separation anxiety disorder	23	–
Specific phobia	12	–
Major depressive disorder	1	–
ADHD (inattentive type)	1	–
ODD	2	–
Tic Disorder	4	–
PDS	2.50 (0.99)	2.54 (1.13)
PARS (six items)	17.76 (4.47)	1.00 (1.88)
SCARED–parent	37.04 (11.87)	10.72 (7.64)
SCARED–child	39.31 (12.48)	3.46 (3.85)

Data presented as mean (SD) unless otherwise noted. ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder; PDS, Peterson Developmental Scale; PARS, Pediatric Anxiety Rating Scale six-item score; SCARED, Screen for Childhood Anxiety and Related Disorders. ^aDiagnostic groups are partially overlapping due to inclusion of comorbid patients. Primary/principle diagnoses were not designated, meaning that percentages for the three diagnostic inclusion groups will not sum to 100.

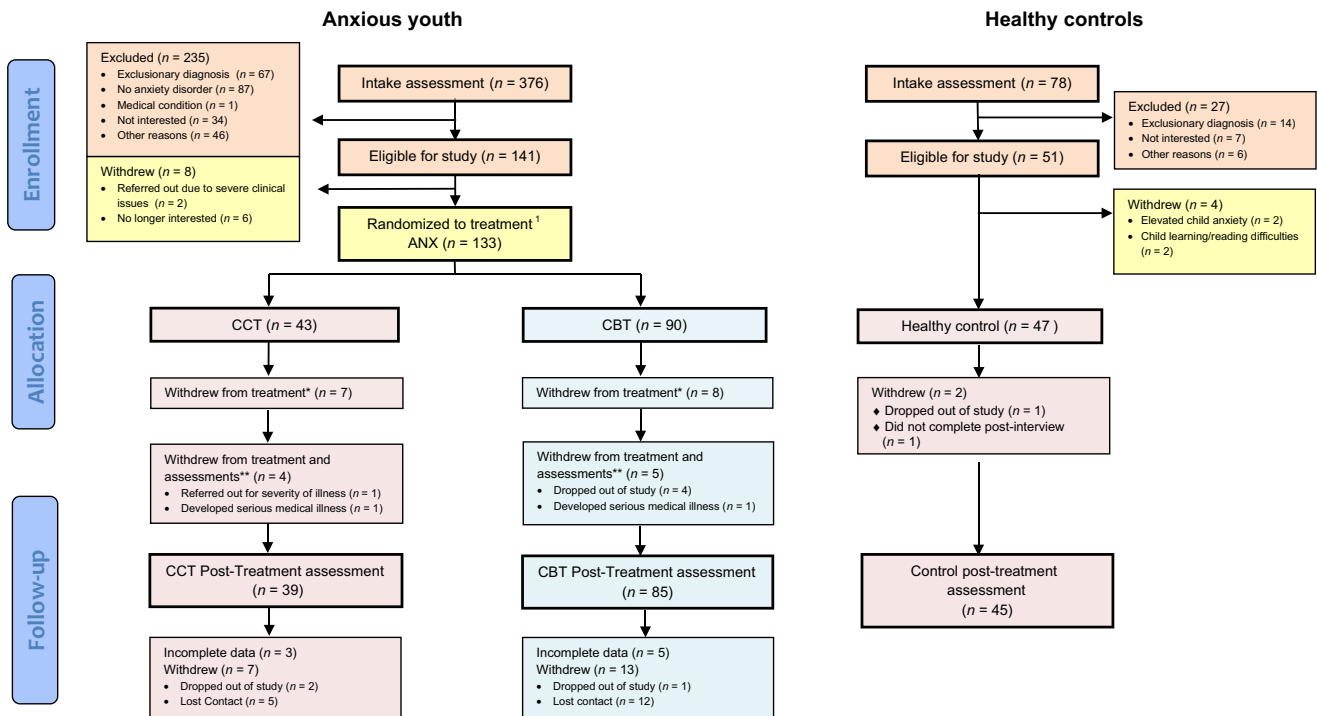


Figure 1 CONSORT flow diagram. ¹Two participants were originally erroneously randomized to treatment, but did not meet inclusion/exclusion criteria for the study. These participants are included above as ‘ineligible’; *Participants who withdrew from treatment continued to do follow-up assessments; **Participants who withdrew from treatment and assessments did not do any follow-up assessments. Figure adapted from Silk et al. (2016)

treatment by an independent evaluator unaware of treatment assignment condition. The ClinicalTrials.gov identifier is NCT00774150.

