EEG Correlates of Affective Processing in Major Depressive Disorder

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ABSTRACT

Background: Individuals with major depressive disorder present with deficits in emotional reactivity. Conflicting models have been proposed to characterise the direction of this effect. Previous studies mostly support the emotional context insensitivity model, which suggests that reactivity to positive and negatively-valenced emotional stimuli is blunted in depression. We sought to test the emotional context insensitivity hypothesis in a preregistered study.

Methods: Forty-one depressed participants and 41 age- and gender-matched healthy controls were shown a series of unpleasant and neutrally-valenced pictures in a passive view paradigm while acquiring electroencephalography (EEG). The late positive potential (LPP), an EEG marker of emotional reactivity, was compared between groups using mixed-effects repeated-measures models and exploratory cluster-based permutation tests.

Results: We found no difference in LPP amplitudes between MDD and healthy individuals using the preregistered analysis plan. However, exploratory permutation analysis revealed a significant reduction in the LPP for MDD participants while viewing unpleasant pictures in EEG electrodes marginally more posterior and within a narrower time interval than specified in our original analysis plan. Secondary analyses found that emotion regulation strategy use and anxiety comorbidity did not influence the LPP.

Conclusions: We found significantly reduced LPP amplitudes to unpleasant pictures in MDD, in support of the emotional context insensitivity hypothesis. However, the parameters used to estimate the LPP deviated from the preregistered analysis plan, suggesting that methodological differences between studies may result in variability in the cortical response to emotional stimuli.
INTRODUCTION

Major depressive disorder (MDD) is a mental illness that presents as persistent low mood, loss of interest in pleasurable activities, or both, in conjunction with other symptoms (American Psychiatric Association, 2013). Consistent with the core symptom of disturbed mood, depressed individuals report altered reactivity to emotion-eliciting contexts of positive or negative affect (Rottenberg et al., 2005). Although the terms mood and emotion are sometimes used interchangeably, mood typically refers to slow-moving affective states that are weakly influenced by external stimuli, whereas emotions are considered to be rapid reactions to meaningful affective stimuli (Watson, 2000). The two are deeply intertwined and an improved understanding of the emotional deficits in MDD may thus provide further insight into mood symptoms (Rottenberg, 2005). Currently, three competing models have been proposed to describe the observed abnormalities in emotional reactivity in depressed individuals. The oldest of these, the positive attenuation model, suggests that the physiological response is diminished to positive stimuli and unchanged for unpleasant, negatively-valenced stimuli (Clark & Watson, 1991). The emotional context insensitivity model argues that depression results in blunted emotional reactivity to positive stimuli as well as to negative emotional contexts (Rottenberg et al., 2005). The most recently proposed negative potentiation hypothesis states that depression increases reactivity towards negative contexts (Browning et al., 2010). These theories disagree with regards to the physiological response in MDD to negative stimuli: positive attenuation predicts no difference in reactivity compared to healthy individuals, negative potentiation predicts increased reactivity, and the emotional context insensitivity predicts decreased reactivity in depression.
Emotional reactivity is commonly assessed using electroencephalography (EEG). Specifically, the late positive potential (LPP) may provide a reliable measure of affective cortical processing (Codispoti et al., 2006, 2007). The LPP is characterized as the mean amplitude of the event-related potential (ERP) within a time window approximately 400-1000ms following the visual presentation of emotionally laden images (Cuthbert et al., 2000; Schupp et al., 2000). EEG studies in depressed individuals have shown mixed findings of the LPP amplitude and do not provide conclusive support in favour of any current model of emotional reactivity in depression. Two studies have demonstrated attenuated LPP amplitudes in response to unpleasant stimuli, lending support to the emotional context insensitivity hypothesis (Foti et al., 2010; MacNamara et al., 2016). In contrast, Zhang et al. (2016) found a significant increase in LPP amplitudes while passively observing pictures of faces showing sad emotional expressions as compared to neutral expressions, in agreement with the negative potentiation hypothesis. Lastly, Weinberg et al. (2016) did not find a significant difference in LPP amplitudes comparing healthy controls to depressed participants. Although most studies on emotional reactivity reveal attenuation of LPP amplitudes in depressed individuals, in agreement with the emotional context insensitivity hypothesis, the evidence is not conclusive.

The primary aim of this study was therefore to test the emotional context insensitivity hypothesis by comparing the contrast in LPP amplitudes for unpleasant vs neutral pictures between MDD participants and healthy controls. As previous studies (Foti et al., 2010; MacNamara et al., 2016; Weinberg et al., 2016; Zhang et al., 2016) did not preregister their study protocols and should hence be considered preliminary, we sought to test the difference in emotional reactivity in MDD participants in a preregistered study. We
hypothesised that the LPP amplitude difference (i.e. unpleasant vs neutral) would be attenuated in MDD participants in support of the emotional context insensitivity model. In addition, studies examining LPP amplitudes in response to emotional images did not investigate the role of emotion regulation in depression. In healthy individuals, the LPP is sensitive to the use of emotion regulation strategies, which refers to conscious or subconscious efforts to exert control over one’s emotional experience (Gross & John, 2003). Differences in the frequency or type of emotion regulation strategy use could partly explain the observed differences in the LPP to unpleasant images in MDD participants compared to healthy controls (Foti & Hajcak, 2008; Hajcak & Nieuwenhuis, 2006; Moser et al., 2009). In addition to emotion regulation strategy, anxiety, a common comorbidity of depression (Brown et al., 1998), has also been found to modulate the LPP. Compared to neutral pictures, MacNamara and Hajcak (2009) showed enhanced LPP amplitudes to aversive pictures in individuals with high self-reported anxiety. Anxiety in depressed individuals may therefore explain the conflicting evidence supporting hypotheses of emotional reactivity in MDD. Therefore, the secondary aims of this study were to determine whether the frequency of emotion regulation strategy use differs between MDD and healthy participants and whether emotion regulation strategy use and comorbid anxiety in MDD participants modulates the LPP amplitude in response to unpleasant pictures. We based the research protocol that we used to test our hypotheses – the required sample size and the EEG preprocessing steps to quantify the LPP amplitude – on previous literature, and documented this in a preregistration form (Nikolin et al., 2020). We anticipated that MDD participants would use emotion regulation strategies less frequently than healthy controls, and that LPP amplitude would be moderated by emotion regulation strategy use and anxiety comorbidity in MDD participants.
MATERIALS AND METHODS

Participants

A total of 82 participants were recruited in this study, of whom 41 were currently depressed and 41 were healthy adults with no current or past diagnosis of a psychiatric illness. Power analysis shows that this sample is sufficient to detect moderate effect sizes of Cohen’s $d = 0.6$ (using $\beta = 80\%$ and $\alpha = 0.05$).

