Subgenual anterior cingulate activation to valenced emotional stimuli in major depression

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Sponsorship: Supported by NIMH Grant MH59259 to Ian H. Gotlib.

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Received 26 July 2005; accepted 22 August 2005

Major depression has been associated with anomalous activation in the subgenual anterior cingulate cortex, but its response to emotional stimuli is poorly understood. The primary goal of this study was to compare levels of activation in the subgenual anterior cingulate cortex of diagnosed depressed and nondepressed participants in response to happy and sad facial expressions of affect. Whereas cognitive theories of depression predict increased activation to negative stimuli, depressed participants were found to exhibit increased activation to both types of stimuli in the subgenual anterior cingulate cortex. Importantly, the loci were in different regions of the subgenual anterior cingulate cortex, suggesting that there is functional specialization in the processing of negatively and positively valenced stimuli. NeuroReport 16:1731–1734 © 2005 Lippincott Williams & Wilkins.

Keywords: affective neuroscience, emotion, functional magnetic resonance imaging, information processing, neurophysiology, unipolar depression

Introduction

The anterior cingulate cortex (ACC) is involved in attentional processes that regulate both cognition and emotion [1] in its caudal and rostral regions [2], respectively; it has also been postulated to play a central role in the neurobiology of depression and affective disorders [3]. Given its role in affect, the rostral ACC and, in particular, the subgenual region of the rostral ACC, has been the focus of a number of studies. A number of investigators using positron emission tomography have found depressed patients to be characterized by hypoactivation in the subgenual ACC at rest, relative to controls [4]. Drevets and colleagues [4] suggested that this subgenual region hypoactivity may be an artifact of reduced cortical volume, although studies examining this possibility have yielded inconsistent results [5].

An alternative approach to the study of the role of the subgenual ACC in depression is to focus on brain activation during cognitive-affective processes. Cognitive theories of depression, for example, predict that depressed individuals should exhibit increased activation to negative stimuli [6]. Several investigators have now examined patterns of activation in the ACC in depressed individuals as they process emotional stimuli. George and colleagues [7], for example, found evidence of ACC hypoactivation in depressed, relative to control, participants on the Stroop task. Importantly, however, hypoactivation was not seen in the subgenual region of the ACC; moreover, George et al. [7] found hypoactivation in response to neutral, rather than to emotional, stimuli. Kumari and colleagues [8] reported greater activation in the subgenual ACC on a cognitive affect-generation task in treatment-resistant depressed patients than in controls. Contrary to expectation, this hyperactivity was found only for positive, and not for negative, affective states. It is possible that this pattern reflects the additional effort required by depressed patients to generate positive rather than negative affect. Indeed, a recent meta-analysis found that differences in task difficulty affect blood flow within the ACC [9]. The aim of the present study was to further delineate the role of the subgenual ACC in the processing of emotional stimuli in depression. To circumvent the possibility that subgenual activation is confounded with cognitive effort, we used a simple sex discrimination task and different categories of emotional and neutral face images. On the basis of cognitive theories of depression (e.g. [6]) and the results of Kumari et al. [8], we predicted that, compared with nondepressed controls, depressed participants would exhibit increased activation in the subgenual ACC to both sad and happy (relative to neutral) facial expressions.

Participants and methods

Study participants

Eighteen individuals with diagnosed major depressive disorder (13 female participants, mean age 35.2 years) and 18 nondepressed controls (13 female participants, mean age 30.8 years) with no psychiatric history participated in this study. Nine of the depressed participants were taking antidepressant medications (two were taking tricyclic antidepressants, one was taking tricyclic and selective
serotonin reuptake inhibitor antidepressants, and six were taking other types of antidepressants). No significant age difference was observed between the groups, t(34)=1.26, P>0.05. All participants (1) were between the ages of 18 and 60 years; (2) had no reported history of brain injury, psychotic ideation, social phobia, panic disorder, mania, or substance abuse in the past 6 months; (3) had no behavioral indications of possible impaired mental status; and (4) had no physical functional magnetic resonance imaging counterindications.

