Research report

Neural response to emotional stimuli associated with successful antidepressant treatment and behavioral activation

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1. Introduction

Major depressive disorder (MDD) is a common, often severe, and chronic illness with high rates of non-recovery (Collins et al., 2011; Warden et al., 2007). Suboptimal outcomes with conventional antidepressants provide the impetus for identifying phenotypic and/or biological markers that would inform treatment decisions to improve likelihood of response. Towards this aim, functional magnetic resonance imaging (fMRI) investigations provide an opportunity to assess direct effects of different treatments on brain circuits that subserve the phenomenology of MDD. In particular, fMRI studies have been used to define the brain networks associated with different emotions (Fu et al., 2004, 2007; Hariri et al., 2002; Kalin et al., 1997; McCabe et al., 2005; Northoff et al., 2000; Phillips et al., 2001; Siegle et al., 2002; Wang et al., 2012). Evaluating antidepressant effects on emotion processing neurocircuitry can provide important insights into illness states, as well as potential biomarkers of response, all of which can contribute to improving selection of current therapies and development of future targeted therapeutics.

A replicated outcome when employing emotional provocation techniques evaluated with fMRI in depressed states is overactivity in the subgenual cingulate, amygdala, insula, and prefrontal cortex (Anand et al., 2005; Harmer et al., 2009; Keedwell et al., 2009; Northoff et al., 2000; Phillips et al., 2001; Siegle et al., 2002; Wang et al., 2012). Evaluating antidepressant effects on emotion processing neurocircuitry can provide important insights into illness states, as well as potential biomarkers of response, all of which can contribute to improving selection of current therapies and development of future targeted therapeutics.

Aim: To identify baseline and 1-week neuroimaging predictors of response to a 6-week trial of fluoxetine/olanzapine combination treatment during an affective processing task.

Methods: Twenty-one MDD patients and 18 healthy controls were enrolled in the study. MDD patients were treated for 6 weeks with fluoxetine (40–60 mg/day) and olanzapine (5–12.5 mg/day). All participants viewed images from the International Affective Picture Rating System during a functional magnetic resonance (fMRI) scan at baseline and 1 week.

Results: There was a 57% response rate (defined as a 50% decrease in Hamilton Rating Scale for Depression-17 item) at 6 weeks. At baseline, responders had increased premotor activity while viewing negative images compared to non-responders and healthy controls. Higher baseline premotor activity was also predictive of greater percent change on the HAMD-17 and improvement in negative disposition and behavioral drive. Non-responders exhibited increased insular activity at baseline compared to responders. Higher activity in the posterior cingulate cortex was also predictive of greater percent change on the HAMD-17. Change from baseline to 1 week did not produce any significant predictive findings.

Conclusions: Treatment with fluoxetine/olanzapine demonstrated similar biomarkers of response to monotherapeutic strategies. In particular, posterior cingulate cortex, anterior insula, and premotor cortex may show predictive differences in their response to affective images prior to treatment. Further research needs to be conducted to determine the utility of early changes in emotion circuitry in predicting antidepressant response.

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serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) (Rosenblau et al., 2012; Davidson et al., 2003). However, it is not clear when these changes begin to occur in the course of antidepressant therapy and whether they are specific to treatment strategy (e.g. monotherapy with an SSRI, SNRI, combination therapy).

The imaging studies of emotional processing conducted thus far have all utilized monotherapeutic approaches primarily with an SSRI or SNRI (Davidson et al., 2003; Fu et al., 2004; Kalin et al., 1997; Rosenblau et al., 2012). However, combination strategies are commonly used and are included in clinical guidelines (Lam et al., 2009).

In particular, there has been a steady increase in the use of atypical antipsychotics to treat depression either as a monotherapy (e.g. quietiapine) or as an augmentation strategy (e.g. olanzapine, risperidone, aripiprazole) (Alexander et al., 2011; Blier et al., 2010; Papakostas, 2009; Chen et al., 2011; Nelson et al., 2012). The combination of fluoxetine and olanzapine has demonstrated efficacy in depression and it is the first medication approved for treatment resistant depression by the FDA (Bobo and Shelton, 2010; Croxtall and Scott, 2010).

