



Neural correlates of inhibitory deficits in depression

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ABSTRACT

The present study used functional magnetic resonance imaging to examine neural correlates of inhibitory dysfunction in individuals diagnosed with major depressive disorder (MDD). Twelve MDD participants and 12 never-depressed controls completed the negative affective priming (NAP) task in the scanner. Results indicated that, in depressed participants, increased activation in the rostral anterior cingulate cortex (rACC) is associated with inhibition of negative, but not positive, words; in contrast, in nondepressed participants, inhibition of positive, but not negative, words is associated with increased activation in the rACC. These findings indicate that abnormalities in neural function, especially in the rACC, may underlie difficulties experienced by depressed individuals in inhibiting negative thoughts. These results underscore the importance of continuing to examine the relation between cognitive and neural functioning in depression in order to gain a broader and more integrative understanding of this disorder.

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1. Introduction

Negative automatic thoughts and persistent rumination about negative events and negative mood states are hallmark features of depressive episodes. Cognitive models postulate that, by facilitating these negative thoughts, mood-congruent selective attention plays a central role in the etiology, maintenance, and recurrence of depression (Beck, 1976; Teasdale, 1988). Research indicates that selective attention involves at least two separate mechanisms: (a) orientation toward relevant stimuli; and (b) active disengagement from irrelevant stimuli through inhibition (Posner, 1995; Milliken and Tipper, 1998). In this context, investigators have suggested that depressed individuals are not biased in their initial orientation toward negative stimuli, but instead, have difficulty disengaging their attention from this material (Joormann, 2004; Joormann et al., 2007).

To examine the formulation that inhibitory deficits underlie attentional biases observed in depression, researchers have recently used the negative affective priming (NAP) task (Joormann, 2005; Goeleven et al., 2006). In negative priming studies, participants typically take longer to respond to a stimulus that they were previously instructed to ignore, or to a semantically related stimulus. This increased response latency is referred to as the negative priming effect, and is postulated to be caused by active inhibitory processes that keep

previously irrelevant stimuli from entering working memory (Milliken and Tipper, 1998; Tipper, 2001). In the NAP task, the negative priming effect is observed when ignoring an emotional stimulus results in a delayed response to a stimulus of the same valence that is presented as a target in a subsequent trial. This task, therefore, assesses individual differences in the inhibition of irrelevant emotional material.

Investigators have demonstrated that individuals diagnosed with current or past major depressive disorder (MDD), as well as dysphoric individuals, exhibited diminished negative priming (reflecting reduced inhibition) for negative words, compared to participants who had never been depressed (Joormann, 2004; Goeleven et al., 2006). Reduced inhibition has also been found to be associated with the tendency to ruminate in response to negative events (Joormann, 2006), suggesting that inhibitory deficits underlie the rumination associated with depression.

These studies suggest that inhibitory deficits play an important role in the onset and maintenance of depression; the neural correlates of these deficits, however, have not yet been identified. An extensive body of literature implicates the anterior cingulate cortex (ACC) in normal inhibitory processing (e.g., Bush et al., 2000; Nieuwenhuis et al., 2003; Leung et al., 2008). More relevant to the present study, activation in the most anterior part of the ACC, the rostral ACC (rACC), has been found in healthy participants while they performed affective versions of tasks involving inhibitory processes, such as the Stroop (Bush et al., 2000) and the go/no-go (Shafritz et al., 2006) tasks. Interestingly, Mayberg (1997) places the rACC at the center of her limbic-cortical dysregulation model of depression. It is possible, therefore, that inhibitory deficits observed in depression are associated with abnormalities in rACC functioning.

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Indeed, Wagner et al. (2006) found that during the interference condition of the Stroop color-word task, depressed participants showed greater activity in the rACC than did healthy controls.

Thus far, however, only a few studies have specifically examined the role of the rACC in the deficits in inhibition of *emotional* material observed in depression. Although George et al. (1997) found no difference in neural activation between mood-disordered and healthy participants during an emotional Stroop task, Mitterschiffthaler et al. (2008) found greater rACC activation in depressed than in healthy participants for negative words on this task. Similar results were obtained by Elliott et al. (2002), who reported that whereas healthy controls showed greater activation in the rACC than did depressed participants when they responded to happy target words on a go/no-go task, this pattern was reversed for sad target words. Although these results suggest that the rACC is involved in the attentional biases observed in individuals diagnosed with MDD, it is difficult to draw strong conclusions about inhibitory processes because these studies used block designs, which make it impossible to isolate activation patterns associated with the inhibitory component of the tasks and, therefore, to determine whether rACC abnormalities are associated with specific deficits in inhibitory processing.

