

# Error-related negativity predicts increases in anxiety in a sample of clinically anxious female children and adolescents over 2 years

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**Background:** An increased neural response to making errors has emerged as a biomarker of anxiety. Error negativity (Ne) or error-related negativity (ERN) is an event-related potential generated when people commit errors; the Ne/ERN is greater among people with anxiety and predicts increases in anxiety. However, no previous study has examined whether the Ne/ERN can be used as a prognostic indicator among people with current anxiety. The present study addressed this gap by examining whether the Ne/ERN prospectively predicts increases in anxiety symptoms in clinically anxious children and adolescents. **Methods:** The sample included 34 female participants between the ages of 8 and 14 years who met the criteria for a clinical anxiety disorder based on clinical interview. The Ne/ERN was measured using a flanker task. **Results:** Increased Ne/ERN at baseline predicted increases in total anxiety symptoms 2 years later, even when accounting for baseline symptoms. The Ne/ERN predicted increases in the symptom domains of generalized anxiety, social anxiety and harm avoidance/perfectionism, but not panic, separation anxiety, school avoidance or physical symptoms. **Limitations:** The sample size was small, which may have inflated the false discovery rate. To mitigate this possibility, we used multiple self-report measures, and the results for the 2 measures (as well as their symptom domains) converged. **Conclusion:** These data suggest that the Ne/ERN can delineate specific risk trajectories, even among those who already meet the criteria for a clinical anxiety disorder. Considering the need for prognostic markers among people with clinical anxiety, the current findings are an important and novel extension of previous work.

## Introduction

Anxiety disorders are the most prevalent form of mental illness and often cause significant distress and impairment across the lifespan.<sup>1</sup> Although anxiety affects adults and children, it most often begins early in life.<sup>2,3</sup> Moreover, relapse of anxiety is common:<sup>4,5</sup> more than half of patients experience recurrence.<sup>6–8</sup> Thus, there is interest in characterizing the developmental pathways that lead to anxiety to improve approaches to prevention and intervention.

To this end, research has focused on characterizing the development of core neural systems associated with the development and maintenance of anxiety.<sup>9</sup> Identifying neural markers that track and predict the onset and trajectory of anxiety may increase our understanding of its underlying neurobiological causes and generate targets for novel prevention strategies. Moreover, there is a critical need to identify prognostic indicators that delineate trajectories of symptoms, even among those who already have clinical anxiety — data that could inform predictors of disease course and risk for relapse (i.e., predict who will experience increases in

anxiety symptoms and what type of symptoms those are likely to be).<sup>10</sup>

A substantial amount of research has focused on the error negativity (Ne) or error-related negativity (ERN; referred to here as the Ne/ERN) as a neural marker of anxiety.<sup>11–14</sup> The Ne/ERN is an event-related potential (ERP) that appears as a negative peak in the ERP waveform at frontocentral electrode sites when people make errors during tasks involving speeded reaction time in the laboratory.<sup>15,16</sup> The generation of error-related neural activity appears to involve the anterior cingulate cortex,<sup>17,18</sup> a region of the medial frontal cortex where information about pain, threat and punishment are integrated to modify behaviour.<sup>17</sup> Errors are conceptualized as motivationally salient events that require immediate corrective action; in this context, we view individual differences in the Ne/ERN as partially reflecting variability in sensitivity to errors (i.e., error sensitivity).<sup>19</sup>

The Ne/ERN has been increased in people with anxiety in more than 50 studies to date.<sup>11–13</sup> The Ne/ERN appears to be increased specifically in disorders that are typically characterized by increased concern about performance, behaviour or

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mistakes (i.e., increased error sensitivity), including generalized anxiety disorder,<sup>20-22</sup> obsessive-compulsive disorder<sup>23-26</sup> and social anxiety disorder.<sup>27-30</sup> In addition to being increased among people with clinical anxiety disorders, the Ne/ERN also appears to index prospective risk for the development of anxiety. For example, children with an increased Ne/ERN were particularly prone to increases in anxiety symptoms following a stressful life event.<sup>31</sup> Moreover, an increased Ne/ERN among 6-year-old children predicted the onset of new anxiety disorders 3 years later.<sup>32</sup> Similarly, the Ne/ERN predicted new-onset generalized anxiety disorder across a year and a half in a large sample of female adolescents.<sup>33</sup> Consistent with these findings, other work has found that children who are high in behavioural inhibition and characterized by an increased Ne/ERN are particularly vulnerable to the onset of anxiety disorders later in life.<sup>34-36</sup>

To date, 4 studies have investigated the Ne/ERN before and after treatment for clinical anxiety.<sup>28,37-39</sup> Findings suggested that traditional cognitive behavioural therapy approaches did not affect the Ne/ERN, despite decreases in anxiety symptoms. For example, children who completed exposure therapy for obsessive-compulsive disorder and no longer met the criteria for the disorder continued to be characterized by an increased Ne/ERN post-treatment.<sup>37</sup> Moreover, in another large treatment study, cognitive behavioural therapy decreased anxiety symptoms but did not affect the Ne/ERN or worry related to performance (i.e., error sensitivity).<sup>38</sup> In another study, people with social anxiety disorder were characterized by an increased Ne/ERN even after treatment with cognitive behavioural therapy or selective serotonin reuptake inhibitors.<sup>28</sup>

Overall, the available data indicate that anxiety relates to individual differences in the Ne/ERN, and that an increased Ne/ERN among healthy individuals can confer risk for the development of anxiety later in life. And yet, successful completion of traditional treatment approaches does not appear to reduce the Ne/ERN. However, relatively few data are available about the clinical utility of increased Ne/ERN in people with clinical anxiety.

