

Brain activation to emotional words in depressed vs healthy subjects

Turhan Canli^{CA}, Heidi Sivers,¹ Moriah E. Thomason,¹ Susan Whitfield-Gabrieli,¹ John D. E. Gabrieli¹ and Ian H. Gotlib¹

Department of Psychology, Stony Brook University, Stony Brook, NY 11794-2500; ¹Department of Psychology, Stanford University, Stanford, CA 94305, USA

^{CA}Corresponding Author: turhan.canli@sunysb.edu

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Depression involves either enhanced processing of negative stimuli or diminished processing of positive stimuli. We used functional magnetic resonance imaging to assess brain activation in depressed vs healthy participants. Fifteen participants diagnosed with major depressive disorder and 15 controls were scanned during a lexical decision task involving neutral, happy, sad, and threat-related words. For happy words, depressed subjects exhibited less

activation than did controls to happy words in fronto-temporal and limbic regions. For sad words, depressed subjects showed more activation than did controls in the inferior parietal lobule and less activation in the superior temporal gyrus and cerebellum, suggesting a complex activation pattern that varies for neural sub-circuits that may be associated with different cognitive or behavioral processes. *NeuroReport* 15:2585–2588 © 2004 Lippincott Williams & Wilkins.

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INTRODUCTION

Cognitive theories of depression have focused primarily on enhanced processing of negative stimuli as an explanation for the etiology and maintenance of depression [1,2]. Consistent with these formulations, depressed subjects have been found to exhibit faster responses to negative stimuli than they do to neutral or positive stimuli [3,4]. A different conceptualization of depression focuses on the absence of positive affect [5]. Consistent with this perspective, studies of depressed individuals have documented significantly diminished responsiveness to positive (but not negative) stimuli [6,7].

Taken together, depression appears to be associated with increased processing of negative stimuli and/or diminished processing of positive stimuli. We used fMRI and a lexical decision task to address the question of whether these response biases are related to differential activation patterns between depressed and healthy control subjects. We predicted that, relative to normal controls, depressed participants would exhibit increased activation to sad (relative to neutral) words and/or decreased activation to happy (relative to neutral) words in brain regions associated with affective reactivity, attention, or single-word processing, such as the amygdala, insula, parietal lobules, and frontal and temporal cortical regions.

SUBJECTS AND METHODS

Subjects: Fifteen individuals with diagnosed major depressive disorder (MDD: 12 females, mean age 35.1 years) and 15 non-depressed control (12 females, mean age 30.7 years) subjects with no psychiatric history participated in this study. Seven of the depressed participants were taking antidepressant medications (two were taking tricyclic antidepressants, one was taking tricyclic and selective

serotonin reuptake inhibitors (SSRI) antidepressants, and four were taking other types of antidepressants). There was no significant age difference between the groups. All participants were between the ages of 18 and 60, had no reported history of brain injury, lifetime history of primary psychotic ideations, social phobia, panic disorder or mania, no reported substance abuse within the past 6 months, no behavioral indications of possible impaired mental status; and no physical limitations that prohibited them from undergoing an fMRI examination. Informed consent was obtained from all participants.

All depressed and 14 of the 15 control subjects completed both the Beck Depression Inventory [8] (BDI) and the Beck Anxiety Inventory [9] (BAI). As expected, depressed subjects had significantly higher BDI scores (mean \pm s.d. 23.9 ± 7.53) than did controls (2.3 ± 2.15 ; $t(27) = 10.36$, $p < 0.0001$), and significantly higher BAI scores (19.5 ± 10.29) than controls (0.8 ± 1.12 ; $t(27) = 6.77$, $p < 0.0001$). All depressed participants met criteria for a DSM-IV diagnosis of major depressive disorder whereas none of the controls met criteria for any current or past Axis I disorder, using the Structured Clinical Interview for DSM Axis I (SCID-I). Depressed individuals with comorbid panic disorder or social phobia were excluded from participation in the study.

Behavioral procedures: Stimuli were developed from a set of 120 emotion and neutral words for use in this task. They were selected for inclusion in this study on the basis of independent ratings provided by three clinical psychologists experienced in the treatment of anxiety and depression, who rated (on 5-point scales) the relevance of each word to depression, social threat, physical threat, and happiness. Words were selected if all three judges rated them

as three or more for relevance to one category and less than three for relevance to the other categories. Words were selected as neutral if all three judges gave ratings of less than two for relevance to any of these emotion categories. Thus, there were four categories of emotion words (sad, socially threatening, physically threatening, and happy) and a set of neutral words. Each category contained 24 words. Each word was rated for content by at least four independent raters so that categories did not overlap in emotion content. Each set of words had equal average word length and frequency.

