Preliminary communication

Emotion-related brain activity to conflicting socio-emotional cues in unmedicated depression

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ABSTRACT

Background: Abnormalities in amygdala function have been implicated in major depression. However, results are inconsistent, and little is known about how the depressed brain encodes conflicting social signals. We sought to determine how the task relevance of socio-emotional cues impacts neural encoding of emotion in depression.

Methods: Eighteen medication-free depressed patients and 18 matched controls participated in an fMRI experiment. Whole-brain analyses and a region-of-interest approach was used to measure amygdala activity during the presentation of fearful, happy, or neutral target faces with congruent, incongruent, or neutral distracters.

Results: Greater amygdala activity to target fearful faces was associated with depression, as was attenuated amygdala activity to target and peripheral happy faces. Although no group differences emerged in the amygdala to unattended fearful faces, we observed reduced ventrolateral and dorsomedial prefrontal activity in depressed individuals during this condition.

Limitations: Nine patients had a history of anti-depressant use, though they were unmedicated for at least three months at testing.

Conclusions: Depression was associated with reduced amygdala reactivity to positive social stimuli. However, enhanced amygdala responsiveness to negative emotional cues was only observed to target (attended) expressions. The results highlight the need to further determine factors that affect emotional reactivity in depression.

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1. Introduction

Depression is associated with a negative cognitive style that is thought to play a key role in initiating and maintaining depressed mood (Beck et al., 1979). However, depression is also often associated with compromised social and interpersonal functioning (Paykel, 2002, Schelde, 1998), which appears to be an important risk factor for the disorder (Kaplan et al., 1987). At a neural level, abnormal activation of emotion-related brain regions to salient socio-emotional stimuli is associated with depression (Surguladze et al., 2004, Dannlowski et al., 2007) and depression vulnerability (Elliott et al., 2012). The majority of studies that examine neural responding to social cues in major depression involve single, static, unambiguous facial expressions. Although social situations are dynamic, involving multiple players, and often discordant social cues, much less is known about how conflicting emotional cues are encoded in the depressed brain. It is particularly unclear how the task-relevance (i.e., central versus peripheral) of competing socio-emotional cues influences the neural regions involved in emotional responding.

There is considerable evidence implicating the amygdala in emotion, and emotional responses to social stimuli (Phelps and LeDoux, 2005). For example, negative mood-induction has been shown to correlate with amygdala sensitivity (Berna et al., 2010, Schmitz et al., 2009), and electrical stimulation of the amygdala induces positive and negative emotions (Lanteaume et al., 2007). The amygdala is metabolically hyperactive (Drevets et al., 2002). In addition, enhanced...
amygdala activity to negative cues, when present, has been found to resolve with treatment (Fales et al., 2009, Sheline et al., 2001, Victor et al., 2010). Collectively, the evidence implicates enhanced amygdala activity with emotional reactivity and depression, and supports using activity in this structure as a physiological index of emotional encoding and responsiveness.

Here we used fMRI to examine how the brain integrates conflicting basic socio-emotional signals in unmedicated depressed patients and matched controls. The study was designed to address the question of how incongruent (happy, fearful and neutral) facial expressions are integrated with task-relevant social cues at a neural level in patients with depression. Specifically, the current study sought to determine whether target versus peripheral socio-emotional cues have a differential impact on neural activity in the amygdala and other emotion-related structures. While others have demonstrated that heterogeneity between groups can influence neural responding to facial expressions (Fournier et al., 2012), the present study is the first to assess whether task demands (i.e., socio-emotional context) influence the within-subject variability of amygdala reactivity observed in other studies. Thus, we tested the prediction that, consistent with a negative information processing bias, depression would be associated with enhanced amygdala activity for negative, and reduced amygdala activity for positive socio-emotional cues irrespective of task-relevance (regardless of whether they were presented centrally or peripherally). On the basis of studies suggesting that the amygdala is modulated by task demands (Mitchell et al., 2007, Pessoa et al., 2002), an alternative prediction is that amygdala reactivity would vary as a function of whether or not the socio-emotional cues were task-relevant.

