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Resting Anterior Cingulate Activity and Abnormal Responses to Errors in Subjects With Elevated Depressive Symptoms: A 128-Channel EEG Study

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Abstract: Depression has been associated with dysfunctional executive functions and abnormal activity within the anterior cingulate cortex (ACC), a region critically involved in action regulation. Prior research invites the possibility that executive deficits in depression may arise from abnormal responses to negative feedback or errors, but the underlying neural substrates remain unknown. We hypothesized that abnormal reactions to error would be associated with dysfunctional rostral ACC activity, a region previously implicated in error detection and evaluation of the emotional significance of events. To test this hypothesis, subjects with low and high Beck Depression Inventory (BDI) scores performed an Eriksen Flanker task. To assess whether tonic activity within the rostral ACC predicted post-error adjustments, 128-channel resting EEG data were collected before the task and analyzed with low-resolution electromagnetic tomography (LORETA) using a region-of-interest approach. High BDI subjects were uniquely characterized by significantly lower accuracy after incorrect than correct trials. Mirroring the behavioral findings, high BDI subjects had significantly reduced pretask gamma (36.5–44 Hz) current density within the affective (rostral; BA24, BA25, BA32) but not cognitive (dorsal; BA24′, BA32′) ACC subdivision. For low, but not high, BDI subjects pretask gamma within the affective ACC subdivision predicted post-error adjustments even after controlling for activity within the cognitive ACC subdivision. Abnormal responses to errors may thus arise due to lower activity within regions subserving affective and/or motivational responses to salient cues. Because rostral ACC regions have been implicated in treatment response in depression, our findings provide initial insight into putative mechanisms fostering treatment response. *Hum Brain Mapp 27:185–201, 2006.* © 2005 Wiley-Liss, Inc.

Key words: cingulate cortex; treatment response; depression; emotion; Eriksen Flanker task; source localization; anhedonia; low resolution electromagnetic tomography; gamma activity

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INTRODUCTION

In the past decade there has been a surge of interest toward attaining a better understanding of the neural underpinnings and neuropsychological deficits of depression. Emerging from this research is a link between depression and wide-ranging neuropsychological deficits, particularly in attention, memory, and problem-solving tasks. Impairment in executive functions, which are critically needed for flexible problem solving, action monitoring, and adaptive behavioral modification, may be one of the core issues underlying cognitive deficits in depression [Austin et al., 2001; Veiel, 1997]. In line with this assumption, executive dysfunctions 1) have been reported in a wide range of patients, including depressed outpatients [Porter et al., 2003] and young patients with dysphoria [Channon and Green, 1999]; 2) predicted poor response to pharmacological treatment [Dunkin et al., 2000]; and 3) were still observed after symptom recovery [Beats et al., 1996; Paradiso et al., 1997].

Substantial progress in cognitive neuroscience has delineated an executive control system centered on the anterior cingulate cortex (ACC) and prefrontal cortex (PFC) critically implicated in governing information processing and response selection in situations requiring adaptive and flexible task performance, such as planning, error monitoring and correction, and response inhibition [Miller and Cohen, 2001; Posner and Dehaene, 1994]. In depression, abnormalities in this distributed network have been described [Davidson et al., 2002], highlighting candidate neural markers of executive dysfunctions that could lead to impaired problem solving, maladaptive behavioral regulation, and abnormal error monitoring. With respect to the ACC, structural [Ballmaier et al., 2004], neurochemical [Auer et al., 2000; Mirza et al., 2004], and functional [Beauregard et al., 1998; Bremner et al., 2004; George et al., 1997; Kumari et al., 2003; Mitterschiffthaler et al., 2003; Okada et al., 2003] abnormalities have been reported in depression.

In order to understand the potential role of ACC dysfunction in depression, it is important to stress that this region is anatomically and functionally heterogeneous, and that "affective" and "cognitive" subdivisions have been described [Bush et al., 2000; Devinsky et al., 1995; Vogt et al., 1995]. Accordingly, the affective subdivision 1) encompasses rostral and ventral areas of the ACC (areas 25, 32, 33, and rostral area 24); 2) has extensive connections with limbic and paralimbic structures; and 3) has been implicated in regulating visceral, autonomic, and emotional responses to stressful behavioral and emotional events. Conversely, the dorsal cognitive subdivision of the ACC (1) includes caudal area 24′, 32′ and the cingulate motor area; (2) has reciprocal connections with the dorsolateral PFC, parietal cortex, and supplementary motor areas; and (3) is involved in detection of response conflict and processing of cognitively demanding information. Echoing this anatomical data, recent neuroimaging studies of executive functions have uncovered important functional specialization within the ACC (Fig. 1A). Specifically, increased activation within dorsal ACC regions extending to the pre-SMA has been observed during conflict monitoring, which can be conceptualized as the online monitoring of conflict between concurrent processes or response competition [Botvinick et al., 2001; Bunge et al., 2002; Bush et al., 2003; Carter et al., 1998; Casey et al., 2000; Fassbender et al., 2004; Hazeltine et al., 2003; Kerns et al., 2004; MacDonald et al., 2000; Ruff et al., 2001]. In contrast, activation in more rostral and inferior regions of the ACC has been observed after error commission [Braver et al., 2001; Garavan et al., 2003; Kiehl et al., 2000; Laurens et al., 2003; Menon et al., 2001; Rubia et al., 2003; Ullsperger and von Cramon, 2001]. Data from recent event-related potentials (ERP) studies lends further support to the notion that dorsal ACC activity may index conflict monitoring that is dissociable from error detection and emotional evaluation of errors mediated by the rostral ACC [Luu et al., 2003; van Veen and Carter, 2002]. Collectively, these data suggest that, in depression, dysfunction in specific regions of the ACC could be associated with distinct functional impairments.

Interestingly, recent neuropsychological studies suggest that executive deficits in depression may be partially due to abnormal responses to negative feedback or oversensitivity to errors and perceived failure [Beats et al., 1996; Elliott et al., 1996, 1997b; Murphy et al., 2003; Steffens et al., 2001; but see Purcell et al., 1997 and Shah et al., 1999]. In one of these first studies, Beats et al. [1996] found that elderly depressed patients solved the same amount of problems as controls during a planning task, but once a mistake was committed a rapid deterioration of performance was observed [see also Steffens et al., 2001]. Elliott et al. [1996, 1997b] replicated and extended these findings by showing that abnormal response to negative feedback was (1) correlated with depression severity, (2) specific to depression, and (3) still present after clinical recovery, suggesting that it may be a trait-like marker of depression. Finally, Murphy et al. [2003]] found that misleading negative feedback disrupted patients' performance in visual discrimination and reversal tasks.

Although these findings invite the possibility that deficits in performance monitoring and abnormal responses to errors may represent a critical link between cognitive deficits and negative affect in depression, little is known about the underlying mechanisms and brain substrates. Thus, abnormal response to errors and negative feedback may arise due to dysfunctional performance monitoring and controlled response strategies for improving performance. Based on the neuroimaging literature reviewed above, these impairments could be linked to dysfunctions in the cognitive (dorsal) subdivision of the ACC. Alternatively, disrupted performance after errors may reflect abnormal affective reactions to internal or external cues signaling that one's own behavior was inappropriate; in this case, dysfunction in affective (rostral) ACC subdivision could be expected.

