Research paper

Ketamine Alters Electrophysiological Responses to Emotional Faces in Major Depressive Disorder

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ABSTRACT

Background: The glutamatergic modulator ketamine rapidly reduces depressive symptoms in individuals with treatment-resistant major depressive disorder (MDD). However, ketamine's effects on emotional processing biases remain largely unknown, and understanding these processes may help elucidate ketamine's mechanism of action.

Methods: Magnetoencephalography (MEG) was used to investigate ketamine's effects on early visual responses to affective stimuli in individuals with MDD ($n = 31$) and healthy volunteers (HVs; $n = 24$). Participants were enrolled in a double-blind, placebo-controlled, crossover clinical trial and were assessed at baseline and after subanesthetic-dose ketamine and placebo-saline infusions. During MEG recording, participants completed an emotional evaluation task in which they indicated the sex or emotional valence (happy-neutral or sad-angry) of facial stimuli. Source-localized event-related field (ERF) M100 and M170 amplitudes and latencies were extracted from regions of interest. Linear fixed effects models examined interactions between diagnosis, stimulus valence, and drug session for behavioral and MEG data.

Results: In baseline behavioral analyses, MDD participants exhibited higher accuracy for sad-angry than happy-neutral faces, and HVs responded faster to happy-neutral than sad-angry faces. In the MEG post-infusion analyses, calcarine M100 amplitudes were larger in MDD than HV participants post-placebo but became more similar post-ketamine. Finally, fusiform M170 amplitudes were associated with antidepressant response in MDD participants.

Limitations: The modest sample size and the need to collapse across responses to happy and neutral faces to increase statistical power limit the generalizability of the findings.

Conclusions: Ketamine rapidly altered emotional stimulus processing in MDD, laying the groundwork for future investigations of biomarkers of antidepressant treatment response.

Clinical Trial: Clinicaltrials.gov, NCT#00088699

Introduction

Traditional antidepressant medications, which primarily target serotonergic and noradrenergic monoamine receptors, typically take weeks to reduce depressive symptoms, and many individuals do not respond to treatment (Bourin et al., 2002; Stahl, 1998). In contrast, the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has been shown to reduce depressive symptoms and suicidal ideation in individuals with treatment-resistant depression within 24 hours, with repeated administration producing a sustained response (Ballard et al., 2014; Berman et al., 2000; Diazgranados et al., 2010; Duman and Aghajanian, 2012; Fava et al., 2020; Murrough et al., 2013; Nugent et al., 2019; Phillips et al., 2019; Zarate et al., 2006). Ketamine's antidepressant effects are thought to arise from a glutamate surge (Moghaddam et al., 1997) that activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Zanos et al., 2016),

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ultimately leading to activation of pathways associated with synaptogenesis and synaptic potentiation (Duman et al., 2019; Liu et al., 2012). The growing body of clinical evidence demonstrating ketamine's rapid-acting antidepressant effects culminated in the 2019 approval of its isomer esketamine by the United States Food and Drug Administration and the European Commission for use in adults with treatment-resistant depression. Despite its clinical efficacy, the extent to which ketamine influences affective stimulus processing in individuals with depression remains unclear.

Studies have found that individuals with major depressive disorder (MDD) demonstrate attentional biases toward negative stimuli and away from positive stimuli (Fritzsche et al., 2010; Gotlib et al., 2004; Leyman et al., 2007) and that MDD participants classify happy—but not sad—facial stimuli less accurately than healthy volunteers (HVs) (Auerbach et al., 2015). Attentional biases are also thought to increase vulnerability to depression (Gotlib and Krasnoperova, 1998) as well as likelihood of relapse (Bouhuys et al., 1999). Nevertheless, mixed findings for negative processing biases in depression persist (Asthana et al., 1998; Bourke et al., 2010; Cheng et al., 2015; Persad and Polivy, 1993). Thus, investigating the neural correlates of emotional processing may help elucidate the mechanisms underlying depression and treatment response.

In this context, neural correlates of emotional face processing in depression have been studied extensively using functional magnetic resonance imaging (fMRI). Numerous fMRI studies in MDD participants found hyperactivation in the blood-oxygen-level-dependent (BOLD) response to emotional negative faces and hypoactivation to positive faces compared to HVs, particularly in limbic regions such as the amygdala and insula and face-sensitive regions such as the fusiform gyrus (Arnone et al., 2012; Sturhmann et al., 2011; Surguladze et al., 2005; Suslow et al., 2010; Victor et al., 2010). Findings in the prefrontal cortex and anterior cingulate cortex are more variable, with both hyper- and hypoactivation to negative faces being reported in MDD depending on the study (Gotlib et al., 2005; Jaworska et al., 2015; Keedwell et al., 2005; Sturhmann et al., 2011; Zhong et al., 2011). While robust fMRI evidence exists for limbic and fusiform hyperactivation to negative faces in MDD, the sluggish hemodynamic response is not ideal for addressing the question of whether emotional processing biases emerge early in visual processing soon after stimulus onset.

To address this question, electroencephalography (EEG) and magnetoencephalography (MEG) can be used to detect precise temporal characteristics of early visual processing of emotional face stimuli. One commonly studied electrophysiological response to faces is an occipital response peaking around 100 ms post-stimulus (P100 in EEG, M100 in MEG) (Hari and Puce, 2017; Luck and Kappenman, 2011). Studies found that P/M100 amplitudes in MDD participants were greater in response to negative emotional faces than happy and/or neutral faces (Dai and Feng, 2012; Dai et al., 2011; Ruohonen et al., 2020; Zhang et al., 2016) and that amplitudes were smaller in response to happy than neutral faces (Zhang et al., 2016). Some studies have found the reverse pattern in HVs, with larger P100 amplitudes in response to happy faces and smaller amplitudes in response to sad faces compared to neutral (Zhang et al., 2016); however, other studies also found that P100 did not vary by emotional valence in HVs (Ruohonen et al., 2020). With regard to comparisons between groups, individuals with MDD appear to have larger P100 amplitudes than HVs in response to sad faces (Dai et al., 2011) as well as to facial stimuli regardless of valence (Zhao et al., 2015). Other studies also found that M100 amplitude did not differ by emotional valence or between individuals with MDD and HVs (Xu et al., 2018). Although additional research is needed, these results provide preliminary evidence that responses as early as P/M100 may index an early visual processing bias to negative stimuli in depression.

The face-sensitive N/M170 electrophysiological response localized to the fusiform cortex occurs after the P/M100 and reflects processing of higher-level characteristics of facial stimuli (Hari and Puce, 2017;

Luck and Kappenman, 2011). While the effect of emotional valence on the N/M170 response has been studied more often in MDD than earlier components, findings are mixed. Some studies supporting a negative bias in depression found greater N170 amplitudes in response to sad faces in MDD participants than in HVs and the reverse pattern for happy faces (Chen et al., 2014; Wu et al., 2016). Similarly, Zhang and colleagues (2016) found greater N170 amplitudes for happy than sad faces in HVs, while MDD participants did not display this positive bias. In contrast, Xu and colleagues (2018) found greater amplitudes in response to sad than happy faces in both HVs and depressed participants, and Ruohonen and colleagues (2020) found the opposite result. An additional study found smaller N170 amplitudes in depressed individuals than in HVs with no valence effects (Dai and Feng, 2012). Taken together, the literature paints a convoluted picture of whether negative bias can be reliably detected in early brain responses to emotional faces in MDD. These inconsistencies may be partly due to the effects of psychiatric medications, clinical heterogeneity, and the frequent use of sensor-based MEG/EEG analyses that may average signals from multiple brain sources.

