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Electrophysiological evidence of mal-adaptation to error in remitted depression

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ABSTRACT

Identifying risk markers for major depressive disorder (MDD) that persist into remission is key to address MDD's high rate of recurrence. Central to MDD recurrence are the disorder's negative information processing biases, such as heightened responses to errors, which may subsequently impair abilities to monitor performance and adjust behaviors based on environmental demands. However, little is known regarding the neurophysiological correlates of *post*-error adaptation in depression. The current study investigated event-related potentials (ERPs) and behavioral performance *following* errors from a flanker task in 58 participants with remitted MDD (rMDD) and 118 healthy controls (HC). Specifically, using trial-level data, we tested: (a) the impact of errors on response-locked ERPs of the current and post-error trials (error-related negativity [ERN] and correct response negativity [CRN]) and (b) longer-term adaptation to errors (ERN/CRN) over the course of the task. Compared to HC, rMDD participants showed a larger ERN to the current trial and smaller habituation in ERN over time. On trials immediately following errors, rMDD participants showed slower reaction times that were predicted by the previous-trial ERN amplitude but comparable accuracy to HC, suggesting a deficient ability to disengage from errors and/or a compensatory effort to mitigate accuracy decrements. Critically, this pattern of responding: (a) was concurrently associated with greater levels of anhedonia symptoms, more severe MDD history, and interpersonal impairment (but lower impairment in life activities) and (b) predicted more anhedonia symptoms at one-year follow-up. Collectively, a hyperactive performance monitoring system may be a useful risk marker for future MDD recurrence.

1. Introduction

Major depressive disorder (MDD) is a leading cause of personal disability and societal burden in the United States (GBD 2019 Diseases and Injuries Collaborators, 2020; Greenberg et al., 2021), with 21 million (8.4%) adults having at least one major depressive episode (MDE) in 2020 (SAMHSA, 2021). Although the majority of individuals with MDD achieve remission within one year of treatment, recurrence is the norm, as individuals typically experience four to nine episodes in their lifetime (Buckman et al., 2018; Burcusa & Iacono, 2007). Given the recurrent course of MDD and the associated heavy cost, it is imperative to identify risk markers of MDD that persist into remission to potentially serve as targets for delaying or preventing recurrence.

Etiological theories of depression and empirical evidence suggest that negative information processing biases are implicated in the onset and recurrence of MDD (Buckman et al., 2018; Gotlib & Joormann, 2010). Particularly, ruminating on negative events interferes with one's ability to flexibly deploy cognitive control, a key component of performance monitoring (Gotlib & Joormann, 2010; Nolen-Hoeksema et al., 2008). To probe the interplay between negative bias and performance monitoring in depression, researchers have extensively examined responses to errors in a variety of speeded choice reaction time tasks, such

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as the flanker task in which participants respond to the direction of a central arrowhead flanked by either congruent (e.g., <<<<<) or incongruent arrowheads (e.g., <<><<). Error responses robustly elicit the error-related negativity (ERN), a negative deflection in the event-related potential (ERP) waveform peaking approximately 50 ms after errors at frontocentral sites (Falkenstein et al., 1991; Gehring et al., 1993; Holroyd & Coles, 2002). The neural generator of ERN likely involves the anterior cingulate cortex (Dehaene et al., 1994; Holroyd et al., 1998; Van Veen & Carter, 2002), which represents a central hub integrating both cognitive and affective/motivational information (Shackman et al., 2011). Consequently, theories diverge regarding the functional significance of the ERN, including: (a) a conflict from error and error-correcting response tendencies (i.e., conflict monitoring theory; Yeung et al., 2004), (b) a phasic dip in midbrain dopamine release when results are worse than expected (i.e., reinforcement learning theory; Holroyd & Coles, 2002), and (c) an aversive signal prompting defensive motivation (Hajcak & Foti, 2008; Weinberg et al., 2012). A commonality in these theories, however, is that ERN acts as a fast alarm within the performance monitoring system, signaling a need to increase cognitive control and adjust behaviors (Cavanagh & Frank, 2014; Ullsperger et al., 2014). The corresponding ERP component after correct responses, the correct response negativity (CRN), is thought to index subthreshold error tendencies that call for fine-grained adaptation (Cavanagh & Frank, 2014; Ullsperger et al., 2014).

Although a negative bias in depression *should* generate a heightened error responsivity, the literature is rather mixed, with ERN amplitudes found to be enhanced, attenuated, and unaffected in depression (Endrass & Ullsperger, 2014; Moran et al., 2017; Olvet & Hajcak, 2008; Pasion & Barbosa, 2019; Weinberg, Meyer et al., 2016). Importantly, it appears that the association between ERN and depression might be influenced by symptom severity (Endrass & Ullsperger, 2014; Moran et al., 2017; Olvet et al., 2010). An enhanced ERN has been primarily observed using samples with mild to moderate levels of depressive symptoms as well as those scoring high on the broader construct of trait negative affect (Chiu & Deldin, 2007; Hajcak et al., 2004; Holmes & Pizzagalli, 2008; Luu et al., 2000). By contrast, studies utilizing severely depressed clinical samples typically observe an attenuated ERN (Schrijvers et al., 2008, 2009), leading some to propose that high levels of anhedonia and apathy that characterize severely depressed samples may diminish the enhancing effect of high negative affect on ERN (Olvet et al., 2010; Schrijvers et al., 2008, 2009). This proposal aligns with the fact that MDD is heterogenous (Cuthbert, 2014) and specific symptom clusters (e.g., negative vs. positive affect) may have differing associations with ERN. In particular, anhedonia has been linked to a chronic down-regulation of the dopaminergic system (Belujon & Grace, 2017), which may prevent effective phasic dips associated with the ERN. In support of this, high levels of anhedonia have been shown to relate to attenuated ERN amplitudes (Olvet et al., 2010; Weinberg, Liu et al., 2016).

