Changes in the neural correlates of implicit emotional face processing during antidepressant treatment in major depressive disorder

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Abstract

An emerging hypothesis regarding the mechanisms underlying antidepressant pharmacotherapy suggests that these agents benefit depressed patients by reversing negative emotional processing biases (Harmer, 2008). Neuropsychological indices and functional neuroimaging measures of the amygdala response show that antidepressant drugs shift implicit and explicit processing biases away from the negative valence and toward the positive valence. However, few studies have explored such biases in regions extensively connected with the amygdala, such as the pregenual anterior cingulate cortex (pgACC) area, where pre-treatment activity consistently has predicted clinical outcome during antidepressant treatment. We used functional magnetic resonance imaging (fMRI) to investigate changes in haemodynamic response patterns to positive vs. negative stimuli in patients with major depressive disorder (MDD) under antidepressant treatment. Participants with MDD (n=10) underwent fMRI before and after 8 wk sertraline treatment; healthy controls (n=10) were imaged across an equivalent interval. A backward masking task was used to elicit non-conscious neural responses to sad, happy and neutral face expressions. Haemodynamic responses to emotional face stimuli were compared between conditions and groups in the pgACC. The response to masked-sad vs. masked-happy faces (SN-HN) in pgACC in the depressed subjects was higher in the pre-treatment condition than in the post-treatment condition and this difference was significantly greater than the corresponding change across time in the controls. The treatment-associated difference was attributable to an attenuated response to sad faces and an enhanced response to happy faces. Pre-treatment pgACC responses to SN-HN correlated positively with clinical improvement during treatment. The pgACC participates with the amygdala in processing the salience of emotional stimuli. Treatment-associated functional changes in this limbic network may influence the non-conscious processing of such stimuli by reversing the negative processing bias extant in MDD.

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Introduction

Major depressive disorder (MDD) consistently has been associated with a tendency to bias stimulus processing towards negative information as compared to positive or neutral information, as evident in behavioural measures that evaluate memory and attention (e.g. Bradley et al., 1995; Murphy et al., 1999; Murray et al., 1999; Gotlib et al., 2004a, b; Mogg et al., 2006), as well as in neurophysiological indices (e.g. Siegle et al., 2002; Murphy et al., 2003; Surguladze et al., 2005; Leppanen, 2006; Taylor Tavares et al., 2008; Suslow et al., 2010; Victor et al., 2010, 2012). Conversely, healthy humans show a normative positive bias in the same
indices (Killgore and Yurgelun-Todd, 2004; Erickson et al., 2005; Sharot et al., 2007; Juruena et al., 2010; Victor et al., 2010). For example, we previously observed that the haemodynamic response of the amygdala is greater to masked-sad vs. masked-happy faces presented below the level of conscious awareness in unmedicated, depressed or remitted individuals with MDD, but greater to masked-happy vs. masked-sad faces in healthy controls (Victor et al., 2010). Functional neuroimaging data suggest that these biases are mediated partly by rapid, non-conscious processing networks involving the amygdala (LeDoux, 1996; Morris et al., 1999). Notably, antidepressant agents from pharmacologically distinct classes shift the processing bias for negative emotional information towards the positive direction (e.g. Harmer et al., 2009; Victor et al., 2010). In depressed subjects, selective serotonin reuptake inhibitor (SSRI) treatment attenuates the exaggerated amygdala response to explicitly presented sad faces (Fu et al., 2004) and implicitly presented fearful faces (Sheline et al., 2001). Reboxetine administration reverses abnormal reductions in the recognition of positive facial expressions, response speed to positive personality adjectives and memory for positive information (Harmer et al., 2009). In healthy subjects, administration of an SSRI for 10 d (Norbury et al., 2009), reboxetine for 1 wk (Norbury et al., 2007) or mirtazapine in one dose (Rawlings et al., 2010) enhances the amygdala or fusiform gyrus response to explicitly presented happy face stimuli. Delineating the extended functional anatomical networks in which function changes to mediate these effects thus may constitute a crucial step towards elucidating the therapeutic mechanisms of antidepressant drugs in MDD.

Neuroimaging studies investigating the functional anatomical effects of treatment on these biases have focused on the amygdala, due to the central role this structure plays in evaluating the emotional salience of sensory stimuli (LeDoux, 1996; Morris et al., 1999). The amygdala interacts, however, with an extended network that includes structures within the medial and orbital prefrontal cortices, the rostral, medial and visuo-temporal cortices, the basal ganglia and thalamus, and the basal forebrain and brainstem, in the modulation of emotional behaviour (Ongur and Price, 2000; Ongur et al., 2003; Price and Drevets, 2010). Several components of this extended network have been implicated in the pathophysiology of MDD by neuropathological and lesion analysis studies, as well as by functional imaging studies that have observed abnormal haemodynamic responses during a variety of emotion processing tasks (reviewed in Price and Drevets, 2010). Nevertheless, the specific regions within this network, where the neural responses to emotional stimuli change in conjunction with the corresponding change in the amygdala response during antidepressant treatment, have not been established.

