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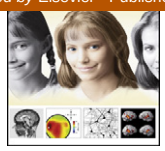

Altered error-related brain activity in youth with major depression

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ABSTRACT

Depression is associated with impairments in cognitive control including action monitoring processes, which involve the detection and processing of erroneous responses in order to adjust behavior. Although numerous studies have reported altered error-related brain activity in depressed adults, relatively little is known about age-related changes in error-related brain activity in depressed youth. This study focuses on the error-related negativity (ERN), a negative deflection in the event-related potential (ERP) that is maximal approximately 50 ms following errors. High-density ERPs were examined following responses on a flanker task in 24 youth diagnosed with MDD and 14 low-risk healthy controls (HC). Results indicate that compared to HC, MDD youth had significantly smaller ERN amplitudes and did not exhibit the normative increases in ERN amplitudes as a function of age. Also, ERN amplitudes were similar in depressed youth with and without comorbid anxiety. These results suggest that depressed youth exhibit different age-related changes in brain activity associated with action monitoring processes. Findings are discussed in terms of existing work on the neural correlates of action monitoring and depression and the need for longitudinal research studies investigating the development of neural systems underlying action monitoring in youth diagnosed with and at risk for depression.

1. Introduction

Childhood-onset major depressive disorder (MDD) is a serious mood disorder that tends to persist into adulthood (Fombonne et al., 2001). MDD is characterized by anhedonia, poor concentration, and diminished positive affect (American Psychiatric Association, 1994). It is associated with high rates of suicide (Keenan-Miller et al., 2007), as well as poor academic, emotional, and social functioning (Lewinsohn et al., 2003). Such poor functioning could be attributed to impairments in cognitive-affective processes, particularly those involved in self-regulation and learning such as rapid behavioral adjustments and adaptive action monitoring (Austin et al., 2001; Nitschke and Mackiewicz, 2005; Paradiso et al., 1997). MDD in adults has been associated with increased sensitivity to errors and negative feedback (Elliott et al., 1998; Steffens et al., 2001) as well as impairments in action monitoring processes and associated brain activity (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008; Ruchsow et al., 2004, 2006), which play an important role in self-regulation of behavior and emotion (Lewis et al., 2006; Luu and Tucker, 1996, 2004; Phillips et al., 2008). However, it is not yet known whether depressed youth also exhibit deficits in action monitoring and associated brain activity. Addressing this question would provide valuable information regarding the pathophysiology of major depression.

Action monitoring represents the ability to monitor and regulate self-initiated actions, which involve the detection and processing of erroneous responses. It is an important set of skills that influence decision-making and goal-oriented behavior. These skills undergo important

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developmental changes in adolescence and depend, in part, on the maturation of a network of prefrontal and subcortical neural regions (Dahl and Spear, 2004; Steinberg, 2005, 2007). One of these neural regions supporting action monitoring includes the anterior cingulate cortex (ACC), which is a structure in the medial wall of the prefrontal cortex that is considered a transitional cortex interfacing emotion, cognition, and action (Devinsky and Luciano, 1993; Devinsky et al., 1995; Vogt and Pandya, 1987).

Researchers have identified an event-related potential (ERP) associated with action monitoring: the error-related negativity (ERN) (Dehaene et al., 1994; Falkenstein et al., 1991; Gehring et al., 1993, 1995; van Veen and Carter, 2002a). The ERN is a response-locked sharp negative deflection in the ERP waveform occurring approximately 50 ms following erroneous responses, with a frontocentral scalp distribution (Falkenstein et al., 1991; Gehring et al., 1993). The ERN is elicited by errors committed in situations where a speeded response is required. In combination with functional magnetic resonance imaging (fMRI), findings from source localization studies point to the dorsal region of the ACC as the primary neural generator of the ERN (van Veen and Carter, 2002b; Yeung et al., 2004). Studies in normative samples of children and adolescents indicate that the ERN can be elicited in childhood (Davies et al., 2004; Kim et al., 2007; Ladouceur et al., 2004, 2007) but reaches adult-like amplitudes in mid to late adolescence (Davies et al., 2004; Ladouceur et al., 2004, 2007). Furthermore, source localization data from developmental studies have also identified the ACC as the primary neural generator of the ERN in children and adolescents (Ladouceur et al., 2007). Although ERN amplitude was found to be associated with post-error slowing, it has been found to predict performance on a flanker task in adults but not in children and adolescents (Ladouceur et al., 2007).

A number of theories and computational models have been formulated to explain the functional significance of the ERN and they all tend to center around the notion that the ERN reflects cognitive control mechanisms involved in monitoring processes (e.g., Bush et al., 2000; Falkenstein et al., 2000). Some proposed that the ERN reflects an error-detection process (e.g., Falkenstein et al., 1991, 2000; Gehring et al., 1993; Nieuwenhuis et al., 2001), a reinforcement-learning signal implicating the mesencephalic dopamine system (Holroyd and Coles, 2002), a conflict-detection process (van Veen and Carter, 2002a; Yeung et al., 2004), or a response to errors in terms of their emotional/motivational salience (Bush et al., 2000; Luu and Tucker, 2004).