Clinical assessments. The Schedule for Affective Disorders and Schizophrenia in School-Age Children—Present and Lifetime version was administered to determine the presence of other Axis-I disorders. Anxiety severity was measured using the six-item score [anxiety severity, frequency, distress, avoidance, and interference during the previous week ($\alpha = .76$)] of the Pediatric Anxiety Rating Scale (PARS) (Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002). Treatment response was defined as a 35% reduction in PARS from pre- to post-treatment. Child- and parent-report of anxiety symptoms were assessed using the Screen for Childhood Anxiety and Related Disorders (Birmaher et al., 1997).

Pubertal maturation. The Pubertal Development Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988) assessed pubertal status based on child self-report about physical development, scored from 1 (no) to 4 (development seems complete).

Eriksen flanker task. An arrow version of the flanker task was administered using E-prime software (Eprime Inc., Pittsburgh, PA). As previously described (Ladouceur et al., 2006), the task included presentation of five arrows, with 50% congruent trials ($\rightarrow\rightarrow\rightarrow\rightarrow$ and $\leftarrow\leftarrow\leftarrow\leftarrow$) and 50% incongruent trials ($\leftarrow\rightarrow\leftarrow\rightarrow$ and $\rightarrow\leftarrow\rightarrow\leftarrow$). Participants were asked to respond as fast and as accurately as possible on a button box using their right and left index fingers according to the direction of the central arrow. There were three blocks of 200 trials each, with 30 practice trials. All stimuli were presented for 200 ms followed by an intertrial interval that varied randomly from 500 and 1,500 ms during which a fixation cross was presented.

Post-task questionnaire. After completing the flanker task, participants rated how they felt about making errors on the task using a Likert scale (1–5) to indicate to what extent they: (a) worried about the feedback about their performance; (b) felt badly about making errors; (c) were certain, when making errors, that their response was incorrect.

EEG data acquisition and processing. Continuous EEG activity was recorded using an ActiveTwo head cap and the ActiveTwo 128-channel BioSemi system (BioSemi, Amsterdam, The Netherlands) sampled at 512 Hz. An elastic lycra cap was placed on the child's head and 128 Ag/AgCl-tipped electrodes were attached to the cap. Also, seven flat electrodes were used to measure electrical activity generated by eye and muscle movements. Specifically, two electrodes were placed at supra and infra orbital sites of the right eye to monitor vertical eye movements and two on the outer canthi of the left and right eyes to monitor horizontal eye movements. In addition, two electrodes were placed on the mastoid (right and left) and one on the tip of the nose.

Offline, all data processing was performed using Brain Electrical Signal Analysis (BESA) software. EEG data were rereferenced to the nose and high-pass (0.01 Hz) and low-pass (30 Hz) filtered. A semiautomated preprocessing procedure was used to reject bad channels and trials with significant signal artifact. After visual inspection to identify bad channels, segments were extracted from the continuous EEG, from 200 ms prior to correct and erroneous responses to 800 ms following responses. ERP data were corrected for blinks and eye movements using the method developed by Gratton, Coles, & Donchin (1983). A semiautomated procedure was used to detect and reject artifact according to the following criteria: a voltage step of more than 50 μV between

data points, a voltage gradient of 150 μV within trials, a signal of $<0.1 \mu\text{V}$ across the trial, or reaction times occurring outside of a 100–2,000 ms window. Visual inspection of the data served to detect and reject any remaining artifacts. After preprocessing, ERN data were excluded from analyses if the EEG was contaminated by excessive artifact or the participant had fewer than 10 errors. As a result, of the 130 ANX and 47 HC youth who completed the baseline ERP assessment as part of their participation in the larger RCT (see Figure 1 for the CONSORT Flow Diagram), 30 ANX and 17 HC youth were excluded from the baseline group comparison analyses. Participants who had good-quality ERN data at both pre- and post-treatment assessments were included in pre/post-treatment-related analyses (ANX: $n = 67$ and HC: $n = 27$).

