Research report

Decreased functional coupling of the amygdala and supragenual cingulate is related to increased depression in unmedicated individuals with current major depressive disorder

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Abstract

Background: Individuals with major depressive disorder (MDD) show abnormal functional coupling (FC) between several nodes of a widely distributed cortico-limbic network that includes the amygdala and anterior cingulate. The aim of this study was to examine the degree to which alterations in amygdala–cingulate FC relate to severity of current depressive symptoms in a group of depressed individuals without significant co-morbidities.

Methods: Fifteen young, unmedicated subjects with current MDD and 16 healthy controls (HC) with no lifetime history of psychiatric illness performed a validated emotional face-matching task during functional magnetic resonance imaging. Amygdala activity and strength of amygdala–cingulate FC during emotional face processing were contrasted between the groups.

Results: Although both groups activated the extended amygdala (EA) during emotion processing, the MDD relative to the HC group showed more task-related co-activation of the subgenual cingulate, which is involved in processing negative self-referential information; and less co-activation of the supragenual cingulate, which is involved in the cognitive control of emotion. Greater depressive symptom severity correlated positively with decreased FC between bilateral EA and supragenual cingulate in MDD subjects.

Limitations: This study included a demographically homogeneous population of subjects, which may limit the generalizability of the findings.

Conclusions: These results elaborate current neurobiological models of MDD by providing unique evidence that decreased FC between the EA and supragenual cingulate is related to increased severity of current depressive symptoms. We speculate that the clinical manifestations of MDD may result in part from a failed ability to co-activate a cognitive control network during emotion processing.

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Keywords: Depression; Amygdala; Cingulate; Faces; Brain imaging

1. Introduction

Functional brain imaging studies have contributed greatly to the development of models (Drevets, 2001; Mayberg, 1997), which characterize the neural system alterations that drive the symptoms of major depressive
disorder (MDD). Converging functional neuroimaging approaches have shown that MDD is associated with altered functioning of several interconnected cortico-limbic structures (Drevets et al., 1998; Mayberg, 1997). Recently, methods have been developed, which allow one to examine the degree to which a given brain region co-activates with other brain regions (Fox et al., 2005; Friston et al., 1997). In order to increase the neurobiological understanding of MDD, these methods have been employed in several studies, which have identified MDD-associated alterations in the functional coupling (FC) of cortico-limbic structures in the resting state (Greicius et al., 2007), and during performance of emotionally evocative tasks (Chen et al., 2008; Pezawas et al., 2005).

Consistent with the evidence that the amygdala and anterior cingulate cortex (ACC) are critical components of the neural network that is dysregulated in MDD, a prior study (Pezawas et al., 2005) reported that the presence of the short allele(s) of the human serotonin transporter gene, which is associated with increased amygdala reactivity and an increased risk of MDD when accompanied by stressful life events (Hariri et al., 2005), is related to increased FC between the amygdala and subgenual cingulate. This study also identified a supragenual portion of the ACC, which showed decreased FC with the amygdala. In a subsequent treatment study (Chen et al., 2008), decreased FC between the amygdala and supragenual ACC was observed at baseline in individuals with current MDD relative to healthy controls (HC), and antidepressant treatment was associated with a significant increase in FC between the amygdala and supragenual ACC in MDD subjects. Related evidence examining steady state blood flow changes using functional magnetic resonance imaging (fMRI) also suggests that resting state FC between the amygdala and supragenual ACC is decreased in MDD relative to non-MDD individuals (Anand et al., 2005). Therefore, compelling evidence supports the notion that the amygdala–ACC circuit is dysregulated in MDD, both at rest and in response to emotionally evocative tasks.

These findings are in line with the evidence that altered functional activity of the amygdala and ACC represents a neural correlate of MDD symptoms. Several positron emission tomography (PET) and fMRI studies indicate that neural substrates such as the amygdala and subgenual cingulate, which are critical for emotion processing, are hyperactive in individuals with MDD both at rest (Mayberg et al., 1999) and during performance of emotional tasks (Drevets et al., 1997; Sheline et al., 2001; Siegle et al., 2002; Siegle et al., 2007). Conversely, brain structures such as the dorsolateral prefrontal cortex and supragenual ACC, which are involved in the cognitive control of behavior (Aron, 2007) and emotion (Ochsner and Gross, 2005), are hypoactive in individuals with MDD both at rest (Mayberg et al., 1999) and during performance of interference processing tasks that require cognitive control (George et al., 1997). In summary, MDD has been repeatedly associated with dysfunction of the amygdala, as well as both the supragenual and subgenual ACC. This dysfunction takes the form of altered functional activation of these structures, as well as dysregulated FC between these brain regions both at rest and during performance of emotional and cognitive tasks.

