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Frontal and Limbic Activation During Inhibitory Control Predicts Treatment Response in Major Depressive Disorder

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Abstract

Background—Inhibitory control or regulatory difficulties have been explored in major depressive disorder (MDD) but typically in the context of affectively salient information. Inhibitory control is addressed specifically by using a task devoid of affectively-laden stimuli, to disentangle the effects of altered affect and altered inhibitory processes in MDD.

Methods: Twenty MDD and 22 control volunteer participants matched by age and gender completed a contextual inhibitory control task, the Parametric Go/No-go (PGNG) task during functional magnetic resonance imaging. The PGNG includes three levels of difficulty, a typical continuous performance task and two progressively more difficult versions including Go/No-go hit and rejection trials. After this test, 15 of 20 MDD patients completed a full 10-week treatment with s-citalopram.

Results: There was a significant interaction among response time (control subjects better), hits (control subjects better), and rejections (patients better). The MDD participants had greater activation compared with the control group in frontal and anterior temporal areas during correct rejections (inhibition). Activation during successful inhibitory events in bilateral inferior frontal and left amygdala, insula, and nucleus accumbens and during unsuccessful inhibition (commission errors) in rostral anterior cingulate predicted post-treatment improvement in depression symptoms.

Conclusions: The imaging findings suggest that in MDD subjects, greater neural activation in frontal, limbic, and temporal regions during correct rejection of lures is necessary to achieve behavioral performance equivalent to control subjects. Greater activation in similar regions was further predictive of better treatment response in MDD.

Keywords

Depression; executive functioning; fMRI; imaging; inhibitory control; mood disorders; SSRIs; treatment response

One prominent theory about the genesis and persistence of major depressive disorder (MDD) relates to failed regulatory mechanisms (e.g., emotion regulation) impacting on attention and cognitive-emotional integration (Rogers *et al.* 2004). In this context, regulatory

ability refers to the ability of neocortical networks to modulate overlearned or automated behaviors (e.g., prepotent responses; Humberstone *et al.* 1997). Failure of regulatory mechanisms in MDD is thought to result in deficient emotional and behavioral functioning (Anand *et al.* 2005; Davidson *et al.* 2002; Kennedy *et al.* 2006; Mayberg 1997; Robertson *et al.* 2005; Zubieta *et al.* 2003). It is suspected that the frontal lobes are the foci for these dysfunctional regulatory systems, subsumed under the construct of executive functioning (Alexopoulos 2002; Austin *et al.* 1999; Bench *et al.* 1993; Drevets and Raichle 1992; Goodwin 1997), although a broader number of the brain areas subserving these skills have been described, including inferior parietal and insular cortex (Rubia *et al.* 2001). Effortful regulatory and problem solving processes are very important in understanding the pathology of MDD, recovery after treatment, and potential for relapse (Dunkin *et al.* 2000; Hooley *et al.* 2005; Marcos *et al.* 2005; Marie-Mitchell *et al.* 2004; Mayberg *et al.* 1997; Mohr *et al.* 2003; Potter *et al.* 2004).

Several imaging studies of executive functioning have been performed with MDD patients, although few have specifically investigated inhibitory control. One study of interference resolution reported decreased left middle cingulate activation (George *et al.* 1997), whereas another reported increased activation for MDD patients (e.g., left dorsolateral prefrontal cortex [DLPFC], anterior cingulate [AC]) compared with the control group (Wagner *et al.* 2006). Studies using working memory and verbal fluency tasks have generally reported more prominent activation in the control groups in frontal, basal ganglia, and parietal areas compared with MDD patients (Audenaert *et al.* 2002; Barch *et al.* 2003; Elliott *et al.* 1997; Holmes *et al.* 2005; Hugdahl *et al.* 2003, 2004; Matsuo *et al.* 2002; Okada *et al.* 2003), whereas three other studies (examining working memory, attention, and interference control, respectively) have noted greater activation in frontal areas for the MDD groups compared with the control groups in the context of preserved behavioral performance (Harvey *et al.* 2005; Holmes *et al.* 2005; Wagner *et al.* 2006). Although the direction of findings in executive function studies remains controversial, prefrontal cortical activity in MDD has been associated with better responses to psychotropic medications (Davidson *et al.* 2003; Mayberg *et al.* 1997; Pizzagalli *et al.* 2001).

