ORIGINAL ARTICLE

Spatiotemporal Dynamics of Error Processing Dysfunctions in Major Depressive Disorder

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Context: Depression is characterized by executive dysfunctions and abnormal reactions to errors; however, little is known about the brain mechanisms that underlie these deficits.

Objective: To examine whether abnormal reactions to errors in patients with major depressive disorder (MDD) are associated with exaggerated paralimbic activation and/or a failure to recruit subsequent cognitive control to account for mistakes in performance.

Design: Between February 15, 2005, and January 19, 2006, we recorded 128-channel event-related potentials while study participants performed a Stroop task, modified to incorporate performance feedback.

Setting: Patients with MDD and healthy comparison subjects were recruited from the general community.

Participants: Study participants were 20 unmedicated patients with MDD and 20 demographically matched comparison subjects.

Main Outcome Measures: The error-related negativity and error positivity were analyzed through scalp and source localization analyses. Functional connectivity analyses were conducted to investigate group differences in the spatiotemporal dynamics of brain mechanisms that underlie error processing.

Results: Relative to comparison subjects, patients with MDD displayed significantly lower accuracy after incorrect responses, larger error-related negativity, and higher current density in the rostral anterior cingulate cortex (ACC) and medial prefrontal cortex (PFC) (Brodmann area 10/32) 80 milliseconds after committing an error. Functional connectivity analyses revealed that for the comparison subjects, but not the patients with MDD, rostral ACC and medial PFC activation 80 milliseconds after committing an error predicted left dorsolateral PFC (Brodmann area 8/9) activation 472 milliseconds after committing an error.

Conclusions: Unmedicated patients with MDD showed reduced accuracy and potentiated error-related negativity immediately after committing errors, highlighting dysfunctions in the automatic detection of unfavorable performance outcomes. New analytic procedures allowed us to show that abnormal reaction to committing errors was accompanied by hyperactivation in rostral ACC and medial PFC regions 80 milliseconds after committing errors and a failure to recruit dorsolateral PFC-based cognitive control. Future studies are warranted to investigate whether these dysfunctions might foster the emergence and maintenance of negative processing biases and thus increase vulnerability to depression.

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COGNITIVE THEORIES OF DEpression have long postulated that automatically activated cognitive schemata and a predisposition to process information in a negative manner are prominent features of depression.[1] Consistent with this, depression is characterized by ineffective inhibition of negative information,[2] difficulty disengaging attention from negative cues,[3] greater interference from negative distractors,[4] amplification of the significance of failure,[5] and increased likelihood of committing errors immediately after an initial mistake.[6-10] Although these negative processing biases have been critically implicated in the etiology and maintenance of depression, little is known about their underlying mechanisms and neural substrates.

Emerging neuroimaging evidence suggests that, in major depressive disorder (MDD), negative processing biases may result from dysfunctions in paralimbic regions implicated in affective responses such as the amygdala and the rostral anterior cingulate cortex (ACC)[11-13] and/or dysfunctions in cortical regions involved in cognitive control (ie, the ability to guide action and thought in accordance with internally generated goals), such as the dorsolateral prefrontal cortex (PFC) and dorsal ACC.[13-18] Moreover, patients with MDD show reduced connectivity between the

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dorsolateral PFC and rostral ACC regions after the presentation of personally relevant negative stimuli.[13] Collectively, these findings suggest that abnormal responses to errors and negative cues in depression[6-10] might be due to exaggerated paralimbic activation, a failure to recruit PFC-based cognitive control after committing an error, or a combination of these 2 factors, possibly resulting from disrupted frontocingulate connectivity. To the best of our knowledge, these hypotheses have yet to be fully investigated.

The goal of this study was to address these important questions. To this end, we capitalized on the high temporal resolution of event-related potentials (ERPs) and on novel approaches to investigate spatiotemporal dynamics of brain mechanisms that underlie error processing in a sample of unmedicated patients with MDD. The ERP analyses focused on error-related negativity (ERN) and error positivity (Pe), 2 components assumed to reflect dissociable aspects of error processing and partially originating from regions within the ACC.[19]

The ERN, a negative voltage deflection measured over midline frontocentral regions beginning with the occurrence of an incorrect response and peaking approximately 50 to 150 milliseconds later,[20,21] is hypothesized to represent a negative reinforcement learning signal conveyed through the mesencephalic dopamine system[22,23]; accordingly, the ERN is assumed to index the automatic initial detection of unfavorable performance outcomes, which then triggers recruitment of PFC-based cognitive control.[24] The Pe, a positive voltage deflection peaking approximately 150 to 500 milliseconds after mistakes, is hypothesized to index conscious error awareness and subjective affective evaluative processes after errors.[20] Fitting these conceptualizations, ERN is not contingent on the conscious experience of errors, whereas the Pe is observed when subjects are aware of having committed an error.[25-27]

Extending reports of abnormal error processing in depression,[6-10] recent ERP studies have described enhanced ERN amplitude in clinically depressed patients,[28] elderly patients with MDD who remain symptomatic after antidepressant treatment,[29] and individuals with increased levels of negative affect[30,31] but not in medicated patients with MDD in remission.[32] Moreover, increased ERN amplitude has been found to predict poor treatment response in a small sample of patients with geriatric depression.[33] Although these ERN findings highlight dysfunctional error processing in depression, at first glance, they appear paradoxical in light of theoretical considerations[22] and empirical findings[21,34] that link increased ERN with adaptive performance adjustments. To reconcile these data, we hypothesized that, in depression, initial exaggerated error processing (increased ERN) is not followed by successful recruitment of PFC-based cognitive control, leading to posterror impairments. Notably, decreased ERN in error trials after a prior mistake[32] has been described in patients with MDD, providing indirect support for this hypothesis.