Further complicating the relation between depression and ERN is the high comorbidity rates between depression and anxiety (Gorman, 1996). In contrast to the mixed results for depression, studies have yielded more consistent evidence for an enhanced ERN in anxiety disorders, and effects are particularly robust for symptoms of obsessive-compulsive disorder (OCD) (for a review, see: Endrass & Ullsperger, 2014; Moser et al., 2013; Pasion & Barbosa, 2019; Riesel, 2019; Weinberg, Dieterich et al., 2015). Thus, it is unclear whether an enhanced ERN found in MDD samples is due to comorbid anxiety symptoms or risk factors shared between depression and anxiety (e.g., high trait negativity; Olvet & Hajcak, 2008; Weinberg, Dieterich, et al., 2015).

Determining whether an enhanced ERN is observable among individuals with remitted MDD (rMDD; i.e., when acute symptoms have subsided) without current anxiety disorders and testing its association with specific symptom clusters (i.e., negative vs. positive affect) is therefore important, as this may clarify whether an enhanced ERN is a trait-like risk for MDD. However, considering that the several studies utilizing rMDD samples have yielded conflicting findings (Georgiadi et al., 2011; Ruchsow et al., 2004, 2006; Schoenberg, 2014; Weinberg, Liu, et al., 2016; Whitton et al., 2017), more research is warranted.

Another gap in the literature is that previous research on error responsivity in depression only focused on averaged ERN amplitudes across trials. This approach ignores trial-by-trial variations of performance monitoring necessary for adapting to changing environmental demands. Indeed, it has been proposed that errors trigger a constellation of automatic and controlled processes, including attentional orienting (Notebaert et al., 2009), motor inhibition (Ridderinkhof, 2002), and upregulation of cognitive control (Botvinick et al., 2001), resulting in reaction time (RT) slowing and possibly increased accuracy of the subsequent trial (Ullsperger et al., 2014; Wessel, 2018). The performance monitoring system also takes into account the course of one's action outcomes. For example, the commission of an error increases subsequent error response (Jocham, Klein, et al., 2009; Jocham et al., 2009; Ruchsow et al., 2004, 2006), a time when a strong need for adaptation is necessary. Over longer periods of time, the motivational salience of errors decreases (e.g., due to repeated exposure or fatigue), resulting in a smaller ERN across time (Volpert-Esmond et al., 2018).

Abnormalities in post-error *behavioral* adaptations have been widely documented in depression, with studies typically, albeit not consistently, showing greater RT slowing and reduced accuracy on trials immediately following errors (Endrass & Ullsperger, 2014; Pizzagalli, 2010). This impairment has been observed even in conjunction with an enhanced trial-averaged ERN for MDD compared to healthy control (HC) participants, indicating a failure to recruit cognitive control resources by the error signal (Holmes & Pizzagalli, 2008). By contrast, only one study with a small sample size investigated abnormalities in post-error *neurophysiological* adaptations in those with depression, showing a smaller enhancement of ERN following errors for rMDD than HC participants without significant impairment in behavioral adaptation (Ruchsow et al., 2004, 2006). Thus, there is preliminary neurophysiological evidence to suggest that depression is associated with a performance monitoring system that fails to adequately adapt to errors.

The objective of the current study was to examine the effect of, and adaptation to, errors in individuals with rMDD using trial-level data from the flanker task. First, we tested the impact of errors on current and subsequent response-locked ERP. Second, we tested the longer-term adaptation to errors over the course of the task (i.e., changes in ERN/CRN). Given prior findings of negative bias particularly linked to depression risk, we hypothesized that individuals with rMDD (vs. HC) would show a heightened response to errors (i.e., larger ERN to current trial error) and a deficient adaptation following errors, both immediately (i.e., smaller enhancement in response-locked ERP on post-error trials) and over longer periods (i.e., smaller ERN habituation over the course of the task). Third, to clarify whether these abnormalities were tied to specific symptom clusters, we explored their association with general depression symptoms as well as specific affective symptoms of dysphoria (high negative affect) and anhedonia (low positive affect). Last, as an enhanced ERN has been suggested to be an adaptive response linked to better control abilities, including better academic performance (Hirsh & Inzlicht, 2010; Moser et al., 2013) and better stress regulation in daily life (Compton et al., 2008), it would be important to clarify whether an enhanced ERN indeed confers maladaptive outcomes to be considered as a risk factor. Thus, we further tested whether the observed abnormalities (a) were related to functional impairment and (b) in a subset of participants, predicted follow-up symptoms of general depression, dysphoria, and anhedonia at one year. Findings will shed light on the neural dynamics of affective and cognitive dysfunction in rMDD, which may aid in the identification of novel risk markers for MDD recurrence.

2. Methods

2.1. Participants

Participants were from a larger NIMH-funded family study of transdiagnostic mechanisms of psychopathology (for recruitment details, see: Gorka et al., 2016; Weinberg et al., 2015). Briefly, sibling pairs aged 18–30 years were recruited from the community and mental health clinics in the Chicagoland area. Recruitment was not based on DSM diagnoses, but individuals with severe internalizing psychopathology symptoms and alcohol use (but not necessarily those with diagnoses) were oversampled. All study procedures were carried out in accordance with the Declaration of Helsinki and approved by the university's Institutional Review Board.