Inclusion criteria shared by both MDD participants and healthy controls were: aged 18 years and above, able to provide informed consent, normal or corrected-to-normal vision, no recent serious head injury in the last 12 months (e.g. loss of consciousness of more than 30 minutes), no current or past neurological condition (e.g. stroke, epilepsy), no history of drug or alcohol dependence in the last three months, not pregnant or possibly pregnant, no past history of distress reaction to affective images, and an ability to cooperate with the EEG procedure (e.g. no tremor).

Depressed participants were recruited from those seeking entry into clinical treatment trials at the Black Dog Institute, Sydney Australia. Healthy controls were recruited via the University of New South Wales (UNSW) School of Psychology Paid Sign-Up System, Black Dog Institute Volunteer Research Register, or from flyers distributed in the local area.

Healthy controls were age- and gender-matched to MDD participants since these factors have previously been shown to influence the latency, amplitude, and topography of ERP components (Kayser et al., 2000; Oliver-Rodriguez et al., 1999; Renfroe et al., 2016). The study protocol was approved by the UNSW Human Research Ethics Committee (HC16617).
Procedure

Participants were instructed to passively view and attend to picture stimuli. Pictures were selected to have valence and arousal ratings consistent with those used in previous EEG studies investigating LPP effects (Hajcak & Nieuwenhuis, 2006; MacNamara et al., 2016; Moser et al., 2006). A total of 168 pictures were selected from the International Affective Picture System (IAPS; Lang et al. (2008)). Of these, 84 were unpleasant (e.g. threatening scenes, violence, weapons) and 84 were neutral (e.g. neutral faces, household objects, landscapes). These pictures were chosen from the IAPS based on published valence and arousal ratings. Valence ratings were lower for unpleasant pictures (2.78 ± 0.54) compared to neutral pictures (5.01 ± 0.21), indicating that they elicited more negative emotional affect. Arousal ratings were higher for unpleasant pictures (5.80 ± 0.61) compared to neutral pictures (3.04 ± 0.52). The pictures were divided into three parallel lists consisting of 56 images each (28 unpleasant and 28 neutral) with similar valence and arousal ratings (see Supplementary Materials for further details).

The stimuli were presented on a 58.4 cm (23-inch) computer screen in a dimly lit, sound-attenuated room using Inquisit 4 software (Version 4, Millisecond Software). Digitised pictures sized 20 × 30 cm were presented on a black background, consistent with previous EEG studies (Dunning & Hajcak, 2009; MacNamara et al., 2016). The pictures were displayed for 5 s in a pre-determined block-randomised order so participants were unable to anticipate the valence of each picture. A black screen with a centered white fixation cross was presented for 2 s between stimuli (Fig. 1). Pictures of the same valence were not presented more than three times consecutively to prevent participants from generating expectations of upcoming stimuli and to avoid over-saturation of emotional salience.
Participants were not informed of any emotional regulation strategies prior to viewing the IAPS images.

Figure 1. Study protocol. Participants passively observed a total of 56 picture stimuli. These were presented in a block-randomised order and consisted of 28 unpleasant images with a negative valence, and 28 neutral images with no emotional valence, sourced from the International Affective Picture System (IAPS). Pictures were displayed for 5 s, followed by a 2 s fixation cross. A sample of two trials, showing a neutral image (a towel) and an unpleasant image (a gun), is displayed.

Behavioural measures

Prior to the experimental session, MDD participants had their mood assessed by a trained rater using the ten-item Montgomery-Asberg Depression Rating Scale (MADRS) for depressive symptoms (Montgomery & Asberg, 1979). All participants completed the 21-item self-reported Depression, Anxiety and Stress Scale (DASS; Lovibond and Lovibond (1995)). The DASS was chosen as it reliably discriminates between depression, anxiety, and stress.
states (Crawford & Henry, 2003). Upon completion of the experimental session, we used an emotion regulation questionnaire adapted from Gross et al. (2003), provided in Supplementary Materials. Participants were able to select from five emotion regulation strategies, including no strategy, reinterpretation, distraction, detachment, and ‘other’ in which participants could specify their strategy. Strategies specified in the ‘other’ category were re-assigned to one of the former strategy options by study personnel.

Electroencephalography data acquisition and processing

EEG data were acquired using a 64-channel setup and a TMSi Refa amplifier (TMS International, Oldenzaal, Netherlands) with a sampling rate of 1024 Hz. Offline EEG processing and analysis was conducted using custom-developed MATLAB scripts (v.R2019a; MathWorks) and the Fieldtrip toolbox (Oostenveld et al., 2011). All scripts used for EEG processing and calculation of neurophysiological measures are available at the following link: https://github.com/snikolin/MDDvsCTRL_IAPS.

EEG data was pre-processed using a Butterworth IIR digital filter to remove 50 Hz electrical line noise. Following this, a second-order band-pass filter with cut-offs of 0.5 and 70 Hz was used to remove low and high frequency noise generated from head movements and muscle activity. The EEG data were then epoched into 6 s intervals, beginning 1 s before each picture onset and continuing for 5 s after picture onset. Epochs were rejected firstly using a semi-automated procedure, and then on visual inspection to identify any remaining trials with large artefacts. Smaller, non-cortical physiological activity (e.g. cardiac, muscle, or ocular) and non-physiological activity (e.g. environmental noise, or movement) were removed using an Independent Components Analysis (ICA) algorithm (Delorme et al., 2007;
Finally, EEG data was re-referenced to the common average reference.

Event-related potentials

ERPs were constructed by separately averaging trials for neutral and unpleasant pictures time-locked to picture presentation. Each averaged ERP was baseline corrected to the mean activity occurring in the 200 ms time interval prior to stimulus onset. The late positive potential (LPP) is a slow, positive wave occurring maximally at centroparietal recording sites, beginning approximately 400 ms after stimulus onset and lasting several seconds (Cuthbert et al., 2000; Schupp et al., 2000). We quantified the LPP component as the mean amplitude of the ERP from 400 to 1000 ms following stimulus onset at a centroparietal cluster of EEG channels (Cz, CPz, Pz, CP1, and CP2), where it has previously been shown to be maximal (Foti et al., 2010; MacNamara et al., 2016). Participants with LPP component amplitudes greater than three standard deviations from the mean, per diagnostic group, were considered outliers and excluded from statistical analyses.