Therefore, on the basis of prior findings,[11,13,28,29] we hypothesized that unmedicated patients with MDD would show (1) decreased performance in trials immediately after errors, (2) increased scalp ERN and rostral ACC activation after committing errors, and/or (3) disrupted connectivity between the rostral ACC and dorsolateral PFC regions, which might explain deficits in the recruitment of cognitive control and the lack of adaptive performance after error commission. With respect to Pe, we hypothesized that patients with MDD would display higher amplitudes, reflecting increased subjective affective evaluation of errors. Because of inconsistent Pe findings in depression,[28,29] we considered this latter hypothesis tentative.

METHODS

STUDY PARTICIPANTS

Between February 15, 2005, and January 19, 2006, 45 study participants were recruited from the community. Individuals of all ethnic origins between 18 and 55 years of age were considered. All participants were right-handed[35] and had normal or corrected vision (including color vision[36]). Patients with MDD were included if the following criteria were met: (1) a *DSM-IV* diagnosis of MDD[37]; (2) absence of any Axis I diagnoses, excluding anxiety disorders (simple phobia; n=1); (3) absence of any psychotropic medication in the last 2 weeks (4 weeks for neuroleptics and benzodiazepines, 6 weeks for fluoxetine hydrochloride, and 6 months for dopaminergic drugs); (4) absence of a history of psychotic symptoms; and (5) absence of electroconvulsive therapy, seizures, or head injuries that resulted in loss of consciousness. Healthy comparison subjects were included if they presented no evidence of current or past psychopathologic disorders, neurologic disorders, or head injuries. Five participants were excluded because of current drug or psychotropic medication use between the Structured Clinical Interview for *DSM-IV* (SCID) and behavioral session (n=3), noncompliance with the SCID interview (n=1), or untreated thyroid condition (n=1). The final sample consisted of 20 comparison subjects and 20 patients with MDD. Groups did not differ with respect to ethnicity, sex, age, or educational level (**Table 1**). Participants provided written informed consent to a protocol approved by the Committee on the Use of Human Subjects at Harvard University and received $10 per hour for their participation.

PROCEDURE

The study consisted of 2 sessions. In the first, study eligibility was established through the patient edition of the SCID, which was performed by a master-level interviewer (A.J.H.). In the following week, participants took part in the experimental session, which included behavioral and ERP testing.

STROOP TASK

Participants performed a variant of the classic Stroop task, which consisted of 3 words (*red*, *green*, and *blue*) printed in 1 of 3 different colors of ink (red, green, and blue). Trials were either congruent (eg, the probe *green* printed in green ink) or incongruent (eg, the probe *red* printed in blue ink). Participants were instructed to respond, as quickly and accurately as possible, to the color of the probe. Responses were made with a button press using 3 fingers of the right hand (index, middle, and ring), with 1 finger representing each color. Before each trial, a fixation cross was presented for 250 milliseconds in the center of a computer screen. Stroop probes were then presented for 150 milliseconds, followed by a variable intertrial interval (1850-1950 milliseconds).

Two practice blocks (24 trials each) were presented to familiarize the participants with the paradigm. During the sec-

Table 1. Demographic Data and Clinical Characteristics

Variable	Patients With MDD (n=20)	Comparison Subjects (n=20)	χ^2_1/t_{38}	*P* Value
Age, mean (SD), y	30.60 (12.16)	28.80 (9.87)	0.51	.15
Educational level, mean (SD), y	15.65 (1.87)	15.65 (1.93)	0.001	.99
Female, %	7 (35)	10 (50)	0.92	.34
White, %	16 (80)	14 (70)	0.53	.46
Beck Depression Inventory II score, mean (SD)	22.55 (9.23)	2.45 (3.31)	9.17	.005
Duration of current episode, mean (SD), mo	2.54 (1.44)	NA	NA	NA
No. of prior episodes, mean (SD)	2.25 (1.26)	NA	NA	NA
History of medication use, %	11 (55)	NA	NA	NA

Abbreviations: MDD, major depressive disorder; NA, not applicable.

ond practice block, reaction times (RTs) were collected to determine, for each participant separately, a threshold for late responses. After the practice blocks, a feedback manipulation was added. Feedback was used to minimize the potential confounders of group differences in error awareness affecting posterror adjustments. Positive feedback (a schematic smiling face) was presented for 250 milliseconds when correct responses were made within the individually titrated response window, which was defined as 85% of each participant's mean RT during the second practice block. Negative feedback (a schematic frowning face) was presented for 250 milliseconds if participants responded incorrectly or outside the response window. To compensate for possible changes in performance over time, the response window threshold was recalculated at the midpoint and end of each block. An 85% accuracy threshold was selected to optimize the psychometric properties of the design (eg, to avoid performance at ceiling levels). To prevent feedback-related activity from interfering with the error-related ERPs, the feedback was presented 1850 to 1950 milliseconds after the Stroop cue; an intertrial interval of 900 to 1100 milliseconds followed the feedback presentation (**Figure 1**).

Each participant completed 6 blocks (total duration, 7 minutes, 48 seconds). To induce more errors, only 35.5% of the trials were incongruent (98 congruent and 54 incongruent). The RT and accuracy measures were collected throughout the task. Participants were allowed to rest between blocks.

APPARATUS

The task was presented on an IBM 2.4-GHz computer using Eprime software (Psychology Software Tools Inc, Pittsburgh, Pennsylvania). Participants' responses were collected via a button box. The 128-channel ERPs were recorded using the Geodesic Sensor Net system (Electrical Geodesic Inc, Eugene, Oregon), with a 250-Hz sampling rate (bandwidth, 0.01-100 Hz) and the vertex electrode (Cz) as recording reference. Impedances were kept below 50 kΩ.

