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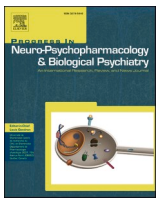

Electrophysiological correlates and predictors of the antidepressant response to repeated ketamine infusions in treatment-resistant depression

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ABSTRACT

Background: Sub-anesthetic ketamine doses rapidly reduce depressive symptoms, although additional investigations of the underlying neural mechanisms and the prediction of response outcomes are needed. Electroencephalographic (EEG)-derived measures have shown promise in predicting antidepressant response to a variety of treatments, and are sensitive to ketamine administration. This study examined their utility in characterizing changes in depressive symptoms following single and repeated ketamine infusions.

Methods: Recordings were obtained from patients with treatment-resistant major depressive disorder (MDD) ($N = 24$) enrolled in a multi-phase clinical ketamine trial. During the randomized, double-blind, crossover phase (Phase 1), patients received intravenous ketamine (0.5 mg/kg) and midazolam (30 μg/kg), at least 1 week apart. For each medication, three resting, eyes-closed recordings were obtained per session (pre-infusion, immediately post-infusion, 2 h post-infusion), and changes in power (delta, theta1/2/total, alpha1/2/total, beta, gamma), alpha asymmetry, theta cordance, and theta source-localized anterior cingulate cortex activity were quantified. The relationships between ketamine-induced changes with early (Phase 1) and sustained (Phases 2,3: open-label repeated infusions) decreases in depressive symptoms (Montgomery-Åsberg Depression Rating Score, MADRS) and suicidal ideation (MADRS item 10) were examined.

Results: Both medications decreased alpha and theta immediately post-infusion, however, only midazolam increased delta (post-infusion), and only ketamine increased gamma (immediately post- and 2 h post-infusion). Regional- and frequency-specific ketamine-induced EEG changes were related to and predictive of decreases in depressive symptoms (theta, gamma) and suicidal ideation (alpha). Early and sustained treatment responders differed at baseline in surface-level and source-localized theta.

Conclusions: Ketamine exerts frequency-specific changes on EEG-derived measures, which are related to depressive symptom decreases in treatment-resistant MDD and provide information regarding early and sustained individual response to ketamine.

Clinical Trial Registration: ClinicalTrials.gov: Action of Ketamine in Treatment-Resistant Depression, NCT01945047

1. Introduction

Major Depressive Disorder (MDD) is a prevalent illness which can have widespread effects on an individual's daily functioning and lifespan (Cuijpers and Schoevers, 2004; Hammer-Helmich et al., 2018). Tragically, it is often comorbid with suicidal ideation (SI, Nock et al., 2010). A significant portion of MDD patients do not respond to currently available treatments (Kennedy et al., 2001; Rush et al., 2006) and are considered to be treatment-resistant (Kasper, 2014). There is also a lag time between treatment initiation and therapeutic response for medications used for depression (Porcelli et al., 2011). The major pharmacological substances used in the treatment of MDD (i.e. selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors, tricyclic derivatives, and

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mirtazapine and bupropion) increase neurotransmitter levels in the synaptic space, leading to enhanced postsynaptic receptor activation (Hillhouse and Porter, 2015). Despite the fact that pharmacological effects begin within hours of drug administration, therapeutic effects only begin to manifest within two to four weeks from treatment initiation. Although this delayed onset of action can be accounted for by adaptive properties of monoamine receptors, the lack of effect for those with treatment-resistant MDD remains to be elucidated (Sanacora et al., 2012).

Ketamine, a dissociative anesthetic, is an *N*-methyl-D-aspartate receptor (NMDAR) antagonist that has been used as a rapid antidepressant agent (McIntyre et al., 2021; Swainson et al., 2021). While the mechanisms through which ketamine exerts its antidepressant effects have yet to be fully elucidated, the current hypothesis is that it acutely increases glutamate neurotransmission in the prefrontal cortex, which leads to increased synaptic plasticity and neurotrophic signaling through downstream molecular cascades (Lener et al., 2017; Zanos and Gould, 2018). A single sub-anesthetic dose of ketamine has repeatedly been shown to exert rapid antidepressant effects in individuals with unipolar and bipolar depression (Bobo et al., 2016; Caddy et al., 2015). Depressive symptom reductions typically manifest within a few hours, with the effect peaking at 24 h, and symptoms returning within one week post-infusion (Kishimoto et al., 2016). A recent meta-analysis also found that a single dose of ketamine effectively and rapidly reduces SI, and that these effects are partially independent of the antidepressant effects (Wilkinson et al., 2018a). Many early randomized ketamine trials used saline as a placebo, while recent studies using the benzodiazepine midazolam as an "active" placebo suggest that midazolam is superior to saline for blind integrity (Grunebaum et al., 2018; Murrough et al., 2015; Murrough et al., 2013a; Phillips et al., 2019; Wilkinson et al., 2019).