The present study considered the possibility that variability in the Ne/ERN might predict longer-term naturalistic outcomes among adolescents with a current anxiety disorder. We tested the novel possibility that the Ne/ERN may delineate differential developmental trajectories among those who already have clinical anxiety. Indeed, there is a critical need for prognostic markers that indicate the likelihood of recurrence among people who have an anxiety disorder.<sup>10</sup> If an increased Ne/ERN among people with a current anxiety disorder can predict later changes in anxiety, the Ne/ERN could be leveraged to identify those most in need of treatment; along similar lines, the Ne/ERN could be a novel target for relapse prevention.

As a first step in addressing this possibility, we examined the extent to which the Ne/ERN predicted changes in anxiety symptoms over 2 years among children and adolescents with anxiety disorders. Thirty-four children and adolescents between the ages of 8 and 14 years at baseline met the diagnostic criteria for an anxiety disorder based on clinical interview.

The Ne/ERN was recorded at baseline, and children and adolescents reported on anxiety symptoms at both assessments via multiple self-report measures. We hypothesized that an increased Ne/ERN at baseline would predict increases in total anxiety symptoms at follow-up 2 years later. Additionally, based on previous work linking the Ne/ERN to anxiety symptoms that are relevant to performance and error sensitivity (i.e., generalized anxiety disorder, obsessive-compulsive disorder, social anxiety), we hypothesized that the Ne/ERN would predict increases in specific anxiety symptom domains (i.e., generalized anxiety, social anxiety and harm avoidance/perfectionism) but likely not in others that have been less related to increased Ne/ERN (i.e., panic, separation anxiety, school avoidance and physical symptoms). In relation to specificity, we also predicted that the Ne/ERN would not predict changes in depressive symptoms.

## Methods

### Participants

Participants were drawn from a larger longitudinal study funded by the United States National Institute of Mental Health. Results for the relationship between the Ne/ERN and anxiety at baseline have been reported previously.<sup>40</sup> Participants were recruited from a commercial mailing list of families that had an 8- to 14-year-old female living at home. Participants were paid \$20 per hour for their participation. Participants in the present study included 34 children and adolescents who met the criteria for a current threshold anxiety disorder at the baseline assessment, based on a clinical interview with the child and parent.

Overall, 79% of the sample identified as White, 12% as Black/African American, 6% as Hispanic and 6% as other. All participants identified as female. At the baseline assessment, children and adolescents were between the ages of 8 and 14 years (6% were 8 years old, 12% were 9 years old, 6% were 10 years old, 9% were 11 years old, 24% were 12 years old, 27% were 13 years old and 18% were 14 years old). All participants provided informed consent, and study procedures were approved by the institutional review board at Stony Brook University.

### Self-report measures

Children and adolescents completed 2 self-report measures related to their current anxiety symptoms at both the baseline and follow-up assessments. The Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire<sup>41</sup> broadly assesses symptoms of anxiety, including symptom subscales of panic, general anxiety, separation anxiety, social anxiety and school avoidance. The SCARED questionnaire contains 41 items, and participants can answer 0 (not true or hardly ever true), 1 (sometimes true) or 2 (true or often true).

Children and adolescents also completed the Multidimensional Anxiety Scale for Children (MASC) questionnaire.<sup>42</sup> The MASC broadly assesses symptoms of anxiety, including subscales of physical symptoms (e.g., tense/restless and

somatic/automatic), social anxiety (e.g., humiliation/rejection and public performance fears), harm avoidance (e.g., perfectionism and anxious coping) and separation anxiety. The MASC contains 39 items, and participants can answer 0 (never true about me), 1 (rarely true about me), 2 (sometimes true about me) or 3 (often true about me).

Children and adolescents also completed the Children's Depression Inventory (CDI) self-report, a measure of depression symptoms.<sup>43</sup> The CDI consists of 10 items that assess symptoms (e.g., sadness) over the preceding 2 weeks. Items on the CDI are rated from 0 (e.g., I am sad once in a while) to 2 (e.g., I am sad all the time).

### *Clinical interview*

We administered the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version for the DSM-IV at baseline.<sup>44</sup> This is a semistructured interview that assesses psychopathology in children and adolescents. Both parent and child were interviewed, and symptom ratings were based on a consensus diagnostic meeting that incorporated all of this information. The interrater agreement across anxiety diagnoses ranged from 0.73 to 0.91. The present study included children who had a threshold anxiety disorder diagnosis at the baseline assessment ( $n = 34$ ). Some of those children met the diagnostic criteria for more than 1 anxiety disorder: 4 children met the criteria for panic disorder, 3 for separation anxiety disorder, 16 for a simple phobia, 7 for social anxiety disorder, 9 for generalized anxiety disorder and 7 for obsessive–compulsive disorder.

### *EEG task*

An electroencephalogram (EEG) was recorded while participants completed an arrowhead version of the flanker task on a computer.<sup>45</sup> During the task, 5 arrowheads appeared on the screen and participants were instructed to press the left or right mouse button as quickly as possible based on the direction of the centre arrowhead. Stimuli were presented for 200 ms, and the interval between the offset of one stimulus and the onset of the subsequent stimulus varied randomly between 2300 and 2800 ms. Participants completed a practice block containing 30 trials and then began the task, which consisted of 11 blocks of 30 trials (330 trials in total). After each block, the message "Please try to be more accurate" was displayed if a participant's performance was 75% correct or lower; the message "Please try to respond faster" was displayed if performance was above 90% correct; and the message "You're doing a great job" was displayed if performance was between 75% and 90%.

