Lack of Ventral Striatal Response to Positive Stimuli in Depressed Versus Normal Subjects

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Objective: Most of the functional neuroimaging studies of depression have focused primarily on the resting state or responses to negatively valenced stimuli. However, depression consists not only of an accentuation of negative affective processing but of an inability to experience pleasure or positive motivation. The authors tested the hypothesis that depressed subjects would show less activation than healthy comparison subjects, in response to positive stimuli, in ventral striatal regions associated with processing of reward and positive stimuli.

Method: Positive, negative, and neutral words were presented to 10 unmedicated depressed patients and 12 healthy comparison subjects in the context of a 3T functional magnetic resonance imaging (MRI) paradigm. Image processing and analysis were performed using statistical parametric mapping with a mixed-effects model. Significant differences in neural responses were assessed, examining group, condition, and interaction effects of interest within the context of a general linear model.

Results: Relative to comparison subjects, depressed patients demonstrated significantly less bilateral ventral striatal activation to positive stimuli, correlating with decreased interest/pleasure in and performance of activities. They also displayed decreased activation to positive stimuli in a dorsomedial frontal region associated with processing of self-related stimuli. Responses of depressed subjects to negative stimuli were consistent with the growing literature on frontolimbic dysfunction in depression.

Conclusions: This finding 1) supports a pathophysiological model of depression that includes reward/motivational pathway dysfunction, 2) suggests a contributing neural substrate of the inability to experience pleasure or engage in rewarding activities, 3) provides greater specification of abnormalities of basal ganglia function in depression, and 4) may help guide treatment approaches.

Most of the previous functional neuroimaging studies of depression have focused, in their design or reporting of results, primarily on the resting state (1–3) or on responses to negative mood induction or other negatively valenced stimuli (4–6) at various stages of treatment. These approaches are valuable and have led to the development of neural circuit models of the disorder. However, in addition to an accentuation of negative affective processing, depression consists of an inability to experience pleasure or positive motivation. While abnormalities in the processing of positive stimuli by depressed subjects have been demonstrated (7, 8), less has been done to investigate the neural correlates of this core component of the illness.

Studies in both animals and humans demonstrate a central role for the ventral striatum—particularly the nucleus accumbens—a region receiving dopaminergic projections from the ventral tegmentum, in behavioral responses to, anticipation of, and/or monitoring of errors in the prediction of reward (9–11). While classically studied in the context of drug addiction (12) or in response to stimuli closely associated with reward per se (9), this role appears to extend to a broad range of positive stimuli (13), including verbal stimuli (14), which is consistent with the conceptualization of happiness as an approach emotion (15). The nucleus accumbens also appears to respond to the emotional intensity and self-relatedness of a variety of stimuli, independent of their valence (16), with both positive and negative valences possibly processed along a rostrocaudal gradient (17).

Multiple neuroimaging studies of depression have demonstrated abnormalities of or changes in basal ganglia function with treatment, but generally these findings have not been specific to the ventral striatum and/or to positive or rewarding stimuli (e.g., 18–22). Conversely, a number of functional neuroimaging studies of depression have included positive stimuli (23–28) but have not reported ventral striatal findings. Two previous studies have touched upon the relation between ventral or medial striatal activity and pleasure or reward in depressed subjects, although without specifically addressing ventral striatal responses to positive stimuli. Dunn and colleagues (29) found a correlation between a psychomotor-anhedonia symptom cluster and lower metabolism in the anteroverentral caudate/puta-
men, among other regions, in depressed subjects performing an (nonemotional) auditory continuous performance task. In another study, Elliott and colleagues (24) reported significantly less activation in depressed patients relative to healthy comparison subjects to the presence of task-related feedback, regardless of its valence, in bilateral medial caudate nuclei and the tail of the left caudate, interpreted as differential activation associated with the expectation of reward. More recently, Surguladze and colleagues (30) found that depressed patients lack the linear increase in right putamen response to facial expressions of increasing happiness observed in healthy comparison subjects.