Anhedonia is a core deficit in MDD, which is inherently related to emotional processing. In addition to being a core abnormality in MDD, aberrations in reward-based phenomenology may be a baseline predictor of treatment outcome with antidepressants. For example, low scores on the interest-activity item on the Hamilton Rating Scale for Depression-17 item (HAM-D-17; Hamilton, 1960), which reflects reward responsiveness and drive, predicted poor outcome in a post-hoc analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Uher et al., 2012) and was a unique negative predictor of time to remission in SSRI resistant adolescents (McMakin et al., 2012). Furthermore evidence also suggests that low reward seeking may be a vulnerability factor for incident MDD and may separately predict functional domain outcomes (Rawal et al., 2013). Neuroimaging studies and quantitative meta-analyses have identified a consistent pattern of abnormal activity in MDD in a corticostriatal “reward circuit” encompassing the ventromedial prefrontal cortex, ventral striatum, and ventral tegmental area (Tremblay et al., 2005; Diekhof et al., 2007, 2012). Reward function might thus be expected to act as a mediator of antidepressant response, both at the behavioral and at the neural level.

The primary aim of the current study was to determine whether brain activation in response to neutral and positive images at baseline and 1 week would predict treatment outcome in a 6-week trial of fluoxetine and olanzapine in patients with MDD. The extent to which behavioral activation (reward responsiveness, drive, and fun seeking) correlates with emotion processing circuitry and is a mediator of antidepressant response was also explored. We hypothesized the following: (1) Differences between responders and non-responders to treatment will be evident at baseline and these changes will predict antidepressant outcome; (2) MDD patients will demonstrate changes in neural activity in response to viewing positive and negative images by 1 week, and these changes will predict antidepressant outcome at 6 weeks; (3) Baseline and changes in behavioral activation in MDD patients will correlate with treatment outcome and brain activity in response to positive and negative images, and (4) MDD patients will exhibit increased pre-treatment activity in limbic and cortical regions compared to healthy controls in response to negative pictures, and successful treatment will normalize this activation pattern.

2. Methods

2.1. Participants

Patients with MDD (n=21) were recruited from the Mood Disorders Psychopharmacology Unit (MDPU) at the University Health Network. Age- and sex-matched healthy controls (n=18) were also recruited from the community through local advertisements. All participants provided written informed consent. The study was approved by the University Health Network Research Ethics Board.

All participants were required to be 18–55 years old, and righthanded. Exclusion criteria for both MDD and healthy controls were: DSM-IV-TR criteria for substance abuse or dependence (except nicotine or caffeine) within the past 3 months; unstable medical illness; history of neurological trauma resulting in loss of consciousness; uncorrected hypothyroidism or hyperthyroidism, including elevated thyroid stimulating hormone (TSH); hyperglycemia or diabetes mellitus as defined by a fasting blood glucose value of > 125 mg/dl; pregnant or nursing status.

Inclusion criteria for the MDD group only included meeting DSM-IV criteria for diagnosis of a Major Depressive Episode as part of Major Depressive Disorder (confirmed with the Mini International Neuropsychiatric Institute (MINI) structured interview), a Hamilton Depression Rating Scale 17-item (HRSD-17) > 17, and antidepressant free for a minimum of 7 days (3 weeks in the case of non-selective MAO-Inhibitors) prior to the baseline visit. The presence of a primary Axis I disorder other than MDD, lifetime history of hypomania/mania, psychosis, obsessive compulsive disorder, or an eating disorder were exclusionary, in addition to prior failure to respond to fluoxetine and olanzapine in combination at adequate dose and duration, failure to respond to two adequate antidepressant trials in the current episode, evidence of serious risk of suicide based on clinician assessment and/or HRSD-17 suicide item > 3, or electroconvulsive therapy in the preceding 6 months.

