Inhibition-related activity in subgenual cingulate is associated with symptom severity in major depression

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**Abstract**

Individuals with major depressive disorder (MDD) show impaired inhibitory control over negative thoughts. However, the brain mechanism underlying impaired inhibitory control in MDD has been incompletely described. The objective of this study was to examine brain function during inhibitory and error processing in a unique population of young, healthy, unmedicated MDD individuals. We hypothesized that MDD subjects would show clinically relevant alterations in brain activation in medial prefrontal and anterior cingulate cortex (ACC) during both inhibitory and error processing. Subjects performed an individualized parametric stop-signal task during functional magnetic resonance imaging (fMRI). MDD subjects (n=15) met DSM-IV criteria for current MDD. Healthy control (HC) subjects (n=16) had no lifetime history of MDD or other psychiatric disorder. The groups were not significantly different in several socio-demographic variables or in behavioral performance. A group by trial difficulty interaction on error-related activation in bilateral inferior frontal gyrus and left supragenual ACC was observed, suggesting a demand-specific failure of this circuitry in MDD. Additionally, a group by trial difficulty interaction on inhibition-related activation in subgenual ACC was observed. Among MDD individuals, inhibition-related subgenual activation correlated with depressive symptom severity, implicating subgenual ACC in inhibitory control processes related to clinical depression.

1. Introduction

Major depressive disorder (MDD) individuals show impaired inhibitory control over negative thoughts, leading to rumination and anhedonia—hallmark symptoms of this debilitating disorder (Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV); American Psychiatric Association, 2000). Although the mechanism of impaired inhibitory control in MDD has been incompletely described, emerging evidence suggests that altered functioning of a specific neural network underlies such impairment. Prior research shows that the inferior frontal gyrus (IFG) is necessary for inhibiting motor responses (Rubia et al., 2003; Aron et al., 2004). Individuals with MDD relative to non-depressed controls show altered inhibition-related activity not only in IFG, but also in a functionally connected network of structures that includes the subgenual anterior cingulate cortex (ACC) (Langenecker et al., 2007), a critical node of the cortico-limbic network that is involved in MDD (Mayberg, 1997). Related evidence shows that pre-treatment levels of activation in IFG (Langenecker et al., 2007) and subgenual ACC (Mayberg, 1997) relate to response to pharmacological treatments in MDD individuals.

Functional neuroimaging studies have shown that a network of structures that includes the medial prefrontal cortex (mPFC) and supragenual ACC (Botvinick et al., 1999; Carter et al., 2000; Brown and Braver, 2005) is involved in error monitoring and correction. Altered error-related activity in this network has been observed in MDD, and such activation has been shown to relate to response to pharmacological treatments (Langenecker et al., 2007). Taken together, these studies suggest that dysfunction of a network of structures that includes mPFC and ACC may underlie impairments in inhibitory control in MDD, which may perpetuate MDD symptoms.

Despite this evidence, MDD is a heterogeneous disorder, and more information is needed regarding the degree to which impairments in inhibitory control are specific to particular MDD subgroups, or are generalizable to the population of MDD individuals at large. Therefore, we examined brain function during inhibitory and error processing in a unique population of young, healthy, unmedicated MDD individuals. We hypothesized that MDD relative to HC subjects would show altered inhibition-related activity in a network of structures that includes IFG and subgenual ACC, and altered error-related activity in a...
neural circuit that includes mPFC and supragenual ACC. We further hypothesized that brain activity during error and inhibitory processing would relate to the severity of current depressive symptoms. To test these hypotheses, we used a previously validated parametric stop-signal task (Matthews et al., 2005), which allowed for the examination of inhibition trials that varied in difficulty and were individualized for each participant.