While ketamine is effective for the rapid reduction of depressive symptoms, including SI, its limitation lies in its transitory nature. Recent work has focused on specific dosing schedules (twice-weekly, thrice-weekly) aimed at prolonging the antidepressant effects (aan het Rot et al., 2010; Cusin et al., 2017; Murrough et al., 2013b; Shiroma et al., 2014; Singh et al., 2016; Vande Voort et al., 2016; Wilkinson et al., 2018b). Phillips et al. (2019) examined single, repeated (thrice-weekly for 2 weeks), and maintenance (once weekly, for a month) infusions, and found that repeated infusions led to cumulative and sustained reductions in depressive symptoms and suicidal ideation (Phillips et al., 2020) that were maintained in responders. Importantly, several non-responders to single infusions responded to repeated infusions (Phillips et al., 2019).

Electroencephalography (EEG) is a promising method for investigating the effects of ketamine and its relation to depressive symptoms (Olbrich and Arns, 2013). There have been many investigations of the acute electrophysiological effects of subanesthetic doses of ketamine in healthy human participants (for a review, see McMillan and Muthukumaraswamy, 2020), with consistent findings of decreases in EEG-derived alpha (8.5–12 Hz) and increases in gamma (30–50 Hz) power. While the data is less consistent with the lower frequency bands, certain studies have shown that sub-anesthetic doses decrease delta (1–4 Hz) power (de la Salle et al., 2016; Forsyth et al., 2018; Knott et al., 2006; McMillan et al., 2019; Shaw et al., 2015; Vlisides et al., 2017, 2018), while increases in frontal theta (4–8 Hz) have been found in studies that employed a bolus dose (Forsyth et al., 2018; McMillan et al., 2019; Muthukumaraswamy et al., 2015). Studies with a slow sub-anesthetic infusion method only, however, have found decreases in theta power (de la Salle et al., 2016; Knott et al., 2006; Vlisides et al., 2018; Vlisides et al., 2017). Prefrontal theta cordance has been found to decrease following ketamine infusion in healthy controls (Horacek et al., 2010; Sanacora et al., 2014), suggesting that it would induce similar physiological changes when used in the treatment of MDD. Horacek et al. (2010) propose that acute ketamine-induced neurophysiological changes were similar to the gradual monoaminergic-based antidepressant changes, and that this change could serve as a marker and a predictor of the rapid antidepressant effect. Changes in beta power have been less clear, but have generally shown decreases. Only a handful of studies have examined ketamine-induced changes in resting EEG power in MDD and their relationship with antidepressant response (Cao et al., 2019; McMillan et al., 2020; Nugent et al., 2019); with widely varying methodologies (e.g. different post-infusion time points, imaging techniques, placebo substances).

The potential for early (i.e. pre-treatment [baseline] or early within treatment [one-two weeks]) identification of treatment responders is crucial; despite the fact that the antidepressant effects of ketamine are rapid, certain patients may not respond until multiple repeated infusions, or may not respond at all. However, baseline and early changes in electrophysiological measures have shown promise in treatment response prediction in depression to a variety of pharmacotherapies and brain stimulation (Iosifescu, 2011; Lai, 2019; Olbrich and Arns, 2013). Most notably, elevated pre-treatment alpha power and left alpha lateralization have shown predictive ability to treatment response (Bruder et al., 2008; Bruder et al., 2001). Recent work has also indicated a relationship between SI and alpha asymmetry (Park et al., 2019; Roh et al., 2020). Frontal theta band power is altered in MDD with patients showing higher activity in the anterior and right hemisphere (Kwon et al., 1996; Ricardo-Garcell et al., 2009). This frontal pattern has been suggested to reflect altered activity in the anterior cingulate cortex (ACC), which has been implicated in affective processing (Jaworska et al., 2012). Indices of theta power have been found to be predictive of response. Frontal theta power (both increased and decreased pre-treatment in responders); reduced relative theta power at one week post-treatment, (Iosifescu, 2011), theta cordance, a quantitative combination of absolute and relative spectral power (a decrease after one week of treatment found to predict response to multiple treatment modalities, Bares et al., 2008, Bares et al., 2007; Broadway et al., 2012; Hunter et al., 2018), and higher pre-treatment source-localized theta ACC activity (Korb et al., 2009; Mulert et al., 2007) have been found to predict antidepressant treatment response.