Additional exclusion criteria for the HC group included a history of psychiatric illness, (based on the MINI), history of psychiatric treatment (antidepressants, anxiolytics, or antipsychotics), and a family history of psychiatric illness or treatment.

2.2. Study design

This was a parallel two group (MDD and healthy control) design, in which the MDD participants underwent 3 separate fMRI sessions at baseline and 1 week after initiation of open-label olanzapine/fluoxetine (12.5 mg/60 mg) combination treatment. The healthy controls also underwent fMRI sessions at baseline and 1 week later. During each session, participants completed a set of questionnaires and subsequently viewed neutral, positive and negative pictures from the International Affective Picture System (IAPS) (Lang et al., 1993). Subsequently, participants rated the extent to which they perceived the pictures to be neutral, positive or negative.

Clinical assessments involving completion of administered depression scales and self-report questionnaires occurred at 1 week, 2 weeks, 4 weeks and 6 weeks after the baseline visit. Medication compliance was monitored by pill counting at each clinical assessment. All participants were reimbursed for their travel expenses up to $20 for each study visit and given $200 in total for compensation of the imaging sessions.

2.3. Clinical outcome measures

The HAMD-17 was the primary clinical outcome measure and was used to define response ( > 50% decrease in total score). The Clinical Global Impression – Severity and Change scales (Guy, 1976) were secondary outcome measures. The change scale is designed such that a 0 reflects no change in symptoms, while negative and positive values represent worsening and improvement, respectively.
The Positive and Negative Affect Schedule (PANAS) was a secondary measure of individual disposition (Watson et al., 1988). This 20-item scale requires participants to rate on a Likert scale how much an attribute (e.g., “excited”) represents them. There are two subscales that reflect negative and positive disposition.

The Behavioral Activation System scale (Carver and White, 1994) was used to assess reward across three subscales: reward responsiveness, drive and fun seeking. A higher score is reflective of greater levels of behavioral activation in the respective domain.

2.4. IAPS paradigm

The IAPS is a series of 114 35 mm color slides specifically selected to elicit a range of positive, neutral and negative affective states (Lang et al., 1993, 1999).

This collection of visual stimuli is one of the most frequently used for the study of affective processing, and there is strong evidence that its utilization reliably elicits affective responses (Lang and Greenwald, 1988a, 1988b). Negative (e.g. mutilated face), positive (e.g. Olympic victories), and neutral (e.g. wicker basket) stimuli were selected based on z score transformed normative ratings of arousal (low to high) and valence (negative to positive), separately for male and female ratings, in order to obtain a derived set of stimuli that reliably elicits maximal affective responses for both sexes (Lang and Greenwald, 1988a).

Positive, negative, and neutral affective visual stimuli were presented in a blocked design. During the imaging session, stimuli were presented in two runs, or data acquisition sets. The first run was composed of alternating blocks (groups) of neutral and positive valence pictures. The second run was composed of alternating blocks of neutral and negative valence pictures (Fig. 1). Each block consisted of 12 photographs with constant affective valence; either negative, positive, or neutral. Within each block, each photograph was displayed for 4 s, with no interphotograph transition delay, resulting in a block length of 48 s. The positive-neutral run (data-acquisition set) consisted of 11 alternating positive-neutral blocks, beginning and ending with neutral blocks for a total duration of 540 s. Similarly, the negative-neutral run was also comprised of 11 alternating negative-neutral blocks for 540 s.

In total 132 visual stimuli were presented in each run. Each stimulus appeared twice per trial. The stimuli were presented in a quasi-random order such that (1) a given stimulus was never repeated with fewer than 12 intervening stimuli, and (2) novel stimuli appeared up to three-quarters of the way through the trial. Each trial began and ended with neutral stimulus blocks.

Subjects were asked to react naturally to the stimuli that were presented on the screen, without thinking about previously presented stimuli, and without any conscious effort to identify or regulate their affect. To ensure viewing compliance, subjects were additionally asked to make a quick non-emotional judgment for each picture presented whether it depicted indoor or outdoor action through pressing one of two buttons on an MR-compatible button pad as quickly as possible (Current Designs, Philadelphia PA).