2. Materials and methods

2.1. Subjects

Thirty-one volunteers provided informed consent and completed this cross-sectional study, which was conducted from January 2005 to August 2006, and was approved by the University of California San Diego Human Research Protection Program. Subjects were recruited via flyers and electronic bulletin boards and completed two study visits. During visit 1, subjects completed the Structured Clinical Interview for DSM-IV (First et al., 1997) and a psychiatric interview (which was administered by a board certified psychiatrist), as well as the Beck Depression Inventory-2 (BDI-2) (Beck et al., 1961). Following visit 1, subjects were assigned to one of two groups. MDD subjects (n=15, 12F, mean age=24.5, age range=19–35) met DSM-IV criteria for current MDD, were experiencing a current major depressive episode and had a BDI-2 score of at least 15 (range=15–43). HC subjects (n=16, 10F, mean age=24.3, age range=19–37) had no lifetime history of MDD, and had a BDI-2 score<5 (range=0–3). The groups did not differ in socio-demographic characteristics, such as age (t(29)=0.06, P=N.S.), ethnicity (χ²=0.168, N.S.), and gender (χ²=1.151, N.S.).

As well as meeting criteria for current MDD, seven of the MDD individuals also met criteria for lifetime (but not current) comorbid depressive and/or anxiety disorders (i.e., dysthymia, n=3; PTSD, n=2; generalized anxiety disorder and panic disorder, n=1; dysthymia and panic disorder, n=1). None of the HC individuals met criteria for a current or lifetime psychiatric disorder. Exclusion criteria for both groups included: (1) lifetime history of alcohol or substance dependence, ADHD, psychotic or bipolar disorder; (2) antidepressive or other psychiatric medications, alcohol or substance abuse within 90 days of study participation; (3) active medical problems or suicidal ideation.

2.2. Stop task

During visit two, subjects again completed the BDI-2, and performed a stop-signal task (Logan et al., 1984; Band et al., 2003; Matthews et al., 2005) during fMRI. During the task, subjects viewed “X” and “O” stimuli that appeared on a black background back-projected to the subjects positioned inside the MRI scanner, at a visual angle of approximately 6°. The “X” and “O” stimuli (i.e., the “go” stimuli) appeared at the beginning of each of the trials. During 25% of the trials, these visual stimuli were followed by an auditory tone (i.e., the “stop” signal). Subjects were instructed to: (1) press the left mouse button when an “X” appeared on the screen; (2) press the right button when an “O” appeared; (3) not press either button when they heard a tone. Before and after each scan subjects were asked to indicate whether they clearly heard the auditory stop signal. Each trial lasted at most 1300 ms, or until the subject responded. Trials were separated by 200 ms interstimulus intervals (blank screen). The individual response latency was used to denote the period of inhibitory processing and provided a naturally jittered reference function. Subjects performed 72 total stop trials, which were pseudo-randomized throughout the task and counterbalanced. Six blocks were performed, each containing 48 total trials (12 stop and 36 non-stop trials in each block). Task instructions were presented for 12 s between blocks. One of the advantages of the task used in this study was that trials were individualized for each participant. Prior to scanning, subjects practiced the task to determine their mean reaction time (RT). Subsequently, individualized hard (i.e., tone delivered at RT, 100 ms less than RT, or 200 ms less than RT) and easy (i.e., tone delivered at 300 ms less than RT, 400 ms less than RT, or 500 ms less than RT) trials were constructed for each individual. Each subject received the same amount of hard and easy trials depending on their own RT. To compare the groups on vigilance during the task, mean RT during the non-stop trials was compared between the groups. Since the task was constructed based on each subject’s RT, the performance on the task was measured by percent correct (i.e., the ability of each individual to successfully inhibit easy and hard trials). To test for main effects of task and group, and for a group by task interaction, error rate for each individual was entered into a two-way analysis of variance (ANOVA), i.e. with task condition (hard/easy) and group (MDD/HC) as factors.