### *Psychophysiological recording and data analysis*

We collected continuous EEG recordings using an elastic cap and the ActiveTwo system (BioSemi). Thirty-four electrode sites were used, as well as 2 electrodes on the left and right mastoids. We measured electrooculograms (horizontal and vertical eye movements) using 4 facial

electrodes. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 1 by an ActiveTwo system. The data were digitized at a 24-bit resolution with a sampling rate of 1024 Hz, using a low-pass, fifth-order sinc filter with a half-power cut-off of 204.8 Hz.

Offline, all data were re-referenced to the average of the left and right mastoids and band-pass filtered between 0.1 and 30 Hz; ocular corrections were conducted as per Gratton and colleagues.<sup>46</sup> Artifact detection and rejection was conducted using an automatic procedure: voltage steps greater than 50.0  $\mu\text{V}$  between sample points, voltage differences of less than 0.50  $\mu\text{V}$  within 100 ms intervals were rejected from channels in each trial. The EEG data were segmented for each trial, from 500 ms before the response to 800 ms after the response. A baseline correction was performed using the interval from 500 ms to 300 ms before the response. Correct and incorrect responses were averaged separately from 0 to 100 ms after the response to obtain the correct-related negativity (CRN) and the Ne/ERN. Analyses focused on the FCz electrode, where error-related brain activity was maximal. We calculated a subtraction-based difference score ( $\Delta\text{Ne/ERN}$ ) by subtracting the CRN from the ERN. We calculated percent accuracy and reaction time by trial type (i.e., reaction time on error and correct trials) as behavioural measures.

### *Data analysis*

We conducted statistical analyses using SPSS version 26. We used the Pearson correlation coefficient ( $r$ ) to examine bivariate associations between study variables. We used repeated-measures analyses of variance to compare reaction time on error and correct trials, as well as the ERN and CRN. We conducted a series of hierarchical multiple regressions wherein baseline anxiety symptoms were entered as the first predictor, the  $\Delta\text{Ne/ERN}$  was entered as the second predictor and follow-up total anxiety symptoms were entered as the criterion variable. These were conducted separately for the total SCARED and MASC scores. We then conducted the same regression analyses (i.e., predicting change in total anxiety symptoms) while controlling for baseline child age, accuracy during the task and reaction time on error and correct trials.

Based on previous work,<sup>47</sup> we examined the individual contributions of error and correct brain activity, as well as their interaction (error  $\times$  correct), in predicting the change in total symptoms on the SCARED and MASC. Next, we examined the extent to which the  $\Delta\text{Ne/ERN}$  predicted specific anxiety subscales on both the SCARED and MASC questionnaires by conducting a series of simultaneous multiple regressions wherein the baseline symptom domain and the baseline  $\Delta\text{ERN}$  were entered as predictors, and the outcome variable was the follow-up symptom domain. Finally, we conducted a simultaneous multiple regression to examine whether the  $\Delta\text{Ne/ERN}$  predicted changes in depression symptoms using the CDI.

## Results

### Behavioural data

Across the sample, mean ( $\pm$  standard deviation [SD]) accuracy was  $80.7 \pm 11.96\%$ . Overall, participants were faster on error trials ( $369.75 \pm 78.02$  ms) than on correct trials ( $473.09 \pm 89.80$  ms;  $F_{1,33} = 166.93$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.84$ ). Neither accuracy nor correct/error reaction time was significantly associated with study variables at baseline (SCARED or MASC), nor was change in anxiety symptoms (SCARED or MASC). Child age was not significantly associated with accuracy or reaction time on error trials, but older children responded more quickly on correct trials ( $r_{32} = -0.52$ ,  $p < 0.05$ ). Correlations between all study variables are reported in Appendix 1, available at [jpn.ca/200128-a1](http://jpn.ca/200128-a1).

### Error-related brain activity predicting changes in total anxiety symptoms

Overall, the ERP response was more negative on error trials (mean  $\pm$  SD =  $1.26 \pm 6.76$ ) than on correct trials ( $4.78 \pm 6.03$ ;  $F_{1,33} = 23.82$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.42$ ). For the regression predicting follow-up SCARED total symptoms (Table 1), the overall model was significant ( $F_{2,33} = 13.22$ ,  $p < 0.001$ ). Baseline SCARED total symptoms and  $\Delta$ Ne/ERN were significant predictors ( $B = 0.66$ , standard error [SE] =  $0.14$ ,  $t = 4.71$ ,  $p < 0.001$ ; and  $B = -1.22$ , SE =  $0.51$ ,  $t = -2.41$ ,  $p < 0.05$ , respectively). Adding the  $\Delta$ Ne/ERN in the second step increased the variance accounted for by an additional 10% ( $R^2$  change =  $0.10$ ,  $p < 0.05$ ). Figure 1 presents a depiction of these results in which we divided the sample based on a median split of the change score on SCARED total symptoms (i.e., follow-up minus baseline). Children and adolescents with clinical anxiety who experienced a greater increase in total symptoms from baseline to follow-up were characterized by increased error-related brain activity at baseline. Figure 2 shows partial regression plots depicting the association between the baseline  $\Delta$ Ne/ERN and changes in total anxiety symptoms on the SCARED questionnaire.