With regard to ketamine in particular, it remains unknown whether this rapid-acting antidepressant can alter early visual responses to affective stimuli in MDD. fMRI studies of MDD participants suggested that ketamine may alter BOLD activation to emotional stimuli in regions such as the anterior cingulate cortex, medial prefrontal cortex (Reed et al., 2018; Reed et al., 2019), and caudate (Murrough et al., 2015) to resemble the activation patterns of HVs. To our knowledge, no studies to date have investigated rapid changes in electrophysiological responses to emotional faces in MDD post-ketamine infusion. However, preliminary evidence suggests that ketamine may alter MEG-based primary somatosensory responses, particularly in participants with MDD who exhibit an antidepressant response (Cornwell et al., 2012; Nugent et al., 2019).

This placebo-controlled clinical trial examined ketamine's impact on MEG event-related fields (ERFs) in response to emotional stimuli in individuals with MDD and HVs. Because MEG has both superior temporal resolution to fMRI and superior spatial resolution to EEG, it is ideal for examining the early stages of emotional face processing in MDD. All participants were unmedicated prior to ketamine infusions, and source localization techniques were used to isolate activity occurring in distinct brain regions. Given the study's focus on ketamine's impact on early visual responses to emotional stimuli, selected neural regions for analysis included calcarine, occipital, and fusiform areas (Furey et al., 2006; Gao et al., 2013; Liu et al., 2002; Perry and Singh, 2014). The study had three main hypotheses. First, we predicted that MDD participants at baseline would display negative processing biases at the behavioral (Auerbach et al., 2015; Fritzsche et al., 2010; Gotlib et al., 2004) and electrophysiological (Chen et al., 2014; Wu et al., 2016; Zhang et al., 2016) levels, such as higher accuracy rates, faster reaction times, larger ERF amplitudes, and shorter ERF latencies to negatively valenced facial stimuli compared to happy and neutral stimuli and compared to HVs. Second, based on evidence from our two prior fMRI studies (Reed et al., 2018; Reed et al., 2019), we predicted that ketamine would exert differential effects on behavioral and M100 and M170 ERF responses to emotional faces in MDD and HV participants and thus normalize depression-specific emotional processing biases. Third, we predicted that post-ketamine ERFs to emotional faces in MDD would be associated with magnitude of treatment response.

Methods

Participants

This study included data from 55 participants, including 31 individuals with MDD and 24 HVs. All participants were 18-65 years old and had no history of serious medical or neurological illness.

Participants were enrolled in an inpatient-based clinical trial (NCT#00088699) at the National Institutes of Health (NIH) and provided written informed consent prior to study onset. The NIH Combined Neuroscience Institutional Review Board approved all study procedures.

MDD diagnoses were confirmed using the Structured Clinical Interview for DSM-IV-TR Disorders (First et al., 2002a and 2002b). MDD participants were treatment-resistant (defined as a lack of response to an adequate trial of at least one antidepressant medication), had an age of illness onset earlier than 40 years, and had a minimum score of 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). MDD participants had no history of drug or alcohol dependence or abuse (except for nicotine or caffeine) within the last three months and no psychotic symptoms. HVs had no personal or first-degree relative history of psychiatric disorders and no history of drug or alcohol abuse; additional inclusion/exclusion criteria can be found in the Supplement.

Study design

All participants were enrolled in a randomized, double-blind, placebo-controlled, crossover clinical trial investigating the antidepressant ketamine (NCT#00088699). Full details regarding research procedures have previously been published (Nugent et al., 2019). Individuals with MDD were tapered off of any psychotropic medications and underwent a drug-free period of at least two weeks (five weeks for fluoxetine), followed by baseline clinical assessments and MEG recording. Participants were then randomized to receive an intravenous infusion of either subanesthetic-dose ketamine (0.5 mg/kg over 40 minutes) or placebo saline. After a two-week period, participants crossed over to the other treatment condition; MDD participants only crossed over if they had a minimum MADRS score of 20 preceding the second infusion. The present analyses focus on three MEG recordings collected at baseline and six to nine hours after ketamine and placebo infusions (see Supplement for additional information). Fifty-five participants had baseline recordings (31 MDD, 24 HV), 45 had post-ketamine recordings (25 MDD, 20 HV), and 40 had post-placebo recordings (22 MDD, 18 HV).

Emotional evaluation task

Participants were told that they would be viewing emotional faces on a projector screen during MEG recording (Fig. 1). In the explicit task condition, participants were asked to press the left button of a button box when they saw a face with a happy or neutral emotional expression (referred to as the "happy-neutral" condition) and to press the right button when they saw a face with a sad or angry emotional expression (referred to as the "sad-angry" condition). In the implicit task condition, participants were asked to press the left button for male faces and the right button for female faces. The task consisted of 130 randomized trials, including two explicit task blocks and two implicit task blocks with 32 or 33 trials per block. Facial stimuli were selected from standardized emotional face databases (Langner et al., 2010; Lundqvist et al., 1998; Tottenham et al., 2009), and unique stimuli were used at each session. Stimuli had an even distribution of happy, neutral, sad, and angry facial expressions. Half of the stimuli were presented in an upright orientation and half were presented in an inverted orientation to increase task difficulty. Each face was presented for 750 ms followed by a 2.5 second fixation period.

MEG data acquisition and processing

Data were acquired using a CTF MEG system (CTF Systems, Inc., Canada) comprising a whole-head array of 275 radial first-order gradiometer/SQUID channels housed in a magnetically shielded room. Synthetic third-gradient balancing was used to remove background noise online. Data were sampled at 1200 Hz with a quarter-Nyquist

hardware filter of 0-300 Hz. Sensors were placed on participants at three fiducial points (nasion, left and right preauricular) for co-registration of the MEG data to structural MRIs. Preprocessing of MEG data was conducted using the CTF software DataEditor. After placing event markers at stimulus onsets, data were high-pass filtered using a zero-phase lag Butterworth filter at 0.61 Hz and notch-filtered at 60 Hz. Next, trials contaminated with artifacts were manually excluded from analysis.

MRI data acquisition and processing

Anatomical T1 weighted 1 mm resolution MRI images were acquired on a 3-Tesla General Electric HDx scanner (GE Signa, Milwaukee, WI) using an eight-channel head coil. Radiology markers were placed on participants' preauricular points and nasion prior to entering the scanner for co-registration. Anatomical images were preprocessed in Analysis of Functional NeuroImages (AFNI; Cox, 1996) to create head models and register anatomical images to Talairach space.