Although this evidence has contributed greatly to understanding the neural basis of MDD, there are methodological issues that limit the scope of this research. For example, the chronic effects of depression on brain activation have not been sufficiently addressed, and most studies have included subjects who have experienced a wide range of depression severity over a variable period of time. To minimize the influence of these potential confounds, we used fMRI to compare the brain responses of a group of young, unmedicated individuals with current MDD to those of a group of age- and education-matched HC subjects with no history of MDD, during performance of a validated emotion emotion-processing task (Paulus et al., 2005). The objective of this study was to expand on the clinical relevance of amygdala–ACC FC by relating these FC measures to severity of current depression. Based on the evidence described above, we hypothesized that greater depressive symptom severity would be related to decreased FC between the amygdala and supragenual ACC, and to increased FC between the amygdala and subgenual cingulate. Support for this hypothesis would provide unique evidence regarding the neurobiological basis of MDD, and elaborate existing models of this common and debilitating disorder.

2. Methods

Thirty-one volunteers provided informed consent and completed this study, which 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, all subjects completed the Structured Clinical Interview for DSM DSM-IV (First et al., 1997) and a psychiatric interview (which were administered by a board certified psychiatrist), as well as the Beck Depression Inventory-II (BDI-2) (Beck et al., 1961). Following visit 1, subjects were assigned to one of two groups (Table 1). MDD subjects (n=15, 12F, mean...
Table 1
MDD subject characteristics

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>BDI-II score</th>
<th>Age of first major depressive episode (MDE)</th>
<th>Lifetime number of MDE</th>
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<tr>
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<td>25</td>
<td>18</td>
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<tr>
<td>15</td>
<td>40</td>
<td>14</td>
<td>3</td>
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</table>

age±S.D.: 24.5±5.5) 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±S.D.: 24.3±5.0) had no lifetime history of MDD, and had a BDI-2 score <5 (range=0–3).

As well as meeting criteria for current MDD, seven of the MDD individuals also met criteria for lifetime (but not current) co-morbid depressive and/or anxiety disorders. Specifically, three MDD subjects met criteria for past but not current dysthymia, two MDD subjects met criteria for past but not current PTSD, one MDD subject met criteria for past but not current generalized anxiety disorder and panic disorder and one MDD subject met criteria for past but not current dysthymia and panic disorder. 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) use of antidepressants or other psychiatric medications within 90 days of study participation, (3) alcohol or substance abuse within 90 days of study participation; and (4) active medical problems or suicidal ideation.

During visit 2, subjects performed during scanning a slightly modified version (Paulus et al., 2005) of a validated emotional face face-matching task (Hariri et al., 2002). During each 5-second trial of this task, a target stimulus was presented on the top of the screen, and two probe stimuli were presented on the bottom of the screen. Subjects were instructed to match the probe that was identical to the target by pressing the left or right button of a computer button box. Emotional (i.e. angry, fearful and happy) faces were presented in the task blocks and shapes (i.e. ovals and circles) were presented in the control blocks. Each block consisted of six consecutive trials and was presented three times in a pseudo-randomized order. A fixation cross was interspersed between blocks. For each trial, response accuracy and reaction time (RT) data were recorded. To determine whether there were significant differences between the groups in mean RT during the two phases of the task, a 2-sample t-test was performed for all face-matching trials and another for shape-matching trials. Two additional t-tests were performed to examine differences between the groups in response accuracy during these two phases.

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 Sigma EXCITE (GE Healthcare, Milwaukee) 3.0T scanner (T2-weighted echoplanar imaging, TR=2000 ms, TE=32 ms, FOV=230 mm×230 mm, 64×64 matrix, 30 2.6 mm axial slices with a 1.4 mm gap, 256 scans, 512 s). BOLD signal acquisition was time-locked to the onset of the task. During the same experimental session, a T1-weighted image (MPRAGE, TR=8.0 ms, TE=3.0 ms, flip angle=12°, FOV=250 mm×250 mm, 256×256 matrix, 172 1 mm sagittal slices) was obtained for cross-registration of functional images.