Next, we conducted a regression predicting follow-up MASC total symptoms (Table 1). The overall model was significant ( $F_{2,33} = 7.66$ ,  $p < 0.05$ ), and both baseline MASC total symptoms and  $\Delta$ Ne/ERN were significant predictors ( $B =$

$0.49$ , SE =  $0.14$ ,  $t = 3.44$ ,  $p < 0.05$ ; and  $B = -1.43$ , SE =  $0.66$ ,  $t = -2.18$ ,  $p < 0.05$ , respectively). Adding the  $\Delta$ Ne/ERN in the second step increased the variance accounted for by an additional 10% ( $R^2$  change =  $0.10$ ,  $p < 0.05$ ). This pattern of results was consistent with findings for SCARED total symptoms.

Although it was not the focus of the current investigation, we collected data from the Child Behavior Checklist externalizing symptoms scale. We examined a model wherein baseline externalizing symptoms and baseline  $\Delta$ Ne/ERN were entered predicting follow-up externalizing symptoms. In this model, the  $\Delta$ Ne/ERN predicted changes in externalizing symptoms at a trend level ( $B = 0.37$ , SE =  $0.19$ ,  $t = 2.0$ ,  $p = 0.057$ ). Thus, a smaller (i.e., more positive)  $\Delta$ Ne/ERN at baseline among clinically anxious children predicted increases in externalizing symptoms, albeit at a trend level.

To examine the potential effect of age and behaviour during the task, we conducted a simultaneous multiple regression in which baseline SCARED total symptoms,  $\Delta$ Ne/ERN, child age, accuracy during the task and reaction time on error and correct trials were all entered to predict SCARED total symptoms at follow-up. Our results suggested that only baseline SCARED total symptoms and  $\Delta$ Ne/ERN were significant predictors in this model ( $B = 0.62$ , SE =  $0.16$ ,  $t = 4.32$ ,  $p < 0.001$ ; and  $B = -1.35$ , SE =  $0.58$ ,  $t = -2.32$ ,  $p < 0.05$ , respectively). Child age, accuracy and reaction times did not reach significance. We found the same pattern of results when using MASC total symptoms (i.e., only baseline MASC and  $\Delta$ Ne/ERN were significant predictors, and child age, accuracy and reaction time did not reach significance). Thus, child age, accuracy and reaction during the task did not appear to play a significant role in predicting changes in anxiety symptoms and were dropped from further analyses.

Based on previous work,<sup>47</sup> we examined the individual contributions of error- and correct-related brain activity, as well as their interaction (error  $\times$  correct), in predicting change in total symptoms on the SCARED and MASC questionnaires. To do so, we conducted a hierarchical multiple regression in which baseline symptoms and the Ne/ERN and CRN were entered as the first set of predictors, the interaction between the Ne/ERN and CRN was entered as the second predictor, and follow-up total symptoms was the criterion variable. Our results suggested that SCARED total symptoms at baseline was significant in this model ( $B = 0.67$ , SE =  $0.15$ ,  $t = 4.45$ ,  $p < 0.001$ ). Although the interaction between the Ne/ERN and

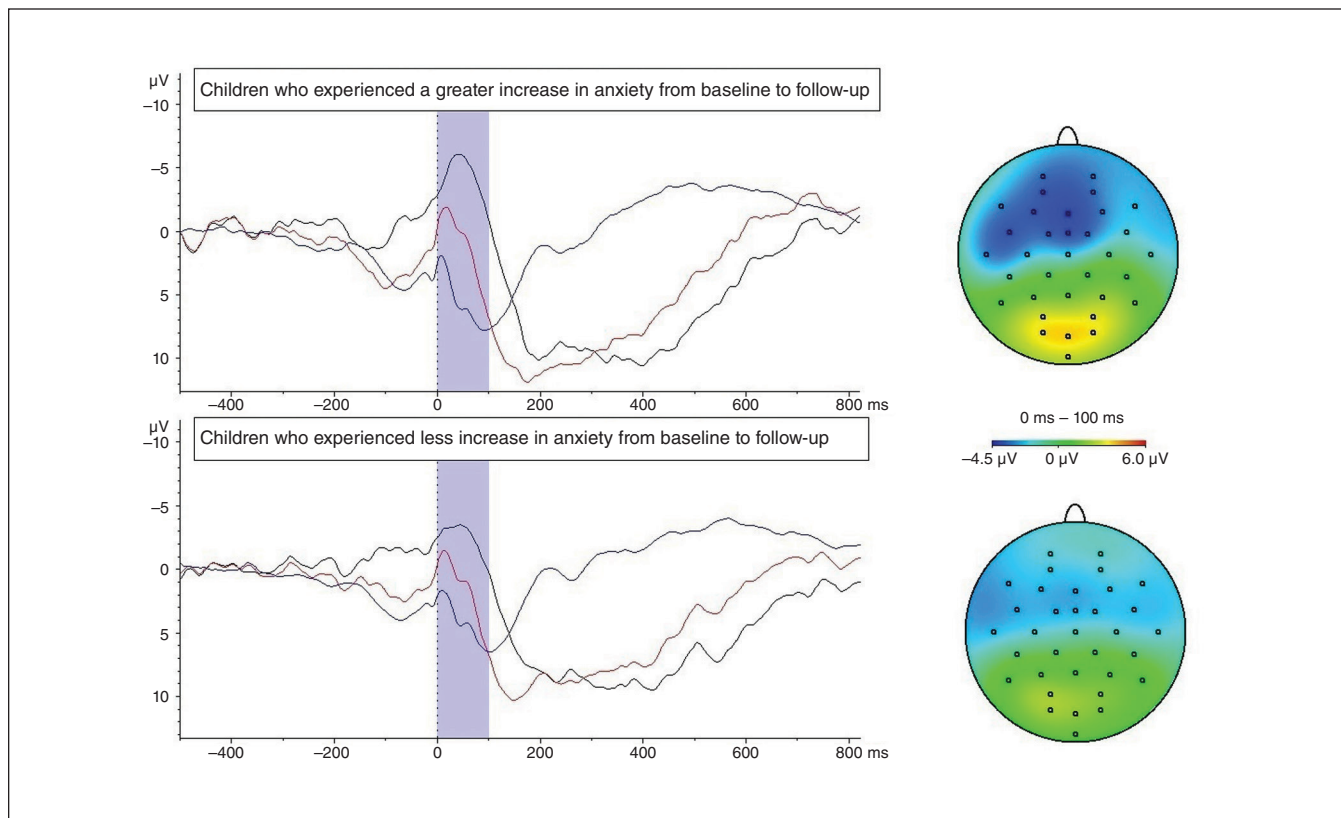
**Table 1: Hierarchical multiple regression predicting follow-up total symptoms**