EEG data reduction and analyses. To quantify the response-locked ERN, averages were computed separately for correct and error trials for each group at pre- and post-treatment. Baseline correction was applied by subtracting from each data point the average activity in a -150 to -50 ms window prior to the response. The ERN and the negative deflection on correct trials (i.e. the correct response negativity, or CRN) were scored as the average activity on error and correct trials, respectively, from 0 to 90 ms window after response onset at scalp site FCz, where error-related brain activity was maximal. To minimize the number of tests, analyses focused on the difference between error and correct trials quantified using the ERN standardized residual score ($\text{ERN}_{\text{resid}}$) (Meyer, Lerner, De Los Reyes, Laird, & Hajcak, 2017). The $\text{ERN}_{\text{resid}}$ is calculated by saving the variance leftover in a regression where CRN was the independent variable and ERN is the dependent variable.

Data analysis

Mixed ANCOVA models were used to analyze, at baseline, behavioral performance and ERP measures, with group (ANX, HC) as between-subject variable, response type (correct, error) as within-subject variables. For behavioral data analyses, trial type (congruent, incongruent) was included as an additional factor.

To address questions regarding treatment-related changes, mixed ANCOVA models were computed with $\text{ERN}_{\text{resid}}$ as the dependent variable,¹ with group (ANX, HC) as between-subject variable and time (pre, post) as a within-subject factor (see Table 2). The effect of treatment type was evaluated in ANX only using treatment type (CBT, CCT) by time (pre, post) repeated measures analyses. Subanalyses were performed examining whether changes correlated with anxiety symptom reduction. Pearson's correlations were computed between change in the $\text{ERN}_{\text{resid}}$ and change in anxiety symptom severity (PARS six-item and SCARED parent and child scores) from pre- to post-treatment. Hierarchical regression analyses and logistic regressions, covarying for age and pre-treatment anxiety symptoms, were performed to examine whether $\text{ERN}_{\text{resid}}$ predicted changes in anxiety symptom severity and treatment response, respectively.

Statistical analyses were performed using SPSS version 23.0 (Armonk, NY). Greenhouse-Geisser correction was applied upon any violations of the assumption of sphericity. Post hoc and secondary analyses included *t*-tests and correlational analyses, with type-I error correction using Bonferroni and false discovery rate (FDR) as appropriate (Benjamini & Hochberg, 1995). Given evidence of age-related changes in ERN amplitude (Davies et al., 2004; Ladouceur et al., 2007), age was included as covariate. Secondary analyses examined differences according to sex and anxiety diagnosis as well as correlations between $\text{ERN}_{\text{resid}}$ and behavioral performance, PDS score, symptom severity, and subjective ratings of task performance.²

Table 2 Summary of behavioral performance, event-related potential (ERP) amplitudes, and symptom severity (means and standard deviations) by group and at pre-treatment and post-treatment in participants with useable ERP data at both time points