MEG source localization

Synthetic aperture magnetometry (SAM) was used to localize MEG ERFs to source space (Robinson and Vrba, 1999). Time series were bandpass filtered from 1-30 Hz for beamformer weight calculation. Data from each trial were projected by those weights onto a grid of 5 mm voxels and downsampled to a time step of 3 ms. For each voxel and participant, time series for each stimulus type were averaged to generate ERFs. Data were then transformed into Talairach space using AFNI. Regions of interest (ROIs) selected for analysis included the calcarine, bilateral middle occipital, and bilateral fusiform regions. Anatomical ROIs for these five regions were used from the Eikhoff-Zilles atlas distributed with AFNI software. For each participant, evoked responses were squared to make all values positive due to the ambiguous polarity of the beamformed signals and then averaged over each ROI. To determine the time window for measurement of participant-level ERFs, grand averages were created by averaging the evoked responses for all sessions, conditions, and participants within each ROI. Peak amplitudes and latencies for each ROI, participant, session, and condition were identified as the maximal ERF value within a time window of 24 ms (or eight time steps) before and after the grand average peak latency. Individual participant ROIs without peaks in the time window, or peaks occurring at the edge of the window, were excluded from subsequent analyses. The time window was determined as a trade-off between including participants but not overlapping with other peaks.

Statistical analysis

Statistical analyses were performed in SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). First, independent samples t-tests and chi-square tests were conducted to compare demographic variables between diagnostic groups. Next, linear fixed effects models were used to investigate behavioral and neural emotional face processing differences between MDD and HV participants at baseline and post-infusions. Because the baseline timepoint was potentially confounded by novelty effects to both the task and the MEG environment, baseline data were analyzed in separate models from the post-infusion data. Sessions with task accuracy rates below 50% were excluded from all analyses.

Separate linear fixed effects models predicted behavioral outcome variables of percent accuracy and reaction time in seconds and MEG outcome variables of log-transformed ERF peak amplitudes and ERF peak latencies independently for the five ROIs (calcarine, bilateral middle occipital, bilateral fusiform). In all models, predictors included fixed effects of diagnosis (MDD, HV), stimulus valence (happy-neutral faces, sad-angry faces), and stimulus orientation (upright, inverted). For treatment analyses, an additional fixed effect of drug session (post-ketamine, post-placebo) was included. For behavioral models, a fixed
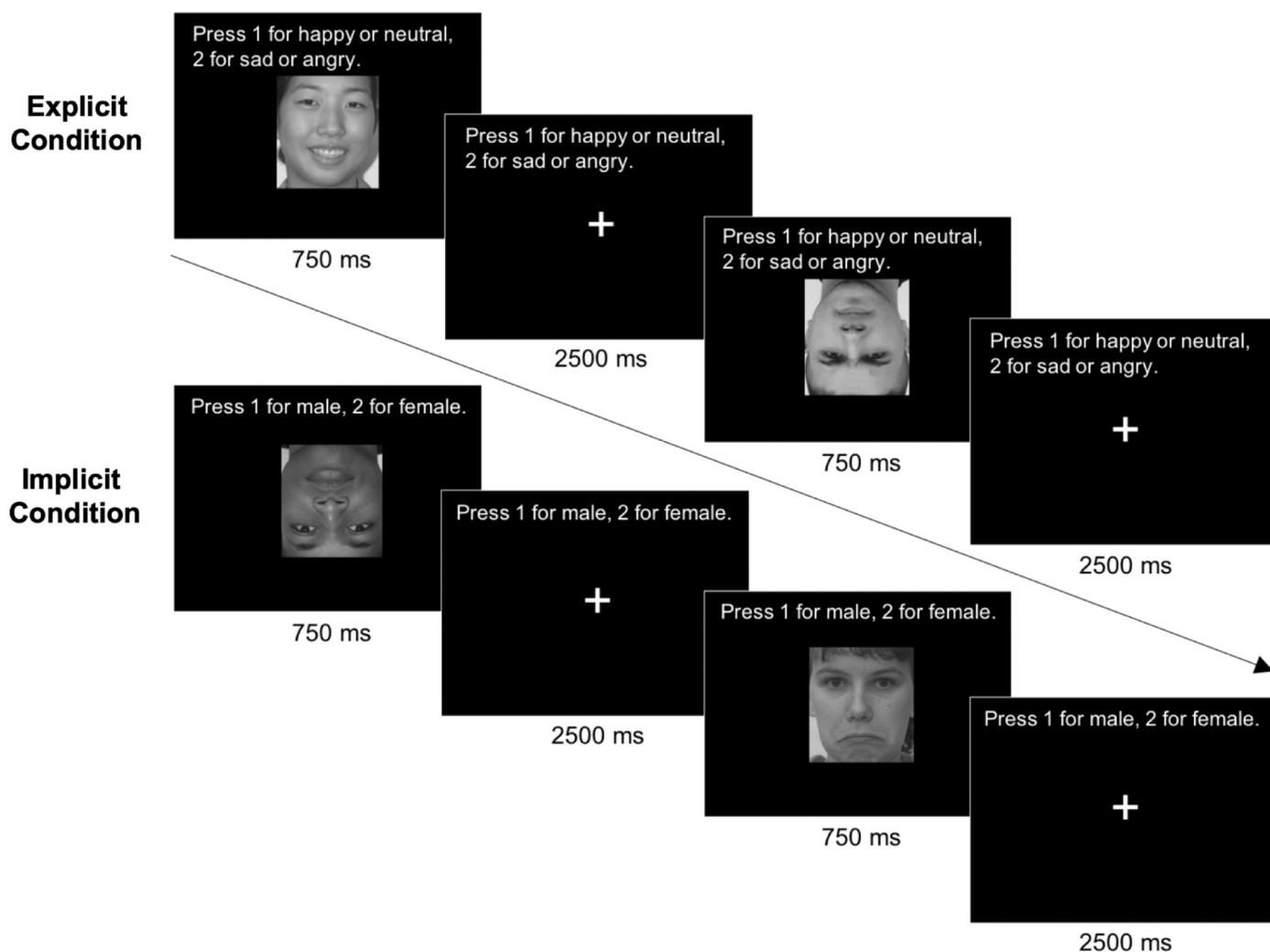
Emotional Evaluation Task

Fig. 1. Schematic representation of example trials from the emotional evaluation task designed in E-Prime software. Participants completed two blocks of each task condition in which they were shown emotional faces and asked to either identify the emotional valence (happy-neutral or sad-angry; explicit condition) or sex (male or female; implicit condition). Figure adapted from Reed et al. (2019), Supplement.

effect of task condition was also included (implicit, explicit). In order to achieve adequate statistical power, trials were collapsed across task conditions for the MEG analysis and across specific emotions within each valence category (happy-neutral and sad-angry) for the MEG and behavioral analyses.

Model interactions of primary interest were those between diagnosis, valence, and drug effects; interactions with a factor of task condition were also conducted in behavioral models to test the specificity of findings. For each model, a compound symmetry or unstructured covariance structure, with or without group estimation, was selected based on best fit. F-tests were considered statistically significant at a threshold of $p < .05$ for behavioral analyses and $p < .01$ for MEG analyses to correct for multiple comparisons over the five ROIs. False discovery rate (FDR)-corrected post-hoc tests ($p_{FDR} < .05$) were conducted for significant interactions.