DATA REDUCTION

Behavioral Data

Only trials in which the participant made a response were considered. To reduce the influence of outliers, trials with RTs (after log transformation) that fell outside the range of mean±3 SDs for each trial type were excluded (mean [SD], 0.28% [0.24%]).

The main analyses of interest focused on behavioral adjustments immediately after error commission. Prior research has shown that individuals increase their RTs and improve their accuracy immediately after committing a mistake, indicating that error monitoring is used to improve behavioral performance.[38,39] Accordingly, posterror adjustments were calculated as [($RT_{\text{After Incorrect Trials}} - RT_{\text{After Correct Trials}}$); Rabbitt effect][39] and [($\text{Accuracy}_{\text{After Incorrect Trials}} - \text{Accuracy}_{\text{After Correct Trials}}$); Laming effect].[38] For either effect, higher scores are indicative of adaptive, posterror behavioral adjustments. As in prior studies,[9] analyses assessing posterror adjustments were restricted to trials performed after incongruent trials so that posterror and congruence adjustment effects were deconfounded.

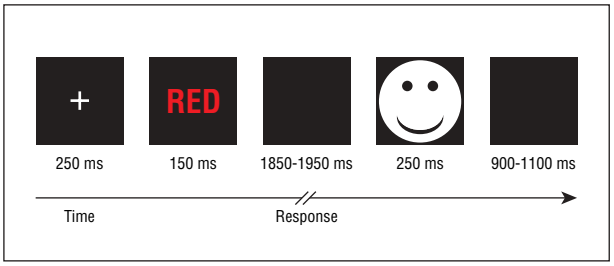

Figure 1. Schematic representation of the task design.

ERP Data

Data were processed using Brain Vision software (Brain Products GmbH, Gilching, Germany). Channels with corrupted signals were replaced with spatially weighted linear interpolations, and artifacts were removed through independent components analysis.[40] A semiautomatic artifact detection was performed to identify remaining artifacts (maximal amplitude, ±75 μV; within-segment absolute amplitude difference, 150 μV; gradients, 50 μV). Subsequently, response-locked ERPs were computed 200 milliseconds before and 924 milliseconds after a response. Four participants (2 in each group) were excluded from the ERP analyses because of excessive movement-related artifacts. Mirroring the behavioral data, ERPs to correct and incorrect responses were computed only for incongruent trials. The ERP data were then bandpass filtered (0.01-30 Hz), baseline corrected (−200 to −100 milliseconds before response), and rederived to an average reference. Finally, grand mean ERPs were calculated by averaging ERPs across conditions and groups.

The ERP analyses focused on the ERN, its counterpart for correct responses (correct-response negativity [CRN]), and the Pe and involved 3 steps. In the first step, conventional scalp ERP waveform analyses were performed by extracting ERN/CRN and Pe amplitudes and latencies from midline sites (Fz, FCz, Cz, and Pz). The ERN and CRN were identified as the maximal negative deflections 50 to 150 milliseconds after a re-

Table 2. Behavioral, Scalp ERP, and LORETA Findings[a]

Variable	Patients With MDD	Comparison Subjects	Group Effects *P* Value[b]
Behavioral data[c]			
Postcorrect accuracy	0.91 (0.08)	0.92 (0.05)	.48
Posterror accuracy	0.87 (0.08)	0.92 (0.06)	.005
Postcorrect RT	340.12 (82.29)	322.34 (54.40)	.43
Posterror RT	380.95 (97.21)	354.89 (68.23)	.33
Scalp ERP data, μV[d]			
ERN	−2.74 (1.83)	−1.42 (1.69)	.01
CRN	0.20 (1.80)	1.33 (2.01)	.08
Early Pe	3.58 (2.33)	3.42 (2.40)	.85
Late Pe	3.61 (2.40)	4.29 (3.52)	.49
LORETA data[e]			
Rostral ACC (BA 32)	−3.50 (0.09)	−3.74 (0.18)	<.00003

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; CRN, correct-response negativity; ERN, error-related negativity; ERP, event-related potential; LORETA, low-resolution electromagnetic tomography; MDD, major depressive disorder; Pe, error positivity; RT, reaction time.

[a] Data are presented as mean (SD).

[b] Findings from unpaired *t* tests (postcorrect RT, posterror RT, early PE, and late PE) or post hoc Newman-Keuls tests (postcorrect accuracy, posterror accuracy, ERN, and CRN) are reported.

[c] Posterior adjustment effects were restricted to trials following incongruent trials. Comparison subjects: n=20; patients with MDD: n=20.

[d] Mean amplitudes (averaged across Fz, FCz, Cz, and Pz) for incongruent trials. Comparison subjects: n=18; patients with MDD: n=18.

[e] Current density, 80 milliseconds after error for incongruent trials. Comparison subjects: n=18; patients with MDD: n=18.

sponse. Following recent reports,[19,41] early Pe and late Pe were defined as the maximal positive deflection that occurs 150 to 250 and 250 to 500 milliseconds, respectively, after an incorrect response. The mean (SD) number of segments available for the ERP analyses did not differ between the patients with MDD (mean [SD], 42.1 [4.2]) and comparison subjects (mean [SD], 35.9 [2.9]) (t_{38}=1.21; P=.24).