Among the regions that share extensive anatomical connections with the amygdala and that also show altered haemodynamic responses to emotionally valenced stimuli in depressed subjects (Victor et al., 2012), the pregenual anterior cingulate cortex (pgACC) has been noteworthy as a region in which pre-treatment activity consistently predicts the clinical response to antidepressant treatment (reviewed in Pizzagalli, 2011). In healthy individuals, the activity in this region has been associated with autonomic, neuroendocrine and monoamine neurotransmitter modulation in response to stressful and emotional stimuli (Price and Drevets, 2010) and with haemodynamic or electrophysiological responses to emotionally valenced stimuli, including pictures and words (for reviews, see Drevets and Raichle, 1998; Whalen et al., 1998; Bush et al., 2000). Moreover, in depressed subject samples, the baseline (pre-treatment) glucose metabolism and blood flow and the haemodynamic, encephalographic or magnetoencephalographic responses to negatively valenced stimuli have correlated positively with the clinical response to various pharmacological and non-pharmacological antidepressant treatments (reviewed in Pizzagalli, 2011). The function of this region thus appears to reliably predict the outcome of antidepressant treatment. However, the relationship between clinical outcome during antidepressant treatment and the haemodynamic response of the pgACC to emotional stimuli presented below the level of conscious awareness has not previously been evaluated.

A useful experimental paradigm for exploring the extended neuroanatomical network underlying emotional processing biases and their responsiveness to antidepressant drugs applies the technique of backward masking (Esteves and Öhman, 1993; Morris et al., 1999) to implicitly presented sad, happy and neutral faces. This design involves the presentation of face stimuli below the level of conscious awareness, allowing the assessment of rapid, automatic neural responses to the masked stimuli while reducing the variability associated with conscious stimulus processing. We developed a backward masking task that capitalized on the tendency of depressed subjects to bias stimulus processing both towards negative and away from positive information, thereby eliciting differential neurophysiological responses in depressives vs. controls (Victor et al., 2010). Thus, unmedicated-depressed
subjects exhibited an abnormally increased haemodynamic response to masked-sad faces and an abnormally decreased response to masked-happy faces in the amygdala. Notably, both of these abnormal amygdala responses reversed towards the normative pattern following sertraline treatment (Victor et al., 2010).

To more fully characterize the functional anatomical effects of antidepressant treatment on emotional processing in MDD, the current study extends our previous work by delineating the network of regions where, in conjunction with the amygdala, changes in the haemodynamic response to implicit emotional stimuli under sertraline are associated with reversal of the negative processing bias. The previous study evaluated differences in the haemodynamic response to masked-emotional faces in a region of interest limited to the amygdala. The current study instead applied to the same image data set a region-of-interest (ROI) analytic approach in the pgACC to test the hypotheses that the pre-treatment haemodynamic responses in this region to sad vs. happy stimuli in depressed subjects would differ relative to healthy controls, would change towards the normative pattern during SSRI treatment and would predict the clinical outcome post-treatment.

**Method**

**Participants**

Current unmedicated, depressed participants with MDD and healthy control subjects were recruited through the National Institutes of Health Clinical Center and newspaper advertisements in the Washington, DC area. Participants underwent screening evaluations to determine eligibility, which included a medical and psychiatric history, laboratory testing, physical examination, electrocardiogram and neuromorphological magnetic resonance imaging (MRI). The psychiatric diagnosis was determined according to DSM-IV-TR criteria (APA, 1994) using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) and an unstructured interview with a psychiatrist. Subjects were excluded if they manifest any of the following conditions: (1) serious suicidal ideation or behaviour; (2) major medical or neurological disorders; (3) exposure to psychotropic drugs or other medications that affect medical or neurological disorders; (3) exposure to (1) serious suicidal ideation or behaviour; (2) major if they manifested any of the following conditions:

Written informed consent was obtained from all subjects, as approved by the National Institutes of Health Combined Neuroscience Institutional Review Board. Subjects received financial compensation for their participation.

Assessments of intelligence were performed prior to scanning using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Illness symptom severity was rated using the Hamilton Depression Rating Scale (HAMD, 24 item; Hamilton, 1960), the Automatic Thoughts Questionnaire (ATQ; Hollon and Kendall, 1980), the Inventory of Depressive Symptomatology: Self-Rating (IDS-SR; Rush et al., 1996), the State-Trait Anxiety Inventory (Spielberger et al., 1970) and the Thought Control Questionnaire (Wells and Davies, 1994). The clinical response to treatment was assessed using the change in HAMD as the primary outcome measure.