The goal of the present study was to examine the relation between rACC activity and inhibitory deficits for negative material in depression. Given previous findings of rACC involvement in selective attention tasks, we predicted that depressed participants would show greater rACC activation than would their nondepressed counterparts when attempting to inhibit negative stimuli. Because previous studies did not find behavioral differences between depressed and nondepressed individuals in negative priming for positive words (e.g., Joormann 2004, 2005), we did not expect to find group differences in rACC activation during inhibition of positive stimuli.

2. Materials and methods

2.1. Participants

Participants were recruited through advertisements in the local community and from two outpatient psychiatry clinics. Participants were first screened with a telephone interview to establish that they were fluent in English and were between 18 and 60 years of age. Trained interviewers administered the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1995) to participants during their first session in the study. Based on a random sample of 15 diagnostic interviews, inter-rater reliability for the SCID was $k = 0.96$. Participants were included in the depressed group if they met the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (DSM-IV; American Psychiatric Association, 1994) criteria for MDD and were not currently taking antidepressant medication. The healthy control (HC) group consisted of individuals with no current or past Axis I disorder. Exclusion criteria included severe head trauma, color blindness, learning disabilities, current panic disorder, psychotic symptoms, bipolar disorder, and alcohol or substance abuse within the past 6 months. Finally, participants also completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), a 21-item, self-report measure of the severity of depressive symptoms.

Participants comprised 12 unmedicated individuals diagnosed with MDD and 12 HC individuals matched for age, gender, and handedness. They participated in the functional magnetic resonance imaging (fMRI) session, conducted within 2 weeks of the SCID administration. This study was approved by the human subjects committee at Stanford University and informed consent was obtained from all participants.

2.2. Procedure

The fMRI session took place at the Richard M. Lucas Center for Magnetic Resonance Spectroscopy and Imaging. To familiarize themselves with the NAP task, participants first completed a set of practice trials on a computer located outside of the scanner room. Once in the

scanner, task instructions and stimuli were back-projected onto a screen placed approximately 6 in. from the participants' eyes.

Blood oxygenation level dependent (BOLD) signal changes were measured while participants completed the NAP task in the scanner. They were instructed that two words would be presented, one above the other, one word in blue letters and one in red letters. They were instructed to look only at the blue (target) word, ignoring the red (distracter) word, and to make affective evaluations of the target words (positive or negative). They were asked to evaluate the target words as quickly and as accurately as possible, and to respond by pressing an assigned key on a button box, using only their right hand. Participants were instructed to focus on the target word and ignore the distracter word for as long as the words remained on the screen. All displays included a positive and a negative word.

Following these instructions, a fixation cross appeared and remained in the middle of the screen for 2 s, signaling the beginning of the task. Immediately following the disappearance of the fixation cross, a prime display (a distracter word in red letters and a target word in blue letters) was presented for 1 s. The spatial position of the target and distracter word (top or bottom word in the display) was randomly assigned in each display. When the display disappeared a fixation cross was again presented (this time for 1 s), after which the next display (probe) was presented. Presentation of the probe display (1 s) was also followed by a fixation cross (1 s). A distinction between prime and probe displays was made only for data analysis; participants were not aware of this distinction. Each trial consisted of a prime display, a fixation cross, followed by a probe display, and another fixation cross. Trials in which negative priming is expected to occur, i.e., trials in which the target word in the probe display has the same valence as the distracter word in the prime display, are referred to as negative priming (NP) trials. Trials in which the target in the probe display does not have the same valence as the distracter word in the prime display are referred to as control (CTL) trials (see Fig. 1). After seeing the instructions, participants completed 160 trials, presented across two runs of 80 trials each. The order of trials within each run was pseudo-randomized in a way that prevented presentation of the same type of trial more than three consecutive times. Reaction times (RTs) and responses were recorded for all stimuli.