Statistical Analyses

All analyses were performed using SPSS software (IBM SPSS Statistics 25, SPSS Inc.), and were in accordance with our preregistered protocol (Nikolin et al., 2020). For the primary analysis, LPPs were investigated using a mixed-effects repeated-measures model (MRMM). The model included a repeated factor of Valence (unpleasant vs neutral) using an unstructured covariance matrix, as well as the between-subjects factor of Group (MDD vs healthy controls), and the Valence × Group interaction. Subject was included as a random effect. Residuals were visually inspected to ensure an adequate fit of the model. Cohen’s $d$
was calculated to estimate the effect size for the LPP amplitude contrast between unpleasant and neutral images comparing MDD participants to healthy controls:

\[ \text{MDD LPP\textsubscript{unpleasant} − MDD LPP\textsubscript{neutral}} \] vs \[ \text{Healthy LPP\textsubscript{unpleasant} − Healthy LPP\textsubscript{neutral}} \]

A follow-up exploratory non-parametric cluster-based permutation test was performed to identify any significant differences between MDD participants and healthy controls beyond the \textit{a priori} time interval and channels operationalised for the LPP. This method controls for multiple comparisons while comparing differences across a large spatiotemporal parameter space (Maris & Oostenveld, 2007). Permutation testing was performed across all EEG channels within the time interval 0 – 1000 ms following presentation of IAPS stimuli.

Participants’ ERPs were permuted 3000 times, and the resulting distributions were compared using independent samples \( t \)-tests. A value of \( \alpha < 0.05 \) was adopted as the two-tailed significance threshold. Statistically significant clusters were required to comprise at least two neighbouring channels.

For secondary analyses, a Fisher’s Exact Test was used to investigate whether there were differences in emotion strategy regulation use between diagnostic groups. Emotion regulation strategies were entered into a 2 x 2 contingency table using the binary variables of Strategy (no strategy vs strategy) and Group (MDD vs healthy controls). Acceptable strategies consisted of reinterpretation, distraction, or detachment.

We performed simple univariate linear regression analyses to confirm whether emotion regulation strategy or comorbid anxiety had an effect on LPP amplitudes. LPP amplitude was included as the dependent variable, with emotion regulation strategy or comorbid anxiety entered separately as independent variables. Strategy was included as a binary categorical
variable (no strategy vs strategy). Anxiety was included as a continuous variable using the anxiety subscore of the DASS. These analyses were initially restricted to LPP amplitudes obtained from MDD participants while viewing unpleasant images. Additional confirmatory multivariate linear regression analyses were then performed using the full dataset of MDD and healthy participants, including both unpleasant and neutral pictures. Independent variables in these regressions included Valence (unpleasant vs neutral), Group (MDD vs healthy controls), as well as Strategy or Anxiety as described previously for univariate analyses.

Scripts for EEG analyses in MATLAB and statistical analyses using SPSS are provided at: https://github.com/snikolin/MDDvsCTRL_IAPS.
RESULTS

Behavioural and EEG measures were assessed in 82 participants (41 with MDD and 41 ageand gender-matched controls). Table 1 shows baseline demographic and clinical information for MDD participants and healthy controls. One participant was excluded from EEG analyses due to values greater than three standard deviations from the group mean, leaving a total of 40 MDD participants and 41 healthy controls.

Table 1. Baseline demographic and clinical information. Means and standard deviations (SD) are shown for continuous measures, and frequency counts for categorical measures.

|                  | MDD    | Controls |
|------------------|--------|----------|
| n                | 41     | 41       |
| Age (years)      | 46.3 (13.2) | 46.0 (13.9) |
| Education (years)| 15.8 (3.6)  | 17.3 (3.6)   |
| Gender (females/males) | 15/26   | 15/26         |
| TRD (yes/no)     | 32/9   | -         |
| Concurrent antidepressants (yes/no) | 31/9   | -         |
| MADRS            | 29.6 (5.0)  | -         |
| DASS Depression  | 33.7 (7.1)  | 4.2 (5.2)    |
| DASS Anxiety     | 11.0 (9.7)  | 3.3 (4.5)    |
| DASS Stress      | 21.3 (9.5)  | 6.8 (5.5)    |
| DASS Total       | 66.5 (19.7) | 14.2 (12.9)  |

MDD: Major Depressive Disorder; TRD: Treatment-Resistant Depression – Defined as failure to respond to at least two adequate courses of antidepressant medication; MADRS: Montgomery-Asperg Depression Rating Scale (Montgomery et al., 1979); DASS: 21-item Depression, Anxiety and Stress Scale (Lovibond et al., 1995). DASS scores were not available for two MDD participants.
Primary Analysis

The LPP amplitude was compared across groups (MDD and controls) and valence conditions (unpleasant and neutral). MRMM results showed a significant main effect of Valence ($F = 19.62, p < 0.001$), indicating increased LPP amplitude for unpleasant compared to neutral images (Fig. 2). The main effect of Group ($F = 0.39, p = 0.54$) and the Group $\times$ Valence interaction ($F = 0.26, p = 0.61$) were not significant. Comparison of the valence difference between MDD participants and healthy controls showed a small effect size ($d = 0.11$).
Figure 2. Preregistered EEG measures of affective processing. The LPP was quantified as the mean EEG amplitude in the time interval from 400 to 1000 ms following stimulus onset for a cluster of centroparietal EEG channels (highlighted in red). ERPs, spatial topographies, and scatter plots of LPP amplitude are presented for MDD participants and controls while viewing unpleasant and neutral images. ERPs are displayed with bootstrapped 95% confidence intervals and with the time interval used to calculate LPPs shaded in light grey. Spatial topographies are of average ERP amplitude from 400 to 1000 ms. Scatter plots show
the mean (black line), median (red line), and the 95% confidence interval (dark grey region).