**Antidepressant drug treatment**

The MDD subjects were imaged before and after 8 wk antidepressant treatment. Following the pre-treatment, baseline functional MRI (fMRI) scan, participants received the SSRI, sertraline hydrochloride (50 mg/d for 3 d, then titrated to 100 mg/d as tolerated). Participants were monitored by a psychiatrist, who increased or decreased the dose as clinically indicated. Participants received a stable dose for at least 4 wk prior to post-treatment scanning. The healthy subjects underwent fMRI scanning before and after a similar time interval as the MDD subjects to control for time and retest effects.

**fMRI Backward masking task**

Participants underwent fMRI while performing a backward masking task (for complete details, see Victor et al., 2010). Briefly, each task-trial displayed sad, happy or neutral faces in pairs of two, including a 26 ms ‘masked’ face immediately followed by a 107 ms ‘masking’ face to inhibit explicit perception of the first face (Esteves and Öhman, 1993; Wiens et al., 2004). Following each face pair, a fixation crosshair was shown as an implicit baseline measure for 10–13 s, allowing the haemodynamic response to return to baseline prior to the next face pair. Each emotion was shown in the masked position and followed by a neutral stimulus: sad-neutral (SN); happy-neutral (HN); neutral-neutral (NN). The SN, HN stimulus types were presented eight times and the NN type 16 times in each of four runs in a pseudo-randomized, mixed-trial design. Before each run, subjects viewed two neutral target faces and were instructed to indicate
by button press whenever a target appeared during the task, regardless of their facial expression. The actors whose faces depicted the happy and sad face stimuli presented during the post-treatment fMRI scan differed in identity from those used to generate the stimuli presented in the pre-treatment fMRI scan.

**Data acquisition, processing and statistical analysis**

Behavioural data acquired to assess the accuracy of the response to each stimulus presentation and the reaction time for initiating a response to target face stimuli during the fMRI task were recorded using E-Prime software and analysed with SPSS 14.0 statistical software (SPSS, Inc., USA).

Echoplanar images were acquired using a General Electric 3.0 T scanner (GE Signa, USA) with an eight-channel phased-array head coil (39 continuous slices, Electric 3.0 T scanner (GE Signa, USA) with an eight-channel phased-array head coil (39 continuous slices, field of view=22 cm, voxel size=3.4×3.4×3.0 mm$^3$). A total of 290 fMRI images were obtained during each of four 10-min runs (four images were discarded at the beginning of each run to allow for steady-state tissue magnetization). An anatomical MRI scan was obtained using a fast spoiled gradient echo sequence (TR=780 ms, TE=2.7 ms, flip angle=12°, FOV=22 cm, matrix=224×224, number of axial slices=128, slice thickness=1.2 mm, in-plane resolution=0.98 mm$^2$) to provide an anatomical framework for the functional imaging analyses. The coordinates were transformed from Montreal Neurological Institute (MNI) coordinates to the stereotaxic array of Talairach and Tournoux (1988) and localized anatomically using stereotaxic atlases (Talairach and Tournoux, 1988; Mai et al., 2003).

Image data were analysed voxel-wise using the general linear model within Statistical Parametric Mapping (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/). Single-subject difference maps were computed between conditions (e.g. masked-sad faces vs. masked-happy faces, SN-HN). At the group level, these difference maps were compared within a pgACC ROI to evaluate differences between the pre- and post-treatment conditions. The pgACC anatomical mask was defined on the MNI brain template provided within SPM, by designating an image corresponding to the anterior cingulate gyrus situated anterior to the genu of the corpus callosum. Voxels that corresponded to Brodmann areas 24 and 32, as depicted in the Talairach and Tournoux (1988) stereotaxic atlas, were included to encompass the rostral ACC region implicated previously in treatment studies of MDD (Vogt et al., 1995; Pizzagalli, 2011).

Paired sample $t$ tests were used to evaluate differences in the blood oxygen level dependent (BOLD) contrast signal in the pgACC between the pre-treatment and post-treatment fMRI scans for the main contrast of masked-sad vs. masked-happy faces (SN-HN). Within this pgACC ROI, the fMRI data were searched for voxels in which the BOLD signal difference between conditions reached the significance threshold set at $p_{\text{corrected}}<0.05$, after applying corrections for multiple comparisons using the family-wise error rate, as constrained by the ‘small-volume correction’ option within SPM5. The sizes of clusters of contiguous voxels for which the voxel level $p_{\text{uncorrected}}\leq 0.001$ were also assessed and clusters that remained significant following cluster-test correction for multiple comparisons were noted (Poline et al., 1997).