Participants made lexical decisions (deciding if letter strings were words or non-words) for neutral or emotional (happy, sad, physical threat, social threat) word sets. Stimuli in each set were of equal average word length and frequency and were presented in 30 s blocks of at a rate of 10 words/block. In each block, eight words were regular English and two were altered to produce non-words. Each condition was presented three times, with each word being presented once.

fMRI scanning procedures: Whole-brain imaging data were acquired on a 3 T MRI Signa LX Horizon Echospeed (GE Medical Systems, 8.2.5 systems revision). T2-weighted flow-compensated spin-echo anatomical images (2000 ms TR; 85 ms TE) were acquired in 32 contiguous 6 mm axial slices. Functional whole-brain images were acquired using a gradient echo T2*-weighted spiral scan (TR=3 s, TE=30 ms, flip angle=83°, FOV=24 cm), smoothed (8 mm FWHM) and normalized (gray-matter SPM99 template). Data preprocessing and statistical analysis was performed using SPM99 (Wellcome Department of Cognitive Neurology). All functional images were realigned to the first one in the time series to correct for motion. The structural volume for each participant was segmented to extract an image of its gray matter. The resulting gray matter images were then spatially normalized to the MNI gray matter template provided in SPM99. The spatial transformations derived from normalizing the segmented gray matter were then applied to all functional volumes and the anatomical volume. After normalization, all volumes were re-sampled in $2 \times 2 \times 2$ mm voxels, using sinc interpolation in space and spatially smoothed with an 8 mm FWHM isotropic Gaussian filter.

Data analysis: Voxel-wise fixed-effects contrast analyses [10] were performed at the single-subject level and random effects analyses [11] were conducted at the group-level to create SPM Z-maps depicting loci that were active across subjects. Areas of significantly different activation between both groups were identified with two-factor (group \times emotion condition) analyses of covariance (ANCOVA), using gender as a covariate. Analyses were conducted with the significance level set at $p < 0.001$ (uncorrected) and an extent threshold of 10 voxels. All coordinates presented here are in Talairach space [12].

RESULTS

Behavioral data: There was no group difference with respect to accuracy: a two-way (group \times emotion condition) ANOVA did not yield a significant main effect for group ($F(1,28)=0.40$, $p=0.50$), or a significant group \times emotion interaction ($F(4,112)=1.25$, $p=0.29$). A significant main effect of emotion condition ($F(4,112)=60.07$, $p < 0.0002$), reflected that, across groups, accuracy for emotional words was

higher than for neutral words (happy $t(29)=5.52$, $p < 0.001$; sad $t(29)=4.0$, $p < 0.001$; social threat $t(29)=2.52$, $p < 0.05$; physical threat $t(29)=2.69$, $p < 0.05$). Accuracy for all stimuli was $> 90\%$, and there were no significant accuracy differences among the emotional words.

There was no significant group difference with respect to reaction times to real words: a two-way (group \times emotion condition) ANOVA yielded no significant main effect for group ($F(1,28)=0.34$, $p=0.93$), or for group \times emotion interaction ($F(4,112)=0.74$, $p=0.49$). Again, however, there was a main effect for emotion condition ($F(4,112)=7.07$, $p < 0.001$), reflecting the finding that, across groups, mean reaction times were fastest for happy (670 ms) and physical threat (671 ms) words, intermediate for neutral (692 ms) and sad (703 ms) words, and slowest for social threat words (727 ms).

fMRI data: Table 1 lists regions of significant differences between depressed participants and controls for happy, sad, and threat-related (all relative to neutral) words. For happy words, controls exhibited greater activation than MDD participants in the amygdala and fronto-temporal regions. In contrast, there were no brain regions in which depressed patients exhibited greater activation than controls. For sad words, the pattern is more complex: controls demonstrated greater activation in the superior temporal gyrus at BA22 and the cerebellum, whereas depressed patients exhibited greater activation in the left inferior parietal lobule. For threat-related words, depressed patients exhibited significantly greater activation than controls in all but one region, located primarily in the frontal cortex (Fig. 1).