2.3. Stimuli

Words used in the NAP task were adjectives selected from the Affective Norms for English Words (Bradley and Lang, 1999) according to their valence ratings. Adjectives with a rating of 7 or more on a

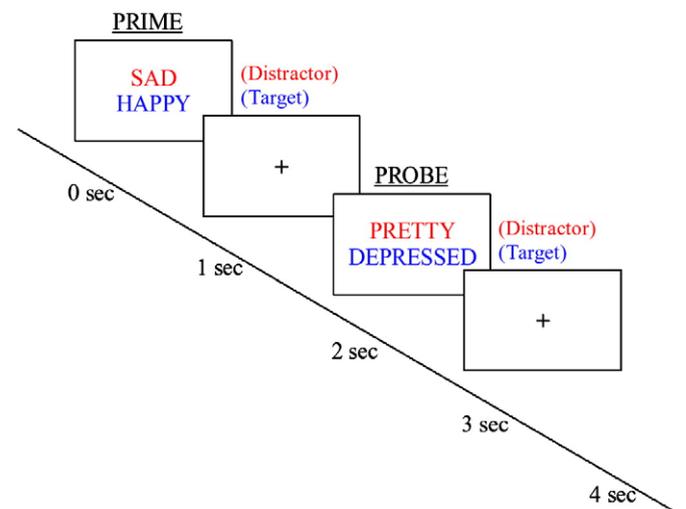


Fig. 1. Negative affective priming design. A trial consists of a prime display and a probe display. Valence of the probe target can either be the same as the prime target (CTL trials) or the same as the prime distracter (NP trials). Adapted from Joormann (2004).

9-point scale were considered to be positive, and adjectives with a rating of 4 or lower were considered to be negative. Positive and negative adjectives were matched on average length, $t(106) < 1$, frequency, $t(104) = 1.91$, and arousal, $t(106) < 1$, all P s > 0.05 .

2.4. Image acquisition

Images were acquired on a 1.5 Tesla system (General Electric, Milwaukee, WI). Twenty-four slices (4 mm thick) were acquired every 2 s (TR = 2000 ms) in a horizontal axial plane. These T2*-weighted functional images were acquired using a spiral-in/out pulse sequence (TE = 40 ms, flip = 70°) designed to minimize signal dropout at the base of the brain (Glover and Law, 2001). Each run was composed of 187 TRs (scan time = 6 min 14 s). The first seven TRs were added to account for the magnet stabilization period and were not included in the analyses. They corresponded to the initial two-second fixation cross display and three NAP trials included to allow time for participants to adjust to the button box (data from these first three trials were not included in the analyses). To facilitate localization and co-registration of functional data, high-resolution structural images were acquired sagittally using a T1-weighted spoiled grass sequence (TE min, flip = 15°, bandwidth = 15.63, slice thickness = 1.5 mm, FOV = 22 cm, scan time = 10 min 41 s).

2.5. Imaging data analysis

Imaging data were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Voxel time series were interpolated to correct for non-simultaneous slice acquisition within each volume. Images for all subjects were realigned to correct for artifacts due to small head movements with AFNI's motion correction algorithm (Fourier interpolation, two-pass). Images were then convolved in space with a three dimensional isotropic Gaussian kernel (full-width at half-maximum = 6 mm) to improve the signal to noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization. Finally a high-pass filter (cut-off frequency = 0.011 Hz) was used to remove possible effects of low frequency changes (e.g., signal drift). Structural and functional images for each participant were co-registered by hand, realigned on the anterior commissure–posterior commissure (AC–PC) axis, and warped into a standard brain atlas (Talairach and Tournoux, 1988).

Each participant's hemodynamic response function (HRF) was convolved with a canonical hemodynamic gamma-variate response function (Cohen, 1997). Contrast analyses were used to compare brain activation during negative priming and in the absence of negative priming. To determine activation associated with inhibition of positive and negative words, activation during CTL trials was subtracted from activation during NP trials, separately for trials with positive and negative probe targets. Effects at every voxel were estimated using the general linear model. Voxel values for each contrast yielded individual statistical parametric maps of the t statistic, which were subsequently transformed into Z scores. For each task, average statistical parametric maps were created, and within-group t tests were conducted to

compare activation during NP and CTL trials, for positive and negative probe targets separately. For between-group comparisons, we conducted a two-way (group repeated over valence) analysis of variance (ANOVA).