In a second step, low-resolution electromagnetic tomography (LORETA)[42,43] was used to calculate the 3-dimensional intracerebral current density at the time of maximal error-related processing. LORETA is a distributed source localization technique that solves the inverse problem without assuming an a priori number of underlying sources and has recently received substantial validation from studies that combine this algorithm with functional magnetic resonance imaging (fMRI),[44] positron emission tomography,[45] and intracranial recordings.[46,47] The solution space (ie, the locations in which sources can be found) includes 2394 voxels (7 mm^3) and is restricted to cortical gray matter and hippocampi, as defined by the Montreal Neurologic Institute template (MNI305). For each subject, LORETA was computed at the times of maximal global field power (GFP) peaks within the ERN/CRN and Pe time windows, which were empirically defined through a data-driven, space-oriented segmentation procedure.[48] The GFP is computed as the average standard deviation within the potential field; the GFP peaks are hypothesized to index time points associated with maximal neuronal activity and thus offer optimal signal-to-noise ratio.[49] Before the statistical analyses, LORETA activity was normalized to a total current density of 1 and log-transformed.

In the third step, functional connectivity analyses were performed to investigate the spatiotemporal dynamics of error processing and putative dysfunctions of these processes in MDD.

STATISTICAL ANALYSES

Behavioral Data

For RT and accuracy scores, we performed separate mixed 2×2 analyses of variance (ANOVAs) with group (patients with MDD vs comparison subjects) as the between-subject factor and condition (after committing an error vs after correct response) as the repeated measure.

Scalp ERP Data Analyses

For the ERN/CRN data, mixed 2×2 ×4 ANOVAs with group, condition (ERN and CRN), and site (Fz, FCz, Cz, and Pz) as factors were run separately on amplitude and latency scores. For the Pe, only group and site were considered. When applicable, the Greenhouse-Geisser correction was applied (adjusted P and ε values are reported). Post hoc Newman-Keuls tests were performed in case of significant ANOVA findings. For the sake of brevity, only effects that involved group are reported. Moreover, since no group differences emerged with respect to ERP latencies (mean [SD] ERN latency across the groups, 97.28 [15.75] milliseconds; CRN, 89.47 [18.16] milliseconds; early Pe, 188.08 [25.71] milliseconds; late Pe, 346.56 [42.79] milliseconds), these variables were not further considered.

LORETA Analyses

For each identified GFP peak (ERN/CRN, 80 milliseconds; early Pe, 184 milliseconds; late Pe, 304 and 472 milliseconds), voxelwise unpaired *t* tests were performed to assess group differences in current density. The output was thresholded at $P<.05$, corrected for multiple comparisons, according to a nonparametric randomization procedure that used 5000 permutations.[50]

Functional Connectivity Analysis

To test the a priori hypothesis that depression would be associated with disrupted recruitment of cognitive control after error commission, functional connectivity analyses that considered current density across different stages of error processing were computed. For patients with MDD and comparison subjects separately, whole-brain Pearson correlation analyses were run between (1) the average current density within regions that showed significant group differences at the time of the ERN GFP peak (80 milliseconds after committing an error) and (2) current density at each voxel computed at later stages of error processing (Pe GFP peaks, 184, 304, and 472 milliseconds). As in prior studies,[51] voxelwise Fisher tests were computed to identify voxels in which the 2 groups showed significantly different correlations (ie, different functional connectivity). To avoid spurious results, findings from the Fisher tests were thresholded at $P<.005$ (uncorrected) with a minimal cluster size of 5 voxels.

RESULTS

BEHAVIORAL ANALYSES

General Performance

Exploratory analyses were conducted to evaluate whether groups differed in their accuracy scores, which could have affected ERP averaging. A mixed ANOVA with group and condition (congruent vs incongruent trials) revealed only