To interpret the interaction between the SN and HN conditions, eigenvariates were extracted from the peak voxel of the cluster-test corrected region identified in the SN-HN contrast. In addition, post hoc contrast evaluations of masked-sad vs. masked-neutral faces (SN-NN) and masked-happy vs. masked-neutral faces (HN-NN) were performed to characterize the nature of the hypothesized differential response to SN-HN. In all of these contrasts, in order to provide continuity with our previously published results (Victor et al., 2010, 2012), regional differences in BOLD activity that did not remain significant after correction for multiple testing were listed in the results if associated with a minimum cluster size of 10 contiguous voxels for which $p_{\text{uncorrected}}\leq 0.001$.

To evaluate whether the haemodynamic response to SN-HN in the baseline condition would predict clinical outcome at the post-treatment scan, a correlation analysis using SPSS 14.0 was performed on the eigenvariate values extracted from the peak voxel identified in the pgACC ($p_{\text{corrected}}<0.05$) for each participant and their HAMD scores from the post-treatment clinical assessment.

To control for test–retest repetition and other non-specific order effects, data for the SN-HN contrast were compared directly between the MDD subjects scanned pre- and post-treatment and the control subjects scanned twice across a similar time interval within the pgACC ROI. The differences in regional BOLD response between scan sessions were compared across groups via independent $t$ tests computed voxel-wise in SPM5.

Finally, exploratory whole brain analyses were performed post hoc to assess differences between the pre- and post-treatment conditions in other regions using paired $t$ tests for the SN-HN, SN-NN and HN-NN contrasts.
Clinical and neuropsychological characteristics

Altogether, 27 depressed patients were assessed for eligibility based on the entrance criteria; 20 volunteers qualified to participate in the study and seven were excluded for not meeting the entrance criteria. The 20 participants underwent treatment with sertraline hydrochloride. Four participants withdrew from the study during the treatment interval. Of the 16 participants who completed the 8 wk treatment course, the image data were excluded from analysis for six subjects due to excessive head motion during either the pre- or post-treatment fMRI scans. The 10 depressed participants who completed treatment and whose image data were included in the analysis (six female, right-handed, aged 33.2±5.0 yr) were group matched to 10 healthy control subjects (seven female, right-handed, aged 28.4±5.7 yr).

Of the 10 MDD participants included in the analysis, nine were diagnosed with recurrent MDD and one with a chronic single episode of MDD. One of the subjects with recurrent MDD was also diagnosed with co-morbid post-traumatic stress disorder and simple phobia and the subject with a single chronic episode of MDD also met criteria for co-morbid social phobia. The mean age of onset (s.d.) of MDD was 18.6 (5.6) yr. Four subjects were treatment naïve. For the six participants who had taken antidepressant medication in the past, the mean number of months (s.d.) off treatment was 21.7 (27.7). The average number of major depressive episodes (s.d.) was 4.1 (2.5) and ranged from one to 10 episodes. The mean WASI score was 122.3 (13.1) for the MDD group and 126.3 (8.1) for the control group.

The mean (s.d.) HAMD score for the MDD participants was 24.8 (5.8) pre-treatment and 6.4 (6.0) following the 8-wk treatment period and the mean change in HAMD scores was significant (p<0.001). The mean (s.d.) HAMD score was 0.0 (0.0) pre- and post-treatment for the control participants. Upon completion of the study, the mean final dose of sertraline for MDD participants was 105 mg/d±50 mg/d; range 50–200 mg/d). Nine MDD participants were sertraline treatment responders, based upon the operational definition of >50% reduction in their HAMD scores under treatment (Nierenberg and DeCecco, 2001). Exclusion of the participant who was non-responsive to treatment did not significantly affect the neuroimaging results. In seven participants, the HAMD scores decreased to the non-depressed range (<7), achieving the operational definition of illness remission (Nierenberg and DeCecco, 2001). Self-reported mood and anxiety questionnaire mean scores (s.d.) were also lower in the post-treatment vs. the pre-treatment condition for MDD participants: ATQ: 72.8 (21.0) vs. 18.1 (13.1), p<0.001; IDS-SR: 31.7 (5.4) vs. 13.6 (9.2), p<0.001; State-Trait Anxiety Inventory-State:

Table 1. Differential accuracy measures for detecting target faces when stimuli were presented in the masked (1st) vs. the masking (2nd) face position

<table>
<thead>
<tr>
<th></th>
<th>Target face in 1st position</th>
<th>Target face in 2nd position</th>
<th>Target face in neither position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct detection</td>
<td>22.8% b</td>
<td>77.2%</td>
<td>–</td>
</tr>
<tr>
<td>Correct rejection</td>
<td>–</td>
<td>–</td>
<td>77.5%</td>
</tr>
<tr>
<td>Incorrect detection (false alarm rate)</td>
<td>–</td>
<td>–</td>
<td>22.5%</td>
</tr>
<tr>
<td>Incorrect rejection</td>
<td>77.2%</td>
<td>22.8%</td>
<td>–</td>
</tr>
</tbody>
</table>

a Categorization of the subject’s response to each stimulus event was divided into four categories: (1) correct detection – the subject correctly identified the face as a target stimulus when shown in the first or second face position; (2) correct rejection – the subject correctly rejected the presence of a target stimulus when a target face was not present in either position; (3) incorrect detection (false alarm rate) – the subject indicated a target face was present when no target face was shown in either face position; (4) incorrect rejection – the subject failed to identify the presence of a target face when it was shown in either the first or second face position.