An *a priori* search strategy was used for each analysis, and a small volume correction was conducted in the rACC. Boundaries for the rACC were drawn based on those described by Bush et al. (2000) and Pizzagalli et al. (2001). The mask used for this ROI contained 183 voxels and had the following boundaries (Talairach and Tournoux (1988) coordinates for the right rACC): $L = 1$, $R = 15$, $A = 54$, $P = 6$, $S = 21$, $I = -13$. Monte Carlo simulations were used to determine that for this ROI a minimum cluster size of 13 voxels used in combination with an individual voxel probability threshold of $P < 0.05$ was equivalent to a ROI-wise probability threshold of $P < 0.05$, corrected for multiple comparisons. For the whole-brain *post hoc* analyses, the same procedure was used to determine that a minimum cluster size of 13 voxels and an individual voxel threshold of $P < 0.001$ were needed to achieve a family-wise probability threshold of $P < 0.001$.

3. Results

3.1. Participant characteristics

Demographic and clinical information about the participants is presented in Table 1. There were no significant differences between the depressed and nondepressed participants in age, $t(22) < 1$, or years of education, $t(20) < 1$. As expected, depressed participants had significantly higher scores on the BDI-II than did control participants, $t(22) = 9.25$, $P < 0.001$. On average depressed participants had experienced 3.8 past episodes, with the first episode occurring 16.4 years prior to their participation in this study. At the time of assessment their current episode had lasted an average of 12.8 months. Although none of the depressed participants was taking antidepressants at the time of the study, six had taken antidepressants in the past.

3.2. Behavioral data

RT data were analyzed following procedures described by Joormann (2004). Outlying RT scores (below 300 and above 2000 ms) were eliminated from the analyses, and only correct responses were analyzed (see Fazio, 1990). Depressed and nondepressed participants did not differ significantly in response accuracy, $t(22) < 1$. A three-way (group [MDD, HC] repeated over valence [positive, negative] and condition [CTL vs. NP trials]) ANOVA conducted on the RT data yielded a significant effect only for valence, $F(1,22) = 41.07$, $P < 0.001$; participants in both groups took longer to respond to negative than to positive probe targets. Neither the main effects for group and trial type nor the interactions were significant (all P s > 0.05). RT data for each group are presented in Table 2.

3.3. fMRI data

Activations during negative priming (inhibition) were contrasted with activations in the absence of negative priming (no inhibition) for

Table 1
Clinical and demographic characteristics of participants.

	HC group	MDD group
	<i>M</i> (S.D.)	<i>M</i> (S.D.)
Age	34.4 (11.7)	33.8 (9.9)
Gender (female; male)	8F / 4M	6F / 6M
Education (years)	16.1 (4.4)	15.8 (3.2)
Depression severity (a)	1.0 (1.6)	29.0 (10.4)

HC = healthy control; MDD = major depressive disorder; (a): Beck Depression Inventory-II score.

Table 2
Group reaction times (ms) for each condition.

	HC group	MDD group
	<i>M</i> (S.D.)	<i>M</i> (S.D.)
CTL trials – positive	682.0 (91.3)	737.4 (102.1)
CTL trials – negative	732.5 (97.2)	776.8 (90.1)
NP trials – positive	704.4 (92.0)	740.3 (84.8)
NP trials – negative	734.3 (86.2)	793.7 (85.1)

CTL = control; NP = negative priming; HC = healthy control; MDD = major depressive disorder.

