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Sustained Engagement of Attention is Associated with Increased Negative Self-Referent Processing in Major Depressive Disorder

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Abstract

This study investigated the link between self-reference and attentional engagement in adults with ($n = 22$) and without (HC; $n = 24$) Major Depressive Disorder (MDD). Event-related potentials (ERPs) were recorded while participants completed the Self-Referent Encoding Task (SRET). MDD participants endorsed significantly fewer positive words and more negative words as self-descriptive than HC participants. A whole-scalp data analysis technique revealed that the MDD participants had larger difference wave (negative words minus positive words) ERP amplitudes from 380–1000ms across posterior sites, which positively correlated with number of negative words endorsed. No group differences were observed for earlier attentional components (P1, P2). The results suggest that among adults with MDD, negative stimuli capture attention during later information processing; this engagement is associated with greater self-referent endorsement of negative adjectives. Sustained cognitive engagement for self-referent negative stimuli may be an important target for neurocognitive depression interventions.

Keywords

cognitive bias; major depressive disorder; psychophysiology; ERP; LPP

The way that one views oneself, one's self-concept or self-schema, is intricately tied with mood. Beck's (1967) cognitive model of depression postulates that the schema— internal

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beliefs and knowledge about the self, the world, and the future—influences how life events are appraised and interpreted. Schemas also prioritize the processing of incoming information, such that environmental stimuli that are consistent with one's self-schema are attended to, processed, and subsequently recalled more readily (Segal, 1988). A negative self-schema may result in biased interpretation of ambiguous stimuli, or cause elaborative processing of over-attended stimuli (Everaert, Koster, & Derakshan, 2012). This in turn has been theorized to facilitate increased recall of negative stimuli, resulting in negatively biased memory. Although other mechanisms clearly also contribute to the maintenance of depression (e.g., emotional blunting), negative self-schema may be an important mechanism that fuels many of the negative cognitive biases thought to maintain depression.

Consistent with the cognitive model, individuals with Major Depressive Disorder (MDD) have been shown to display negatively biased attention, interpretation, and memory (Everaert et al., 2012). Further, depressed people often do not display protective positive cognitive biases that are observed in healthy individuals (Walker, Skowronski, & Thompson, 2003; Disner, Beevers, Haigh, & Beck, 2011). Major depression instead privileges negative processing and, as a result, individuals with MDD are likely to view themselves as having more negative and fewer positive characteristics than non-depressed individuals.

One method of measuring self-schema is the self-referent encoding task (SRET; Derry & Kuiper, 1981). The SRET is a binary-choice, affective decision-making task combined with incidental recall of SRET stimuli. The SRET is generally a computer-based task, where positive and negative adjectives are presented one at a time to participants who determine as quickly as possible whether each word is self-descriptive or not. Following presentation of the word stimuli, participants are then asked to recall as many of the SRET stimuli as possible. Studies have shown strong correlations between endorsement of negative (but not positive) words and depressive symptoms (e.g., Disner, Shumake, & Beevers, 2016); increased endorsement of negative words (and decreased endorsement of positive words) on the SRET is also predictive of depression symptom course (Disner et al., 2016; Connolly, Abramson, & Alloy, 2015). Responses on the SRET also appear to be consistent over time particularly when depression symptoms remain relatively stable (Goldstein, Hayden, & Klein, 2015; Auerbach et al., 2016).

These studies provide a clear link between negative self-referent cognition, as measured by the SRET, and depressive symptoms. Understanding the neural architecture of negative self-referent bias is important, as it could provide a more comprehensive understanding of this important cognitive bias and point to translational treatment targets for neurocognitive interventions.

In the current project, we used electroencephalography (EEG) to measure the temporal characteristics of cognitive processes involved in self-appraisal. Although the spatial resolution of EEG is not ideal, EEG is extremely effective at measuring information about the time course of cognitive phenomena (Kappenman & Luck, 2012). Thus, collecting event-related potentials (ERPs) during the SRET can provide information as to whether biased self-referent processing is occurring at an early processing level; whether it occurs at

a later level of cognitive evaluation; or whether both processes contribute to this negative self-referent processing bias.

Early ERP processes include the P1 and P2, both positive deflections in an ERP waveform thought to reflect automatic processing of attentional information that may nonetheless be influenced by emotion (Hajcak, Weinberg, MacNamara, & Foti, 2012; Delplanque, Lavoie, Hot, Silvert, & Sequeira, 2004). These peaks occur between 100 and 300 ms following a stimulus. The P2 in particular may index post-perceptual selective attention, as it occurs late enough (peaking approximately 180 ms after stimulus onset) to be related to the association of new information with prior comprehension (Hajcak et al., 2012; Luck & Hillyard, 1994). As both occur early, they are understood to be related to early attentional engagement; both are typically increased when attending to emotional stimuli (Delplanque et al., 2004).

The late positive potential (LPP), conversely, is a component often considered an index of cognitive evaluation and engagement with stimuli. The LPP begins around 300 ms post-stimulus and continues up to 1,500 ms (Hajcak et al., 2012; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000). The LPP is often either posterior or central in localization (Hajcak et al., 2012). The LPP increases in positive amplitude in response to prioritization of information, indicating increased engagement, especially to negative information. Schupp and colleagues (2004) demonstrated that the LPP is greater in response to unpleasant or negative images as compared to neutral or positive images, regardless of mood state; others have shown that attending to non-arousing images reduces the LPP (Hajcak, MacNamara, Foti, Ferri, & Keil, 2013). Moreover, some studies have shown a generally diminished LPP in participants with MDD (Blackburn, Roxborough, Muir, Glabus, & Blackwood, 1990; Proudfit, Bress, Foti, Kujawa, & Klein, 2015; Weinberg, Perlman, Kotov, & Hajcak, 2016).

Several studies have attempted to use EEG to identify the key ERP components that contribute to negative self-referent processing during the SRET. A prior study found that both current and remitted MDD groups had increased amplitudes for negative stimuli in an early component of attentional capture (the P2) in comparison to healthy controls (Shestyuk & Deldin, 2010). They also found that individuals who were currently depressed showed more positive amplitudes in the late positive potential (LPP) for negative stimuli than the other groups. This suggests that MDD participants selectively attended to negative information (due to the initial P2 amplitude difference from controls) and were engaging in increased cognitive evaluation of negative information (due to the increases in the LPP compared to healthy controls). Similarly, in a sample of depressed and healthy female adolescents, depressed girls were shown to exhibit greater early (P1) amplitudes in response to negative words, and greater later (LPP) amplitudes to negative words (Auerbach, Stanton, Proudfit, & Pizzagalli, 2015). These findings are consistent with the results of prior work, with the MDD group showing early attention to negative words that continues over the time-course of the ERP.

Further work with a large sample of younger female participants ($N=121$) found indications that risk for depression (i.e., maternal history of MDD) was also associated with greater LPP amplitudes to negative words when compared to those at low risk for MDD (Speed, Nelson, Auerbach, Klein, & Hajcak, 2016). This study used a principle components analysis (PCA),

which builds components from the EEG electrode channels that most strongly contribute to an outcome. With the LPP described by the PCA, there was no difference between positive and negative valence within groups; however, in response to negative words only, the at-risk participants showed increased LPP amplitudes and increased subsequent recall of negative stimuli compared to positive. This study did not find differences in the earlier waveforms (P1 or P2). An additional study investigated depressive response on the SRET from a semantic processing perspective (i.e., the N400 waveform), arguing that a diminished N400 suggests stronger self-reference (Kiang et al., 2017). This study demonstrated that participants with MDD had a diminished N400 in response to negative, but not positive, adjectives.

A recent SRET study using PCA techniques with ERPs in a large community sample of adults ($N = 128$) found that individuals with elevated depressive symptoms had enhanced negativity to both positive and negative words in early frontal regions (Waters & Tucker, 2016). A waveform that they believed to be an element of the late positive complex or P300, at a similar time frame to the LPP, was attenuated in response to all stimuli in parietal regions. Notably, these findings are in the opposite direction to the results reported above (e.g., the LPP measured at a similar point in time was increased in depressed female adolescents in Auerbach et al., 2015).

