A Differential Pattern of Neural Response Toward Sad Versus Happy Facial Expressions in Major Depressive Disorder

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**Background:** Accurate recognition of facial expressions is crucial for social functioning. In depressed individuals, implicit and explicit attentional biases away from happy and toward sad stimuli have been demonstrated. These may be associated with the negative cognitions in these individuals.

**Methods:** Using event-related functional magnetic resonance imaging (fMRI), neural responses to happy and sad facial expressions were measured in 14 healthy individuals and 16 individuals with major depressive disorder.

**Results:** Healthy but not depressed individuals demonstrated linear increases in response in bilateral fusiform gyri and right putamen to expressions of increasing happiness, while depressed individuals demonstrated linear increases in response in left putamen, left parahippocampal gyrus/amygdala, and right fusiform gyrus to expressions of increasing sadness. There was a negative correlation in depressed individuals between depression severity and magnitude of neural response within right fusiform gyrus to happy expressions.

**Conclusions:** Our findings indicate preferential increases in neural response to sad but not happy facial expressions in neural regions involved in the processing of emotional stimuli in depressed individuals. These findings may be associated with the above pattern of implicit and explicit attentional biases in these individuals and suggest a potential neural basis for the negative cognitions and social dysfunction in major depression.

**Key Words:** Major depression, fMRI, facial expressions, activation trends

Facial expressions are important signals of individual emotional states. Accurate recognition of and appropriate response to these stimuli are critical for successful interpersonal function in the social environment (Darwin 1872/1998). In individuals with major depressive disorder (MDD), cognitive models have emphasized the presence of negative schemata (Beck 1976), which are frequently associated with impaired interpersonal functioning. These schemata include unconscious and conscious negative attentional biases toward stimuli and events within the environment, such as facial expressions, promoting a more negative view of the world, self, and others.

To date, studies examining the nature of unconscious and conscious evaluative processing biases toward emotional stimuli in depressed individuals have used tasks measuring implicit and explicit attentional biases toward these stimuli. Findings from studies employing implicit attentional tasks have indicated implicit attentional biases toward negative emotional stimuli during memory (Bradley et al 1996), performance on the emotional Stroop task (Williams et al 1996), and an affective go/no-go task with “happy” and “sad” words (Murphy et al 1999) in depressed individuals. An increased frown response to happy expressions was demonstrated in dysphoric healthy individuals in a study measuring facial electromyography (EMG) reactivity to facial expressions, suggesting abnormal implicit processing of these expressions during dysphoria (Sloan et al 2002).

Studies employing a measure of explicit attentional and evaluative processing of emotional stimuli, facial expression discrimination, have reported in depressed individuals a negative emotion-specific discrimination bias, with neutral faces misinterpreted as sad and happy faces as neutral (Gur et al 1992), and in a mixed group of mood-disordered individuals, a greater than normal tendency to identify ambiguous faces as negative (Bouhuys et al 1999). Other investigators have shown in individuals with MDD a specific impairment in the recognition of positive facial expressions (Suslow et al 2001), interpreted as being consistent with a negative discrimination bias. We have also previously demonstrated a significantly smaller discrimination bias toward the labeling as happy of happy facial expressions in depressed individuals compared with healthy volunteers (Surguladze et al 2004). Other studies, however, have reported a generalized perceptual deficit (Asthana et al 1998) or no specific impairment in emotional facial expression identification (Feinberg et al 1986) in depressed populations. Together with the findings from the above studies, these findings provide some evidence for both implicit and explicit attentional biases away from happy and toward sad stimuli in depressed individuals.

Studies employing functional neuroimaging techniques have highlighted the role of a distributed neural system involving ventral striatum, including the caudate nucleus and ventral putamen, the amygdala, and anterior insula in the response to negative facial expressions (Phillips et al 2003a). In addition to these regions, increased response has been demonstrated in visual cortex during attention to presentations of emotional compared with nonemotional signals (Junghoefer et al 2001), irrespective of the visual complexity of the stimuli (Taylor et al 2000) or eye movements in response to these (Lang et al 1998). The visual cortical response, the modulation of which may be mediated via the amygdala (Morris et al 1998), may therefore be an additional component of the distributed neural system important for the response to visually presented emotionally salient stimuli, in particular, facial expressions. Previous findings also suggest that visual cortical responses may be individually specific: Fredrikson et al (1995) demonstrated increases in visual
cortical responses toward phobogenic pictures in phobia patients, whereas Amin et al (2004) demonstrated an association between visual cortical response and extraversion in healthy individuals to pictures of positively and negatively valenced scenes (Lang et al 2001).