The current analysis included 118 participants without any lifetime disorder diagnosis (HC) and 58 with a lifetime MDD but not any current disorder diagnosis (rMDD), as determined by the Structured Clinical Interview for DSM-5 Disorders (First et al., 2015). Demographic and clinical information of the participants is shown in Table 1. Groups significantly differed in race/ethnicity, which was added as a covariate in all analyses involving group comparisons.

At one year after the initial assessment, participants were invited for a follow-up assessment of depression and anxiety symptom severity. Fifty-three participants (30.1% of the total sample) returned for the one-year follow-up (see Table 1). Participants who did (vs. did not) complete the follow-up did not significantly differ in any baseline demographic or clinical characteristics (see Table S1).

Table 1
Participant Demographic and Clinical Characteristics.

	Healthy Control $n = 118$	Remitted MDD $n = 58$	Test Statistics
Demographic			
Female *n* (%)	74 (62.7)	41 (70.7)	$\chi^2(1) = 0.77$, $p = .38$
Age *M* (*SD*)	21.45 (2.88)	22.12 (2.98)	$t(174) = 1.44$, $p = .15$
Race/Ethnicity *n* (%)			$\chi^2(4) = 15.87$, $p = .003$
White	37 (31.4)	34 (58.6)	
Hispanic	30 (25.4)	12 (20.7)	
Black	11 (9.3)	6 (10.3)	
Asian	29 (24.6)	4 (6.9)	
Other	11 (9.3)	2 (3.4)	
Education *n* (%)			$\chi^2(2) = 0.39$, $p = .82$
High School or Below	11 (9.3)	7 (12.1)	
Some College	69 (58.5)	34 (58.6)	
College or Above	38 (32.2)	17 (29.3)	
Clinical			
IDAS *M* (*SD*)			
General Depression Symptoms	31.28 (7.92)	37.74 (10.90)	$t(91.59) = 4.11$, $p < .001$
Dysphoria Symptoms	13.79 (4.36)	18.03 (6.79)	$t(92.42) = 4.68$, $p < .001$
Anhedonia Symptoms	21.46 (6.88)	21.03 (5.53)	$t(173) = -0.41$, $p = .68$
OCD Composite Symptoms	20.12 (6.42)	21.48 (5.95)	$t(173) = 1.67$, $p = .097$
Age of Onset of MDD *M* (*SD*)	–	16.59 (4.32)	–
Number of MDE *M* (*SD*)	–	2.13 (1.62)	–
Months in Remission *M* (*SD*)	–	23.31 (24.05)	–
Current Psychotropic Medication *n* (%)	–	10 (17.2)	–
Functional Impairment: WHODAS			
Getting Along	1.03 (0.16)	1.17 (0.31)	U=2582, $p < .001$
Life Activities	1.07 (0.22)	1.29 (0.52)	U=2540, $p < .001$
Participation	1.05 (0.19)	1.25 (0.36)	U=2184.5, $p < .001$
Follow-Up			
n (% total)	38 (32.2)	15 (25.9)	$\chi^2(1) = 0.47$, $p = .49$
IDAS *M* (*SD*)			
General Depression Symptoms	33.82 (11.62)	40.67 (12.64)	$t(51) = 2.11$, $p = .040$
Dysphoria Symptoms	15.21 (6.20)	19.73 (8.26)	$t(51) = 2.39$, $p = .020$
Anhedonia Symptoms	22.87 (7.08)	23.07 (7.04)	$t(51) = 0.092$, $p = .93$
OCD Composite Symptoms	19.79 (5.58)	24.00 (8.30)	$t(51) = 2.08$, $p = .042$

Note. MDD = major depressive disorder, MDE = major depressive episode, IDAS = Inventory of Depression and Anxiety Symptoms, OCD = obsessive-compulsive disorder, WHODAS = World Health Organization Disability Assessment Schedule. For group comparisons on WHODAS scores, Mann-Whitney *U* tests were used due to non-normally distributed data.

2.2. Measures

Depression and anxiety symptoms at baseline and follow-up were assessed using the expanded Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012). The IDAS-II is a self-report measure that assesses symptoms over the past two weeks, with each item rated on a 5-point scale from 1 (*not at all*) to 5 (*extremely*). Depression severity was indexed by the General Depression subscale (20 items; baseline $\alpha = 0.88$, follow-up $\alpha = 0.92$). Additionally, symptoms of high negative affect and low positive affect were respectively indexed by the Dysphoria subscale (10 items; baseline $\alpha = 0.85$, follow-up $\alpha = 0.90$) and the Well-Being subscale (8 items, reverse-coded to reflect anhedonia; baseline $\alpha = 0.86$, follow-up $\alpha = 0.88$). As a covariate, a composite measure of OCD symptoms (baseline $\alpha = 0.85$, follow-up $\alpha = 0.87$) was created by summing across the three OCD subscales: Checking (3 items), Ordering (5 items), and Cleaning (7 items).

Functional impairment at baseline was assessed using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS), 36-item interviewer-administered version (Üstün et al., 2010). The WHODAS assesses disability in six domains of functioning over the past 30 days, with each item rated on a 5-point scale from 1 (*none*) to 5 (*extreme or cannot do*). Analyses focused on three domains: getting along with people (5 items; $\alpha = 0.68$), life activities (household and school/work, 8 items; $\alpha = 0.90$), and participation in society (8 items; $\alpha = 0.84$), as the other domains (e.g., mobility) were less relevant to a young, physically healthy sample.