Follow-up analyses were conducted to test the hypothesis that antidepressant response would relate to post-ketamine neural response to emotional faces. Antidepressant response was calculated as percent change in MADRS score from baseline (60 minutes pre-infusion) to Day 1 (24 hours) post-ketamine infusion. Linear fixed effects models in the MDD group were conducted for ROIs that exhibited significant drug

effects on ERF amplitude or latency with mean-centered MADRS percent change as a covariate. Main effects modeled included orientation, valence, drug, and MADRS change, and interactions modeled included MADRS*drug and MADRS*drug*valence. For interactions significant at a threshold of $p < .05$, post-hoc tests were conducted for the slope of the amplitude or latency versus change in MADRS score at each drug session and for each valence.

Results

Participants

Task accuracy rates below 50% resulted in the exclusion of one HV baseline recording, one MDD post-ketamine recording, and two HV post-ketamine recordings (see Table 1 for final sample sizes per time-point). MDD and HV groups did not significantly differ based on age (t (53) = 1.05, $p = .299$), sex ($\chi^2(1) = 0.05$, $p = .824$), or race/ethnicity ($\chi^2(3) = 1.9$, $p = .593$) (Table 1). Groups also did not differ based on infusion order ($\chi^2(1) = 0.04$, $p = 1$). The MDD group had not responded to an average of six antidepressant trials and had an average baseline MADRS score of 33.29. For additional information regarding infusion

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Table 1
Participant demographics and clinical symptom scores.

	HV	MDD
N		
Total	24	31
Baseline	23	31
Ketamine	18	24
Placebo	18	22
Age, years	32.96 (10.21)	35.77 (9.61)
Sex (F/M)	14/10	19/12
Race/ethnicity[a]		
Asian	1	1
Black	4	2
Caucasian	16	26
Hispanic	2	2
MADRS total		
Baseline	1.3 (1.4) [range: 0-4]	33.29 (4.98) [range 24-41]
Post-ketamine Day 1	2.57 (3.84) [range 0-16]	23.9 (11.28) [range 2-43]
Post-placebo Day 1	0.74 (1.2) [range 0-4]	31.1 (5.58) [range 14-40]

Values are presented as mean (standard deviation). Abbreviations: HV: healthy volunteer; MDD: major depressive disorder; F: female; M: male; MADRS: Montgomery-Åsberg Depression Rating Scale. [a]Data missing for one HV participant.

randomization and antidepressant response rates, see Supplementary material and Supplementary Figure S1.

Baseline behavioral results

Baseline behavioral analyses for reaction time revealed that all participants responded faster to upright than inverted faces ($F(1,48.7) = 56.05$, $p < .001$) and to stimuli in the implicit versus the explicit condition ($F(1,47.6) = 54.23$, $p < .001$). There was a diagnosis*valence interaction ($F(1,52) = 4.18$, $p = .046$) as well as a diagnosis*valence*task interaction ($F(1,51.6) = 6.43$, $p = .014$) (Fig. 2A). Post-hoc tests for the diagnosis*valence interaction showed that HVs had faster reaction times to happy-neutral compared to sad-angry stimuli ($p_{FDR} = .031$), and post-hoc tests for the three-way interaction revealed that this was particularly evident in the explicit condition ($p_{FDR} = .024$).

Similarly, all participants had higher accuracy rates in response to upright than inverted faces ($F(1,53) = 45.96$, $p < .001$) and to stimuli in the implicit condition than the explicit condition ($F(1,40.7) = 34.84$, $p < .001$). Overall, MDD participants exhibited higher accuracy than HVs ($F(1,33.4) = 16.82$, $p < .001$). There was again both a diagnosis*valence interaction ($F(1,38.4) = 9.91$, $p = .003$) as well as a diagnosis*valence*task interaction ($F(1,44.9) = 7.29$, $p = .01$) (Fig. 2B). For the diagnosis*valence interaction, post-hoc analyses revealed that MDD participants responded more accurately to sad-angry than happy-neutral faces ($p_{FDR} = .001$) as well as more accurately than HVs for sad-angry faces ($p_{FDR} < .001$). Post-hoc tests for the three-way interaction showed that MDD participants responded more accurately to sad-angry than happy-neutral faces specifically in the explicit emotion condition ($p_{FDR} = .002$) and responded more accurately than HVs in all conditions except the happy-neutral explicit emotion condition. Exploratory follow-up analyses in the explicit emotion condition based on a limited number of trials suggested that: 1) MDD participants identified neutral faces less accurately than the other three emotions; and 2) MDD participants more accurately identified sad and angry faces than HVs, though the groups had similar accuracy rates for happy and neutral faces (Supplementary Figure S2).

Ketamine vs. placebo behavioral results

Post-infusion behavioral analyses for reaction time showed that all participants responded more quickly to upright than inverted faces ($F(1,596) = 48.99$, $p < .001$), to happy-neutral than sad-angry faces (F

($1,596) = 31.22$, $p < .001$), and in the implicit versus the explicit task condition ($F(1,596) = 49.74$, $p < .001$). A significant diagnosis*drug interaction was observed for reaction time ($F(1,600) = 18.13$, $p < .001$) (Fig. 2C). Specifically, post-hoc tests indicated that MDD participants had slower reaction times post-ketamine than post-placebo ($p_{FDR} = .018$), whereas HVs showed the reverse pattern ($p_{FDR} = .003$).

Similar to the reaction time findings, results from the accuracy analyses showed that all participants responded more accurately to upright than inverted faces ($F(1,597) = 93.31$, $p < .001$), to happy-neutral than sad-angry faces ($F(1,597) = 109.85$, $p < .001$), and to the implicit versus the explicit task condition ($F(1,597) = 55.03$, $p < .001$). Aligning with the baseline findings, a significant main effect of diagnosis indicated overall higher accuracy rates in MDD participants than in HVs ($F(1,44) = 4.29$, $p = .044$). Post-hoc tests from a significant diagnosis*drug interaction ($F(1,626) = 8.11$, $p = .005$; Fig. 2D) showed that MDD participants were more accurate than HVs post-placebo ($p_{FDR} = .012$). Finally, a diagnosis*valence*task interaction was observed ($F(2,597) = 10.35$, $p < .001$), with post-hoc tests indicating that accuracy rates were higher for the implicit than the explicit condition with the exception of HVs and happy-neutral faces (Fig. 2E).

Grand average ERF peak timing

The grand average ERF peak in the calcarine region occurred at 103 ms, corresponding with the M100 response. The remaining grand average ERFs corresponded with the M170 response, peaking at 145 ms and 133 ms in the left and right middle occipital lobe, respectively, and at 148 ms and 145 ms in the left and right fusiform area, respectively.

Baseline MEG results

Significant main effects were observed for stimulus orientation at baseline. Specifically, M170 amplitudes in the left middle occipital cortex were greater for inverted than upright faces ($F(1,106) = 8.13$, $p = .005$), and M170 latencies in the right fusiform were longer for inverted than upright faces ($F(1,130) = 17.98$, $p < .001$). No other effects were significant for any of the ROIs.