As an initial attempt to better characterize abnormal reactions to errors in depression, a modified version of the Eriksen Flanker task [Eriksen and Eriksen, 1974] was used in the present study to assess conflict monitoring and post-error behavioral adjustments in subjects with elevated levels of depressive symptoms. The rationale for using the Eriksen

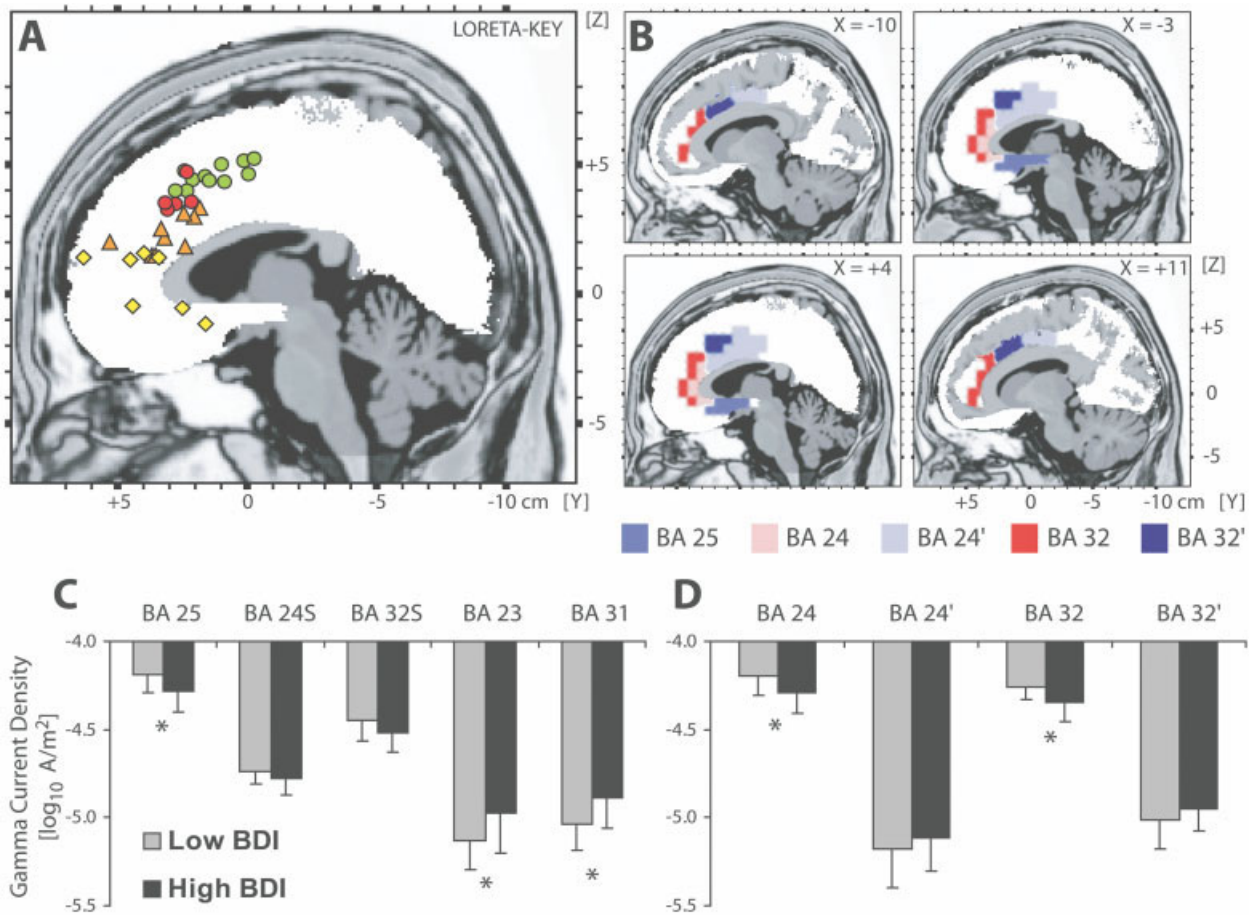

Figure 1.

A: Summary of neuroimaging studies highlighting functional specialization within the ACC. Green and red circles denote locations of increased activation during increased conflict monitoring and interference effects [Braver et al., 2001; Bush et al., 2003; Carter et al., 1998, 2000; Fassbender et al., 2004; Kerns et al., 2004; Kiehl et al., 2000; Laurens et al., 2003; MacDonald et al., 2000; Menon et al., 2001; Ruff et al., 2001]. The red circles denote activations associated with the compatibility (Eriksen) or conflict-adaptation (Gratton) effects in studies using the Eriksen task [Botvinick et al., 2001; Bunge et al., 2002; Casey et al., 2000; Hazeltine et al., 2003; van Veen et al., 2001]. Orange triangles denote activations during error commission, predominantly during go/nogo tasks [Braver et al., 2001; Fassbender et al., 2004; Garavan et al., 2003; Kiehl et al., 2000; Laurens et al., 2003; Menon et al., 2001; Rubia et al., 2003; Ullsperger and von Cramon, 2001]. Yellow diamonds denote the locations of rostral ACC regions that have been linked to treatment response in depression [Buchsbaum et al., 1997; Davidson et al., 2003; Mayberg et al., 1997; Pizzagalli et al., 2001; Saxena et al., 2003; Smith et al., 1999; Wu et al., 1999]. Note that this region is pregenual, i.e., slightly more inferior and anterior than the one implicated in error processing. **B:** Location and extent of various ACC subdivisions as defined by the Structure-Probability Maps [Lancaster et al., 1997] and displayed on the LORETA template. Coordinates in mm (MNI space); origin at anterior commissure; (X) = left(–) to right(+); (Y) = posterior(–) to anterior(+); (Z) = inferior(–) to superior(+). **C:** Mean (and SD) gamma current density within five general ACC regions for low (n = 16) and high (n = 17) BDI subjects. **D:** Mean (and SD) gamma current density within the affective and cognitive ACC subdivisions for low (n = 16) and high (n = 17) BDI subjects. *Group differences ($P < 0.05$).

task was twofold. First, prior studies using this or similar speeded-response tasks have shown that performance can be dissected into different subcomponents, including behavioral adjustments during or after high-conflict (incompatible) trials, as well as after errors. For example, subjects typically slow down their reaction time (RT) and improve their accuracy on trials following errors, suggesting that they utilize errors to monitor and improve their performance [Laming, 1968; Rabbitt, 1966b]. Second, and more importantly, neuroimaging studies have shown that dorsal and rostral ACC regions are primarily recruited during conflict monitoring and error detection, respectively, elicited by the Eriksen or similar speeded tasks [Botvinick et al., 1999; Casey et al., 2000; Hazeltine et al., 2003; Kerns et al., 2004] (Fig. 1A).

In addition to testing whether elevated levels of depressive symptoms in a nonclinical sample would modulate

conflict monitoring and post-error behavioral adjustments, the second aim of this study was to investigate whether resting electroencephalographic (EEG) activity within specific territories of the ACC assessed *before* the Eriksen task predicted behavioral performance, and whether specific dysfunction in such ACC regions would explain performance abnormalities in subjects with elevated depressive symptoms. Due to our a priori hypotheses regarding the ACC, EEG analyses were restricted to the theta (6.5–8 Hz) and gamma (36.5–40 Hz) band. This choice was justified by animal and human findings showing that: (1) the ACC is critically implicated in the generation and/or modulation of theta activity [Asada et al., 1999; Gevins et al., 1997; Ishii et al., 1999]; and (2) theta and gamma activity are functionally coupled [Bragin et al., 1995; Burgess and Ali, 2002; Duzel et al., 2003; Penttonen et al., 1998; Hajos et al., 2003; Fell et al., 2003; Schack et al., 2002] such as gamma bursts occur within periods of the theta phase [Buzsaki, 1996, for review]. Since both animal and human studies have also demonstrated links between ACC function and theta oscillations [Feenstra and Holsheimer, 1979; Nishida et al., 2004; Pizzagalli et al., 2003; Talairach et al., 1973] as well as between theta and gamma rhythms [Cape and Jones, 2000; Chrobak and Buzsaki, 1998; Mann and Paulsen, 2005] during task-free, resting periods, the focus on these EEG bands was warranted.

SUBJECTS AND METHODS

Participants

Forty-eight female subjects were recruited from the Introductory Psychology pool at the University of Wisconsin–Madison. Subjects were selected based on their score on the Beck Depression Inventory (BDI) [Beck et al., 1961], which was administered to 1,495 students. Control subjects were required to have a BDI score of six or less (low BDI group; n = 22), whereas subjects with elevated depressive symptoms were required to have a BDI of 18 or above[1] (high BDI group; n = 26). On the day of the experiment (on average, 30.35±19.42 days postscreening), high and low BDI subjects were required to have a BDI score of ≥12 and ≤4, respectively. Among the 48 subjects identified at the prescreening, 11 failed to meet the BDI criteria at the day of the experiment, and three had data loss for the Eriksen task due to equipment malfunctions. This resulted in a final sample of 17 subjects with high BDI scores (19.94 ± 6.75, range: 12–38) and 17 subjects with low BDI scores (1.53 ± 1.23, range: 0–4). For one low BDI subject, EEG data were lost due to technical problems. Participants were right-handed [Chapman and Chapman, 1987] and between the ages of 18 and 22. Subjects provided written informed consent to a protocol approved by the Human Subjects Committee of the University of Wisconsin, and received course credit for their participation.