2.3. Task

An arrowhead version of the flanker task (Eriksen & Eriksen, 1974) was administered using the Presentation software (Neurobehavioral Systems, Berkeley, CA). On each trial, participants were presented with a row of five arrowheads for 200 ms and were asked to indicate the direction of the central arrowhead with the left or right mouse button as quickly and accurately as possible (ITI=2300–2800 ms). Half of the trials were congruent, and half were incongruent (trial order was randomized). Participants first completed a practice block of 30 trials to ensure they understood the task. The actual task consisted of 11 blocks of 30 trials (330 trials in total), with each block initiated by the participant. At the end of each block, participants received one of three types of performance feedback: if accuracy was 75% or lower, the message "Please try to be more accurate" was displayed; if accuracy was above 90%, the message "Please try to respond faster" was displayed; if accuracy was between 75% and 90%, the message "You're doing a great job" was displayed.

2.4. EEG recording and processing

During the flanker task, continuous EEG activity was recorded at a sampling rate of 1024 Hz using the ActiveTwo BioSemi system (BioSemi,

Amsterdam, Netherlands). Recordings were taken from 64 Ag/AgCl electrodes placed according to the 10/20 system. All electrodes were recorded online with respect to the signal formed by the common mode sense active electrode placed between PO3 and POz and the driven right leg passive electrode placed between POz and PO4. Electrode offsets were kept within + /- 40 mV to ensure high quality signal. EEG data was filtered online using a low-pass fifth order sinc filter with 3 dB cutoff at 208 Hz. Offline signal processing was conducted in MATLAB following established procedures (Miyakoshi, n.d.; see supplement for details).

After preprocessing, response-locked epochs were segmented from −1500 to 1500 ms, with large windows to accommodate edge artifacts. All epochs were then low-pass filtered at 30 Hz and baseline corrected using the −500 to −300 ms pre-response interval. On average, HC had 34.48 error trials (*SD*=14.36, range=12–82) and rMDD had 29.72 error trials (*SD*=12.58, range=11–57). For each trial, based on topographic maps and waveforms collapsed across groups, ERN and CRN were defined as the average voltage from 0 to 80 ms following response at FCz. Reliability of ERN, CRN, and ΔERN (i.e., ERN minus CRN) was quantified by the generalization theory's index of dependability calculated using the ERP Reliability Analysis toolbox (Clayson & Miller, 2017) and was as follows: (a) ERN for HC: 0.88, 95% CI [0.84, 0.90], (b) ERN for rMDD: 0.88, 95% CI [0.83, 0.92], (c) CRN for HC: 0.98, 95% CI [0.98, 0.99], (d) CRN for rMDD: 0.99, 95% CI [0.98, 0.99], (e) ΔERN for HC: 0.88, 95% CI [0.84, 0.91], and (f) ΔERN for rMDD: 0.88, 95% CI [0.82, 0.92].

2.5. Statistical analyses

All analyses were performed using R (R Core Team, 2022). Unless otherwise specified, trial-level behavioral and electrophysiological data were examined using multilevel models including random intercepts of families and of participants nested within families.

First, group differences in post-error adaptation in behavioral performance (accuracy and RT on correct trials) were tested using Previous Trial Accuracy (Correct vs. Error) X Group (HC vs. rMDD). To examine whether the magnitude of the error response predicted subsequent behavioral adaptation, a Previous Trial ERN (i.e., error trials only) X Group (HC vs. rMDD) was also conducted for accuracy and RT. Previous trial congruency (congruent vs. incongruent) was included as a covariate to account for potential adaptation arising from stimulus incongruence, as recommended by previous research (Holmes & Pizzagalli, 2008). A generalized multilevel model was conducted for accuracy, with binomial error distribution with one trial and logit link.

Second, group differences in error response and post-error adaptation in ERP were tested using Current Trial Accuracy (Correct vs. Error) X Group (HC vs. rMDD) + Previous Trial Accuracy (Correct vs. Error) X Group (HC vs. rMDD).[1] Again, previous trial congruency (congruent vs. incongruent) was included as a covariate.

Following previous studies (Brush et al., 2018), to examine group differences in changes of ERN/CRN across the course of the task, a multilevel model of Trial Number X Accuracy (Correct vs. Error) was conducted with additional predictors of group (to test whether groups differed in the initial response), interaction between group and trial (to test whether group moderated changes in the response to correct trials across time), and interaction between group, accuracy, and trial (to test whether group moderated changes in the difference between error and correct trials across time). Trials were re-coded so that the first trial corresponded with the intercept (i.e., trial=0) and then divided by 30 so that coefficients associated with trial would be large enough to be interpretable. Random effects additionally included random slopes of trial. All above models included the demographic covariate of race/ethnicity, where a significant group difference was observed, as well as baseline depression and OCD symptoms to test a specific relation with remission status.

Next, the association of ERN/CRN with baseline clinical characteristics and functional impairment was tested in similar models described previously, adding an interaction between group and the depression symptom/functioning measure along with covariates of race/ethnicity and baseline OCD symptoms. Models testing associations with MDD history were only examined within the rMDD group where data were available. In models testing associations with functional impairment, baseline depression symptoms were also included as a covariate to test for effects above and beyond residual symptoms.

Last, across the rMDD and HC groups, the association of ERN/CRN with depression symptoms at one-year follow-up was examined, again using similar models (i.e., replacing group with the follow-up symptom measure). Specifically, residualized scores were first calculated by regressing baseline on follow-up symptom scores; the residualized scores were then entered as the predictor. Residualized follow-up OCD symptoms were included as a covariate.