Image processing and analysis was performed with the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). Echoplanar image intensity images were co-registered to the 128th image using a 3D-coregistration algorithm. Three motion parameters (droll, dpitch, dyaw) were used as nuisance regressors to account for motion artifacts. Four orthogonal task regressors (i.e. happy, angry, fearful, circle/oval) were convolved with a modified gamma variate function (Boynton et al., 1996) to account for the delay and the dispersion of the BOLD signal due to hemodynamics. Two additional regressors were used to model baseline and linear trends. The AFNI program 3dDeconvolve was used to calculate the estimated voxel-wise response amplitude. Data were spatially smoothed with a 4 mm full-width half-maximum (FWHM) Gaussian filter.

Data for each individual were normalized to Talairach coordinates (Talairach and Tournoux, 1998). We examined activation differences between the groups for all face-matching minus all shape-matching trials by entering the regression coefficients from the AFNI program 3dDeconvolve into a two-sample t-test. To estimate the task effect, a one-sample t-test was performed for all face-matching minus all shape-matching trials. A region of interest (ROI) analysis was conducted using an extended amygdala (EA) mask.

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which included the amygdala proper and the uncus, as defined by the Talairach Daemon Atlas (Lancaster et al., 2000). Based on Monte-Carlo simulations using AFNI’s program AlphaSim, it was determined that a voxel-wise a priori probability of 0.05 would result in a corrected cluster-wise activation probability of 0.05 if a minimum volume of 128 μl and 2 connected voxels was considered. The ROI mask was superimposed on each individual’s voxel-wise percent signal change brain image. The corrected voxel-wise probability in the ROI corresponded to p < 0.0001.

Based on prior evidence that FC between the amygdala and ACC during an emotional task is disrupted in MDD individuals (Chen et al., 2008), we measured the strength of the echoplanar signal covariation between the bilateral EA and all voxels in the ACC. The average activation from the clusters in the left and right EA, as defined by the task effect, were extracted and used for this analysis. Prior to this analysis, the individual raw signal datasets were: (a) band-pass filtered (0.009 < f < 0.08), (b) corrected for slice-dependent time shifts, (c) corrected for interleaved acquisition, (d) corrected for rigid body head motion, and (e) warped to conform to the Talairach atlas. The FC analysis performed in the present study was based on validated methods (Fox et al., 2005; Friston et al., 1997), which have been employed in several other published studies investigating the degree of co-activation between brain regions during performance of emotional tasks (Heinz et al., 2005; Pezawas et al., 2005). Based on these studies, our FC estimates used the whole time series of the task, and not the difference between specific task stimuli. Individual time courses in the processed raw signal datasets were extracted for the seed ROIs in left and right EA. These two seeds were identified based on the task-related activation in all 31 subjects related to all face-matching minus all shape-matching trials. Time points in each individual’s time course were censored if they were more than 2 S.D. from the individual’s average activation. The extracted time courses were temporally smoothed (circular convolution) and entered as regressors of interest, along with the three movement (droll, dpitch, dyaw) regressors, and baseline and linear trend regressors into a deconvolution analysis. The resulting correlation coefficients were then calculated for each voxel in the ACC, providing correlation maps of the relationships between the time courses of activation in the voxels within the seeded ROI’s and all voxels in the ACC. The Fisher’s z transforms of these correlation maps were then warped to conform to the Talairach atlas and a Gaussian blur of 4 mm FWHM was applied to allow for a between-groups comparison using a two-sample t-test. Correlational analyses between the strength of FC and depressive symptom severity were then carried out with SPSS 10.0 (Norusis 1990).

3. Results

3.1. Sociodemographic and clinical

By design, the MDD relative to the HC subjects had significantly higher depression ratings (Table 1). However, 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.).

3.2. Behavioral

The MDD and HC groups were not significantly different in RT for faces (MDD: mean RT = 1.37 s (S.D. = 0.27), HC: mean RT = 1.35 s (S.D. = 0.36); t(26) = 0.05, p = N.S.), or shapes (MDD: mean = 0.83 s (S.D. = 0.04), HC: mean = 0.91 s (S.D. = 0.06); t(26) = 1.3, p = N.S.). Additionally, the groups were not significantly different in percent correct for faces (MDD: mean = 98% (S.D. = .04), HC: mean = 98% (S.D. = .05); t(26) = 0.05, p = N.S.) or shapes (MDD: mean = 98% (S.D. = .01), HC: mean = 97% (S.D. = .01); t(26) = 0.6, p = N.S.).