Procedure

After obtaining written informed consent, the state forms of the Positive and Negative Affect Schedule [PANAS; Watson et al., 1988] and State Trait Anxiety Inventory [STAI; Spielberger et al., 1970] were administered to assess pre-task levels of affect. Next, preparations for the EEG recording were made. Following standard procedures, EEG recording consisted of eight contiguous 1-min trials (four with eyes open and four with eyes closed), alternating according to an order counterbalanced across subjects. After the EEG recording, instructions for the Eriksen task and a practice block were provided and subjects subsequently performed 10 blocks of the Eriksen task (without EEG recording).[2] After the task, subjects filled out the BDI, the state forms of the PANAS and STAI, the trait form of the PANAS, the Mood and Anxiety Symptom Questionnaire [MASQ; Watson et al., 1995], and a post-task questionnaire assessing subjects' experience with the task. Subjects were then debriefed and compensated.

Task

A modified version of the Eriksen Flanker task was used [Eriksen and Eriksen, 1974]. Each trial started with the presentation of a warning cue (a line) for 1,000 ms in the center of the screen, directly above where a target letter was to be presented. Immediately thereafter, one of four equiprobable letter strings (HHHHH, SSSSS, SSHSS, and HHSHH) was presented. The participants' task was to decide via button press whether the center letter in the string (the target letter) was an "H" or "S." The target-key press assignment was counterbalanced across subjects. In so-called compatible trials, the target letter was the same as the distracter letters (i.e., SSSSS, HHHHH), whereas in incompatible trials, the target and distracter letters were different (i.e., SSHSS, HHSHH). Trials were separated by 1,000 ms (ITI), and each participant completed 10 blocks (50 trials/block), separated by a short break, in which subjects received feedback about their performance (the number of correct responses in a particular block and the cumulative correct responses). The task lasted about 25 min.

Unlike the original Eriksen task, our task included a stimulus degradation function to increase task difficulty and thus elicit more errors. Task parameters (e.g., level of degradation) were first piloted on 18 independent subjects. The

[1]A BDI score of 12 is the cutoff point for mild depression [Kendall et al., 1987]. For the initial screening, a more stringent cutoff of 18 was used in order to increase the likelihood that the subjects in the high BDI group would still report elevated depressed symptoms at the experimental session.

[2]No EEG was recorded during the Eriksen Flanker task because the present study was designed to investigate (1) behavioral differences in conflict monitoring and error processing in subjects differing in depressive symptoms; and (2) relations between tonic, task-free ACC activity and individual differences in conflict monitoring and error processing.

center letter (target) degraded after each trial depending on the subject's performance according to the formula: [(Block Score + 1)/(Trial in Block + 15)], where *Block Score* is the running total correct score in a given block, and *Trial in Block* is the trial number in the block (range: 1–50). Therefore, if a participant maintained a high accuracy on the task (high *Block Score*), the stimulus was degraded more than if the participant maintained a lower accuracy.

Apparatus

The Eriksen task was run on a PowerMac 6214CD using PsyScope software [Cohen et al., 1993]. A 128-channel EEG was recorded using the Geodesic Sensor Net system (Electrical Geodesic, Eugene, OR). The sampling rate was 250 Hz (16 bit precision; bandwidth: 0.01–100 Hz), and the vertex electrode (Cz) served as recording reference. Amplifier gains and zeros were measured prior to each recording session. Following standard procedures [e.g., Luu et al., 2003; Tucker et al., 2003], impedances were kept below 50 KΩ.

Data Reduction and Analyses

Behavioral data

In addition to analyzing overall RT and accuracy, compatibility (Eriksen), post-error adjustment (Laming/Rabbit), and conflict-adaptation (Gratton) effects were computed, since these variables have been previously associated with conflict monitoring and post-error behavioral adjustments as well as ACC activation. Specifically, neuroimaging studies have shown that the compatibility [Botvinick et al., 1999; Bunge et al., 2002; Hazeltine et al., 2003; van Veen et al., 2001] and conflict-adaptation [Botvinick et al., 1999; Kerns et al., 2004] effects recruit the dorsal ACC, whereas error of commissions are typically associated with rostral ACC activation [e.g., Kiehl et al., 2000; Menon et al., 2001; Ullsperger and von Cramon, 2001] (Fig. 1A).

The *Compatibility (Eriksen) effect* refers to longer RTs and lower accuracies for incompatible than compatible trials [Eriksen and Eriksen, 1974] due to high response competition between the distracters and the center stimulus in an incompatible trial. Accordingly, this effect was computed as: [$RT_{\text{Incompatible trials}} - RT_{\text{Compatible trials}}$] and [$\text{Accuracy}_{\text{Compatible trials}} - \text{Accuracy}_{\text{Incompatible trials}}$]. The *post-error adjustment (Laming) effect* reflects longer RT but higher accuracy on trials following incorrect than correct responses [Laming, 1968], suggesting that subjects utilize errors to monitor and adjust their performance. Thus, this effect was computed as: [$RT_{\text{After incorrect trials}} - RT_{\text{After correct trials}}$] and [$\text{Accuracy}_{\text{After incorrect trials}} - \text{Accuracy}_{\text{After correct trials}}$]. Finally, the *Conflict-adaptation (Gratton) effect* reflects shorter RT and higher accuracy for incompatible trials following incompatible trials than incompatible trials following compatible trials [Gratton et al., 1992], likely due to increased recruitment of cognitive control during the preceding incompatible trial. Thus, this effect was computed as: [$RT_{\text{Incompatible trials following compatible trials}} - RT_{\text{Incompatible trials following incompatible trials}}$] and [$\text{Accuracy}_{\text{Incompatible trials following incompatible trials}} - \text{Accuracy}_{\text{Incompatible trials following compatible trials}}$].

Finally, to exclude the possibility that the post-error adjustment and conflict adaptation effects affected each other, control analyses, deconfounding the putative overlap between these effects, were performed. To this end, for the post-error adjustment effect, analyses were restricted to trials subsequent to incompatible trials; for the conflict adaptation effect, analyses of preceding compatibility were restricted to post-correct trials.

Baseline EEG data

After gain and zero calibration to microvolts, data were converted to Matlab-compatible format (MathWorks, Natick, MA). Using in-house software, EEG channels were first automatically checked for values greater than ±200 μV dynamic range and time frames exceeding this threshold were marked as artifact. Second, a zero-phase 60 Hz notch filter was used to remove power noise. Third, the 128-channel EEG data were manually scored for eye movement, blink, muscle, and other artifacts. Channels with artifacts exceeding more than 50% of the 1-min recording were marked as corrupted (3.30% of the channels) and were later interpolated using a spline interpolation method [Perrin et al., 1989]. Low and high BDI subjects did not differ in the number of sensors requiring interpolation (4.44 ± 3.52 vs. 3.53 ± 2.68, $t(31) = 0.84$, $P > 0.40$). Next, all available artifact-free 2048-ms EEG epochs from the eyes-closed trials were extracted (high BDI: 33.29 ± 23.47 vs. low BDI: 31.31 ± 22.00; $t(31) = 0.25$, $P > 0.80$), and subjected to standard spectral analyses via Discrete Fourier Transform (DFT) using a boxcar window [Brillinger, 1981]. As in our prior studies in clinical depression [e.g. Pizzagalli et al., 2001], only EEG data extracted from the eyes-closed trials were used for the analyses to (1) avoid potential artifacts deriving from eye movements, blinks, etc.; and (2) increase comparability across studies.

Subsequently, Low-Resolution Electromagnetic Tomography [LORETA; Pascual-Marqui et al., 1994, 1999] was used to estimate the three-dimensional intracerebral current density distribution of the theta (6.5–8 Hz) and gamma (36.5–44 Hz) EEG band. For the theta band, the 6.5–8 Hz frequency range was selected based on prior factor analysis EEG studies of resting EEG data [Kubicki et al., 1979]. This distributed source localization technique has recently received important cross-modal validation from studies combining LORETA with functional MRI (fMRI) [Mulert et al., 2004; Vitacco et al., 2002], structural MRI [Worrell et al., 2000], and PET [Pizzagalli et al., 2004; but see Gamma et al., 2004]. LORETA estimates location(s) of electrical source activity by assuming similar activation among neighboring neuronal sources (i.e., no assumption is made about the number of generating sources). This core assumption is implemented by computing the "smoothest" of all possible activity distributions. In the present study, a three-shell spherical head model [Ary et al., 1981] and EEG electrode coordinates derived from cross-registrations between spherical and re-

alistic head geometry [Towle et al., 1993] were utilized, which were both registered to the digitized MRI available from the Brain Imaging Centre, Montreal Neurologic Institute [MNI305; Evans et al., 1993; Collins et al., 1994].[3] According to the digitized MNI probability atlases, the solution space was restricted to cortical gray matter and hippocampi and included 2,394 voxels (voxel dimension: 7 mm^3). After conversion from MNI to Talairach coordinates [Brett et al., 2002], the Structure-Probability Maps atlas [Lancaster et al., 1997] was used to identify voxels belonging to distinct ACC subdivisions. Based on prior functional and anatomical data [Bush et al., 2000; Devinsky et al., 1995; Paus, 2001; Vogt et al., 1995], voxels belonging to the affective (BA25: 17 voxels, 5.83 cm^3; BA24: 12 voxels, 4.12 cm^3; BA32: 25 voxels, 8.58 cm^3) and cognitive (BA32′: 20 voxels, 6.86 cm^3; BA24′: 48 voxels, 16.46 cm^3) ACC subdivision were identified (Fig. 1B). To test the regional specificity of putative differences, posterior cingulate regions were also investigated (BA23: 12 voxels, 4.12 cm^3; BA31: 45 voxels, 15.44 cm^3).