3. Results

3.1. Behavioral performance

Accuracy. Neither the main effect of previous trial accuracy or group nor their interaction was significant (all $ps > 0.23$). Further, accuracy was not significantly predicted by the previous ERN amplitude nor was this effect different by group (both $ps > 0.78$).

Reaction time on correct trials. There was a main effect of previous trial accuracy, $F(1, 49220.98) = 59.61$, $p < .001$: participants were slower following error than correct trials ($\beta = 0.11$, SE=0.014, $p < .001$). There was a main effect of group, $F(1171.90) = 4.82$, $p = .030$: the rMDD group was slower than HC ($\beta = 0.18$, SE=0.080, $p = .028$). A significant interaction between previous trial accuracy and group was observed, $F(1,49220.55) = 12.56$, $p < .001$. The RT slowing effect by previous error (vs. correct) trials was larger for rMDD than HC ($\beta = 0.10$, SE=0.028, $p < .001$). Further, RT was significantly predicted by the previous ERN amplitude, $F(1, 4922.16) = 5.77$, $p = .016$: a larger ERN on error trials predicted slower subsequent response ($\beta = -0.036$, SE=0.015, $p = .016$). The previous ERN amplitude by group interaction was not significant ($p = .32$).

3.2. ERN/CRN

There was a main effect of current trial accuracy, $F(1,53371.43) = 2216.82$, $p < .001$, and a main effect of previous trial accuracy, $F(1,53372.41) = 3.86$, $p = .049$. ERN was larger than CRN (i.e., a significant ΔERN; $\beta = -0.66$, SE=0.014, $p < .001$). ERPs were larger following error than correct trials ($\beta = -0.028$, SE=0.014, $p = .049$).

A significant interaction between current trial accuracy and group was observed, $F(1,53372.61) = 17.63$, $p < .001$. ΔERN was larger for rMDD than HC ($\beta = -0.12$, SE=0.028, $p < .001$; see Fig. 1). The previous trial accuracy by group interaction was not significant ($p = .30$).

3.3. Changes in ERN/CRN across trials

There was a main effect of trial number, $F(1308.18) = 20.64$, $p < .001$, a main effect of accuracy, $F(1,55308.45) = 789.17$, $p < .001$, and a trial by accuracy interaction, $F(1,55194.14) = 47.93$, $p < .001$. ERN became smaller across time ($\beta = 0.026$, SE=0.004, $p < .001$) but not CRN ($\beta = 0.0003$, SE=0.002, $p = .90$). There was not a main effect of group ($p = .75$) nor an interaction between group and trial ($p = .79$), but there was a significant three-way interaction between trial, accuracy, and group, $F(1,55352.46) = 13.00$, $p < .001$. The attenuation in the difference between ERN and CRN (i.e., ΔERN) was smaller for rMDD than HC ($\beta = -0.015$, SE=0.004, $p < .001$; see Table 2 and Fig. 2).

[1] We omitted the interaction between current and previous trial accuracy given the low rates of making two errors in a row (*M*=3.51, *SD*=4.04, range=0–24).

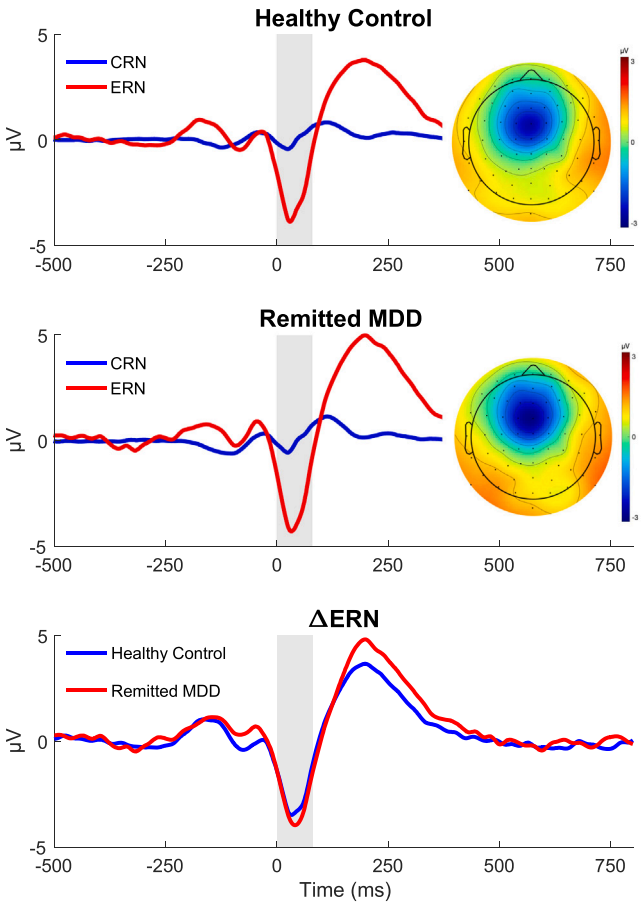

Fig. 1. Response-locked waveforms at FCz by current trial accuracy. Shaded regions indicate the time window (0–80 ms) used in analysis. Topographical maps indicate the difference between ERN and CRN (ΔERN) in the selected time window.

Table 2
Fixed Effects of Multilevel Model for the Group Differences in ERN/CRN Across Trials.