This present electrophysiological study was a component of a larger clinical trial (NCT01945047) aimed at enhancing and prolonging the antidepressant effect of ketamine through repeated infusions (Phillips et al., 2019). The primary objectives of this EEG study were 1) to assess the pharmacodynamic actions of ketamine in patients with treatment-resistant depression (TRD) using resting EEG measures (power, alpha asymmetry, theta cordance, theta ACC-indexed activity) and using midazolam as an active control, 2) to assess how these acute changes, in combination with baseline EEG measures, correlated with acute changes in depressive/SI symptom changes, and 3) to assess the utility of these EEG measures (baseline and early changes) and depressive/SI symptoms (baseline and early changes) in predicting initial and prolonged treatment response to repeated ketamine doses.

Consistent with previous work, we expected that alpha power would decrease and gamma would increase with acute ketamine administration, and that baseline electrophysiological measures (power, alpha asymmetry, theta cordance, ACC activity) and acute changes in these measures, in combination with baseline and acute changes in depressive symptoms, would be useful in characterizing and predicting the early and sustained antidepressant response to ketamine. As there have been few studies examining these response predictors with ketamine in patients with TRD, we had no specific hypotheses regarding which predictors (or combination of predictors) would be most effective.

2. Methodology

2.1. Participants

24 outpatients (males and females, aged 18–65) with TRD who were enrolled in larger single-center randomized controlled trial comprising a total of 41 patients (Phillips et al., 2019) chose to participate in this add-

on electrophysiological arm. Participant recruitment was from physician referrals and media advertisements. Assessments were conducted in the University of Ottawa Institute of Mental Health Research at the Royal Ottawa Mental Health Centre in Ottawa, Canada.

Participants were required to (i) have a primary Axis I diagnosis of MDD, single or recurrent and without psychotic features (confirmed using the Mini-International Neuropsychiatric Interview, Sheehan, 1998), as assessed using criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) (American Psychiatric Association, 2000), and (ii) have treatment-resistant MDD, defined as a failure to respond adequately to at least two trials of medications for depression (of different pharmacological classes) and two augmentation strategies for a minimum of six weeks during the present depressive episode (defined using the Antidepressant Treatment History Form, Sackeim, 2001). Participants had to maintain their stable dosages of concomitant psychotropic medications for at least 6 weeks prior to treatment initiation, with no medication changes permitted throughout the trial. Medication types and doses are provided in Table S2 (Supplemental). A MADRS (Montgomery and Asberg, 1979) total score of $\geq$25 was required at screening and randomization, with no more than 20% improvement between these two visits. Exclusion criteria included: (i) current or past substance abuse or dependence (defined by DSM-IV-TR criteria or positive urine screen), (ii) psychotic symptoms, (iii) a history of mania or hypomania, (iv) a body mass index of $\geq$35, and (v) any unstable medical conditions identified through physical examination, vital signs, weight, electrocardiogram, blood tests, and urinalysis (including pregnancy testing for female participants).

All participants provided informed consent for both the clinical trial and add-on EEG arm. The study was approved by the Research Ethics Boards of the Royal Ottawa Health Care Group. This study was conducted in accordance with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans.

2.2. Study design

The clinical study involved three phases (Fig. 1a). Phase 1 followed a randomized, double-blind cross-over design, with participants randomly assigned to receive either ketamine (KET) or an active placebo (midazolam, MID). The participants and the study staff in immediate contact with the participants were blind to the treatment. Participants were required to return to 80% of their baseline MADRS scores in order to receive the second infusion (at least 7 days between sessions). The same criteria (i.e. return to 80% of the baseline MADRS score) were used to determine their progression to Phase 2. All participants entered Phase 2, which involved the acute repeated administration of 6 open-label ketamine infusions, thrice weekly over a period of 2 weeks. Only participants meeting antidepressant response criteria, responders (i.e. $\geq$50% decrease in MADRS total score from baseline [prior to first infusion in Phase 1] to the end of Phase 2), were enrolled in Phase 3, the maintenance phase, which involved the administration of 4 open-label ketamine infusions, once weekly over a period of 4 weeks.