The exploration of regulatory abilities, particularly cognitive regulation abilities like task switching and inhibitory control, could highlight whether there is a generalized regulatory problem in MDD or whether the problem pertains specifically to emotional regulation. Previous studies by our group have highlighted the fact that patients with MDD exhibit difficulties in the Parametric Go/No-go (PGNG) task, a measure of sustained attention, set-shifting, processing speed, and inhibitory control (Langenecker *et al.* 2005; Langenecker *et al.*, in press). One particular benefit of using a Go/No-go, event-related design in functional magnetic resonance imaging (fMRI) is that successful behavioral inhibition (correct lure rejections) can be separated from failed inhibition (commissions), allowing for sounder attribution of behavioral and activation differences.

The present study used an event-related design with the PGNG to directly address the question of whether there are dysfunctional inhibitory mechanisms in depression, specifically addressing those involved in successful and unsuccessful inhibition. The first hypothesis was that MDD patients would perform less efficiently than the control group on behavioral measures, consistent with our previous findings. The second hypothesis was that MDD patients would exhibit increased activation compared with the control group in areas known to be important for inhibitory control, for example, right inferior frontal, anterior insula, and inferior parietal areas as well as bilateral dorsal AC (Langenecker and Nielson 2003) at comparable levels of performance. It was also expected that the MDD patients would exhibit greater activation for errors of commission compared with the control group in AC and prefrontal areas. Although prior imaging studies in MDD have yet to explore

activation related to errors, the clinical and behavioral phenomenology of depression suggests excessive error processing and rumination (Watkins and Brown 2002; Young and Nolen-Hoeksema 2001). A final hypothesis was that greater functional activation and better performance for the PGNG would be associated with greater treatment response to a serotonin-selective reuptake inhibitor antidepressant (Davidson *et al.* 2003; Mayberg *et al.* 1997; Pizzigalli *et al.* 2001).

Methods and Materials

Participants

Twenty-two control and 20 MDD participants were recruited via newspaper advertisements, campus fliers, and word of mouth with institutional review board–approved informed consent. Demographic information is listed in Table 1, and there were no differences in these parameters (all $ps > .22$). Three of the 42 participants were left handed, ascertained by self-report and fine motor dexterity performance (Costa *et al.* 1963); one left-handed control subject was excluded for methodological reasons, whereas a left-handed MDD patient and a control subject were matched on age, handedness, gender, and education and included. Patients with MDD were unmedicated and had been medication-free for a minimum of 90 days for fluoxetine or 30 days for all other medications (including birth control) to eliminate medication effects on functional activation and behavioral parameters. Cigarette smokers, those with alcohol abuse, and those who had used illegal drugs in the past 2 years were excluded.

All participants were interviewed with the Structured Clinical Interview for the DSM-IV (First *et al.* 1995) and Hamilton Rating Scale for Depression (HDRS; Hamilton 1960, 1967) and self-completed the Beck Depression Inventory-II (BDI-II; Beck *et al.* 1961). Patients had a score of 15 or higher on the 17-item HDRS (moderate to severe depression). The depressed and control groups differed in HDRS, BDI-II, and Global Assessment of Functioning (p values $< .0001$, Table 1). The HDRS reliability assessments were excellent [Virginia Murphy-Weinberg, VMW, LMG; $r(23) = .91$, $p < .0001$]. The MDD patients were then treated with *s*-citalopram (Lexapro, Forest Laboratories, New York) for 10 weeks. Dosing was 5 mg during the 1st week, then 10 mg to week 4, then to 20 mg if $< 50\%$ improvement of symptoms. Repeat HDRS measurements took place upon completion of the trial ($n = 15$).

PGNG

The PGNG measures attention (hits) and set-shifting, processing speed, and correct (rejections) and incorrect (commissions) responses to lure trials as a part of inhibitory control (Langenecker *et al.* 2005). The PGNG consists of three separate levels. For all three levels, a serial stream of letters is presented (navy blue letter in 120 point Arial font on a yellow background) for 500 msec with no interstimulus interval. Responses were made by button press with the right index finger. No targets were repeated without at least one intervening distractor.