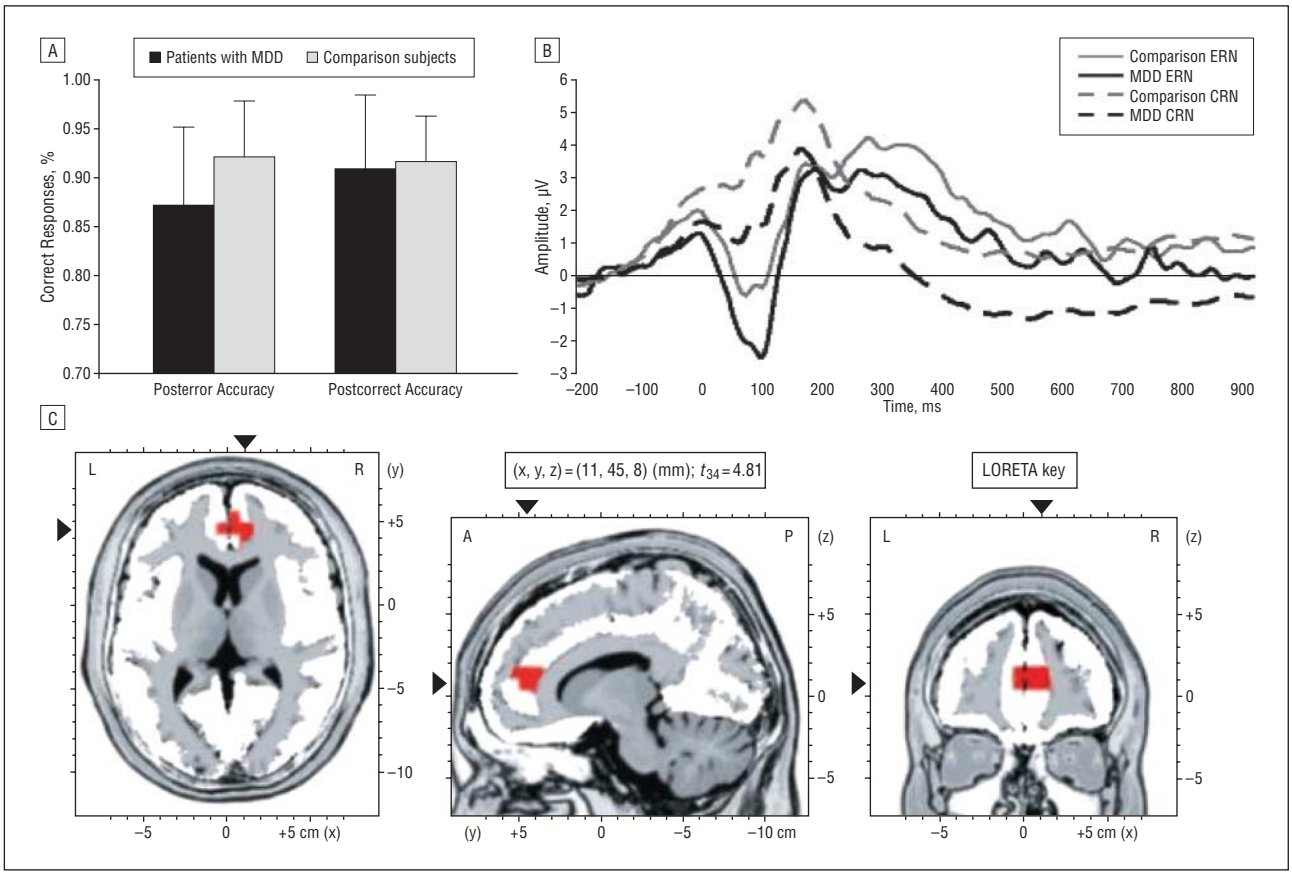

Figure 2. Summary of behavioral and event-related potential findings highlighting abnormal error processing in major depressive disorder (MDD). A, Mean (SE) accuracy for the patients with MDD (n=20) and comparison subjects (n=20). B, Response-locked grand mean waveforms (averaged across Fz, FCz, Cz, and Pz) for correct-response negativity (CRN) and error-related negativity (ERN) responses. C, Rostral anterior cingulate cortex and medial prefrontal cortex cluster in which patients with MDD had significantly higher current density than comparison subjects 80 milliseconds after committing an error (Brodmann area 10/32; 13 voxels; peak voxel Montreal Neurologic Institute coordinates: x=11, y=45, z=8; t_{34}=4.81; P<.05, corrected). LORETA indicates low-resolution electromagnetic tomography; L, left; R, right; A, anterior; and P, posterior.

a main effect of condition ($F_{1,38}$=44.17; P<.001; partial η^2=0.54) due to higher accuracy for congruent (mean [SD], 0.93 [0.05]) than incongruent trials (mean [SD], 0.86 [0.08]). Notably, the main effect of group ($F_{1,38}$=0.81; P=.38) and the group × condition interaction ($F_{1,38}$=2.61; P=.12) were not statistically significant. Accordingly, patients with MDD (mean [SD], 0.89 [0.06]) and comparison subjects (mean [SD], 0.90 [0.06]) did not differ in their overall error rates.

Posterror Adjustments

For RT, neither the group ($F_{1,38}$=0.86; P=.36) nor the group × condition interaction ($F_{1,38}$=0.46; P=.50) emerged. For accuracy, the main effect of group was not statistically significant ($F_{1,38}$=2.10; P=.16; **Table 2**). However, replicating findings in patients with elevated depressive symptoms,[8,9] a significant group × condition interaction emerged ($F_{1,38}$=9.28; P=.004; partial η^2=0.20), indicating that the 2 groups differed in their Laming effect (Cohen d=0.96). Post hoc Newman-Keuls tests revealed that patients with MDD (P<.001), but not comparison subjects (P=.54), had significantly lower accuracy scores after incorrect than correct responses (**Figure 2**A and Table 2). Moreover, patients with MDD had significantly lower posterror accuracy (P<.001) but similar accuracy after correct responses (P=.48) relative to comparison subjects. On an individual level, 15 of the 20 patients with MDD (binomial P=.02) but only 9 of the 20 comparison subjects (binomial P=.16) had a negative Laming effect (Fisher exact test, P=.05).

SCALP ERP WAVEFORM ANALYSES

ERN Amplitudes

In addition to significant main effects of site (Fz=FCz>Cz=Pz; P<.001) and condition (ERN>CRN; P<.001), the only other finding of relevance was the main effect of group ($F_{1,34}$=5.53; P=.03; partial η^2=0.14; Table 2). On the basis of a priori hypotheses that postulated abnormal error processing in patients with MDD, post hoc Newman-Keuls tests were performed to further explore this finding. Relative to comparison subjects, patients with MDD had significantly larger ERN (P=.006; Cohen d=0.75) but comparable CRN (P=.19; Figure 2B). To ensure that the ERN findings were not confounded by potential group differences in motor preparation, control analyses were performed using a 600- to 400-millisecond pre-response baseline and a peak-to-peak measure (using the preceding positive peak). The