DISCUSSION

Depression can be conceptualized as enhanced processing of negative emotional stimuli or diminished processing of positive emotional stimuli. Using fMRI and samples of healthy control subjects and participants diagnosed with MDD, we identified specific brain regions that may be implicated in these forms of dysfunctional processing.

In group comparisons of patterns of brain activation in response to happy-neutral words, depressed participants showed consistently blunted reactivity, relative to normal controls, in a number of brain regions associated with language-related processes, affective and visceral states, and motor systems. For example, depressed subjects exhibited less activation to happy-neutral words than did normal controls in the left inferior frontal gyrus (BA 47), a region previously associated with semantic processing [13]. The greater activation in BA 47 in controls than in depressed subjects is consistent with findings from another imaging study that investigated mood-congruent processing biases during an emotional go/no-go task [14]. In the present study, control subjects showed modestly increased amygdala activation to happy, relative to neutral, words, compared to depressed participants, who showed strongly decreased amygdala activation. The decreased amygdala response of depressed individuals is consistent with the results of one study that found blunted amygdala responsiveness to emotional faces in depressed children [15], but stands in contrast to findings from other studies of sustained amygdala activation to emotional stimuli [16,17]. Increased amygdala activation in normal controls to happy words stimuli is consistent with reports in which positive

Table 1. Differential activation between control and depressed subjects.

Condition/region	Cluster size (voxels)	Talairach coordinates			Z score
		X	Y	Z	
Happy-Neutral					
<i>Control > Depressed</i>					
L Inferior frontal gyrus (BA 47)	31	-18	17	-18	3.43
L Superior temporal gyrus					
Sylvian fissure	43	-46	5	-12	3.59
L Middle temporal gyrus (BA 21)	52	-61	-48	6	3.56
R Amygdala	10	22	-6	-13	3.54
R Insula	12	42	8	-2	3.35
R Cerebellum, ant. lobe, culmen	11	4	-39	-6	3.26
<i>Depressed > Control</i>					
Sad-Neutral					
<i>Control > Depressed</i>					
L Superior temporal gyrus (BA 22)	22	-57	6	-5	3.51
R Cerebellum, ant. lobe, nodule	82	4	-46	-30	3.47
<i>Depressed > Control</i>					
L Inferior parietal lobule (BA 40)	19	-53	-54	43	3.37
Social Threat-Neutral					
<i>Control > Depressed</i>					
<i>Depressed > Control</i>					
L Middle frontal gyrus	18	-36	12	45	3.63
Physical Threat-Neutral					
<i>Control > Depressed</i>					
R Cerebrum	18	2	8	-19	3.70
<i>Depressed > Control</i>					
R Inferior frontal gyrus	58	55	28	8	3.58
L Medial frontal gyrus	52	-8	27	39	3.54
L Middle temporal gyrus	12	-42	-63	18	3.37

Coordinates indicate location in Talairach space [12] of the maximally significant voxel within each significant cluster of activation ($p < 0.001$, uncorrected; spatial extent threshold of 10 contiguous voxels). L=left hemisphere, R=right hemisphere. Z-value refers to the Z-transformed t-statistic for the maximally significant voxel within a cluster.

words were used to generate emotional feeling states [18]. Given the mixed findings regarding depression-associated blunting or activation of the amygdala, it is clear that more research is required to elucidate the parameters of amygdala response in depression.

Depressed subjects also had significantly less activation than did normal control subjects in a region of the cerebellum. Because the cerebellum is primarily regarded as a motor region, it is possible that this activation pattern reflects the lack of motor action often associated with depression. Alternatively, it has been suggested that the cerebellum plays an important role in the processing of emotional stimuli by acting as a relay station for limbic, parietal, temporal, and frontal regions [19], based on the observation that damage to the cerebellum can produce a constellation of affective changes that have been termed cerebellar cognitive affective syndrome [19]. Future research needs to examine depression-associated patterns of activation in this area more systematically.

With respect to the processing of sad words, depressed subjects showed evidence of blunted activation in some regions and increased activation in others. Relative to controls, depressed individuals exhibited significantly greater activation to sad words in the left inferior parietal lobule. One interpretation of this finding is that depressed individuals exhibit greater attention than do controls to sad emotional stimuli, given the role of the inferior parietal lobule in attentional processing of emotional stimuli [20]. An alternative interpretation is that the relatively greater activation represents processes related to word reading,

given a neuroimaging literature that has implicated the inferior parietal lobule in the processing of written language [21]. In either case, our data are consistent with the view that depressed persons display enhanced responsiveness to negative stimuli, whereas control subjects may engage in an emotion-regulation strategy that minimizes the processing of such input.