To allow time for the MR signal to reach a steady-state, subjects viewed the word “BEGIN” and a 12 s countdown timer before the presentation of the first neutral block. The runs were presented in a fixed order to all subjects; neutral-positive followed by neutral-negative. The positive and negative trials were not counterbalanced because of evidence that a negative affective state may linger and interfere with the elicitation of a positive affective state (Davidson et al., 2003; Ekman et al., 1980). Visual stimuli were displayed with an XGA LCD projector onto a projection screen that was visible from within the bore of the magnet through a periscope mirror attached in the headcoil. The presentation of stimuli, recording of reaction times and appropriate response button (indoor/outdoor) was implemented in MATLAB 7.4.0 (Natick, MA) using a custom script written in COGENT2000.

Fig. 1. Affective induction paradigm.
2.5. fMRI acquisition

All neuroimaging was performed with a 1.5 T GE Echospeed magnetic resonance imaging system (GE Medical Systems, Milwaukee, WI) fitted with a standard quadrature head coil. Subjects were placed into the scanner in a supine position with dense foam padding around the head to minimize movement within the scanner. The MRI compatible button box was attached to the subject’s right quadriceps with medical tape, and was operable using the right index and middle finger. Prior to entry into the scanner, all subjects were acquainted with use of the button box with the presentation of 20 photographs selected from the IAPS that were not included in the trial runs, and appropriate button press recording.

Two experimental runs of 9 min were performed after a 4.5 min high-resolution three-dimensional (3D) anatomical scan of the whole head was acquired. For the anatomical scan, 120 axial slices, with a 256 × 256 matrix, and a 20 × 20 cm² field of view were acquired using a T1-weighted 3D spoiled gradient. Voxel sizes with .78 × .78 × 1.10 mm³ dimensions were obtained using an echo sequence with a flip angle of 45°, echo time (TE), 5 ms, repetition time (TR), 25 ms, and a slice thickness of 1.1 mm. Whole-brain functional imaging employed a spiral gradient echo imaging (Glover and Lee, 1995) of 25 axial slices with a 64 × 64 matrix, and a 20 × 20 cm² field of view. Voxel sizes with 3.13 × 3.13 × 4.40 mm³ dimensions were obtained using a T2*-weighted sequence with a flip angle of 85°, TE=25 ms, and TR=2000 ms, and a slice thickness of 4.4 mm. A total of 270 functional volumes were acquired for each run. The first three scan volumes were automatically removed to allow for signal equilibration, three additional volumes corresponding to the last six seconds of viewing of the BEGIN countdown timer were additionally removed.

3. Data analysis

3.1. Clinical data

Statistical significance between responders vs. non-responders and MDD vs. healthy controls was assessed using the student’s t-test in instances where the data met criteria for normality and Mann–Whitney U tests when normality was not met. Similarly, Spearman’s Rho was used to assess the correlation and prediction between non-normal continuous measures and Pearson correlation coefficients for normal variables. A repeated measures analysis of variance was employed to evaluate the effect of time on depression measures.

3.2. Neuroimaging

A first level analysis was performed for each subject at each time point (baseline, week 1, week 6), using FEAT (Beckmann et al., 2003), part of the FSL analysis package (FMRIb’s Software Library, www.fmrib.ox.ac.uk/fsl). The first six volumes were deleted to allow for signal stabilization. Pre-processing consisted of high pass filtering (192 s cutoff), slice timing correction, motion correction using MCFLIRT (Jenkinson et al., 2002) and spatial smoothing using a Gaussian kernel of 8 mm FWHM. Non-brain voxels were extracted using BET (Smith, 2002). Data were pre-whitened using FILM (Woolrich et al., 2001). A simple block design (48 s on, 48 s off) was convolved with an ideal hemodynamic response. Additionally 6 motion covariates (1–S, 1–R, A–P, pitch, yaw and roll) were included in the model. Time series data for each voxel were modeled as the linear sum of all regressors and the resulting maps registered to the subject’s anatomical image and then to standardized (MNI) space.