b A direct comparison showed no significant difference in the correct detection rate for a target face in the first position vs. the incorrect detection rate for a target face in neither position (shown in bold). These data demonstrate the efficacy of the backward masking paradigm.
50.6 (8.9) vs. 35.7 (10.7), \( p = 0.003 \); State-Trait Anxiety Inventory-Trait: 62.3 (3.3) vs. 43.1 (9.4), \( p < 0.001 \).

**Behavioural results during scanning**

Upon debriefing after completion of the fMRI, no participant reported awareness of having seen a masked face stimulus. Moreover, participants performed at the chance level in detecting the target face when these stimuli were masked. Similar to the accuracy results reported in Victor et al. (2010, 2012), the present study found that the ‘correct detection’ rate of trials when the target face was present in the first position did not differ from the ‘incorrect detection’ rate (false alarm rate) of trials when no target face was present in either face position for both MDD and control participants across both the pre- and post-treatments scans, demonstrating the effectiveness of the masking technique (\( t_{39} = 0.23, p = 0.83 \); Table 1). Separately, no difference in the correct and incorrect detection rates was found between MDD participants (\( t_{19} = 0.62, p = 0.54 \)) or control participants (\( t_{19} = 0.40, p = 0.70 \)) for the pre- and post-treatment scans. An analysis of variance (five stimulus types×four groups) revealed no differences between groups by emotion (\( F_{3,39} = 0.65, p = 0.59 \)). Separately, no accuracy differences were found to the presentation of a masked target face between groups (pre vs. post) by emotion (SN, HN, NS, NH, NN) for MDD participants (\( t_{18} = 0.31, p = 0.76 \)) or control participants (\( t_{18} = 0.53, p = 0.61 \)).

An analysis of participant reaction time to masked-sad and masked-happy target faces revealed no
significant difference between groups. In addition, the reaction times did not differ significantly between sessions in either group.

**fMRI results**

The MDD participants showed a greater haemodynamic response to masked-sad vs. masked-happy faces (SN-HN) in the right pgACC in the pre-treatment condition compared to the post-treatment condition ($t_{10}=7.79$, $p_{\text{corrected}}<0.001$; Fig. 1a-c). The haemodynamic response to SN-NN was also greater in the pre-treatment condition than in the post-treatment condition in the right pgACC ($t_{10}=8.95$, $p_{\text{corrected}}<0.001$; Fig. 1b). The results for SN-HN and SN-NN remained significant following both the family-wise error rate and cluster-test corrections in the right pgACC (Fig. 1b). The HN-NN contrast did not reveal a significant difference between the pre-treatment vs. post-treatment conditions.

The clinical response to treatment correlated positively with the pre-treatment BOLD response in the SN-HN condition in the pgACC ($r=0.67$; $p<0.05$), such that a greater BOLD response to masked-sad vs. masked-happy faces at baseline was predictive of a greater reduction in HAMD scores during treatment (Fig. 2).

The results of the exploratory whole brain analyses performed post hoc to assess regional differences in the haemodynamic response to SN-HN, SN-NN and HN-NN in participants before and after 8 wk antidepressant treatment appear in Tables 2 and 3. The analyses revealed several areas of the visual association cortices and the extended visceromotor network that share reciprocal connections with the amygdala. The MDD participants showed a greater haemodynamic response to SN-HN in the baseline condition compared to the post-treatment condition in the right pgACC (Fig. 1, Table 2), left caudal superior temporal gyrus and left anterior inferotemporal gyrus (ITG; Table 2). The MDD participants showed a greater haemodynamic response to SN-NN in the pre- vs. post-treatment conditions in the right pgACC (Fig. 3a), left and right medial thalamus (Fig. 3a), right anterior and posterior insula (Fig. 3b), left ventrolateral prefrontal cortex (vIPFC; 3b), left medial and lateral orbitofrontal cortex (Fig. 3a, c), left caudate (Fig. 3d), right anterior putamen (Fig. 3d), left fusiform gyrus, left anterior ITG, right posterior hippocampus, right anterior thalamus, right paracentral lobule, right occipital gyrus and left precentral gyrus. The MDD participants showed a greater haemodynamic response to HN-NN in the pre- vs. post-treatment conditions in the left precentral gyrus and left inferior parietal cortex.