All of the depressed participants were diagnosed with major depressive disorder on the basis of the Structured Clinical Interview for DSM (SCID) [10]. None of the control participants met criteria for any current or past axis-I disorder; axis-II disorders were not assessed. In addition, all participants completed the Beck Depression Inventory-II [11], a 21-item self-report measure of cognitive, affective, behavioral, and physiological symptoms of depression that has demonstrated validity and reliability in this population [12]. As expected, depressed participants had significantly higher Beck Depression Inventory-II scores (mean±SD: 24.6±8.3) than did controls (mean±SD: 1.9±2.1; t(33)=12.80, P<0.001). All participants gave informed consent and were paid $25 per hour for their participation. All aspects of this study complied with American Psychiatric Association ethical standards for treatment of human participants.

Behavioral procedures
Participants were instructed that they would see a series of faces, and that their task was to indicate the sex of each face. Participants were presented with blocked presentations of pictures of emotional (happy, sad, angry, fearful), neutral, and scrambled faces used in previous studies [13–15]. Blocks of 10 faces from each of the six categories (fearful, angry, sad, happy, neutral, and scrambled) were presented at a rate of 3 s per face. Each category was presented three times, for a total of 30 novel face images. Two different stimulus orders were created and counterbalanced across participants. To make the judgments on sex, participants pressed one button for male faces and a different button for female faces. The accuracy of the judgments on sex, multivariate F(34,1)=2.85, P<0.05, M=791 ms. Given these findings, therefore, group differences in patterns of neural response to sad and happy faces cannot be attributable to differences in behavioral performance.

Functional magnetic resonance imaging imaging data
Depressed and nondepressed participants did not differ in the magnitude of stimulus-correlated motion, t(34)=1.83, P>0.05. As predicted, for the sad–neutral contrast (Table 1

Table 1 Whole-brain analysis of emotional minus neutral faces: areas of significant differential blood oxygen level-dependent response

<table>
<thead>
<tr>
<th>Direction of results</th>
<th>Brain region</th>
<th>Volume (mm³)</th>
<th>Coordinates of maximum intensity voxel (R/L, A/P, S/I)</th>
<th>Z-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sad minus neutral faces</td>
<td>L inferior frontal gyrus (BA 47)</td>
<td>152</td>
<td>-14, +15, -19</td>
<td>4.22</td>
</tr>
<tr>
<td></td>
<td>L subgenual ACC (BA 25)</td>
<td>96</td>
<td>+46, -3, -18</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td>R inferior frontal gyrus (BA 45/47)</td>
<td>552</td>
<td>+55, 18, 1</td>
<td>3.42</td>
</tr>
<tr>
<td>Happy minus neutral faces</td>
<td>L subgenual ACC (BA 24/32)</td>
<td>160</td>
<td>-8, +31, -7</td>
<td>3.50</td>
</tr>
<tr>
<td></td>
<td>L middle frontal gyrus (BA 9)</td>
<td>176</td>
<td>-26, +40, -15</td>
<td>3.45</td>
</tr>
<tr>
<td></td>
<td>R superior frontal gyrus (BA 6)</td>
<td>368</td>
<td>+38, +20, +54</td>
<td>4.03</td>
</tr>
<tr>
<td></td>
<td>R inferior temporal gyrus (BA 20)</td>
<td>344</td>
<td>+57, -5, -30</td>
<td>3.60</td>
</tr>
<tr>
<td></td>
<td>L insula (BA 13)</td>
<td>72</td>
<td>-40, +8, -14</td>
<td>3.32</td>
</tr>
</tbody>
</table>

ACC, anterior cingulate cortex; NC, nondepressed control group; MDD (major depressive disorder), depressed group; BA, Brodmann’s area; L, left; R, right.