During each of the two sessions of Phase 1, EEG recordings were performed before, immediately following, and two hours post-infusion (Fig. 1b).

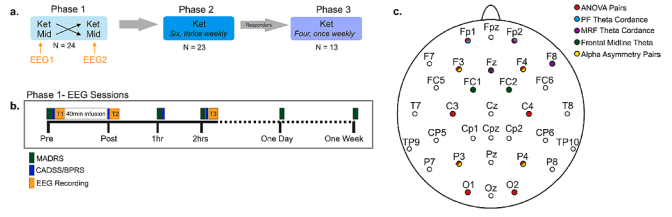

Fig. 1. Timeline of three study phases (a), timeline of EEG recording sessions of Phase 1 (b), and electrode recording montage and electrode groupings for analysis (c).

2.3. Drug administration

Ketamine hydrochloride (Ketalar®, ERFA Canada Inc., Montreal, QC; 0.5 mg/kg, diluted in 0.9% saline) was given throughout the three phases, and midazolam (30 μg/kg diluted in saline) was administered once during Phase 1. Medications were administered by IV pump over 40 min by a study physician and research nurse within an outpatient setting. Vital signs (blood pressure, pulse, oxygen saturation) were monitored throughout the infusion and post-infusion to ensure a return to pre-infusion levels. Participants were required to abstain from benzodiazepines from the preceding day (Frye et al., 2015) and grapefruit juice on the day of infusion (Peltoniemi et al., 2012).

2.4. EEG acquisition

Three minutes of resting activity (eyes closed) was acquired according to standard pharmaco-EEG procedures (Jobert et al., 2012). The montage included 32 $Ag^{+}/Ag^{+}Cl^{-}$ passive electrodes (10–20 international EEG system; Fig. 1c); an electrode placed on the nose served as a reference and a mid-forehead electrode (AFz) served as the ground. Additional electrodes were placed on the supra- and sub-orbital ridges of the right eye and on the external canthus of both eyes to record vertical (VEOG) and horizontal (HEOG) electro-oculographic activity. Recordings were performed using a Brain Vision® Quickamp amplifier and Brain Vision Recorder® (Brain Products, Germany), with amplifier bandpass filters and sampling rate set to 0.1–100 Hz and 500 Hz, respectively. Electrode impedances were maintained below 5 kΩ.

2.5. EEG analysis

2.5.1. Scalp surface-level power and derived measures

Off-line processing was performed using Brain Vision® Analyzer Version 2.1 software (Brain Products, Munich, Germany). First, raw data was visually inspected for prominent ocular/muscle/cardiac contamination; any contaminated segments were removed. Data was then re-referenced to linked mastoids, bandpass filtered from 0.1–70 Hz (24 dB/oct; 60 Hz notch filter), ocular-corrected (Gratton et al., 1983), segmented (2.048 ms) and inspected for artifacts (voltages ±75 μV, faulty channels, drift). The resulting corrected, non-overlapping epochs (Means ± S.D. Ketamine: Time 1 = 84.2 ± 9.2; Time 2 = 84.8 ± 8.6; Time 3 = 82.0 ± 6.8; Midazolam: Time 1 = 84.3 ± 8.8; Time 2 = 81.0 ± 10.2; Time 3 = 83.3 ± 6.6) were subjected to a Fast Fourier Transform algorithm (Hanning window with 10% cosine taper) for computation of absolute (μV^2) spectral power at delta (1–4 Hz), theta1 (4–6 Hz), theta2 (6–8 Hz), theta total (4–8 Hz), alpha1 (8.5–10.5 Hz), alpha2 (10.5–12.5 Hz), alpha total (8.5–12.5 Hz), beta (12.5–30 Hz), and gamma (30–50 Hz). Values were then ln-transformed (Gasser et al., 1982) for statistical analyses. Alpha (alpha1, alpha2, and alphaT) power asymmetry was calculated from ln-transformed data from frontal electrodes (F4-F3/F4 + F3) and posterior electrodes (P4-P3/P4 + P3) (Arns et al., 2016). A positive score indicates greater left hemisphere activation (higher left alpha). Theta cordance values were computed via a custom Matlab script of the cordance algorithm provided by the developers, as defined in Leuchter et al. (1999). This algorithm involves the computation of a re-attributed montage (30 pairs, 19 electrodes) in which absolute (μV^2) and relative (%) power are calculated for each bipolar pair of neighbouring electrodes, followed by a square-root and a z-transformation. The normalized absolute and relative values are then summed for each electrode and for each frequency band. Average cordance values were derived from two main regions of interest: prefrontal (PF; Fp1, Fp2) and midline and right frontal (MRF; Fz, Fp2, F4, F8) for the theta band only. The MRF region was previously identified through a hierarchical cluster analysis demonstrating medication-specific changes (Leuchter et al.,

