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The Neural Basis of Difficulties Disengaging From Negative Irrelevant Material in Major Depression

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Abstract

Recurrent uncontrollable negative thoughts are a hallmark of depressive episodes. Deficits in cognitive control have been proposed to underlie this debilitating aspect of depression. Here, we used functional neuroimaging during an emotional working memory (WM) task to elucidate the neural correlates of these difficulties in cognitive control. In a WM manipulation involving depressed participants, the dorsal anterior cingulate and parietal and bilateral insular cortices were activated significantly more when negative words were removed from WM than when they were maintained in WM; in contrast, nondepressed participants exhibited stronger neural activations in these regions for positive than for negative material. These findings implicate anomalous activation of components of the task-positive network, known to be modulated by cognitive effort, in depression-associated difficulties in expelling negative material from WM. Future studies should examine the association between these aberrations and the maintenance of depressive symptoms.

Keywords

depression, functional MRI, working memory, dorsal anterior cingulate cortex, insula, neuroimaging, brain

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Recurrent negative thoughts are not only a symptom of depression, but have also been associated with vulnerability to the onset and recurrence of depressive episodes and the maintenance of negative affect (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Recent studies suggest that deficits in working memory (WM), a limited-capacity system that maintains the representations of which a person is aware, may underlie these ruminative thoughts. Indeed, one of the most consistent findings in research on major depressive disorder (MDD) is that people with MDD have difficulty in disengaging from the processing of negative material. In addition to having problems directing attention away from negatively valenced stimuli (Fritzsche et al., 2010; Gotlib, Krasnoperova, Yue, & Joormann, 2004) and related difficulties inhibiting the initial processing of irrelevant negative information (Goeleven, Raedt, Baert, & Koster, 2006; Joormann, 2004), depressed individuals are less able than are nondepressed persons to remove task-irrelevant negative thoughts and memories from WM (Berman et al., 2011; Joormann & Gotlib, 2008; Joormann, Nee, Berman, Jonides, & Gotlib, 2010; Levens & Gotlib, 2010).

Difficulties expelling irrelevant negative material from WM may contribute to the sustained negative affect that characterizes MDD (Joormann & Gotlib, 2010). Given that the activated contents of WM influence the experience of emotions (Isen, 1984; Siemer, 2005), getting "stuck" processing negative information is likely to have deleterious effects on mood. Difficulties disengaging from negative thoughts may also have adverse effects on individuals' ability to successfully regulate sad mood; because WM is a limited-capacity system (Hasher & Zacks, 1998), material in WM must be expelled as it becomes irrelevant in order to allow the individual to process new, relevant information that could facilitate the flexible reappraisal or reinterpretation of events (Siemer, 2005). Finally, problems managing the contents of WM are likely to influence the strength and duration of rumination (Joormann

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& Gotlib, 2008). In fact, Demeyer, De Lissnyder, Koster, and De Raedt (2012) recently found that difficulties in disengaging from the processing of irrelevant, negative material in WM were associated with a worsening of depressive symptoms at follow-up and that this relation was mediated by rumination.

Despite these findings implicating WM dysfunction in persistent negative mood in depression, the neural mechanisms underlying depressed individuals' difficulty expelling negative material from WM are not well understood. Indeed, although researchers are beginning to elucidate neural correlates of dysfunctional processing of negative stimuli in depression (Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Eugène, Joormann, Cooney, Atlas, & Gotlib, 2010; Mitterschiffthaler et al., 2008), investigators have not yet examined the neural mechanisms underlying difficulties in expelling negative material from WM in this disorder.

We addressed this issue by scanning depressed and nondepressed individuals as they participated in a modified Sternberg task. In this task, participants memorize two lists of simultaneously presented words. An instruction cue then indicates which of the two lists they should forget and which they should remember for the following word-recognition procedure. During the word recognition, or "probe," epoch, participants are instructed to endorse probe words that came from the list they were previously cued to remember (i.e., the relevant list) and to reject probe words that either came from the list they were cued to forget (i.e., the no-longer-relevant list) or did not come from either list. Thus, successful performance on this task requires that participants actively manipulate the contents of WM during the instruction-cue epoch by retaining only words identified by the cue as relevant and expelling those identified as irrelevant.

Our lab has previously adapted this task behaviorally to examine the ability of depressed individuals to remove positively and negatively valenced words from WM (Joormann & Gotlib, 2008). In that study, depressed individuals, compared with their nondepressed counterparts, took a longer time to respond to negative (but not positive or neutral) probe words that came from the no-longer-relevant word lists; these longer latencies reflect difficulties removing no-longer-relevant negative information from WM. In the current investigation, we used this emotional version of the Sternberg task to assess the neural correlates of these difficulties in a sample of clinically depressed participants. More specifically, we examined whether difficulties experienced by participants with MDD in removing negative material from WM are associated with anomalous patterns of brain activation during the presentation of the instruction cue, when participants are required to actively forget, or expel from WM, one of the just-encoded lists. On the basis of previous research showing greater activation of cognitive-control regions such as the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) in depressed individuals during the processing of irrelevant negative material than of irrelevant positive material (Eugène et al., 2010; Kerestes et al., 2012), we hypothesized that depressed participants would also exhibit increased activation in these areas during the removal of negative material from WM. Further, given evidence that the ability to update the contents of WM in depression is related to the tendency to ruminate (Joormann & Gotlib, 2008), we examined whether heightened activation in these brain regions in depression is associated with increased levels of trait rumination.