Variables	Pre-treatment		post-treatment	
	Anxious youth (<i>n</i> = 67)	Healthy controls (<i>n</i> = 27)	Anxious youth (<i>n</i> = 67)	Healthy controls (<i>n</i> = 27)
Reaction time				
Overall	526.16 (100.14)	507.18 (111.46)	502.19 (86.08)	484.34 (87.85)
Correct	537.56 (99.04)	518.92 (107.12)	512.00 (85.19)	496.31 (88.81)
Error	426.47 (115.80)	430.49 (134.46)	428.33 (110.56)	409.22 (94.56)
Congruent	500.09 (95.13)	482.35 (106.62)	479.19 (83.99)	464.88 (88.37)
Incongruent	552.24 (107.25)	532.01 (116.95)	525.19 (89.53)	503.81 (87.82)
Percentage of errors				
Overall	8.37 (4.50)	10.21 (4.99)	8.06 (2.99)	10.01 (4.37)
Congruent	3.74 (3.51)	4.27 (3.01)	3.39 (2.05)	4.04 (3.22)
Incongruent	12.95 (6.30)	16.15 (8.14)	12.73 (5.07)	15.97 (6.91)
ERP data (FCz)				
Correct trials	-1.36 (2.50)	-0.13 (1.38)	1.75 (2.42)	0.69 (2.65)
Error trials	-2.63 (3.70)	-1.45 (2.52)	-1.92 (3.86)	-1.98 (3.23)
ERN _{resid}	-0.18 (1.10)	0.38 (0.79)	-0.03 (1.07)	0.09 (0.78)
Symptom severity				
PARS (six items)	17.41 (4.77)	1.11 (1.95)	9.08 (6.50)	0.41 (1.58)
SCARED-parent	36.95 (12.74)	3.08 (3.66)	22.02 (13.76)	3.74 (3.66)
SCARED-child	40.60 (12.06)	9.81 (6.99)	18.12 (15.56)	5.44 (4.98)
Subjective ratings about task performance				
Worried about feedback	2.35 (1.18)	1.60 (0.71)	2.03 (1.10)	1.41 (0.69)
Felt badly	3.32 (0.66)	3.16 (0.62)	3.33 (0.72)	3.00 (0.73)
Felt certain	3.53 (1.29)	3.32 (1.38)	3.48 (1.34)	3.07 (1.59)

ERP, event-related potentials; PARS, Pediatric Anxiety Rating Scale six-item score; SCARED, Screen for Childhood Anxiety and Related Disorders. ERN_{resid}: Error-related negativity standardized score. Pre-treatment: Anxious youth: *n* = 65, Healthy controls: *n* = 25; Post-treatment: Anxious youth: *n* = 66, Healthy controls: *n* = 27.

Results

Participant characteristics

As shown in Table 1, ANX and HC groups did not differ on distribution of sex, mean age, and pubertal status (*ps* > 0.25). Compared to HC, ANX had significantly higher scores on the six-item PARS (*t* = 19.97, *df* = 126, *p* < .001), SCARED-parent (*t* = 23.92, *df* = 124, *p* < .001) and SCARED-child (*t* = 15.03, *df* = 124, *p* < .001). As shown in Table 2, anxious youth showed a reduction in symptom severity pre- to post-treatment (*t* = 9.09, *df* = 65, *p* < .001), SCARED-parent (*t* = 9.57, *df* = 65, *p* < .001), and SCARED-child (*t* = 11.98, *df* = 61, *p* < .001) rating scales. Furthermore, there were no significant differences in the number of anxious youth who responded to CBT (*n* = 39 ANX; 62% responders) or CCT (*n* = 27 ANX; 60% responders) treatment ($\chi^2 = 0.35$, *p* = .85).

Behavioral data

There were no significant main effects of group or interactions for accuracy or reaction times (*ps* > .05). There were significant trial type and response type main effects, indicating that reaction times were slower for incongruent than congruent trials (*F* = 4.79, *df* = 1,124, *p* = .03, $\eta_p^2 = .04$) and faster for incorrect than correct responses (*F* = 13.46, *df* = 1,124, *p* < .001, $\eta_p^2 = .10$).

As shown in Table 2, there were no significant changes in accuracy or reaction times from the first

to second assessment (*ps* > .10). However, in this subset of participants, ANX were more accurate than HC at both time points (*F* = 5.61, *df* = 1,92, *p* = .02, $\eta_p^2 = .06$). Regarding reaction times, there was no significant main effect of group or interactions (*ps* > .50). However, both groups were faster at the second compared to the first assessment (*F* = 5.96, *df* = 1,91, *p* = .02, $\eta_p^2 = .06$).

Event-related potential data: The error-related negativity

Figure 2 presents baseline response-locked ERP data for correct and error trials at FCz for the ANX (*n* = 100) and HC (*n* = 30) groups. Amplitude was significantly more negative for error compared to correct trials (*F* = 58.02, *df* = 1,127, *p* < .001, $\eta_p^2 = .32$) and there was a significant group by response type interaction (*F* = 13.11, *df* = 1,127, *p* = .001, $\eta_p^2 = .09$). Independent *t*-tests performed on ERN_{resid} indicated that ERN amplitude was greater for ANX than HC (*t* = -2.63, *df* = 128, *p* = .009, *d* = 0.59).