Studies specifically examining neural responses to emotional stimuli in individuals with MDD have indicated increased response within the left amygdala to masked, and particularly fearful, facial expressions (Sheline et al 2001) and sad faces (Fu et al 2004); decreased attenuation of the amygdalar response to negative words (Siegle et al 2002); and increased response within lateral orbitofrontal cortex to negative emotional stimuli during an affective go/no-go task (Elliott et al 2002). During sad mood induction in these individuals, findings indicate increased blood flow in a number of regions, including ventral striatum, insula, and ventrolateral prefrontal cortex, and decreased blood flow within medial prefrontal and orbitofrontal cortex (Liotti et al 2002). Other studies have demonstrated in depressed individuals at rest increased blood flow within the amygdala (Drevets et al 1992), anterior insula, and ventral striatum (Mayberg et al 1999), with positive correlations between amygdalar metabolism and severity of depressed mood (Abercrombie et al 1998). Taken together, these findings indicate in depressed compared with healthy individuals a pattern of predominantly increased activity in neural regions important for the response to emotional stimuli. Further examination of the nature of neural responses and the relationship to clinical parameters is required.

We have previously demonstrated increased activity within visual cortex and striatum to expressions of increasing intensity (mild to prototypical) of happiness and decreased activity within visual cortex and hippocampus to expressions of increasing intensity of sadness in healthy individuals (Surguladze et al 2003). These stimuli may be of particular relevance to the negative schemata demonstrated by depressed individuals (Beck 1976), who may identify with displays of sadness, but not happiness, in others. The employment of facial expressions of both mild and prototypical intensity of emotion allows for the inclusion of milder intensity facial expressions, which are more frequently observed in everyday life, and also allows the examination of the nature of linear trends in neural responses to facial expressions of varying intensity of emotion (Surguladze et al 2003).

We wished to examine the neural basis of the reported implicit and explicit attentional biases in depressed individuals by examining the pattern of neural response to varying intensities of happy and sad facial expressions in a group of individuals with MDD. A subgroup of the depressed individuals in the current study had previously been reported as demonstrating an explicit discrimination bias away from labeling the happy facial expressions as happy (Surguladze et al 2004). The task used in this study was a gender decision task, allowing individuals to attend implicitly rather than explicitly to the emotional content of the face. This may also involve more explicit emotion evaluative processes at longer stimulus presentation durations. We also wished to determine the extent to which abnormal patterns of neural response to these stimuli were associated with depression severity within the depressed individuals.

Findings to date allowed us to predict in depressed compared with healthy individuals:

1. A significantly greater increase in response in neural regions important for the response to emotional stimuli, in particular, ventral striatum, amygdala, and visual cortex, to facial expressions of increasing sadness (neutral to mild to prototypical emotion) and a significant decrease in response within these regions to facial expressions of increasing happiness.

2. Significant correlations between these patterns of neural response to happy and sad expressions and depression severity.

**Methods and Materials**

**Participants**

Sixteen individuals with a diagnosis of major depressive disorder diagnosed using DSM-IV criteria by the psychiatrist responsible for the patient’s management at the Maudsley Hospital, London (American Psychiatric Association 1994) were recruited from the hospital and community services of the South London and Maudsley National Health Service Trust. Fourteen healthy individuals without a history of previous depressive episodes or other psychiatric history, determined by interview, were recruited from the community and staff of the Institute of Psychiatry, London, United Kingdom, nine of whom had participated in a previous study (Surguladze et al 2003). Ethical approval was obtained from the Ethical Committee of the South London and Maudsley Trust and Institute of Psychiatry. Written consent was obtained from all subjects prior to participation in the study. All participants were right-handed (Oldfield 1971). Both groups were matched for age, sex ratio, and years of education. Although the healthy individuals were younger, there was no significant difference between groups with regard to age. Exclusion criteria included a history of head injury, illicit substance abuse, and a score of less than 24 on the Mini-Mental State Examination (MMSE) (Folstein et al 1975). Depression severity was measured in both groups using the Beck Depression Inventory (BDI) (Beck et al 1986). All healthy individuals scored <10 on this measure. Depressed individuals had significantly higher BDI scores compared with healthy individuals (t(28) = −9.7; p < .001), and all scored >15 on this measure. All data on duration of illness in depressed individuals were collected from the medical records and interview with each depressed individual. The mean duration of illness in this group was 7.5 years (SD 5.1) (Table 1).