In summary, these studies reveal some conflicting results in terms of the waveforms associated with the SRET, raising a question of whether there is attenuation or augmentation of the early selective attention components (P1, P2) and later cognitive evaluation (LPP) in response to negative stimuli in depressed participants relative to healthy controls. Many of the above-reviewed studies were conducted in young, female participants; it is important to determine which of these findings, if any, extend to adult samples. Further, relatively few studies have been completed in a sample with a clinical diagnosis of MDD. Additionally, given the recent emphasis in psychology to replicate novel research (e.g., Munafó et al., 2017), this study's potential to independently replicate prior work in this area is important.

In the current study, we anticipated that behavioral results would follow in the same vein as previous work, with more endorsements of negative words as self-referent in participants diagnosed with MDD compared to healthy controls. Based on prior research and the cognitive model of depression, we predicted that adults with MDD, in comparison to healthy controls, would show early, differential attention between negative and positive words in the P1 and P2. We also predicted that MDD-diagnosed participants, as compared to healthy controls, would show increased cognitive evaluation in later components (similar to the LPP) for negative stimuli. Were this confirmed, it would imply that differential processing of self-referential information results from both the early components involved in perception and selective attention of negative stimuli, and also from the way that these stimuli are elaborated, processed, and encoded.

To better assess the full span of attentional processing in response to word presentations, we conducted analyses using a non-parametric technique often applied to functional neuroimaging analyses (Nichols & Holmes, 2002), which identified spatiotemporal areas that might be strongly differentiating between the MDD and HC groups during self-

referential processing. This technique, discussed further below, uses randomized permutations of the data to conduct point-by-point *t*-tests, correcting for multiple comparisons, which allows spatiotemporal areas with strong differences to rise to the forefront. This data-driven method identifies the onset of differential between-group responses in a manner that is conservative compared to standard parametric approaches because, first, no assumptions of normality are required and, second, no *a priori* (and possibly biased) choices of time window or electrode region are necessary. This is in contrast to the traditional, parametric approach to ERP analysis, which examines activity within a limited number of electrode sites averaged across specified time windows. Nevertheless, we also conducted a limited number of parametric analyses to allow for easier comparisons of results from past work and the current study.

Method

Participants

Adults were recruited from the Austin, TX community through the use of advertisements posted on websites (Craigslist, a UT-Austin message board, and Indeed) and fliers. Postings described a study on “mood” and “emotional experiences” but highlighted the need for both healthy and depressed subjects. The advertisements directed participants to a website to determine eligibility. At this website, participants provided informed consent for the screening and filled out a brief survey of current mood and demographics. Research assistants and graduate students trained on diagnostic interviewing conducted phone screenings on eligible participants, using the Mini International Neuropsychiatric Interview (version 6.0, Sheehan et al., 1998). The MINI is a standardized instrument used for brief screenings to diagnose a variety of psychiatric disorders. Research assistants took part in a training workshop during which they learned interview skills, role-played interviews, and reviewed diagnostic criteria. After the workshop, they listened to calls conducted by experienced researchers and had their initial screening interviews monitored for fidelity. Phone calls were audio-recorded with consent from participants throughout the study for fidelity analyses. An independent assessor (J.D.B.) randomly selected and rated 20% of MDD and HC interviews. Agreement for MDD diagnosis between study interviewers and the independent assessor was excellent ($k = 1.00$, $p < .0001$).

Inclusion and Exclusion Criteria

Participants were included in the current study if they were between the ages of 18 and 55 and spoke fluent English. Participants who scored less than 13 or greater than 16 on the Center for Epidemiologic Studies – Depression Scale (CESD) during online screening were invited to complete the MINI interview over the phone. Participants with CESD > 16 who met DSM-5 criteria for MDD ($N = 22$; *Diagnostic and statistical manual of mental disorders*, 2013) were included in the study. Nine participants met criteria for a current single major depressive episode, while 12 met criteria for recurrent MDD. Participants with MDD were included whether or not they met criteria for a current anxiety disorder; for all participants in this group, MDD was the primary diagnosis as assessed during the MINI. Of those diagnosed with MDD, 12 met criteria for one or more DSM-IV anxiety or trauma-based

disorders (seven for Generalized Anxiety Disorder, two for Social Anxiety Disorder, five for panic attacks, and four for PTSD).

Healthy control participants had a CESD < 13 and did not meet diagnostic criteria for past or current MDD or a current anxiety disorder ($N = 24$). Importantly, all participants (HC and MDD) were excluded from the study if they met diagnostic criteria for the following disorders: current alcohol or substance abuse or dependence; mania or hypomania; bipolar disorder; or psychosis. Participants were also excluded based on criteria that could affect EEG collection, including a history of seizures or epilepsy, head trauma, current use of beta-blockers, and current use of anti-psychotic drugs (Keil et al., 2014).

Sample Characteristics

Data from one participant in each condition were excluded because of poor EEG data quality. Demographics are reported in Table 1; participants were in their mid-twenties, mostly female, and approximately half were white (53% white, 28% Hispanic/Latino, 16% Asian, and 2% Black). Groups did not differ significantly on the basis of age ($t[41.82] = -0.33, p = .74$), gender ($\chi^2[2] = 2.30, p = .32$), or race ($\chi^2[2] = 0.77, p = .85$). Groups did of course significantly differ on depression severity, as measured by the CESD, $t(31.6) = -14.0, p < .001$.

Power Analysis

A priori power analyses were conducted to determine sample size necessary to achieve a medium-to-large effect size ($\eta^2 = 0.22$), as per Auerbach, Stanton, Proudfit, and Pizzagalli (2015) for multivariate ANOVA; with the current sample size, we would achieve 80% power.

Procedure

The institutional review board at the University of Texas at Austin provided approval for the study (IRB # 2014-08-0078). Participants who were eligible for the study following phone screening were scheduled for a 1.5-hour session in the lab. Informed consent was obtained, and participants completed several self-report questionnaires. Following this, Easycap EEG caps were placed on the participant's head and prepared for EEG collection, and then participants completed experimental tasks on a computer. Participants were paid \$20 for completing the study and were provided with a list of local mental health resources.

Measures

Center for Epidemiologic Studies – Depression Scale (CES-D)—The CES-D (Radloff, 1977) is a self-report scale designed to assess depressive symptoms over the past week using 20 items. Scores may range from 0 to 60; a score greater than 16 is often used as a cut-off for elevated depressive symptoms (Radloff, 1977; Santor, Zuroff, Ramsay, Cervantes, & Palacios, 1995). The CES-D was used for screening and was assessed again during the laboratory visit when it was confirmed that the CES-D remained above 16 for participants with MDD and below 13 for healthy controls.

Mood and Anxiety Symptoms Questionnaire (30-item version; MASQ)—The MASQ (Clark & Watson, 1991) is a 90-item self-report scale designed to measure the tripartite model of depression, anxiety, and general distress. A short (30-item) adaptation of this questionnaire has been developed, which maps closely onto the original questionnaire (Wardenaar et al., 2010), and was used in the present study. The MASQ provides sub-scales of General Distress, Anhedonic Depression, and Anxious Arousal. The Anxious Arousal subscale was used as a covariate in a final set of analyses to determine if anxiety symptoms altered observed findings.

Self-Referent Encoding Task (SRET)—The SRET (Derry & Kuiper, 1981, see Figure 1) is an affective decision-making task where participants make binary-choice decisions about whether positive and negative words are self-descriptive. Participants view the words on a computer screen and make rapid judgments following the word's display. In this version, participants viewed 40 negative and 40 positive words (as in Auerbach et al., 2015¹) selected from the Affective Norms for English Words (Bradley & Lang, 2010) for a total of 80 trials.

Stimuli were presented in random order for 200 ms, followed by 1,800 ms of a fixation cross. Since subjects were instructed to withhold their motor response during this fixation cross, event-related potentials to word presentation and decision-making remained uncontaminated by motor responses. Only after offset of the fixation cross were participants presented with the question prompt, “Does this word describe you?” Participants used a Logitech gaming controller's shoulder buttons to respond “yes” or “no”. Although the 1800ms period between the stimulus offset and behavioral response allows for the recording of neural response to stimuli, this extended period renders the reaction time response less meaningful and difficult to interpret². Thus, we focus on ERP responses to word stimuli rather than reaction time in our analyses, which is consistent with prior work in this area (e.g., Auerbach et al., 2015). Participants completed several neutral practice trials before the task began to ensure that they knew to wait to respond until the question appeared. A jittered intertrial interval followed each trial, between 1,500 and 1,700 ms in length.