Figure 3 presents response-locked ERP data (at FCz) for pre-treatment (left) and post-treatment (right) assessments for participants with good quality data at both time points: ANX (*n* = 67) (top) and HC (*n* = 27) (bottom) groups. Results indicated that across groups, there was no significant change in ERN_{resid} from pre- to post-treatment (*F* = .26, *df* = 1,91, *p* = .61), and that there was no significant

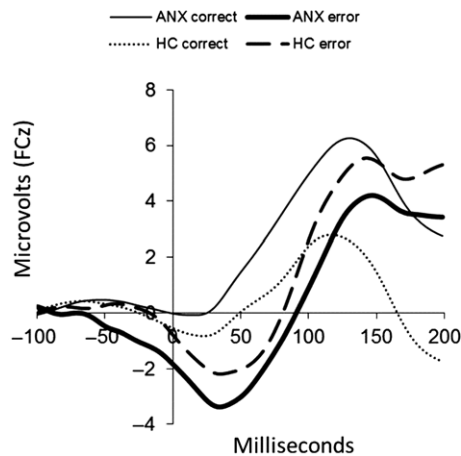


Figure 2 Baseline grand average event-related potential (ERP) waveforms are plotted at FCz following correct and error responses in anxious (ANX, $n = 100$) and healthy youth (HC, $n = 30$)

group by time interaction ($F = 3.03$, $df = 1,91$, $p = .09$). With regard to the effects of treatment type (CBT vs. CCT) on ERN_{resid} in ANX youth, results indicated that treatment type did not have any significant effects on changes in ERN_{resid} ($F = 1.21$, $df = 1,64$, $p = .28$). There were also no group by treatment type interaction when analyses were conducted only on ANX youth who responded to treatment ($n = 40$) ($F = 0.46$, $df = 1,37$, $p = .50$). There were no significant correlations between change in ERN_{resid} and change in symptom severity from pre- to post-treatment (PARS 6-item score: $r = -.03$, $df = 57$, $p = .81$; SCARED-parent: $r = .23$, $df = 57$, $p = .08$; SCARED-child: $r = -.11$, $df = 57$, $p = .42$).

Regression analyses in ANX youth showed that, after controlling for age and anxiety severity at baseline, baseline ERN_{resid} ($\beta = 0.11$, $t = 0.99$, $p = .32$) did not significantly predict post-treatment anxiety severity ($F = 1.21$, $df = 3,84$, $p = .31$). Moreover, baseline ERN_{resid} did not significantly reliably distinguish between treatment responders and non-responders ($\chi^2 = 3.92$, $p = .27$ with $df = 3$). Also, there were no significant effects of age or anxiety severity ($ps > .15$).

Interestingly, results indicated that ANX youth were significantly more worried about feedback on their performance than HC youth ($F = 10.57$, $df = 1,87$, $p = .002$, $\eta_p^2 = .11$) at both pre- ($t = 2.99$, $df = 88$, $p = .004$, $d = .78$) and post-treatment ($t = 2.71$, $df = 91$, $p = .008$, $d = 0.65$). Also, mean ratings did not significantly change following treatment ($F = .52$, $df = 1,87$, $p = .47$) and baseline ratings did not significantly distinguish between treatment responders and nonresponders ($\chi^2 = 1.47$, $p = .23$ with $df = 1$). ANX youths' subjective ratings about how badly they felt about making errors and how certain they felt about their errors were not significantly different from HC youths' ratings at both time points ($ps > .05$).

Findings from secondary analyses on behavioral performance and ERN_{resid} indicated that there were

no significant effects related to sex or significant correlations with behavioral performance, PDS, parent and child total SCARED scores, or subjective ratings in ANX or HC at pre- and post-treatment ($p_{FDR} > .05$). However, when comparing HC and ANX youth at baseline based on anxiety disorder diagnosis (GAD only, SocAD and/or SAD only, GAD with SocAD and/or SAD), results indicated a trend for a main effect of group ($F = 2.61$, $df = 3,126$, $p = .05$). Independent t -tests revealed that ERN_{resid} was significantly greater, compared to HC, for GAD only ($t = 2.67$, $df = 83$, $p = .009$) or GAD with either SocAD and/or SAD ($t = 2.53$, $df = 45$, $p = .015$), but not for ANX youth with SocAD and/or SAD only ($t = 1.52$, $df = 56$, $p = .13$).