Characteristic	B	SE	t	p	R <sup>2</sup>	R <sup>2</sup> change
<b>SCARED</b>						
Baseline total symptoms	0.66	0.14	4.71	< 0.001	0.36	0.36*
Baseline $\Delta$ Ne/ERN	-1.22	0.51	-2.41	0.022	0.46	0.10†
<b>MASC</b>						
Baseline total symptoms	0.49	0.14	3.44	0.002	0.23	0.23†
Baseline $\Delta$ Ne/ERN	-1.43	0.66	-2.18	0.037	0.31	0.10†

MASC = Multidimensional Anxiety Scale for Children;  $\Delta$ Ne/ERN = change in error negativity/error-related negativity; SCARED = Screen for Child Anxiety-Related Emotional Disorders; SE = standard error.

\* $p < 0.01$ .

† $p < 0.05$ .



**Figure 1:** On the left, waveforms for error (dotted line), correct (grey line) and the difference (error minus correct; black line) at electrode FCz. On the right, topographical headmaps for error minus correct, 0–100 ms after the response. Results are depicted based on a median split of the change scores for total anxiety symptoms on the Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire from baseline to follow-up (across 2 years). All children and adolescents had a clinical anxiety disorder at baseline. Children and adolescents on the top experienced a greater increase in anxiety symptoms from baseline to follow-up; children and adolescents on the bottom experienced less of an increase or a decrease in anxiety symptoms from baseline to follow-up. Children and adolescents who would go on to experience greater increases in anxiety symptoms were characterized by increased error-related brain activity at baseline.

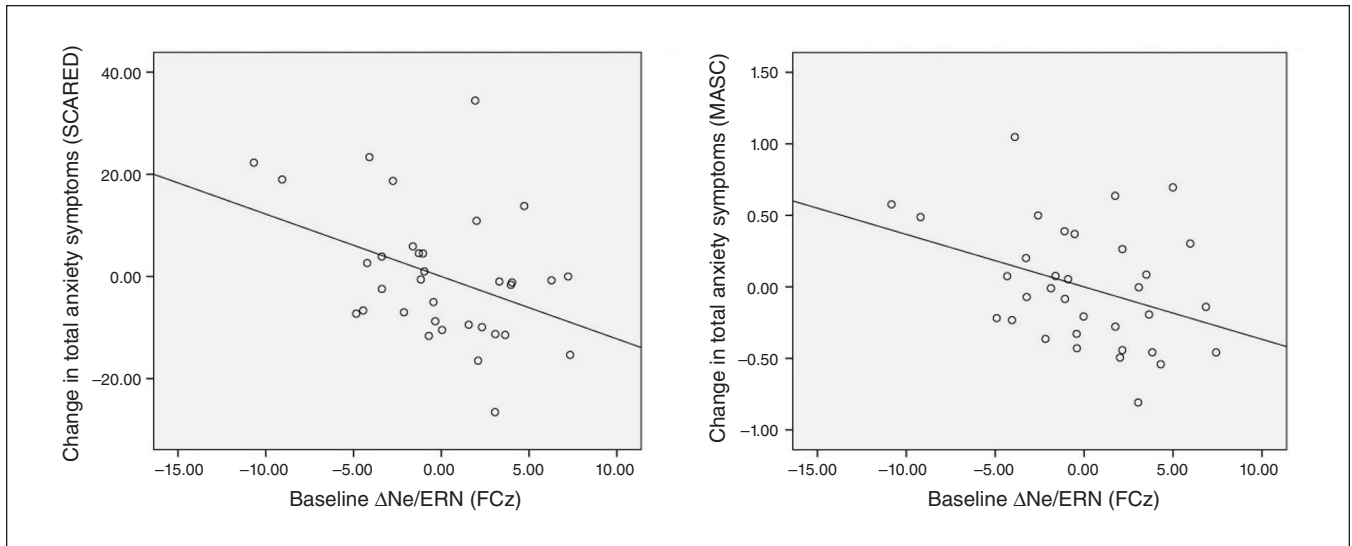
CRN did not reach significance ( $p = 0.78$ ), both the Ne/ERN and the CRN were significant predictors ( $B = -1.21$ ,  $SE = 0.52$ ,  $t = -2.32$ ,  $p < 0.05$ ; and  $B = 1.26$ ,  $SE = 0.60$ ,  $t = 2.10$ ,  $p < 0.05$ , respectively). It should be noted that the Ne/ERN and the CRN predicted changes in SCARED total symptoms in the opposite direction, such that a greater Ne/ERN predicted increased symptoms and a smaller CRN predicted increased symptoms. When we examined the same model using MASC total symptoms, results suggested that baseline MASC total symptoms were significant ( $B = 0.47$ ,  $SE = 0.15$ ,  $t = 3.22$ ,  $p < 0.05$ ). Similar to the results described above, the interaction between the Ne/ERN and CRN did not reach significance ( $p = 0.56$ ). The Ne/ERN was a significant predictor in this model ( $B = -1.47$ ,  $SE = 0.67$ ,  $t = -2.19$ ,  $p < 0.05$ ). However, the CRN did not reach significance ( $B = 1.28$ ,  $SE = 0.77$ ,  $t = 1.67$ ,  $p = 0.11$ ).