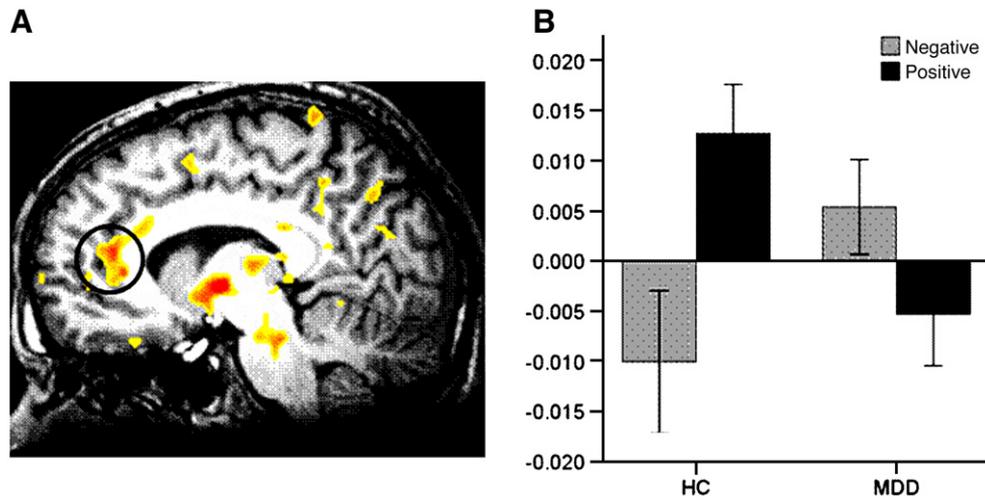


Fig. 2. Group by valence interaction during negative priming. Significant interaction was found in the right rACC (circled in A). Percent signal change associated with inhibition of positive and negative words in the right rACC is presented in B. HC = healthy control; MDD = major depressive disorder.

positive and negative words. A two-way (group repeated over valence) ANOVA yielded a significant interaction of group and valence in the right rACC (BA 32; see Fig. 2). In the nondepressed group, increased activation in this region was associated with inhibition of positive, but not of negative, words. The opposite pattern of results was obtained in the MDD group: increased activation in right rACC was associated with inhibition of negative words, but not with inhibition of positive words. Consistent with these findings, we found a significant negative correlation ($r = -0.48$; $P = 0.017$) between rACC activation for positive words and severity of depressive symptoms as measured by the BDI-II.

Subsequent whole-brain analyses indicated that, in the MDD group, inhibition of negative words was also associated with a significant increase in activation in the left putamen; there were no significant activations in the MDD group for positive stimuli. There were no additional activations associated with inhibition of either positive or negative stimuli in the nondepressed participants. Results from the contrast analyses are presented in Table 3.

4. Discussion

Previous research has demonstrated that depression is associated with difficulties inhibiting the processing of emotional material (Joormann, 2004; Goeleven et al., 2006). Importantly, these studies have proposed that these inhibitory deficits play a significant role in the maintenance of

depressive episodes (Joormann et al., 2007). The present study was designed to examine neural correlates of these deficits in the inhibition of emotional material and, more specifically, to investigate whether these deficits are related to abnormalities in rACC activation. Currently depressed and never-depressed participants completed the NAP task, which assesses the ability to inhibit the processing of emotional words, while their BOLD response was recorded.

Consistent with our hypothesis, inhibition of negative stimuli was associated with increased activation in the rACC in the depressed, but not in the nondepressed, participants. This finding suggests that depressed individuals' difficulty disengaging attention from negative stimuli is related to anomalous functioning in rACC. This result is consistent with data reported recently by Mitterschiffthaler et al. (2008), who found that depressed individuals exhibited greater rACC activation than did nondepressed individuals when responding to negative words in an emotional Stroop task. The present results extend the findings of Mitterschiffthaler et al. by demonstrating increased rACC activation in depression is specific to inhibition of negative words; MDD participants did not exhibit greater rACC activation during inhibition of positive stimuli.

Taken together, these results underscore the links among depression, inhibition of negative material, and abnormalities in rACC functioning. The rACC is involved in tasks that require selective attention and conflict monitoring (Bush et al., 2000; Shafritz et al., 2006), and is a critical component in neural models of depression, particularly with respect to assessing the emotional salience of stimuli (Mayberg, 1997). In this context, the increased activation of this area in response to negative irrelevant material in depression could reflect both the increased salience of this material for the depressed participants, leading to increased conflict when negative material has to be ignored, and the difficulties experienced by these participants when they attempt to override automatic responding to these salient stimuli. Indeed, previous work has implicated the engagement of rACC in conflict monitoring and overriding responses (Botvinick et al., 1999), and has documented the role of rACC in solving interference from irrelevant emotional material (Etkin et al., 2006).

Importantly, in the current study rACC activation was associated with inhibition of positive stimuli in HC but not in MDD participants. Although not predicted, this double dissociation is important in suggesting that depression is associated with abnormal processing not only of negative, but also of positive, stimuli. This formulation is supported by correlational analyses showing that more severe depressive symptoms are associated with lower activity in the rACC during inhibition of positive words. Indeed, some authors have suggested that depressed individuals not only preferentially process negative stimuli, but also lack a bias for the preferential processing of

Table 3
ANOVA results.