Method

Participants

The study was approved by Stanford University's institutional review board, and each participant provided written informed consent. Participants were recruited through advertisements posted in numerous locations (e.g., Internet bulletin boards, university kiosks, supermarkets). The Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996) was administered to all participants to assess current and lifetime diagnoses for anxiety, mood disorders, psychotic symptoms, alcohol and substance use, somatoform, and eating disorders. Participants who met criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* for current MDD were included in the depressed group, and participants with no current or past Axis I disorders were included in the control group. We also administered the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) and the second edition of the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) to assess current severity of depressive symptoms, and the Ruminative Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991) to assess trait rumination.

Fourteen individuals diagnosed with MDD and 15 nondepressed control subjects met inclusion criteria and were included in this study (Table 1). Eight of the depressed participants met criteria for one or more comorbid anxiety disorders (panic disorder: $n = 1$, social phobia: $n = 5$, posttraumatic stress disorder: $n = 2$, generalized anxiety disorder: $n = 2$), and 3 were taking one or more psychotropic medications at the time of scanning (buproprion: $n = 3$, atypical antipsychotic: $n = 1$, duloxetine: $n = 1$, benzodiazepine: $n = 1$, citalopram, $n = 2$).

Emotional Sternberg task

The modified emotional Sternberg task has been described in a previous article (Joormann & Gotlib, 2008). Briefly, on each trial, subjects viewed an encoding display (8 s), an instruction cue (4 s), and a probe display (4 s; Fig. 1). In the encoding display, two lists of three words each, taken from the Affective Norms for English Words list (Bradley & Lang, 1999) were presented simultaneously. One word list was presented in blue, and the other was presented in red. The two lists also differed in word valence: One of the lists contained neutral words only, and the other contained positive, negative, or neutral words.[1]

Table 1. Characteristics of the Sample

Characteristic	Control group	Major-depressive-disorder group
Gender	8 females, 7 males	7 females, 7 males
Mean age in years	35.4 (11.4)	41.9 (13.2)
Mean years of education	16.1 (2.1)	15.3 (1.9)
Mean Hamilton Depression Rating Scale score[a]	0.9 (2.1)	16.8 (3.9)
Mean Beck Depression Inventory score[a]	4.8 (8.9)	35.4 (7.4)
Mean RRS-Reflection score[a]	3.8 (1.4)	7.9 (1.8)
Mean RRS-Brooding score[a]	7.1 (2.9)	15.1 (3.2)
Mean duration of current depressive episode in months[b]	—	36.2 (54.0)
Mean number of prior depressive episodes[b]	—	8.8 (7.7)
Number of participants with comorbid anxiety	—	8
Number of participants taking medication	—	4

Note: Standard deviations are given in parentheses. RRS = Ruminative Response Scale.
[a]The two groups differed significantly on these measures ($p < .05$). [b]Several depressed participants reported too many months or episodes to count.

After the offset of the words, the instruction cue informed participants which of the two word lists would be relevant for the recognition task that followed: a red frame signaled that the red list should be maintained and the blue list be expelled from WM, and a blue frame signaled that the blue list should be maintained and the red list should be expelled. Finally, a single word was presented in black in the probe display, during which participants indicated whether the word came from the relevant (i.e., maintained) list by pressing a specific key on the response box or did not come from the relevant list (i.e., was from the irrelevant list or was not from either list) by pressing a different key (the keys were counterbalanced across participants). Trials were separated by a fixation cross that lasted for 2, 4, or 6 s; the average trial length was therefore 20 s. In total, 108 trials were presented to each participant in a random order, and all trials were divided among three separate scanning runs,