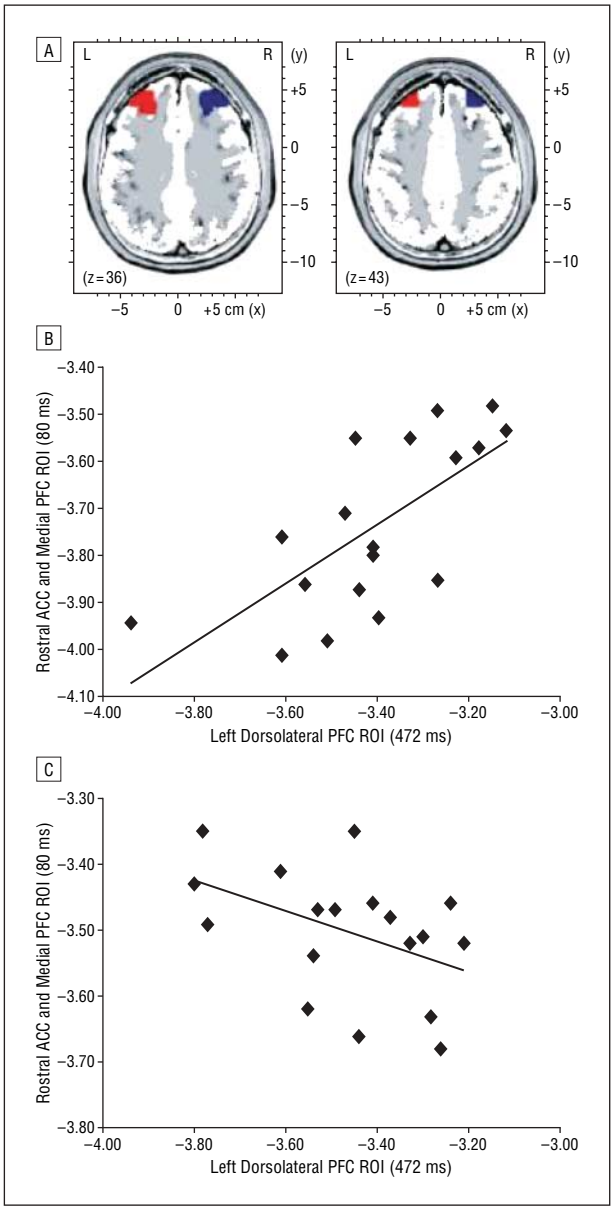

Figure 3. Summary of functional connectivity findings. A, Red denotes regions of interest (ROIs) with significantly lower correlations in patients with major depressive disorder (MDD) than comparison subjects between current density within the rostral anterior cingulate cortex (ACC) and medial prefrontal cortex (PFC) cluster 80 milliseconds after error (Figure 2C) and the current density at the late error positivity global field power peak (472 milliseconds). The only ROI showing group differences in functional connectivity was the left dorsolateral PFC cluster shown in red (Brodmann area 8/9; 12 voxels; $P<.005$; peak voxel Montreal Neurologic Institute coordinates: x=−24, y=38, z=36). Blue represents the homologous right dorsolateral PFC cluster, which was used to formally evaluate laterality. L indicates left; R, right. B and C, Scatterplots of the current density (averaged across voxels) within the rostral ACC and medial PFC cluster 80 milliseconds after committing an error and the late error positivity (472 milliseconds) in the left dorsolateral PFC ROI for the comparison subjects (B) ($r=0.69$; $P=.001$) and patients with MDD (C) ($r=-0.46$; $P=.06$).

main effect of group was confirmed ($F_{1,34}=7.12$; $P=.01$; partial $\eta^2=0.17$).

Early and Late PE Amplitudes

The only significant finding was the main effect of site because of the maximal Pe at the frontocentral sites (early Pe: FCz=Cz>Fz>Pz; all $P<.01$; late Pe: FCz=Cz>Fz>Pz; all $P<.02$). No effects that involved group emerged (all $F<2.78$; all $P>0.84$; Table 2).

LORETA ANALYSES

Error-Related Negativity

The only region that exceeded the statistical threshold ($t_{34}>4.31$; corrected $P<.05$) at the time of maximal ERN GFP peak (80 milliseconds) was a cluster (13 voxels) that involved the rostral ACC (Brodmann area [BA] 32) and medial PFC (BA 10). As shown in Figure 2C, patients with MDD had significantly higher current density than comparison subjects 80 milliseconds after an incorrect response ($t_{34}=4.81$; corrected $P<.05$; Cohen d=1.61; Table 2).

Error Positivity

When considering the Pe GFP peaks (184, 304, and 472 milliseconds after response), no significant findings emerged.

FUNCTIONAL CONNECTIVITY ANALYSES

Only 1 region exceeded the statistical thresholding of the voxelwise Fisher tests. These analyses revealed significant group differences between (1) the mean current density within the rostral ACC and medial PFC cluster 80 milliseconds after committing an error and (2) current density within a left dorsolateral PFC cluster (BA 8 and BA 9; 12 voxels) at the late Pe GFP peak (472 milliseconds; maximum voxel $z=4.21$; $P<.001$; **Figure 3**A). This effect was due to significant positive correlation between rostral ACC and medial PFC current density 80 milliseconds after committing an error and current density in the left dorsolateral PFC 472 milliseconds after committing an error for the comparison group ($r=0.69$; $P=.001$; Figure 3B) and a trend in the opposite direction for patients with MDD ($r=-0.46$; $P=.06$; Figure 3C).

Two additional analyses were performed to formally test this laterality effect. In the first analysis, we evaluated whether group differences were specific to the left dorsolateral PFC. Thus, the mean z value (averaged across voxels) was extracted for the left dorsolateral PFC and its homologous right dorsolateral PFC region and compared using the following formula[52]: $z' = [(z_{Left}-z_{Right})/\sqrt{2}]$. A significant difference emerged ($z'=2.43$; $P=.008$), indicating that patients with MDD had significantly lower functional connectivity than comparison subjects between the rostral ACC and medial PFC and the left, but not right, dorsolateral PFC. In the second analysis, we tested whether the correlation between the rostral ACC and medial PFC and the left dorsolateral PFC cluster was significantly different from the one between the rostral ACC and medial PFC and the right dorsolateral PFC cluster.[53] For comparison subjects, these correlations were significantly different ($r=0.69$ for the left vs $r=-0.11$ for the right; $z=2.15$; $P=.02$). For patients with MDD, the

2 correlations were not significantly different ($r=-0.46$ for the left vs $r=0.001$ for the right; $z=-1.64$; $P=.10$).