In our study, we used functional magnetic resonance imaging (fMRI) to examine neural responses to positive, negative, and neutral words in depressed patients relative to healthy comparison subjects. We hypothesized that depressed subjects would demonstrate decreased ventral striatal, particularly nucleus accumbens, activation in response to positive stimuli. While our study focused on the positive condition, we also predicted, based on the literature (31, 32), intergroup differences in the negative condition in the following regions: medial and lateral prefrontal cortex, anterior cingulate, amygdala and hippocampus.

Method

Subjects

Participants were 10 unmedicated subjects with DSM-IV major depression (nine women and one man; mean age=35.6 years, range=26–49; eight right-handed, two left-handed) and 12 healthy comparison subjects (seven women and five men; mean age=32.0 years, range=23–53; all right-handed). All subjects completed at least some education beyond high school, with level of education matched across subject groups. Apart from depression in the patient group, all participants were free of major psychiatric diagnoses, substance abuse, and significant neurological or medical disorders. After full explanation of the study to the participants, written informed consent was obtained. Hamilton Rating Scale for Depression (33) scores were obtained on the same day as the scan.

Image Acquisition

All image data were acquired with a GE Signa 3 Tesla MRI scanner (max gradient strength 40mT/m, max gradient slew rate 150T/m/s, General Electric Company, Waukesha, Wisc.) using blood-oxygen-level-dependent fMRI, which measures hemodynamic and oxygenation changes associated with localized neuronal activity in the brain (34). After shimming to maximize homogeneity, a series of fMRI scans was collected using gradient echo-planar imaging (TR=1200; TE=30; flip angle=70°; field of view=240 mm; 15 slices; 5 mm thickness with 1 mm interslice space; matrix=64x64), with a single-shot version of a z-shimming algorithm to reduce susceptibility artifact at the base of the brain (35). Echoplanar images were acquired in the axial plane parallel with the anterior commissure-posterior commissure (AC-PC) plane. The first five volumes of each session were discarded. A reference T1-weighted anatomical image with the same slice placement and thickness and a matrix of 256x256 was acquired immediately preceding the echo-planar imaging acquisition. A high-resolution T1-weighted anatomical image using a spoiled-gradient sequence with a resolution of 0.9375x0.9375x1.5 mm³ was also acquired.

Stimuli

Stimuli consisted of 24 positive words, 24 negative words, and 24 neutral words (adjectives, nouns, and verbs) balanced across categories for frequency, length and part of speech, with the exception that within the neutral list, verbs were substituted for adjectives. This was done because adjectives, which are important components of the valenced categories, are by nature generally not free of valence. Verbs were substituted rather than nouns, since their imageability is more similar to that of adjectives. Stimuli were designed to be relevant to depressive and counter-depressive themes, as defined by the literature and clinical experience, and were rated for suitability by a panel of three experienced clinicians. They were based on a similar list of words that were piloted on 34 healthy subjects who rated the three word types as significantly different in valence (p<0.001) and rated positive and negative words as not significantly different in intensity (p=0.26). Examples of such words are as follows: success, admired, heroic (positive words); worthless, bleak, burden (negative words); transfer, trunks, fasten (neutral words).

Image Processing and Data Analysis

SPM99 software (Wellcome Department of Imaging Neuroscience) was used for processing the data (36), which included manual AC-PC reorientation of all anatomical and echo-planar images; realignment of functional echo-planar images based on intracranial voxels to correct for slight head movement between scans; coregistration of functional echo-planar images to the corresponding high-resolution anatomical image based on the transformation of the reference anatomical image to the latter for each individual subject; stereotactic normalization to the standardized coordinate space of Talairach and Tournoux (Montreal Neurological Institute [MNI] average of 152 T1 brain scans) based on the high-resolution anatomical image; and spatial smoothing of the normalized echo-planar images with an isotropic Gaussian kernel (7.5 mm, full width at half maximum). To perform image data analyses, a whole-brain voxel-by-voxel multiple linear re-
Results

Behavioral Data

Affective ratings. Within the group of healthy subjects, the three word types were rated as significantly different in valence (negative versus neutral: Z=−3.10, p<0.001; negative versus positive: Z=−3.03, p<0.001; positive versus neutral: Z=3.02, p=0.001), and the positive and negative words were rated as not significantly different in intensity (Z=1.06, p=0.29). Depressed subjects did not differ significantly from healthy comparison subjects on their ratings of positive or neutral words but did rate negative words as significantly more negative (Z=−2.74, p=0.003).