**Functional Neuroimaging Task**

All participants participated in two, 6-minute experiments employing event-related functional magnetic resonance imaging
In one experiment, participants were presented with happy and neutral expressions and in the other experiment, sad and neutral expressions from a standardized series of prototypical facial expressions posed by 10 different volunteers (4 male volunteers) (Ekman and Friesen 1976). The 10 prototypical expressions of happiness and sadness were further manipulated by morphing software to depict expressions 50% along the neutral-prototypical expression continuum (Young et al 2002). Data indicate that in healthy individuals, labeling of these 50% emotion—50% neutral morphed stimuli as depicting the appropriate emotion rather than neutral is not significantly above chance level for either the happy-neutral or sad-neutral stimuli (Young et al 2002).

In one experiment, participants therefore viewed 20 prototypically happy (i.e., expressions of 100% happiness), 20 mildly happy (i.e., expressions of 50% happiness), and 20 neutral expressions, and in the other experiment, they viewed 20 mildly and 20 prototypically sad and 20 neutral expressions. The order of presentation of the two experiments was counterbalanced across participants within each group to avoid practice effects on patterns of neural response to the neutral stimuli presented again in the second experiment. Additionally, there were equal numbers of happy, sad, and neutral expressions overall, ensuring that participants did not become familiarized to one specific emotional category. Each facial stimulus was presented for 2 seconds. All stimuli were presented in a pseudorandomized order. Each stimulus type was preceded by similar numbers of each of the other two stimulus types to minimize the effect of the preceding stimulus type on neural responses to the stimulus of interest. The duration of the interstimulus interval (ISI) varied from 3 to 8 seconds according to a Poisson distribution to prevent participants from predicting the timing of the next stimulus presentation, with average interval 4.9 seconds. During the ISI, participants viewed a fixation cross. In subsequent analyses, the fixation cross was used as the baseline stimulus in each of the two experiments. In the current study, participants decided on the gender of each face and pressed one of two buttons accordingly.

**Image Acquisition**

Magnetic resonance (MR) images were acquired using a GE Signa 1.5T Neuro-optimised MR system (General Electric, Milwaukee, Wisconsin) for gradient echo echoplanar imaging (EPI) at the Maudsley Hospital, London, United Kingdom. A quadrature birdcage headcoil was used for radio frequency (RF) transmission and reception. An inversion recovery EPI dataset was acquired at 43 near-axial 3-mm thick planes parallel to the anterior commissure-posterior commissure (AC-PC) line: echo time (TE) 73 milliseconds, time to inversion (TI) 180 milliseconds, repetition time (TR) 16 seconds, in-plane resolution 1.72 mm, interslice gap .3 mm, matrix size: 128 × 128 pixels. This higher resolution EPI dataset was used to register the fMRI datasets acquired from each individual in standard stereotactic space. One hundred eighty T2*-weighted images depicting blood oxygenation level dependent (BOLD) contrast (Kwong et al 1992) were acquired at each of 16 near-axial noncontiguous 7-mm thick planes parallel to the intercommissural (AC-PC) line: TE 40 milliseconds, TR 2 seconds, in-plane resolution 3.44 mm, interslice gap .7 mm, matrix size: 64 × 64 pixels.

**Neuroimaging Data Analysis**

The data were analyzed using the Institute of Psychiatry software (Brammer et al 1997; Bullmore et al 1999a). Neural responses to neutral expressions and each emotion intensity compared with baseline and to each emotion intensity compared with neutral expressions were determined by time series analysis using gamma variate functions (peak responses at 4 and 8 seconds) to give the best-fit (least-squares) model of the time series of the BOLD response at each intracerebral voxel. A goodness-of-fit statistic, the sum of squares (SSQ) ratio, was then computed at each voxel. This was the ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time series) divided by the sum of squares due to the residuals (original time series minus model time series). To sample the distribution of SSQ ratio under the null hypothesis that observed values of SSQ ratio were not determined by experimental design (with minimal assumptions), the time series at each voxel was permuted using a wavelet-based resampling method described in detail in Bullmore et al (1999a, 2001).