After completing the task, participants completed an image-based task for approximately 12 minutes. Following this distraction, they were asked to recall as many adjectives as possible from those presented during the SRET, within five minutes. Participants were not previously informed that they would be asked to perform this recall task. The primary behavioral outcome from the SRET is the number of positive and negative words endorsed as self-referential. An alternative method (see e.g., Goldstein, Hayden, & Klein, 2015) involves calculating processing bias scores, with a negative score calculated as

¹The following 80 words were included in the SRET: Positive words were: admired, adorable, alive, beautiful, bold, bright, capable, carefree, confident, cute, devoted, dignified, elated, engaged, famous, festive, friendly, gentle, grateful, happy, honest, hopeful, inspired, jolly, joyful, lively, loyal, lucky, masterful, outstanding, proud, satisfied, silly, surprised, terrific, thoughtful, untroubled, useful, vigorous, wise. Negative words were: afraid, alone, angry, anguished, bored, brutal, burdened, cruel, crushed, defeated, depressed, disgusted, disloyal, displeased, distressed, dreadful, fearful, frustrated, guilty, helpless, hostile, insane, insecure, lonely, lost, morbid, obnoxious, rejected, rude, scared, shamed, sinful, stupid, terrible, terrified, troubled, unhappy, upset, useless, violent. Positive and negative words were matched for arousal, frequency, and length (Auerbach et al., 2015).

²Indeed, we tested whether group and valence predicted reaction times, and found no significant effect.

$\frac{\text{number of negative words endorsed}}{\text{number of any words endorsed}}$ and the reverse for positive valence. Thus, individuals with an increased number of negative words endorsed, or a negative processing bias closer to one, have a stronger negative processing bias.

EEG Recording and Data Analysis

EEG was recorded using a 64-channel active electrode system placed in the Easycap recording cap and recorded with the BrainVision actiCHamp amplifier and PyCorder software. In addition to the 64 cap channels, an additional four channels were collected to track vertical and horizontal eye movements. All head channels were located based on extended 10/20 system locations; cap sizes were chosen based on the circumference of participant's heads. Electrode impedances were reduced using an electrical conducting gel to below 10 k Ω . Continuous EEG were sampled at 500 Hz, initially referenced to Cz. Offline, data were processed using BrainVision Analyzer 2.0 software where the data were re-referenced to an average reference of all head channels.

Electrooculogram (EOG) channels were created by subtracting active electrodes placed below the eyes from above-eye (Fp1 and Fp2) sites for vertical EOG, and by subtracting sites placed outside of the left and right canthi of the eyes for horizontal EOG. A Butterworth infinite impulse response filter was applied to bandpass filter the data from 0.1 to 30 Hz (slope of 12 dB/oct), and sections with major artifacts identified by visual inspection were marked and excluded from analysis. Several participants ($N = 6$) had one or two faulty electrodes; these participants had the faulty channel(s) interpolated using a linear triangulation algorithm before further analyses were conducted. An independent component analysis (ICA) transform was then conducted in order to identify and remove the effects of eye blinks and eye movements, using both vertical and horizontal EOG channels. Each participant's whole dataset was used to calculate the ICA matrix, and a restricted Infomax rotation was used to decompose the ICA and remove components relating primarily to eye blinks and eye movements (Jung et al., 2000; Lee, Girolami, & Sejnowski, 1999).

Individual trials were split into 1,500 ms epochs selected from 200 ms before stimulus onset to 1,300 ms following stimulus onset. Epochs were created separately for positively- and negatively-valenced words. Following the creation of these epochs, intervals were further artifact assessed using the following semi-automated criteria based on Auerbach et al. (2015): a maximal voltage step of 50 $\mu\text{V}/\text{ms}$; a voltage difference above 300 μV within an epoch; amplitudes above 200 μV or below $-200 \mu\text{V}$; and periods longer than 100 ms with activity under 0.5 μV . Epochs that did not pass these parameters were rejected from further analysis. A linear de-trend³ was then applied to the data based on the 100 ms before stimulus onset and the 100 ms at the end of the epoch, and a baseline correction was applied by averaging the period from 200 ms preceding stimulus onset until that onset.

³Given the possibility that a linear de-trend would alter differences in longer lasting, late ERP components, all analyses were repeated without the de-trend. Results were not substantially different except in one test indicated in the text, below; nor did the visual inspection of waveforms reveal substantial differences.

Average responses were created per-participant, for negative and positive words separately. A minimum of 20 valid epochs were required per participant, per each valence; all participants had at least this many. On average, 36 ($SD = 2.9$) epochs per participant were included for negative word stimuli trials, and 36.1 ($SD = 2.7$) epochs were included for positive word stimuli trials. Difference waves were generated by subtracting positive from negative word stimuli trials.

The data were examined using pointwise non-parametric randomized permutation t -tests, which were corrected for multiple comparisons across time and site (Trujillo, Allen, Schnyer, & Peterson, 2010; Sanguinetti, Trujillo, Schnyer, Allen, & Peterson, 2015; Nichols & Holmes, 2002; Pernet, Latinus, Nichols, & Rousselet, 2015). This cluster-based method allows for the identification of differential responses between MDD and HC groups in a manner that is more conservative than standard t -tests, avoids putative *a priori* choices of regions of analysis by utilizing the full scalp recorded data. This analysis was performed on the difference waves (negative words minus positive words) in a between-subjects analysis.

This non-parametric statistical method consists of a three-step process to create an empirical null distribution for the between-group ERP difference waves to be used for hypothesis testing the between-group differences. First, we computed a statistical significance threshold for the between-group difference waves at electrode and time point. As the ERP responses were recorded from 62 channels over a 1.5 sec (1,500 ms) epoch at a 500 Hz sampling rate, this amounted to a total of $62 \times 1.5 \times 500 = 46,500$ independent thresholds. We determined these thresholds by computing a distribution of 20,000 between-group t -statistics for each data point under the null hypothesis. Each t -statistic was computed after exchanging (permuting) the data of a randomized subset of participants in each group (the size of each subset equaled the number of individuals in the smaller of the two subject groups, i.e., $n = 22$). If the null hypothesis is true and there are no between-group differences, then the t -value computed after this exchange is still an element of the null distribution (because exchanging subjects across groups should make no difference if there truly are no between-group differences). This process was repeated 20,000 times to create a distribution of t -values from which we determined the two-tailed $p = 0.05$ threshold for each of the 46,500 data points.

Because such a large number of independent tests will inflate type-I error, it was necessary to correct for multiple comparisons. We accomplished this in a second step by using these significance thresholds to determine contiguous t -statistic clusters across electrodes and time points. We then computed the distribution of maximal t -statistic clusters under the null hypothesis. This was accomplished by computing a second round of 20,000 between-group data permutations, where during each permutation new t -values were computed for each data point. Those t -values that were above the $p = 0.05$ thresholds determined in the first step of this procedure were then divided into contiguous clusters. Data was arranged into a three-dimensional structure (anterior-posterior electrode dimension, left-right electrode dimension, time dimension) and t -statistic clusters were defined as three-dimensional neighborhoods of contiguous points (26-connected point neighborhoods). Then, for each identified cluster, we computed its exceedance mass, defined as the summed total of t -values within the cluster (i.e. “the integral of the statistic image above the primary threshold within the suprathreshold

cluster”; Nichols & Holmes, 2002, p.8). We then selected the largest exceedance mass for a given permutation, yielding a distribution of 20,000 maximal exceedance mass values under the null hypothesis.

In a final step, we used the previously-obtained null distribution of maximal cluster exceedance masses to hypothesis test the cluster exceedance masses observed in the non-permuted data. Cluster exceedance masses calculated from the non-permuted data with sizes greater than the null distribution’s $p = 0.05$ criterion exceedance mass were considered to be significant at the two-tailed level with strong control for type-I error. All p -values were corrected for multiple comparisons using a step-down procedure (Holmes, Blair, Watson, & Ford, 1996). As each cluster corresponded to a spatiotemporal extent of between-group ERP differences, this method allowed us to simultaneously identify where on the scalp and when in time those differences were statistically significant.

In an effort to compare our findings with prior work, event-related potential (ERP) components were also calculated as the mean area under the curve for relevant electrode sites and time windows. Consistent with previous studies (e.g., Auerbach et al., 2015), the P1, P2, and the early late positive potential (LPP), components were calculated using averages across Pz, POz, P1, P2, PO3, and PO4. The P1 was quantified as the mean average from 100 to 200 ms following the stimulus; the P2, from 200 to 300 ms; and the early LPP, from 400 to 600 ms. The late LPP was calculated as the average of Fz, FCz, and Cz, from 600 to 1,200 ms following the stimulus.