2.3. Functional imaging data acquisition and analysis

A fast event-related functional magnetic resonance imaging (fMRI) design was used. During the task, an fMRI run sensitive to blood oxygenation level-dependent (BOLD) contrast (Ogawa et al., 1990) was collected for each subject using a Signa EXCITE (GE Healthcare, Milwaukee) 3.0 T scanner (T² weighted echoplanar imaging, TR=2000 ms, TE=32 ms, FOV=230×230 mm, 64×64 matrix, 30 2.6 mm axial slices with a 1.4 mm gap, 256 scans, 512 s). fMRI acquisitions were time-locked to the onset of the task. During the same experimental session, a T₁-weighted image (MPRAGE, TR=8.0 ms, TE=4.0 ms, flip angle=12°, FOV=250×250, 1 mm³ voxels) was obtained for cross-registration of functional images. Image processing and analysis were performed with the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). Two types of multiple regression analysis were performed to test the proposed hypotheses regarding alterations in the neural substrates of error and inhibitory processing in MDD.

To test the hypothesis regarding altered error processing in MDD, preprocessed time series data for each individual were analyzed using a multiple regression model consisting of four task-related regressors: 1) error responses during hard trials (i.e., RT, RT-100, RT-200), 2) error responses during easy trials (i.e., RT-300, RT-400, RT-500), 3) correct responses during hard trials, 4) correct responses during easy trials. To test the hypothesis regarding altered inhibitory processing in MDD, preprocessed time series data for each individual were analyzed using a multiple regression model consisting of three task-related regressors: 1) non-inhibit trials, i.e., trials where no auditory stop signal was administered, 2) hard stop trials, i.e., difficult to inhibit trials (RT, RT-100, RT-200), and 3) easy stop trials, i.e., easy to inhibit trials (RT-300, RT-400, RT-500). Five additional regressors were included in each model as nuisance regressors: three movement regressors to account for residual motion (in the roll, pitch, and yaw directions), and regressors for baseline and linear trends to account for signal drifts. A Gaussian filter with a full width-half maximum of 6 mm was applied to the voxel-wise percent signal change data to account for individual variation in the anatomical landmarks. Data from each subject were normalized to Talairach coordinates (Talairach and Tournoux, 1998).

Primary contrasts between regression coefficients from the AFNI program 3DDeconvolve were entered into two-sample t-tests. We examined activation differences between the groups for: 1) [all errors—all correct] trials during the first regression analysis and 2) [hard inhibit—easy inhibit] trials during the second regression analysis. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false positive areas of activation (Forman et al., 1995). Based on the whole brain analysis,
an a priori voxel-wise probability of $P<0.05$ in a cluster of 1024 μL with 16 connected voxels resulted in an a posteriori cluster-wise probability of $P<0.05$. Only activations which satisfied the volume and voxel connection criteria were extracted and used for post-hoc correlations between brain activation and behavioral performance (i.e., error rate), as well as between brain activation and severity of depressive symptoms (i.e., BDI-2 scores). Due to equipment failure behavioral responses were not recorded in three MDD and one HC subjects; thus, the error-related analyses shown represent data from 12 MDD and 15 HC subjects.

3. Results

3.1. Behavioral

The groups did not differ in their mean RT ($F(1,21)=0.055$, N.S.) during the non-stop trials, suggesting that the groups did not differ in vigilance during the task. By design, a significant effect of task (easy/hard) on error rate was observed, i.e. significantly more errors during hard than during easy trials in both groups ($F(1,23)=184.2, P<0.0001$). The MDD and HC groups were not significantly different in mean % correct during hard (HC: mean=31.3%, S.D.=26.0; MDD: mean=24.0%, S.D.=20.2) or easy (HC: mean=95.1%, S.D.=5.5; MDD: mean=87.2%, S.D.=15.9) trials. No significant group ($F(1,23)=1.789$, N.S.) or group by task ($F(2,23)=0.006$, N.S.) effects on error rate were observed indicating that the MDD and HC groups were not significantly different in their accuracy during hard or easy trials.