**Region of Interest Analyses**

To demonstrate further the nature of the between-group differences in linear trends in magnitude of neural response, SSQ values were extracted from regions in which between-group differences in the above trends were demonstrated, and statistical comparison of the effects of group, emotion intensity, and the interaction between the two were performed on this measure for both emotion categories.

**Type I Error Control**

Using the above data-driven, permutation-based approaches set out in detail in Bullmore et al (1999b), the critical threshold of cluster mass (integrated SSQ ratio over all voxels of a cluster) for individual brain activation maps was determined for any given probability of occurrence. The analysis proceeded as follows. First, a BOLD model was fitted to the time series data at each voxel. The model was then refitted a large number of times at each voxel after wavelet-based permutation of the time series to destroy the relationship between the stimulus and the experimental response (the validity of this approach has been established in detail in Bullmore et al 2001). Any “observed” SSQ ratio
(or any other statistic chosen to be tested) could then be compared with its own distribution under the null hypothesis and its probability of chance occurrence assessed. This approach was extended to cluster level by connecting activated voxels into three-dimensional (3-D) clusters, computing the integral of SSQ ratio over the cluster, doing the same for the permuted data, and using the data to establish the critical threshold for cluster mass at a given level of probability under the null hypothesis of no experiment effect. The critical threshold for cluster mass was thereby set to less than .5 clusters per experiment (corresponding to a threshold of \( p < .001 \)) under the null hypothesis. The 95% confidence limit for cluster occurrence was determined by bootstrapping null data and was such that \( >1 \) false-positive cluster would only be observed once in 20 experiments. The approach was further extended to the group level, and between-group analyses, and to the fitting of linear trends in response to facial expressions of increasing intensity of emotion (i.e., neutral–50%–100% intensity) at individual, group, and between-group levels.

**Analysis of Between-Group Differences in Noise Levels**

Between-group differences in noise levels (residual changes in the MRI signal after removing the stimulus-related effects) were then calculated for each emotional condition. This was to ensure that any between-group differences in the above trends in these regions reflected signal (BOLD response) changes rather than changes in noise.

**Between-Group Differences in Percentage BOLD Signal (Effect Size)**

To confirm any findings of between-group differences in SSQ for the above contrasts, time series analysis was employed to determine between-group differences in the magnitude of percentage changes in BOLD signal to happy and sad expressions. Here, time series were extracted in each individual from each voxel within all clusters in which between-group differences in SSQ had been demonstrated in the above analyses. The voxel-derived time series were then averaged per cluster per individual. Group-averaged time series were then computed for each cluster. Between-group differences in percentage change in BOLD signal were then determined for each voxel within the clusters for SSQ had been demonstrated in the above analyses. Within-group analyses of emotional-neutral facial expression contrasts were also performed using similar \( t \) tests.

**Results**

The nature of linear trends in neural response to happy and sad expressions in healthy individuals has been described previously (Surguladze et al. 2003). We were interested in examining between-group differences in larger numbers of healthy and depressed individuals in linear trends in neural response to these stimuli.

**Behavioral Results**

There were no significant between-group differences in accuracy in the gender decision tasks for happy or sad expressions processing tasks (Table 1). In both groups, however, the accuracy of gender decision for these expressions was low. This was due to the masked nature of the facial expressions, i.e., hair and any other nonfacial features were cropped, which renders gender decision difficult. We then performed a \( 2 \times 2 \) repeated measures ANOVA to analyze between-group differences in reaction time, with emotion (happy, sad) as the within-subject variable and group (depressed, healthy) as the between-group variable. There was a main effect of group: \( F(1,24) = 5.5, p = .027 \). In other words, mean reaction time to both types of emotion (happy and sad) was longer in depressed compared with healthy individuals. There was no interaction of group \( \times \) emotion: \( F(1,24) = .53, p = .5 \). Post hoc \( t \) tests revealed that healthy individuals had shorter reaction times for sad expressions than depressed individuals \( (t(26) = -3.1, p = .002) \). There were no other significant between-group differences in reaction time (Table 1).

**Neuroimaging Results**

**Happy Facial Expressions.** The value of the absolute fit of the gamma variate model (SSQ ratio) representing neural responses to each expression intensity versus baseline for each group was computed for each of the clusters obtained by group analysis. At the significance level \( p = .003 \), the \( F(2,17) \) for these fits corresponded to the range between 5.5–6.2 in both depressed and healthy groups of individuals. (Degrees of freedom for these \( F \) values were calculated on the basis of three types of facial expression and 180 whole brain images in each GBAM).