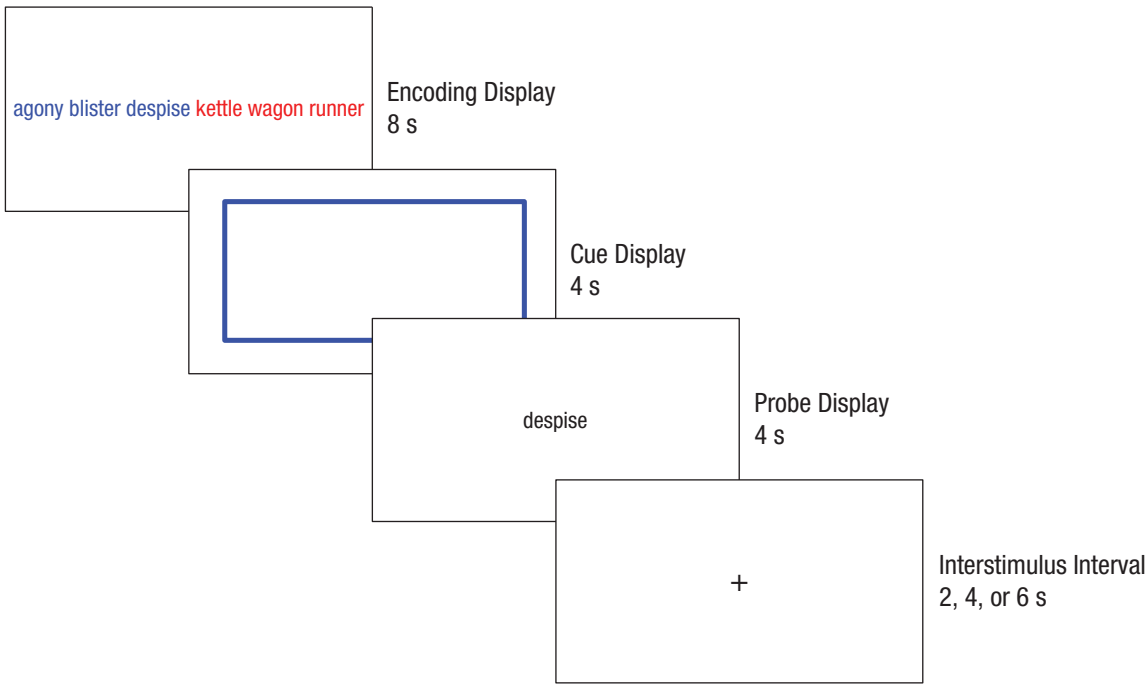

Fig. 1. Example trial sequence from the present study. At encoding, participants were presented with two lists, each consisting of three positive, three negative, or three neutral words. Each list was presented in a different color (this example shows negative words in blue and neutral words in red). After encoding, a colored cue display informed participants which of the two lists to hold in mind (the negative word list in this example). During the subsequent probe display, participants indicated whether the probe word was from the cued list (i.e., was relevant) or not from the cued list (i.e., was irrelevant). Trials were separated by an interstimulus interval of varying length.

each lasting 12 min. Participants were asked to respond as quickly and as accurately as possible; accuracy and reaction times were recorded.

Image acquisition

Blood-oxygen-level-dependent (BOLD) data were acquired with a 3 Tesla strength General Electric Signa magnetic resonance scanner using a spiral pulse sequence (Glover & Law, 2001), 29 axial slices, field of view (FOV) = 240 mm, slice thickness = 4 mm, gap = 0 mm, repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°. A structural T1-weighted volume (29 axial slices, FOV = 240 mm, slice thickness = 4 mm, gap = 0 mm, TR = 3,000 ms, TE = 68 ms, FA = 90°) was acquired in overlapping slices of the functional scans. We describe functional MRI (fMRI) data-preprocessing procedures in Section 1 of the Supplemental Material available online.

Behavioral data analysis

Accuracy and reaction times for correct responses to probe words were analyzed using a mixed-design analysis of variance (ANOVA). The effects of between-subjects factors (diagnostic group: MDD, control) and within-subjects factors (probe valence: negative, positive; probe relevance: relevant, irrelevant) were modeled to assess the main effects of each variable and their interactions.

fMRI data analysis

Statistical analyses of neuroimaging data were conducted using the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Because multiple runs were conducted for each participant, time-series statistical analyses were carried out at a single-run intrasubject level using a generalized linear model that modeled the encoding, instruction cue, and probe epochs using a synthetic hemodynamic response function and its first derivative. To test our main hypotheses that depressed participants would exhibit aberrant activation during the removal of no-longer-relevant negative material from WM, we conducted a direct comparison at this first level between activations that were greater when participants expelled than when they maintained negative words and activations that were greater when participants expelled than when they maintained positive words. By contrasting activations in "expel" versus "maintain" trials separately for each valence and then comparing these differences within subjects and between groups, we could assess depression-associated abnormalities in activation that were specific to the process of removing negatively valenced information from WM versus activations that may be involved in any WM manipulation (removal or maintenance) of stimuli with either valence (positive or negative).

Single-run intrasubject maps were taken to a multiple-run fixed-effects intrasubject level to provide subject-specific summaries of activation. Subject-specific activation summary maps were carried to higher-level intergroup analyses using FMRIB's Local Analysis of Mixed Effects (FLAME; Woolrich, Behrens, & Smith, 2004) program in FSL to assess the interaction of group, valence, and cue instruction. The threshold for the resulting statistical images for these higher-level analyses was $Z > 2.3$, and the cluster probability was $p < .05$, corrected for whole-brain multiple comparisons using Gaussian random-field theory (Worsley, Marrett, Neelin, & Evans, 1992).

We decomposed multifactor effects in clusters resulting from the direct comparison between groups—that is, clusters that showed a significant interaction of group (control, MDD), valence (negative, positive), and cue instruction (expel, maintain) by first extracting parameter estimates (proportional to fMRI signal change) of BOLD signal response for each condition, separately for each cluster, using featquery (fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/featquery.html), a regions-of-interest toolbox in FSL. In separate analyses conducted with SPSS (www.ibm.com/software/analytics/spss/), we used parameter estimates to examine two-way interactions of valence and instruction type within groups. Pairwise comparisons were used to decompose significant two-way (within-groups) interactions. Additional analyses examining the effects of medication and comorbid anxiety on these activations are presented in Section 2 of the Supplemental Material.