Predictor	β	*SE*	*t*	*df*	*p*
Intercept	0.12	0.060	2.11	170.90	0.036
Trial #	0.0007	0.003	0.25	176.14	0.80
Error (vs. Correct)	-0.78	0.028	-28.09	55308.45	< 0.001
Trial # X Error	0.030	0.004	6.92	55194.14	< 0.001
rMDD (vs. HC)	0.024	0.073	0.32	174.31	0.75
Trial # X rMDD	-0.001	0.005	-0.26	178.60	0.79
Trial # X Error X rMDD	-0.015	0.004	-3.60	55352.46	< 0.001
IDAS General Depression	0.025	0.032	0.80	159.96	0.42
IDAS OCD Composite	0.022	0.031	0.74	167.19	0.46

Note. The demographic covariate, race/ethnicity, was included in the model (results not shown). ERN = error-related negativity, CRN = correct response negativity, rMDD = remitted major depressive disorder, HC = healthy control, IDAS = Inventory of Depression and Anxiety Symptoms, OCD = obsessive-compulsive disorder.

3.4. Association of ERN/CRN with baseline clinical characteristics and functional impairment in rMDD and HC

A significant association with baseline depression symptoms was only observed for the rMDD but not HC group, with greater levels of anhedonia associated with a larger ΔERN to current trial error (by group interaction: $F(1,53370.35) = 9.69$, $p = .002$; see Table 3 for simple slopes) and smaller attenuation in ΔERN over the course of the task (by group interaction: $F(1,55351.06) = 9.51$, $p = .002$; see Table 4 for simple slopes). That is, a pattern of greater responsivity to errors was associated with greater anhedonia in rMDD. Additionally, within the rMDD group, greater error responsivity was associated with more lifetime MDEs, shorter time in remission (ΔERN to current error only), and taking psychotropic medication.[2]

With respect to functional impairment, greater error responsivity was associated with greater difficulties in getting along with people for both rMDD and HC (Tables 3 and 4), with these associations not significantly different between groups (both $ps > 0.61$). Interestingly, whereas greater error responsivity was associated with greater difficulties in life activities for HC, it was associated with *fewer* difficulties in this domain for rMDD (by group interactions: $F(1,52557.66) = 41.28$, $p < .001$ and $F(1,54487.76) = 33.94$, $p < .001$). Further, for the HC group only, greater error responsivity was additionally associated with greater difficulties in participation in society (by group interactions: $F(1,52560.78) = 21.23$, $p < .001$ and $F(1,54487.89) = 10.38$, $p = .001$).

3.5. Association of ERN/CRN with follow-up depression symptoms across rMDD and HC

Greater residualized follow-up anhedonia scores (i.e., adjusting for baseline anhedonia) were associated with a larger ΔERN to current trial error ($\beta = -0.062$, SE=0.023, $p = .008$) and smaller attenuation in ΔERN over the course of the task ($\beta = -0.010$, SE=0.003, $p = .004$). Additionally, greater residualized follow-up dysphoria scores were associated with a larger attenuation in ΔERN over the course of the task ($\beta = 0.008$, SE=0.004, $p = .046$), but not ΔERN to current trial error ($\beta = 0.046$, SE=0.026, $p = .070$). Residualized follow-up general depression scores were not associated with either ΔERN to current trial error ($\beta = 0.041$, SE=0.025, $p = .096$) or ΔERN changes over the course of the task ($\beta = 0.007$, SE=0.004, $p = .055$).

4. Discussion

The present investigation examined trial-by-trial adaptations to errors in rMDD to aid in the identification of risk markers for future MDD recurrence. Compared to HC, rMDD participants showed a pattern of greater responsivity to errors characterized by larger trial-averaged ΔERN and smaller ΔERN habituation across the course of the task – an effect that was independent of residual depressive and OCD symptoms. Greater error responsivity: (a) was concurrently associated with greater levels of anhedonia, a worse MDD history, worse interpersonal, yet better household and school/work functioning among rMDD participants and (b) after adjusting for baseline anhedonia, predicted greater levels of anhedonia at one-year follow-up. Overall, converging findings indicate that rMDD individuals are characterized by a hyperactive performance monitoring system, which may be considered as a marker of risk given its association with interpersonal impairment and future escalation in anhedonia.

Despite numerous cognitive models of depression assigning a causal role to negative information processing biases (Beck, 1987; Roiser et al., 2012; Teasdale, 1983), previous studies have obtained conflicting findings in the association between error responsivity and depression. We found that rMDD had a larger ΔERN than HC participants. This finding is consistent with a handful of studies reporting an enhanced ERN (Georgiadi et al., 2011) as well as hyperactivity in the anterior cingulate cortex in rMDD (Liotti et al., 2002; Pizzagalli, 2010; Ray et al., 2022; Schöning et al., 2009). Nevertheless, the majority of prior studies on rMDD and ERN reported null findings (Ruchsow et al., 2004, 2006; Schoenberg, 2014; Whitton et al., 2017). In contrast to our young adult sample, these studies utilized older adults (average age ~40–50 years old). Given that ERN has been found to decrease with age (Nieuwenhuis

[2] All findings remained the same after including psychotropic medication status as a covariate.