In subsequent analysis, fitting of linear trends in response to facial expressions of increasing intensity of happiness enabled us to identify linear trends in neural responses to expressions of increasing intensity of happiness in each group and between-group differences in these linear trends (\( p < .001 \); corresponding to \( <.5 \) clusters per between-group comparison).

Our aim was to determine between-group differences in response to expressions of increasing intensity of happiness, and therefore we report here findings for the between-group differences in linear trends. These were demonstrated in three clusters: within right and left fusiform gyrus (Brodmann area [BA] 19) and right putamen, with increases in neural response within these regions to expressions of increasing happiness in healthy individuals and decreases in depressed individuals.

To examine these linear trends further, SSQ values reflecting the goodness-of-fit of neural response within each cluster to the contrast of each expression intensity versus baseline were entered into a \( 3 \times 2 \) repeated measures ANOVA, with expression intensity (neutral, 50%, 100%) as the within-subject and group (depressed, healthy) as the between-subject factor. There were significant interactions between intensity and group for SSQ values extracted from left fusiform gyrus \( (F(2,27) = 9.5; p = .007) \), right fusiform gyrus \( (F(2,27) = 4.9; p = .04) \), and right putamen \( (F(2,27) = 5.1; p = .04) \). There were no other significant effects or interactions. The interactions between intensity and group reflected significant increases in goodness-of-fit of the model in each of the clusters to expressions of increasing intensity of happiness (i.e., neutral to 50% to 100%) in healthy compared with depressed individuals (Table 2; Figure 1).

Analysis of between-group differences in noise levels did not reveal any significant findings in the above neural regions. This indicated that the between-group differences in the above trends demonstrated with SSQ as the dependent measure were a true reflection of signal (i.e., BOLD signal) changes rather than changes in noise.

After extraction of time series of changes in percentage BOLD signal in the above regions for each group of individuals, \( t \) tests (unequal variance) further revealed significant between-group differences (control subjects > depressed) in BOLD signal to expressions of 100% intensity happiness at 6 seconds poststimu-
Table 2. Between-Group Differences in Trends in Neural Response to Increasing Intensities of Happy and Sad Facial Expressions

<table>
<thead>
<tr>
<th>Emotion</th>
<th>Brain Region (BA)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Size</th>
<th>Patients</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happy</td>
<td>L Fusiform Gyrus (19)</td>
<td>−31</td>
<td>−79</td>
<td>−12.5</td>
<td>27</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>R Fusiform Gyrus (19)</td>
<td>34</td>
<td>−70</td>
<td>−12.5</td>
<td>17</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>R Putamen</td>
<td>22</td>
<td>11</td>
<td>−2</td>
<td>10</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Sad</td>
<td>R Fusiform Gyrus (19)</td>
<td>29</td>
<td>−59</td>
<td>−18</td>
<td>41</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>L Putamen</td>
<td>−25</td>
<td>4</td>
<td>−2</td>
<td>10</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>L Parahippocampal Gyrus/Amygdala</td>
<td>−25</td>
<td>0</td>
<td>−23.5</td>
<td>7</td>
<td>Increase</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Between-group ANOVAs of linear trends in neural response. Coordinates of regions in which significant between-group differences were demonstrated are presented. Voxelwise and clusterwise differences at p = .05 and p = .001, respectively. Brodmann areas are indicated in parentheses. BA, Brodmann area; L, left; R, right; ANOVA, analysis of variance.

Between-group differences in linear trends in neural response to increasing intensity of sadness in healthy individuals, but increases within these regions in depressed individuals (Table 2). The coordinates for the parahippocampal gyrus/amygdala in Table 2 refer to the center of mass of the cluster, whereas the upper part of this cluster was positioned at x = −25, y = 0, and z = −12, extending to the left amygdala.