A) ERPs and topographies for MDD participants. B) ERPs and topographies for healthy controls. C) ERPs and spatial topographies of the valence difference (unpleasant – neutral) for MDD participants and healthy controls. D) Scatter plots of LPP amplitude for unpleasant (U) and neutral (N) images at the centroparietal cluster. E) Spatial topography of the valence difference (unpleasant – neutral) contrasting MDD participants with healthy controls.

Exploratory non-parametric cluster-based permutation testing compared the difference scores (unpleasant – neutral stimuli) between MDD participants and healthy controls. These revealed a significant cluster (Fig. 3). The time interval for the significant cluster fell within the preregistered LPP window (662 – 755 ms). EEG channels identified in this cluster were slightly more posterior than those for our preregistered LPP analysis and included CPz, CP1, Pz, POz, P1, and P2. Three of these channels are also found in the preregistered cluster (CPz, CP1, and Pz). See Supplementary Material for further details regarding cluster channels.

Repeating the MRMM using the EEG channels and time interval identified in the exploratory cluster revealed a main effect of Valence (F = 9.55, p = 0.003) and a significant Group × Valence interaction effect (F = 15.59, p < 0.001). The main effect of Group was not significant (F = 0.56, p = 0.46). Post-hoc independent t-tests found that the MDD group had lower LPPs while viewing unpleasant images compared to healthy controls (p = 0.02), but there was no difference for neutral images (p = 0.23). Comparison of the valence differences between MDD participants and healthy controls showed a large effect size of Cohen’s $d = 0.88$. 
Figure 3. Exploratory EEG measures of affective processing. Exploratory cluster-based permutation testing revealed a significant cluster from 662 to 755 ms in EEG channels CPz, CP1, Pz, POz, P1, and P2 (highlighted in red). ERPs, spatial topographies, and scatter plots of LPP amplitude are presented for MDD participants and controls while viewing unpleasant and neutral images. ERPs are displayed with bootstrapped 95% confidence intervals and with the time interval used to calculate the mean amplitude within the exploratory cluster.
shaded in light grey. Spatial topographies are of average ERP amplitude from 662 to 755 ms. Scatter plots show the mean (black line), median (red line), and the 95% confidence interval (dark grey region). A) ERPs and topographies for MDD participants. B) ERPs and topographies for healthy controls. C) ERPs and spatial topographies of the valence difference (unpleasant – neutral) for MDD participants and healthy controls. D) Scatter plots of LPP amplitude for unpleasant (U) and neutral (N) images at the exploratory cluster. E) Spatial topography of the valence difference (unpleasant – neutral) for the time interval 662 – 755 ms contrasting MDD participants with healthy controls.

Secondary Analyses

As a secondary analysis, we compared the emotion regulation strategies used by MDD participants and control. The majority of participants reported that they did not use a strategy (Table 2). A Fisher’s Exact Test revealed that strategy use was not significantly different between both groups (p = 0.34).

Table 2. Emotion regulation strategy use.

|                  | MDD (n = 40) | Controls (n = 41) |
|------------------|--------------|-------------------|
| No strategy      | 30           | 26                |
| Strategy         |              |                   |
| Reinterpretation | 1            | 5                 |
| Distraction      | 2            | 5                 |
| Detachment       | 7            | 5                 |

MDD: Major Depressive Disorder
We also investigated the association between strategy use and anxiety on the LPP amplitude. We performed simple univariate linear regression analyses, restricting the dataset to LPP values obtained from MDD participants while viewing unpleasant images. Strategy was not significantly associated with LPP amplitudes ($r = 0.13$, $r^2 = 0.02$, $\beta = -0.18$, $p = 0.44$; Supp Fig. 1A). Similarly, Anxiety was not significantly associated with the LPP ($r = 0.21$, $r^2 = 0.05$, $\beta = 0.01$, $p = 0.20$; Supp Fig. 1B). Next, we performed multivariate linear regression analyses using the full dataset (incorporating healthy controls as well as neutral images), including Group and Valence as independent variables. Neither the regression model including Strategy ($r = 0.18$, $r^2 = 0.03$, $p = 0.17$), nor the model including Anxiety ($r = 0.17$, $r^2 = 0.03$, $p = 0.20$), met the significance threshold.

Univariate regression analyses were repeated for the exploratory cluster identified during permutation testing with similar results. Neither Strategy ($r = 0.02$, $r^2 = 0.00$, $\beta = -0.04$, $p = 0.90$) nor Anxiety ($r = 0.05$, $r^2 = 0.00$, $\beta = -0.00$, $p = 0.76$) were significantly associated with LPP amplitudes. After expanding the dataset to incorporate healthy controls and neutral images, and including Group and Valence as independent variables, neither the model including Strategy ($r = 0.14$, $r^2 = 0.02$, $p = 0.39$), nor Anxiety ($r = 0.21$, $r^2 = 0.04$, $p = 0.08$), were significant.
We performed a preregistered study to test the emotional context insensitivity model by comparing the LPP amplitude for unpleasant and neutral stimuli in depressed participants and age- and gender-matched healthy controls. Our preregistered data analysis plan found no difference in emotional reactivity between MDD participants and controls within the preregistered centroparietal region of interest and time interval, which were based on previous studies. However, exploratory permutation analysis revealed a significant difference between MDD participants and healthy individuals in the hypothesised direction. The difference in amplitudes between unpleasant pictures relative to neutral pictures was lower for MDD participants compared to healthy controls, in agreement with the emotional context insensitivity model of depression. The exploratory results revealed a significant cluster of parietal EEG channels slightly posterior to the preregistered region of interest and within a narrower post-stimulus time interval (662-755 ms). We also investigated the effect of strategy use and anxiety comorbidity but found no evidence that emotion regulation strategy use differed between diagnostic groups, nor that strategy use or anxiety influenced the LPP in a passive view paradigm.