For analyses of change over time, a higher level fixed effects analysis was run for each subject, contrasting parameter estimates within subject for the response to slides at the two time points of interest.

All group analyses were modeled as mixed effects (subject as a random factor and condition as a fixed factor) using FLAME (FMRIb’s Local Analysis of Mixed Effects). Analyses were corrected for multiple comparisons with a cluster based correction for multiple comparisons (z = 1.96, p < 0.05) using Gaussian Random Field Theory (Forman et al., 1995; Worsley et al., 1992) except where noted below.

An initial group analysis was conducted on baseline data to determine whether depressed subjects differed from healthy controls in response to positive or negative slides. To determine whether these effects were associated with treatment response, we ran a between group analysis comparing non-responders to responders and healthy controls. Within the omnibus map of group differences, we conducted a post-hoc analysis looking for regions where either responders or non-responders differed significantly from the two other groups (intersection of contrast maps of one of the depression groups with the other and with healthy controls, z = 1.96, p < 0.05 corrected).

Mean values from each subject were extracted from clusters significant at the group level to determine whether results correlated with key outcome variables.

4. Results

4.1. Participants

A total of 21 MDD patients and 18 healthy controls were enrolled in the trial. At 6 weeks, 17 patients had completed the antidepressant trial and had repeat fMRI scans at 1 week and 6 weeks, while 11 healthy controls had repeat fMRI scans. Due to high levels of movement, scans from 2 of the MDD patients were not included in the imaging analyses.

The healthy control and MDD group were similar in age and percentage of females (Table 1). Responders and non-responders also did not differ on these variables, as well as severity, duration of episode and family history (Table 2).

4.2. Behavioral findings

There were no differences across patients or healthy controls on button press accuracy. At baseline, the MDD group rated negative images as more aversive than healthy controls [−3.4 (.78) vs. −2.8 (.89), p = .044]. The only difference between responders and non-responders on the picture ratings was at week 6, where non-responders rated negative pictures as more aversive [−3.8 (.27) vs. −2.8 (.15), p = .011].

4.3. Clinical findings

There was a significant change in HAMD-17 scores over time in the MDD group [F(4) = 6.54, p < .001], with a 57% response rate and 48% remission (HAMD-17 < 7) rate at 6 weeks.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDD (N=21)</th>
<th>HC (N=18)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.9 (11.4)</td>
<td>36.2 (10.3)</td>
<td>.44</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>14/21</td>
<td>12/18</td>
<td>1.00</td>
</tr>
</tbody>
</table>
CGI-Severity score at baseline predicted change in HAMD-17 scores at week 6 ($r = .69$, $p = .001$). Depression severity also correlated with increased negative disposition (measured on PANAS; $r = -.53$, $p < .001$) but not positive disposition ($r = .053$, ns) at baseline. This finding persisted over the 6 week trial where the percent change in the HAMD score correlated with the change in negative disposition, $r = .58$, $p = .015$, but not positive disposition.

Baseline behavioral activation measures did not significantly predict depression outcomes. However, BAS-reward responsiveness correlated with both positive and negative disposition at baseline ($r = .49$, $p = .035$; $-.50$, $p = .030$, respectively). Furthermore, both BAS-reward responsiveness and BAS-drive change from baseline to week 6 significantly correlated with % HAMD change ($r = .47$, $p = .050$; $r = .65$, $p = .003$, respectively). BAS-drive change from baseline to week 6 was also associated with PANAS-negative scale change ($r = .53$, $p = .03$). Neither baseline nor change in BAS-fun seeking significantly correlated with the HAMD-17. However, baseline CGI severity and the PANAS-positive scale predicted BAS-fun seeking change ($r = .50$, $p = .037$; $r = -.50$, $p = .043$, respectively), which in turn, correlated with CGI Severity change from baseline to week 6 ($r = .65$, $p = .003$).