Results of the comparisons of regional differences in BOLD response in the SN-HN contrast between MDD participants studied across treatment vs. control participants studied across a similar time interval appear in Table 4, Fig. 1d. The MDD participants showed a greater BOLD signal difference relative to the controls in the pre- vs. post-treatment conditions in the right pgACC in the ROI analysis ($t_{10}=3.98$, $p_{\text{corrected}}<0.001$) as well as in the whole brain analysis. The latter analysis also showed differences in the same direction in the right posterior cingulate cortex and left temporopolar cortex. In contrast, the MDD participants showed an increased response compared to the controls in the post- vs. the pre-treatment conditions in the right lateral frontal polar cortex.

**Discussion**

Chronic sertraline treatment was associated with differential changes in the haemodynamic response to emotional stimuli presented below conscious awareness in the pgACC, a region that shares substantial, reciprocal anatomical connections with the amygdala (Carmichael and Price, 1995). The limbic circuits between these structures form part of an extended medial prefrontal network, which plays major roles in evaluating the salience of emotional stimuli and in modulating emotional experience and behaviour.
Our most striking result specifically showed a decrease in the haemodynamic response to masked-sad vs. masked-happy faces following treatment in the pgACC. These differences reflect a change in the pattern of haemodynamic activity that had existed prior to treatment, indicating a shift in the neurophysiological correlates of the negative emotional processing bias observed in MDD, in the same direction as our previously published findings in the amygdala (Victor et al., 2010). The treatment-associated modulation of this bias appears compatible with the hypothesis that the therapeutic mechanism of antidepressant pharmacotherapy involves shifts in the emotional processing bias towards the positive direction (Harmer, 2008). Nevertheless, our study design did not permit us to fully explore this model, as we were unable to establish whether the shift in this bias leads mechanistically to symptom reduction or to differentiate whether the shift occurs independently of the direct drug effect (e.g. on the basis of clinical response) or to determine the specific time that the processing shifts occurred during the course of treatment.

Extensive literature has implicated the pgACC as a region where function changes during effective antidepressant treatment. Depressed subjects who improve during antidepressant treatment show higher pgACC metabolism and electrophysiological activity before treatment than non-responders or healthy controls (e.g. Mayberg et al., 1997; Pizzagalli et al., 2001; Salvadore et al., 2010). During effective treatment, glucose metabolism in the pgACC decreases towards normative levels (reviewed in Drevets et al., 2002). Our data more specifically suggest that the function of this cortex changes in association with SSRI treatment, such that the significant reduction in BOLD response in the SN-HN contrast was attributable to a significant decrement in the haemodynamic response to implicitly presented sad stimuli coupled with an enhancement of the haemodynamic response to implicitly presented happy stimuli (Fig. 1c). In addition, our data show that increased haemodynamic activity to implicitly sad stimuli in the pre-treatment condition is predictive of a greater decrease in depressive symptoms during treatment (Fig. 2).

In addition to the pgACC, several orbitofrontal cortical regions showed a decrease in the haemodynamic response to masked-sad faces vs. masked-neutral faces following antidepressant treatment (Table 3, Fig. 3). Under the classification of prefrontal cortical networks by Ongur and Price (2000), the orbitofrontal cortex areas implicated herein localize to the orbital (or ‘sensory’) network, whereas the pgACC forms part of the medial (or ‘visceromotor’) network. These regions share substantial, reciprocal anatomical connections with the amygdala, although the density of such projections is greater for the pgACC (Amaral and Insausti, 1992). The orbital network receives extensive anatomical projections from sensory association cortices and plays a major role in interpreting the

<table>
<thead>
<tr>
<th>Condition</th>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Cluster size</th>
<th>Z value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD-pre&gt;MDD-post</td>
<td>Right pregenual anterior cingulate cortex</td>
<td>14</td>
<td>42</td>
<td>−5</td>
<td>101**</td>
<td>4.20</td>
</tr>
<tr>
<td></td>
<td>Left caudal superior temporal gyrus</td>
<td>−61</td>
<td>−35</td>
<td>2</td>
<td>21</td>
<td>3.83</td>
</tr>
<tr>
<td></td>
<td>Left anterior inferotemporal gyrus</td>
<td>−42</td>
<td>−14</td>
<td>−18</td>
<td>11</td>
<td>3.44</td>
</tr>
</tbody>
</table>

BOLD, Blood oxygen level dependent; MDD, major depressive disorder; SN, masked-sad face followed by unmasked-neutral face; HN, masked-happy face followed by unmasked-neutral face.

A significant increase in the BOLD response within the left amygdala for SN-HN was reported previously for the same dataset in Victor et al. (2010), established using an analysis limited to an amygdala region of interest.

The statistical t values for these regions are reported in the text, while corresponding z values are reported in the table (#p ≤ 0.001).