Contrast	Region	BA ^a	K ^b	Coordinates ^c			Z score	Corrected P value
				x	y	z		
Group	None	–	–	–	–	–	–	
Valence	None	–	–	–	–	–	–	
Group × valence	R. rACC	32	192	15	38	16	3.85	0.001
<i>HC group:</i>								
Positive words	R. rACC	32	31	5	36	19	3.05	0.001
Negative words	None	–	–	–	–	–	–	–
<i>MDD group:</i>								
Positive words	None	–	–	–	–	–	–	–
Negative words	R. rACC	32	19	8	41	4	2.67	0.013
	L. putamen		13	-19	8	1	3.91	0.001

Brain activations associated with negative priming as a function of group and word valence.

L = left; R = right. HC = healthy control; MDD = major depressive disorder.

^a Brodmann's area.

^b Cluster size (voxels).

^c Talairach coordinates (mm).

positive stimuli (see Leppänen, 2006). Our findings suggest that while depressed participants recruit rACC when inhibiting negative stimuli, healthy individuals recruit this brain area when inhibiting positive stimuli. These findings may reflect depression-associated differences in the relative difficulty of disengaging from negative and positive material and, thus, support our interpretation of increased rACC activation as reflecting greater difficulty in disengaging from a stimulus.

It is noteworthy that investigators have found that greater activation in the rACC during a depressive episode predicts better response to treatment (e.g., Ebert et al., 1991; Mayberg et al., 1997; Wu et al., 1992, 1999; Pizzagalli et al., 2001; Davidson et al., 2003). Because these studies focused on resting-state metabolism or on rACC activation during passive viewing of emotional stimuli, while the present study focused on rACC activation during the effortful inhibition of negative stimuli, it is not clear whether the current findings are related to clinical outcome in depression. It remains for future research, therefore, to examine more explicitly whether the magnitude of rACC activation during the inhibition of negative stimuli predicts treatment response in MDD.

The whole-brain analyses revealed that inhibition of negative words was also associated with increased activation in the putamen in depressed participants. Although some investigators have found depressed participants to be characterized by reduced putamen activity during selective attention tasks (e.g., Halari et al., 2009), it is important to note that these findings were obtained with tasks using emotionally neutral material. Interestingly, our findings are consistent with those reported by Surguladze et al. (2005), who found putamen activation in depressed individuals to be associated with passive viewing of negative stimuli. Thus, even though participants were instructed to ignore the negative distracters, we obtained activation in the present study in a neural structure that has been found to be activated by passive viewing of negative material in MDD. This result provides further support for our hypothesis that MDD participants had difficulty disengaging from the processing of negative material and suggests that depression is associated with increased activation in neural regions, such as the putamen, that are posited to be involved in the response to emotional stimuli, even when participants are instructed to ignore the stimuli (e.g., Phillips et al., 2003).

We should note two limitations of the present study. First, we did not find significant behavioral differences between depressed and nondepressed participants. Because this task was used successfully in previous behavioral studies (e.g., Joormann, 2004), it is likely that we did not obtain significant group differences in RT because of the scanning environment. Interestingly, it is frequently the case that group differences observed in behavioral studies are not replicated in fMRI studies using similar designs (e.g., Wagner et al., 2006). Second, because we did not include a psychiatric control group in this study, we cannot address the issue of the specificity of our findings to depression. Indeed, it is likely that combined rACC and inhibitory dysfunctions are also involved in other disorders, such as posttraumatic stress disorder (Shin et al., 2001; Bremner et al., 2004) and schizophrenia (Carter et al., 2001; Rubia et al., 2001). Future research should address this issue by examining how neural correlates of inhibition differ in participants diagnosed with other psychiatric disorders.

In closing, we have demonstrated in this study that inhibitory difficulties that prevent diagnosed depressed individuals from disengaging their attention from negative information in their environment are associated with increased rACC response. By demonstrating a potential link between neural functioning and inhibitory processing in MDD, this study represents an important step in developing a more comprehensive understanding of depression through the integration of neural and cognitive models of this disorder.

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