The primary aim of the study was to obtain stronger evidence for the emotional context insensitivity model through registered predictions (Nosek et al., 2018), and to replicate the reduced LPP to unpleasant stimuli in depression. We found a large reduction (Cohen’s $d = 0.88$) in LPP amplitude in the predicted direction for negatively-valenced stimuli. However, the reduction was not statistically significant when using the preregistered analysis plan to quantify the LPP (i.e. mean ERP amplitude in a time interval of 400-1000ms following simulation presentation in a cluster of predefined EEG electrodes). The predicted reduction
in LPP amplitude was only observed when using a narrower time window (662-755 ms) and slightly more posterior EEG electrodes, which were determined using a data-driven approach. Ledgerwood (2018) made a distinction between two types of preregistration: preregistering a theoretical, a priori, directional prediction to ensure a study tests (rather than informs) a theory and preregistering an analysis plan to help control type I error. The current findings matched the a priori directional prediction (i.e. lower LPP in the MDD group while viewing unpleasant images compared to healthy controls) and as such provides evidence supporting the emotional context insensitivity model of depression. While the predicted difference was not observed with the preregistered analysis plan, we used a cluster-based permutation test that controls the family-wise error rate (Maris et al., 2007; Pernet et al., 2015). Cluster-based permutation tests should not be used to make inferences about the latency or location of effects (Sassenhagen & Draschkow, 2019), but the current results show that the temporal and spatial extent of the LPP – as outlined in the preregistered analysis plan and based on previous literature – may not necessarily generalise across stimulus steps and measurement contexts (Yarkoni, 2019).

Relatively few EEG studies have investigated the emotional reactivity of depressed individuals (Foti et al., 2010; MacNamara et al., 2016; Weinberg et al., 2016; Zhang et al., 2016). These have reported mixed effects, including studies suggesting reduced reactivity to unpleasant stimuli in MDD relative to a healthy cohort (Foti et al., 2010; MacNamara et al., 2016), increased reactivity (Zhang et al., 2016), and no difference between unpleasant and neutral stimuli (Weinberg et al., 2016). The discrepancy observed in the present study between preregistered and exploratory analyses, as well as in outcomes between previously mentioned studies, suggests that relatively minor differences in the protocol used to
generate and operationalise the LPP may contribute to mixed findings. These include the selection of EEG electrodes for analysis, the LPP time interval, as well as other methodological choices such as the set of images used to evoke a physiological response.

The set of images used to generate the LPP differs markedly between studies, specifically with regards to the selection of aversive, unpleasant stimuli. Zhang et al. (2016) and Foti et al. (2010) used pictures of faces bearing emotional expressions. The former using faces depicting sadness, whereas the latter displayed angry and fearful expressions. In contrast, Weinberg et al. (2016) and MacNamara et al. (2016) chose their stimuli from the IAPS, which contains a broader array of picture options (e.g. photographs of people, faces, everyday objects, and scenes). However, even working from the same image set, the choice of unpleasant stimuli was substantially different between these studies. Weinberg et al. (2016) selected threatening images, defined as “images of mutilation, death, and animal and human threat”, whereas MacNamara et al. (2016) used less restrictive criteria to pick their negatively-valenced content. Although there is overlap in the brain regions used to process faces and emotionally evocative scenes, specialised regions of the brain activate in response to human faces, i.e. both image types activate the visual cortex, amygdala, posterior hippocampus, and ventromedial prefrontal cortex, whereas only images of expressive faces activated the superior temporal gyrus, insula and anterior cingulate (Britton et al., 2006). Furthermore, angry or fearful facial expressions have been shown to produce a stronger amygdala response in comparison to matched fearful or threatening scenes (Hariri et al., 2002). Consequently, this has important implications for the expected neurophysiological response measured using EEG, which may differ between these image types (Mavratzakis et al., 2016).
Regarding the EEG electrodes preselected for measuring the LPP, the exploratory cluster identified in the present study was marginally more posterior than the centroparietal region of interest used in previous studies of depression, but in agreement with studies of healthy participants reporting that a maximum effect occurred parietally (Hajcak, Moser, et al., 2006; Kessel et al., 2017; Liu et al., 2012). Interestingly, there is evidence to suggest that the LPP is initially largest parietally, and then shifts to a more centroparietal location in the latter stages of affective processing (Hajcak et al., 2012).

Studies of affective processing have operationalised the LPP using a diverse range of time intervals. These report it as commencing as early as 300 ms (Liu et al., 2012; Thiruchselvam et al., 2011), and as late as 600 ms (Mehmood & Lee, 2016). The LPP has been suggested to terminate as early as 500 ms (Schupp et al., 2003; Schupp et al., 2004), and as late as 1700 ms (MacNamara, Foti, et al., 2009; Thiruchselvam et al., 2011). Lastly, the duration of the LPP interval has been defined to be as narrow as 50 ms (Schupp et al., 2003), and as wide as 1400 ms (Liu et al., 2012). Broadly, the cluster identified in our exploratory analysis falls within the time interval of previous LPP studies.

Our secondary hypotheses stated that LPP amplitude would be moderated by emotion regulation strategy use and anxiety comorbidity in MDD participants. Contrary to these hypotheses, emotion regulation strategy use did not differ between diagnostic groups. Further, we found no evidence to suggest that emotion regulation strategy use attenuated LPP amplitudes to unpleasant pictures, in contrast to previous EEG studies. Extensive research has shown reduced LPP amplitude to unpleasant pictures when reinterpretation/reappraisal (Foti et al., 2008; Hajcak, Moser, et al., 2006; Hajcak & Nieuwenhuis, 2006; Moser et al., 2006) or distraction were used to regulate negative
emotions (Dunning et al., 2009; Hajcak et al., 2007; Thiruchselvam et al., 2011; Uusberg et al., 2014; Zhang et al., 2014). A possible reason for this discrepancy may be that the majority of healthy and depressed participants in the current study reported no emotion regulation strategy use (MDD: 30/40; healthy controls: 26/41), thus limiting the ability to statistically infer the effects of strategy on LPP amplitudes. We also did not find evidence that anxiety levels modulate LPP amplitudes. The prevailing view is that anxiety increases attentional resources towards emotionally salient, aversive, stimuli thereby resulting in enhancement of LPP amplitude (MacNamara & Hajcak, 2009). Previous research has shown enhanced LPP to aversive pictures in healthy individuals with high self-reported anxiety (MacNamara & Hajcak, 2009), and patients suffering from generalized anxiety disorder (MacNamara & Hajcak, 2010; MacNamara et al., 2016). Although our results differ considerably from these studies, they are corroborated by Weinberg et al. (2016), who found that a diagnosis of anxiety did not modulate the LPP. The reason for these disagreements in the field is unclear but may be related to idiosyncratic features of the study samples, including criteria used to estimate anxiety symptoms.

