Subgenual anterior cingulate activation to valenced emotional stimuli in major depression

Ian H. Gotlib[a], Heidi Sivers[a], John D.E. Gabrieli[a], Susan Whitfield-Gabrieli[a], Philippe Goldin[a], Kelly L. Minor[a] and Turhan Canli[b]

[a]Department of Psychology, Stanford University, Stanford, California and [b]Department of Psychology, SUNY Stony Brook, Stony Brook, New York, USA.

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

Correspondence and requests for reprints to Ian H. Gotlib, PhD, Department of Psychology, Building 420, Jordan Hall, Stanford, CA 94305-2130, USA
Tel: + 1 650 725 9216; fax: + 1 650 725 5699; e-mail: gotlib@psych.stanford.edu

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 $\pm$ SD: 24.6 ± 8.3) than did controls (mean $\pm$ 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 on a button box in their right hand. Given the focus of this paper on perception of emotional faces by depressed individuals, we restricted our consideration here to activations to the sad, neutral, and happy faces.

Functional magnetic resonance imaging procedures

Whole-brain imaging data were acquired on a 3 T magnetic resonance imaging Signa LX Horizon Echospeed (G.E. Medical Systems, Fairfield, Connecticut, USA, 8.2.5 systems revision) using structural and functional imaging parameters and preprocessing methods described in detail elsewhere [16]. Briefly, functional images were acquired using a gradient echo T2*-weighted spiral scan (TR=3 s, TE=30 ms, flip angle=83°, FOV=24 cm, matrix=80 $\times$ 80), smoothed (8 mm full-width at half maximum), normalized [gray matter statistical parametric mapping (SPM)99 template], and preprocessed using SPM99 (Wellcome Department of Cognitive Neurology, University of London, UK).

Data analysis

Voxel-wise fixed-effects contrast analyses were performed at the single-participant level and random effects analyses were conducted at the group level to create SPM{Z} maps depicting loci that were active across participants. Significant activations were subjected to a significance threshold of $P<0.001$ and five voxels extent threshold. As SPM reports all significant clusters in space devised by the Montreal Neurological Institute, all coordinates were converted into Talairach space, using the conversion algorithm by Brett [17].

Results

Behavioral data

During scanning, depressed and nondepressed participants did not differ in their performance on the sex identification task. No group differences were observed with respect to the accuracy of the judgments on sex, multivariate $F(34,1)<1$, with both groups correctly identifying the sex of more than 95% of the faces. Similarly, the depressed and nondepressed participants did not differ in their reaction times to make judgments on sex for the faces, 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 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

Direction of results	Brain region	Volume (mm^3)	Coordinates of maximum intensity voxel (R/L, A/P, S/I)[a]	*Z*-value
Sad minus neutral faces				
MDD > NC	L inferior frontal gyrus (BA 47)	152	−14, +15, −19	4.22
	L subgenual ACC (BA 25)			
NC > MDD	R middle temporal gyrus (BA 21)	96	+46, −3, −18	3.42
	R inferior frontal gyrus (BA 45/47)	552	+55, +18, +1	3.42
Happy minus neutral faces				
MDD > NC	L subgenual ACC (BA 24/32)	160	−8, +31, −7	3.50
	L middle frontal gyrus (BA 11)	176	−26, +40, −15	3.45
	R superior frontal gyrus (BA 8)	368	+38, +20, +54	4.03
NC > MDD	R inferior temporal gyrus (BA 20)	344	+57, −5, −30	3.60
	L insula (BA 13)	72	−40, +8, +14	3.32

ACC, anterior cingulate cortex; NC, nondepressed control group; MDD (major depressive disorder), depressed group; BA, Brodmann's area; L, left; R, right.
[a]From Talairach and Tournoux [18]; coordinates are presented as follows: right (+), left (−); anterior (+), posterior (−); superior (+), inferior (−).