To explore the nature of these differences further, SSQ values reflecting the goodness-of-fit of neural response within each cluster region were entered into a 3 × 2 repeated measures ANOVA, with intensity (neutral, 50%, 100% sad intensity) and group (depressed, healthy) as the between-subject factors. There were significant interactions between intensity and group for SSQ values extracted from right fusiform gyrus [F(2,26) = 6.1; p = .026], left putamen [F(2,26) = 11.6; p = .004], and left parahippocampal gyrus/amygdala [F(2,26) = 5.9; p = .02]. There were no other significant effects or interactions. There were fewer degrees of freedom compared with those observed in the experiment with happy facial expressions (26 vs. 27), since one healthy individual was not able to complete the sad faces task. The interactions between intensity and group reflected significant increases in goodness-of-fit of the model within the three brain regions to expressions of increasing intensity of sadness (i.e., neutral, 50%, 100%) in depressed individuals and a decrease in healthy individuals.
Neutral Faces Versus Baseline. To ensure that differences between groups were not due to between-group differences in neural responses to faces per se (i.e., the contrast of neutral expressions and the fixation cross), SSQs for these contrasts were extracted from all the clusters showing significant differences in linear trends between depressed individuals and healthy volunteers and were entered into a $6 \times 2$ ANOVA, with cluster (six regions in total for the two emotional experiments) as the within-subject variable and group (patients, comparison subjects) as the between-subject factor. Analysis revealed no significant effects of group and cluster and no significant interaction between group and cluster. 

Further Region of Interest Analyses. Sums of squares were extracted from anatomically defined coordinates for the regions (Talairach and Tournoux 1988) of right and left amygdalae, ($\pm 23, -4, -16$, respectively) and for the right and left subgenual cingulate gyri ($\pm 2, 6, -6$ respectively) (Mayberg et al 1999). There were no significant differences in SSQ in any of the four between-group comparisons (100% intensity happy versus baseline, 100% intensity sad versus baseline, neutral versus baseline in each experiment). Between-group comparison of mean percentage change in BOLD signal to the 100% intensity happy expressions revealed a significantly greater mean percentage change in BOLD signal in healthy compared with depressed individuals within the left subgenual cingulate gyrus, $t(27) = -2.2; p < .05$. There were no significant between-group differences in percentage change in BOLD signal to the 100% intensity sad expressions extracted from the same four clusters.

Correlations. The statistical parameters for detection of clusters showing significant correlations between BDI score and whole-brain responses were set at levels (voxelwise $p = .05$, clusterwise $p = .001$) at which the expectation of false-positive clusters was less than .1 over the entire brain volume tested. To prototypically happy versus neutral facial expressions, significant negative correlations were demonstrated in depressed individuals between BDI score and power of neural response within the right fusiform gyrus ($x = 22; y = -61; z = -11$) and left fusiform gyrus ($x = -35; y = -75; z = -18$). To determine further the significance of these negative correlations, SSQs to the contrast of prototypically happy versus neutral facial expressions were extracted from these two clusters in the fusiform gyrus in all within these regions to these expressions in healthy individuals (Table 2; Figure 3).

Analysis of between-group differences in noise levels did not reveal any significant findings in the above neural regions. This indicated that the between-group differences in the above trends demonstrated with SSQ as the dependent measure were a true reflection of signal (i.e., BOLD response) changes rather than changes in noise.

After extraction of time series of changes in percentage BOLD signal in the above regions, $t$ tests (unequal variance) further revealed significant between-group differences in BOLD response (control subjects < depressed subjects) to expressions of 100% intensity sadness at 6 seconds poststimulus onset within the left parahippocampal gyrus/amygdala ($t[26] = -4.65; p = .00193$) and a near-significant between-group effect in the right fusiform gyrus ($t[26] = 1.84; p = .085$). Within the groups, depressed but not healthy individuals demonstrated significant increases in BOLD signal to these expressions compared with neutral expressions at this time point in these regions ($t[14] = -3.45; p = .0023$, and $t[14] = -4.38; p = .000163$, respectively). Examples of the time series for the right fusiform gyrus and left parahippocampal gyrus/amygdala in both groups are shown in Figure 4.

Figure 4. Time series of percent change in blood oxygenation level dependent (BOLD) signal to neutral and both intensities of sad expression in the left parahippocampal/amygdalar region. The figure represents the time course of BOLD signal change in left parahippocampus/amygdala—average for 16 depressed and 14 healthy individuals. HI, healthy individuals; DI, depressed individuals.
Medication Effects