LORETA computes current density as the linear, weighted sum of the scalp electrical potentials and then squares this value for each voxel to yield power of current density (unit: amperes per square meter, A/m^2). Before statistical analyses, for every subject and every band, the LORETA solution was normalized to a total power of 1 and log-transformed for normalization purposes. For each cluster, activity was finally averaged across the voxels.

Statistical Analyses

Self-report measures

For the state PANAS scale, a mixed analysis of variance (ANOVA) was run with *Time* (pre-, post-task), *PANAS Scale* (positive, negative) as repeated measures, and *Group* (low vs. high BDI subjects) as the between-subject factor. For the trait PANAS scale, a 2 (*PANAS Scale*) × 2 (*Group*) ANOVA was performed. For the STAI, a 2 (*Time*) × 2 (*Group*) ANOVA was run. For the MASQ, a 4 (*MASQ subscales*) × 2 (*Group*) ANOVA was performed. For the sake of brevity, only effects involving *Group* are reported.

Behavioral data

Mixed ANOVAs were run separately for RT and accuracy variables with *Condition* and *Group* as factors. To assess compatibility effects, the performance for compatible vs. incompatible trials was entered as the repeated measure. To investigate post-error adjustments, the performance following a correct or incorrect response was analyzed. Finally, to test conflict-adaptation effects, the performance for incompatible trials following a compatible vs. incompatible trials was considered.

To test whether group differences were further modulated by self-report measures of mood, Pearson correlation and hierarchical regression analyses between the MASQ scores and behavioral performance (compatibility, post-error adjustment, and conflict-adaptation effects) were performed. To limit the number of tests performed in these analyses only the MASQ scores were used as predictors. The MASQ was selected because it allows for an independent assessment of depressive and anxious symptoms, thus providing a test of the specificity of putative findings

Baseline EEG data

For the LORETA data, a mixed ANOVA analyses with Brodmann Area (BA; BA25, BA24S, BA32S, BA23, BA31) as repeated measure and *Group* as the between-subject factor was performed for each band separately. Note that "BA 24S" (= BA24+BA24′) and "BA32S" (= BA32 + BA32′) refer to the sums of the respective affective and cognitive subdivisions. To directly test putative group differences in cognitive vs. affective ACC subdivisions, a 3-way ANOVA with *BA* (BA24, BA32), *ACC subdivision* (affective, cognitive), and *Group* as factors was run. Finally, hierarchical regression analyses were run separately for low and high BDI subjects to test whether 1) resting activity in the affective ACC subdivision predicted individual differences in post-error adjustments after controlling for the activity in the cognitive ACC subdivision; and 2) activity in the cognitive ACC subdivision predicted compatibility or conflict-adaptation effects after controlling for the affective ACC subdivision.

RESULTS

Self-Report of Mood and Affect

For both the state and trait form of the PANAS, the *Group* × *PANAS scale* interaction was significant (both $F(1,32) > 13.40$, $P < 0.001$), reflecting significantly higher negative affect but significantly lower positive affect in high BDI subjects (Table I) at both the pre- and post-task assessment. Similarly, for the STAI only the *Group* main effect was significant ($F(1,32) = 13.62$, $P < 0.001$), due to higher state anxiety in high BDI subjects at both assessments. For the MASQ, higher scores in high BDI subjects, particularly in the two depression subscales, resulted in both the *Group* and the *Group* × *MASQ subscale* effects reaching significance (both $F(1,32) > 23.50$, $P < 0.001$).

Behavioral Data

Overall performance

As shown in Table I, no differences emerged in overall RT ($t(32) = -0.29$, $P > 0.70$) or accuracy ($t(32) = 0.48$, $P > 0.60$)

[3]Although the LORETA version used in the present study received important cross-modal validation through fMRI and PET [e.g., Mulert et al., 2004; Pizzagalli et al., 2004; Vitacco et al., 2002], it is important to stress that a number of factors likely weaken the spatial resolution of this approach. In future studies, the use of (1) a more complex head model (rather than a three-shell spherical head model); (2) individual anatomical scans (rather than a general brain template); and (3) individual digitization of electrode positions (rather than general positions), is expected to improve the spatial resolution of LORETA.

TABLE I. Self-report measures and behavioral performance in the Eriksen Task for low (N = 17) and high (N = 17) BDI subjects

	Low BDI*	High BDI*	*t*	*P*
Self-report measures				
BDI	1.53 ± 1.23	19.94 ± 6.75	11.06	0.001
PANAS-trait				
PA	34.47 ± 4.99	26.06 ± 4.96	−4.93	0.001
NA	16.24 ± 2.33	24.94 ± 6.53	5.17	0.001
PANAS-state[a]				
PA	28.03 ± 5.25	23.21 ± 5.25	−2.68	0.015
NA	13.91 ± 0.92	16.09 ± 2.53	3.33	0.005
STAI state[a]	28.82 ± 4.76	36.96 ± 7.74	3.69	0.001
MASQ				
GDA	14.24 ± 3.25	24.18 ± 8.71	4.41	0.001
AA	19.35 ± 3.46	31.88 ± 11.91	4.17	0.001
GDD	17.12 ± 4.00	34.82 ± 8.29	7.93	0.001
AD	43.82 ± 5.84	75.00 ± 11.76	9.79	0.001
Eriksen task				
Overall performance[b]				
RT (ms)	508.32 ± 52.88	502.68 ± 59.65	−0.29	0.77
Accuracy	0.84 ± 0.046	0.85 ± 0.039	0.48	0.64
Compatibility (Eriksen) effect[c]				
RT (ms)	6.06 ± 20.04	9.41 ± 24.49	0.44	0.66
Accuracy	−0.12 ± 0.11	−0.09 ± 0.11	1.04	0.31
Post-error (Laming) adjustment[d]				
RT (ms)	20.76 ± 19.10	26.59 ± 17.56	0.93	0.36
Accuracy	0.01 ± 0.052	−0.02 ± 0.030	−2.05	0.048
Conflict-adaptation (Gratton) effect[e]				
RT (ms)	0.59 ± 8.02	2.62 ± 16.00	0.47	0.64
Accuracy	−0.00 ± 0.03	0.01 ± 0.05	1.09	0.28

*Values are expressed as mean ± SD.

[a] For the state PANAS and STAI scales, values are averaged between the pre- and post-task assessment because no significant effects involving *Time* (pre- vs. post-task) emerged.

[b] Mean RT and accuracy (averaged across trial types).

[c] Compatibility effect: $[RT_{Incompatible\ trials} - RT_{Compatible\ trials}]$; $[Accuracy_{Compatible\ trials} - Accuracy_{Incompatible\ trials}]$.

[d] Post-error adjustment effect (including both compatible and incompatible trials): $[RT_{After\ incorrect\ trials} - RT_{After\ correct\ trials}]$; $[Accuracy_{After\ incorrect\ trials} - Accuracy_{After\ correct\ trials}]$.

[e] Conflict-adaptation effect (including both post-correct and post-error trials): $[RT_{Incompatible\ trials\ following\ compatible\ trials} - RT_{Incompatible\ trials\ following\ incompatible\ trials}]$; $[Accuracy_{Incompatible\ trials\ following\ incompatible\ trials} - Accuracy_{Incompatible\ trials\ following\ compatible\ trials}]$.