3.2. Functional neuroimaging

For the error analysis, a significant group (MDD versus HC) by condition (correct versus error) interaction on activation in left supragenual ACC and bilateral IFG/insular cortex (IC) was observed (Fig. 1). The error-related brain activation of the MDD and HC groups during hard error, easy correct and hard correct trials was not significantly different ($t(24)'s<1.7, P's>0.1$, Fig. 1). However, despite the lack of behavioral differences between the groups, the MDD relative to the HC group showed significantly less activation in left supragenual ACC ($t(24)=2.11, P<0.05$) and bilateral IFG/IC (right: $t(24)=3.09, P<0.01$; left: $t(24)=2.85, P<0.01$) during easy error trials (Fig. 1), suggesting a demand-specific failure of this circuitry in MDD. No significant correlations were observed between activation in any of these three regions with either error rate or BDI-2 score in the MDD, HC or combined groups ($R's$ between $-0.39$ and $-0.04$, $P's>0.05$, uncorrected).

For the inhibitory processing analysis, a significant group (MDD versus HC) by condition (hard versus easy) interaction on subgenual ACC activation was observed such that the MDD individuals showed less activation during hard versus easy trials, whereas the HC subjects showed more activation for this contrast (Fig. 2). Although a significant correlation was not observed between subgenual ACC activity and error rate in the MDD, HC or combined group ($R's$ between $-0.3$ and $0.37$, $P's>0.05$), symptom severity in the MDD group (as indicated by total BDI-2 scores on the day of scanning) correlated positively with the percentage of BOLD signal change in the left subgenual ACC ($r=0.50$, $P<0.01$, two-tailed).

![Fig. 1. Error processing. Decreased activation during all errors minus all correct trials was observed in subjects with current major depressive disorder (MDD) compared to healthy control (HC) subjects within bilateral inferior frontal gyrus/insular cortex (IFG/IC) [right: $x=29/y=26/z=11, t=3.0$; left: $x=-13/y=24/z=11, t=2.5$] and left supragenual ACC (supra ACC) [$x=-7/y=38/z=27, t=1.7$]. Bar graphs show extracted % signal changes within these areas during each trial type in each group.](https://example.com/fig1.png)
subgenual ACC for hard trials ($R^2 = 0.64$, $P<0.05$) and easy trials ($R^2 = 0.64$, $P<0.05$, Fig. 2).

4. Discussion

Consistent with our a priori hypotheses, we observed altered inhibition-related subgenual ACC activity, which was related to the severity of current depressive symptoms. Although both MDD and HC subjects showed subgenual ACC deactivation during performance of hard and easy inhibit trials, the MDD subjects exhibited more subgenual ACC deactivation as inhibitory load was increased, whereas the HC individuals displayed less. Prior research in healthy volunteers indicates that attending to one’s internal emotional state activates the subgenual ACC (Lane et al., 1997). Related evidence indicates that the subgenual ACC is also activated when healthy volunteers rest passively (Raichle et al., 2001), a behavioral state during which individuals focus frequently on autobiographical thoughts and memories (Mazoyer et al., 2001). Conversely, accumulating evidence suggests that the subgenual ACC is deactivated during performance of demanding cognitive tasks that require an external focus of attention (Kennedy et al., 2006; Marsh et al., 2006). Such deactivation may be an indicator of the degree to which affective processing is inhibited (Gusnard et al., 2001). Therefore, one speculative interpretation of our subgenual ACC finding is that the increased inhibitory load was distracting to MDD subjects (i.e. less focus on their emotional state and thereby more subgenual ACC deactivation), and frustrating to HC subjects (i.e. more affective processing and thereby less subgenual ACC deactivation). This interpretation is consistent with research indicating that MDD is associated with an impaired ability to disengage from negative affective processing (Lyubomirsky et al., 1998; Wenzlaff and Bates, 1998; Ellenbogen et al., 2002; Siegle et al., 2002). In light of this evidence, our findings implicate the subgenual ACC in inhibitory control of emotion processing, and suggest that MDD symptom severity may relate to the ability to regulate and “put the brakes on” subgenual ACC activity, which presumptively frees inhibitory cognitive resources that are necessary for discrete and adaptive emotional experiences that are not sustained or prolonged.