2. Methods

2.1. Participants

Eighteen medication-free outpatients with a primary diagnosis of major depressive disorder (MDD) were recruited for study participation from London Health Sciences Centres and via community advertisements in London, Ontario ($M_{\text{age}} = 26.61, \text{SD} = 11.7$, range = 16–59; 12 female, 6 male). Nine patients were antidepressant naïve at the time of scan, and the remainder were medication-free for at least three months ($M_{\text{months}} = 30.8$, range = 3–60 months); all were experiencing a major depressive episode at the time of scanning, as determined by trained individuals using the Structured Clinical Interview for the DSM-IV-TR (First et al., 2002). Patients with a history of head injury, neurologic illness, or depression resulting from a general medical condition or substance were excluded. Patients with a comorbid diagnosis other than anxiety or past alcohol abuse were also excluded; and all reached diagnostic criterion for MDD, which was not attributed to any other comorbid diagnosis. Six patients were experiencing their first major depressive episode at the time of the scan, while the remainder were experiencing at least their second major depressive episode. Six patients had comorbid anxiety disorders: two with social anxiety disorder (SAD) without agoraphobia, three with post-traumatic stress disorder (PTSD), one with PTSD and SAD without agoraphobia; and two had a history of alcohol abuse (not within a month of testing). We performed independent t-tests contrasting depressed patients with and without comorbid anxiety revealing no significant differences between the two subgroups of patients ($p > 0.25$ for all), and confirming their inclusion did not significantly bias the results presented. Patients who reported claustrophobia, or who had any contraindications for MRI were not enrolled. A control group (CTL) of 18 healthy volunteers matched for age, sex and handedness were recruited from the community. CTLS had no history of psychiatric illness as determined by the SCID, and reported having no first-degree relative with a known DSM-IV Axis-I or Axis-II disorder ($M_{\text{age}} = 27.89, \text{SD} = 11.26$, range = 18–54; 12 female, 6 male). There was no significant group difference in age, $t(34) = 0.333; p > 0.7$, or IQ based on the Wechsler Abbreviated Scale of Intelligence [WASI; $t(31) = 1.07, p > 0.3$; WASI scores were missing from three participants (two in the MDD group) due to attrition]. Prior to scanning, participants completed the Beck Depression Inventory (BDI; Beck et al., 1996). Participants with MDD had significantly higher scores than controls [BDIscore; MDD = 24.56(9.8), CTL = 1.6(2.4); $t(36) = 9.64, p < 0.001$; the mean BDI score was indicative of moderate depression (severity ranging from mild to severe). All subjects granted informed written consent, and the study was approved by the Health Science Research Ethics Board at the University of Western Ontario, Canada.

2.2. Mixed emotions task

To test the impact of task-relevant and task-irrelevant emotional cues on the neural response of individuals with depression, participants completed a variant of the “mixed emotions task” (Amting et al., 2009; supplementary Fig. 1). Participants viewed greyscale stimuli consisting of a central facial expression surrounded by four distracter faces. Throughout the experiment, participants were instructed to maintain fixation on cross-hairs located at the centre of the screen, and judge the emotion of the central (target) facial expression while ignoring the peripheral distractor faces. Participants entered their responses “as quickly and as accurately as possible” via button presses. The target-response pairings were counter-balanced across participants. There were 36 trials for each of the nine conditions, for a total of 324 trials divided equally between six “runs” of the task. The run order was counter-balanced across subjects.

2.3. fMRI data acquisition

Participants were scanned at the Centre for Metabolic Mapping, in the Robarts Research Institute’s 3T Siemens scanner equipped with a 32-channel head coil. BOLD changes were measured using a T2-gradient echo-planar sequence (time to repetition=3000 ms, time to echo=30 ms; voxel dimensions=2.5 mm x 2.5 mm x 2.5 mm). The session ended with a high resolution T1-weighted whole-brain anatomical scan (time to repetition=2300 ms, time to echo=42.5 ms; field of view=25.6 cm; 192 axial slices; voxel dimensions=1 mm isovoxels; 256 x 256 mm$^2$ matrix).