The peak coordinate reported here for the whole brain analysis was also revealed in the pregenual anterior cingulate cortex region-of-interest analysis and was significant after applying family-wise error rate and cluster-test corrections for multiple comparisons. The differences identified in other regions would not have been significant after applying corrections for multiple testing across the whole brain.
salience of sensory stimuli in relation to context (Ongur and Price, 2000). The medial network, in contrast, is implicated in the regulation of the autonomic, endocrine and behavioural aspects of emotional behaviour (Ongur et al., 2003; Price and Drevets, 2010). Both networks are extensively interconnected with the vlPFC (Price and Drevets, 2010). The medial network shares reciprocal projections to the posterior cingulate cortex and temporopolar cortex, which also showed differential responses to implicitly presented emotional stimuli under sertraline in the MDD subjects relative to the controls (Table 4). The pgACC and other regions within this extended medial network also function as part of a ‘default system’ of the brain, which is hypothesized to subserve self-referential functions that include the self-absorption and obsessive ruminations manifest in depression (Gusnard et al., 2001; Raichle et al., 2001; Drevets et al., 2002; Grimm et al., 2009; Berman et al., 2011), symptoms that often appear outside explicit cognitive control. Similarly, the data presented herein suggest that these regions play a role in processing emotion during tasks that involve automatic neural responses to negative emotional stimuli.

Finally, our results comparing changes across time or treatment in the control and MDD groups, respectively, revealed a significant difference in the haemodynamic response of the frontal polar cortex

### Table 3

Regional differences in the BOLD response to masked-sad faces vs. masked-neutral faces and masked-happy vs. masked-neutral faces in patients with MDD before and after 8 wk antidepressant treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Region</th>
<th>SN-NN</th>
<th>HN-NN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD-pre</td>
<td>R pregenual ACC</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>&gt;MDD-post</td>
<td>L fusiform G</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>L anterior inferotemporal G</td>
<td>−44</td>
<td>−4</td>
</tr>
<tr>
<td></td>
<td>R posterior hippocampus</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>R caudate</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>R posterior insula</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>R posterior insula</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>R anterior putamen</td>
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<td>24</td>
</tr>
<tr>
<td></td>
<td>R anterior insula</td>
<td>36</td>
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</tr>
<tr>
<td></td>
<td>R anterior insula</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Paracentral lobule</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>L medial orbitofrontal C</td>
<td>−14</td>
<td>−14</td>
</tr>
<tr>
<td></td>
<td>L lateral OFC</td>
<td>−44</td>
<td>−44</td>
</tr>
<tr>
<td></td>
<td>L ventrolateral PFC</td>
<td>−38</td>
<td>−38</td>
</tr>
<tr>
<td></td>
<td>L medial thalamus</td>
<td>−6</td>
<td>−6</td>
</tr>
<tr>
<td></td>
<td>R anterior thalamus</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>R medial thalamus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Right occipital G</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>L precentral G</td>
<td>−12</td>
<td>−12</td>
</tr>
<tr>
<td></td>
<td>L inferior parietal C</td>
<td>−12</td>
<td>−12</td>
</tr>
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</table>

BOLD, Blood oxygen level dependent; MDD, major depressive disorder; SN-NN, masked-sad faces vs. masked-neutral faces; HN-NN, masked-happy faces vs. masked-neutral faces; MDD-pre, participants scanned prior to antidepressant treatment; MDD-post, participants scanned following 8 wk antidepressant treatment; R, right; L, left; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; G, gyrus; C, cortex.

*The regions reported correspond to clusters containing at least 10 voxels for which the voxel $p_{uncorrected} \leq 0.001$.

**The peak coordinate reported here for the whole brain analysis was also revealed in the pregenual anterior cingulate cortex region-of-interest analysis and was significant after applying family-wise error rate and cluster-test corrections for multiple comparisons. The differences identified in other regions would not have been significant after applying corrections for multiple testing across the whole brain.
to implicitly presented emotional stimuli. The BOLD signal in the lateral frontal polar cortex increased in response to masked-sad vs. masked-happy faces in the MDD group following treatment, while no change was observed in the control group. In previous studies, the correlation between depression severity

**Fig. 3.** Neuroimaging results for the masked-sad vs. masked-neutral (SN-NN) contrast in the pre-treatment condition relative to the post-treatment condition. (a–d) Voxels showing greater haemodynamic response to SN-NN in major depressive disorder (MDD) participants at baseline vs. after 8 wk antidepressant treatment, shown on horizontal slices in the (a) right pregenual anterior cingulate cortex, (b) right anterior insula (c) left medial orbitofrontal cortex (OFC) and (d) right caudate. Contrast eigenvariate values are shown for SN-NN at the peak voxel within a cluster for several regions identified in the whole brain analysis. vlPFC, Ventrolateral prefrontal cortex.
ratings and resting blood flow or glucose metabolism was opposite in direction between the left amygdala and the left vlPFC/lateral frontal polar cortex (Drevets et al., 1992, 1995). These and other neuroimaging data suggest the hypothesis that neural activity in the vlPFC/lateral frontal polar cortex exerts an inhibitory influence over depression severity (reviewed in Drevets et al., 2008). The current results showing an increase in this region in MDD vs. control subjects across time to implicit sad stimuli appear compatible with this hypothesis, since they suggest that an antidepressant response is associated with enhanced function in a region that may modulate the limbic response to negative stimuli.