4.4. Baseline fMRI

4.4.1. Positive images

4.4.1.1. MDD vs. healthy controls. In response to positive images, depressed patients showed greater activity in the caudate head, subgenual cingulate and ventral medial prefrontal cortex (BA24/25/32/10) than healthy controls (Fig. 2) (Table 3).

4.4.1.2. Responders, non-responders and healthy controls. The omnibus test searching for differences between healthy controls, responders and non-responders revealed differences in activation in the precuneus, posterior cingulate and occipital cortex (BA18) among groups. Subsequent contrasts showed activity was greater in the: (1) posterior cingulate gyrus (Area 30) in responders compared to non-responders and healthy controls, (2) precuneus in responders compared to non-responders (Fig. 3) (Table 3).

4.4.2. Negative images

4.4.2.1. MDD vs. healthy controls. Healthy controls had less activity than the MDD group in the occipital cortex (BA18), cuneus and precuneus while viewing negative images (Table 4).

4.4.2.2. Responders, non-responders and healthy controls. When groups were further broken down into response status vs. healthy controls, non-responders displayed increased activation in the bilateral insula compared to responders and healthy controls (Fig. 4) (Table 4). There was increased activity in the premotor cortex in the responders compared to non-responders and healthy controls (Fig. 5) (Table 4).

5. Discussion

To our knowledge, this is the first study to assess fMRI biomarkers of response at baseline and 1 week during an antidepressant combination (i.e. olanzapine/fluoxetine) treatment trial. We demonstrated that high baseline response to positive images in the posterior cingulate cortex and to negative images in the premotor cortex predicted change in depression scores from baseline to 6 weeks. High baseline premotor activity also correlated with greater increases in drive and decreases in negative disposition at endpoint. Insula activity at baseline was significantly lower in responders compared to non-responders, but did not
predict other outcomes. Changes in emotional processing by week 1 were also not predictive of outcome.

Our results are consistent with other imaging studies assessing the effects of antidepressants on emotional processing, which have consistently shown activation in the insula, anterior cingulate cortex, prefrontal areas, parietal cortex (precuneus) as well as subcortical structures (caudate, putamen, amygdala) in response to negative pictures (Davidson et al., 2003; Diener et al., 2012; Fu et al., 2004; Samson et al., 2011; Sheline et al., 2001). In particular, premotor cortex hypoactivity has consistently been shown in response to negative stimuli in depression (Diener et al., 2012) and successful treatment with antidepressants, psychotherapy, and neurostimulation increase activity in this area (Delaveau et al., 2011; Fu et al., 2008; Goldapple et al., 2004; Lozano et al., 2008; Mayberg et al., 2000). Considering this region demonstrates increased activity with good antidepressant outcomes, it follows that in the present study responders exhibited higher activity in the premotor cortex than non-responders at baseline.

The correlation of premotor cortex activity with BAS-drive and the PANAS-negative subscale raises an interesting question of the relationship between emotional processing and reward processing. Traditionally, the reward system is discussed in terms of the roles of the nucleus accumbens, striatum, prefrontal and orbitofrontal cortices in motivation, anticipation, reward valuation and consummatory pleasure (Dunlop and Nemeroff, 2007; Narango et al., 2001; Nestler and Carlezon, 2006). However, several studies suggest that high activity in the premotor cortex is indicative of greater reward value (Elliot et al., 2003; Roesch and Olson, 2003) and premotor planning associated with greater reward (Ernst et al., 2004), as well as reduced occurrences of habitual action to no-longer rewarding outcomes (de Wit et al., 2012). The reward role of the premotor cortex in the context of depression is less clear, but there are reports of increased premotor activity in response to positive stimuli after antidepressant therapy