2.4. fMRI analysis

Individual and group analyses were conducted using Analysis of Functional NeuroImages software (Cox, 1996) following procedures adopted in our previous work (Greening et al., In Press). In brief, following motion correction, the functional data were aligned to the anatomical data and both were transformed into the standard space of Talairach and Tournoux. The dataset for each subject was spatially smoothed (4 mm isotropic Gaussian kernel) and scaled to per cent signal change from the mean voxel activity. Regressors were produced by convolving the train of stimuli for each condition (from distracter onset to target-with-distracter offset) with the gamma-variate hemodynamic response function. General linear model regression was performed with a regressor for each of the nine conditions (error trials were modelled separately as regressors of no-interest). Baseline plus linear drift and quadratic trend were also modelled. This produced beta
coefficients and t-values for each of our experimental conditions at each voxel, which were then used in the group analyses.

To test our primary hypotheses concerning the impact of attended and unattended emotional cues on the neural response, we compared four critical experimental conditions across groups. These conditions were: a fearful target with neutral distracters (FN), a happy target with neutral distracters (HN), a neutral target with fearful distracters (NF), and a neutral target with happy distracters (NH). This between-group analysis was performed using the mixed effects meta-analysis function in the AFNI software package (Chen et al., 2012). As the amygdala was our primary region-of-interest (ROI), we used a small volume correction (SVC) to identify clusters of significant activity within the anatomically defined right and left amygdala consistent with previous studies of emotional reactivity and depression (Fales et al., 2008, Victor et al., 2010). For the ROI analysis, clusters within the amygdala were identified that survived a family-wise error (FWE) correction to \( p < 0.05 \), requiring \( k > 5 \) contiguous voxels to be significant at \( p < 0.01 \), two-tailed. An exploratory whole-brain analysis was also performed, which identified significant clusters that survived an FWE correction to \( p < 0.05 \) (\( k > 30 \) contiguous voxel; \( p < 0.005 \), two-tailed).

3. Results

3.1. Behavioural results

Behavioural performance was analysed with a 2 (group: MDD, CTL) by 3 (target: fear, happy, neutral) by 3 (distracter: fear, happy, neutral) repeated measures ANOVA for both reaction time (RT; for correct responses) and accuracy data (proportion of target emotions correctly categorised; see supplementary Table 1 for details). The RT analysis revealed a main effect of target \([F(2,34)] = 44.34; p < 0.001\). RTs were significantly faster to happy relative to both fearful \([F(1,14)] = 64.6; p < 0.001\) and neutral targets \([F(1,14)] = 42.1; p < 0.001\), and to neutral relative to fearful targets \([F(1,14)] = 5.6; p < 0.05\). No other effects were significant.

The analysis of accuracy revealed a main effect of target \([F(2,68)] = 19.5; p < 0.001\). Participants responded more accurately to happy targets relative to both fearful \([F(1,14)] = 23.9; p < 0.001\) and neutral targets \([F(1,14)] = 7.3; p < 0.05\). In addition, participants responded more accurately to neutral relative to fearful targets \([F(1,14)] = 18.7; p < 0.001\). No other effects were significant.

3.2. FMRI results

To evaluate the neural encoding of task-relevant negative cues in MDD, we first contrasted conditions with emotional targets and neutral distracters across the MDD and control groups. In response to task-relevant negative emotional cues (FN condition), patients with MDD displayed significantly greater right amygdala activity relative to controls (Fig. 1, left; threshold of \( p < 0.01 \), SVC to \( p < 0.05 \)). Conversely, when the task-relevant emotional cue was positive (HN condition), the MDD group displayed significantly less right amygdala activity than CTLs (Fig. 1, middle; threshold of \( p < 0.01 \), SVC to \( p < 0.05 \)). The whole-brain analyses revealed no significant group differences during the presentation of either positive or negative task-relevant emotional cues.

To examine the encoding of non-target emotional stimuli in the presence of neutral social cues, we contrasted conditions with neutral targets and emotional distracters across the two groups.