*From Talairach and Tournoux [18]; coordinates are presented as follows: right (+), left (−); anterior (+), posterior (−); superior (+), inferior (−).
[18] and Fig. 1), depressed participants produced a significantly greater blood oxygen level-dependent (BOLD) response that encompassed parts of both the left inferior frontal gyrus [Brodman’s area (BA) 47] and the left subgenual anterior cingulate cortex (BA 25). Nondepressed participants showed right-lateralized enhanced BOLD response in the middle temporal gyrus (BA 21) and in the inferior frontal gyrus (BA 45, 47). For the happy–neutral contrast (Table I [18] and Fig. 1), depressed participants exhibited significantly greater differential BOLD response than did nondepressed participants in frontal cortical regions, including the left subgenual anterior cingulate cortex (BA 24/32), left middle frontal gyrus (BA 11), and right superior frontal gyrus (BA 8). Nondepressed participants produced significantly greater BOLD responses than did depressed participants in the right inferior temporal gyrus (BA 20) and left posterior insula (BA 13).

**Discussion**

Ours is the first study to show greater activation, to both negative and positive emotional stimuli in the subgenual ACC, in depressed than in nondepressed individuals. To date, few functional imaging studies of depression have examined activations to both positive and negative stimuli. Kumari and colleagues [8] used an affect-generation task and reported greater activation in depressed than in nondepressed individuals in the subgenual ACC. As this effect was specific to positive affect, it was possible that the ACC activation reflected a greater effort on the part of depressed patients to generate positive rather than negative affect. Despite the fact that, in the present study, identifying the sex of the happy faces was no more difficult than identifying the sad faces, depressed participants exhibited significantly greater activation to happy faces than did nondepressed controls. The precise location of this activation cluster was the border region between BA 24 and 32 in the rostral ACC ventral to the genu; according to anatomical studies [4,19], BA 24 is clearly part of the subgenual ACC. Importantly, depressed participants also exhibited significantly greater activation to sad faces than did controls within BA 25, which is located posterior to BA 24. Unlike BA 24, all of BA 25 is located in the subgenual ACC, leading some investigators to regard only BA 25 as subgenual ACC proper. If we adopted this convention, our data would fully support the prediction derived from cognitive theories that depressed patients would exhibit increased activation to sad, but not to happy, facial expressions of emotion in the subgenual (i.e. BA 25) ACC. This conclusion, however, would oversimplify the results of this study.

Instead, it is instructive to consider the anatomical projections that are associated with BA 24 and 25. BA 24 is interconnected with the ventrolateral prefrontal cortex (BA 47) [20]. Interestingly, BA 47 has been found to activate in response to film-induced sadness [21] and in response to attributing emotional statements to oneself [22]. It is possible that the increased activation in BA 24 to happy faces in depressed individuals activates a circuit that engages in self-referential analysis and the generation of sad affect. In contrast, BA 25 is interconnected with the ventral orbitofrontal cortex (BA 13) [23], a region involved in regulation of autonomic functions such as respiration and blood pressure. Thus, increased activation in BA 25 in response to sad faces in depressed persons may activate a circuit that is engaged in autonomic output of affect, rather than affect generation per se. In the absence of concurrent psychophysiological measures, however, we cannot be certain that the presentation of sad, but not happy, faces was associated with change in autonomic functioning.

Another region that has been reported to differ in activation between depressed participants and controls is the amygdala. We found no evidence for differential activation of this region in our study. This finding is consistent with results reported by Lawrence and colleagues [24], who also found no differences between depressed and nondepressed participants in amygdala activation to unmasked emotional faces. On the other hand, Sheline and colleagues [25] reported stronger amygdala response in depressed participants than in healthy controls to masked emotional faces. It is possible that masked stimuli elicit different patterns of neural activity compared with unmasked face presentations. Future research is required to examine more explicitly depression-associated differences in neural response to subliminally versus supraliminally presented faces expressing different emotions.

**Conclusion**

The present study demonstrates, for the first time, that carefully diagnosed depressed individuals exhibit greater activation in the subgenual ACC than do nondepressed controls to both negative and positive emotional stimuli. It will be critical in future investigations to examine the role of these patterns of neural activation in the onset and course of this disorder.
Acknowledgement
We thank Etienne Benson, Amy Tso, Moriah Thomason, and Maulik Shah for their assistance in the data collection and analysis process.

References