Several studies have found that adults with MDD exhibit abnormal responses to negative feedback (Douglas et al., 2009; Elliott et al., 1997) or oversensitivity to errors and perceived failure (Beats et al., 1999; Elliott et al., 1996, 1997). Studies focusing on ERN amplitudes as an index of the neural correlates of action monitoring in MDD have been rather inconsistent. Some studies have reported reduced ERN amplitudes in mid-to-moderate depressed patients in remission relative to healthy controls using a flanker task (Ruchsow et al., 2004) and a modified go/no-go task (Ruchsow et al., 2006). However, such findings were restricted to erroneous trials that followed error trials. More recent studies, however, using a flanker task and a modified Stroop task have reported greater ERN amplitude in moderately depressed adults (acute state of the illness) relative to healthy controls (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2010). Another study, also using a flanker task, reported comparable ERN amplitudes between acutely depressed patients and healthy control participants (Schrijvers et al., 2009). Taken together, the evidence to date suggests the existence of some abnormalities in error-related brain activity associated with depression. The inconsistencies of the above findings could be attributed in part by differences in the clinical profile of participants included in some of those studies (e.g., currently depressed, remitted, presence of comorbid anxiety disorder). Examining ERN amplitudes in unmedicated youth diagnosed with major depression could therefore provide additional information regarding action monitoring and MDD pathophysiology.

If we consider depression as an internalizing disorder that often co-occurs with anxiety disorders (Kessler et al., 2003), it would seem highly relevant to also examine error-related brain activity associated with anxiety or high negative affect (Olvet and Hajcak, 2008). Findings have consistently demonstrated greater ERN amplitudes associated with anxiety disorders. For instance, greater ERN amplitude were reported in patients with obsessive-compulsive disorder (OCD) (Gehring et al., 2000; Hajcak and Simons, 2002; Johannes et al., 2001), college students high on negative emotionality and trait anxiety (Hajcak et al., 2003, 2004; Luu et al., 2000), and adults with generalized anxiety disorder (GAD) (Weinberg and Hajcak, 2010). Greater ERN was also reported in children with OCD (Hajcak et al., 2008), and children with anxiety disorders (Ladouceur et al., 2006). Hajcak and colleagues also demonstrated that ERN does not appear to change with treatment in children with OCD (Hajcak et al., 2008). A more recent prospective longitudinal study reported greater ERN in adolescents who in infancy and early childhood were described as being behaviorally inhibited (BI). More importantly, those BI children with greater ERN were at increased risk for a diagnosis of anxiety disorder (McDermott et al., 2009). Together these findings suggest that children with an anxiety disorder exhibit overactivity of the ACC associated with action monitoring processes and that greater ERN amplitude may represent a potential neural marker of risk for anxiety disorders.

Given evidence that anxiety and depression are highly comorbid conditions (Kessler et al., 2003; Mineka et al., 1998), that anxious children are at increased risk of future onset of major depression in adolescence or adulthood (Pine et al., 1998), and that both of these disorders appear to share a common core neuropsychological vulnerability pertaining to processing errors and feedback (Elliott et al., 1997; Holmes and Pizzagalli, 2008; Weinberg and Hajcak, 2010), findings of greater ERN amplitude in childhood anxiety have important implications with regard to interpreting neural correlates of action monitoring in depressed youth. For instance, the consistent findings of greater ERN amplitude in anxious youth had been interpreted in terms of overactivity of the ACC associated with action monitoring processes. As such, observation of greater ERN amplitude

in depressed youth could provide some support to the notion that anxiety and depression share a common core neuropsychological vulnerability associated with action monitoring processes.

The primary goal of this study was to examine differences in ERN amplitude between children and adolescents diagnosed with MDD and low-risk healthy controls. Given evidence of normative increases in ERN amplitude as a function of age (Davies et al., 2004; Ladouceur et al., 2007), the second goal of this study was to examine associations between ERN amplitude and age in depressed youth relative to low-risk healthy controls. On the basis of previous findings of abnormally reduced ACC activity associated with a clinical state of depression (George et al., 1997; Liotti and Mayberg, 2001), we hypothesized that, relative to low-risk healthy controls, depressed youth would show reduced ERN amplitude and fail to show the normative age-related increases in ERN amplitude previously documented in normative samples. In addition, exploratory analyses were performed to examine the influence of comorbid anxiety disorders and other comorbid diagnoses as well as depression symptom severity on group differences in ERN amplitude.

2. Methods

2.1. Participants

Children and adolescents aged 7 years 6 months to 17 years 11 months who were participating in a larger project examining the neurobehavioral aspects of childhood depression were included in this study (Birmaher et al., 2000; Dahl et al., 2000). The initial sample consisted of a total of 36 participants diagnosed with a Major Depression (MDD) and 25 low-risk healthy controls (HC) (mean age = 12.80, SD = 2.76). Of these, 12 MDD and 11 HC youth were excluded from analyses for the following reasons: (a) too few error trials (i.e., less than 20), (b) too many errors (i.e., more than 200), or (c) high level of artifact in the EEG. Thus, a total of 38 participants were included in the final analyses. Of these, 24 were selected into the MDD group (9 males) and 14 into the HC group (5 males) (mean age = 13.54, SD = 2.48). Data from 8 out of the 14 HC have been published previously (Ladouceur et al., 2006). The majority were right-handed (91%), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) (see Table 1).

Participants in the MDD group were recruited from outpatient clinics at the Western Psychiatric Institute and Clinic, Pittsburgh, PA and by advertising and met diagnostic criteria for major depression according to DSM-III-R and DSM-IV criteria (American Psychiatric Association, 1994). All participants were medication-free at the time of the assessment. A subset of the participants in the MDD group had comorbid conditions (number of diagnoses, mean = 1.7, SD = 1.1, range 0–4): generalized anxiety disorder ($n = 12$), social phobia ($n = 6$), simple phobia ($n = 2$), panic disorder ($n = 2$), agoraphobia ($n = 1$), separation anxiety disorder ($n = 1$), attention deficit disorder: inattentive subtype ($n = 8$), oppositional defiant disorder ($n = 7$), conduct disorder ($n = 1$), adjustment disorder ($n = 1$).

Table 1
Demographic information and clinical variables.