2008). The PF region has been examined in more studies, though neither region has been found to be superior (de la Salle et al., 2020).

2.5.2. Theta source-localized ACC activity

In order to derive ACC theta activity, EEG data was referenced to the average (Jaworska et al., 2012) and computed using exact low-resolution electromagnetic tomography software (eLORETA; version 2,081,104; 89). eLORETA is a weighted minimum non-linear inverse solution method applied to EEG recordings for computation of three dimensional distribution of electric cortical activity with zero location error (Pascual-Marqui et al., 2011). Current density (A/m^2) was estimated as at three regions of interest (Fig. S1, Supplemental): rostral ACC (BA24, 32 voxels), dorsal ACC (BA32, 91 voxels) and the subgenual ACC (BA25, 12 voxels). These regions were defined based on the Montreal Neurologic Institute average MRI brain (MNI152) (Mazziotta et al., 2001) consisting of 6239 voxels ($5 \times 5 \times 5\ mm^3$/voxel) and restricted to cortical gray matter/hippocampus. This method has been cross-validated with functional and structural MRI, PET and intracranial recordings (Mulert et al., 2004; Pizzagalli et al., 2004; Seeck et al., 1998; Vitacco et al., 2002; Worrell et al., 2000).

2.6. Clinical outcomes and dissociative symptom assessment

For this sub-sample of patients who completed the EEG component of Phase 1, mean (±S.D.) MADRS total scores and item 10 (to assess SI) are presented. MADRS item 10 has been found to be a reliable assessment of rapid decrease in SI with ketamine (Ballard et al., 2015). Baseline measures were derived from the first session (regardless of drug). Comorbid disorders were assessed using the MINI at screening. Responders were patients who demonstrated ≥50% decrease in MADRS total score 24 h after the infusion(s). During Phase 1, the Brief Psychiatric Rating Scale–Positive Symptoms subscale (BPRS-P; Grunebaum et al., 2018; Overall and Gorham, 1962), which assesses conceptual disorganization, mannerisms and posturing, grandiosity, hostility, suspiciousness, hallucinatory behaviour, unusual thought content, and excitement, was administered at pre-infusion, immediately post-infusion, 1 and 2 h post-infusion.

2.7. Statistical analysis

Statistical analyses were carried out with the Statistical Package for Social Sciences (IBM, 2016). To assess the acute regional and frequency specific changes, power values for each frequency band were analyzed with separate repeated measures analysis of variance (rmANOVA) involving drug condition (midazolam, ketamine), time (pre-infusion, post-infusion, 2 h post-infusion), region (prefrontal [Fp1, Fp2], frontal [F3, F4], central [C3, C4], posterior [P3, P4], occipital [O1, O2]) and laterality (left, right) factors. The main effects and interactions of interest were drug condition and time. A priori planned contrasts for drug condition × time interactions are reported regardless of F test significance, unless there is a significant 'drug condition × time × region' or 'drug condition × time × hemisphere' interaction. Similar ANOVAs (with drug condition and time) were carried out for alpha asymmetry (pair: F4-F3, P4-P3), theta cordance (separately for PF, MRF), frontal midline theta power, and source-localized ACC power (BA: rACC, sgACC, dACC). Significant ($p < .05$) Greenhouse-Geisser estimates were followed up with Bonferroni adjusted pairwise comparisons.