Discussion

Findings from this study suggest that despite changes in ratings of anxiety symptoms, ERN amplitude does not significantly change following treatment. This conclusion holds whether anxious youth were treated with a well-validated CBT program for anxious youth or a child-centered therapy. With this study, we also replicate, in a larger sample ($n = 100$), previous findings (Ladouceur et al., 2006; Meyer et al., 2012; Weinberg et al., 2010) showing that youth diagnosed with an anxiety disorder, particularly in those with GAD, exhibit a larger ERN compared to healthy youth. Such elevated neural response to errors in anxious individuals has led some researchers to suggest that elevated error-related brain activity could represent a potential diagnostic biomarker of anxiety disorders. Findings from the present study, together with evidence documenting that a larger ERN predicts future onset of anxiety disorders in at-risk youth (Meyer et al., 2015), seem to support this idea.

Our finding of greater ERN amplitude in anxious youth that persists following treatment is consistent with previous treatment studies (Hajcak et al., 2008). It is also consistent with findings in youth and adults with social anxiety disorders indicating that a larger ERN continues to persist following treatment with CBT or SSRI (Kujawa et al., 2016) and with findings showing that ERN amplitude is independent of ongoing treatment (SSRI or CBT) in youth with OCD or other anxiety disorders (Carrasco, Hong, et al., 2013). By randomizing a sample of clinically anxious youth to CBT or CCT, we were able to address many of the limitations from previous treatment studies and demonstrate that greater error-related brain activity persists following individual psychotherapy. Furthermore, through the use of a post-task questionnaire, we discovered that ANX youth reported feeling more worried about performance feedback than their peers and that, like the ERN, such worries about feedback persisted following treatment. Other ratings about their performance on the task (i.e. how badly they felt or how certain