Note: BDI: Beck Depression Inventory [Beck et al., 1961]; PANAS: Positive and Negative Affect Schedule [PA: positive affect, NA: negative affect; Watson et al., 1988]; STAI: State Trait Anxiety Inventory [State form; Spielberger et al., 1970]; MASQ: Mood and Anxiety Symptom Questionnaire [Watson et al., 1995; GDA: General Anxiety; AA: Anxious Arousal; GDD: General Depression; AD: Anhedonic Depression].

scores, suggesting no general dysfunctions (e.g., attention, motivation) in high BDI subjects. In line with these findings, low and high BDI subjects did not differ in the amount (mean: 0.51 ± 0.02 vs. 0.51 ± 0.02) or variance (standard deviation (SD): 0.16 ± 0.01 vs. 0.16 ± 0.01) of stimulus degradation, which was contingent upon global performance in the task ($t(32) < 0.04$, $P > 0.90$).

Compatibility effect: Performance for compatible vs. incompatible trials

For RT, the ANOVA revealed a nearly significant effect of *Condition* ($F(1,32) = 4.06$, $P = 0.052$). As expected from prior studies [Eriksen and Eriksen, 1974], RT was longer for incompatible (508.85 ± 49.02 ms) than compatible (501.12 ± 66.18 ms) trials. The main effect of *Group* and the *Group* × *Condition* interaction were not significant ($F < 0.19$). Thus, high and low BDI subjects did not differ in their relative RT slowing during incompatible trials (compatibility effect: $t(32) = 0.44$, $P > 0.60$; Table I).

For accuracy, the ANOVA showed a significant effect of *Condition* ($F(1,32) = 32.15$, $P < 0.01$), which resulted from unexpectedly higher accuracy for incompatible (0.90 ± 0.060) than compatible (0.80 ± 0.076) trials. As above, the main effect of *Group* and the interaction were not significant ($F < 1.1$). Thus, high and low BDI subjects did not differ in their relative accuracy adjustments during incompatible trials (compatibility effect: $t(32) = 1.04$, $P > 0.30$; Table I).

Post-error adjustment effect: Performance following correct vs. incorrect responses

For RT, only the main effect of *Condition* ($F(1,32) = 56.65$, $P < 0.001$) was significant (all $F < 0.90$). As in prior studies [Laming, 1968; Rabbit, 1966a], this effect was due to significantly longer RT for trials following incorrect (524.79 ± 64.13 ms) than correct (501.12 ± 55.24 ms) responses. Thus, the two groups did not differ in RT slowing after errors (post-error adjustment: $t(32) = 0.44$; Table I).

For accuracy, the only significant effect emerging was the *Group* × *Condition* interaction ($F(1,32) = 4.22$, $P < 0.05$; all other $F < 0.80$), suggesting that high and low BDI subjects differed in their post-error adjustment effect (Table I). Critically, the *Group* × *Condition* interaction was confirmed also in the control analyses in which the post-error adjustment effect was restricted to trials subsequent to incompatible trials ($F(1,32) = 7.66$, $P < 0.009$; all other $F < 0.95$). As shown in Figure 2A, high BDI subjects had significantly lower accuracy after incorrect than correct trials ($t(16) = 2.41$, $P < 0.03$), an effect that was not present in low BDI subjects ($t(16) = -1.43$, $P > 0.15$). Moreover, high BDI subjects had significantly lower accuracy after incorrect trials than low BDI subjects ($t(32) = -2.22$, $P < 0.04$), whereas the two groups did not differ in their accuracy after correct trials ($t(32) = 0.55$, $P > 0.50$). On an individual level (Fig. 2B), 12 of the 17 high BDI subjects [binomial probability $P(12/17) < 0.05$] but only 5 of the 17 low BDI subjects [$P(5/17) < 0.05$] showed a negative post-error adjustment effect (= $\text{Accuracy}_{\text{after incorrect trial}} - \text{Accuracy}_{\text{after correct trials}}$), $\chi = 5.77$, $P < 0.05$.

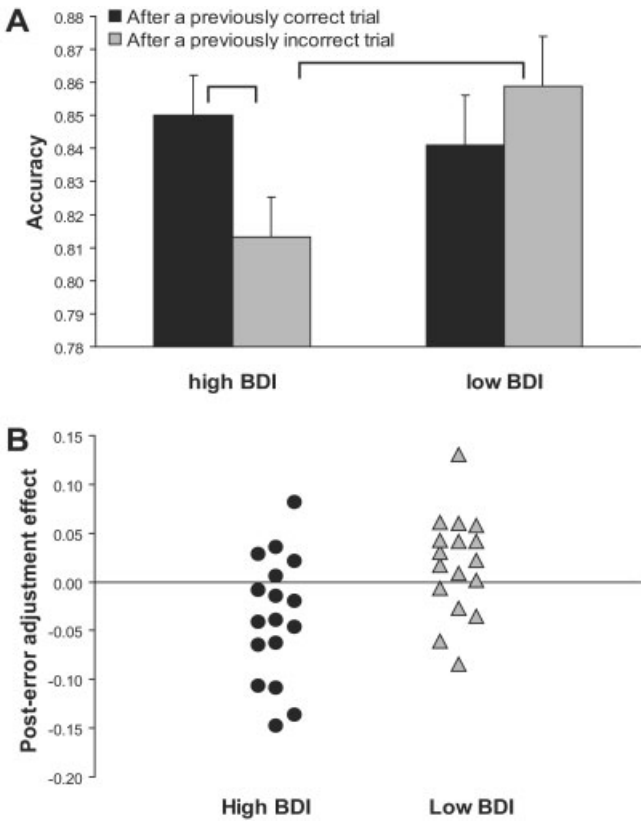

Figure 2.

A: Mean accuracy (and SE) after incorrect and correct trials for high BDI (n = 17) and low BDI (n = 17) subjects. **B:** Individual scores for the post-error adjustment (Laming) effect [$\text{Accuracy}_{\text{After incorrect trial}} - \text{Accuracy}_{\text{After correct trials}}$] for low (gray triangles) and high (dark circles) BDI subjects. To eliminate potential overlap between the post-error adjustment and conflict adaptation effects, values were derived from trials subsequent to incompatible trials.

Conflict-adaptation effect: Performance for incompatible trials following compatible vs. incompatible trials

For both RT and accuracy, no significant results emerged (all $F < 1.19$, all $P > 0.25$). Additionally, no significant effects emerged when the control analyses of preceding compatibility were restricted to post-correct trials (all $F(1,32) < 1.77$, all $P > 0.19$). Thus, high and low BDI subjects did not differ in their behavioral adjustment following incompatible trials (conflict-adaptation effect: $t(32) < 1.10$, $P > 0.30$; Table I).

Correlations Between Behavioral Measures and the Self-Report Measures of Mood

For high BDI subjects, Pearson correlations were run between behavioral measures (compatibility, post-error adjustment, and conflict-adaptation effects) and self-report measures of mood (MASQ subscales). (For low BDI subjects, the restricted range on the self-report measures prevented these analyses.) When considering RT, no significant correlations emerged (all $P > 0.12$). When considering accuracy, the post-error adjustment effect was negatively correlated with the Anhedonic Depression score ($r = -0.58$, $P < 0.015$; Fig. 3A) and with the General Depression score ($r = -0.50$, $P < 0.05$; Fig. 3B), whereas no reliable correlations emerged when considering the Anxious Arousal ($r = -0.16$, ns) or General Anxiety Scores ($r = -0.27$, ns). No significant correlations emerged between the MASQ scores and the compatibility (all $|r| < 0.34$, all $P > 0.17$) or the conflict-adaptation (all $|r| < 0.32$, all $P > 0.21$) effect.