Relationships between baseline electrophysiological measures known to be related to treatment outcome (theta, alpha power, alpha asymmetry) as well as absolute change in electrophysiological measures (i.e. post-infusion – pre-infusion, Δ post-infusion and 2 h post-infusion – pre-infusion, Δ 2 h post-infusion) were examined in relation to absolute change in MADRS and MADRS SI assessments (early change scores [i.e. 2 h post-infusion – pre-infusion, 'Δ 2 h'; one day – pre-infusion, 'Δ 1d'), sustained change scores [i.e. Post-Phase 2 – Baseline, 'Δ Ph2'; Post-Phase 3 – Baseline, 'Δ Ph3']) using Pearson correlations. Only variables that exhibited ketamine-induced changes were examined. Correlations were also carried out for change in BPRS-P symptoms (ΔBPRS-P) with alpha power, as this band has been found to be related to perceptual/dissociative symptoms with ketamine (de la Salle et al., 2016).

Electrophysiological variables (baseline and ketamine-induced changes) that were correlated with early and sustained change in MADRS were examined in terms of their predictive ability. Separate stepwise multiple regressions (Criteria: Probability-of-F-to-enter ≤ 0.05, Probability-of-F-to-remove ≥ 0.10) were performed with Δ 2 h, Δ 1d, Δ Ph2, and Δ Ph3 for MADRS total score and MADRS SI as dependent variables. As baseline and early change in depressive symptoms can be predictive of later response, we included baseline MADRS scores for all models, and early change in MADRS in the regressions for later response times (i.e. Δ 2 h within the model predicting Δ 1d, and Δ 2 h and Δ 1d within models predicting Δ Ph2, Δ Ph3). As an exploratory measure, baseline variables were compared with Mann-Whitney *U* tests in responders and non-responders at 1d and end of Ph2.

To explore baseline influence on change in gamma power and depressive symptoms (as reported in Nugent et al., 2019), separate linear fixed effects models with immediately post- and 2 h-post-infusion gamma power as the dependent variable, Δ 2 h MADRS and Δ 1d MADRS as main effects, and baseline gamma power as a covariate, were conducted.

3. Results

3.1. Demographics, clinical outcome, and dissociative symptom measures

Clinical outcome measures for the primary study and specific outcomes related to SI are presented in Phillips et al. (2019) and Phillips et al. (2020), respectively. Twenty-four patients were included in the EEG portion of the study, and 23 completed both EEG sessions of Phase 1. One patient withdrew from the study during Phase 2 after receiving three infusions. None of the patients had mania, hypomania, post-traumatic stress disorder, alcohol or substance abuse or dependence, psychotic features, anorexia nervosa, bulimia nervosa, or antisocial personality disorder. Demographic features and clinical characteristics of the participants are listed in Table 1.

The response rate to a single ketamine infusion at 2 h post-infusion

Table 1
Demographic features and clinical characteristics of participants ($N = 24$). Means and standard deviations are presented.

Variable	Means (± S.D.), Ns
Sex	14F/10M
Age (years)	41.7 ± 12.3
Weight	81.1 (17.7)
Body mass index	27.1 (4.8)
Length of current episodes (years)	5.7 (4.4)
Major Depressive Episodes, Single/Recurrent	12/12
Failed Antidepressant Trials[a], Mean (SD)	3.1 (1.5)
Failed Augmentation Strategies[a], Mean (SD)	2.8 (1.0)
ECT Nonresponder in Current Episode, *n* %	5, 21%
rTMS Nonresponder in Current Episode, *n* %	1, 4%
Lifetime History of Suicide Attempt, *n* %	6, 25%
Comorbid Panic Disorder[b], *n* %	2, 8%
Comorbid Agoraphobia[b], *n* %	6, 25%
Comorbid Social Phobia[b], *n* %	6, 25%
Comorbid Obsessive Compulsive Disorder[b], *n* %	2, 8%
Comorbid Generalized Anxiety Disorder[b], *n* %	5, 21%

ECT, Electroconvulsive therapy; F, female; M, male; MADRS, Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979); rTMS, repetitive Transcranial Magnetic Stimulation.

[a] Number of failed antidepressant trials and augmentations during current episode according to the Antidepressant Treatment History Form (Sackeim, 2001).

[b] Assessed with the Mini-International Neuropsychiatric Interview (Sheehan, 1998).

was 16.7% and 25% at 24 h (one day) post-infusion. The response rate for midazolam was 0% at all time points. The average number of days between the two sessions of Phase 1 was 9.7 (±4.6 S.D., range 7–22 days). The response rate at the end of Phase 2 following repeated infusions was 57%. Thirteen patients were entered into Phase 3, and 77% of participants continued to meet treatment response criteria at the end of Phase 3 (Table 2).