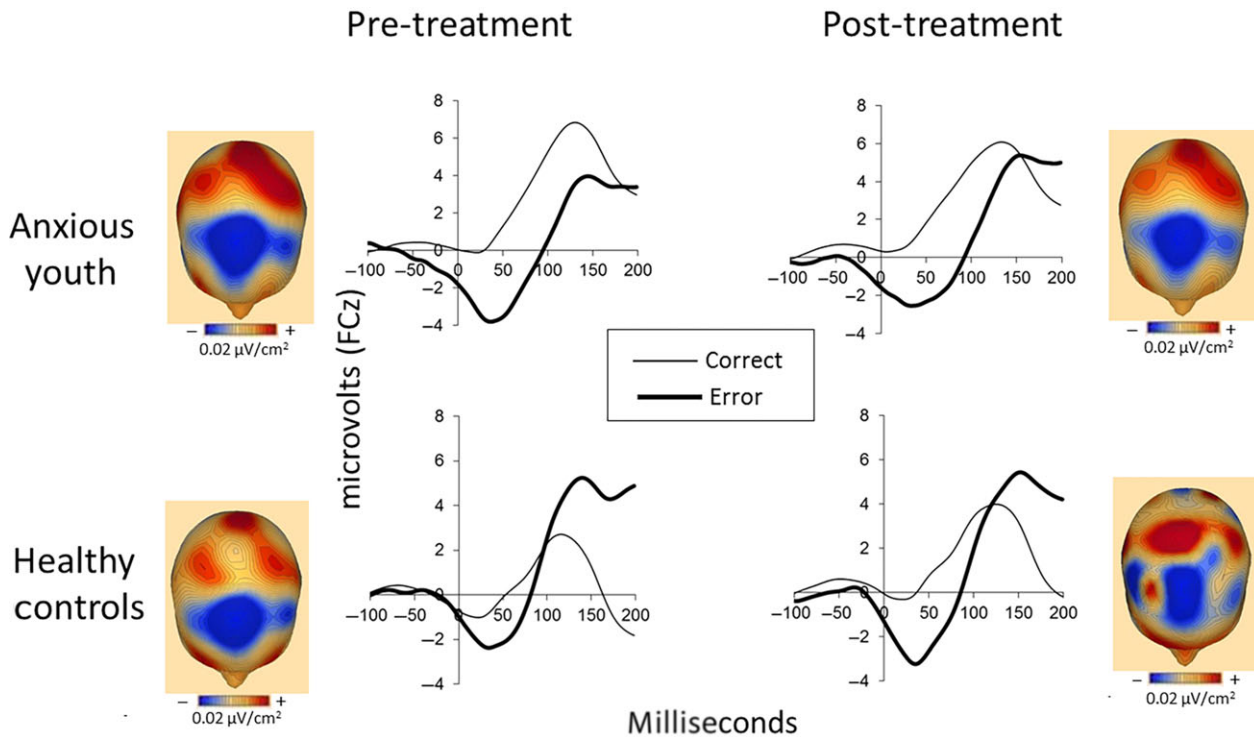


Figure 3 Grand average event-related potential (ERP) waveforms are plotted at FCz following correct and error responses in anxious ($n = 67$) and healthy youth ($n = 27$) with useable ERP data at both pre- and post-treatment. Topographic current source density (CSD) maps display the projection of the currents on the scalp surface after onset of incorrect responses at their maximal peaks between 0 and 100 ms (note: blue = more negative; red = more positive; reference free, $0.02 \mu\text{V}/\text{cm}^2/\text{step}$)

they were about committing an error) were not significantly different than HC youth at both assessments, suggesting that concern about performance feedback seems to be an important factor. The lack of correlations between ERN amplitude and these subjective ratings as well as symptom severity is consistent with findings from other studies with clinical samples (Ladouceur et al., 2006; Weinberg, Klein, & Hajcak, 2012), suggesting these may be parallel processes.

Our findings that larger ERN and feeling worried about performance feedback remain unchanged following treatment and do not predict treatment response suggest that anxiety disorders may implicate a stable overactive action monitoring system. Such an overactive system seems to cut across domains, including fast-occurring error processing brain activity as well as subjective self-monitoring processes, and suggest that it could represent a trait-like feature that appears to be independent of symptom severity or treatment effects (Carrasco, Harbin et al., 2013; Endrass, Riesel, Kathmann, & Buhmann, 2014; Hajcak et al., 2008; Kujawa et al., 2016). Nevertheless, it has yet to be determined the extent to which altered error-related brain activity contributes to subjective self-monitoring processes or vice versa. Our findings that participants reported significantly fewer anxiety symptoms following treatment without significant change in these action monitoring processes is

intriguing. The relationship between elevated error-related brain activity and specific clusters of anxiety symptoms remains unclear. The dimension of action monitoring is not very well represented in self-report or clinical measures of anxiety disorders and as such, it is possible that it is an aspect that may not change with psychotherapy. Would targeting such an overactive monitoring system in anxious youth enhance treatment outcome or prevent relapse? Future research is needed to determine whether there is a need to develop complimentary cognitive and emotional training programs that can modify these processes. One strategy could be to employ a multipronged approach, for instance, through a combination of neurofeedback and targeted exposure sessions focused on habituation to making errors in the context of negative performance feedback from peers. If error-related brain activity in anxious individuals is a marker of elevated threat processing (Weinberg et al., 2016), another strategy could be to target this brain activity through attention bias modification (ABM), which trains individuals to disengage attention from potential threat. Nelson, Jackson, Amir, and Hajcak (2015) reported that ERN amplitude was less negative among undergraduates who completed a single session of ABM before relative to those who completed ABM after the ERN assessment using a flanker task (Nelson et al., 2015). Another study reported that ERN amplitude in

OCD patients was significantly less negative (and comparable to healthy controls) when assessed during dual-task demands compared to the standard conditions with the flanker task (Klawohn, Endrass, Preuss, Riesel, & Kathmann, 2016). A more recent study showed that engaging in expressive writing compared to a control writing condition was associated with reductions in ERN amplitude in individuals with chronic worry (Schroder, Moran, & Moser, 2018). The authors reasoned that expressive writing may serve to enhance cognitive control processes underlying action monitoring by reducing the distracting effects of worry. Together these findings suggest that focusing on how attentional resources are being deployed during task performance may be an important factor to consider. The question remains, however, would targeting such an overactive action monitoring system significantly improve clinical outcome? It is possible that anxiety symptom reduction occurs prior to changes in action monitoring systems and that further follow-up may be needed to detect such changes.