Conclusion

In conclusion, exploratory analyses found significantly reduced EEG amplitudes to unpleasant pictures in MDD, in support of the emotional context insensitivity hypothesis. However, we did not find a difference in emotional reactivity between MDD participants and healthy controls using our preregistered analysis plan, which was based on the existing literature. Compared to preregistered LPP features, the parietal EEG cluster identified in exploratory analyses was marginally more posterior and subtended a narrower time interval.
These results suggest that methodological differences between studies may play an important role in variability in the cortical response to emotional stimuli, limiting the generalisability of the findings. Neither emotion regulation strategy use, nor comorbid anxiety, were found to modulate LPP amplitude. Although the pathophysiology of depression remains poorly understood, arising possibly due to its inherent heterogeneity (Fried & Nesse, 2015), our findings indicate that a core feature and promising biomarker of depression may be reduced emotional reactivity to unpleasant stimuli. The presence of heterogeneity in EEG correlates of affective processing indicates the need for standardised EEG tests and analyses of emotional reactivity in depression.
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SUPPLEMENTARY MATERIALS

Some participants repeated the experimental protocol over three separate session. Only results from the first of these sessions is reported in the present study. To prevent carryover effects between sessions, the set of pictures participants viewed at each session was randomised and counterbalanced from the available parallel lists described below:

| IAPS List A | Description      | Valence | Arousal |
|-------------|------------------|---------|---------|
|             |                  | Mean    | SD      | Mean   | SD    | Class       |
| 6230        | AimedGun         | 2.37    | 1.57    | 7.35   | 2.01  | Unpleasant  |
| 2053        | Baby             | 2.47    | 1.87    | 5.25   | 2.46  | Unpleasant  |
| 9620        | Shipwreck        | 2.70    | 1.64    | 6.11   | 2.10  | Unpleasant  |
| 2745.1      | Shopping         | 5.31    | 1.08    | 3.26   | 1.96  | Neutral     |
| 7035        | Mug              | 4.98    | 0.96    | 2.66   | 1.82  | Neutral     |
| 2691        | Riot             | 3.04    | 1.73    | 5.85   | 2.03  | Unpleasant  |
| 7950        | Tissue           | 4.94    | 1.21    | 2.28   | 1.81  | Neutral     |
| 6821        | Gang             | 2.38    | 1.72    | 6.29   | 2.02  | Unpleasant  |
| 9520        | Kids             | 2.46    | 1.61    | 5.41   | 2.27  | Unpleasant  |
| 7150        | Umbrella         | 4.72    | 1.00    | 2.61   | 1.76  | Neutral     |
| 3300        | DisabledChild    | 2.74    | 1.56    | 4.55   | 2.06  | Unpleasant  |
| 2570        | Man              | 4.78    | 1.24    | 2.76   | 1.92  | Neutral     |
| 2688        | Hunters          | 2.73    | 2.07    | 5.98   | 2.22  | Unpleasant  |
| 2703        | SadChildren      | 1.91    | 1.26    | 5.78   | 2.25  | Unpleasant  |
| 2516        | ElderlyWoman     | 4.90    | 1.43    | 3.50   | 1.88  | Neutral     |
| 5532        | Mushrooms        | 5.19    | 1.69    | 3.79   | 2.20  | Neutral     |
| 1302        | Dog              | 4.21    | 1.78    | 6.00   | 1.87  | Unpleasant  |
| 2811        | Gun              | 2.17    | 1.38    | 6.90   | 2.22  | Unpleasant  |
| 2393        | FactoryWorker    | 4.87    | 1.06    | 2.93   | 1.88  | Neutral     |
| 2683        | War              | 2.62    | 1.78    | 6.21   | 2.15  | Unpleasant  |
| 7185        | AbstractArt      | 4.97    | 0.87    | 2.64   | 2.04  | Neutral     |
| 7034        | Hammer           | 4.95    | 0.87    | 3.06   | 1.95  | Neutral     |
| 2710        | DrugAddict       | 2.52    | 1.69    | 5.46   | 2.29  | Unpleasant  |
| 7100        | FireHydrant      | 5.24    | 1.20    | 2.89   | 1.70  | Neutral     |
| 5731        | Flowers          | 5.39    | 1.58    | 2.74   | 1.95  | Neutral     |
| 7037        | Trains           | 4.81    | 1.12    | 3.71   | 2.08  | Neutral     |
| 6260        | AimedGun         | 2.44    | 1.54    | 6.93   | 1.93  | Unpleasant  |
| IAPS List B | Description          | Valence Mean | Valence SD | Arousal Mean | Arousal SD | Class       |
|-------------|----------------------|--------------|------------|--------------|------------|-------------|
| 6210        | AimedGun             | 2.95         | 1.83       | 6.34         | 2.14       | Unpleasant  |
| 2661        | Baby                 | 3.90         | 2.49       | 5.76         | 2.13       | Unpleasant  |
| 5740        | Plant                | 5.21         | 1.38       | 2.59         | 1.99       | Neutral     |
| 2717        | DrugAddict           | 2.58         | 1.32       | 5.70         | 2.16       | Unpleasant  |
| 7493        | Man                  | 5.35         | 1.34       | 3.39         | 2.08       | Neutral     |
| 2095        | Toddler              | 1.79         | 1.18       | 5.25         | 2.34       | Unpleasant  |
| 2120        | AngryFace            | 3.34         | 1.91       | 5.18         | 2.52       | Unpleasant  |
| 7050        | HairDryer            | 4.93         | 0.81       | 2.75         | 1.80       | Neutral     |
| 3220        | Hospital             | 2.49         | 1.29       | 5.52         | 1.86       | Unpleasant  |
| 7009        | Mug                  | 4.93         | 1.00       | 3.01         | 1.97       | Neutral     |
| 2810        | Boy                  | 4.31         | 1.65       | 4.47         | 1.92       | Unpleasant  |
| 2840        | Chess                | 4.91         | 1.52       | 2.43         | 1.82       | Neutral     |
| 7590        | Traffic              | 4.75         | 1.55       | 3.80         | 2.13       | Neutral     |
| 5535        | StillLife            | 4.81         | 1.52       | 4.11         | 2.31       | Neutral     |
| 3500        | Attack               | 2.21         | 1.34       | 6.99         | 2.19       | Unpleasant  |
| 2455        | SadGirls             | 2.96         | 1.79       | 4.46         | 2.12       | Unpleasant  |
| 7705        | Cabinet              | 4.77         | 1.02       | 2.65         | 1.88       | Neutral     |
| 7008        | Fork                 | 5.27         | 1.09       | 2.32         | 1.84       | Neutral     |
| 2981        | DeerHead             | 2.76         | 1.94       | 5.97         | 2.12       | Unpleasant  |
| 2750        | Bum                  | 2.56         | 1.32       | 4.31         | 1.81       | Unpleasant  |
| 6020        | ElectricChair        | 3.41         | 1.98       | 5.58         | 2.01       | Unpleasant  |
| 2200        | NeutFace             | 4.79         | 1.38       | 3.18         | 2.17       | Neutral     |
| 1930        | Shark                | 3.79         | 1.92       | 6.42         | 2.07       | Unpleasant  |
| 6212        | Soldier              | 2.19         | 1.49       | 6.01         | 2.44       | Unpleasant  |
| 2191        | Farmer               | 5.30         | 1.62       | 3.61         | 2.14       | Neutral     |
| 2305        | Woman                | 5.41         | 1.12       | 3.63         | 2.04       | Neutral     |
| 7000        | RollingPin           | 5.00         | 0.84       | 2.42         | 1.79       | Neutral     |
| 6200        | AimedGun             | 2.71         | 1.58       | 6.21         | 2.28       | Unpleasant  |
| 7500        | Building             | 5.33         | 1.44       | 3.26         | 2.18       | Neutral     |
| 9920        | CarAccident          | 2.50         | 1.52       | 5.76         | 1.96       | Unpleasant  |
| 7004        | Spoon                | 5.04         | 0.60       | 2.00         | 1.66       | Neutral     |
| 7010        | Basket               | 4.94         | 1.07       | 1.76         | 1.48       | Neutral     |
| 7235        | Chair                | 4.96         | 1.18       | 2.83         | 2.00       | Neutral     |
| 2700        | Woman                | 3.19         | 1.56       | 4.77         | 1.97       | Unpleasant  |
| 6834        | Police               | 2.91         | 1.73       | 6.28         | 1.90       | Unpleasant  |
|   | Category     | Mean | SD  | Median | Unpleasant |
|---|--------------|------|-----|--------|------------|
| 2595 | Women       | 4.88 | 1.24 | 3.71   | 1.88       |
| 9902 | CarAccident | 2.33 | 1.38 | 6.00   | 2.15       |
| 9421 | Soldier      | 2.21 | 1.45 | 5.04   | 2.15       |
| 7043 | Drill        | 5.17 | 1.26 | 3.68   | 2.09       |
| 7003 | Disk         | 5.00 | 1.22 | 3.07   | 1.98       |
| 2900 | CryingBoy    | 2.45 | 1.42 | 5.09   | 2.15       |
| 7036 | Shipyard     | 4.88 | 1.08 | 3.32   | 2.04       |
| 1111 | Snakes       | 3.25 | 1.64 | 5.20   | 2.25       |
| 7547 | Bridge       | 5.21 | 0.96 | 3.18   | 2.01       |
| 7175 | Lamp         | 4.87 | 1.00 | 1.72   | 1.26       |
| 3230 | DyingMan     | 2.02 | 1.30 | 5.41   | 2.21       |
| 9050 | PlaneCrash   | 2.43 | 1.61 | 6.36   | 1.97       |
| 3350 | Infant       | 1.88 | 1.67 | 5.72   | 2.23       |