Level 1 is designed to build and sustain prepotent responding to the set of working memory (WM) target letters (“x,” “y,” and “z”; see Figure 1). In the fMRI version of the task there are 84 targets, 344 distractors, and a time of 3’30”/run.

In Level 2, participants are required to respond to the WM target letters (“x” and “y,” “z” is absent in this level) each time they appear, in alternation or non-repeating order. This “non-repeating rule” stipulates that once the participant responds to the target “x,” the WM target set is “y” and the WM lure set (lures trials) is “x.” Here there are 80 targets, 17 lures, and 311 distractors and a time of 3’21”/run.

Level 3 decreases the participant's ability to anticipate the next correct response by adding an additional target to the WM target set (targets “x,” “y,” and “z”). After each target response (say “x”), the other two targets become part of the WM target set (“y,” “z”) and “x” is in the WM lure set. Here there are 80 targets, 17 lures, and 311 distractors and a time of 3'21”/run.

Procedures

Participants completed a practice run of the PGNG before fMRI. This baseline data was acquired, questions were answered, and the participants were familiarized with the task. Participants then performed the task again while in the scanner, twice in a counterbalanced order (Results following). The PGNG Levels were presented in six separate runs in either an order of 123:132 or 132:123 to maintain prepotency (each level once in each set) and to counterbalance practice and fatigue effects, with no difference between groups in order [$X(21) = 2.1, p > .34$]; order of completion did not affect any of the behavioral analyses (all $p > .27$). The lure and target events were jittered in presentation with the average interlure and intertarget intervals of 5.9 repetition times (TRs) (SD = 2.2, range = 2.5–11) and 1.4 TRs (SD = .8, range = .5–6), respectively.

The visual stimulus was presented via goggles attached to the head coil. Earplugs and foam padding were used to attenuate the 95 dB scanner noise and limit head movement. Participants used the index finger of their right hand to respond to the target stimuli to record accuracy and reaction time through the parallel port of an IBM compatible computer.

Participants also completed an emotion processing task inside of the scanner before completing the PGNG (reported elsewhere) that might have changed their predisposition to the PGNG but would be unlikely to affect event-related analyses. In our previous work, the PGNG was also preceded by an emotion processing task (Langenecker *et al.* 2005; Langenecker *et al.* in press).

MRI Parameters

Whole brain imaging was performed with a GE Sigma 3T scanner (release VH3, Milwaukee, Wisconsin). The fMRI series consisted of 30 contiguous oblique-axial sections, 4-mm thick to cover the brain acquired with a forward spiral sequence (Glover and Thomason 2004). The image matrix was 64×64 over a 24-cm field of view for a $3.75 \times 3.75 \times 4$ mm voxel. The 30-slice volume was acquired serially at 2000 msec temporal resolution in six counterbalanced runs of 3'30 each for a total of 720 time points for PGNG. One hundred six high-resolution fast spoiled gradient-echo inverse recovery axial anatomic images (echo time [TE] = 3.4 msec, TR = 10.5 msec, 27° flip angle, number of excitations = 1, slice thickness = 1.5 mm, field of view = 24 cm, matrix size = 256×256) were performed on each participant for co-registration. Processing of images was conducted with Statistical Parametric Mapping (SPM 2, Friston *et al.* 1995) standard event-related analyses (see Supplement 1).

Statistical Analyses for Behavioral and Functional MRI Comparisons

A $p < .05$ was used for the behavioral repeated measures analysis of variance (ANOVA), and $p < .0001$, uncorrected, with a minimum cluster size of 20 voxels (160 mm^3) was used for imaging comparisons and predictions of treatment response, more stringent than the $p < .001$, 20-mm^3 threshold used by Wagner *et al.* (2006) with a similar task and design. Combined cluster size by threshold correction is effective in reducing type I error (Ward *et al.* 1998). The fMRI analyses included one-group random effects t tests for each group for rejections, hits, and commissions. Two-group t test comparisons were then made between MDD and control groups for event-related hemodynamic response function (HRF) changes

to rejections (successful inhibition, no response to WM lure set), commissions (failed inhibition, response to WM lure set), and hits (correct response to WM target set). Behavioral performance measures; clinical measures; and voxel $\times$ voxel, whole brain, fMRI activation after rejections, and commissions were then used to predict treatment response (HDRS score change from pre- to post-treatment) with the random effects simple regression procedure in SPM2.