Because the post-error adjustment effect is computed as [$\text{Accuracy}_{\text{after incorrect trial}} - \text{Accuracy}_{\text{after correct trials}}$], these correlations suggest that the higher the depressive symptoms, the lower the accuracy after incorrect trials compared to correct trials. Consistent with this interpretation, for high BDI subjects a negative correlation was observed between the Anhedonic Depression score and the accuracy after incorrect ($r = -0.61$, $P < 0.01$; Fig. 3C) but not correct ($r = -0.31$, $P > 0.20$) trials. The correlations involving incorrect and correct trials were significantly different ($Z = -1.94$, $P < 0.05$) [Meng et al., 1992]. Similarly, for high BDI subjects a significant negative correla-

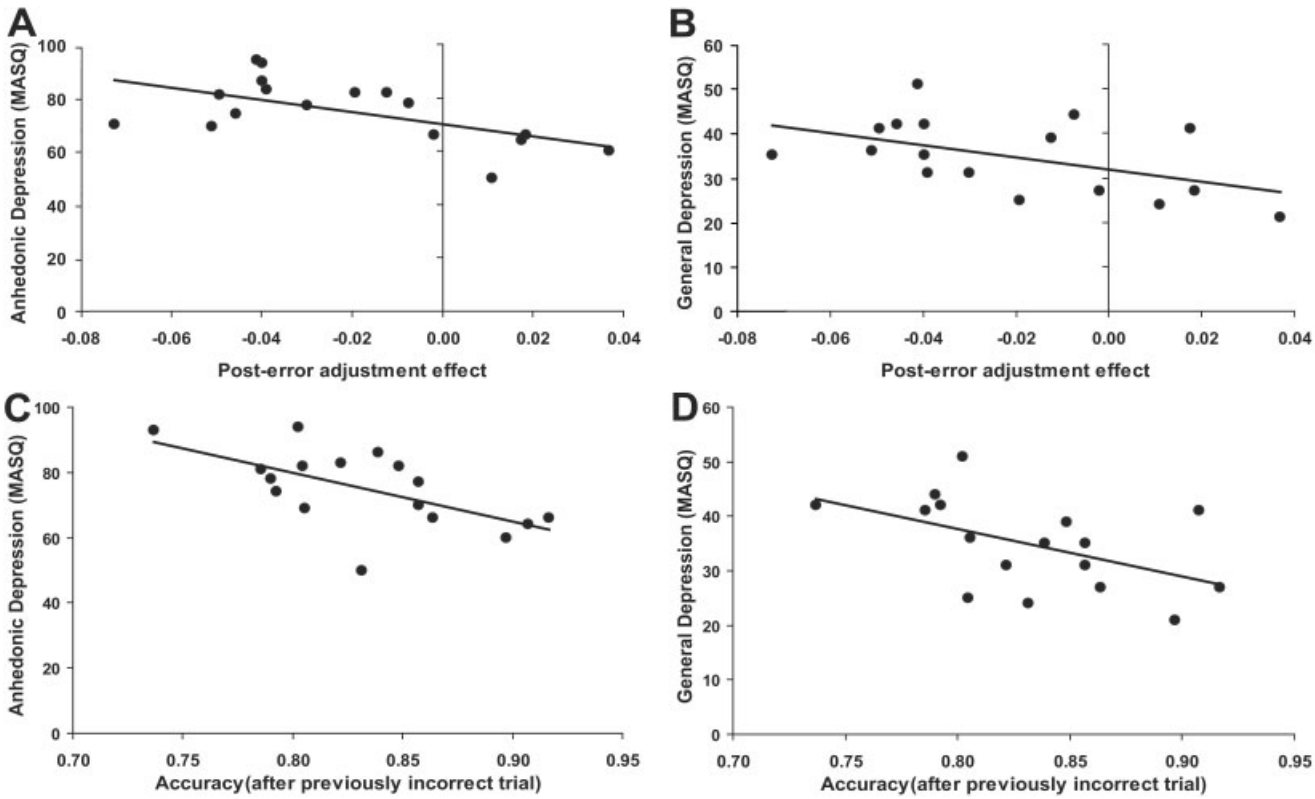

Figure 3.

Scatterplot and Pearson's correlation between (**A**) the post-error adjustment (Laming) effect and the MASQ Anhedonic Depression scores; (**B**) the post-error adjustment (Laming) effect and the MASQ General Depression scores; (**C**) the mean accuracy after incorrect trials and the Anhedonic Depression scores; and (**D**) the mean accuracy after incorrect trials and the General Depression scores. High BDI subjects only (n = 17).

tion emerged between the General Depression score and accuracy after incorrect ($r = -0.50$, $P < 0.05$; Fig. 3D) but not correct ($r = -0.24$, $P > 0.30$) trials. Yet these correlations were not significantly different ($Z = -1.60$, ns).

To assess the specificity of the link between depressive symptoms and diminished post-error adjustment effect, hierarchical regression analyses predicting the post-error adjustment effect (calculated with accuracy scores) were performed. In the first, trait negative affect (NA) score was entered in a first step followed by the Anhedonic Depression score. In the second analysis, the MASQ General Anxiety scores were entered first, Anxious Arousal scores entered second, and Anhedonic Depression scores were entered last. The third analyses tested whether the Anhedonic Depression scores predicted the post-error adjustment effect after controlling for General Anxiety, Anxious Arousal, and trait NA scores. Results showed that the Anhedonic Depression scores continued to explain unique variance in the post-error adjustment effect when controlling for trait NA scores, $\Delta R^2 = 0.27$, $\Delta F(1,14) = 6.72$, $P < 0.025$, both MASQ anxiety scales, $\Delta R^2 = 0.27$, $\Delta F(1,13) = 5.59$, $P < 0.035$, or all three measures of anxiety/negative affect, $\Delta R^2 = 0.25$, $\Delta F(1,12) = 5.08$, $P < 0.045$.

Baseline EEG Data

ANOVA analyses

Contrary to our prediction, the ANOVA conducted on theta current density with Brodmann Area (BA25, BA24S, BA32S, BA23, BA31) and *Group* as factors revealed no significant effects involving *Group* (all $F < 2.69$, all $P > 0.10$). For gamma, the main effect of *Brodmann Area* ($F(4,124) = 194.81$, $P < 0.001$), and most importantly, the *Group* × *Brodmann Area* interaction ($F(4,124) = 6,21$, Greenhouse-Geisser $\epsilon = 0.35$, $P < 0.01$) were significant. Post-hoc *t*-tests (Fig. 1C) revealed that, compared to low BDI subjects, high BDI subjects had higher gamma current density in the posterior cingulate cortex (BA23: $t(31) = 2.20$, $P < 0.035$; BA31: $t(31) = 2.66$, $P < 0.015$) but lower gamma current density in BA25 ($t(31) = -2.50$, $P < 0.020$); groups did not differ in BA24S ($t(31) = -1.46$, $P > 0.15$) or BA32S ($t(31) = -1.63$, $P > 0.10$). Highlighting the frequency specificity of the results, identical 2 × 2 × 2 ANOVAs performed on delta (1.5–6 Hz), alpha1 (8.5–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2

(18.5–21 Hz), and beta3 (21.5–30 Hz) revealed no reliable effects involving *Group* (all $F < 2.03$, all $P > 0.15$).

To investigate with more precision whether dysfunctional gamma activity was localized to cognitive or affective subdivisions of the ACC, a 3-way ANOVA with *BA* (BA24, BA32), *ACC subdivision* (affective, cognitive), and *Group* as factors was run. Apart from the main effects of *BA* and *ACC subdivision* and a significant *BA* × *ACC subdivision* interaction (all $F(1,31) > 22.53$, all $P < 0.001$), the only other significant result was the *Group* × *ACC subdivision* interaction ($F(1,31) = 7.49$, $P < 0.010$). Post-hoc tests (Fig. 1D) clarified that, compared to low BDI subjects, high BDI subjects had significantly lower gamma activity in the affective (BA24: $t(31) = -2.88$, $P < 0.007$; BA32: $t(31) = -2.19$, $P < 0.040$) but not cognitive (BA24′: $P > 0.15$; BA32′: $P > 0.30$) subdivisions of the ACC. As above, analogous 3-way ANOVAs run separately for delta, theta, alpha1, alpha2, beta1, beta2, or beta3 current density revealed no reliable effects involving *Group* (all $F < 2.69$, $P > 0.10$).

Regression analyses

For low BDI subjects, the first analysis predicted the post-error adjustment effect (calculated with accuracy scores), with gamma current density in the cognitive ACC subdivisions (BA24′, BA32′) entered as the first predictor followed by gamma current density in the affective ACC subdivisions (BA24). As expected, the post-error adjustment effect was not significantly predicted by gamma current density in the cognitive subdivisions (BA24′: $\beta = -0.25$; BA32′: $\beta = 0.07$; ns). However, pre-task gamma activity within the affective subdivision of the ACC (BA24) was a significant predictor of the post-error adjustment effect even after removing the variance associated with gamma activity within BA24′ and BA32′ ($\beta = 0.68$; $\Delta R^2 = 0.31$, $\Delta F(1,12) = 5.72$, $P < 0.035$), as shown in Figure 4. For high BDI subjects, the relation between BA24 gamma activity and the post-error adjustment effect was reversed. Thus, gamma within the affective subdivision of the ACC was a nearly significant negative predictor of this effect ($\beta = -0.51$; $\Delta R^2 = 0.20$, $\Delta F(1,13) = 3.36$, $P = 0.090$) after removing the variance associated with gamma activity within BA24′ ($\beta = 0.20$, ns) and BA32′ ($\beta = -0.18$, ns).