Ketamine vs. placebo MEG results

In the MEG post-infusion analyses, a significant diagnosis*drug interaction was observed for M100 amplitude in the calcarine region ($F(1,24.4) = 9.37$, $p = .005$) (Fig. 3A). Post-hoc tests revealed that MDD participants had greater peak amplitudes than HVs post-placebo ($p_{FDR} = .038$), and that HVs exhibited greater amplitudes post-ketamine than post-placebo ($p_{FDR} = .025$).

In the left middle occipital cortex (Fig. 3B), a significant diagnosis*valence interaction was noted for M170 latency ($F(1,20.1) = 18.02$, $p < .001$). Post-hoc tests showed that MDD participants had shorter latencies to happy-neutral than sad-angry faces ($p_{FDR} = .006$), and that MDD participants had shorter latencies to happy-neutral faces than HVs ($p_{FDR} = .047$). In the right middle occipital cortex (Fig. 3C), participants overall had greater M170 amplitudes in response to sad-angry than happy-neutral stimuli ($F(1,21) = 8.9$, $p = .007$).

In the left fusiform region (Fig. 4A), participants overall had larger M170 amplitudes post-ketamine than post-placebo ($F(1,210) = 13.33$, $p < .001$). In the right fusiform region, a diagnosis*drug interaction was observed for M170 amplitude ($F(1,34.3) = 7.69$, $p = .009$; Fig. 4B), but post-hoc tests were not significant after FDR correction.

MEG ERF relationship to antidepressant response in MDD participants

Follow-up linear fixed effects models with a MADRS percent change covariate were conducted in the MDD group for the regions with significant drug effects described above (calcarine amplitudes, left middle occipital latencies, bilateral fusiform amplitudes). No significant

Baseline Behavioral Results
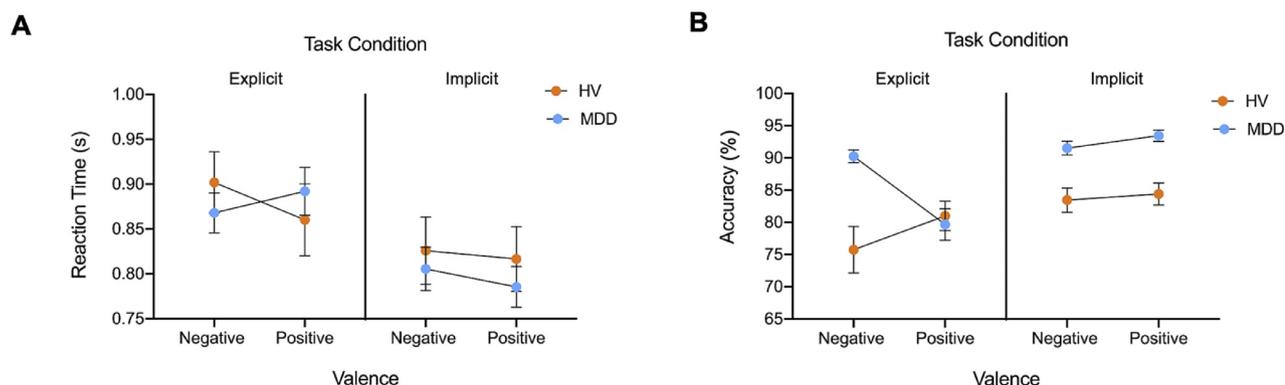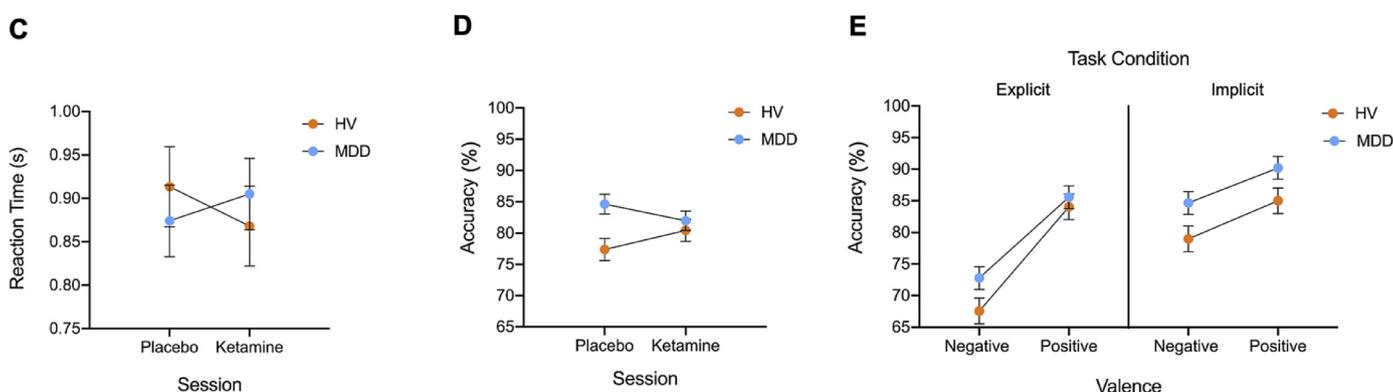

Ketamine vs. Placebo Behavioral Results

Fig. 2. Behavioral results illustrated by plots of marginal means from the linear fixed effects models. **A)** Diagnosis*valence*task interaction for baseline reaction time. **B)** Diagnosis*valence*task interaction for baseline percent accuracy. **C)** Diagnosis*session interaction for ketamine vs. placebo reaction time. **D)** Diagnosis*session interaction for ketamine vs. placebo percent accuracy. **E)** Diagnosis*valence*task interaction for ketamine vs. placebo percent accuracy.
Error bars represent ± 1 standard error of the mean.
Abbreviations: MDD: major depressive disorder; HV: healthy volunteer. Positive: happy or neutral faces; Negative: sad or angry faces.

relationship was observed between ERF amplitude in the calcarine region or ERF latency in the left middle occipital cortex and percent change in MADRS score post-ketamine. A significant MADRS*drug*valence interaction was found for left fusiform M170 amplitudes ($F(1,86.5) = 4.07$, $p = .047$). Post-hoc tests showed that MDD participants who experienced greater antidepressant response to ketamine exhibited lower M170 amplitudes in response to sad-angry faces and higher amplitudes in response to happy-neutral faces post-ketamine ($p = .008$) (Fig. 5A). A significant MADRS*drug interaction was also observed for right fusiform M170 amplitudes ($F(1,118) = 3.98$, $p = .048$). Post-hoc tests indicated that the relationship between MADRS and M170 amplitudes was significantly greater in the post-ketamine than post-placebo condition ($p = .048$), with participants who experienced greater antidepressant effects exhibiting lower ERF amplitudes post-ketamine (Fig. 5B). Exploratory analyses to evaluate the predictive power of fusiform ERFs found that higher baseline M170 amplitudes in the right, but not the left, fusiform significantly correlated with greater antidepressant response to ketamine (Supplementary Figure S3).

Discussion

This study, which used MEG to examine the impact of ketamine on emotional face processing, found that ketamine exerted differential effects on task reaction time and early visual and face-sensitive ERF responses in treatment-resistant MDD participants compared to HVs. In addition, fusiform M170 amplitudes in MDD participants at baseline and post-ketamine were associated with antidepressant response.