Participant characteristics	Groups			
	MDD ($n = 24$)		HC ($n = 14$)	
	M	*SD*	*M*	*SD*
Age	13.82	2.5	13.05	2.7
Illness duration (months)	24.4	20	–	–
CGAS	56	11	–	–
Z-score CDI/BDI-child	0.58	0.9	−0.88	0.2
MFQ-parent	23.9	11.7	1.8	2.8
SCARED-child	31	13.8	5.4	5.9
SCARED-parent	29.14	3.5	3.8	3.5

Note: MDD: Major Depression Disorder; HC: Low-risk healthy control; C-GAS: Child Global Assessment of Severity; CDI: Children's Depression Inventory; BDI: Beck Depression Inventory; MFQ: Mood and Feelings Questionnaire; SCARED: Screen for Childhood Anxiety and Related Disorders; *M*: mean, SD: standard deviation.

Low-risk healthy controls were recruited through advertisements in the local newspaper. Participants in this group were required to be free of (1) any lifetime psychopathology, and (2) first-degree relative with a lifetime episode of any mood or psychotic disorder, no second-degree relative could have a lifetime history of childhood-onset, recurrent, psychotic, or bipolar disorder or schizoaffective or schizophrenic disorder, and no more than 20% of their second-degree relative could have a lifetime single episode of major depression (Stein et al., 2000).

The University of Pittsburgh Institutional Review Board approved the study. To participate, children and their parents were required to sign assent and informed consent forms, respectively.

2.2. Measures

2.2.1. Clinical assessment

The Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Versions (K-SADS-PL) (Kaufman et al., 1997) was used to establish diagnosis. This interview provides assessments of present episode and lifetime history of psychiatric illness in children according to DSM-III-R and DSM-IV criteria. Child and parent report of children's behaviors were gathered by experienced interviewers. Meetings with a child psychiatrist were conducted to confirm diagnoses.

2.2.2. Self-reports

Participants and their parents or guardians completed the following self-report measures: (a) the Screen for Childhood Anxiety and Related Disorders (SCARED) child and parent versions (Birmaher et al., 1997), (b) the Children's Depression Inventory (CDI) (Kovacs, 1985) (children, 8–12 years old), and (c) the Beck Depression Inventory (BDI) (Beck et al., 1961) (adolescents, 13–18 years old), and (d) the Mood and Feelings Questionnaire (MFQ), to assess parent report of depression symptoms (Angold et al., 1995).

2.2.3. Experimental task

A modified version of the Erikson flanker task was performed by all participants. The task was comprised of congruent (e.g., →→→→→) and incongruent conditions

(e.g., ←←→←←) (Eriksen and Eriksen, 1974). The five-arrow stimuli were presented using E-prime (Psychological Software Tools, Pittsburgh, PA). Each trial was preceded by the presentation of a central fixation point '+' (3000 ms duration). Following the fixation cross, one of four stimulus arrays appeared on the computer screen. The probability of each stimulus array was .25. Using a button, participants responded with their left index finger if the central arrow pointed to the left and with their right index finger if the central arrow pointed to the right. Consistent with previous studies (van Veen and Carter, 2002a), the flanker stimuli appeared 100 ms prior to the target stimulus. Stimuli remained on the screen until a response was made followed by a fixation point, which indicated an inter-trial interval (randomized between 500 and 1500 ms). EEG data were recorded during the task's duration.

2.3. Procedure

Upon entry into the study, participants stayed in the Child and Adolescent Sleep and Neurobehavioral Laboratory at Western Psychiatric Institute and Clinic for a three-day assessment, which included completing a series of computer tasks. Diagnoses were established using a semi-structured interview and self-report questionnaires. The interview was administered independently with the child and one parent about the child by clinically experienced interviewers. Monthly reliability meetings were conducted under the supervision of a child psychiatrist to establish reliability of clinical diagnoses. Inter-rater reliabilities for diagnoses assessed during the course of this study were found to be $k \geq 0.70$. A best estimate procedure for diagnoses based upon all available information was employed to establish diagnosis (Leckman et al., 1982).

During the flanker task, participants sat .5 m back from the computer monitor. The task was described and participants were instructed to respond as quickly and accurately as possible. In order to facilitate compliance and motivation, participants were also informed that it would be possible for them to earn extra money if they performed well on this task (all were told that they did very well and received an extra $5). A 60-trial practice block was performed, followed by seven blocks of 120 trails each. Participants were permitted to rest between blocks. To measure ERPs associated with task performance, the experimenter applied the dense-array electrode net (Tucker, 1993). The percentage of correct responses was computed after each block in order for the experimenter to give feedback to participants about the need to adjust their speed and accuracy.

2.3.1. EEG data acquisition and processing

EEG data were recorded with a 128-channel dense-array Geodesic Sensor Net (Tucker, 1993) and was analyzed using EGI software (EGI, Eugene, OR) with a sampling rate of 250 Hz. Data were filtered online with a .1–100 Hz band pass hardware filter. All channels were referenced to Cz. Electrode impedances were kept at below 50 kΩ.

Processing EEG data included (1) digital filtering using a .3–30 Hz band pass filter, (2) segmenting the EEG −400 to +800 ms prior to and following response onset (button press), and (3) dividing EEG segments according to correct and error trials. Response-locked epochs were baseline corrected at −150 to −50 ms prior to response onset and artifacts were screened using automatic detection methods (Net Station, Electrical Geodesics, Inc.). Channels were interpolated if fast average amplitude was 200 μV, differential amplitude >100 μV, channel had 0 variance, or was bad more than 20% of the time. Segments were eliminated if they contained more than 10 bad channels, movement artifacts or reaction times before 100 ms and after 2000 ms. Bad channel data were replaced using spherical spline interpolation (PARE) of neighboring channel values (Perrin et al., 1987). Eye movement artifacts were corrected using eye movement correction procedure (EMCP) (Gratton et al., 1983; Miller et al., 1988). No significant group differences in the number of EEG segments excluded due to artifact (i.e., eye blinks, eye movements, or number of bad channels) were observed. Data were re-referenced against the average reference (Bertrand et al., 1985).