Behavioral data cleaning, modeling, and visualization was conducted in RStudio (version 1.0.136) running R (version 3.3.2) with the following packages: dplyr (Wickham & Francois, 2015), tidyr (Wickham, 2015), ggplot2 (Wickham, 2009), lme4 (Bates, Mächler, Bolker, & Walker, 2015), lmerTest (Kuznetsova, Brockhoff, & Christensen, 2016), and compute.es (Re, 2013). EEG data were prepared in BrainVision Analyzer 2.0 and analyzed in MATLAB via in-house scripts.

Results

Summary Statistics and Analyses of Behavioral Data

Behavioral SRET data are summarized in Table 2. Two-way mixed effects ANOVAs were conducted with factors of group and valence. For processing bias, the group \times valence interaction was significant, $F(1, 40) = 138.8$, $p < .001$, generalized $\eta^2 = .78$, with the MDD group having a greater negative processing bias than the HC group, $t(27.3) = -11.21$, $p < .001$, Cohen’s $d = -3.47$, 95% CI $[-4.46, -2.48]$. Given that processing bias is a ratio, the test for positive processing bias return inverse results with opposite signs, and is thus not repeated here.

For each valence, participants could endorsed between 0 and 40 words. In the HC group, participants endorsed from 0–8 negative words, and 12–36 positive words. In the MDD group, participants endorsed 2–30 negative words, and 8–27 positive words. In the two-way mixed effect ANOVA, the group \times valence interaction was significant, $F(1, 40) = 115.3$, $p < .001$, generalized $\eta^2 = .62$, with the MDD group endorsing more negative words than the HC

group, $t(20.9) = -10.08$, $p < .001$, Cohen's $d = -3.12$, 95% CI $[-4.06, -2.19]$, and the HC group endorsing more positive words than the MDD group, $t(40.0) = 5.90$, $p < .001$, Cohen's $d = 1.83$, 95% CI $[1.08, 2.57]$. Within the MDD group, there was a near-significant effect of valence, with more negative words endorsed than positive, $t(33.3) = 2.02$, $p = .051$, Cohen's $d = 0.66$, 95% CI $[-0.02, 1.33]$. Within the HC group, there was a significant effect of valence, with significantly more positive words endorsed than negative, $t(27.3) = -16.8$, $p < .001$, Cohen's $d = -4.94$, 95% CI $[-6.14, -3.75]$.

Non-Parametric Statistical Analysis

Grand averages were generated for HC and MDD participants separately and used to create topographic maps (see Figure 2). The topographic maps were used to visualize the scalp distribution of the group by valence differences, and how they change over time. As temporal interval increases, consistent frontal and posterior differences develop between groups, with the MDD group demonstrating greater differences than healthy control participants in responses to negative versus positive words. Central differences were especially apparent from 600 – 1,000 ms, indicating periods where the HC group's responses to negative minus positive words were increased compared to the MDD group. Thus, these topographic maps indicated heightened differential activation at central sites during a time window that is consistent with the LPP. Early time periods show relatively minor differences between groups, primarily in frontocentral regions.

We computed permutation tests using negative word stimuli minus positive word stimuli difference waves, comparing between groups (HC subtracted from MDD). The permutation tests were performed over all electrode sites following data processing, using an interval from 0 – 1,000 ms post-stimulus, thus encompassing the waveforms that were significantly different between groups in previous work described above, including P1, P2, and the LPP.

The results of the permutation tests are displayed in Figures 3 and 4. The upper portion of Figure 3 depicts the ERPs averaged across all electrodes that showed statistically significant differences between groups. The lower portion of Figure 3 indicates the electrodes and time periods where the difference waveform for negative vs. positive word stimuli was significantly different between MDD and HC groups. Darker colors, concentrated at left-frontal and central sites, indicate where the MDD group showed a more negative difference waveform relative to controls; that is, where the negative minus positive difference waveform was more negative in the MDD group compared to controls. Permutation tests indicated significant differences from 380 to 866 ms. Lighter colors indicate the converse: that the MDD group showed a more positive difference waveform, primarily in the posterior sites; these differences were most evident in a later time-period, from 380 ms through the end of the analysis window at 1,000 ms.

To facilitate interpretation of the difference waveforms observed in Figure 3, we also plotted the average waveforms across frontal, central and posterior scalp locations collapsed across all electrodes that showed significant differences in the statistical maps (i.e., those indicated in the lower section of Figure 3), in response to negative and positive stimuli separately for the MDD and HC groups. These plots are shown in Figure 4. Beginning around 450 ms in frontal and central sites, more positive ERPs to positive words than to negative are evident in

data from the MDD participants, whereas HC participants show little difference between stimuli. The posterior differences were inverted relative to the frontal effects. Beginning around 500 ms in posterior sites, the MDD participants showed more positive ERPs to negative words than to positive; HC participants showed the opposite effect. This pattern over posterior sites begins late and grows more positive over time. The waveform is less positive in response to positive words for the MDD group, whereas it is less positive in response to negative words for the HC group. There were not apparent differences for either group in early responses to positive and negative words, either between or within groups.

Relationship Between Behavioral and Neural Outcomes

Based on the results described above, we exported timepoint-by-timepoint voltage per participant, averaged across all spatiotemporal clusters marked as significantly different between MDD and HC groups in the difference waves (i.e., the mean per-group of the ERPs depicted in Figure 3). We then examined whether the ERP response to negative words minus positive words predicted behavioral outcomes (i.e., processing bias and endorsements).

For ERP response predicting endorsements of word stimuli on the SRET, a linear mixed model regression with a factor of valence (positive or negative words) and a continuous predictor of the non-parametric test voltage values found an interaction between valence and the voltage values, $t(78) = -2.80$, $p = .006$, Cohen's $d = -0.86$, 95% CI $[-1.51, -0.21]$. A more positive ERP difference was related to an increased number of negative words endorsed, $t(39) = 2.28$, $p = .029$, Cohen's $d = 0.5$, 95% CI $[0.06, 0.95]$. Conversely, a less positive ERP difference was non-significant in predicting the number of positive words endorsed, $t(39) = -1.64$, $p = .11$, Cohen's $d = -0.41$, 95% CI $[-0.83, 0.08]$. These results are consistent with the above-discussed group effects, as MDD participants are more likely to show more positive ERP difference waves (to negative minus positive words), especially in posterior sites.

A final model tested whether the behavioral and ERP results were independent predictors of depression group status, using logistic generalized linear models with group status modeled as 1 for MDD and 0 for HC. An additive model with three predictors: positive words endorsed, negative words endorsed, and permutations test voltage values (rescaled with a standard deviation of 1, from 0 – 4, to result in odds ratios [OR] that were interpretable), revealed a significant effect for number of negative words endorsed, $OR = 1.66$, 95% CI $[1.21, 3.49]$, $z = 2.04$, $p = .04$; MDD diagnosis was 1.66 times more likely for every additional negative word endorsed. This model had a non-significant effect of the number of positive words endorsed, $OR = 0.81$, 95% CI $[0.51, 1.05]$, $z = -1.31$, $p = .19$ and the permutations test voltage values, $OR = 0.82$, 95% CI $[0.10, 5.00]$, $z = -0.23$, $p = .82$.

These predictors were correlated with one another but measured separate constructs. The number of negative words endorsed was strongly negatively correlated with the number of positive words endorsed, $r = -.63$, 95% CI $[-.42, -.79]$, $p < .001$; it was positively correlated with the permutations test voltage values, $r = .34$, 95% CI $[.04, .59]$, $p = .03$; the number of positive words endorsed was not significantly correlated with the permutations test voltage values, $r = -.25$, 95% CI $[-.52, .06]$, $p = .11$. There was a marginally-significant positive

correlation between permutations test voltage values and score on the CESD, $r = .26$, 95% CI $[-.05, .52]$, $p = .09$.

ANOVA: Early Attentional Components

We performed parametric analyses of variance (ANOVA) to compare ERP responses between groups at specific time-windows; these waveforms are shown in Figure 5. Area under the curve was calculated for each component and entered into a mixed-level ANOVA, with fixed factors of group and valence, and a random factor of participant. There was no significant interaction of group \times valence for the area under the P1 waveform, 100 to 200 ms following stimulus presentation, $F(1, 40) = 0.03$, $p = .87$, generalized $\eta^2 < .001$. There were no significant main effects of group or valence: for group, $F(1, 40) = 0.02$, $p = .90$, generalized $\eta^2 < .001$, or for valence, $F(1, 41) = 0.21$, $p = .65$, generalized $\eta^2 < .001$.