3.3. Functional neuroimaging

To validate prior evidence that the amygdala is hyperactive in MDD (Drevets et al., 1997; Sheline et al., 2001; Siegle et al., 2002; Siegle et al., 2007), a between-groups ROI (i.e. bilateral EA) 2-sample t-test was performed on task-related (i.e. face-matching minus shape-matching) brain response. Consistent with prior evidence, we observed significantly increased activity in bilateral EA in MDD relative to the HC subjects (Table 2).

Table 2

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<thead>
<tr>
<th></th>
<th>Volume</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t-val</th>
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<tr>
<td>(A) Group effect</td>
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<td></td>
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<tr>
<td>MDD&gt;controls</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Right extended</td>
<td>192</td>
<td>30</td>
<td>-4</td>
<td>-29</td>
<td>3.06</td>
</tr>
<tr>
<td>Amygdala (EA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left EA</td>
<td>128</td>
<td>-22</td>
<td>1</td>
<td>-24</td>
<td>2.90</td>
</tr>
<tr>
<td>(B) Task effect</td>
<td></td>
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<td></td>
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<tr>
<td>MDD + controls</td>
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<tr>
<td>Right EA</td>
<td>896</td>
<td>24</td>
<td>-6</td>
<td>-14</td>
<td>4.56</td>
</tr>
<tr>
<td>Left EA</td>
<td>1216</td>
<td>-22</td>
<td>-5</td>
<td>-16</td>
<td>4.33</td>
</tr>
</tbody>
</table>
In addition to the small but significant between between groups difference in bilateral EA activity, a large area in the bilateral EA was observed for the face-matching minus shape-matching contrast in all 31 subjects (Fig. 1).

3.4. Functional coupling (FC)

The average activation in each of the clusters (i.e. from the task effect in all 31 subjects) in the bilateral EA was extracted and used for FC analysis. As described above, the relationships between the time courses of activation in the right and left EA seed ROIs, and all voxels in the ACC were examined. We observed increased FC (i.e., Fisher’s z score) between bilateral EA and subgenual cingulate, and attenuated FC between bilateral EA and supragenual ACC in MDD relative HC individuals (Fig. 1).

3.5. Brain–behavior relationships

Pearson correlations were examined between the severity of depressive symptoms (i.e. BDI-2 scores) and the strength of FC (i.e. Fisher’s z score) between the bilateral EA and supragenual and subgenual cingulate in the MDD group. Individuals with higher scores on the BDI-2 showed weaker FC between bilateral EA and supragenual ACC (right: \( r = -0.67 \), left: \( r = -0.73 \), \( p < 0.05 \), corrected for multiple comparisons) (Fig. 1). In comparison, there was no significant correlation between depressive symptom severity and the strength of FC between bilateral EA and subgenual cingulate (right: \( r = -0.29 \), left: \( r = -0.09 \), \( p > 0.3 \)).

4. Discussion

This investigation yielded three main results. First, consistent with the a priori hypotheses, the MDD relative to HC subjects showed increased activity in bilateral EA during performance of a validated emotion-processing task. Second, supporting the idea that MDD is associated with dysregulated cortico-limbic connectivity, we observed decreased FC between the supragenual cingulate and bilateral EA and increased FC between the subgenual cingulate and bilateral EA in MDD relative to HC subjects. Third, decreased FC between the supragenual cingulate and bilateral EA was positively related to greater depressive symptoms in MDD individuals. Taken together, these findings support the conceptualization of MDD as a dysregulated networks disorder characterized by overactivity of an emotion emotion-processing circuit and underactivity of functionally connected control network.

The amygdala is critically involved in several affective processes that are related directly to mood disorders, such as fear conditioning (LeDoux et al., 1990), recognizing emotion in human faces (Adolphs, 2002), interoception (Craig, 2002), and autonomic modulation (Critchley, 2005). This structure is necessary for the acquisition of emotional memories (LaBar et al., 1995), and it has been proposed that the amygdala hyperactivity observed in MDD may represent a neural correlate of rumination on depressogenic thoughts (Drevets, 2001). Our findings suggest that amygdala hyperactivity is present early in the course of MDD. One possibility is that the EA hyperactivity observed in the MDD subjects was related to differential connectivity of this structure to the ACC. Our results indicate that, although both groups activated the EA during emotion processing, the MDD relative to the HC group showed more co-activation of circuitry (i.e. subgenual cingulate) that is involved in processing negative self-referential information, and less co-activation of circuitry (i.e. supragenual cingulate) that is involved in the cognitive control of emotion (Ochsner and Gross, 2005). We speculate that MDD symptoms may result in part from an impaired ability to appropriately co-activate a cognitive control network during emotion processing.