2.3.2. EEG data reduction and analyses

To quantify the amplitude of the response-locked ERN, averages of the minimum peak amplitudes were computed separately for correct and error trials for each participant. The ERN was defined as the highest negative peak amplitude in the window 0–100 ms following error response onset (Ladouceur et al., 2006).

2.3.3. Statistical analyses

Statistical analyses were performed on the behavioral and ERP measures using SPSS (version 17). Specifically, behavioral measures were analyzed using a mixed MANCOVA model with group (MDD, HC) as between-subject variable and trial type (congruent, incongruent) and response type (correct, error) as within-subject variables. ERP measures were analyzed using a mixed MANCOVA model with group (MDD, HC) as between-subject variable and response type (correct, error) as within-subject variables. Age was included as a covariate variable in both models. The multivariate test statistic reported is Wilks' lambda. Greenhouse–Geisser correction was applied upon any violations of the assumption of sphericity. Follow-up analyses included univariate analyses of variance and *t*-tests with Bonferonni correction. Secondary exploratory analyses included examining ERN amplitude in depressed youth with versus without comorbid anxiety disorders (i.e., generalized anxiety disorder, social phobia, separation anxiety disorder, agoraphobia). Secondary analyses also included re-examining group differences in ERN amplitude by excluding participants with other comorbid conditions (e.g., ADHD – attentive subtype, oppositional defiant disorder, conduct disorder). Because of the low number of participants in each cell, we were unable to examine the influence of each of the other comorbid conditions separately. Finally, we examined whether differences in ERN amplitude was associated with symptom severity in the MDD group. Thus, we examined correlations between the ERN difference waveforms (incorrect–correct trials) and total scores on the self-report measures of depression and anxiety symptoms in the MDD group.

3. Results

3.1. Clinical variables

Results from independent *t*-test analyses indicated that the MDD group had significantly higher total scores than the HC group on the SCARED-child, $t(35) = -6.5$, $p < .001$, SCARED-parent, $t(35) = -6.4$, $p < .001$, and CDI/BDI *z*-scores, $t(35) = -5.8$, $p < .001$ (see Table 1).

3.2. Performance measures

With regard to reaction times, results did not reveal any significant main effect of diagnostic group, $F(1, 35) = .14$, $p = .71$, partial $\eta^2 = .004$, diagnostic group by trial type interaction, $F(1, 35) = .02$, $p = .89$, partial $\eta^2 = .001$, nor diagnostic group by response type interaction, $F(1, 35) = .23$, $p = .64$, partial $\eta^2 = .006$. As expected, however, results yielded significant main effects of trial type and response type, indicating that reaction times were slower on incongruent than congruent trials, $F(1, 35) = 14.82$, $p < .001$, partial $\eta^2 = .30$, and faster on errors than correct responses, $F(1, 35) = 71.02$, $p < .001$, partial $\eta^2 = .67$, respectively.

With regard to accuracy, there was no significant main effect of diagnostic group, $F(1, 36) = 1.3$, $p = .26$, partial $\eta^2 = .04$, nor significant diagnostic group by trial type interaction, $F(1, 36) = .16$, $p = .69$, partial $\eta^2 = .004$. As expected there was a significant main effect of trial type indicating that all participants made more errors on incongruent than congruent trials, $F(1, 36) = 114.8$, $p < .001$, partial $\eta^2 = .76$.

In addition to reaction times and accuracy, we examined participants' response slowing on correct trials following errors. Response slowing after having made an error is a well-known indicator of the recruitment of cognitive control processes that support behavioral adjustment on a particular task (Rabbitt, 1966). We computed the difference in reaction times between correct trials following error trials and correct trials following correct trials. Results indicated that overall participants were slower on correct trials that followed an initial error, $F(1, 36) = 6.67$, $p < .05$, partial $\eta^2 = .16$. However, there were no significant group differences in post-error reaction times, $F(1, 36) = .06$, $p = .81$, partial $\eta^2 = .002$, nor was there any significant group by trial type interaction, $F(1, 36) = .72$, $p = .40$, partial $\eta^2 = .02$ (see Table 2).

Table 2
Summary of performance measures for youth with Major Depression and low-risk healthy controls.

Variables	Groups			
	MDD ($n = 24$)		HC ($n = 14$)	
	M	*SD*	*M*	*SD*
Reaction time				
Overall	480.4	92.9	492.1	175.7
Correct trials	490.9	90.4	502.5	177.7
Error trials[a]	397.7	105.1	420.4	178.7
Congruent trials	451.2	87.9	456.2	172.1
Incongruent trials[b]	509.6	99.1	527.9	180.2
Post-error slowing[c]	515.2	124.7	536.0	246.7
Percentage of errors				
Overall	11.8	9.2	8.8	4.5
Congruent trials	5.4	7.9	2.9	3.6
Incongruent trials[d]	18.3	11.6	14.8	6.2

M: mean, *SD*: standard deviation.
[a] Participants were faster on error than correct trials, $p < .001$.
[b] Participants were slower on incongruent than congruent trials, $p < .001$.
[c] Participants were slower on post-error trials than post-correct trials, $p < .05$.
[d] Participants made more errors on incongruent than congruent trials, $p < .001$.