Results

Behavioral Results

Interaction Between Response Time, Hits, and Rejections/Commissions—The better performance in reaction time and nominally better performance in responses to target trials (percent correct target trials) for the control group compared with the MDD group and the inverse relationship in inhibitory control or lure rejections (percent correct inhibitory trials) were important and suggested an interaction of different behavioral parameters with the PGNG and diagnostic group. To analyze this potential interaction a $2 \times 3 \times 3$ repeated measures ANOVA was computed with group $\times$ behavioral parameter $\times$ PGNG level [$F(4,160) = 1.44, p = .24, \eta^2 = .034$], which was not significant. The interaction between behavioral parameter and group was significant [$F(4,160) = 4.67, p = .03, \eta^2 = .10$]. This interaction is graphed in Figures 2A and 2B. The control group had faster and more accurate performance for the more frequently occurring targets, whereas the MDD group exhibited better performance in the less frequently occurring lure trials.

fMRI Results

Because there were no significant interactions across PGNG levels for the groups and behavioral parameters, events were collapsed across PGNG levels into hits (Levels 1–3), rejections, and commissions (both from Level 2 and 3). The parametric element of activation in MDD and control subjects was not analyzed for the present work and will be described elsewhere. Four MDD and 4 control participants were not included in the brain activation comparisons, owing to data acquisition problems, and 1 additional control participant was removed, owing to image artifacts, leaving 17 control subjects' and 16 patients' data for behavioral and functional analyses.

Activation for Hits

Activation for hits emphasizes motor responses, sustained attention, and set-shifting with WM updating (Table 2, Figure 3, Panels A–D). Significant activation for control subjects was observed in bilateral AC; inferior parietal lobule/post-central gyrus; right inferior temporal and middle occipital gyri; and left inferior frontal, middle temporal, fusiform, and inferior occipital gyri. The MDD patients demonstrated far fewer activation foci, which were located in bilateral inferior parietal lobule, right medial frontal and middle temporal gyri, as well as left superior frontal and middle temporal gyri (Figure 3, A–D). However, there were no significant differences between groups in activation for hits.

Activation for Rejections

Activation for rejections, or correct lure rejections, emphasizes inhibitory control and is also dependent upon sustained attention with set maintenance (Table 3, Figure 3, Panels E–H). For control subjects, there was significant activation in bilateral middle frontal and middle temporal gyri, with right middle occipital gyrus, cuneus, posterior cerebellum, and left postcentral gyrus/insula. Areas of activation for rejection trials in MDD patients were noted in some similar regions (left middle frontal, right middle temporal, and middle occipital gyri), yet substantially more areas were involved in these processes in the MDD group.

These included bilateral inferior frontal/superior temporal gyri, AC/medial frontal gyri, right ventral basal ganglia/caudate, and left supramarginal gyrus. In direct comparisons, there was greater activation in the MDD group compared with the control group in bilateral inferior frontal/superior temporal gyri and left subgenual AC gyrus (Table 3, Figure 4).

Activation for Commissions

Activation for commissions emphasizes failed inhibition for lure trials and could include the affective response to commission errors (Table 4, Figure 3, Panels I–L). Activation foci for control subjects related to commission errors was observed in similar foci as for rejections: the left inferior frontal and AC gyri, bilateral middle occipital gyrus, and right cuneus. The MDD patients exhibited activation for commissions in right superior temporal and fusiform gyri and left medial frontal/orbital, middle occipital, and inferior occipital gyri as well as left cerebellum. Areas of greater commission activation for the MDD participants compared with the control group were in the left medial frontal gyrus (near the frontal pole) and right precuneus (Table 4, Figure 4, Panel B). The control group exhibited greater activation compared with the MDD participants in left superior frontal gyrus in the supplementary motor area (Figure 4, Panel C).