Reaction times. Within the group of normal subjects, reaction time was significantly faster for positive versus neutral words (Z=−2.85; p=0.003). Within the depressed group, there was no significant difference in reaction time across word categories. Depressed subjects did not show significantly different reaction times than healthy comparison subjects for any category of words.

Recognition memory. Recognition memory performance was calculated by adjusting the percentage of positive responses to target stimuli (p) by the rate of positive responses to distractor stimuli (fp) using the following formula: p′=(p−fp)/(1−fp). Within the group of healthy subjects, there were no significant differences in recognition memory performance among word types. Across groups, there were no differences in performance on positive words, but depressed subjects did recognize negative words at a significantly higher rate than healthy comparison subjects (Z=1.98, p=0.02). Within the depressed group, negative words were recognized at significantly higher rates than both neutral (Z=1.73, p=0.04) and positive (Z=1.73, p=0.04) words.

fMRI Data

Between-group contrasts revealed significantly less activation to positive stimuli in depressed patients relative to healthy subjects in bilateral ventral striatal regions, including ventral head of caudate and putamen and nucleus accumbens, with the left contrast maximum falling in the region of the nucleus accumbens (right: [15, 6, −3], Z=−3.66, voxel-wise p=0.0001, p<0.008; left: [−15, 15, −6], Z=3.52, voxel-wise p=0.0002, p<0.005) (Figure 1A). Within-group analyses (reported at the statistical maxima of the between-group findings) revealed that these findings were due to a decrease in activation to positive stimuli in depressed subjects (right: [15, 6, −3], Z=−1.42, p=0.08; left: [−15, 15, −6], Z=−3.23, p=0.004), coupled with an increase in healthy comparison subjects (right: [15, 6, −3], Z=3.75, p<0.0001; left: [−15, 15, −6], Z=1.82, p=0.04) (Figure 1B). Decreased activity in bilateral ventral striatum was also found in depressed patients relative to healthy comparison subjects in response to positive versus neutral stimuli (right: [15, 9, −3], Z=−2.43, voxel-wise p=0.008; left: [−18, 9, −6], Z=−3.23, voxel-wise p=0.0006, p<0.05) (corrected). No significant between-group differences in ventral striatal activation were seen in any other contrast. The fMRI data are available as a supplement in the online version of this article.

In order to determine whether the differential response to positive stimuli might be occurring in the setting of differential regional baseline activity, a between-group comparison of regional (relative to global) activity during rest (at the statistical maxima of the between-group finding for the positive condition) was performed by sampling two different time points in the experiment before subjects were exposed to valenced stimuli. The two time points are as follows: 1) before the blood-oxygen-level-dependent response to the initial stimulus began to emerge and 2) at the end of the 24-second rest period following the first neutral presentation block. No significant between-group differences were seen for either comparison (Time point 1: right: [15, 6, −3], Z=−0.27, p=0.40; left: [−15, 15, −6], Z=−0.83,
p=0.20. Time point 2: right: [15, 6, –3], Z=–0.40, p=0.35; left: [−15, 15, −6], Z=−0.83, p=0.20. While the analysis does not constitute an integrated measure of baseline activity, it represents a relevant sampling of baseline activity in these subjects before valenced stimuli were delivered, which is useful for interpreting the main finding.