Likewise, there was no interaction of group \times valence for the area under the P2 waveform, 200 to 300 ms following stimulus presentation, $F(1, 40) = 0.06$, $p = .80$, generalized $\eta^2 < .001$. There were also no significant main effects of group or valence: for group, $F(1, 40) = 0.12$, $p = .73$, generalized $\eta^2 = .003$, for valence, $F(1, 41) = 0.11$, $p = .74$, generalized $\eta^2 < .001$. These results demonstrate that for these early components, neither group showed significant effects of valence nor significantly differed from the other.

ANOVA: Late Positive Potential (LPP)

For the early LPP, calculated at the same sites as the P1 and P2 components, from 400 to 600 ms, there was a significant group \times valence interaction, $F(1, 40) = 7.51$, $p = .009$, generalized $\eta^2 = .014$. This interaction, visualized in Figure 5, indicates that the depressed group exhibited greater activity following negative versus positive words and healthy controls demonstrating the opposite pattern. This difference (i.e., amplitudes to positive – negative stimuli between groups) was a medium to large effect (MDD: $M = -0.16 \mu\text{V}$, $SD = 0.34$; HC: $M = 0.15 \mu\text{V}$, $SD = 0.38$). For the comparison of difference waves, Cohen's $d = 0.85$, 95% CI $[0.20, 1.50]$.

The late LPP was calculated across Fz, FCz, and Cz from 600 to 1200 ms. A mixed-effects ANOVA with factors of group and valence found no group \times valence interaction, $F(1, 40) = 0.01$, $p = .92$, generalized $\eta^2 < .001$. After dropping the interaction, there was a significant effect of group, $F(1, 40) = 6.09$, $p = .018$, generalized $\eta^2 = .13$, with the depressed participants showing greater amplitudes across both valences compared to healthy controls. These group differences are apparent in the right portion of Figure 5. There was also a main effect of valence, with a greater amplitude to negative words compared to positive words, $F(1, 41) = 4.89$, $p = .03$, generalized $\eta^2 = .04$.

Anxiety as a Covariate

For three of the primary analyses reported above, we repeated the ANOVA analyses with the Anxious Arousal subscale of the MASQ as a covariate. For the prediction of negative

⁴For this test only, analyses with data that had not had a linear de-trend applied during the data processing pipeline found a different result – the interaction was no longer significant, $F(1, 39) = 2.65$, $p = .11$, generalized $\eta^2 = .003$. A main effect of valence was also not significant, $F(1, 40) = 0.87$, $p = .36$, generalized $\eta^2 = .02$.

processing bias, the group \times valence interaction remained significant after including anxious arousal as a covariate, $F(1, 79) = 274.2, p < .001$, generalized $\eta^2 = .78$. For ERP response predicting endorsements of word stimuli, with anxious arousal as a covariate, the interaction between word valence and the voltage values remained significant, $t(77) = -2.85, p = .006$, Cohen's $d = -0.86$, 95% CI $[-1.50, -0.22]$. Finally, for the early LPP (from 400 to 600 ms) as the outcome, a significant group \times valence interaction remained when including anxious arousal as a covariate, $F(1, 39) = 7.51, p = .009$, generalized $\eta^2 = .01$.

Discussion

This study examined the electrocortical corollaries of positive and negative self-referent processing in depression using the SRET. Using a novel analytic technique, pointwise non-parametric randomized permutations, we compared significant spatiotemporal differences between MDD and healthy control groups. Our primary findings indicated that across posterior sites, beginning immediately but becoming strongest by 380 ms and increasing until the end of the analysis window (1,000 ms), MDD participants demonstrated more positive ERP amplitudes in response to negative words than positive words, whereas HC participants showed an inverse configuration. This pattern of findings may be driven by the late positive potential (LPP), which is associated with sustained attentional engagement and increased cognitive evaluation of negative material in MDD (Shestyuk & Deldin, 2010; Auerbach et al., 2015). Further, these results could not be accounted for by the presence of anxious arousal symptoms.

Findings in the current study indicate differential cortical responses between MDD and healthy controls over centroparietal sites that are generally consistent with previously observed LPP responses in MDD (Shestyuk & Deldin, 2010; Auerbach et al., 2015). As indicated in Figure 3, these effects are most evident across central and posterior sites in a time period suggestive of cognitive evaluation (i.e., from approximately 350 to 900 ms). Further, using parametric analyses, we observed a group \times valence interaction for the early portion of the LPP (400 to 600ms). The depressed group exhibited greater activity following negative versus positive words and healthy controls demonstrated the opposite pattern. This effect replicates past work (Auerbach et al., 2015), which found depression group differences for amplitudes to positive versus negative words during this same time window at the same electrode locations.

Recent research in participants with MDD has shown less positive LPP amplitudes in response to rewarding images compared to HC participants (Weinberg et al., 2016; MacNamara, Kotov, & Hajcak, 2016). Our findings of reduced LPPs in response to positive stimuli in the MDD group are consistent with these findings. Indeed, recent work indicates that MDD affects reward-processing as well as negative information-processing (Proudfit, 2014). This reduction in evaluation of reward thus fits with the RDoC concept of depression as a failure of a positive valence system (Proudfit, 2014; Cuthbert & Insel, 2013).

For the later portion of the LPP, the parametric analysis of variance revealed a main effect for group (not an interaction between stimuli condition and group), where MDD participants had more positive amplitudes to both word valences compared to healthy controls. However,

valence differences during this time period between MDD and healthy controls were captured in the pointwise non-parametric randomized permutation analyses, suggesting that approach may have been more sensitive than parametric analyses. Thus, results of the non-parametric analyses suggest that depressed individuals show greater late-stage cognitive evaluation of negative stimuli, which is consistent with prior work examining the LPP in depression.

In contrast to the findings at posterior locations, non-parametric analyses also revealed negative amplitudes in frontal and some central regions for negative versus positive words in MDD but not HC participants, with consistent differences appearing from approximately 380 ms to 866 ms. However, the functional significance of these left frontal differences is unclear. Additionally, interpretation of these frontal effects must be tempered by the fact that we did not employ recording sites over frontopolar regions.

It is possible that these negative amplitudes reflect an N2 wave (although the N2 often appears earlier in the time course). The N2 or N200 waveform is a scalp potential with negative polarity that is located in frontal and central regions and appears to be linked to error monitoring, cognitive monitoring, and response inhibition (Schmajuk, Liotti, Busse, & Woldorff, 2006; Ramautar, Kok, & Ridderinkhof, 2004). The N2 is more negative when inhibition of response is successful in a Stop-Signal task (Schmajuk et al., 2006). Given that in our data, MDD participants showed a more negative amplitude during this time-frame in response to negative words, it is possible that this reflects increased cognitive evaluation and monitoring of the correct response to these negative stimuli. It is also possible, however, that this waveform results from participants inhibiting their behavioral response on the task until they were permitted to respond. Future research will need to tease apart these competing explanations should this pattern be replicated.

Past ERP studies have also found that early attentional responses, including the P1 and P2, differentiated MDD from HC participants (Shestyuk & Deldin, 2010; Auerbach et al., 2015; Waters & Tucker, 2016). However, the current study did not find these distinctions in the nonparametric analysis, nor in parametric analysis of variance performed on time-locked waveforms, although such differences were hinted at in the waveforms seen in Figure 5. These findings indicate that there were not large differences in these stages of processing of emotional stimuli. Instead, the results of the current study seem to indicate that the primary differences between groups were evident in later, more elaborative stages of processing and cognitive evaluation. Given that we based the design of our task on past work (Auerbach et al., 2015), there were no major methodological differences that should have resulted in this lack of early attentional difference (in the P1 or P2) between groups. Thus, differences across studies could be due in part to developmental stage (adolescents in prior work versus adults in current work), symptom severity, or other factors. Future work that examines the ERP responses to the SRET in depressed samples across the lifespan could address this question directly.