3.3. Electrophysiological data

Before conducting between-group analyses, we examined the amplitudes at the four frontocentral electrode sites where ERN activity has been located in previous studies (EGI sites 11 or Fz, 6 or FCz, 129 or Cz, and 62 or Pz) and selected the site that showed the greatest amplitude. Difference waveforms for each electrode site (i.e., subtracting the signal elicited on correct trials from the signal elicited on error trials) were included in a repeated measure ANOVA with channel as a within-subject variable. Results indicated that the more negative amplitude was at site 6 (FCz) for the ERN, $F(2, 36) = 5.99$, $p = .002$. Therefore, amplitude data at FCz were included as a dependent variable in subsequent statistical analyses. Furthermore, preliminary analyses focusing on latency did not yield any significant differences and as such this variable was not included the final analyses.

First, there was a significant response type main effect, $F(1, 36) = 27.8$, $p < .001$, $\eta^2 = .44$, confirming that overall amplitude was more negative for error trials compared to correct trials. Consistent with our hypothesis, there was a significant diagnostic group by response type interaction, $F(1, 34) = 10.76$, $p = .002$, $\eta^2 = .24$. Post hoc comparisons indicated that ERN amplitude was significantly less negative on error trials in the MDD compared to the HC group, $p < .05$ with Bonferroni correction (see Fig. 1). As illustrated by topographic maps depicting differences in surface-level brain electrical activity across the FCz electrode sites in error versus correct responses, the most negative amplitude was at approximately 40–50 ms following response onset in both the MDD and HC groups (Fig. 2A and B, respectively). Furthermore, results yielded a significant group by response type by age interaction, $F(1, 34) = 13.26$, $p = .001$, $\eta^2 = .28$. Post hoc correlational analyses between ERN amplitude (ERP difference waveform: error minus correct trials) and age in each of the groups indicated that age was significantly negatively correlated with ERN amplitude in the HC group ($r = -.74$, $p = .002$) but not in the MDD group ($r = .13$, $p = .56$) (Fisher's $Z = -2.9$, $p = .004$) (Fig. 3).

3.4. Secondary exploratory analyses

3.4.1. Analyses of MDD youth with versus those without comorbid anxiety

A mixed MANCOVA model with group (MDD_withoutanxiety ($n = 10$), MDD_withanxiety ($n = 14$)) as between-subject variable, response type (correct, error) as within-subject variable, and age as covariate did not yield a significant group by response type interaction, $F(1, 22) = 1.8$, $p = .19$, $\eta^2 = .08$ (Fig. 4).

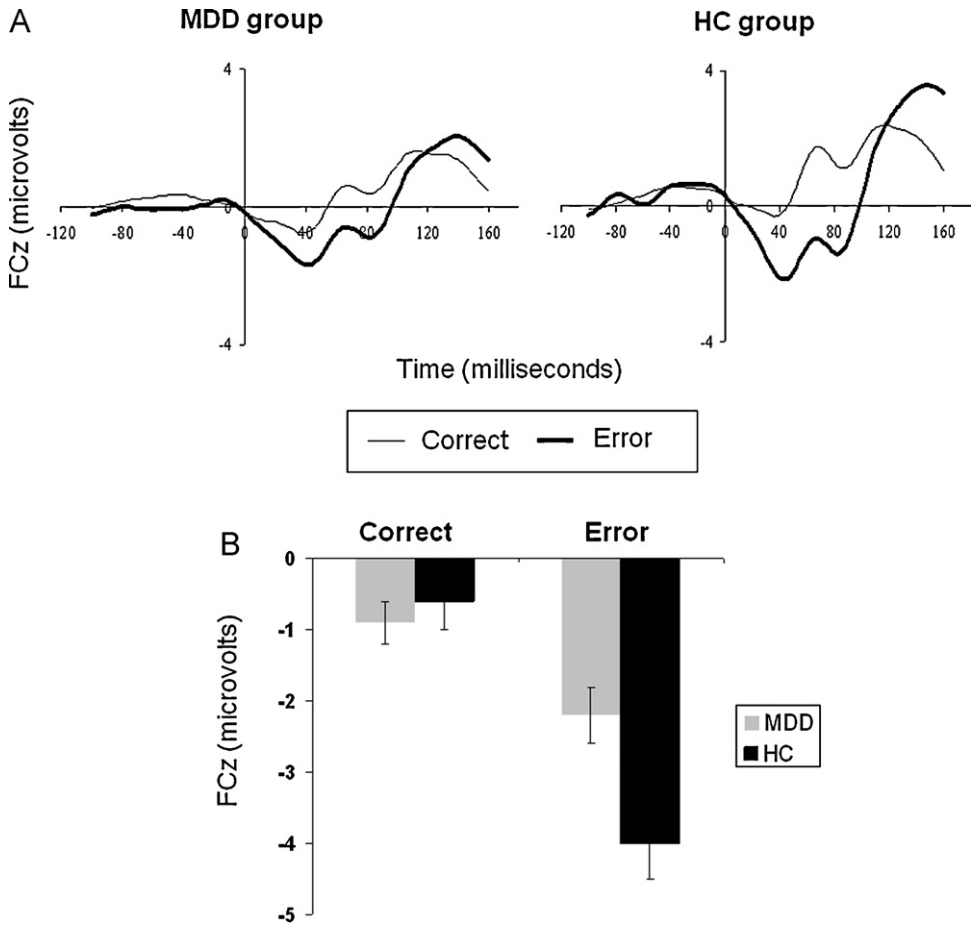

Fig. 1. (A) Response-locked waveforms at FCz for error and correct trials for youth with Major Depression (MDD, $n = 24$) (left) and low-risk health controls (HC, $n = 14$) (right). Response onset occurred at 0 ms. (B) Estimated marginal mean amplitude scores (with age as a covariate) for ERPs response-locked to correct and error trials for MDD and HC groups. Error bars represent standard errors of the means.