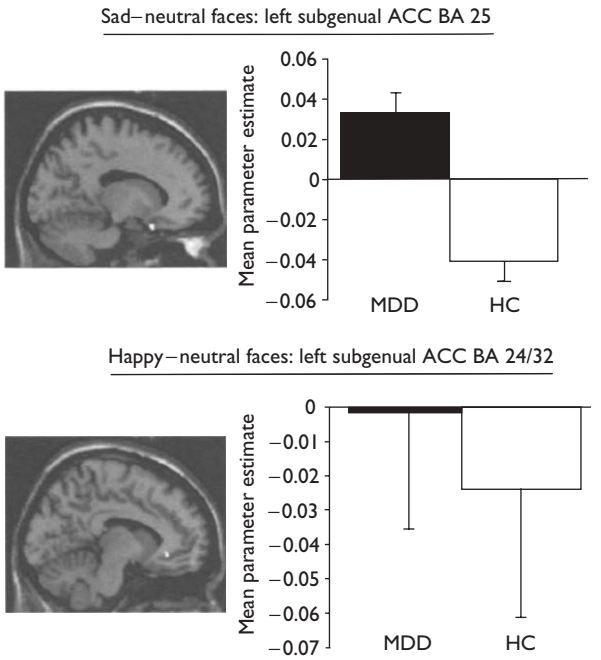

Fig. 1 Areas of significant differences in blood oxygen level-dependent response to valenced minus neutral faces between depressed and nondepressed participants. ACC, anterior cingulate cortex; BA, Brodmann's area; MDD, major depressive disorder; HC, healthy controls.

[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 [Brodmann'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 1 [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 over-simplify 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

1. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* (2000); **4**:215–222.
2. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain* (1995); **118 (Pt 1)**:279–306.
3. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annu Rev Psychol* (2002); **53**: 545–574.
4. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* (1997); **386**:824–827.
5. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, *et al*. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci* (2005); **8**:828–834.
6. Beck AT. *Cognitive therapy and the emotional disorders*. New York: International University Press; 1976.
7. George MS, Ketter TA, Parekh PI, Rosinsky N, Ring HA, Pazzaglia PJ, *et al*. Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). *J Neuropsychiatry Clin Neurosci* (1997); **9**:55–63.
8. Kumari V, Mitterschiffthaler MT, Teasdale JD, Malhi GS, Brown RG, Giampietro V, *et al*. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biol Psychiatry* (2003); **54**: 777–791.
9. Paus T, Koski L, Caramanos Z, Westbury C. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. *Neuroreport* (1998); **9**:R37–R47.
10. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV*. Washington, District of Columbia: American Psychiatric Association; 1996.
11. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive therapy of depression*. New York: The Guilford Press; 1979.
12. Steer RA, Ball R, Ranieri WF, Beck AT. Further evidence for the construct validity of the Beck Depression Inventory-II with psychiatric outpatients. *Psychol Rep* (1997); **80**:443–446.
13. Gotlib IH, Krasnoperova E, Neubauer Yue D, Joormann J. Attentional biases for negative interpersonal stimuli in clinical depression. *J Abnorm Psychol* (2004); **113**:127–135.
14. Yang TT, Menon V, Eliez S, Blasey C, White CD, Reid AJ, *et al*. Amygdalar activation associated with positive and negative facial expressions. *Neuroreport* (2002); **13**:1737–1741.
15. Yang TT, Menon V, Reid AJ, Gotlib IH, Reiss AL. Amygdalar activation associated with happy facial expressions in adolescents: a 3T functional MRI study. *J Am Acad Child Adolesc Psychiatry* (2003); **42**:979–985.
16. Canli T, Sivers H, Thomason ME, Whitfield-Gabrieli S, Gabrieli JD, Gotlib IH. Brain activation to emotional words in depressed vs healthy subjects. *Neuroreport* (2004); **15**:2585–2588.
17. Brett M. *The MNI brain and the Talairach atlas*. Cambridge, MRC Cognition and Brain Sciences Unit; www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml; 1999.
18. Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain*. New York: Thieme; 1988.
19. Brambilla P, Nicoletti MA, Harenski K, Sassi RB, Mallinger AG, Frank E, *et al*. Anatomical MRI study of subgenual prefrontal cortex in bipolar and unipolar subjects. *Neuropsychopharmacology* (2002); **27**:792–799.
20. Koski L, Paus T. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Exp Brain Res* (2000); **133**:55–65.
21. Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, *et al*. Neural circuitry underlying voluntary suppression of sadness. *Biol Psychiatry* (2003); **53**:502–510.
22. Blackwood NJ, Howard RJ, ffytche DH, Simmons A, Bentall RP, Murray RM. Imaging attentional and attributional bias: an fMRI approach to the paranoid delusion. *Psychol Med* (2000); **30**:873–883.
23. Barbas H, Pandya DN. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *J Comp Neurol* (1989); **286**:353–375.
24. Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, *et al*. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol Psychiatry* (2004); **55**:578–587.
25. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* (2001); **50**:651–658.