Analyses examining the effects of treatment on behavioral performance did not yield significant group differences or changes with treatment. These findings are consistent with previous findings in OCD (Hajcak et al., 2008), but are inconsistent with the Kujawa et al. (2016) study, which reported correlations between ERN amplitude and accuracy at pre-treatment and ERN amplitude and reaction times at post-treatment in the combined sample. Furthermore, baseline comparisons across anxiety disorder diagnosis and HC suggest that ERN amplitude was greater than HC in anxious youth with GAD (i.e. with or without SocAD and/or SAD) but not in those without GAD (i.e. with SocAD and/or SAD). These findings are inconsistent with those in Kujawa et al. (2016), which reported no significant differences between individuals with GAD and HC. The discrepancy in findings could be due to the fact that our study focused on 9- to 14-year-old youth, whereas the Kujawa et al. sample included children, adolescents, and adults (8- to 26-year olds; mean age = 17.40, $SD = 4.13$) along with anxious participants with higher levels of depression symptoms. Nevertheless, further research is needed to elucidate how alterations in action monitoring systems may vary as a function of anxiety disorder symptom profile. Also, we did not find any main effects or interactions with puberty or sex. The potential moderating effects of sex on the relationship between anxiety and the ERN may emerge later (Moser, Moran, Kneip, Schroder, & Larson, 2016).

Findings from the present study include certain limitations. Data loss was higher in ANX than HC due to slightly higher levels of EEG artifact related to movement in ANX youth. Helping anxious youth remain still during EEG assessments may be an

important factor to consider in future follow-up studies. Also, youth were primarily Caucasian and treatment was delivered in an academic medical setting with high quality conditions for treatment delivery, which are factors that could limit generalizability to more diverse samples in community settings. That said, there is little reason to think that in a more diverse or less optimally treated sample, the ERN would be more predictive, or would change more in treatment.

In conclusion, findings from this study provide evidence supporting the idea that error-related brain activity and subjective feelings of worry about performance feedback are elevated in anxious youth and persist regardless of the type of individual therapy in pediatric anxiety disorders. These findings along with those in OCD (Hajcak et al., 2008) suggest that an overactive action monitoring system may represent a trait-like transdiagnostic marker underlying these disorders. Complimentary intervention strategies specifically targeting this system at multiple levels may be warranted to improve treatment outcome.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. CONSORT 2010 Checklist.

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Key points

- Anxious youth exhibit a larger error-related negativity (ERN), which is thought to be a biomarker for anxiety disorders.
- Few studies have investigated the effects of treatment on the ERN in pediatric anxiety disorders.
- Findings show that ERN amplitude and subjective feelings of worry about performance feedback remain elevated in youth treated with CBT or CCT.
- An overactive action monitoring system could represent a trait-like characteristic of anxiety disorders.
- Studies examining the effects of intervention strategies targeting the action monitoring system in anxious youth may be warranted.

Notes

1. All analyses performed on the ERN_{resid} were also performed on the mean amplitude of the difference waveform (Δ ERN: ERN-CRN). The pattern of results was similar across the two sets of analyses.

2. Secondary analyses included: (a) separate diagnostic group by sex ANCOVAs, with age as a covariate, on accuracy, reaction times, and ERN_{resid} to examine group by sex interactions and main effects of sex at baseline, (b) group [HC, GAD only ($n = 55$), SocAD and/or SAD only ($n = 28$), GAD with SocAD and/or SAD ($n = 17$)] ANCOVA, with age as a covariate, on ERN_{resid} to examine differences in ERN amplitude based on anxiety disorder diagnosis at baseline, (c) mixed ANCOVA, with group (ANX, HC) and sex (male, female) as between-subject variables and time (pre, post) as a within-subject factor to examine whether there were sex differences in the effects of treatment on ERN amplitude, (d) computation of Pearson correlations (pre- and post-treatment) between ERN_{resid} and accuracy, reaction times, PDS score, symptom severity, and subjective ratings of task performance.

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