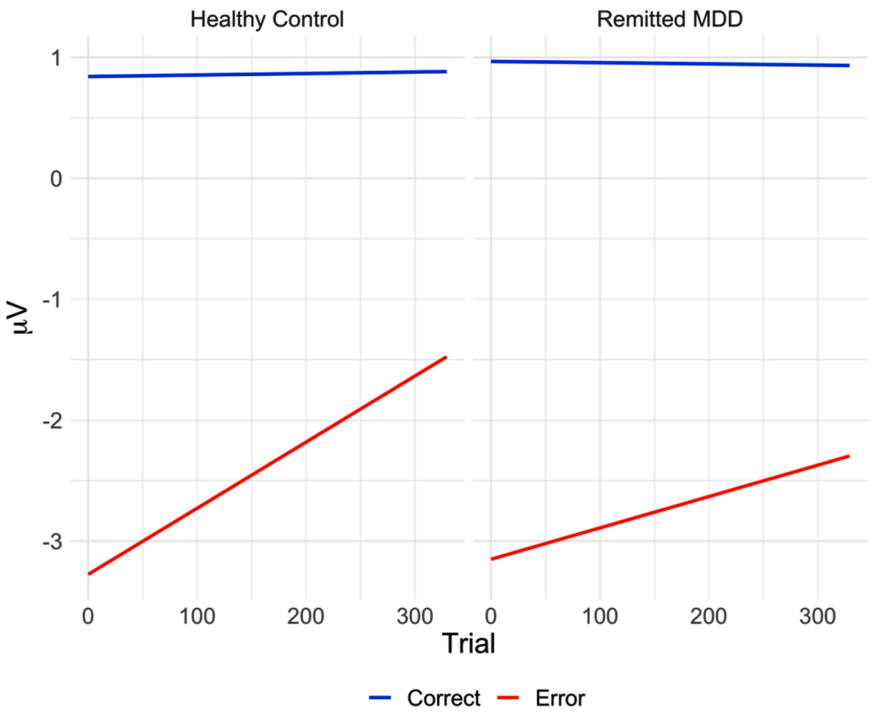

Fig. 2. Estimated slopes of ERN and CRN at FCz across the course of flanker task.

Table 3
Simple Slopes Displaying the Association of ERN/CRN with Clinical Characteristics and Functional Impairment in Remitted MDD and Healthy Control Groups.

	Remitted MDD						Healthy Control					
	Current Error (vs. Correct)			Previous Error (vs. Correct)			Current Error (vs. Correct)			Previous Error (vs. Correct)		
	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*	β	*SE*	*p*
Clinical Characteristics												
IDAS												
General Depression	0.019	0.021	0.37	-0.012	0.021	0.55	-0.003	0.019	0.88	-0.007	0.019	0.70
Dysphoria	0.035	0.020	0.076	< 0.001	0.020	1.00	-0.008	0.020	0.68	-0.026	0.020	0.20
Anhedonia	-0.11**	0.027	< 0.001	-0.052 *	0.027	0.053	-0.011	0.015	0.46	0.008	0.015	0.57
Age of Onset of MDD	0.006	0.024	0.80	-0.004	0.024	0.86	–					
Number of MDE	-0.070	0.024	0.004	-0.016	0.024	0.50	–					
Months in Remission	0.055	0.023	0.020	0.036	0.023	0.12	–					
Currently Taking Psychotropic Medication	-0.19	0.064	0.003	-0.036	0.065	0.58	–					
Functional Impairment												
Getting Along	-0.065	0.018	< 0.001	-0.027	0.018	0.13	-0.075	0.029	0.009	-0.024	0.029	0.40
Life Activities	0.038***	0.017	0.023	-0.022	0.017	0.19	-0.17	0.027	< 0.001	-0.028	0.027	0.30
Participation	0.027***	0.019	0.16	-0.009	0.019	0.63	-0.12	0.027	< 0.001	-0.036	0.027	0.18

Note. Stars denote significant group differences in slope (* $p < .05$, ** $p < .01$, *** $p < .001$). ERN = error-related negativity, CRN = correct response negativity, MDD = major depressive disorder, MDE = major depressive episode, IDAS = Inventory of Depression and Anxiety Symptoms.

et al., 2002), with some evidence suggesting that age-related reduction in ERN is more pronounced for rMDD than HC individuals (Georgiadi et al., 2011), it is possible that prior null findings may be a function of the older age masking risk-related ERN enhancement.

Another possibility underlying these conflicting findings is that previous studies have largely ignored the trial-level dynamics across the course of the task. Specifically, we found that rMDD did not significantly differ from HC in the initial ERN/CRN amplitude at trial 1 but evidenced less ΔERN habituation over the course of the task. Thus, the enhanced average error responsivity in rMDD (vs. HC) is better characterized as a greater maintenance of the motivational salience of errors across time. Interestingly, one previous study examining ERN amplitude averaged by blocks (four blocks of 200 trials each) found that ERN was greater for individuals with high (vs. low) trait negative affect for the first block, after which group differences were reversed (Luu et al., 2000). That is, individuals with high trait negative affect might have disengaged from the task when the task becomes too long and taxing. In light of this finding, it should be noted that our task was relatively short with numerous breaks in between blocks (11 blocks of 30 trials each), whereas previous studies that observed null findings typically used tasks with much larger number of trials (~500) with few breaks (Ruchsow et al., 2004, 2006; Schoenberg, 2014; Whitton et al., 2017).

The negative bias in rMDD is also evident in the post-error behavioral adaptation. On trials immediately following errors, rMDD participants showed greater RT slowing yet comparable accuracy than HC, with neither group showing a post-error increase in accuracy. Further, the RT, but not accuracy, on post-error trials was predicted by the previous ERN amplitude. This pattern is suggestive of errors eliciting an orienting response (Notebaert et al., 2009), with rMDD (vs. HC) individuals taking more time to disengage from errors and re-orient to the next trial due to the aversiveness of errors (Hajcak & Foti, 2008). It is also possible that the source of distraction comes from negative information external to the task (e.g., ruminating past negative events; Paulus, 2015), with rMDD (vs. HC) individuals expending greater effort to compensate the

Table 4
Simple Slopes Displaying the Association of ΔERN Habituation with Clinical Characteristics and Functional Impairment in Remitted MDD and Healthy Control Groups.