To determine whether the differences displayed between depressed patients and comparison subjects in positive blocks represented prolonged processing of negative stimuli (27, 40) rather than a differential response to positive stimuli, we examined each block of positive stimuli individually to determine whether a lack of ventral striatal activation in depressed patients, compared with healthy subjects, was observed predominantly following blocks of negative stimuli. No such pattern was revealed. Similarly, because decreases in basal ganglia volumes have been reported in depressed patients (41), a voxel-based morphometric comparison (42) of depressed patients relative to comparison subjects was performed. This revealed no significant differences in gray matter volume in ventral striatal regions (right: 15, 6, −3 [Z=−1.01, p=0.16]; left: −15, 15, −6 [Z=−0.33, p=0.37]) that might account for our findings.

A correlation analysis was performed within the depressed group to investigate the association between the blood-oxygen-level-dependent activation levels in depressed subjects in the positive condition and their day-of-scan scores on question 7 of the Hamilton depression scale, which assesses interest and pleasure in and subsequent performance of activities. A significant negative correlation was observed, with those subjects who had higher scores (i.e., less interest/pleasure/performance of activities) showing less activation in bilateral ventral striatal regions (right: 27, 6, −9 [Z=−2.20, p=0.01]; left: −18, 0, −6 [Z=−1.84, p=0.03]). In areas outside the region of interest (at the level of p<0.001), negative correlations with question 7 of the Hamilton depression scale were also found in the left dorsolateral prefrontal cortex (−33, 60, 18) and right frontal operculum (60, 9, 12), while a positive correlation was found in the left posterior cerebellum (−24, −72, −45).

Between-group differences outside the ventral striatum for positive, negative, neutral, positive versus neutral and negative versus neutral contrasts are shown in the Table (available in the online version of this article as a data supplement) and will be commented upon in the discussion section.

Discussion

The key finding of this study is the failure of depressed patients relative to healthy comparison subjects to activate ventral striatal regions in response to positive stimuli. This relative decrease is specific to the positive (as well as positive versus neutral) condition and is not due to medication effects. In addition, this decrease does not appear to reflect differential baseline activity or prolonged processing of negative stimuli by the depressed patients (27, 40), nor does it appear to reflect a failure to process the positive words, since there were no between-group differences in recognition performance for positive words. This relative decrease is also unlikely to be secondary to volume effects, given its condition-specific nature as well as the lack of significant between-group differences in ventral striatal gray matter volume found on voxel-based morphometric comparison.

A significant correlation was found between depressed subjects’ failure of activation to positive stimuli and their same-day scores on question 7 of the Hamilton depression scale, such that those with the least ventral striatal activation reported the least interest and pleasure in, and subsequent performance of activities. At the same time, behavioral data revealed that depressed subjects failed to display the significantly faster reaction time to positive versus neutral words shown by healthy comparison sub-

FIGURE 1. Activation Differences in Ventral Striatal and Dorsomedial Frontal Regions in Response to Positive Words in Depressed Patients Compared With Healthy Subjects*
subjects, yet displayed no significant differences from healthy comparison subjects on either affective rating or recognition of positive words. Taken together, these correlational and behavioral findings suggest that the paucity of ventral striatal activation observed in the depressed patients relates more to the translation of motivational information into behavior than to affective evaluation or encoding per se, which is consistent with a model of the nucleus accumbens as the limbic-motor interface (43).

Decreased activation in response to positive stimuli in depressed patients relative to comparison subjects was also found in regions outside the ventral striatum, including the (left) dorsomedial frontal gyrus (Brodmann’s area 9), a region associated with social cognition (44) and self-reflection (45) (see Figure 1A). In healthy subjects, both this region and the nucleus accumbens have been shown to display increased activation to stimuli perceived as self-related (16, 46). In previous studies, dorsomedial frontal abnormalities have been found in depressed patients (31, 32), although not, to our knowledge, specifically in response to a positively valenced probe. In our study, decreased parahippocampal gyrus activation was also found in depressed subjects in response to positive as well as negative stimuli, an interesting finding in light of recent research on hippocampal abnormalities in depression, and their possible relevance to its pathophysiology and treatment (47). Depressed patients also displayed decreased activation to positive stimuli in left dorsal head-of-caudate and bilateral dorsal thalamus, which is consistent with the literature and the role of frontal-subcortical-thalamic circuits in the regulation of emotion (48, 49). Finally, decreased activation to positive stimuli was found in depressed patients at a lower level of significance in the hypothalamus, a region associated with lower-level drive and motivational processing (3, –9, –6 [Z=–2.89, p=0.002]).