In this study, behavioral data from the SRET consistently showed that participants in the MDD group but not the HC group endorsed more negative words and fewer positive words as self-descriptive compared to healthy controls. We also found a significant relationship

between the ERP responses and the behavioral results—most prior studies have not linked these levels of analysis. This relationship indicated that electrical activity within frontal, central, and posterior scalp sites across all electrodes that showed significant differences between the MDD and healthy control groups were predictive of the number of negative words endorsed—i.e., that a more positive amplitude to negative words (relative to positive words) was related to an increased endorsement of negative words. This supports the idea that the brain responses to negative stimuli found herein are associated with self-referential processing, rather than simply representing an ERP response to word valence. Moreover, this relationship falls within the negative valence system (Woody & Gibb, 2015; Cuthbert & Insel, 2013), demonstrating how electrocortical activity in MDD may be strongly connected to negative self-reference. Indeed, the increased cognitive evaluation of negative stimuli may be linked to rumination, which is common in MDD (Nolen-Hoeksema, 2000). How rumination may differ from increased cognitive evaluation bears further scrutiny in psychophysiological work with the SRET.

Although the non-parametric analytic techniques used in this study were conservative, and there are several strengths to our methods, it is important to acknowledge that our sample was relatively small, which limits our ability to detect large effects. Larger samples could also further examine the role of anxiety symptoms or other mental illness in self-referent processing, or allow us to fully explore potential gender differences in the results (although results were consistent when a covariate of gender was added). Consistent with past work, the SRET did not include an other-reference condition, focusing solely on self-reference. Given the nature of the stimuli, many of the healthy participants did not endorse many negative words, and many of the participants in the MDD group endorsed few positive words. This makes subdividing ERPs into cells by valence and self-reference difficult, due to empty cells for many participants. Including neutral words in future studies using the SRET could provide an alternative ERP difference wave model that would provide further evidence of the presence or absence of LPP differences between groups. Additionally, although this study did perform a structured diagnostic interview with participants, diagnoses were performed over the phone and not by clinicians. It is possible that inclusion in the study would have been modified slightly had participants instead been diagnosed by clinicians.

The current study is consistent with recent efforts in other areas of research to develop literatures that are robust and replicable, an effort that proves increasingly important in the current neuropsychological landscape (Munafó et al., 2017). One important aspect of this effort is for independent laboratories to conduct replications of prior work to determine whether previously observed results are consistent across settings and are robust to changes in methods or samples. The current study attempted to replicate prior findings and indeed found support for later stage cognitive evaluation of negative information in MDD. We believe that conducting additional replication studies for important clinical phenomenon is a critical direction for psychopathology research in general. Engaging in large scale, multi-site, and pre-registered collaborative studies should be central to this endeavor (Tackett et al., in press).

In summary, the current study provides evidence of increased cognitive evaluation of negative compared to positive self-referent stimuli in major depression, without evidence of

differential early attentional engagement. These results are evident both behaviorally and in later posterior ERP components thought to reflect cognitive evaluation. Negative stimuli appear to capture and sustain attention among participants with MDD to a greater degree than positive stimuli during the later stages of information processing. Importantly, brain responses during the cognitive evaluation stage were also predictive of the number of negative words endorsed, even after statistically controlling for anxiety symptoms, indicating that this component of the ERP is related to self-referential processing. Given these results, late-stage event-related potentials that support biased processing of self-referential stimuli appear to be a stable feature of depression. As such, future work should investigate whether this processing can be ameliorated through treatment. Results from the present study indicate that interventions should target later, more elaborative stages of information processing and provide important direction for identifying the brain responses that should be targeted by such treatments in major depressive disorder.

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Highlights

- Depression is associated with endorsement of negative adjectives as self-descriptive.
- ERP analyses used a whole-scalp technique and parametric analyses of variance.
- Depression is associated with greater late, posterior ERP activity to negative words.
- Sustained attention for negative stimuli may be an important target for depression interventions.

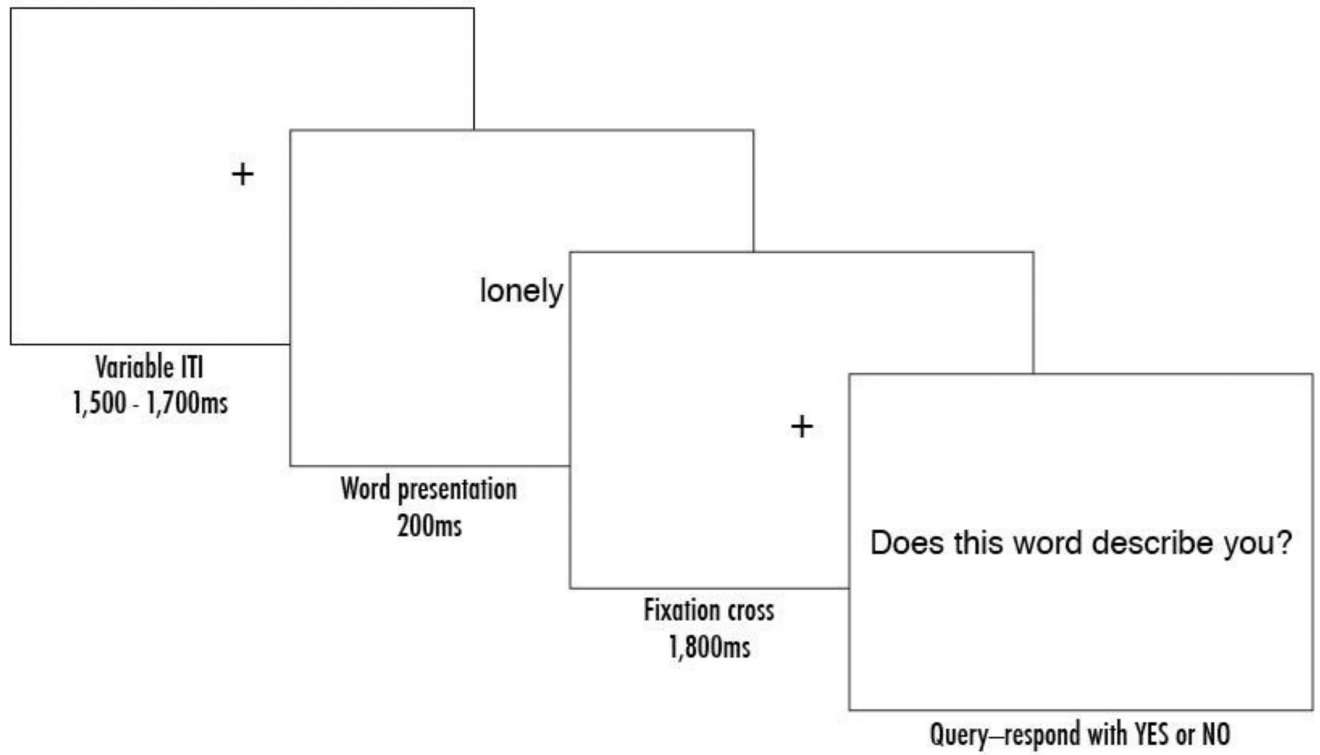


Figure 1.
The SRET (Self-Referent Encoding Task). Event-related potential epochs are based on the moment of word presentation.

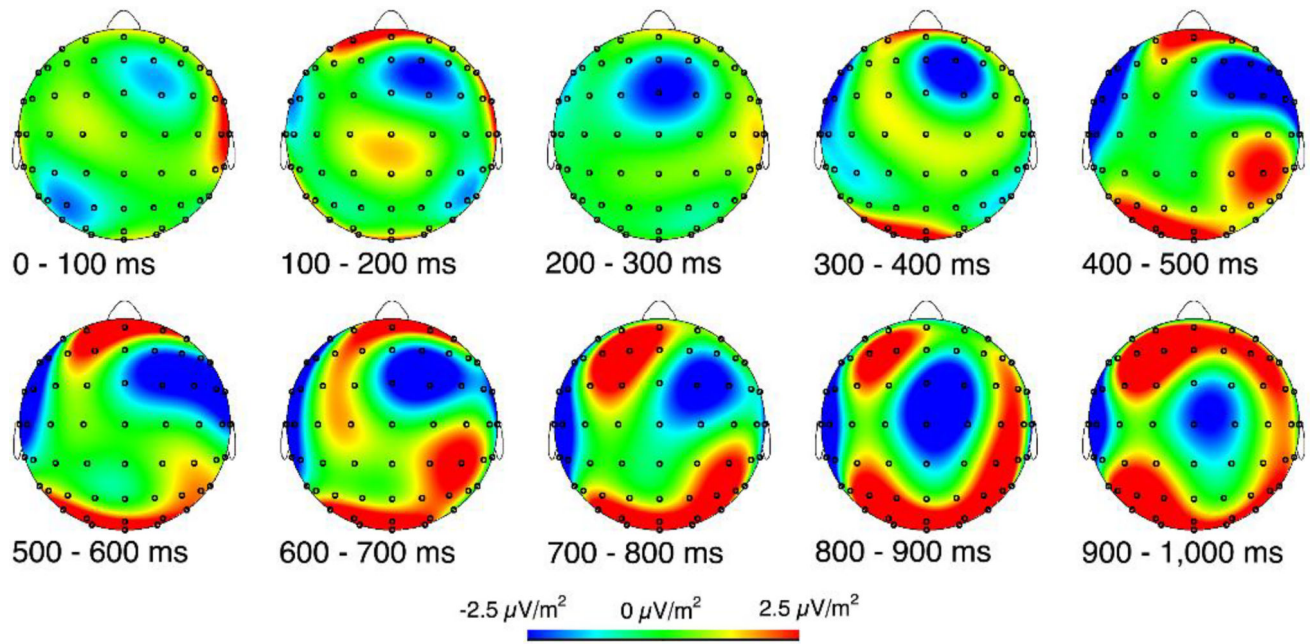


Figure 2.