	Remitted MDD			Healthy Control		
	β	*SE*	*p*	β	*SE*	*p*
Clinical Characteristics						
IDAS						
General Depression	0.002	0.003	0.53	0.001	0.003	0.71
Dysphoria	0.005	0.003	0.11	0.002	0.003	0.46
Anhedonia	-0.016**	0.004	< 0.001	-0.001	0.002	0.54
Age of Onset of MDD	0.001	0.003	0.76	–		
Number of MDE	-0.010	0.004	0.006	–		
Months in Remission	0.005	0.003	0.11	–		
Currently Taking Psychotropic Medication	-0.025	0.010	0.008	–		
Functional Impairment						
Getting Along	-0.008	0.003	0.003	-0.010	0.004	0.012
Life Activities	0.006***	0.002	0.017	-0.021	0.004	< 0.001
Participation	0.002**	0.003	0.41	-0.013	0.004	< 0.001

Note. Stars denote significant group differences in slope (** $p < .01$, *** $p < .001$). ERN = error-related negativity, MDD = major depressive disorder, MDE = major depressive episode, IDAS = Inventory of Depression and Anxiety Symptoms.

low availability of their cognitive resources (Eysenck et al., 2007; Moser et al., 2013). In contrast to our hypothesis, we failed to observe any significant group differences in post-error ERP. The one previous study that examined post-error ERP indicated a smaller enhancement of ERN following errors (i.e., for sequential errors) in rMDD (Ruchsow et al., 2004, 2006). We were unable to examine the sequential error effect due to the low rates of making two errors in a row; future studies may wish to employ longer tasks with more difficulty to elucidate this effect.

Notably, within the rMDD group, responsivity to errors was associated with a number of clinical characteristics and functional outcomes. Specifically, greater error responsivity was associated with greater levels of anhedonia both concurrently and one-year later, which is the opposite of the previous proposal of high anhedonia attenuating the ERN amplitude (Schrijvers et al., 2008, 2009). This finding should be interpreted in the context of moderate levels of anhedonia in our rMDD group, which was at approximately 40th percentile according to community sample norms (Nelson et al., 2018). Thus, similar to the pattern of findings previously observed for general depression symptom severity and ERN (Endrass & Ullsperger, 2014; Moran et al., 2017; Olvet et al., 2010), there may exist a non-linear relation between anhedonia severity and error responsivity, such that mild to moderate levels of anhedonia (as in this sample) enhances error responsivity whereas extreme levels attenuate it. Additionally, greater error responsivity was associated with a more severe history of MDD and greater levels of functional impairment in terms of getting along with other people, but *lower* impairment in life activities, such as carrying out household chores and school/work tasks. The finding with interpersonal impairment dovetails with previous evidence of an enhanced ERN in individuals with elevated social anxiety (Barker, Troller-Renfree et al., 2015; Endrass et al., 2014), with one study showing that among a sample with social anxiety disorder, greater ERN amplitude was associated with greater depression symptoms (in the mild-to-moderate range; Endrass et al., 2014). Given that error responsivity is suggested to reflect compensatory effort (Moser et al., 2013), it is possible that a heightened focus on negative events might engender stress and rejection in interpersonal relationships through processes such as excessive reassurance seeking and negative feedback seeking (Hames et al., 2013). By contrast, such a compensatory effort may be conducive to ensure completion of day-to-day activities (e.g., paying rent on time, studying for an upcoming exam) for rMDD individuals, in light of error responsivity's association with *better* household and school/work functioning.

There are several limitations of the current study that warrant consideration. Chiefly, longitudinal analyses were limited by the small sample size, precluding analysis separately by group. Thus, findings of heightened error responsivity predicting escalation in anhedonia should be considered preliminary and await replication from larger-scale longitudinal studies. Moreover, the arrowhead version of the flanker task used in the current study is a fairly easy task (*M* accuracy=0.89), which could have contributed to our lack of post-error increase in accuracy and group differences therein. Last, while we focused on rMDD, it is likely that a heightened error responsivity, especially diminished habituation to errors, plays a key role in recurrence for other internalizing disorders due to shared risk factors (Olvet & Hajcak, 2008; Weinberg, Dieterich, et al., 2015). These factors may include greater motivational salience of aversive errors and/or greater compensatory effort from rumination in depression and worry in anxiety. It would be important for future studies to compare individuals with rMDD vs. those with remitted anxiety disorders to tease out the shared and unique mechanisms for heightened error responsivity, which could shed light on issues of comorbidity.

In sum, the present investigation revealed that rMDD individuals exhibited a heightened response to error characterized by a diminished habituation to errors over the course of the task. Findings highlight the utility of taking into account trial-by-trial dynamics to explicate prior conflicting findings and afford critical insights into abnormal error responsivity in depression. Critically, this error mal-adaptation was linked to impaired interpersonal functioning and predicted future escalation in levels of anhedonia. It is possible that the diminished ability to adapt to errors, and perhaps other motivationally relevant negative events, not only creates cognitive control difficulties but also dampens positive affect and creates interpersonal stressors that may ultimately trigger a recurrent depressive episode.

Conflicts of interest

None.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2023.108555.

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