### Table 3
Baseline activation differences in response to positive images.

<table>
<thead>
<tr>
<th>Side</th>
<th>Brain Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Peak activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased activation in MDD patients compared to healthy controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Medial frontal gyrus (BA10), Anterior</td>
<td>−6</td>
<td>38</td>
<td>−18</td>
<td>2.49</td>
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<tr>
<td></td>
<td>Cingulate BA24/25/32, Caudate Head</td>
<td>−4</td>
<td>40</td>
<td>−14</td>
<td>2.47</td>
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<td></td>
<td></td>
<td>−8</td>
<td>20</td>
<td>−8</td>
<td>2.88</td>
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<tr>
<td>R</td>
<td>Frontal pole, Anterior Cingulate</td>
<td>18</td>
<td>30</td>
<td>−10</td>
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<tr>
<td></td>
<td>BA24/25/32, Caudate Head</td>
<td>6</td>
<td>14</td>
<td>−10</td>
<td>2.71</td>
</tr>
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<td></td>
<td></td>
<td>4</td>
<td>40</td>
<td>−12</td>
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<td>Increased activation in responders compared to non-responders</td>
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<tr>
<td>L</td>
<td>Posterior cingulate</td>
<td>−6</td>
<td>−50</td>
<td>18</td>
<td>2.77</td>
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### Table 4
Activation differences in response to negative images.

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<th>Peak activation</th>
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<td>Increased baseline activation in MDD patients compared to healthy controls</td>
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<tr>
<td>R</td>
<td>Occipital lobe cuneus (BA18), precuneus BA31/7</td>
<td>26</td>
<td>−90</td>
<td>26</td>
<td>3.2</td>
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<td></td>
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<td>20</td>
<td>−68</td>
<td>26</td>
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<td>Increased baseline activation in non-responders compared to responders and healthy controls</td>
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<tr>
<td>L</td>
<td>Insula</td>
<td>−44</td>
<td>18</td>
<td>−4</td>
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<tr>
<td>R</td>
<td>Insula BA13</td>
<td>36</td>
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<tr>
<td>L</td>
<td>Premotor cortex BA6</td>
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<tr>
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<td>Postcentral gyrus BA2/3/7/40</td>
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<td>Precentral gyrus BA4</td>
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Results support an association between higher insular activity at Phillips et al., 1998; Sugiura et al., 2005; Vogt et al., 2003). This is supported by suggesting that activation in this area may not be valence negative stimuli in depressed patients (Delaveau et al., 2011), reports of increased activation in response to both positive and negative stimuli in depressed patients (Samson et al., 2011). There are also treatment revealed activity in the posterior cingulate in response to positive stimuli has not been consistently demonstrated, with some authors reporting no changes (Davidson et al., 2003), and others reporting increased activity in the left insula, anterior cingulate, and the right caudate, and decreases in the left posterior cingulate (Delaveau et al., 2011). Interestingly, an fMRI study in patients who received mirtzapine and venlafaxine treatment revealed activity in the posterior cingulate in response to negative faces was the area most strongly correlated with change in HAMD-17 scores (Samson et al., 2011). There are also reports of increased activation in response to both positive and negative stimuli in depressed patients (Delaveau et al., 2011), suggesting that activation in this area may not be valence dependent. This is supported by findings demonstrating the role of the posterior cingulate in self-relevant emotional and non-emotional information and self-reflection (Bernstein et al., 2002; Phillips et al., 1998; Sugiura et al., 2005; Vogt et al., 2003). Insular activity is thought to be involved in awareness of the self and body, as well as emotion regulation (Craig, 2009; Farrer and Frith, 2002; Samson et al., 2011; Sprengelmeyer et al., 2011). Differences between depressed patients and healthy controls in this area have been frequently reported in depression, along with significant change in activity after successful treatment (Kennedy et al., 2001, 2007; Mayberg et al., 2000). However, there are reports of hypoactivity in depression with subsequent increase with treatment (Delaveau et al., 2011), as well as the reverse (Samson et al., 2011). These differences may reflect the nature of the stimuli presented (increased insular activation in response to facial expressions of disgust – (Surguladze et al., 2011) or successful vs. unsuccessful attempts at adaptation (Mayberg, 2009). Our results support an association between higher insular activity at baseline and non-response. Given the conflicting findings in the literature, the potential role of this area as a biomarker of treatment effects requires further study.