3.4.2. Analyses of the MDD group without participants having other comorbid conditions

After removing participants with other comorbid conditions (mostly disruptive disorders), the group by response type, $F(1, 26) = 6.4$, $p = .018$, $\eta^2 = .20$, and the group by response type by age interactions, $F(1, 26) = 9.2$, $p = .005$, $\eta^2 = .26$, remained significant.

3.4.3. Associations with clinical variables

Associations between ERN amplitudes and symptom severity in MDD youth, there were no significant correlations between ERN difference wave amplitude and scores on the SCARED-child ($r = -.01$, $p = .97$) and SCARED-parent ($r = .14$, $p = .53$). There was a significant negative correlation between ERN difference wave amplitude and scores on the depression scales ($r = -.48$, $p < .05$) in the MDD group. However, upon examination of the scatter plot, it appeared that the relationship may have influenced by measures from one participant exhibiting high levels of depression symptoms; indeed, this correlation was no longer significant upon removal of this participant ($r = -.29$, $p = .18$) (see Supplemental Figure). Further, ERN difference wave was not correlated with parents' report of child depression symptoms assessed with the MFQ ($r = .08$, $p = .73$).

4. Discussion

Findings from the current study demonstrate that children and adolescents diagnosed with MDD exhibit reduced ERN amplitude relative to the low-risk healthy controls. More importantly, unlike healthy controls, depressed youth did not exhibit the normative increase in ERN amplitude as a function of age, suggesting that depression may be associated with altered age-related changes of neural systems implicated in action monitoring processes. We also found that ERN amplitudes were comparable in depressed youth with and without comorbid anxiety disorders and that the presence of comorbid disruptive behavior disorders did not influence findings of reduced ERN amplitude in depressed youth relative to healthy controls. Furthermore, there were no significant associations between ERN amplitudes and severity of depression symptoms.

Our findings of reduced ERN amplitude in depressed youth relative to low-risk healthy controls are consistent with some findings in depressed adults (Ruchsow et al.,

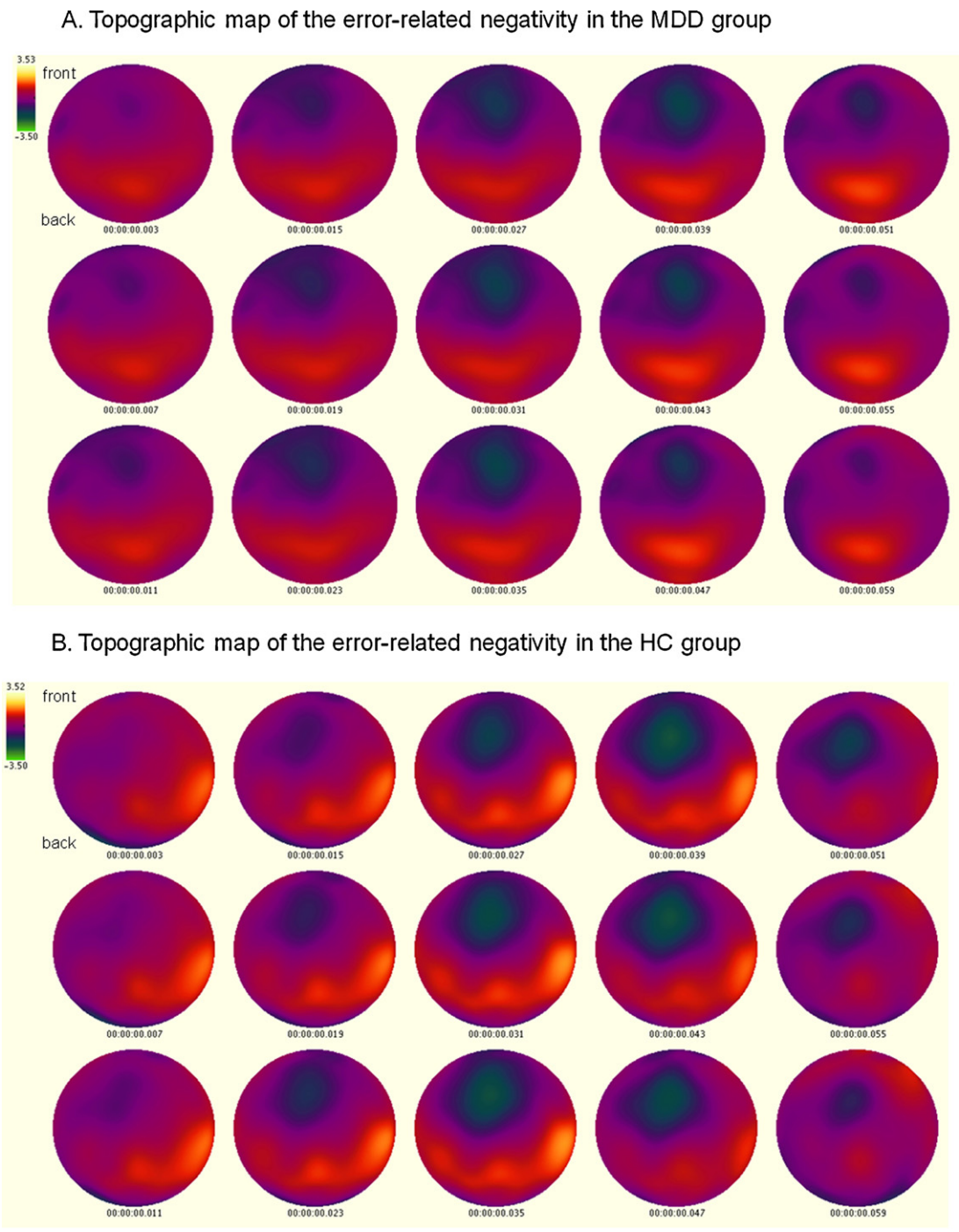

Fig. 2. Data are presented as a topographical map and illustrates differences in surface-level brain electrical activity (microvolts) between error and correct trials in youth with Major Depression (MDD, $n = 24$) (A) and low-risk healthy controls (HC) (B). Separate maps are displayed between 3 and 59 ms following response onset. The front of the head is toward the top and the back of the head is toward the bottom. The colored scale on the left illustrates changes in brain activity at the scalp in microvolts.