Correlation of neural activations with rumination

Finally, to examine whether depression-related abnormalities in activation were related to levels of self-reported rumination, we conducted correlation analyses within the MDD group between parameter estimates extracted from regions that showed a significant interaction of group, valence, and cue instruction, and scores on the HAMD, BDI, and the Reflection and Brooding subscales of the RRS (see Whitmer & Gotlib, 2011, for scoring on these two subscales).

Results

Participant characteristics

The depressed group did not differ significantly from the healthy control group in age, gender composition, or education level (characteristics of the sample are shown in Table 1). As expected, the depressed participants obtained significantly higher scores on the BDI, HAMD, and RRS than did the nondepressed participants.

Behavioral data

Means and standard errors for accuracy of responses and reaction times for correct responses are presented in Figure 2. The ANOVA conducted on reaction times yielded a main effect of relevance, $F(1, 25) = 5.31$, $p = .014$, $\eta_p^2 = .32$; participants responded more quickly to relevant than to irrelevant probe

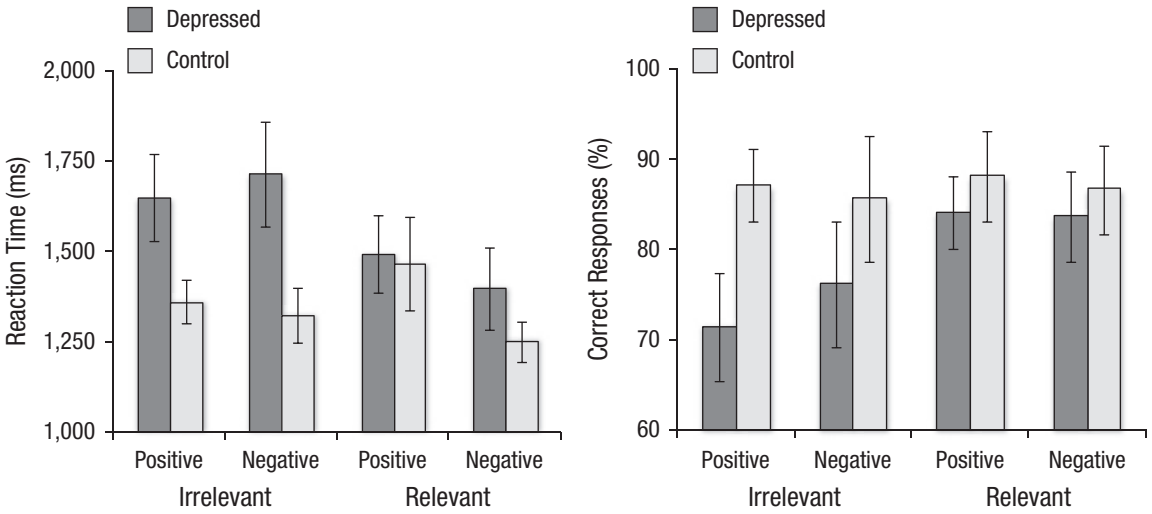

Fig. 2. Mean reaction time for correct responses (left) and mean accuracy (right) as a function of the valence of probe words and whether they came from the relevant or irrelevant encoding list. Results are shown separately for participants with major depressive disorder and control participants. Error bars represent standard errors of the mean.

words. The ANOVA conducted on accuracy of responses also yielded a significant main effect of relevance, $F(1, 25) = 5.31$, $p = .031$, $\eta_p^2 = .19$; participants were more accurate in responding to relevant than to irrelevant probe words. No other main effects or interactions were significant.

Imaging data

Analyses of fMRI data yielded a significant interaction of group, valence, and cue instruction in four distinct brain regions: the left and right insula, the left dorsal ACC (dACC), and the left superior parietal lobule (Figs. 3–5, Table 2). Follow-up analyses revealed that in control participants, there was a significant interaction of valence and cue instruction in each region, Fs(1, 14) > 5.12, ps < .040, η_p^2s > .26. In MDD participants, there was a significant interaction of valence and cue instruction in the dACC, $F(1, 13) = 5.20$, $p = .04$, $\eta_p^2 = .29$, and the left and right insula, Fs(1, 13) > 13.13, ps < .03, η_p^2s > .39), but not in the superior parietal lobule, $F(1, 13) = 3.776$, $p = .074$, $\eta_p^2 = .23$, where there was only a significant main effect of cue instruction, $F(1, 13) = 7.98$, $p = .014$, $\eta_p^2 = .38$.

Pairwise comparisons showed that in control participants, the dACC, superior parietal lobule, and left insula were activated significantly more when positive material was removed from WM than when it was maintained in WM, ts(14) > 2.52, ps < .03; this pattern of activation was not obtained for negative material, ts(14) < 1.81, ps > .05. In contrast, MDD participants showed significantly greater activation in each region when negative material was removed from WM than when it was maintained in WM, ts(13) > 2.57, ps < .03; this pattern of activation was not obtained for positive material. Depression-related abnormalities in activation of the dACC in particular appeared to have been driven by functional patterns that were specific to the process of maintaining negative material in WM: There was both a significant main effect of group in this region for trials in which participants were instructed to maintain negative words, $t(27) = 2.29$, $p = .029$, and a significant main effect of valence in this region for trials requiring MDD participants to maintain emotional words, $t(13) = 2.19$, $p = .046$.