| 7233 | Plate        | 5.09 | 1.46 | 2.77   | 1.92       |
| 6244 | AimedGun     | 3.09 | 1.78 | 5.68   | 2.51       |
| 9430 | Burial       | 2.63 | 1.59 | 5.26   | 2.55       |
| 2190 | Man          | 4.83 | 1.28 | 2.41   | 1.80       |
| 7491 | Building     | 4.82 | 1.03 | 2.39   | 1.90       |
| 6831 | Police       | 2.59 | 1.50 | 5.55   | 2.16       |
| 9600 | Ship         | 2.48 | 1.62 | 6.46   | 2.31       |
| 2514 | Woman        | 5.19 | 1.09 | 3.50   | 1.81       |
| 7056 | Tool         | 5.07 | 1.02 | 3.07   | 1.92       |
| 6370 | Attack       | 2.70 | 1.52 | 6.44   | 2.19       |
| 7006 | Bowl         | 4.88 | 0.99 | 2.33   | 1.67       |
| 7180 | NeonBuilding | 4.73 | 1.31 | 3.43   | 1.95       |
| 1301 | Dog          | 3.70 | 1.66 | 5.77   | 2.18       |
| 2102 | NeuMan       | 5.16 | 0.96 | 3.03   | 1.87       |
| 7038 | Shoes        | 4.82 | 1.20 | 3.01   | 1.96       |
| 1201 | Spider       | 3.55 | 1.88 | 6.36   | 2.11       |
| 5510 | Mushroom     | 5.15 | 1.43 | 2.82   | 2.18       |
| 2880 | Shadow       | 5.18 | 1.44 | 2.96   | 1.94       |
| 9941 | Fire         | 2.91 | 1.54 | 5.83   | 2.14       |
| 7090 | Book         | 5.19 | 1.46 | 2.61   | 2.03       |
| 7211 | Clock        | 4.81 | 1.78 | 4.20   | 2.40       |
| 2512 | Man          | 4.86 | 0.84 | 3.46   | 1.75       |
| 2130 | Woman        | 4.08 | 1.33 | 5.02   | 2.00       |
| 1300 | PitBull      | 3.55 | 1.78 | 6.79   | 1.84       |
| 2480 | ElderlyMan   | 4.77 | 1.64 | 2.66   | 1.78       |
| 7002 | Towel        | 4.97 | 0.97 | 3.16   | 2.00       |
| 2385 | Girl         | 5.20 | 1.32 | 3.64   | 1.81       |
| 3301 | InjuredChild | 1.80 | 1.28 | 5.21   | 2.26       |
| IAPS List C | Description     | Valence | Arousal | Class   |
|-------------|-----------------|---------|---------|---------|
| 8485        | Fire            | 2.73    | 1.62    | 6.46    | 2.10    | Unpleasant |
| 7059        | Keyring         | 4.93    | 0.81    | 2.73    | 1.88    | Neutral    |
| 2495        | Man             | 5.22    | 1.10    | 3.19    | 1.76    | Neutral    |
| 9427        | Assault         | 2.89    | 1.47    | 5.50    | 2.09    | Unpleasant |
| 6150        | Outlet          | 5.08    | 1.17    | 3.22    | 2.02    | Neutral    |
| 9590        | Injecting       | 3.08    | 1.63    | 5.41    | 2.23    | Unpleasant |
| 8230        | Boxer           | 2.95    | 1.88    | 5.91    | 2.15    | Unpleasant |
| 7546        | Bridge          | 5.40    | 1.13    | 3.72    | 2.16    | Neutral    |
| 9491        | DeadBody        | 2.78    | 1.71    | 5.69    | 2.22    | Unpleasant |
| 7032        | Shoes           | 4.82    | 1.46    | 3.18    | 1.88    | Neutral    |
| 7062        | Sewing          | 5.27    | 1.06    | 3.40    | 1.94    | Neutral    |
| 6555        | Knife           | 3.33    | 1.59    | 5.69    | 2.21    | Unpleasant |
| 6220        | BoysW/Guns      | 3.10    | 1.91    | 5.89    | 2.43    | Unpleasant |
| 9120        | OilFires        | 3.20    | 1.75    | 5.77    | 1.94    | Unpleasant |
| 7025        | Stool           | 4.63    | 1.17    | 2.71    | 2.20    | Neutral    |
| 9250        | WarVictim       | 2.57    | 1.39    | 6.60    | 1.87    | Unpleasant |
| 7365        | Meat            | 5.20    | 1.57    | 4.13    | 1.93    | Neutral    |
| 9424        | Bomb            | 2.87    | 1.62    | 5.78    | 2.12    | Unpleasant |
| 9611        | PlaneCrash      | 2.71    | 1.95    | 5.75    | 2.44    | Unpleasant |
| 9621        | Ship            | 3.22    | 1.76    | 5.76    | 2.05    | Unpleasant |
| 7020        | Fan             | 4.97    | 1.04    | 2.17    | 1.71    | Neutral    |
| 9480        | Skull           | 3.51    | 2.08    | 5.57    | 1.87    | Unpleasant |
| 7030        | Iron            | 4.69    | 1.04    | 2.99    | 2.09    | Neutral    |
| 6250        | AimedGun        | 2.83    | 1.79    | 6.54    | 2.61    | Unpleasant |
| 9909        | BurningCar      | 2.78    | 1.45    | 5.98    | 2.04    | Unpleasant |
| 7255        | Cracker         | 5.07    | 1.18    | 3.36    | 1.99    | Neutral    |
| 2214        | NeuMan          | 5.01    | 1.12    | 3.46    | 1.97    | Neutral    |
| 2397        | Men             | 4.98    | 1.11    | 2.77    | 1.74    | Neutral    |
| Item          | Valence | Arousal | Valence | Arousal |
|--------------|---------|---------|---------|---------|
| Police       | 2.45    | 1.44    | 5.80    | 2.09    |
| Zipper       | 4.97    | 0.76    | 3.32    | 1.96    |
| AimedGun     | 3.57    | 1.84    | 5.64    | 2.03    |
| Couple       | 4.91    | 1.05    | 3.34    | 1.83    |
| CandleStick  | 5.22    | 0.75    | 2.95    | 1.91    |
| Jet          | 3.10    | 1.90    | 6.26    | 1.98    |
| Truck        | 4.77    | 1.03    | 3.35    | 1.90    |
| Guns         | 2.82    | 1.81    | 6.21    | 2.23    |
| Baskets      | 4.99    | 1.12    | 2.60    | 1.78    |
| Terrorist    | 2.91    | 1.52    | 5.86    | 2.06    |
| Lightbulb    | 4.90    | 0.64    | 3.02    | 1.83    |
| RoachOnPizza | 2.46    | 1.42    | 5.88    | 2.44    |
| Bomb         | 2.96    | 1.72    | 6.06    | 2.22    |
| FileCabinet  | 4.45    | 1.36    | 2.81    | 1.94    |
| Attack Dog   | 3.09    | 1.72    | 6.51    | 2.25    |
| NeuWoman     | 5.09    | 1.35    | 2.94    | 1.93    |
| Scissors     | 5.15    | 0.97    | 3.25    | 2.03    |
| Skinhead     | 2.04    | 1.57    | 6.05    | 2.71    |
| Video        | 5.18    | 1.07    | 3.12    | 1.97    |
| Girl         | 5.07    | 0.85    | 2.86    | 1.84    |
| CarTheft     | 2.85    | 2.05    | 5.59    | 2.50    |
| CarAccident  | 2.39    | 1.36    | 6.08    | 2.06    |
| Attack       | 2.46    | 1.58    | 6.96    | 2.09    |
| AbstractArt  | 5.07    | 1.02    | 2.30    | 1.75    |
| Vomit        | 2.81    | 2.14    | 6.24    | 2.23    |
| Fruit        | 5.50    | 1.84    | 3.81    | 2.01    |
| Twins        | 4.95    | 1.09    | 2.95    | 1.87    |
| Mushroom     | 5.15    | 1.45    | 3.69    | 2.11    |
Emotion Regulation Questionnaire

An emotion regulation questionnaire adapted was used to identify which strategy, if any, participants used to moderate their emotional response while passively viewing pictures.

Choose only one option:

While viewing unpleasant pictures:

1. I did not use any strategy
2. I looked on the bright side
3. I thought about something else
4. I distanced myself from the picture
5. I did not do any of the above, I did...
Exploratory Cluster Channels

Channels from the significant cluster identified by the exploratory cluster-based permutation testing are displayed below. These are sorted as a proportion of the length of time they were identified relative to the total duration of the cluster time interval. Channels that were present for >75% of the cluster time interval were used in follow-up analyses.
Secondary Analyses of Emotion Regulation Strategy and Anxiety

Supplementary Figure 1. Effects of emotion regulation strategy and anxiety on LPP amplitude. A) The LPP for the preregistered centroparietal cluster and time interval in both MDD participants and healthy controls who used an emotion regulation strategy or not. Black lines show the mean, red lines show the median, light grey shaded boxes indicate the standard deviation, and dark grey regions indicate the 95% confidence interval. B) Association between the anxiety subscore from the 21-item DASS and LPP amplitude for MDD participants while viewing unpleasant images. Dotted line shows the regression slope ($p > 0.05$; ns).