#### *Error-related brain activity predicting changes in specific anxiety scales and depression*

To examine whether error-related brain activity predicted changes in specific anxiety symptom domains, we conducted a series of simultaneous multiple regressions in which base-

line symptom domain scores and baseline  $\Delta$ Ne/ERN were entered as predictors, and the outcome variable was follow-up symptom domain scores. We repeated this analysis for the SCARED subscales (panic, generalized anxiety, separation anxiety, social anxiety and school avoidance) and the MASC subscales (physical symptoms, social anxiety, separation anxiety and harm avoidance).

For the SCARED subscales, the  $\Delta$ Ne/ERN predicted changes in generalized anxiety symptoms ( $B = -0.34$ ,  $SE = 0.17$ ,  $t = -2.00$ ,  $p < 0.05$ ) and social anxiety symptoms ( $B = -0.42$ ,  $SE = 0.11$ ,  $t = -3.74$ ,  $p < 0.001$ ), but not changes in panic symptoms ( $B = -0.18$ ,  $SE = 0.19$ ,  $t = -0.95$ ,  $p = 0.35$ ), separation anxiety symptoms ( $B = -0.15$ ,  $SE = 0.12$ ,  $t = -1.29$ ,  $p = 0.21$ ) or school avoidance ( $B = -0.08$ ,  $SE = 0.08$ ,  $t = -0.98$ ,  $p = 0.33$ ). For the MASC subscales, the  $\Delta$ Ne/ERN predicted changes in social anxiety symptoms ( $B = -0.05$ ,  $SE = 0.03$ ,  $t = -1.99$ ,  $p = 0.056$ ) and harm avoidance ( $B = -0.04$ ,  $SE = 0.02$ ,  $t = -1.99$ ,  $p = 0.056$ ), both at a trend level, but did not predict changes in physical symptoms ( $B = -0.03$ ,  $SE = 0.02$ ,  $t = -1.48$ ,  $p = 0.15$ ) or separation anxiety ( $B = -0.03$ ,  $SE = 0.02$ ,  $t = -1.56$ ,  $p = 0.13$ ). Overall, error-related brain activity predicted changes in anxiety symptoms related to social anxiety,



**Figure 2:** Partial regression plots depicting the association between baseline  $\Delta$ Ne/ERN and change in total anxiety symptoms (Screen for Child Anxiety-Related Emotional Disorders [SCARED] on the left and Multidimensional Anxiety Scale for Children [MASC] on the right).  $\Delta$ Ne/ERN = change in error negativity/error-related negativity.

generalized anxiety (i.e., worry) and harm avoidance, but not panic, separation, school avoidance or physical symptoms.

To examine the specificity of error-related brain activity in predicting changes in anxiety versus depression symptoms, we also conducted a simultaneous multiple regression in which baseline  $\Delta$ Ne/ERN and total CDI scores were entered to predict follow-up CDI total score. The  $\Delta$ Ne/ERN did not significantly predict changes in depression symptoms ( $B = -0.26$ ,  $SE = 0.28$ ,  $t = -0.95$ ,  $p = 0.35$ ).

## Discussion

Results from the present study suggest that increased error-related neural activity, even among clinically anxious children and adolescents, can predict increases in anxiety symptoms measured 2 years later. These findings extend previous work, insofar as the Ne/ERN has never been shown to predict the developmental trajectory of anxiety in people with anxiety. We also found that the Ne/ERN predicted increases in relatively specific anxiety symptom domains: generalized anxiety, social anxiety and harm avoidance/perfectionism, but not panic, separation anxiety, school avoidance or physical symptoms. These data suggest that variability in the Ne/ERN may delineate specific trajectories of symptoms among people with anxiety. Importantly, these are the symptom domains that have most consistently been related to increased Ne/ERN in previous cross-sectional studies.<sup>48</sup> Considering the need for prognostic markers among people with clinical anxiety,<sup>10</sup> the current findings are an important and novel extension of previous work.