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**Fig. 1.** BOLD response in the amygdala using a region of interest approach displays evidence for the preferential processing of central but not peripheral negative emotional faces. Left—greater activity in the right amygdala (\( t \)-value = 3.01; centre of mass: \( x = 16, y = -6, z = -11 \)) during the fearful target with neutral distracter condition in patients with MDD relative to controls \([\%\text{signal change (SE): MDD} = 0.253(0.037); \%\text{signal change (SE): CTL} = 0.037(0.043)]\). Middle—attenuated right amygdala activity (\( t \)-value = 3.23; centre of mass: \( x = 22, y = -7, z = -9 \)) during the happy target neutral distracter condition in patients with MDD relative to controls \([\%\text{signal change (SE): MDD} = -0.042(0.030); \%\text{signal change (SE): CTL} = 0.106(0.031)]\). Right—attenuated activity in a region including the amygdala and parahippocampal gyrus (\( t \)-value = 3.41; centre of mass: \( x = -2, y = 19, z = -23 \)) during the neutral target with happy distracter condition in patients with MDD relative to controls \([\%\text{signal change (SE): MDD} = -0.267(0.023); \%\text{signal change (SE): CTL} = -0.008(0.022)]\). ROI-based correction analysis was performed at a two-tailed threshold of \( p < 0.01 \), corrected to a family wise error rate of \( p < 0.05 \). In order to depict the full extent of activation, all contiguous voxels that reached an uncorrected \( p \)-value ranging from 0.001 to 0.05 are displayed. Active clusters are displayed on the T1-weighted Talairach-Tournoux template (TT_N27) in AFNI.
When negative distracters were presented along with a neutral target, there were no significant differences between the two groups within the amygdala. However, when positive distracters were presented along with a neutral target, we observed significantly reduced activity in the left amygdala (extending into anterior parahippocampal gyrus) of the MDD group relative to the CTLs (Fig. 1, right; threshold of \( p < 0.01 \), SVC to \( p < 0.05 \)).

The whole-brain analysis revealed that there were significant group differences when negative distracters were present with a neutral target (see Table 1). Specifically, we observed that the MDD group had reduced activity relative to CTLs in regions implicated in the executive control of emotion (Mitchell, 2011, Ochsner and Gross, 2005), including dmPFC and left vlPFC (Fig. 2, threshold of \( p < 0.005 \), whole-brain FWE corrected to \( p < 0.05 \)).

Two exploratory analyses comparing the conditions with competing facial expressions (FH and HF) independently across groups revealed no significant group differences in either the amygdala, or whole-brain. In none of the analyses was BOLD activity significantly correlated with depression severity.

### 4. Discussion

The present study examined how the brain integrates conflicting basic socio-emotional signals in unmedicated depressed patients and matched controls. We observed exaggerated amygdala activity to negative stimuli in participants with MDD only when negative stimuli were task-relevant. Consistent with the idea that negative reactivity in depression is modulated by task relevance, amygdala activity associated with peripheral negative expressions was not significantly different from controls. However, amygdala activity was significantly reduced in patients with MDD relative to controls in the presence of positive stimuli (happy faces) regardless of task relevance. Lastly, the presence of task-irrelevant negative expressions was associated with greater activity in controls relative to...
5. Relationship to previous studies

The empirical picture concerning emotional reactivity and the amygdala in depression is complex. Previous studies examining amygdala reactivity to facial emotions in depression have found hypo-activity (Lawrence et al., 2004, Ritchey et al., 2011), hyper-activity (Victor et al., 2010, Suslow et al., 2010), and no significant differences (Almeida et al., 2010) relative to controls. This consistency may at least in part be accounted for by the heterogeneous nature of major depression (Fournier et al., 2012). The present study provides evidence that, even within a sample of patients with MDD, abnormal emotion-related activity can vary as a function of task demands. One possibility is that some of the disparate findings observed in the literature may in part be due to how task demands influence negative stimulus encoding, and the extent to which stimuli map onto depressive schema (e.g., sad faces may be more readily integrated than fearful ones, Neumeister et al., 2006). However, it is important to note that variability may exist between attentional manipulations (e.g., Fales et al., 2008). These results highlight the need for future work in further defining the parameters influencing amygdala reactivity in depression.