Baseline behavioral analyses demonstrated that MDD participants more accurately identified negatively valenced faces than HVs, supporting the existing evidence for negative processing biases in depression (Gotlib et al., 2004; Joormann and Gotlib, 2007). Some studies have suggested that individuals with MDD may identify negative faces particularly accurately because of increased attention to salient negative emotional information, resulting in the allocation of fewer resources for evaluating other task-relevant information (Koster et al., 2011). Notably, in this study, MDD participants responded more accurately to sad-angry than happy-neutral faces in the explicit emotion condition but not in the implicit condition. Participants as a whole responded more quickly and accurately to stimuli in the implicit condition than in the explicit condition; it is therefore possible that the ease of identifying the sex of facial stimuli decreased the likelihood of detecting a negative bias. Finally, echoing prior findings (Auerbach et al., 2015; Fritzsche et al., 2010), HVs displayed faster reaction times in response to happy-neutral than sad-angry faces, a positive bias that was absent in MDD participants.

Behavioral results from the post-infusion analyses suggested that
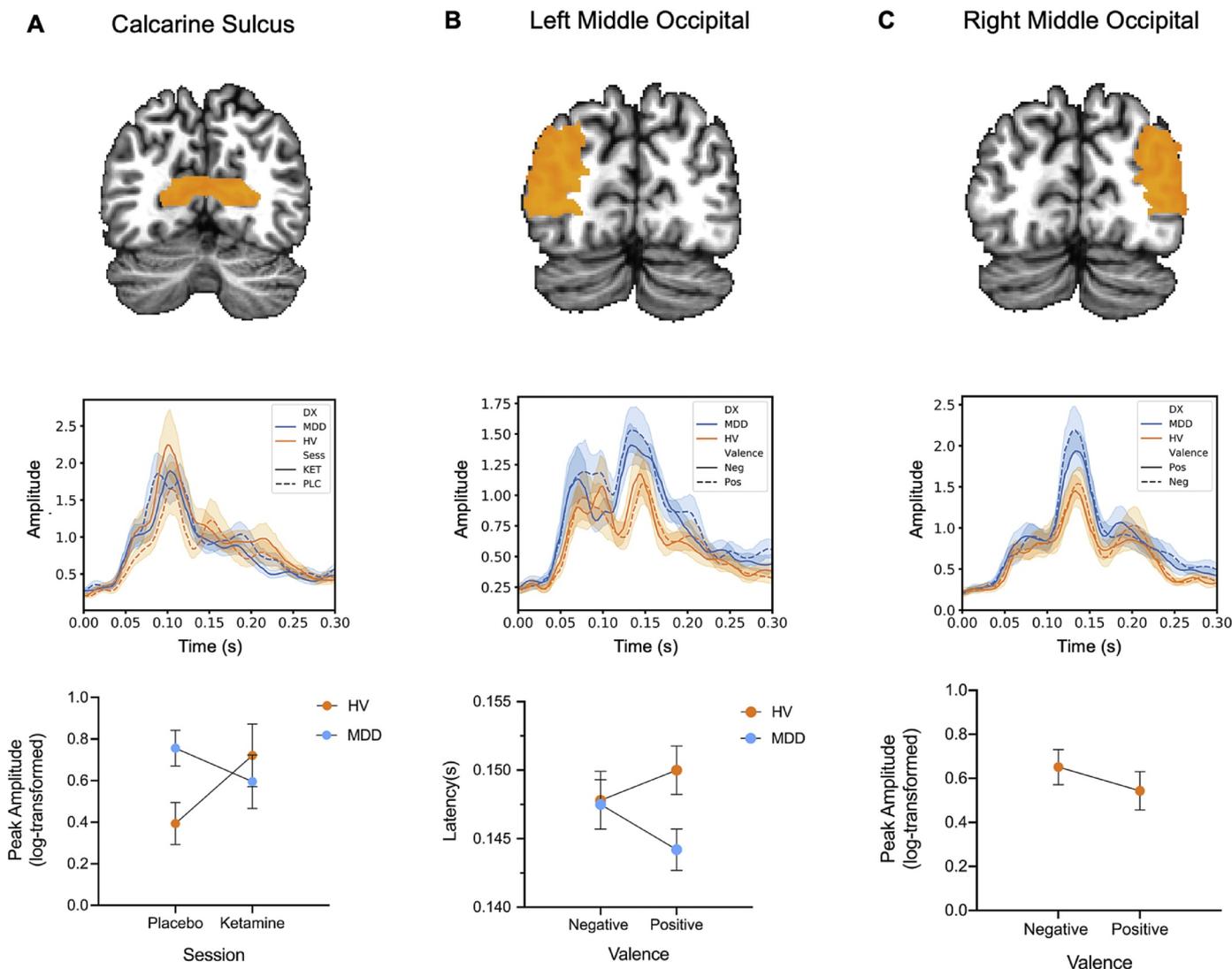
Ketamine vs. Placebo MEG Results

Fig. 3. Illustrations of the ketamine vs. placebo magnetoencephalography (MEG) results for the **A)** calcarine, **B)** left middle occipital, and **C)** right middle occipital regions. *Top*: graphic of the anatomically defined regions of interest (ROIs). *Middle*: Plots of the mean event-related field (ERF) from the ROI, separated by model predictors to illustrate the statistical results. *Bottom*: Plots of the ERF (M100 for calcarine, M170 for middle occipital) marginal means from each significant result from the linear fixed effects models.

Shaded areas on waveform plots represent 95% confidence intervals, and error bars represent ± 1 standard error of the mean.

Abbreviations: DX: diagnosis; MDD: major depressive disorder; HV: healthy volunteers; KET: ketamine; PLC: placebo; Pos: happy or neutral faces; Neg: sad or angry faces.

ketamine had differential effects on task performance for MDD participants compared to HVs. Specifically, MDD participants exhibited slower reaction times post-ketamine than post-placebo, whereas HVs exhibited the opposite pattern. While ketamine's opposing effects on MDD participants and HVs were expected based on our prior fMRI studies (Reed et al., 2018; Reed et al., 2019), these effects were not expected to emerge regardless of stimulus valence. Also unexpectedly, MDD participants exhibited overall higher task accuracy than HVs across sessions, contradicting prior findings suggesting that individuals with MDD may be impaired in terms of recognizing the valence of emotional faces (Asthana et al., 1998; Gotlib et al., 2004; Gur et al., 1992; Persad and Polivy, 1993). However, it is possible that the highly treatment-resistant MDD participants in this sample were more invested in the research study than the HVs, given the prospect of direct benefit

from the trial, and thus devoted more effort to the task. Moreover, the time-intensive nature of the inpatient-based clinical trial may have targeted different samples of participants than other emotional bias studies that comprise only brief, single-day assessments.