Like other prior studies (Chen et al., 2008), the methods employed in the present study do not allow one to draw conclusions regarding a directional relationship between the regions of interest. Future studies could expand on the present results by employing an event related task and effective connectivity (Friston and Buchel, 2000) methods to test directional hypotheses, i.e. altered modulation of the amygdala by the ACC in MDD. Support for such a hypothesis is provided by elegant animal studies which have identified efferent projections from the ACC to the amygdala (Paus, 2001), and by a recent comprehensive characterization of ACC connectivity, in which 16 seed ROIs within the ACC were identified, and areas across that brain that co-activated with each of these ROIs were identified (Margulies et al., 2007). This study reported that activity in ROIs which closely overlap the supragenual cingulate area in the current study, predicted activity in the amygdala and related medial temporal lobe structures.

We also observed increased FC between the EA and subgenual cingulate, which is consistent with a prior study that implemented an independent components...
A. Task-related activation in all 31 Subjects

B. Group Differences in EA-Cingulate FC

C. Relationship between Depressive Symptom Severity and Strength of EA-Supragenual Cingulate FC in MDD

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analysis and reported greater co-activation of the subgenual cingulate, thalamus, pregenual and orbitofrontal cortex in MDD relative to HC subjects (Greicius et al., 2007). That study also found that the length of current depressive episode correlated positively with the strength of subgenual cingulate FC. These findings were interpreted as evidence that alterations in resting state FC in MDD are driven by activity in the subgenual cingulate. In addition to the Pezawas study (Pezawas et al., 2005), in which the presence of the short allele(s) of the human serotonin transporter gene was related to increased FC between the amygdala and subgenual cingulate, at least one prior study has reported decreased FC between the amygdala and subgenual cingulate in individuals with MDD during performance of an emotional task (Chen et al., 2008). We agree with the authors of this study who suggested that the differences in directionality between the studies, i.e. amygdala–subgenual cingulate FC was increased in the Pezawas study (and in the current study), and decreased in the Chen study, are likely partially the result of methodological differences between the tasks. Additionally, the subjects in the Chen study were significantly older than the subjects in the current study. Our findings extend this work and provide support for the notion that FC within an emotion emotion-processing circuit that includes the subgenual cingulate is abnormal in MDD both at rest and during emotion processing. Converging results suggest that the subgenual cingulate is hyperactive in MDD individuals at rest, and in healthy volunteers during induced sadness (Mayberg et al., 1999), as well as in healthy volunteers attending to their internal emotional states (Lane et al., 1997). Related evidence suggests that this structure is deactivated by performing difficult cognitive tasks that require an external focus of attention and that prompt inhibitory control processes (Kennedy et al., 2006; Marsh et al., 2006).

In summary, the present study contributes unique evidence that MDD is associated with hyperactivity of a network that includes the amygdala and subgenual cingulate, and with hypoactivity of an amygdala–supragenual cingulate circuit. This study was limited by a modest sample size and potentially limited generalizability. Therefore, future studies should investigate amygdala–ACC FC alterations in other specifically defined subpopulations of MDD patients (i.e. older vs. younger age, many vs. few co-morbidities, earlier vs. later age of MDD onset). Similarly, prior studies have shown that the extended EA is critically involved in the phenomenology of anxiety disorders (Etkin and Wager, 2007), and future studies should also examine the degree to which the current findings generalize to MDD individuals with lower levels of anxiety. In this study, we aimed to bring together two fields of research in depression, i.e. neural systems basis of this disorder and the cognitive behavioral conceptualization of depression, to identify the potential brain mechanism underlying altered emotion processing in these individuals. Our findings replicate prior evidence that amygdala–ACC connectivity is altered in MDD, and provide unique evidence that such alterations are related to severity of current depressive symptoms.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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References


Fig. 1. (A) Significantly greater task-related activation was observed for face-matching minus shape-matching trials in the combined [MDD and healthy control (HC)] group of individuals (n=31). (B) Significantly weaker correlations between activity in the extended amygdala (EA) and supragenual cingulate (supra ACC), and significantly stronger correlations between activity in the EA and subgenual cingulate (sub ACC) were observed in the MDD relative to the HC group, reflecting stronger EA–subgenual cingulate functional coupling (FC) and weaker EA–supragenual cingulate FC in MDD. (C) Increased severity of current depressive symptoms [i.e. greater scores on the Beck Depression Inventory-II (BDI-2)] was related to weaker EA–supragenual cingulate FC in the MDD group.

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