In the present study, the Ne/ERN predicted increases in total anxiety symptoms using 2 different self-report measures (SCARED and MASC). Although baseline self-report measures accounted for 23% to 36% of the variance in follow-up anxiety symptoms, adding the Ne/ERN increased the variance

accounted for by an additional 10%. These findings were consistent with previous work, which found that the Ne/ERN predicted increases in anxiety over a similar time frame in healthy individuals.<sup>32,33</sup> The current findings extend this work insofar as they suggest that the Ne/ERN may be a prognostic indicator of the course of illness among people with clinical anxiety. These data also suggest that the Ne/ERN could be a predictor of course, based on work on biomarkers for depression that suggests predicting variance in outcomes of over 6% is clinically significant.<sup>49</sup>

The ability of the Ne/ERN to predict changes in anxiety symptoms was relatively specific. For example, the Ne/ERN predicted increases in some symptom domains (i.e., generalized anxiety disorder, social anxiety and harm avoidance/perfectionism), but not others (i.e., panic, separation, school avoidance and physical symptoms). Moreover, this pattern of results was convergent between the 2 self-report measures (e.g., both the SCARED and the MASC questionnaires indicated that the Ne/ERN predicted increases in social anxiety but not separation anxiety). These findings were in line with previous work suggesting that the Ne/ERN may serve as a transdiagnostic marker across anxiety disorders, indexing anxiety related to performance, one's own behaviour or mistakes (i.e., error sensitivity).<sup>11,19,50</sup> To our knowledge, this is the first study to examine whether the Ne/ERN can predict prospective changes in anxiety symptom dimensions differentially among people with anxiety (e.g., predicting change in social anxiety but not change in panic symptoms). It should also be noted that the Ne/ERN did not predict increases in depression symptoms, suggesting that the Ne/ERN is a specific indicator of anxiety and not of depression. Taken together, these findings suggest that the Ne/ERN may be used as a specific prognostic indicator among people with anxiety, shedding light on the course of illness in terms of severity and type of anxiety across time.

## Limitations

The present study had several limitations. Most notably, the sample size used in the present study was somewhat small, and this may have inflated the false discovery rate. To mitigate this possibility, we used multiple self-report measures, and the results between the 2 measures (as well as their symptom domains) converged. However, future work should be conducted to replicate findings from the present study.

## Conclusion

Our results suggest that variability in the Ne/ERN, even among people with anxiety, confers risk for future increases in anxiety. In light of the current findings, it is reasonable to infer that an elevated Ne/ERN following treatment might confer risk for future relapse among people with anxiety, although studies are needed to confirm this possibility. It will be important to test these findings in the context of treatment–outcome studies, such as those that have examined the Ne/ERN before and after traditional cognitive behavioural therapy and pharmacological interventions.<sup>28,37–39</sup>

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**Competing interests:** None declared.

**Contributors:** A. Meyer and G. Hajcak designed the study. A. Meyer acquired the data, which A. Meyer, L. Mehra and G. Hajcak analyzed. A. Meyer wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

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## References

- Kessler RC, Berglund P, Demler O et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593-602.
- Pine DS, Cohen P, Gurley D et al. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry* 1998;55:56-64.
- Wittchen HU, Lieb R, Pfister H et al. The waxing and waning of mental disorders: evaluating the stability of syndromes of mental disorders in the population. *Compr Psychiatry* 2000;41(Suppl 1):122-32.
- Bruce SE, Yonkers KA, Otto MW et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am J Psychiatry* 2005;162:1179-87.
- Hendriks SM, Apijker J, Licht CMM et al. Two-year course of anxiety disorders: different across disorders or dimensions? *Acta Psychiatr Scand* 2013;128:212-21.
- Batelaan N.M., Bosman RC, Muntingh A et al. Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials. *BMJ* 2017;258:j3927.
- Batelaan NM, Rhebergen D, Spinhoven P et al. Two-year course trajectories of anxiety disorders: Do DSM classifications matter? *J Clin Psychiatry* 2014;75:985-93.
- Spinhoven P, Batelaan N, Rhebergen D et al. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. *J Anxiety Disord* 2016;44:92-101.
- Pine DS. Research review: a neuroscience framework for pediatric anxiety disorders. *J Child Psychol Psychiatry* 2007;48:631-48.
- Cosci F, Mansueto G. Biological and clinical markers to differentiate the type of anxiety disorders, in anxiety disorders. *Adv Exp Med Bio* 2020;1191:197-218.
- Meyer A. Developing psychiatric biomarkers: a review focusing on the error-related negativity (ERN) as a biomarker for anxiety. Springer Nature, 2017.
- Weinberg A, Meyer A, Hale-Rude E et al. Error-related negativity (ERN) and sustained threat: conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology* 2016;53:372-85.
- Moser JS, Moran TP, Schroder HS et al. On the relationship between anxiety and error monitoring: a meta-analysis and conceptual framework. *Front Hum Neurosci* 2013;7:466.
- Hajcak G. What we've learned from mistakes. *Curr Dir Psychol Sci* 2012;21:101-6.
- Falkenstein M, Hohnsbein J, Hoormann J et al. Effects of cross-modal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalogr Clin Neurophysiol* 1991;78:447-55.
- Gehring WJ, Goss B, Coles MGH et al. A neural system for error detection and compensation. *Psychol Sci* 1993;4:385-90.
- Shackman AJ, Salomons TV, Slagter HA et al. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 2011;12:154-67.
- Agam Y, Hämäläinen MS, Lee AKC et al. Multimodal neuroimaging dissociates hemodynamic and electrophysiological correlates of error processing. *Proc Natl Acad Sci U S A* 2011;108:17556-61.
- Chong LJ, Meyer A. Understanding the link between anxiety and a neural marker of anxiety (the error-related negativity) in 5 to 7 year-old children. *Dev Neuropsychol* 2019;44:71-87.
- Weinberg A, Klein DN, Hajcak G. Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *J Abnorm Psychol* 2012;121:885-96.
- Weinberg A, Hajcak G. Electrocardiac evidence for vigilance-avoidance in generalized anxiety disorder. *Psychophysiology* 2011;48:842-51.
- Xiao Z, Wang J, Zhang M et al. Error-related negativity abnormalities in generalized anxiety disorder and obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:265-72.
- Endrass T, Klawohn J, Schuster F et al. Overactive performance monitoring in obsessive-compulsive disorder: ERP evidence from correct and erroneous reactions. *Neuropsychologia* 2008;46:1877-87.
- Gehring WJ, Himle J, Nisenson LG. Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychol Sci* 2000;11:1-6.
- Weinberg A, Kotov R, Proudfoot GH. Neural indicators of error processing in generalized anxiety disorder, obsessive-compulsive disorder, and major depressive disorder. *J Abnorm Psychol* 2015;124:172.
- Riesel A, Klawohn J, Grützmann R et al. Error-related brain activity as a transdiagnostic endophenotype for obsessive-compulsive disorder, anxiety and substance use disorder. *Psychol Med* 2019;49:1207-17.
- Endrass T, Riesel A, Kathmann N et al. Performance monitoring in obsessive-compulsive disorder and social anxiety disorder. *J Abnorm Psychol* 2014;123:705-14.
- Kujawa A, Weinberg A, Bunford N et al. Error-related brain activity in youth and young adults before and after treatment for generalized or social anxiety disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2016;71:162-8.
- Barker TV, Troller-Renfree SV, et al. Social influences of error monitoring in adolescent girls. *Psychophysiology* 2018;55:e13089.
- Barker TV, Troller-Renfree S, Pine DS et al. Individual differences in social anxiety affect the salience of errors in social contexts. *Cogn Affect Behav Neurosci* 2015;15:723-35.
- Meyer A, Danielson CK, Danzig AP et al. Neural biomarker and early temperament predict increased internalizing symptoms after a natural disaster. *J Am Acad Child Adolesc Psychiatry* 2017;56:410-6.