In addition to behavioral responses to emotional stimuli, the study examined the degree to which emotional valence and ketamine treatment affected ERF responses indexing early stages of face processing in MDD and HV participants. Average ERF responses across all participants peaked at approximately 100 ms in the calcarine region, corresponding with the M100 response, and at approximately 135-150 ms in the middle occipital and fusiform regions, corresponding with the M170 response (Furey et al., 2006; Meeren et al., 2013; Monroe et al., 2013). In the ERF baseline analyses, participants had greater M170 amplitudes and longer latencies to inverted than upright faces in the left middle
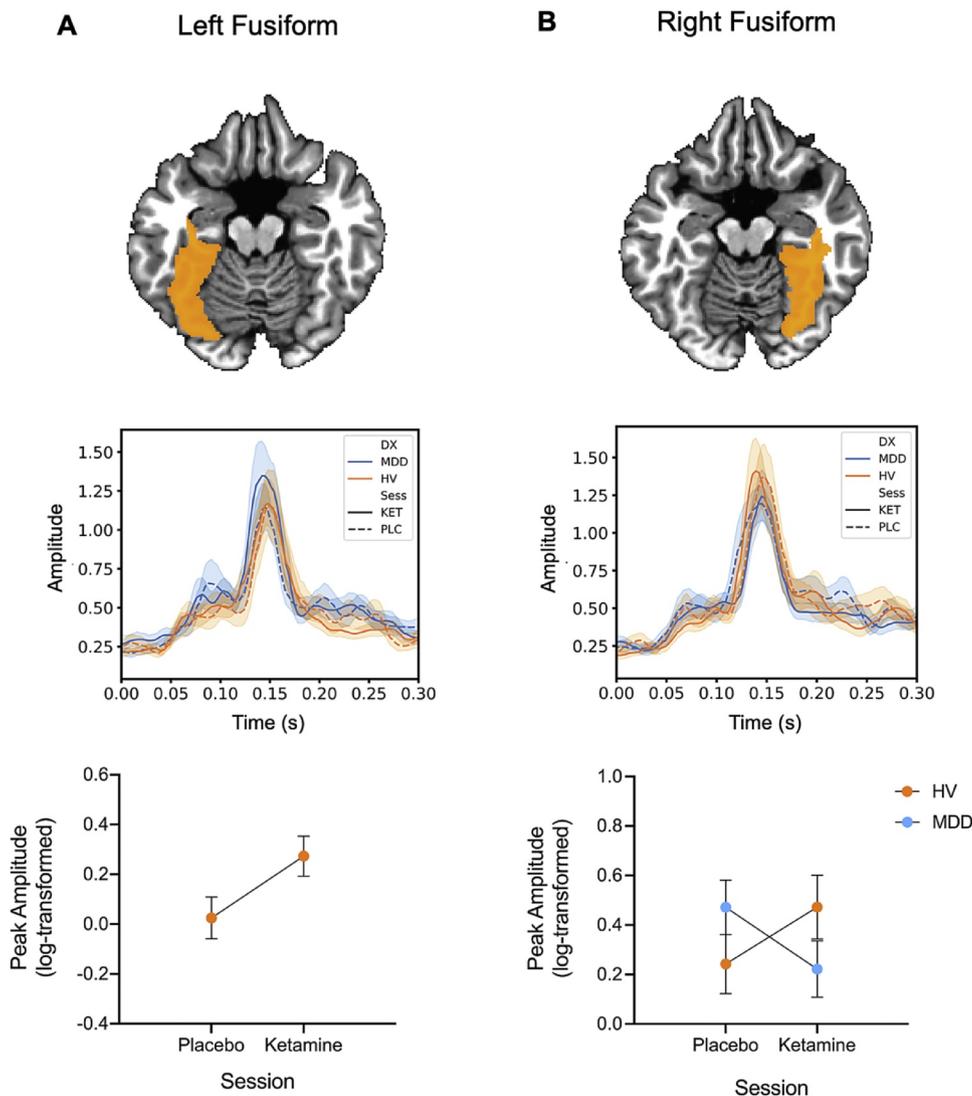
Ketamine vs. Placebo MEG Results

Fig. 4. Illustrations of the ketamine vs. placebo magnetoencephalography (MEG) results for the **A)** left fusiform and **B)** right fusiform regions. *Top:* graphic of the anatomically defined regions of interest (ROI). *Middle:* Plots of the mean event-related field (ERF) from the ROI, separated by model predictors to illustrate the statistical results. *Bottom:* Plots of the M170 ERF marginal means from each significant result from the linear fixed effects models. Shaded areas on waveform plots represent 95% confidence intervals, and error bars represent ± 1 standard error of the mean. Abbreviations: DX: diagnosis; MDD: major depressive disorder; HV: healthy volunteer; KET: ketamine; PLC: placebo

occipital and right fusiform regions, respectively, aligning with prior literature (see Rossion and Gauthier, 2002 for review). Baseline MEG results did not support our hypothesis that MDD participants would display significantly altered early visual responses to sad-angry faces compared to HVs. While some studies found MDD-specific increases in amplitude in response to negative stimuli in the N/M170 (Chen et al., 2014; Wu et al., 2016; Zhao et al., 2015), others found these biases only in the P/M100 (Dai and Feng, 2012; Zhang et al., 2016), and still others did not find robust negative biases in either component (Jaworska et al., 2012).

Interestingly, while no significant effect of valence on ERFs was observed at baseline, the post-infusion MEG results showed a diagnosis-by-valence interaction for left middle occipital cortex latencies. Specifically, MDD participants had shorter M170 latencies in response to happy-neutral than sad-angry stimuli and shorter latencies in response to happy-neutral stimuli than HVs. This differs from the results of Chen and colleagues (2014), which identified shorter latencies in response to sad versus happy and neutral faces in MDD. However, other studies found no N/M170 latency differences by emotional valence (Jaworska et al., 2012; Xu et al., 2018). Moreover, many N/M170 studies solely measure peak amplitude; it is therefore less clear how emotional processing biases might manifest in evoked response latency.

In the right middle occipital cortex, participants had greater M170 amplitudes in response to sad-angry than happy-neutral stimuli. These findings support results obtained by Xu and colleagues (2018) that found overall higher M170 amplitudes in response to sad than happy faces in depressed and healthy participants, but differs from results indicating a negative bias specific to MDD (Chen et al., 2014; Wu et al., 2016). However, interpreting both middle occipital findings is complicated by the fact that these results were specific to the post-infusion analyses and were not observed at baseline.

Post-infusion MEG analyses additionally revealed that ketamine had differential effects on ERF amplitudes in HV versus MDD participants. Significant diagnosis-by-drug interactions were noted for the M100 calcarine and M170 right fusiform responses. The calcarine results in particular suggested that MDD participants had greater ERF amplitudes than HVs post-placebo, and that these were comparable to amplitudes observed in HVs post-ketamine. These differential effects in MDD participants and HVs broadly support our prior fMRI findings (Reed et al., 2018; Reed et al., 2019). While those studies measured the slower BOLD response, the present results suggest that ketamine's effects may also be evident in early visual processing. The findings correspond with evidence suggesting that ketamine's mechanism of action is due in part to restoring homeostasis in some individuals with MDD and disrupting