Prediction of Treatment Response

Seventy-five percent (15 of 20) of MDD patients completed 10 weeks of treatment with *s*-citalopram, with an average symptom reduction (HDRS scores) of 61.5%. Behavioral performance and voxel $\times$ voxel activation (for correct lure rejections and incorrect commissions) were used to predict percent change in HDRS score with treatment in the 15 patients who completed treatment. Percent HDRS change was not significantly correlated with behavioral performance measures during fMRI nor with age, age of onset, or education [r values $> .36$, p values $> .18$]. Percent improvement in HDRS score did not achieve significant correlations with commission [$r = .25$, $P = .36$] and omission [$r = -.13$, $p = .63$] errors. Initial HDRS score was marginally correlated with the percent HDRS change [$r = -.46$, $p < .07$]. The reduction in HDRS scores after treatment was correlated with pretreatment activation during rejections in the insular cortex bilaterally, right middle frontal gyrus (Brodmann area [BA] 9/46), left inferior frontal gyrus (BA 47), amygdala, and cerebellar vermis (Figure 5, Table 5). For activation after commission errors, those with greater treatment response also exhibited more activation in the rostral AC/medial prefrontal gyrus before selective serotonin reuptake inhibitor (SSRI) treatment (Figure 5, Table 5).

Discussion

Regulatory difficulties were explored in MDD with a PGNG, which comprises stimuli without obvious emotional characteristics, characteristics that might complicate cognitive data interpretation in patients diagnosed with MDD. The control and MDD groups seemed to have a different approach to the task, with a significant interaction between percent correct rejections, percent correct hits, and response time for hits. The control group was faster and made fewer errors of omission, or had more correct hits “Go.” They also had nominally more incorrect “No-go” responses compared with the MDD group but not significantly so. The MDD group seemed more willing to accept errors of omission, or missed “Go” responses, putatively in the context of greater behavioral inhibition, or reduced errors of commission for “No-go” events. The present results provide greater contextual differences to demonstrate executive functioning performance decrements in MDD (Alexopoulos *et al.* 2005; Channon and Green 1999; Degl’Innocenti *et al.* 1998; Jones *et al.* 1988; Watkins and Brown 2002). The MDD patients do show greater behavioral inhibition or decreased responding, whereas behavioral activation or approach behaviors are decreased (Campbell-Sills *et al.* 2004; Kasch *et al.* 2002).

The MDD patients had greater functional activation compared with the control group during successful rejections in areas known to be important for successful inhibitory control (Rubia *et al.* 2001). The increased activation in the MDD patients in AC, inferior frontal/superior temporal gyri, insula, and inferior parietal lobe are consistent with recruitment to aid in successful task completion, similar to work with healthy aging and other clinical groups (Fitzgerald *et al.* 2005; Langenecker *et al.* 2004; Robinson and Starkstein 1989). It is also possible that behavioral inhibition control systems involving regulation of behavior and emotions are overactive in MDD to counteract the intense emotional experiences of this group or as an intrinsic part of their symptom constellation. It is also possible that, because of recent negative life events, depressed patients are less likely to engage in any behaviors, which is why psychotherapies aimed at increasing proactive behaviors are as effective as pharmacotherapies in treating MDD and seem to be less prone to relapse.

The increased activation for MDD patients in primarily frontal areas during inhibitory control is consistent with a recent study of the cognitive Stroop test by Wagner *et al.* (2006) as well as with two other studies of MDD using a working memory (Harvey *et al.* 2005) and a continuous performance (Holmes *et al.* 2005) task. It should be noted that increased activation during rejection in the present study was during correct trials only, or better performance, which suggests that this activation is compensatory in nature, opposite to the pattern observed by Wagner *et al.* (2006), where increased left DLPFC and AC activation was associated with greater interference, or worse performance. These studies underline the importance of obtaining behavioral performance markers during functional imaging tasks and in using this information to understand the nature of group activation differences.

In contrast to the activation for the rejection trials, commission trials led to increased activation for the control group in the supplementary motor area (SMA) and for the MDD group in the anterior superior frontal gyrus. The SMA activation in the control group, which was significantly greater than the MDD group, is in a prominent area in the inhibitory control literature, thought to reflect the stopping or withholding component of the motoric response (Humberstone *et al.* 1997). The activation for the MDD adults in the anterior portion of the rostral anterior cingulate gyrus extending into the medial frontal gyrus, is a known site related to error processing and error correction (Botvinick *et al.* 1999; Carter *et al.* 2000). The activation differences herein suggest that the MDD patients might be processing the errors more intensely toward engaging in better strategies to avoid future errors, whereas for the control subjects the increased activation might represent attempts at stopping the current response. Noting that increased activation for commission errors was related to greater treatment responsivity, as noted in the preceding text, this activation might be related to the preserved ability of some MDD subjects to observe and learn from their own errors.