3.2. Regional- and frequency-specific changes with ketamine and midazolam

rmANOVA main effects (drug, time, and drug × time interactions) are presented in Table 3. Ketamine induced widespread changes in low and high resting EEG frequency bands. There were no significant main effects for alpha asymmetry (Table S2, Supplemental). Average power and topographical headmaps at each time point and drug condition are displayed in Figs. 2–5. Average gamma and spectral plots for frontal sites at each time point and drug condition are displayed in Fig. 5.

The fixed effects models did not result in significant interactions between baseline frontal gamma power and Δ 2 h MADRS (Δ post frontal gamma: $F[1,19] = 0.43$, $p = .52$; Δ 2 h post frontal gamma: $F[1,19] = 0.42$, $p = .52$) or Δ 1d post-infusion MADRS (Δ post frontal gamma: $F[1,19] = 0.19$, $p = .67$; Δ 2 h post frontal gamma: $F[1,19] = 0.36$, $p = .56$).

3.3. Relationship between baseline and ketamine-induced changes in EEG measures with acute and sustained change in MADRS and SI

Relationship between baseline EEG and changes in MADRS/SI: correlations indicated negative relationships between baseline rACC theta1, sgACC theta2, rACC theta2, and sgACC thetaT with Δ 1d post-infusion MADRS total score; between baseline sgACC theta2 and rACC theta2 with Δ 1d post-infusion MADRS SI; between baseline rACC theta1 and Δ Ph2 MADRS, and between alphaT parieto-occipital power and Δ Ph3 MADRS SI (Fig. 6).

Relationship between ketamine-induced changes in EEG and changes in MADRS/SI: correlations indicated a positive relationship between Δ post-infusion FMT1 and PF theta cordance with Δ 2 h post-infusion MADRS, while a negative relationship was observed between Δ post-infusion and Δ 2 h post-infusion frontal gamma with Δ 2 h post-infusion MADRS, and between Δ 2 h post-infusion frontal gamma change with Δ Ph3 MADRS. A positive relationship was also observed between Δ post-infusion FMT1 and Δ 1d post-infusion MADRS (Fig. 7). Negative relationships between Δ alphaT power and Δ MADRS SI at all time points were observed. Similar correlations were observed with alpha1 (Supplemental Material). Correlations with alpha total are displayed in Fig. 8.

Relationship between ketamine-induced changes in EEG and changes in BPRS-P: a negative correlation was found between Δ post-infusion parietal alphaT power and ΔBPRS-P symptoms ($r = -0.43$, $p = .04$, $N = 22$).

3.4. Prediction of acute and sustained response to ketamine

Models containing only EEG measures as well as models containing EEG and MADRS predictors were examined (a list of variables can be found in Table S2, Supplemental). The model parameters (Beta coefficient [B], standard error [S.E.)], t-statistic [t-value] and significance [p value]) for all regression analyses are reported in Table 4.

3.4.1. MADRS total score

Significant stepwise regression models were found for the prediction of Δ 2 h, Δ 1d, Δ Ph2, and Δ Ph3 using just EEG variables. With the addition of baseline total MADRS score (to all) and Δ 2 h (to Δ 1d, Δ Ph2, Δ Ph3) and Δ 1d MADRS (to Δ Ph2, Δ Ph3), the model predicting Δ 1d was altered and resulted in two models, containing 1) Δ 2 h MADRS, and 2) Δ 2 h MADRS+ sgACC theta2. The other models remained unchanged.

3.4.2. MADRS SI

Significant stepwise regression models containing only EEG measures were found for the prediction of Δ 2 h, Δ 1d, and Δ Ph3. The prediction of Δ Ph2 MADRS SI did not yield a significant model. With the addition of baseline MADRS SI (to all) and Δ 2 h (to Δ 1d, Δ Ph2, Δ Ph3) and Δ 1d MADRS SI (to Δ Ph2, Δ Ph3), all models were altered. The models predicting Δ 2 h and Δ Ph3 had baseline MADRS SI entered as their only predictor. The model predicting Δ Ph2 was significant with Δ 2 h MADRS SI as a predictor. The model predicting Δ 1d was altered: the analysis produced two models, containing 1) Δ 2 h MADRS SI, and 2) Δ 2 h MADRS+ rACC theta2.