We also observed altered error-related activity in the IFG/IC and supragenual ACC. Specifically, although both groups deactivated the left supragenual ACC and bilateral IFG/IC during hard error trials, HC subjects activated whereas MDD subjects deactivated these regions during easy error trials. Prior work in non-depressed volunteers indicates that distraction by negative pictures during performance of a working memory task is associated with increased IFG activity, and that less IFG activity to emotional distractors is observed in subjects who rated emotional distractors as less distracting (Dolcos and McCarthy, 2006). These findings show that the IFG is critically involved in the successful inhibition of emotional information. Our observation that both groups deactivated bilateral IFG during hard error trials suggests that hard trials were implicitly appraised as more challenging, and subjects were unable to effectively engage circuitry for responding correctly during these trials. In contrast, the finding that HC subjects activated whereas MDD subjects deactivated these regions during easy error trials suggests a demand-specific failure of this network in MDD, an interpretation that is supported by a recent study in which hypoactivity of a network of structures that included
bilateral IFG was observed during performance of an oddball detection task in MDD individuals (Wang et al., 2008). Importantly, group differences were observed not only in bilateral IFG, but also in the supragenual ACC and IC—structures that are necessary for error awareness (Klein et al., 2007). Therefore, our findings suggest that MDD is associated with an inability to appropriately activate a neural network that is involved both in the awareness of one’s internal state and in the modulation of that state.

Taken together, our results are consistent with an extensive body of evidence indicating that MDD as a disorder resulting from altered activation within a network of cortico-limbic structures (Mayberg et al., 1999) that is involved in emotion processing and regulation. However, our results need to be considered in the context of a recent study that implemented a parametric go/no-go task (PGNG) in MDD and non-MDD individuals (Langenecker et al., 2007). In both studies, altered inhibition-related activity in subgenual ACC and dysregulated error-related activity in supragenual ACC and IFG were observed, emphasizing the critical role that these structures play in regulatory processing in MDD. Whereas our results suggest that MDD individuals have an impaired ability to engage neural circuitry involved in error processing and correction, Langenecker observed that MDD subjects showed increased activity during error processing. This directional difference may be partially explained by the fact that functionally different areas were engaged, an interpretation that is supported by the correlation between error-related activity in the Langenecker study, which was not observed in the current study. Similarly, we observed correlations between subgenual ACC activity and a measure of clinical depression symptom severity, which was not observed in the Langenecker study, suggesting that functionally distinct ACC subregions were engaged in each study. Additionally, the PGNG and stop tasks engage slightly different constructs (i.e., inhibiting a not yet initiated motor response in the PCNG task versus stopping an already initiated response in the stop task), which may partially explain the differences between the current and Langenecker experiments.

In summary, the present findings add to prior work suggesting that the specific subregions of the mPFC and ACC are involved in regulatory processes related to MDD symptoms. Improving inhibitory control processes and inhibiting negative thoughts in particular is important in cognitive-based psychotherapies for MDD (Beck, 1963). In the context of prior intervention studies (Mayberg et al., 2005; Sible et al., 2006), the present findings agree with the notion that a therapeutic focus on thought processes that are particularly difficult to inhibit may affect activity within the mPFC–ACC network and have beneficial therapeutic effects. One unique strength of the current study was the design of the task, which included individualized easy and hard trials. This procedure effectively controlled for potential differences between the groups on measures such as arousal and processing speed, which could otherwise have confounded our findings. However, it is possible that our findings may have been related to general intellectual ability. Although we did not obtain direct measures of IQ, there was no indication that MDD individuals had different levels of an indirect proxy of IQ, level of education. The MDD subjects in the current study were unmedicated, young and healthy, which eliminated effects of medication and medical comorbidities. Because prior studies have shown that executive functioning deficits such as context processing do not necessarily generalize across major psychiatric disorders (Holmes et al., 2005), it will be important to examine the degree to which the current findings generalize to other MDD subpopulations. Therefore, future studies should examine inhibitory and error processing in treatment-seeking MDD individuals, as well as MDD subjects with lower levels of anxiety.

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