Perhaps most noteworthy was the increased activation in right dorsolateral prefrontal and left ventral cingulate, amygdala, nucleus accumbens, and insula areas during successful inhibitory trials and rostral cingulate during failed inhibitory trials that were associated with the extent of treatment response. This is the first fMRI study to show that pretreatment activation patterns during a cognitive challenge were related to therapeutic response after a standard antidepressant trial. Increased AC resting metabolic function and activity has been associated with greater response to treatment with another SSRI (fluoxetine) in two studies, a prior positron emission tomography and an electroencephalogram study (Mayberg *et al.* 1997; Pizzigalli *et al.* 2001). Activation in this area has also been shown to more closely approximate activation patterns in healthy control subjects after successful treatment with venlafaxine (Davidson *et al.* 2003). In the present study, the greater rostral AC activation associated with treatment response was observed during incorrect inhibitory trials (commissions). The increased rostral AC activation during errors associated with greater

treatment response suggests that there might be fundamental changes in the ability to detect errors in those who respond less well to treatment, whereas this activation pattern remains intact in those who will respond to treatment with SSRIs (Botvinick *et al.* 1999). It further implicates the function of the rostral, pregenual AC in treatment response (Mayberg *et al.* 1997) and pathophysiology (Drevets 1998) of MDD.

Limitations in the present study are typical for functional neuroimaging studies of depression. The sample sized was relatively small if larger than most imaging studies of MDD. Regardless, the significant differences between groups were robust and meaningful. Furthermore, our ability to show treatment related effects in activation that were not present in behavioral performance or clinical data is compelling. The present study avoided risks of including patients with high severity or duration of symptoms as well as showing medication and partial treatment activation effects. While avoiding these confound, we were still able to recruit a moderately to severely depressed group of patients who had an average of 13 years of illness, which is likely representative of the larger sample of patients with MDD. The inclusion of one left-handed subject in each of the groups might have weakened any laterality affects that could be related to motoric responses in inhibitory control, or set-shifting. Analyses without these two subjects were nearly identical to those presented herein. Finally, because we used an uncorrected threshold, there is a greater possibility of type I error. To guard against this possibility, we also used a combined cluster $\times$ volume threshold, which generally protects against excessive type I error (Ward *et al.* 1998). A final potential limitation of the present study was that all subjects completed an emotion processing task within the scanner 5–10 min before beginning the PGNG. It was possible that this might have changed the subjects approach to the task but was unlikely to affect an event-related fMRI analysis as conducted herein. The different approaches to the PGNG evident in the MDD and control groups could have been caused by emotional “priming” effects.

In summary, the present study supports an excessive or hyperactive inhibitory control system in MDD, both in behavioral data and in functional activation, in a sample of patients who were moderately to severely depressed and who were unmedicated at the time of the assessment. Notably, the increased behavioral performance in inhibition was related to worse performance in obtaining correct hits and, subsequently, nonsignificantly related to treatment response. In contrast, for correct rejections, greater activation in the inhibitory and emotion-processing systems was related to a better treatment response. The present study does support the contention that regulatory ability is potentially disrupted in MDD, even for stimuli and tasks that do not have overt emotional stimuli or processing requirements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 2. Behavioral performance interaction between major depressive disorder (MDD) and control groups. The MDD group was significantly slower and marginally less likely to respond to target stimuli. The MDD group was also less likely to respond to lure trials (e.g., commissions) if not significantly so.

Figure 3.

Panels **A–D** illustrate statistically significant activation for control (red) and depressed (blue) groups in the random effects analysis for correct target trials, at +50, +4, –4, and –50 mm right to left, respectively. Panels **E–H** depict activation for control (red) and depressed (blue) groups in the random effects analysis for correct inhibitory trials (rejections) at +54, +4, –13, and –54 mm right to left, respectively. Panels **I–L** illustrate activation for control (red) and depressed (blue) groups in the random effects analysis for incorrect inhibitory trials (commissions) at +50, +4, –4, and –50 mm right to left, respectively. Images are displayed on an anatomically standardized magnetic resonance image. Threshold is $T > 3.4$, $p < .0001$, cluster $> 160 \text{ mm}^3$ for all images.