Correlations with rumination

Given the main findings from our analysis (i.e., that there were depression-associated anomalies in neural activation in the difference between trials requiring words to be expelled and trials requiring words to be maintained) and that the identified patterns differed as a function of the valence of the stimuli, we computed correlations within the MDD group between the difference in activation (as indexed by parameter estimates of BOLD signal response) between "expel" and "maintain" trials within each valence and self-reported rumination. These analyses yielded no significant correlations (all ps > .05).

Discussion

Depressed individuals experience difficulties in removing negative thoughts and memories from WM once they are no longer relevant (Berman et al., 2011; Joormann & Gotlib, 2008; Levens & Gotlib, 2010). Previous research has linked these difficulties to recurrent negative thoughts and difficulties in emotion regulation that lead to the sustained negative affect that characterizes depressive disorders (Joormann & Gotlib, 2010). The present study was designed to delineate the neural correlates of these difficulties. Results of our investigation showed that, consistent with our hypothesis, the process of

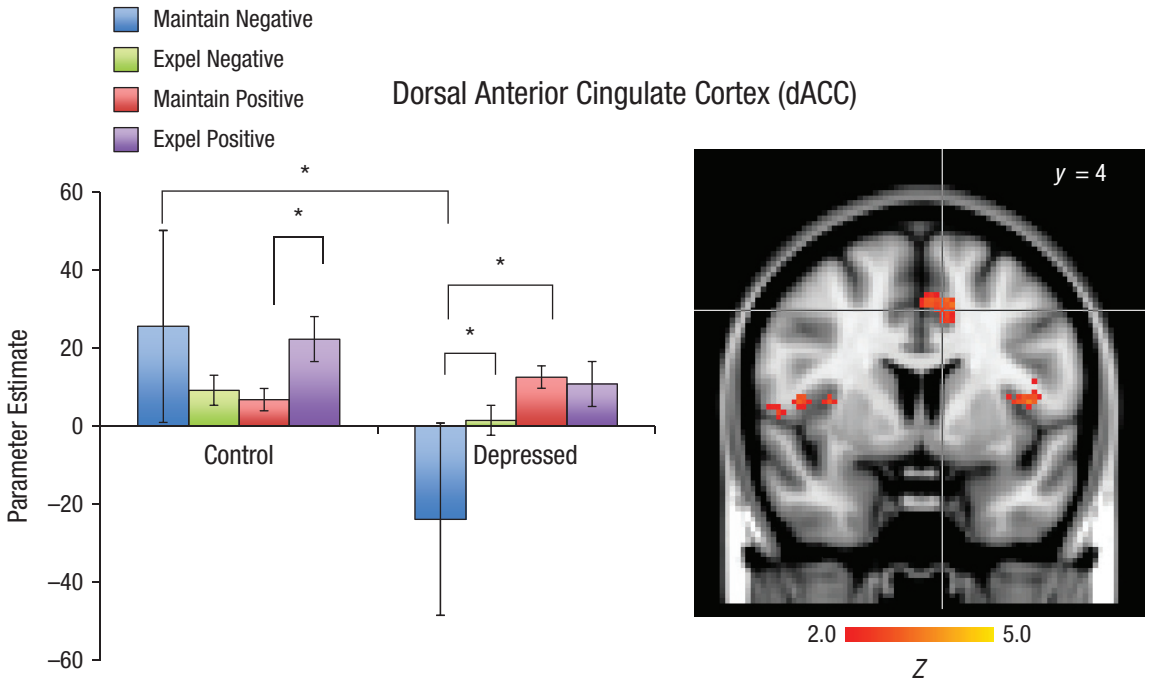

Fig. 3. Results showing activation in the dorsal anterior cingulate cortex (dACC) during the manipulation of working memory contents. The graph on the left shows parameter estimates (indicating the amount of signal change measured in arbitrary units) of blood-oxygen-level-dependent signal response in dACC as a function of group and whether participants were instructed to maintain or expel either negative words or positive words from working memory. Error bars represent standard errors of the mean. Asterisks indicate significant differences between conditions or groups ($p < .05$). The brain image on the right is a coronal cross-section showing the location of voxels in which there was a significant Group × Cue Instruction × Valence interaction in the dACC (crosshairs) and other areas.