Although baseline amygdala and subgenual activity in response to negative stimuli have been reported as predictors of antidepressant outcome (Bryant et al., 2008; DeRubeis et al. 2008; Fu et al., 2008; McCormick et al., 2007), our findings did not implicate these regions in predicting treatment response. The use of combination therapy raises the question of whether the addition of an atypical antipsychotic alters the typical changes seen in emotion processing studies with SSRIs. For example, increased amygdala activity in depressed patients compared to healthy controls is frequently reported in response to fearful faces, an effect that SSRIs have been shown to attenuate (Fu et al., 2004; Sheline et al., 2001; Wagner et al., 2010); however, it is unclear what effect an atypical antipsychotic alone would have on emotion processing in depression. Drawing from the schizophrenia literature, one study reported 8 weeks of olanzapine reduced amygdala activity to negative stimuli lower than that of healthy controls (Blasi et al., 2009), while another study demonstrated no difference in amygdala activity on an emotional valence task between schizophrenia patients on an atypical antipsychotic compared to healthy controls (Sachs et al., 2012). There is also evidence to suggest differences in emotion processing when risperidone is given in a short acting conventional depot form versus a long-acting injectable form (Surguladze et al., 2011). Given that atypical antipsychotics have a different pharmacological mechanism of action from conventional antidepressants, it is plausible to suggest they work on different neural networks, and this requires further exploration.

Several authors have noted changes in emotional processing to negative stimuli within days of antidepressant administration in both healthy controls and depressed patients (Harmer et al., 2006; Keedwell et al., 2009; Keedwell et al., 2010; Murphy et al., 2009). Keedwell et al. (2010) conducted a study in depressed patients who had initiated an antidepressant trial within 2 weeks of conducting an emotional faces task. Increased activation in the right subgenual cingulate and right visual areas in response to sad faces was predictive of good clinical outcome at 12 weeks. In contrast, another study assessed the effects of 8 weeks of mirtzapine or venlafaxine on emotion processing and demonstrated changes in insular and anterior cingulate activity in response to negative stimuli after 2 weeks, although 2 week activation predictors of outcome were not reported (Davidson et al., 2003). A recent study of 7-day escitalopram treatment demonstrated increased amygdala activity in response to fearful faces post-treatment, but these changes were not linked to longer-term outcomes (Godlewksa et al., 2012). In the present study, the failure to find predictors at 1 week suggests this time point may be too early to see strong enough effects, or that the sample size and proportion of responders to non-responders was not balanced enough to identify outcome-predictive changes in neural activity.

Limitations of this study include the small sample size, habituation effects that may occur in an fMRI block-design, and the lack of a group on SSRI monotherapy in order to elicit specific effects of olanzapine augmentation. In order to detect maximal brain responses, we also did not use IAPS pictures that covered the entire dynamic range of positive and negative pictures. As a result we cannot make any conclusions on the potential neural predictors of antidepressants using images of varying intensity.

In summary, the examination of baseline neural activity underlying emotional processing reflects a feasible avenue to identify biomarkers of treatment response using combination antidepressant therapy. Specifically, posterior cingulate cortex, anterior insula, and prefrontal cortex may show predictive differences in their response to positively and negatively valenced visual stimuli prior to treatment. The exploration of several research avenues is vital to advance our understanding of MDD and treatment precision. Firstly, there is a need to identify baseline predictors of outcome and assess the utility of early brain changes in predicting antidepressant response to disparate treatment strategies (e.g. psychotherapy, combination therapy, neurostimulation). Secondly, the concept of “outcome” needs to be expanded to include behaviors that may be proxies for stable response and which

Fig. 5. Baseline premotor cortex activation in responders greater than non-responders and healthy controls while viewing negative images.
are not captured in depression scales (e.g. improved reward, social and occupational function). Thirdly, modeling antidepressant outcome through the integration of neuroimaging data (functional and structural) with molecular and clinical information may produce results that enable us to identify at risk individuals, develop preventative strategies, guide treatment selection and develop novel targets. Likewise, further research in this vein may help to identify clinically meaningful subtypes within the heterogeneous disease entity of major depressive disorder.

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Conflict of interest
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