We were interested in examining the potential effects of antidepressant medication on the above observations of between-group differences in percentage change in BOLD signal to happy and sad expressions of 100% intensity versus baseline. Medication dose was therefore coded from 1 (low dose) to 4 (high dose), according to the approach proposed by Sackeim (2001). Depressed individuals were divided into two subgroups depending on medication dose: 9 patients comprised medium-high dosage subgroup (levels 3–4) and 7 patients comprised low dosage subgroup (levels 1–2). There was no significant difference in BOLD score between low-dose versus high-dose subgroups. Between-subgroup analyses of variance were then performed within each emotional condition using mean percentage change in BOLD signal as the dependent variable. In response to happy expressions, there was a significantly greater mean percentage change in BOLD signal to happy expressions compared with sad expressions at baseline. This difference was observed in both the right fusiform gyrus (47, −63, −24; 29, −63, −24) and left fusiform gyrus (−47, −63, −18) in response to sad expressions, there was a significantly greater mean percentage change in BOLD signal to sad expressions compared with neutral faces at baseline. This difference was observed in both the right fusiform gyrus (51, −59, −24) and left parahippocampal gyrus/amygdala (−14, −7, −18), again in the low-dose versus the high-dose medication group.

Discussion

Previous reports have emphasized in depressed individuals implicit and explicit attentional biases toward sad and away from happy stimuli. We aimed to examine the neural basis of attentional biases to happy and sad facial expressions in these individuals. Medication dose was therefore coded from 1 (low dose) to 4 (high dose), depending on medication dose: 9 patients comprised medium-high dosage subgroup (levels 3–4) and 7 patients comprised low dosage subgroup (levels 1–2). There was no significant difference in BOLD signal to happy and sad expressions at baseline. In response to sad expressions, there was a significantly greater mean percentage change in BOLD signal compared with sad expressions at baseline. This difference was observed in both the right fusiform gyrus (47, −63, −24; 29, −63, −24) and left fusiform gyrus (−47, −63, −18) in response to sad expressions, there was a significantly greater mean percentage change in BOLD signal compared with neutral faces at baseline. This difference was observed in both the right fusiform gyrus (51, −59, −24) and left parahippocampal gyrus/amygdala (−14, −7, −18), again in the low-dose versus the high-dose medication group.

Significant between-group differences were demonstrated in linear trends in neural response to facial expressions of increasing happiness versus baseline. This was observed in the goodness-of-fit statistic within the right putamen and bilateral fusiform gyri in healthy compared with depressed individuals to these expressions. Further analyses also revealed significant between-group differences in percentage change in BOLD signal to expressions of 100% intensity happiness at 6 seconds poststimulus onset within the right fusiform gyrus. Here, healthy but not depressed individuals demonstrated significant increases in this measure to these compared with neutral expressions. Furthermore, a significant negative correlation was demonstrated between depression severity and neural response, using both measures, to intense happy facial expressions in depressed individuals within a nearby region of the right fusiform gyrus.

Significant between-group differences were also demonstrated in linear trends in neural response to facial expressions of increasing sadness versus baseline. In contrast, findings for happy expressions, our data revealed a significant linear increase in the goodness-of-fit statistic within the left putamen and bilateral fusiform gyri in healthy compared with depressed individuals to these expressions. Further analyses also revealed significant between-group differences in percentage change in BOLD signal to expressions of 100% intensity sadness at 6 seconds poststimulus onset within the left parahippocampal gyrus extending to the left amygdala, and right fusiform gyrus to expressions of increasing sadness in depressed compared with healthy individuals. Further analyses revealed significant between-group differences in percentage change in BOLD signal to expressions of 100% intensity sadness at 6 seconds poststimulus onset within the left parahippocampal gyrus/amygdala and a near-significant between-group effect in the right fusiform gyrus. Here, depressed but not healthy individuals demonstrated significant increases in this measure to these compared with neutral expressions. There was no significant between-group difference in both measures within the amygdala as predefined by the Talairach coordinates and based on the region of interest analysis. The cluster with the center of mass in the parahippocampal gyrus we observed in the above contrasts did extend, however, into the inferior aspect of the left amygdala, consistent with previous studies highlighting in-

Figure 5. Correlations of responses to prototypical happy faces versus baseline and the scores of Beck Depression Inventory. The graph depicts the significant negative correlation of neural response in the right fusiform gyrus between BDI score and percentage change in BOLD signal in depressed individuals in response to the contrast of prototypical happy faces versus neutral faces. X-axis: BDI score. Y-axis: BOLD % change. BDI, Beck Depression Inventory; BOLD, blood oxygenation level dependent.
increased left amygdala responses to negative facial expressions in depressed compared with healthy individuals (Sheline et al 2001; Fu et al 2004).