For both the low and high BDI subjects, regression analyses testing whether activity in the cognitive ACC subdivision predicted the compatibility or conflict-adaptation effects (calculated with both RT and accuracy scores) after controlling for the activity in the affective ACC subdivision were nonsignificant (all $\Delta F(1,13) < 2.17$, all $P > 0.15$).

Theta-gamma functional coupling

Apart from BA25 ($r = 0.24$, ns), all correlations between theta and gamma current density within a given cluster were significant (BA23: $r = 0.53$; BA24: $r = 0.59$; BA31: $r = 0.51$; BA32: $r = 0.51$; all $P < 0.002$; n = 33).

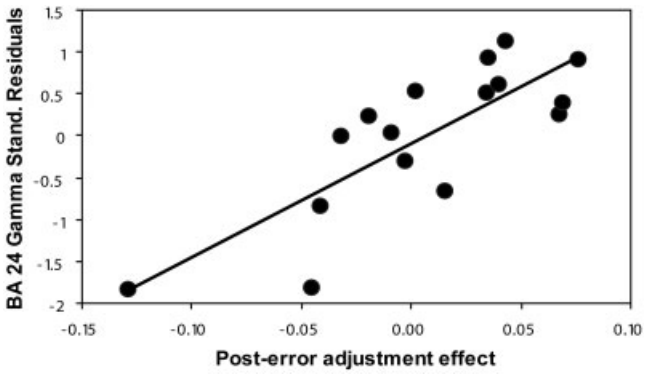

Figure 4.
Scatterplot and regression slope between the post-error adjustment (Laming) effect and (standardized) residuals of the gamma current density in the affective ACC subdivision (BA24) after removing variance associated with the cognitive ACC subdivision (BA24′ and BA32′). The Pearson's correlation between the post-error adjustment effect and BA24 gamma residuals is $r = 0.81$, $P < 0.005$. Low BDI subjects only (n = 16).

DISCUSSION

The present study had two related objectives. First, using an experimental task allowing us to independently assess conflict monitoring and behavioral adjustments after errors, we aimed to investigate with more precision putative mechanisms underlying executive dysfunctions in subjects with elevated depressive symptoms. Second, we tested whether resting EEG activity within specific territories of the ACC assessed *before* the task predicted performance on the Eriksen task, and more importantly, whether specific dysfunctions in such ACC regions would explain task performance deficits in subjects with elevated depressive symptoms.

The following findings emerged. First, unlike subjects with low BDI scores, subjects with elevated depressive symptoms showed lower accuracy in trials following errors than trials following correct responses (i.e., they had a significantly reversed post-error adjustment effect); compared to low BDI subjects, they also had significantly lower accuracy after incorrect, but not correct, trials. Further highlighting the specificity of this finding, high and low BDI subjects did not differ in their overall RT and accuracy scores, suggesting the absence of general dysfunctions in high BDI subjects. The two groups also did not differ in their behavioral adjustments during or following high-conflict (incompatible) trials (Eriksen and Gratton effects), suggesting that high BDI subjects had intact conflict monitoring abilities and were able to recruit cognitive control to overcome high-conflict situations. Second, among the high BDI subjects the post-error adjustment effect was negatively correlated with the Anhedonic Depression and the General Depression scores of the MASQ. These results suggest that the higher the depressive symptoms, the lower the accuracy after er-

rors. Regression analyses further clarified that Anhedonic Depression scores continued to explain unique variance in the post-error adjustment effect even after controlling for various measures of anxious symptoms and distress, suggesting that the findings were specific to depressive symptoms and not due to general psychopathology. Third, mirroring the behavioral findings of abnormal responses to errors despite intact conflict monitoring abilities, high BDI subjects had significantly reduced EEG gamma current density *before* the task within affective (rostral; BA24, BA25, BA32) but not cognitive (dorsal; BA24′, BA32′) subdivisions of the ACC. Fourth, for low, but not high, BDI subjects, pre-task resting gamma activity within the affective ACC subdivision (BA24) was a significant predictor of the post-error adjustment effect even after controlling for gamma activity within the cognitive ACC subdivisions. This latter finding extends a recent report that gamma band response over frontocentral regions during an unrelated task predicted later performance in a variety of neuropsychological tests probing the frontal lobe, including working memory and executive functioning (Karakaş et al., 2003). Finally, consistent with animal and human findings of functional coupling between theta and gamma activity [Bragin et al., 1995; Burgess and Ali, 2002; Duzel et al., 2003; Fell et al., 2003; Hajos et al., 2003; Penttonen et al., 1998; Schack et al., 2002] and reports of concurrent oscillations at theta and gamma frequencies in various limbic/prelimbic regions [Chrobak and Buzsaki, 1998; Fellous and Sejnowski, 2000; Fischer et al., 2002], these two EEG rhythms were positively and significantly correlated within the ACC.

Physiologically, decreased resting gamma current density in subjects with elevated depressive symptoms can be interpreted as a marker of decreased tonic activity in rostral ACC regions. This interpretation is based on a broad range of evidence, including human intracortical EEG findings of: (1) increased gamma activity during various mental processes [perception: Rodriguez et al., 1999; learning: Miltner et al., 1999; motor responses: Crone et al., 1998; memory: Fell et al., 2001]; (2) dose-dependent decreases of gamma activity during anesthesia [Uchida et al., 2000]; and (3) systematic decreases in gamma activity throughout the sleep/wake cycle (highest during wakefulness, intermediate during REM sleep, and lowest during slow wave sleep [Gross and Gotman, 1999]). Consistent with the notion that gamma is a direct indicator of activation, a recent study using concurrent EEG and PET measurements found that the gamma band had the highest number of positive correlations between current density and glucose metabolism [Oakes et al., 2004]. From a functional perspective, gamma oscillations are assumed to reflect large-scale integration of and synchrony among widely distributed neurons [Konig et al., 1995; Mann and Paulsen, 2005]. Accordingly, decreased resting gamma activity may highlight putative dysfunctional coupling and connectivity of underlying neuronal networks leading to impaired rostral ACC function, and, ultimately, to post-error adjustment deficits.

Candidate Mechanisms Underlying Abnormal Response to Errors in Depression

Behavioral studies have consistently shown that humans utilize errors and negative feedback to monitor their performance and adjust behavior accordingly [Laming, 1968; Rabbitt, 1966a,b]. In a seminal study, Rabbitt [1966b] found that subjects can detect and correct errors without receiving any external feedback concerning their performance, indicating that internal monitoring is sufficient to correct behavioral responses.[4] Together with prior findings of abnormal responses to negative feedback and oversensitivity to errors in clinical depression [Beats et al., 1996; Elliott et al., 1996, 1997b; Murphy et al., 2003; Steffens et al., 2001], the present findings suggest that such adaptive processes following errors are impaired in depression. Specifically, depressed and dysphoric subjects appear to be less efficient in utilizing the information conveyed by errors to monitor and guide subsequent performance. Unlike prior studies, however, the present findings offer initial insight about putative mechanisms underlying abnormal response to errors. Thus, whereas prior studies could not disentangle whether abnormal responses to errors was due to inefficiency in monitoring performance vs. abnormal affective reactions to perceived failure, the present behavioral and EEG findings suggest that the latter mechanism may be responsible. That is, at least in a nonclinical population of subjects with elevated depressive symptoms, conflict monitoring and dorsal ACC regions subserving this function were intact, whereas behavioral adjustments after errors and rostral ACC activity known to subserve error detection were dysfunctional.