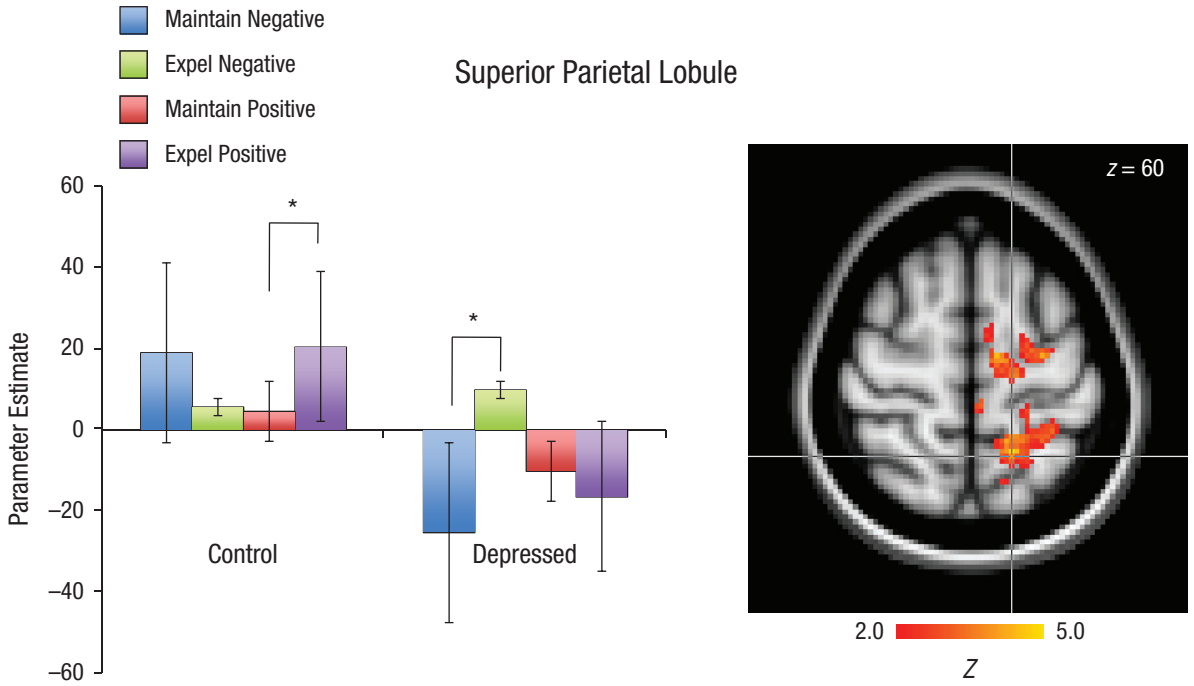

Fig. 4. Results showing activation in the left superior parietal lobule during the manipulation of working memory contents. The graph on the left shows parameter estimates (indicating the amount of signal change measured in arbitrary units) of blood-oxygen-level-dependent signal response in left superior parietal lobule as a function of group and whether participants were instructed to maintain or expel either negative words or positive words from working memory. Error bars represent standard errors of the mean. Asterisks indicate significant differences between conditions ($p < .05$). The brain image on the right is a horizontal cross-section showing the location of voxels in which there was a significant Group × Cue Instruction × Valence interaction in the left superior parietal lobule (crosshairs) and other areas.