Together, these data provide support for our first prediction: Significant increases in neural response were demonstrated within some, although not all, components of a distributed neural system important for the processing of visually presented emotional stimuli (Phillips et al 2003a) to facial expressions of increasing sadness, and significant decreases in response were demonstrated within regions to facial expressions of increasing happiness in depressed compared with healthy individuals. Our findings also provide partial support for our second prediction: A significant negative correlation was demonstrated in depressed individuals between depression severity and the magnitude of neural response in the right fusiform gyrus to happy expressions.

Individuals judged the gender of each facial expression, an implicit emotion-processing task. The relatively long presentation duration of each facial expression (2 seconds), however, may have allowed individuals to perform more explicit evaluation of the emotional content of these stimuli. While reaction time data for the gender decision task indicated that all individuals were able to perform the task within the 2-second period, healthy individuals did demonstrate relatively longer reaction times to the happy compared with sad expressions, suggestive of an attentional bias toward happy expressions in this population. Depressed individuals demonstrated similar mean reaction times for both categories of facial expressions and significantly longer reaction times than healthy individuals for sad expressions. The interaction between emotion and group was not significant, however. These findings, therefore, provide partial support for the absence of a positive attentional bias in depressed individuals and are consistent with findings from an earlier study (Surguladze et al 2004). It is noted, however, that because of the masked nature of the facial expressions, accuracy was low for both groups during performance of the gender decision task.

Dysfunction within the subgenual cingulate gyrus has previously been demonstrated in depressed individuals (e.g., Mayberg et al 1999; Phillips et al 2003b). We, therefore, performed between-group analyses of neural response within right and left subgenual cingulate gyrus using the goodness-of-fit statistic and percentage change in BOLD signal. These revealed a significant between-group difference in percentage change in BOLD signal within the left subgenual cingulate gyrus to happy expressions versus baseline but no between-group differences in neural responses within the right subgenual cingulate gyrus to either the happy, sad, or neutral facial expressions versus baseline. Interestingly, there was no significant between-group difference in SSQ within the left subgenual cingulate gyrus. A deviation between findings for between-group differences in the model fit (SSQ) versus those for the magnitude of BOLD signal change can occur because of the fact that the model fit is computed as a ration of signal: noise, as opposed to signal alone (the BOLD effect size). In all other analyses in the study, however, findings for SSQ and BOLD signal change were consistent. This finding of a decreased subgenual cingulate gyrus response to happy facial expressions is consistent with our main findings of decreases in response to these expressions within neural regions important for the response to visually presented emotional stimuli in depressed individuals.

It is unlikely that antidepressant medication dose had a significant effect on the above patterns of between-group difference in neural response to emotional expressions. Furthermore, analyses in depressed individuals revealed that higher compared with lower doses of antidepressant medication were associated with decreases in mean percentage change in BOLD signal, predominantly within fusiform gyrus and cerebellum, to both types of emotional expression; there were no differences in BDI score between high-dose and low-dose medication subgroups. These findings do not account for the significant increases in BOLD response to sad expressions, nor do they explain the negative correlation between BDI score and right fusiform gyrus response to happy expressions in depressed compared with healthy individuals. Rather, our findings indicate a specific effect of emotion, but not antidepressant medication dose, on patterns of neural response to these facial expressions in depressed compared with healthy individuals. As there were no significant between-group differences in response to neutral expressions compared with baseline, it is unlikely that between-group differences in neural responses to happy and sad expressions were the result of differences in neural responses to faces per se. Clearly, future studies examining unmedicated depressed patients are required.

Another possibility is that movement and visual scanning differences between groups may have contributed to the observed pattern of between-group differences in neural response to happy and sad expressions. The differential pattern of between-group differences in neural response to happy and sad expressions suggests, however, that increases (or decreases) in movement or visual scanning in depressed compared with healthy individuals are unlikely to explain these findings. Additionally, the neuroimaging data analysis software corrected for stimulus-correlated motion artifacts in all subjects (Bullmore et al 1999a).

Our findings suggest that preferential increases in neural response to sad rather than happy facial expressions within neural regions important for the response to visual presentations of emotional stimuli are associated with depression. These findings are consistent with clinical observations in depressed individuals of prominent negative cognitions and may underlie the poor social interaction frequently demonstrated by these individuals. Future studies employing other nonfacial emotional stimuli will help to clarify the extent to which abnormal neural responses reflect biases away from happy and toward sad emotional material per se in major depressive disorder.

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