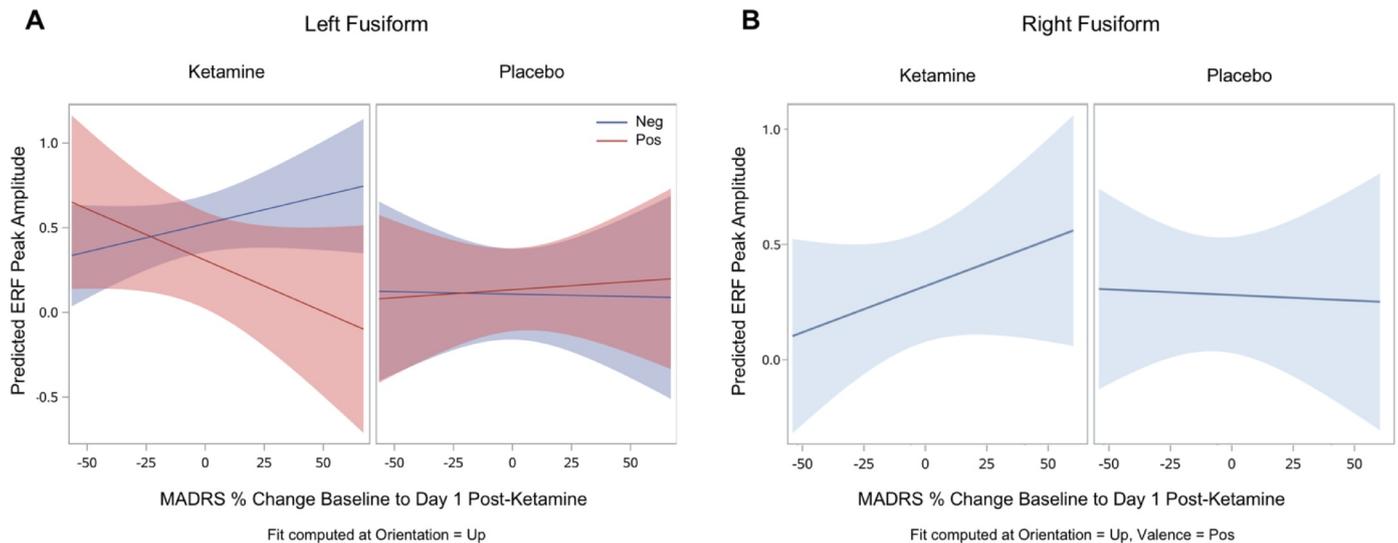# ERF Relationship to Antidepressant Response

Fig. 5. Model predictions of post-infusion event-related field (ERF) amplitudes in participants with major depressive disorder. **A)** Plot of MADRS*drug*valence interaction for left fusiform M170 log-transformed amplitudes. **B)** Plot of MADRS*drug interaction for right fusiform M170 log-transformed amplitudes. Shaded areas represent 95% confidence intervals. Negative x-axis values indicate greater antidepressant response. MADRS change scores were mean-centered. Abbreviations: MADRS: Montgomery-Åsberg Depression Rating Scale; Pos: happy or neutral faces; Neg: sad or angry faces.

pre-existing homeostasis in HVs (Duman and Aghajanian, 2012; Nugent et al., 2019). Given that the diagnosis-by-drug effects did not depend on stimulus valence, it is possible that ketamine may have broadly altered emotional face processing when not accounting for participants' antidepressant response.

Finally, ERF amplitudes in response to emotional faces during the ketamine session were associated with the magnitude of participants' antidepressant response. In the right fusiform, M170 amplitudes in MDD participants post-ketamine became more similar to those of HVs post-placebo, an effect that was most pronounced in those exhibiting the greatest antidepressant response. In addition, while MDD and HV participants exhibited overall larger left fusiform M170 amplitudes post-ketamine than post-placebo, follow-up analyses also showed that MDD participants with a greater antidepressant response had smaller left fusiform amplitudes in response to sad-angry faces and larger amplitudes in response to happy-neutral faces post-ketamine. In conjunction with the exploratory correlational results, these findings suggest that individuals with MDD who experienced a robust antidepressant response to ketamine had larger fusiform M170 amplitudes at baseline, and that these decreased following ketamine infusion. Taken together, these results broadly support prior fMRI findings in MDD demonstrating normalization of neural activation in response to emotional stimuli post-treatment with ketamine (Murrough et al., 2015) and with selective serotonin reuptake inhibitors (Arnone et al., 2012; Victor et al., 2013). In this context, ketamine's impact on early visual responses to emotional faces six to nine hours post-infusion may potentially predict an individual's response to treatment.

This study had several limitations. First, the sample size was relatively small; findings are thus preliminary and require replication. Second, collapsing across happy and neutral stimuli to increase statistical power potentially weakened the findings given that some studies have found that depressed individuals have a tendency to interpret neutral or ambiguous faces as negative (Bouhuys et al., 1999; Gollan et al., 2008). Third, given that saline placebo does not induce ketamine's psychotomimetic side effects, participants may have been aware of which infusion they received. However, ketamine trials that use an "active control," such as the benzodiazepine midazolam (Murrough et al., 2013), have their own shortcomings. Specifically, while midazolam induces some side effects that overlap with those of

ketamine, it does not mimic ketamine's dissociative effects, and studies are warranted to assess whether active controls alter neural activity. Fourth, the effects of the explicit emotion versus implicit task conditions could not be examined in the MEG analysis due to the limited number of trials. This constrained the ERF investigation to early visual responses unlikely to be influenced by top-down cognitive decision-making. Finally, future emotion processing studies in depression should evaluate how ratings of arousal or perceived stimulus intensity impact participants' judgments of emotional valence.

In conclusion, this study provides evidence that ketamine may exert differential effects on behavioral and ERF responses to emotional stimuli in individuals with MDD and HVs. Importantly, our results suggest that greater antidepressant response may be related to reductions in fusiform M170 amplitudes to negatively valenced faces in MDD. Further research is needed to determine whether differences in emotional stimulus processing can serve as reliable biomarkers of MDD symptomology and antidepressant response to ketamine.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon request. The data are not publicly available due to privacy or ethical restrictions.

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Author Contributions

NBL: helped conceptualize, investigate, and administer the project; processed and analyzed the data; wrote the original draft of the manuscript; created the supplementary material; approved the final version of the manuscript.

LS-F: processed and analyzed the data; wrote the original draft of the manuscript; created the figures; approved the final version of the manuscript.

JRG: reviewed the manuscript for critical intellectual content; provided research supervision; approved the final version of the manuscript.

FWC: prepared and optimized the analysis methodology and software; processed and analyzed the data; reviewed the manuscript for critical intellectual content; provided research supervision; approved the final version of the manuscript.

MLF: helped conceptualize, investigate, and administer the project; reviewed the manuscript for critical intellectual content; provided research supervision; approved the final version of the manuscript.

CAZ: acquired funding; helped conceptualize, investigate, and administer the project; reviewed the manuscript for critical intellectual content; provided research supervision; approved the final version of the manuscript.

ACN: helped conceptualize, investigate, and administer the project; prepared and optimized the analysis methodology and software; processed and analyzed the data; created the figures; reviewed the manuscript for critical intellectual content; provided research supervision; approved the final version of the manuscript.

Declaration of Interests

CAZ is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (*2R,6R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisometric dehydro and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (*2R,6R*)-hydroxynorketamine and (*2S,6S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. MLF is identified as a co-inventor on a patent application for the use of scopolamine in mood disorders. She has assigned her patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. MLF is a full-time employee of Janssen Pharmaceuticals of Johnson & Johnson, Inc. All other authors report no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.10.007.

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