Figure 4.

Figure demonstrating statistically greater activation in the major depressive disorder (MDD) group compared with the control group for correct (rejections, panel **A**, blue, Left 10 mm) and incorrect (commissions, panel **B**, blue, Left 17 mm) inhibitory trials. The figure also illustrates statistically greater activation in the control group compared with the MDD group for incorrect (commissions, panel **C**, red, right 2 mm) inhibitory trials. The viewing threshold on these images was relaxed to $T > 2.8$, $p < .003$, cluster $> 10 \text{ mm}^3$ for ease in viewing.

Figure 5.

Activation during successful inhibition (rejections, blue) and failed inhibitory trials (commissions, red) significantly correlated with degree of post-treatment change in the Hamilton Depression Rating Scale (HDRS). Activation foci indicate significantly increased activation during rejections (panels **A** and **B**, blue) and commission events (panel **C**, red). Images are right to left +50, -19, and +4mm; respectively. Correlations of percent depression change in HDRS after treatment are plotted against mean signal change from the Statistical Parametric Mapping (SPM) analyses for each region of interest (ROI). The percent change in HDRS is computed with the following formula $(HDRS1 - HDRS2)/HDRS1$ and thus represents the percentage of symptoms that have dissipated with treatment.

Table 1

Demographic, Clinical, and Behavioral Data for the Depressed and Control Groups

Measure	MDD M (SD)	Control M (SD)
Age	41.0 (12.2)	34.2 (11.0)
Education	15.3 (3.2)	16.1 (2.4)
Gender	15 F, 7 M	14 F, 8 M
Age of Onset	27.9 (15.1)	NA
BDI-II (Time 1, Pre-treatment) ^a	25.0 (9.7)	1.2 (1.8)
HDRS (Time 1, Pre-treatment) ^a	20.4 (7.6)	1.1 (2.0)
GAF (Time 1, Pre-treatment) ^a	56.3 (3.5)	95.0 (4.3)
BDI-II (Time 2, Post-treatment) ^b	7.5 (7.9)	NA
HDRS (Time 2, Post-treatment) ^b	6.8 (5.8)	NA
s-Citalopram Dose at Trial Completion	14.1 (5.4)	NA

MDD, major depressive disorder; M, mean; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning.

^aSignificant difference between groups.

^bSignificant difference between time 1 and time 2, $p < .05$.

Table 2

Activation in Response to Targets in Healthy Control Subjects and MDD Patients

Targets		Control Subjects			MDD Patients		
Location	BA	x, y, z Coordinates (mm)	Z	Cluster Size (voxels)	x, y, z Coordinates (mm)	Z	Cluster Size (voxels)
B. Med. Frontal	9				3, 47, 23	3.67	337
B. Ant. Cingulate	24	1, 32, 1	4.40	1155			
L. Inf. Frontal	9	-50, 18, 24	3.47	146			
L. Sup. Frontal	10				-15, 57, -4	3.59	59
R. Postcentral	3	40, -23, 55	4.08	1060			
L. Postcentral	2				-48, -27, 49	3.95	253
R. Inf. Temporal	37	47, -71, 0	4.94	1190			
R. Inf. Temporal	20	57, -32, -13	4.37	2638			
R. Mid. Temporal	19/39				48, -73, 22	3.79	247
L. Mid. Temporal	21	-57, -26, -3	4.75	1165			
R. Sup. Temporal	4				54, -30, 10	3.69	1133
L. Sup. Temporal	22				-59, -13, 6	3.71	1691
L. Inf. Parietal	40	-50, -30, 47	4.81	1600			
L. Fusiform	20	-52, -29, -23	3.88	182			
L. Inf. Occipital	18	-45, -79, -10	3.83	335			
R. Mid. Occipital	18	27, -96, 23	3.33	106			

Conversion of voxels to mm^3 is voxel $n \times 8$. MDD, major depressive disorder; BA, Brodmann area; Med., medial; Ant., anterior; B., bilateral; L., left; Inf., inferior; Sup., superior; R., right; Mid., middle.