Depressed subjects showed significantly diminished activation relative to control subjects in the left superior temporal gyrus in response to sad words. This activation difference was primarily driven by increased activation to sad words (relative to neutral stimuli) in the control subjects, rather than by decreased activation in the depressed subjects. Given that the left superior temporal gyrus encompasses Wernicke's area, which is believed to access semantic lexical information [22], it is possible that control subjects exhibited normal activation to sad words whereas depressed subjects exhibited blunted lexical processing. Indeed, electrophysiological studies of semantic processing demonstrate reduced activation in depressed patients in response to negative, but not positive word stimuli [23].

The blunted neural activation pattern exhibited by the depressed patients in response to happy or sad stimuli does not generalize to all negative stimuli. For example, group comparisons for threat-related words indicate that depressed subjects can, in fact, demonstrate significantly greater activation than do controls, consistent with their elevated anxiety scores and with cognitive studies in which depressed individuals exhibited heightened attention for threat-related words [3].

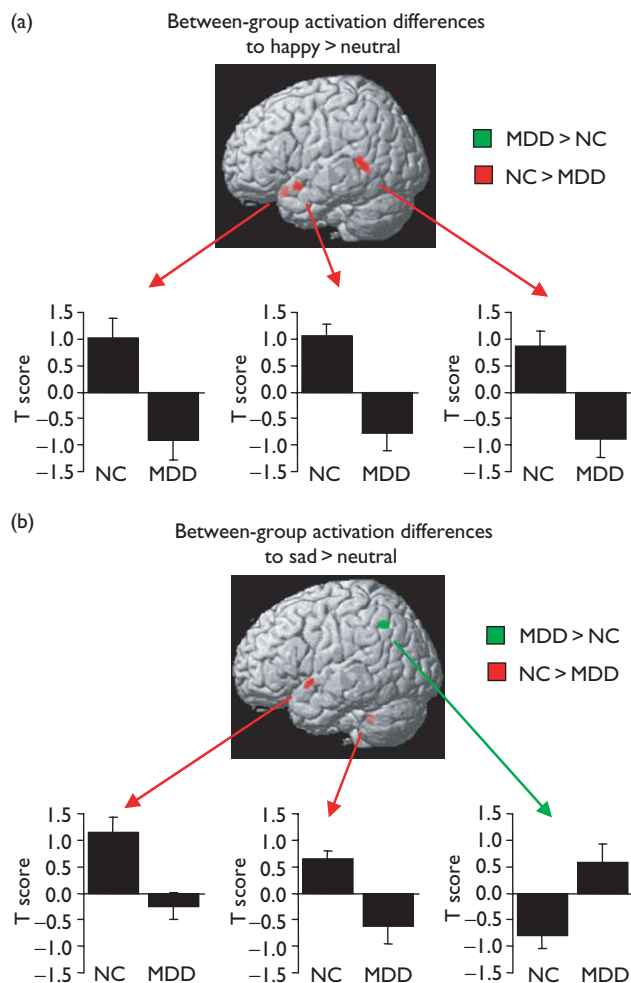


Fig. 1. Between-group activation differences to happy-neutral (a, top) and sad-neutral (b, bottom) words. Figure shows projections of left-sided loci onto a single template brain (sagittal view). Red blobs identify regions where normal control (NC) subjects had greater activation than depressed subjects; green blobs identify regions where patients diagnosed with major depressive disorder (MDD) had greater activation than controls. Arrows point to bar graphs that identify activation (as expressed in average T score within functionally defined region of interest, plus s.e.m.) to emotional-neutral words for each group.

One limitation of the present study is that a subset of seven patients received medication at the time they were scanned. Although it is possible that medication affected some of the brain activation patterns observed here, it is important to note that the medicated patients received different types of psychotropic agents (tricyclic, SSRI, and others). It is unlikely that these different medications would have had identical effects on the brain, but the present results should be replicated in a group of non-medicated depressed patients.

CONCLUSIONS

Using fMRI and a lexical decision task, we found that, relative to control subjects, depressed patients exhibit decreased activation to positive stimuli throughout the

brain, but a complex pattern of decreased activation in superior temporal and cerebellar regions and increased activation in the parietal cortex in response to sad stimuli. Future studies should examine the functional implications of these complex network activation patterns.

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