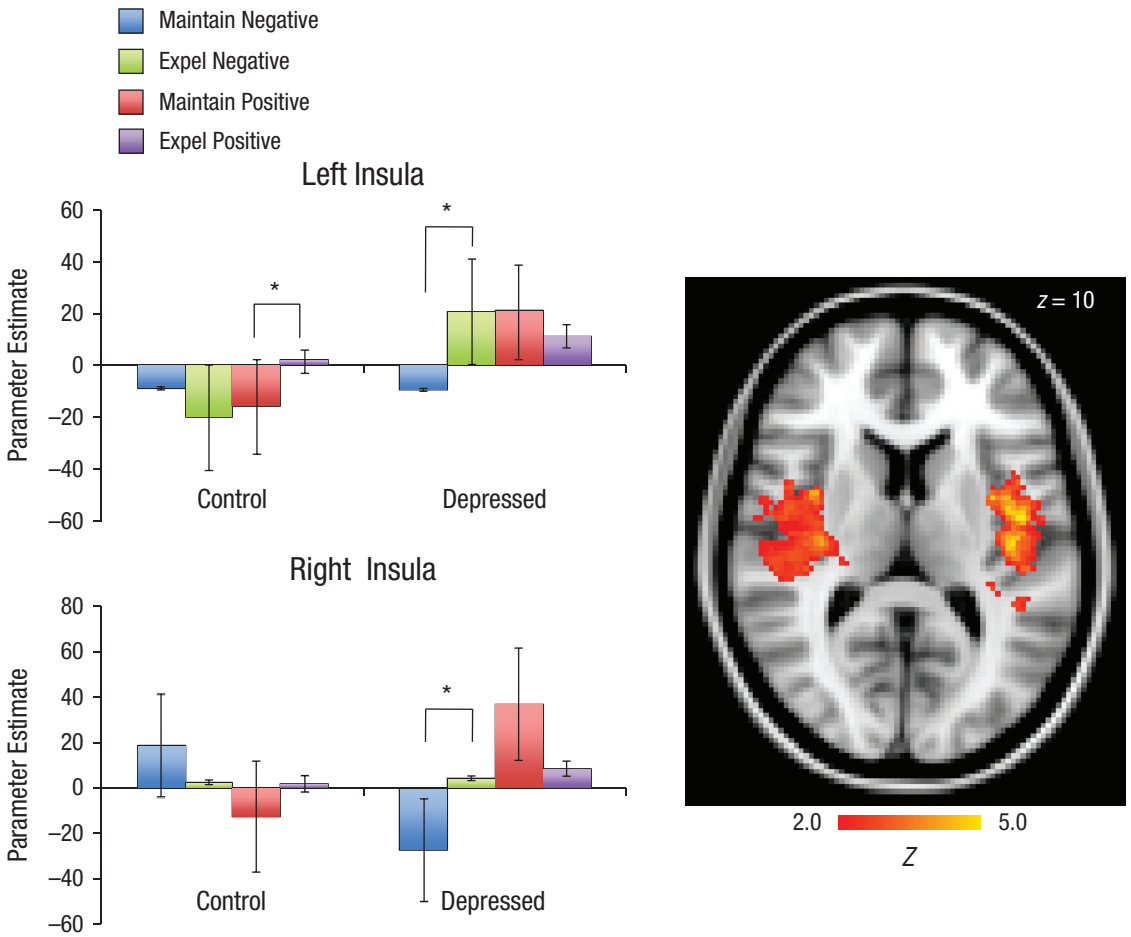

Fig. 5. Results showing activation in the left and right insula during the manipulation of working memory contents. The graphs on the left show parameter estimates (indicating the amount of signal change measured in arbitrary units) of blood-oxygen-level-dependent signal response in the left insula (top) and right insula (bottom) as a function of group and whether participants were instructed to maintain or expel either negative words or positive words from working memory. Error bars represent standard errors of the mean. Asterisks indicate significant differences between conditions ($p < .05$). The brain image on the right is a horizontal cross-section showing the location of voxels in which there was a significant Group × Cue Instruction × Valence interaction in the left and right insula.

removing no-longer-relevant negative material from WM is associated in depression with abnormalities in activation of the dACC, a region that subserves cognitive control. In addition, we found a similar pattern of abnormal response in the insula and the superior parietal lobule in depressed individuals. More specifically, MDD participants showed a greater increase in activation in these areas when negative material was removed from WM than when it was maintained in WM,

Table 2. Brain Regions Showing an Interaction of Group, Valence, and Cue Instruction

	MNI coordinates				
Brain region	*x*	*y*	*z*	Number of voxels	*Z*
Left insula	−40	−16	10	1,082	4.58
Right insula	34	−18	10	811	3.55
Superior parietal lobule	−30	−46	62	603	4.40
Dorsal anterior cingulate cortex	−10	−14	60	485	3.78

Note: Coordinates represent voxels in each region with the most significant magnitude, identified at $Z > 2.3$, with a (corrected) cluster-significance threshold of $p = .05$. MNI = Montreal Neurological Institute.

though this effect did not hold for positive material; in contrast, nondepressed participants showed greater activation in each of these regions when positive material was removed from WM than when it was maintained in WM, though this effect did not hold for negative material.

It is important to note that all four of the regions identified in our voxel-wise analyses—the dACC, left and right insula, and superior parietal lobule—are critical components of the task-positive network (TPN). Previous research has documented that the TPN comprises regions that mediate cognitive control and becomes activated during a wide range of cognitive tasks (Corbetta, Patel, & Shulman, 2008; D'Esposito et al., 1995; Dosenbach et al., 2007; Dove, Brett, Cusack, & Owen, 2006; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Moreover, greater recruitment of this network occurs with increasing cognitive demand (Allen, Bigler, Larsen, Goodrich-Hunsaker, & Hopkins, 2007; Paus, Koski, Caramanos, & Westbury, 1998; Wager et al., 2005). In fact, the results of a recent meta-analysis of neural and cognitive functioning in aging adults indicated greater activation of the TPN in older than in younger adults during the performance of a range of cognitive tasks known to be more demanding for older samples (Spreng, Wojtowicz, & Grady, 2010). Therefore, the increased activation of the TPN that we observed in the depressed participants as they attempted to remove negative material from WM suggests that they required additional neural and cognitive resources to perform this mental operation.

The fact that reliable patterns of TPN activation can be obtained across a range of tasks (Spreng et al., 2010) suggests that investigating the TPN is useful not only in gaining a deeper understanding of the neural underpinnings of cognitive effort in general, but also for elucidating the nature of cognitive dysfunction in MDD more specifically. Indeed, dysfunction in one or more TPN regions has been observed in MDD in a number of studies (see Pizzagalli, 2010, for a review). It is important to note, however, that although the four TPN regions found in our analysis collectively subserve general cognitive-control processes, specific individual subregions may mediate unique aspects of cognitive control in the context of WM. For example, in a meta-analysis of WM studies, Wager and Smith (2003) found that whereas the dACC was primarily activated in WM tasks requiring selective attention or navigation of competing stimuli, the insula (and, in particular, its anterior aspect) and the superior parietal lobule were involved in the manipulation of the content of WM.