Table 3
Activation in Response to Correct Rejections in Healthy Control Subjects and MDD Patients

Lures		Control Subjects			MDD Patients		
Location	BA	x, y, z Coordinates (mm)	Z	Cluster Size (voxels)	x, y, z Coordinates (mm)	Z	Cluster Size (voxels)
R. Mid. Frontal	8	50, 12, 37	3.72	177			
L. Mid. Frontal	6/8	-47, 10, 41	3.60	114	-43, 6, 44	3.46	79
R. Inf. Frontal, Sup. Temporal	43/41/22				59, -15, 6	5.30	3301
L. Inf. Frontal, Sup. Temporal	43/41/22				-59, -15, 8	4.04	2363
L. Sup. Frontal	10				-8, 55, -1	3.97	2198
R. Precentral	6				50, 3, 37	3.38	161
L. Postcentral	2	-45, -29, 53	3.55	193			
R. Mid. Temporal	21/39	59, -29, -4	3.60	213	50, -71, 17	3.60	250
L. Mid. Temporal	39	-45, -73, 17	3.65	209			
L. Supramarginal	40				-61, -46, 33	3.41	87
R. Cuneus	19	24, -91, 23	3.73	365			
R. Mid. Occipital	18/19	41, -79, 4	4.31	349	40, -83, 8	3.87	217
L. Mid./Inf. Occipital	18/19				-43, -75, -1	4.20	1207
R. Post. Cerebellum		40, -85, -26	3.36	115			
R. Ventral Basal Ganglia					13, 4, 7	3.48	79
Control > MDD							
L. Ant. Cingulate	11				-13, 24, -8	3.16	47
R. Inf. Frontal, Sup. Temporal	6, 42, 44				61, -13, 10	5.16	357
R. Insula	13				45, -13, 1	3.17	72
L. Postcentral	43				-66, -5, 14	3.71	176
R. Middle Temporal	22				63, -30, 3	3.16	35
L. Fusiform	37				-44, -54, -20	3.25	195

Conversion of voxels to mm³ is voxel $n \times 8$. Post., posterior; other abbreviations as in Table 2.

Table 4
Activation in Response to Commissions in Healthy Control Subjects and MDD Patients

Commissions		Control Subjects			MDD Patients		
Location	BA	x, y, z Coordinates (mm)	Z	Cluster Size (voxels)	x, y, z Coordinates (mm)	Z	Cluster Size (voxels)
L. Ant. Cingulate	32	-6, 43, 0	3.65	430			
L. Med. Frontal	10				-17, 61, -4	3.52	702
L. Inf. Frontal	9	-50, 12, 29	3.73	439			
R. Sup. Temporal	22				63, -50, 18	3.45	28
R. Fusiform	18				31, -95, -16	3.36	90
R. Mid. Occipital	37	45, -71, 3	6.00	693			
L. Mid. Occipital	18	-13, -102, 16	3.40	714			
L. Inf. Occipital	17				-27, -102, -11	3.32	56
R. Cuneus		20, -102, 3	3.67	208			
L. Post. Cerebellum					-45, -79, -27	3.37	73
Control > MDD							
R. Sup. Frontal	6	-3, 22, 57	3.14	168			
L. Sup. Frontal	10				20, 57, -3	3.38	62

Conversion of voxels to mm³ is voxel $n \times 8$. Abbreviations as in Tables 2 and 3.

Table 5

Activation for Rejections and Commissions Associated With Extent of Treatment Response (HDRS % change)

Location	BA	x, y, z Coordinates (mm)	Z	Cluster Size (Voxels)
Rejections				
R. Mid. Frontal	9/46	56, 20, 27	4.12	27
R. Inf. Frontal	9	48, 4, 26	3.54	89
L. Inf. Frontal/Insula/Amygdala/Nucleus Accumbens	13/47	-21, -1, -16	3.79	405
B. Cerebellum, Vermis		-4, -62, -7	3.88	206
Commissions				
R. Ant. Cingulate/Med. Frontal	32/9	-3, 22, 57	3.5	31

All p values $< .0001$. Conversion of voxels to mm^3 is voxel $n \times 8$. HDRS, Hamilton Depression Rating Scale; other abbreviations as in Tables 2 and 3.