Topographies from 0 to 1,000 ms, for negative minus positive, for HC minus MDD participants. Red shading indicates where the HC group showed a greater difference between negative and positive adjectives in a given spatiotemporal area; blue shading indicates where the MDD group showed a greater difference. HC = healthy control; MDD = Major Depressive Disorder.

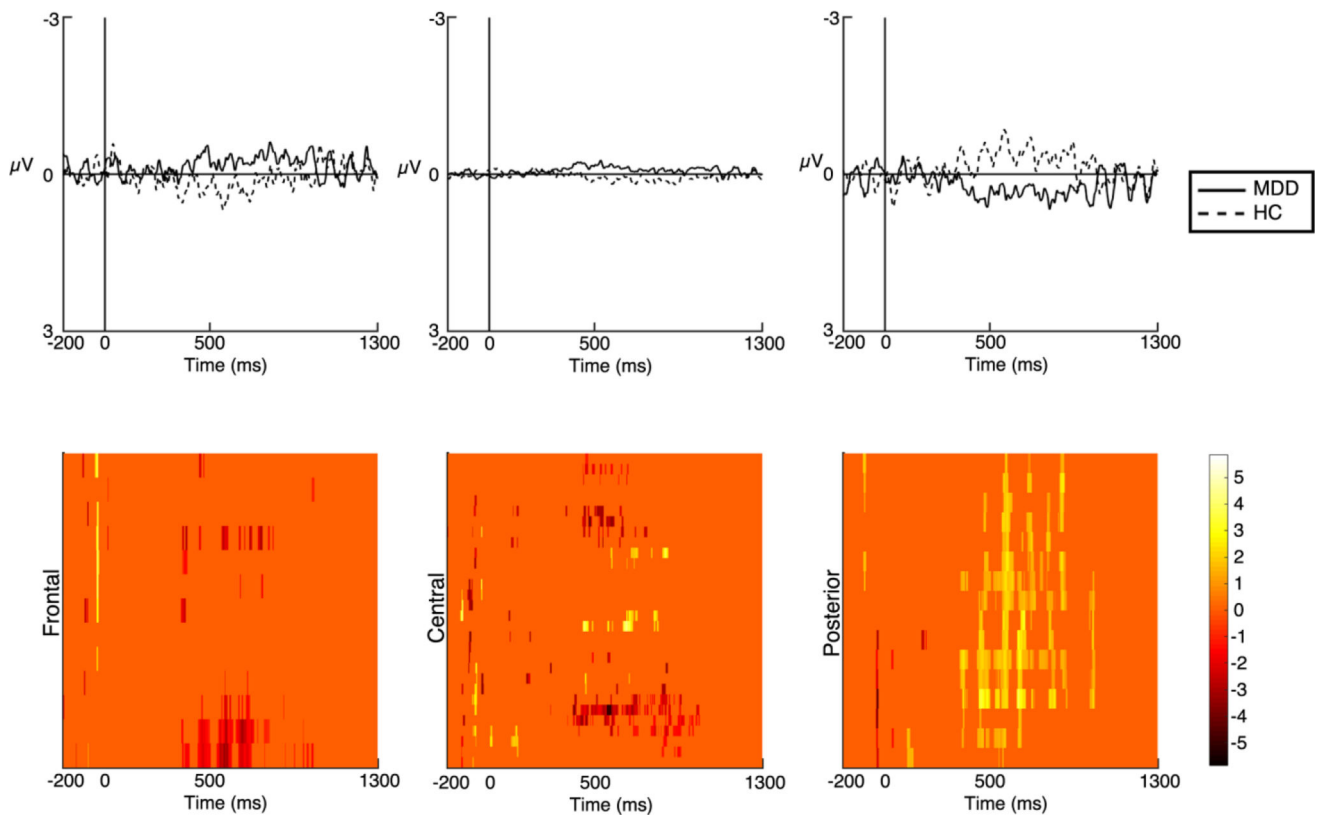


Figure 3.

Event-related potential (ERP) differences by group. Top: ERP difference waves elicited by negative minus positive words, for MDD group (solid line) and HC group (dashed line), recorded at frontal scalp sites (left), central (middle), and posterior (right). Stimulus presentation is indicated by the solid black line at time 0; negative voltage is plotted up. ERPs are averaged across the electrodes that showed statistically significant differences between groups. Bottom: Color values indicate significant ($p < .05$) t -values for clusters comparing MDD to HC groups across positive and negative images. Clusters are arrayed by time (x-axis) and by laterality (y-axis, with left at the bottom and right on the top). Orange (primary shading) indicates no significant spatiotemporal difference; darker colors indicate that the MDD group showed a more negative waveform, and lighter that the MDD group showed a more positive waveform.

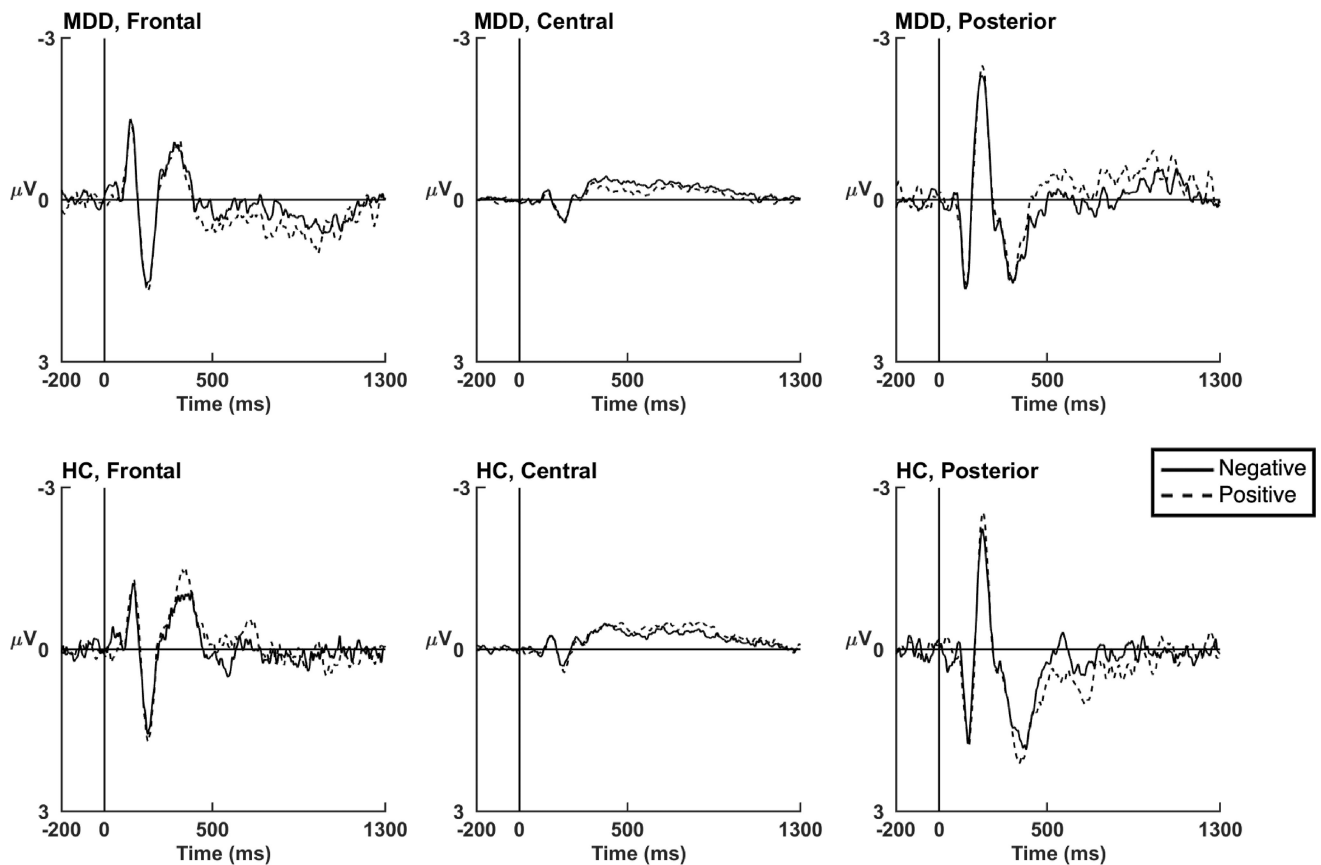


Figure 4.