For comparison subjects, a positive correlation emerged between the rostral ACC and medial PFC and the left dorsolateral PFC activation. On the basis of prior fMRI findings that indicated that ACC activation predicted greater dorsolateral PFC recruitment, which in turn led to better behavioral adjustments,[54] we reasoned that the patients with MDD who showed the strongest left dorsolateral PFC activation would show better posterror behavioral adjustments compared with patients who did not recruit the left dorsolateral PFC after mistakes. To test this hypothesis, a median-split procedure was used to identify patients with MDD with the highest (n=9) and those with the lowest (n=9) left dorsolateral PFC activation 472 milliseconds after committing an error. The MDD subgroups were then compared using PFC group × condition (after committing an error vs after a correct response) ANOVAs run on RT and accuracy scores.

For RT, a significant PFC group × condition interaction emerged ($F_{1,16}=6.11$; $P=.03$; partial $\eta^2=0.28$). A post hoc Newman-Keuls test indicated that patients with MDD with the highest left dorsolateral PFC activation had significantly longer RTs after incorrect than correct responses (mean [SD], 416.65 [90.63] milliseconds vs 350.32 [76.01] milliseconds; $P<.001$), whereas patients with MDD with the lowest left dorsolateral PFC activation failed to show adaptive behavioral adjustments after committing errors ($P=.18$; **Figure 4**A). Moreover, although the 2 MDD subgroups had virtually identical RTs after correct responses ($P=.96$), patients with MDD with the strongest left dorsolateral PFC activation had significantly slower posterror RTs compared with the other MDD subgroup.

For accuracy, the only significant finding was the main effect of condition ($F_{1,16}=9.47$; $P=.008$; partial $\eta^2=0.37$), which was due to significantly lower accuracy after incorrect than correct responses. Targeted analyses revealed, however, that only patients with MDD with the lowest left dorsolateral PFC activation showed significantly reduced accuracy after incorrect relative to correct responses ($P=.02$); moreover, patients with MDD with the lowest left dorsolateral PFC activation had significantly reduced accuracy relative to the other MDD subgroup after incorrect ($P=.03$) but not correct ($P=.18$) responses (Figure 4B).

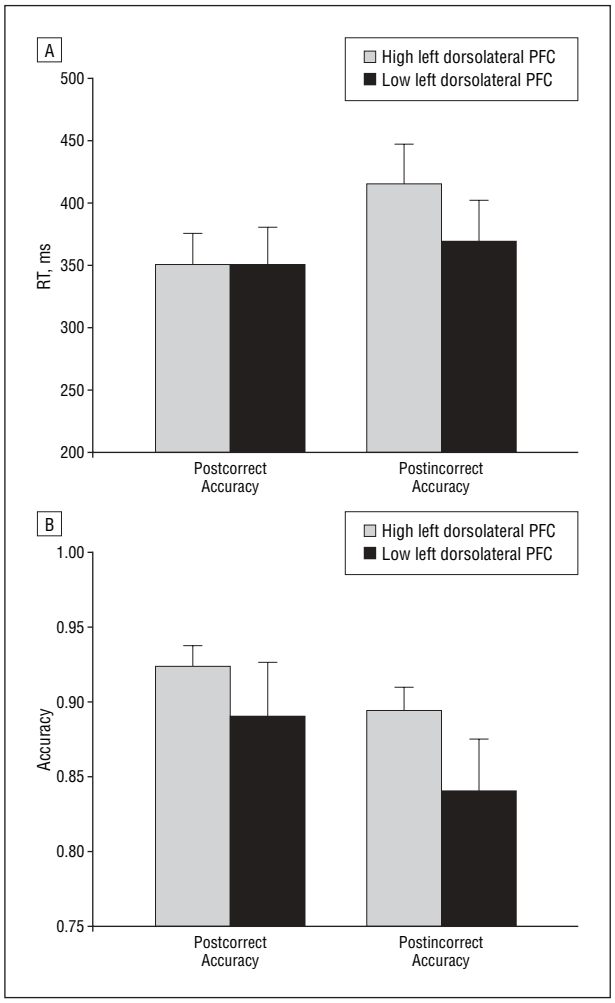

Figure 4. Reaction time (RT) and accuracy for the patients with major depressive disorder (MDD). Mean (SE) RT (A) and mean (SE) accuracy (B) for the patients with MDD with the highest (n=9) and the lowest (n=9) left dorsolateral prefrontal cortex (PFC) activation 472 milliseconds after committing an error.

COMMENT

Emerging evidence indicates that depression is characterized by impairments in executive control required for adaptive responding[15,55] and particularly by deficits in adjusting behavior after errors or negative feedback.[7,8,15,56] In this study, patients with MDD had significantly lower accuracy in Stroop trials immediately after a mistake but were unimpaired in trials after a correct response. Replicating recent findings, this study indicated that patients with depression showed significantly larger ERN at frontocentral sites[28,29,33] but unaffected Pe.[28] The lack of group differences in Pe is not surprising given prior inconsistent findings in the literature.[28,29] When interpreted within the framework of prior ERP studies,[22,23] the present findings indicate that depression is characterized by hypersensitivity to errors during early stages of the information-processing flow but unimpaired conscious experience and recognition of errors. Thus, larger ERN might reflect dysfunctions in the automatic detection of an unfavorable performance outcome, which could convey a signal that errors are large and salient. Interestingly, the only finding of abnormal Pe in depression was observed in geriatric patients with depression who remained symptomatic after an 8-week treatment with escitalopram oxalate.[30] In light of the present and prior[28,29] Pe null findings, it is possible that disruption in later stages of error processing might emerge only in samples of treatment-resistant patients and/or geriatric patients with depression. Future studies will be needed to test this hypothesis.