2004, 2006). They are also consistent with neuroimaging findings in depressed adults of reduced ACC metabolism and reduced dorsal ACC activity while performing a Stroop task (George et al., 1997; Pizzagalli et al., 2001). Our findings also support evidence from neuroimaging studies in depressed youth of reduced ACC activity on cognitive (Halari et al., 2009) and reward processing tasks (Forbes et al., 2006). However, they do not support findings of comparable ERN amplitudes between depressed adults relative to healthy controls (Schrijvers et al., 2008, 2009) and greater ERN amplitude in depressed adults relative to healthy controls (Chiu and Deldin, 2007; Holmes and

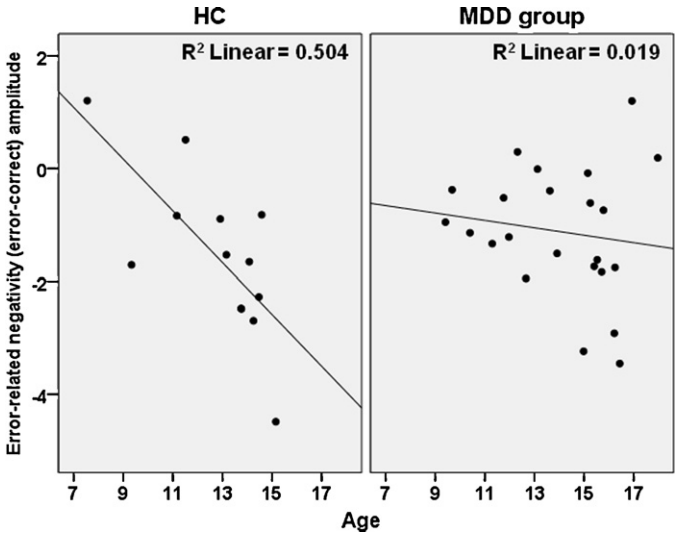

Fig. 3. Scatter plots illustrating relationships between difference waveforms (error minus correct trials) in microvolts and age for youth with Major Depression (MDD, $n = 24$) (right) and low-risk health controls (HC, $n = 14$) (left).

Pizzagalli, 2010). One important factor to consider when comparing our findings to those in adults is the fact that all of our participants were unmedicated whereas participants in several of the adult studies were taking psychotropic medications (Schrijvers et al., 2008, 2009). Another factor to consider is the influence of age on the development of action monitoring processes in childhood and adolescence.

By including age in our statistical model, we were able to examine the relationship between age and ERN amplitude in the MDD relative to the HC group. The significant interaction with age revealed that ERN amplitudes were associated with age in the HC group but not in the MDD group. Such associations between ERN amplitudes and age in the HC group are consistent with previous findings in normative samples (Davies et al., 2004; Ladouceur et al., 2007). For instance, using a similar arrow flanker task, Davies et al. (2004) and Ladouceur et al. (2007) reported increases in ERN amplitudes with age in childhood and adolescence, with ERN reaching adult-like amplitudes in mid to late adolescence. Although recent studies have documented ERNs in younger children using age-appropriate tasks, it is important to note that neural regions that support action monitoring processes, including the ACC, continue to mature in childhood through adolescence (Casey et al., 1997; Cunningham et al., 2002). Also, there are changes in the dopamine system that occur in adolescence, including changes in dopamine receptor distribution and tonic increase in the availability of dopamine (Wahlstrom et al., 2010). Such maturational changes are thought to be associated with more efficient cognitive control processes,

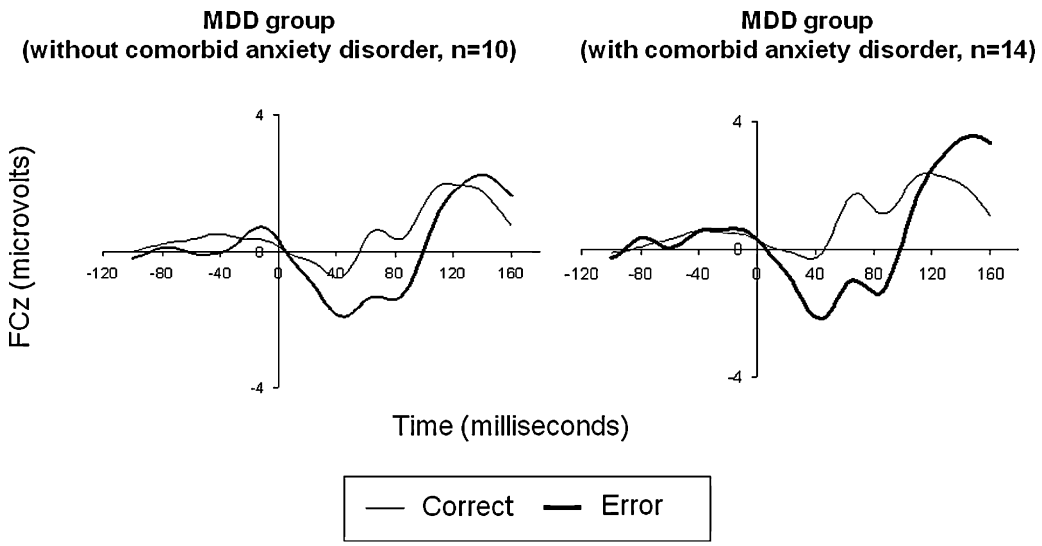

Fig. 4. Response-locked ERPs at FCz for error and correct trials for youth with Major Depression without comorbid anxiety disorder ($n = 10$) (left) and those with comorbid anxiety disorder ($n = 14$) (right). Response onset occurred at 0 ms.