Average Event-Related Potentials for each group, collapsed across regional electrode sites that were significantly different in the permutations tests; negative is plotted upwards. Any electrode that showed significant differences in the permutations tests is included in its regional average. The solid line shows negative words and the dashed line positive words; difference waves for permutations tests were calculated as negative minus positive. The MDD group is in the top row, and HC in the bottom row; plots show grand averages across subjects in that group, for significant electrode sites in that region. In frontal and central sites, the MDD group on average shows a more negative amplitude towards negative words, whereas the HC group shows a more negative amplitude towards positive words. In posterior sites, the trend is reversed; MDD shows a more positive amplitude trend towards negative words, whereas the HC group shows a more positive amplitude trend towards positive words.

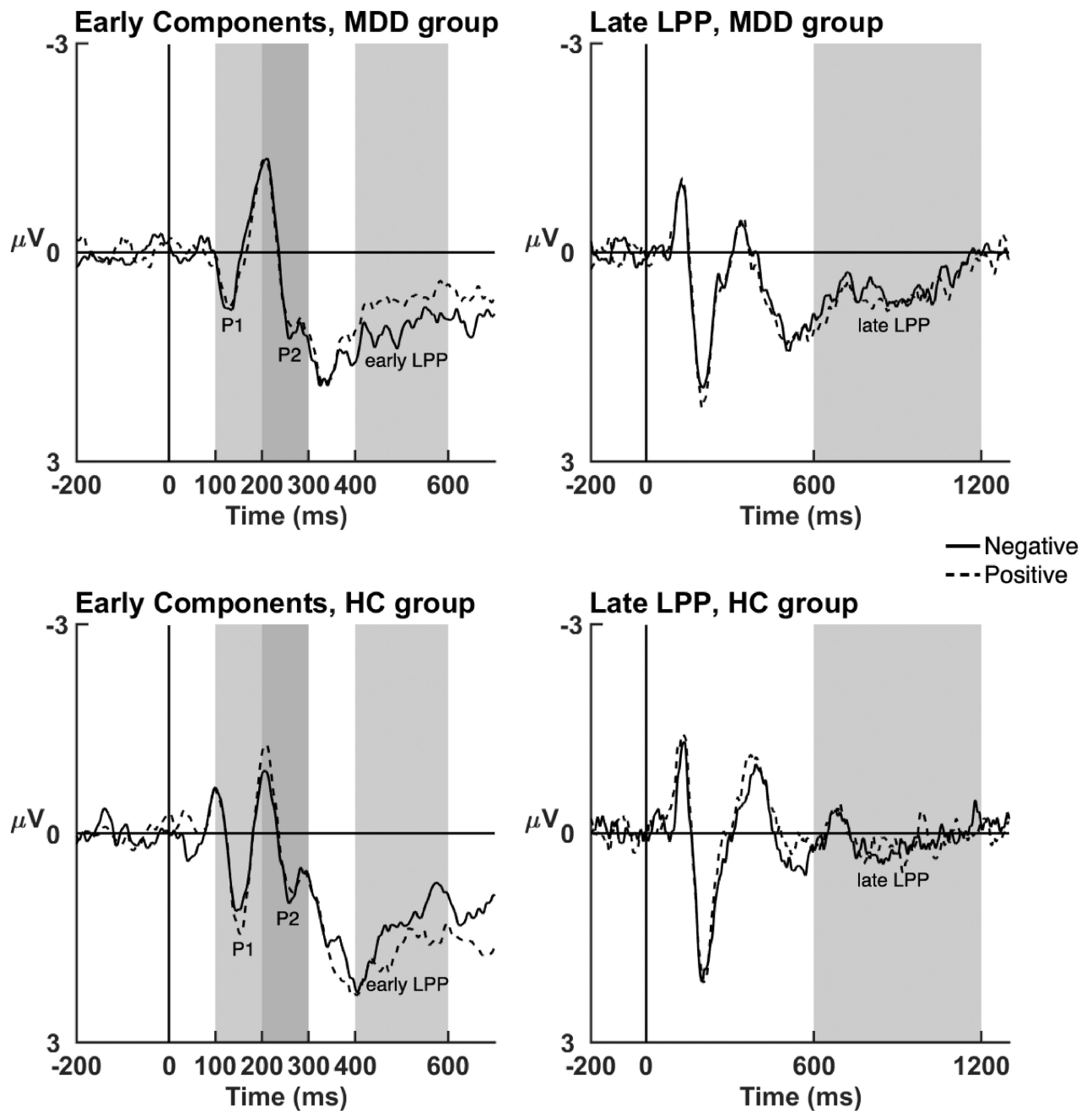


Figure 5.

Parametric event-related potential components compared between groups. Negative is plotted upwards. The solid line shows negative words and the dashed line positive words. Shaded regions indicate the time-frame for the labeled waveforms. Early attentional components (at left; as indicated, P1, P2, and early LPP) are shown from 200 ms before stimulus presentation to 700 ms following, and are averages across Pz, POz, P1, P2, PO3, and PO4. The late LPP can be seen at right; the waveform is plotted from 200 ms before

stimulus presentation to 1,300 ms following, and is an average across Fz, FCz, and Cz. The MDD group is shown at the top, and the HC group at the bottom.

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Table 1

Characteristics of participants included as healthy controls (HC) and diagnosed as depressed (MDD).

	HC (N = 23)	MDD (N = 21)
Age, mean (<i>SD</i>)	25.3 (7.9)	24.6 (6.7)
Female	15 (65%)	16 (76%) ⁵
White	13 (57%)	10 (48%)
Hispanic	6 (26%)	10 (48%)
Psychiatric Medication		
None	22	15
Current medication usage	1 ⁶	6
Current SSRI, for > 10 weeks	1	4
Other antidepressant	0	2
Anti-anxiety medication	0	1
CESD, mean (<i>SD</i>)	4.9 (5.2)	34.7 (7.93)
MASQ, Anxious Arousal subscale	11.3 (2.0)	19.6 (6.1)
MASQ, General Distress subscale	13.9 (4.2)	32.3 (8.3)
MASQ, Anhedonic Depression subscale	24.2 (6.4)	40.5 (5.6)

⁵One participant in this group identified as agender.

⁶This participant reported long-term medication usage, but otherwise met inclusion criteria. Analyses were conducted without this participant and showed no significant differences.

Table 2

Behavioral data for the Self-Referential Encoding Task.

	HC		MDD	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Positive Processing Bias	0.92	0.091	0.45	0.16
Negative Processing Bias	0.084	0.091	0.55	0.16
Positive Words Endorsed	25.30	6.27	14.84	5.23
Negative Words Endorsed	2.09	2.19	18.89	6.99
Positive Recall	9.78	3.81	7.79	2.86
Negative Recall	6.00	3.19	8.63	3.62
Self-Referential Positive Recall	6.74	3.26	3.32	1.92
Self-Referential Negative Recall	0.78	1.00	4.37	2.61
Positive RT	409.5	183	506.4	274
Negative RT	400.9	169	497.7	272

Number of positive and negative words endorsed are sums; processing biases are ratios calculated as the number of positive/negative words endorsed over the total number of words endorsed. Recall is the number of words of that valence recalled; self-referential recall only includes words that were endorsed during the task. HC = healthy control; MDD = Major Depressive Disorder; RT = reaction time.