It is noteworthy that we did not find depression-associated differences in activation of default-mode network (DMN) structures (e.g., posterior cingulate cortex, medial PFC). Recent research suggests that anomalies in reducing DMN activity in depression during effortful cognitive processing lead to interference in task performance from internal emotional states (Sheline et al., 2009). We think the absence of such a finding in the present study is important in suggesting that difficulties removing negative material from WM in depression are not necessarily the result of increased self-relational processing of this material, as has been previously suggested (Amir, Coles, Brigidi, & Foa, 2001; Sheline et al., 2009). Moreover, the absence of a group difference in activation of the inferior frontal gyrus, a region critically involved in inhibition and discussed by Berman et al. (2011) in their investigation of the probe epoch of a directed forgetting task, suggests that difficulties disengaging from the processing of negative information in depression are not secondary to neural impairments in this region of inhibitory circuits.

It is interesting to note that the interactions of valence, group, and WM manipulation type in the dACC, an area for which we generated specific predictions, were driven largely by group differences in activation occurring during the maintenance of negative material in WM; decomposing the interaction effects in this region revealed that MDD participants showed significantly less activation than did control participants. This pattern of findings is consistent with our interpretation that the group differences in activation are related to differences in the level of cognitive effort required for depressed and nondepressed participants to perform the mood-congruent operation indicated by the cue. That is, as suggested by previous research (Joormann & Gotlib, 2008), it is likely less cognitively demanding for depressed than for nondepressed individuals to maintain negative material in WM. These findings in the dACC may also relate more specifically to the role of this region in conflict monitoring (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). As the contents of WM undergo updating during presentation of the instruction cue, interference arises as the previously encoded representations compete for cognitive resources. To cope with this interference, the dACC works to resolve conflict between competing WM representations by suppressing maintenance of the no-longer-relevant word list that was just encoded and enhancing maintenance of the word list identified by the cue as relevant. However, because depressed individuals have difficulty disengaging from negative material once it initially captures their attention (Caseras, Garner, Bradley, & Mogg, 2007), the process of selecting this material moving forward is likely facilitated and may consequently demand less activation by the dACC to resolve interference between two competing word lists.

It is important to consider that, although our interpretations of the above data link neural function with previous behavioral findings concerning depression-specific difficulties in removing and disengaging from no-longer-relevant negative information, the design of the present study was optimized to examine neural, rather than behavioral, anomalies associated with manipulation of information in WM in MDD; thus, we cannot determine conclusively whether the depressed participants in our study experienced such a behavioral difficulty. Nevertheless, previous studies (Berman et al., 2011; Joormann & Gotlib, 2008) that have used longer versions of the emotional Sternberg WM task have found that depressed participants exhibit longer response latencies to words presented during the probe epoch when these words came from negative

word lists and were identified by the cue as no longer relevant, compared with novel probes of the same valence. This difference in reaction times, also known as an intrusion effect, is posited to reflect the strength of the residual activation of the no-longer-relevant word lists in WM, with larger differences indicating greater difficulties in people's ability to expel word lists that are no longer relevant (Oberauer, 2001). Given these behavioral findings in depression with a longer version of the task used in the present study, we believe that our interpretations of our neural findings are appropriate.

We should note two limitations of our study. First, some of the participants in the depressed sample were receiving medication ($n = 4$; 29% of the sample) or had one or more anxiety disorders in addition to depression at the time of scanning ($n = 8$; 57% of the sample); depression-associated abnormalities in activation may have been influenced by one or both of these factors. However, our findings remained significant when we included these variables as covariates in our statistical model; thus, it does not appear that either factor had a significant confounding effect. Second, because our task design did not incorporate a separate baseline between the different task epochs, it is possible that activations observed during the cue epoch also reflected some amount of residual activity occurring during the encoding epoch. We present details concerning additional exploratory analyses designed to examine this possibility in Section 3 of the Supplemental Material.

In conclusion, the present study is important because it begins to elucidate neural dysfunction as depressed individuals attempt to remove no-longer-relevant, mood-congruent material from WM. The results of our investigation, showing that depressed individuals overrecruit the TPN during the removal of irrelevant negative material from WM, provide critical new information for a neural model of depression in which difficulties controlling the processing of no-longer-relevant negative material are associated with abnormalities in brain functioning in these areas. Our findings also highlight important avenues for future research. In particular, future studies should examine whether biases in WM processes and corresponding anomalies in TPN activation are modulated by biases in the initial (attentional) processing of this information. In this context, it will be important for investigators to examine whether and how cognitive-control training, aimed at ameliorating negative cognitive biases in depression, might reverse these patterns of TPN dysfunction in depressed individuals. Finally, investigators might profitably examine whether the patterns of activation documented in MDD participants in this study differentiate individuals who are able to control negative cognitions from persons who initiate a vicious cycle of increasingly negative thoughts.

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Declaration of Conflicting Interests

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Supplemental Material

Additional supporting information may be found at http://pss.sagepub.com/content/by/supplemental-data

Note

1. If we had used a fully balanced design, we would have included trials in which positive and negative word lists were encoded simultaneously; however, both because of time limitations imposed by scanning and because including these trials would make interpretations of activations that occurred during the subsequent instruction cue nonspecific with respect to valence, we did not include such trials in this study.

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