Although the behavioral and scalp ERP analyses replicated prior reports of abnormal reactions to error in depression, the present study provided novel insights about the spatiotemporal dynamics of brain mechanisms that

underlie these abnormalities. Specifically, through an integration of a distributed source localization technique and functional connectivity analyses, we showed that depression is associated with (1) increased activation within midline regions that encompass the rostral ACC and the medial PFC 80 milliseconds after committing an error and (2) disrupted connectivity between the rostral ACC and the left dorsolateral PFC.

Increased posterror activation in the rostral ACC and medial PFC is intriguing when considering the functional roles of these regions. In prior studies, rostral ACC activation has been reported during (1) processing of negatively valenced stimuli in emotional Stroop tasks,[57-59] emotional distracters,[60] and errors associated with monetary loss[61]; (2) increased physiological reactions to behavioral stressors during a challenging Stroop task[62]; and (3) induction of sad mood.[63] Collectively, these findings underscore the role of the rostral ACC in affective responses to errors and in processing the subjective and/or emotional significance of events.[19,61,64,65]

The medial PFC (BA 10), on the other hand, has been strongly implicated in self-reflective judgments[66-70] and cognitive aspects of self-evaluation,[71] raising the possibility that this region plays a key role in automatic self-evaluations.[72] On the basis of these findings, we speculate that heightened rostral ACC and medial PFC activation after committing errors might reflect exaggerated affective appraisal of a perceived failure and potentiated self-relevant negative processing bias. Future studies are warranted to test this hypothesis and evaluate whether abnormalities within frontomedial regions may foster the emergence and maintenance of automatically activated cognitive schemata that might confer increased vulnerability to depression.[1]

The functional connectivity analyses revealed that, for the comparison group, activity within the rostral ACC and medial PFC region at the point of maximal ERN (80 milliseconds after committing an error) was positively correlated with subsequent left dorsolateral PFC activity (472 milliseconds after committing an error). Accordingly, healthy subjects who most strongly activated the rostral ACC 80 milliseconds after committing an error were also the ones recruiting most strongly the left dorsolateral PFC 472 milliseconds after committing an error. This pattern mirrors recent fMRI findings that show that dorsal ACC activation elicited by the Stroop interference predicted greater dorsolateral PFC recruitment, which in turn decreased the incongruency effect on the next trial.[54] The present findings provide strong support for the theory that in healthy participants the ACC and ERN signal that an outcome is worse than expected, facilitating the subsequent recruitment of cognitive control.[22-24] According to these conceptualizations, activity within the ACC and PFC regions should be positively correlated during the generation of adaptive behavioral adjustments. In prior research, the limited temporal resolution of fMRI has made it difficult to investigate the temporal unfolding of ACC and dorsolateral PFC interactions. To our knowledge, the present study is the first demonstration that activity within the rostral ACC and medial PFC at the point of the ERN predicts subsequent dorsolateral PFC activity and provides direct empirical evidence that supports the role of the ERN in the recruitment of executive control processes necessary for adaptive behavioral adjustments after mistakes.

Notably, among patients with MDD, those with the highest left dorsolateral PFC activation 472 milliseconds after committing errors showed more adaptive posterror behavioral adjustments (ie, higher accuracy and longer RTs after committing errors) compared with patients with MDD who failed to recruit the left dorsolateral PFC after mistakes. Interestingly, the behavioral differences emerged despite virtually identical depression severity (mean [SD] Beck Depression Inventory scores: 22.22 [9.46] vs 22.11 [9.45]). These findings are intriguing, particularly when considering the role of dorsolateral PFC regions in cognitive control[24] and emotional regulation,[73,74] as well as data indicating that relatively increased left PFC activity during resting states predict better physiological recovery after negative pictures.[75] Overall, these findings suggest that, in a subgroup of patients with MDD, dorsolateral PFC–based compensatory processes might protect against performance deterioration despite hyperresponsiveness to errors and rostral ACC and medial PFC hyperactivation during early stages of the information-processing flow. Since in healthy samples increased ERN amplitude has often, albeit not consistently, been associated with adaptive behavioral adjustments,[21,34,76] failure to recruit dorsolateral PFC–based cognitive control might explain the apparent contradictory finding of larger ERN but worse posterror behavioral adjustments in MDD. In summary, our findings support the claim that patients with depression may not be able to effectively recruit their dorsolateral PFC to account for changes in affective state or task difficulty[13] and thus help reconcile prior behavioral and ERP findings of abnormal error processing in depression.

Several limitations of the present study should be emphasized. First, although the source localization used in the present study has received considerable empirical support from more traditional tomographic methods (eg, fMRI,[44] positron emission tomography,[45] and intracranial recordings[46]), its relatively low spatial resolution is one of the primary limitations of this study. Second, although the ERN findings occurred well before the onset of the feedback cues, we cannot fully exclude the possibility that the reported results were partially affected by group differences in feedback processing (eg, failure on the part of the patients to disengage from negative feedback). Although future studies will be required to resolve this issue, the present findings replicate prior reports of increased ERN in paradigms with[28] and without[29] feedback. Thus, when seen within the framework of prior literature, it is parsimonious to interpret our findings as reflecting dysfunctional error processing in depression. Third, it is unclear how the present findings relate to recent evidence that decreased resting (ie, task-free) ventral ACC activity predicted impaired posterror behavioral adjustments in a nonclinical sample characterized by elevated depressive symptoms.[9] Future studies will be required to directly test the relationship between resting and task-related ACC activation in conjunction with abnormal error processing along a continuum of depression severity. These limitations notwithstanding, the present study sheds new light into the spatiotem-

poral dynamics of brain mechanisms underlying the dysregulated action-monitoring system in depression and suggests that rostral ACC and medial PFC hyperresponsiveness to internal representations of errors and failures to recruit cognitive control have the potential to explain abnormal responses to errors in MDD, as well as the emergence and maintenance of negative processing biases in depression.

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