including those implicated in action monitoring processes (Luna et al., 2004; Luna and Sweeney, 2004; Velanova et al., 2008). Furthermore, neuroimaging studies report abnormalities of the ACC in depression, including abnormalities in structure (Ma et al., 2007; Salvadore et al., 2011), metabolism (Mirza et al., 2004; Rosenberg et al., 2005), and function (Davidson et al., 2002; Elliott et al., 1997; Halari et al., 2009; Harvey et al., 2005). Thus, our findings suggest that altered age-related changes in ACC function associated with action monitoring processes could be associated with altered functioning of neural regions implicated in self-regulation of behavior and emotion and potentially mediate poor functioning in depressed youth. In particular, it is possible that such reduced error-related brain activity in children and adolescents with MDD may be associated with altered volition, which is an important aspect of depression that is supported by both dorsal and rostral ACC (Nitschke and Mackiewicz, 2005). Future longitudinal studies that include both ERP and fMRI measures of ACC function associated with action monitoring and other self-regulatory processes are needed to investigate further the development of these neural systems in depressed youth.

In light of previous findings of increased ERN amplitudes in anxious youth relative to healthy controls (Ladouceur et al., 2006), we explored the potential influence of comorbid anxiety disorders on ERN amplitudes in MDD youth. Our findings suggest that the presence of comorbid anxiety disorders did not influence ERN amplitudes in MDD relative to HC youth. Given the paucity of research studies specifically examining the influence of comorbid anxiety disorders on error-related brain activity, such a null finding would require replication with a larger sample. Furthermore, research studies in adult depression vary in terms of including or excluding patients based on the presence of comorbid diagnoses. Several studies excluded depressed patients with comorbid conditions (Georgiadi et al., 2011; Ruchsow et al., 2004, 2006; Schrijvers et al., 2008), with the exception of simple phobia (Holmes and Pizzagalli, 2008, 2010), and some did not exclude participants with anxiety disorders (Chiu and Deldin, 2007). Nevertheless, in light of findings of increased ERN amplitude associated with anxiety disorders in adults and youth (Johannes et al., 2001; Ladouceur et al., 2006; Weinberg and Hajcak, 2010), it is possible that onset of depression may be associated with differential patterns of altered error-related ACC functioning. It can be speculated that reduced ERN amplitude in depressed youth may index blunted ACC activity associated with action monitoring processes and that the presence of depression symptoms eclipses all other influences on the ACC, including the influence of anxiety on ERN amplitudes. Another possible interpretation, according to the reinforcement learning model, is that reduced ERN may be associated with altered functioning of the dopamine system specific to depression. Such reduced ERN signal may contribute to neuropsychological deficits or learning impairments often reported in depressed youth (Favre et al., 2009) or it may contribute to feelings of indecisiveness or poor decision making also associated with depression. Given the role of anxiety disorders in the development of major depression, future studies are needed to examine the mediating role of increased error-related ACC function associated with anxiety disorders in childhood on future onset of MDD in adolescence and adulthood.

While these findings suggest altered age-related changes in error-related brain activity in unmedicated depressed youth relative to low-risk healthy controls, certain limitations should be considered. First, the sample included a large number of depressed youth with comorbid anxiety disorders which may have introduced a potential confound related to illness severity. Such a high proportion of participants with an anxiety disorder in our MDD group allowed us, however, to specifically examine whether ERN amplitudes were different in depressed youth depending on whether they had comorbid anxiety disorders. Future studies with larger samples are needed to compare groups of youth with an anxiety disorder, those with depression, and those with comorbid anxiety-depression in order to better address the issue of comorbidity. Another limitation was the use of a cross-sectional design to examine age-related associations on ERN amplitude. Although our sample did include a rather large age range (7–17 years), future longitudinal studies with larger sample sizes are needed to parse out the influence of anxiety on error-related brain activity and how such an influence changes across development. Given recent evidence that ERN amplitudes in young children are associated with affective behaviors (Buss et al., 2011) and that ERN amplitudes do not appear to change with treatment (Hajcak et al., 2008), such studies investigating the development of error-related brain activity could help elucidate the pathophysiology of mood disorders in youth. Finally, although the current study provides preliminary findings suggesting group differences in the association between ERN amplitude and age, there was no evidence of any group differences in behavioral performance. Consequently, we were unable to draw any conclusions regarding deficits in action monitoring processes per se in depressed youth. Future research studies are needed to address this question. These would require more in-depth analyses of trial-by-trial adjustments in behavior guided by a specific developmental cognitive neuroscience model (e.g., Larson et al., 2012; Maier et al., 2010).

In conclusion, this study shows for the first time that unmedicated children and adolescents with MDD exhibit reduced ERN amplitudes relative to healthy controls. Such findings may be attributed to altered age-related changes of neural systems supporting action monitoring processes as findings from this cross-sectional study suggest that depressed youth fail to show the normative increase in ERN amplitude as a function of age previously documented in normative samples. Such alterations in error-related brain activity do not appear to be influenced by comorbid conditions such as anxiety disorders or to be associated with symptom severity. However, future longitudinal ERP and functional neuroimaging studies are needed to investigate the development of neural systems implicated in error processing and other action monitoring processes and to examine whether such alterations may be associated with impairments in self-regulation of behavior and emotion often observed in depression and perhaps present before illness onset. Moreover, future studies in youth at high familial risk of depression could help determine whether

abnormalities in error-related brain activity constitute an endophenotype of MDD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dcn.2012.01.005.

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