In the negative condition—in addition to the decreases in bilateral posterior parahippocampal gyri previously discussed—depressed patients, relative to comparison subjects, displayed decreases in a region of right middle frontal gyrus (Brodmann’s area 9), which is consistent with earlier findings (31), and in the left insula/claustrum, posterior to regions previously implicated in depression (49). Increased activation to negative stimuli was found in depressed patients in midline subgenual anterior cingulate, which is consistent with the literature (49), and in the right orbital gyrus, anterior to regions previously implicated in depression (31, 32).

In the positive versus neutral and negative versus neutral contrasts, depressed patients showed decreased activation to positive versus neutral stimuli and both increased and decreased activation to negative stimuli and negative versus neutral stimuli in right-sided regions involved in visual processing, suggesting a differential impact of valenced emotional content at the level of perceptual function. In the negative versus neutral contrast, depressed patients also displayed decreased activation in left extended amygdala.

This decrease was due to a double dissociation wherein healthy subjects displayed increased activation to negative stimuli and decreased activation to neutral stimuli, while depressed patients showed the opposite pattern (reacting to neutral words as the comparison subjects reacted to negative words and to negative words as comparison subjects reacted to neutral words). This is consistent with the clinical/cognitive phenomenology of depression in which patients negatively interpret phenomena viewed by others as neutral. Depressed subjects also displayed decreased activation in both the positive versus neutral contrasts and negative versus neutral contrasts in the right superior temporal sulcus, which is a region associated with social processing (50).

Our study provides greater specification of the potential localization and significance of previous reports, in depressed patients, of abnormalities of (19, 21, 24) or changes in (18, 20) basal ganglia function with treatment, as well as the association of such abnormalities with anhedonia (29). Along with the recent study by Surguladze and colleagues (30), our study suggests that depressed patients lack the striatal activation to positive stimuli found in healthy subjects (13), and it further correlates decreased ventral striatal response with a lack of interest and pleasure in and subsequent performance of activities. A variety of reasons may be posited for the absence of prior reports of this finding, despite the inclusion of positive stimuli in a number of previous functional neuroimaging studies of depression (23–28). These include differences in a priori regions and comparisons of interest, modality and content of stimuli, task demands (including presence of a motor component), and image acquisition parameters (including those associated with susceptibility artifact at the base of the brain).

Our study has a number of limitations. The uneven distribution of men and women in our patient and comparison groups could be a factor in the results, although this is unlikely given that gender was used as a covariate of no interest in all between-group analyses and that our finding held up in a single-sex subanalysis. Another possible confound arises from the fact that neutral and valenced words were not completely balanced for part of speech, as described previously, or for imageability. This also appears unlikely, given the presence of our finding in the between-group positive (not only positive versus neutral) condition. Finally, although analysis of our data was performed with a mixed-effects model, which takes subject-by-subject variability into account and allows population-based inferences to be drawn (51), we feel that additional subjects will be helpful to further assess this finding and its generalizability.

In conclusion, this study confirms our hypothesis of decreased activation to positive stimuli in depressed patients versus healthy subjects in ventral striatal regions, including the nucleus accumbens. Our findings support a pathophysiological model of depression that includes re-
ward/motivational pathway dysfunction (32, 52, 53) and suggest a possible contributing neural substrate of the inability to experience pleasure and engage in rewarding activities. This line of investigation is thus likely to enhance our understanding of depression and to encourage further studies targeting ventral striatal regions for therapeutic modulation of affective symptoms (54, 55).

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