Several limitations of our study design merit comment. First, the MDD sample was small in size and included only one treatment non-responder. Therefore, we were unable to compare responders and non-responders or to address whether the negative processing bias reverses during sertraline administration even when the therapeutic response proves inadequate. Also, the MDD sample included both treatment-naïve and previously medicated patients, which could contribute to the biological heterogeneity of the group. Second, presumably also due to the small sample size, we were unable to show significant behavioural differences in reaction time to masked-sad vs. masked-happy faces in the pre- vs. post-treatment conditions. Third, we were unable to address the generalizability of these results to other mood disorders, other treatment durations or other antidepressant drugs. Additionally, we excluded subjects from the study with a previous history of non-response to sertraline or of intolerable or adverse side-effects during sertraline treatment, thereby limiting generalization of our findings to these subject populations. Finally, we did not include a sample of MDD subjects who received only placebo in the treatment phase, so we were unable to establish a casual effect of pharmacotherapy on the emotional processing bias.

In conclusion, the pgACC BOLD response to masked-sad and masked-happy faces showed a differential response in MDD participants before vs. after chronic sertraline treatment. The pgACC and several areas of the orbitofrontal cortex and the extended medial prefrontal network showed treatment-associated decrements in response to non-consciously presented sad faces compared to happy or neutral faces, while a reciprocal pattern was observed following treatment in the lateral frontal polar cortex that putatively functions to modulate depression severity. Future studies are needed to explore the mechanisms through which antidepressant pharmacotherapy may produce changes in the salience of emotional stimuli and to assess whether the resolution of emotional processing biases may provide a sensitive and specific biomarker of antidepressant treatment response.

Acknowledgements

The experiments described herein were performed at the National Institute of Mental Health, Division of Intramural Research Programs, in the Section on Neuroimaging in Mood and Anxiety Disorders at the National Institutes of Health, Bethesda, MD. Funding

Table 4. Regional differences in the BOLD response to masked-sad faces vs. masked-happy faces in patients with MDD vs. healthy controls across the treatment interval*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Region</th>
<th>Stereotaxic coordinates</th>
<th>Cluster size</th>
<th>Z value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD&gt;control, pre- vs. post-treatment</td>
<td>Right pregenual anterior cingulate C*#</td>
<td>14 43 0 34</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right posterior cingulate C</td>
<td>6 −53 30 23</td>
<td>3.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left temporopolar C</td>
<td>−44 14 −19 21</td>
<td>3.11</td>
<td></td>
</tr>
<tr>
<td>MDD&gt;control, post- vs. pre-treatment</td>
<td>Right lateral frontal polar C</td>
<td>38 58 −3 14</td>
<td>3.72</td>
<td></td>
</tr>
</tbody>
</table>

BOLD, Blood oxygen level dependent; MDD, major depressive disorder; SN-HN, masked-sad faces vs. masked-happy faces; G, gyrus; C, cortex.

* The statistical t values for these regions are reported in the text, while corresponding z values are reported in the table (p<0.001).

# Denotes a significant change in BOLD response also revealed within a pregenual anterior cingulate cortex region-of-interest analysis using the small volume correction option in SPM5 (p<0.001, KE=18, corrected for multiple comparisons using the family-wise error rate and cluster-test within SPM5).
support for this research was provided by the Intramural Program of the National Institutes of Health, National Institute of Mental Health (Z01-MH002792) and The William K. Warren Foundation. We thank Dr Harvey Iwamoto for programming the fMRI backwards masking task, Joan Williams, Michele Drevets and Dr Paul Carlson for recruitment of study participants and clinical assessment support, Drs Allison Nugent and Sean Marrett for fMRI technical support and scientific direction with scanning and data analysis and Jeanette Black and Renee Hill for technologist support during the fMRI sessions.

Statement of Interest

Dr Furey and Dr Drevets declare relevant financial activities outside the submitted work: a pending patent, US Patent Application No: 2006/0270,698 entitled ‘Scopolamine for the Treatment of Depression and Anxiety’. NIMH is the primary patent holder and no money has been paid to date. Dr Drevets also declares for the work under consideration for publication: grant money to his institution (NIMH DIRP) and for relevant financial activities outside the submitted work: consultancy (money paid to him) at Myriad, Esai, Johnson and Johnson and Pfizer; grant money to his institution from the William K. Warren Foundation in support of the Laureate Institute for Brain Research; payment for development of educational presentations (lecture honoraria) at the University of Pennsylvania, Washington University, University of California-Davis and CME Incorporated.

References