6. Emotion control and prefrontal cortex

It is noteworthy that relative to the control group, depressed patients showed significantly reduced dmPFC and vlPFC activity in response to trials involving negative distractors. Both areas have been implicated in regulating or representing the influence of emotional distracters on brain and behaviour (Ochsner and Gross, 2005, Mitchell, 2011). It is tempting to speculate that the observed abnormalities may be contributing to dysregulated mood in depression. However, interpreting this effect in the current study may be complicated by the absence of a significant group by distracter interaction at the behavioural level. Nevertheless, even without such behavioural effects, the BOLD response has provided a sensitive metric of stimulus encoding at a neural level in healthy (e.g., Mitchell et al., 2007, Pessoa et al., 2002) and depressed (e.g., Elliott et al., 2002, Suslow et al., 2010) groups. Indeed, lack of group differences can be advantageous, as the results are less susceptible to confounds related to time-on-task differences or sampling error (Elliott et al., 2002, Knutson et al., 2008). Interestingly, depression has been associated with functional abnormalities in both dmPFC and vlPFC (Johnstone et al., 2007, Mitterschiffthaler et al., 2008). Further research is required to determine whether depression is related predominantly to dysfunction in “bottom-up” emotion-related areas, or is combined with abnormalities in “top-down” cortical regions associated with emotion regulation.

7. Implications for neurocognitive models of depression

Depression has long been associated with a negative bias that prioritises negative information processing (Beck, 2008). One of the mechanisms by which abnormalities in amygdala responsiveness is thought to influence negative information processing is by enhancing the salience of sensory representations of either internal or external emotional information (Amting et al., 2010, Vuilleumier, 2005). At a neural level, the amygdala in depressed individuals may augment endogenous depressive representations (and associated stimuli) at the expense of dissimilar ones.

In support, enhanced amygdala activity has been observed in studies involving task-relevant facial expressions (Fu et al., 2004, Surguladze et al., 2005). However, our results suggest that the extent to which negative external stimuli elicit pathological neural processes is influenced by their relevance to the current task. Thus, depression was associated with enhanced amygdala activity to target fearful faces, but not peripheral fearful faces. For positive stimuli, however, depression was associated with significantly reduced amygdala activity relative to controls regardless of whether the stimuli were task-relevant. These latter findings appear partially consistent with an alternate theory of depressive cognitive style, emotion context insensitivity (ECI). ECI posits that MDD is associated with attenuated emotional reactivity to both positive and negative cues (Rottenberg et al., 2005). Indeed, individuals with depression have displayed reduced amygdala activity (Drevets, 2001, Thomas et al., 2001) in response to negative facial expressions, and reduced mPFC activity to emotional displays of social groups (Elliott et al., 2012). Our results together with prior studies illustrate the complexity of emotional processing in depression, and suggest that future work is required to further delineate the factors that influence emotional reactivity in the disorder.

8. Limitations

Our depressed sample combined individuals who were medication naïve with those who had previously taken antidepressants. Given that anti-depressants have been shown to cause neurological changes (Bessa et al., 2009), future research involving medication naïve patients combined with longitudinal assessments following treatment would offer further insight into depression. Additionally, the present study used fearful expressions as negative stimuli, and differential effects might be observed with the inclusion of other emotions, particularly sadness (Victor et al., 2010), which might map onto existing depressive representations.

9. Conclusion

The findings of the current study suggest that while a negative processing bias was evident at a neural level when sufficient attention was directed to socio-emotional cues, reactivity to unattended emotional cues in depressed patients relative to controls may be either blunted (for positive distracters) or at similar levels (for negative distracters). One possibility is that preoccupation with idiosyncratic endogenous negative schemas in depression may reduce the capacity to integrate external cues, particularly discordant cues, or those that are not relevant to the current task. This work reconciles some of the apparent contradictions in the literature by suggesting that the extent to which a negative-encoding bias manifests depends on task-demands, and highlights the fact that heterogeneity may exist in emotional encoding even within a sample of depressed patients.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2013.05.053.

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