Although the behavioral and EEG data nicely converge toward this interpretation, it is important to stress that the present version of the Eriksen task with target degradation was only partially successful in triggering conflict monitoring. Indeed, with the exception of the classic finding of RT slowing for incompatible trials, the compatibility (Eriksen) and conflict-adaptation (Gratton) effects were not significant, representing a main limitation of the present study. One possibility is that the target degradation used in this task required greater resources for visual perception at the expense of cognitive control, making the task not sensitive enough for triggering conflict monitoring. Moreover, the balanced (50%/50%) proportion of compatible and incompatible trials may have also prevented the development of a

[4]Consistent with this notion, high BDI subjects showed in the present study a negative correlation between post-error adjustments (calculated with accuracy scores) and scores on the post-task questionnaire items, "How well do you think you did on the task" (from 1, "very well" to 5, "very poor"; $\rho = -0.65$, $n = 17$, $P < 0.005$) and "How satisfied are you with your performance" (from 1, "very satisfied" to 5, "very unsatisfied"; $\rho = -0.68$, $n = 17$, $P < 0.005$). Thus, the bigger the dissatisfaction with own performance and the more negative evaluation of own performance, the lower the post-error adjustments. These findings suggest that the subjects were aware of committing errors.

powerful prepotent responses leading to increased conflict. These methodological limitations could explain the lack of correlation between activity in the cognitive ACC subdivision and the Eriksen/Gratton effects. In sum, whereas the present behavioral and EEG findings suggest that affective reactions to errors and their underlying neural correlates were dysfunctional in subjects with elevated depressive symptoms, future studies utilizing tasks capable of eliciting simultaneously strong conflict monitoring and error commission will be required for testing the precise mechanisms underlying executive dysfunction in depression. More importantly, studies measuring brain activity while participants are engaged in similar paradigms will be needed for conclusive interpretations about links between ACC dysfunction and abnormal responses to errors. Specifically, to more directly assess brain mechanisms underlying behavioral adjustments after errors in depression, it would be particularly interesting to investigate two event-related potential (ERP) components that have been implicated in action monitoring, the error-related negativity (ERN) and feedback-related negativity (FRN). These negative-going ERP waveforms occur maximally over frontocentral scalp regions after error commission and error feedback, respectively. Critically, rostral ACC regions have been implicated in their generation [e.g., van Veen and Carter, 2002], possibly through oscillatory processes in the theta range [Gehring and Willoughby, 2004; Luu et al., 2004]. Based on the present EEG findings as well as prior evidence emphasizing a functional coupling between theta and gamma oscillations (see above), it would be interesting to assess the putative role of gamma oscillations in the generation of the ERN and FRN. Consistent with our findings of abnormal error processing in high BDI subjects, ERN and FRN have been recently found to be abnormal in depression [Ruchsow et al., 2004; Tucker et al., 2003].

Finally, we note that, in the present study, no formal clinical interviews (e.g., Structured Clinical Interview for the DSM-IV, SCID) or detailed personality evaluations were performed to assess current psychopathology, family history of psychopathology, medication use, and personality traits. Because family history of psychopathology and personality traits (e.g., neuroticism) may partially contribute to individual differences observed between high and low BDI subjects, future studies should assess these important variables.

Limitations notwithstanding, the present findings indicate—we believe for the first time—that abnormal reactions to errors in depression are associated with reduced tonic activity within the rostral ACC, a brain region known to be implicated in error processing. More generally, the finding that post-error adjustments were predicted by resting activity within the rostral ACC sheds new light on brain substrates underlying individual differences in action monitoring. Collectively, the present and prior findings [Elliott et al., 1997b; Murphy et al., 2003] suggest that abnormal responses to perceived failure (errors) may be an important link between cognition and emotion affecting behavioral performance in depression that warrants further empirical inquiry.

Functional Role of the Rostral ACC

Intriguingly, this selective impairment in adjusting behavioral performance immediately after committing an error was accompanied by decreased baseline (i.e., pre-task) activity in ventral and rostral areas of the ACC (BAs 24/25/32) in the absence of differences in more dorsal regions (BA24′/BA32′). In light of its role in monitoring conflicting response demands, detecting errors, and evaluating the emotional significance of events, the ACC has been considered a site of convergence and integration between affective and cognitive processes [Bush et al., 2000; Mayberg, 1997; Davidson et al., 2002]. The rostral ACC, in particular, by acting as an interface between limbic/prelimbic and frontal regions, is assumed to integrate salient affective and cognitive information, such as that derived from error processing, and modulate attentional processes within more dorsal (cognitive) subdivision accordingly. In depression, such convergence of affective and cognitive processes as well as executive functions governing adaptive task performance may be dysfunctional, since decreased ACC activity has been reported during resting periods [Bench et al., 1993; Drevets et al., 1997; Mayberg et al., 1994], executive tasks [Bremner et al., 2004; George et al., 1997; Okada et al., 2003], and affective manipulations [Beauregard et al., 1998; Kumari et al., 2003; Mitterschiffthaler et al., 2003]. Thus, translating a large neuroimaging literature to the present findings, decreased rostral ACC activity in subjects with elevated depressive symptoms points to disturbed affective and/or motivational responses to errors [Bush et al., 2000; Gehring and Willoughby, 2002; Luu et al., 2003; Tucker et al., 2003; Whalen et al., 1998] and provides a possible physiological explanation for prior neuropsychological findings of abnormal responses to negative feedback or oversensitivity to errors and perceived failure [Beats et al., 1996; Elliott et al., 1996, 1997b; Murphy et al., 2003; Steffens et al., 2001].

Interestingly, in addition to decreased gamma activity within the rostral ACC, high BDI subjects had increased gamma activity within the posterior cingulate cortex (BAs 23/31), a finding, however, that was not hypothesized. Based on reports of increased posterior cingulate/retrosplenial activation during (1) trauma-related experiences [Fischer et al., 1996]; (2) somatic arousal [Critchley et al., 2000b]; and (3) processing of arousing stimuli [Critchley et al., 2000a], posterior cingulate hyperactivity in high BDI subjects may be associated with increased negative affect and somatic arousal. Notably, in clinical depression the posterior cingulate cortex has been found to be hypoactive during resting periods [e.g., Mayberg et al., 2000; Pizzagalli et al., 2002] and cognitive challenges [Elliott et al., 1997a], a pattern that normalized after symptom remission [Martin et al., 2001; Mayberg et al., 2000]. In light of these findings, posterior cingulate hypoactivity may thus be a state marker of clinical depression, particularly in patients with deficient autonomic/somatic arousal; subjects with elevated levels of

depressive symptoms, on the other hand, may show increased posterior cingulate activity, potentially due to elevated physiological arousal and increased negative affect. Future studies are needed to test these conjectures.

Potential Relevance to Mechanisms Underlying Treatment Response in Major Depression

Of note, prior findings in clinically depressed patients have shown that increased rostral ACC activity *before* treatment was a predictor of treatment response [Awata et al., 2002; Davidson et al., 2003; Mayberg, 1997; Pizzagalli et al., 2001; Saxena et al., 2003; Wu et al., 1999] (Fig. 1). Based on evidence suggesting that the affective (rostral) ACC subdivision is critical for assessing the presence of possible conflicts between the current functional state of the organism and cues that are motivationally and emotionally salient, we speculated that rostral ACC hyperactivation in treatment responders might reflect an increased sensitivity to affective conflict that may eventually foster treatment response [Davidson et al., 2002; Pizzagalli et al., 2001]. Successful affective conflict monitoring would in turn lead to a call for further processing and recruitment of additional cognitive control (likely provided by dorsolateral PFC regions) to resolve the conflict. The present finding of a lawful relation between resting rostral ACC activity and post-error behavioral adjustments is not only consistent with this speculation but provides initial insight into putative *mechanisms* underlying treatment response. As a result, we propose that, in eventual treatment responders, rostral ACC hyperactivity may foster the individual's ability to monitor the outcome of actions and adjust behavior when expected outcomes are violated. In treatment-nonresponders, adaptive action monitoring relying on the rostral ACC may be dysfunctional, particularly after negative outcomes. Future studies in clinical samples are clearly needed to test this hypothesis and the precise functional significance of rostral ACC hyperactivity, particularly since the rostral ACC regions associated with treatment response and error detection only partially overlap (Fig. 1A).

In summary, cognitive theories of depression [Beck et al., 1979] have suggested that people vulnerable to depression show enduring negative cognitive schemata and negative processing biases. Depressed and dysphoric subjects, particularly those with dysfunctional attitudes, have been found to display: amplification of the significance of failure [Wenzlaff and Grozier, 1988]; difficulty in suppressing thoughts associated with failure [Conway et al., 1991]; increased self-focus after failure feedback [Greenberg and Pyzszczynski, 1986]; and increased depressed mood after occurrence of a negative event [Abela and D'Alessandro, 2002] or negative social feedback [Henriques and Leitenberg, 2002]. Abnormal affective/motivational response to errors or perceived failures, as shown in the present study, is not only consistent with these findings but deepens our understanding of candidate mechanisms and brain correlates underlying negative processing biases in depression.

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