32. Meyer A, Hajcak G, Torpey-Newman DC et al. Enhanced error-related brain activity in children predicts the onset of anxiety disorders between the ages of 6 and 9. *J Abnorm Psychol* 2015;124:266-74.
33. Meyer A, Nelson B, Perlman G et al. A neural biomarker, the error-related negativity, predicts the first onset of generalized anxiety disorder in a large sample of adolescent females. *J Child Psychol Psychiatry* 2018;59:1162-70.
34. Lahat A, Lamm C, Chronis-Tuscano A et al. Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *J Am Acad Child Adolesc Psychiatry* 2014;53:447-55.
35. McDermott JM, Perez-Edgar K, Henderson HA et al. A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biol Psychiatry* 2009;65:445-8.
36. Tang A, Crawford H, Morales S et al. Infant behavioral inhibition predicts personality and social outcomes three decades later. *Proc Natl Acad Sci U S A* 2020;117:9800-7.
37. Hajcak G, Franklin ME, Foa EB et al. Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *Am J Psychiatry* 2008;165:116-23.
38. Ladouceur CD, Tan PZ, Sharma V et al. Error-related brain activity in pediatric anxiety disorders remains elevated following individual therapy: a randomized clinical trial. *J Child Psychol Psychiatry* 2018;59:1152-61.
39. Riesel A, Endrass T, Auerbach LA et al. Overactive performance monitoring as an endophenotype for obsessive-compulsive disorder: evidence from a treatment study. *Am J Psychiatry* 2015;172:665-73.
40. Meyer A, Carlton C, Crisler S et al. The development of the error-related negativity in large sample of adolescent females: associations with anxiety symptoms. *Biol Psychol* 2018;138:96-103.
41. Birmaher B, et al. The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. *J Am Acad Child Adolesc Psychiatry* 1997;36:545-53.
42. March JS, Parker JD, Sullivan K et al. The multidimensional anxiety scale for children (MASC): factor structure, reliability, and validity. *J Am Acad Child Adolesc Psychiatry* 1997;36:554-65.
43. Kovacs M. *Manual for the children's depression inventory*. North Tonawanda (NJ): Multi-Health Systems; 1992.
44. Kaufman J, Birmaher B, Brent D et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-8.
45. Eriksen B, Eriksen C. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception Psychophysics* 1974;16:143-9.
46. Gratton G, Coles MGH, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 1983;55:468-84.
47. Meyer A, Lerner MD, De Los Reyes A et al. Considering ERP difference scores as individual difference measures: issues with subtraction and alternative approaches. *Psychophysiology* 2017;54:114-22.
48. Meyer A. A biomarker of anxiety in children and adolescents: a review focusing on the error-related negativity (ERN) and anxiety across development. *Dev Cogn Neurosci* 2017;27:58-68.
49. Uher R, Tansey KE, Malki K et al. Biomarkers predicting treatment outcome in depression: what is clinically significant? *Pharmacogenomics* 2012;13:233-40.
50. Weinberg A, Dieterich R, Riesel A. Error-related brain activity in the age of RDoC: a review of the literature. *Int J Psychophysiol* 2015;98:276-99.