3.5. Baseline EEG differences and ketamine-induced changes between early (1d) and sustained (end of Ph2) treatment responders

An examination of baseline and ketamine-induced change variables in dichotomized responder vs. non-responder groups at early (1d) and sustained (Ph2) time points, in order to compare our findings to previous work. Early responders had significantly larger theta activity at both the scalp and source level, as well as a greater ketamine-induced decrease. Sustained responders had significantly larger theta source activity and a greater decrease with ketamine (Table S3, Fig. S2, Supplemental).

4. Discussion

This electrophysiological study examined the acute effects of sub-anesthetic ketamine (compared to the active placebo midazolam) within the randomized, double-blind phase of a multi-phase trial examining single and repeated ketamine infusions in individuals with

Table 2

a. Montgomery-Åsberg Depression Rating Scale (MADRS) means ± S.D.; b. Changes in Brief Psychiatric Rating Scale – Positive Symptoms (BPRS-P), means ± S.D.

a.		Baseline	Pre infusion	2 hours post	One day post	One week post	End of phase 2	End of phase 3
MADRS Total Score	KET	34.7 (4.1)	34.3 (4.5)	25.1 (8.5)	23.1 (8.8)	28.7 (9.3)	20.4 (13.1)	11.2 (6.7)
	MID		34.1 (5.3)	30.5 (6.4)	31.0 (5.3)	33.0 (6.6)		
MADRS SI	KET	2.96 (1.4)	2.75 (1.6)	1.2 (1.5)	1.2 (1.5)	1.8 (1.8)	1.1 (1.6)	0.4 (0.9)
	MID		2.6 (1.6)	2.2 (1.7)	1.8 (1.7)	2.5 (1.7)		
Response	KET	–	–	16.7% (4 R/20 NR)	25.0% (6 R/18 NR)	8.3% (2 R/22 NR)	56.5% (13 R/10 NR)	76.9% (10 R/3 NR)
	MID	–	–	0.0% (24 NR)	0.0% (23 NR)	0.0% (23 NR)		

b.		Pre-infusion	Post-infusion	1 h post-infusion	2 h post-infusion
BPRS-P Score	KET	8.2 (0.4)	10.7 (3.5)	8.0 (0.0)	8.0 (0.0)
	MID	8.0 (0.0)	8.0 (0.2)	8.0 (0.0)	8.0 (0.2)

BPRS-P, Brief Psychiatric Rating Scale – Positive Symptoms; KET, ketamine; MADRS, Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979); MID, midazolam; NR, non-responder; R, responder; SI, suicidal ideation.

Table 3
Results from rmANOVAs for all frequency bands examined and significant pairwise comparisons.

Frequency band	Variable	Main effect	F (df)	p	ηp^2	Pairwise comparisons
Delta	Delta μV^2	D	(1,22) = 7.09	0.01**	0.24	MID > KET ($p = .01$)
		T	(2,44) = 1.94	0.16	0.08	n.d.
		D × T	(2,44) = 2.03	0.14	0.09	MID: Post>Pre ($p = .04$) Post: MID > KET ($p = .009$)
Theta	Theta1 μV^2	D	(1,22) = 8.50	0.008**	0.29	MID > KET ($p = .008$)
		T	(2,44) = 5.69	0.006**	0.21	Pre > Post ($p = .02$) Pre > 2 h Post ($p = .04$)
		D × T	(2,44) = 2.34	0.11	0.01	KET: Pre > Post ($p = .02$) Pre > 2 h Post ($p = .02$) Post: MID > KET ($p = .003$)
	Theta2 μV^2	D	(1,22) = 4.59	0.04*	0.17	MID > KET ($p = .008$)
		T	(2,44) = 12.79	0.0001**	0.39	Pre > Post ($p > .0001$) Pre > 2 h Post ($p = .004$)
		D × T × R	(2.5,54.9) = 3.13	0.04*	0.12	MID: Pre > Post at PF ($p = .002$), F ($p = .0001$), and C ($p = .0001$) KET: Pre > Post at PF($p = .03$), F ($p = .005$), C ($p = .001$), P ($p = .0001$), and O ($p = .02$) Pre > 2 h at PF ($p = .003$), F ($p = .001$), C ($p = .001$), and P ($p = .001$). Post: MID > KET at C ($p = .03$) and P ($p = .02$)
	ThetaT μV^2	D	(1,22) = 7.73	0.01**	0.26	MID > KET ($p = .01$)
		T	(2,44) = 11.21	0.0001**	0.34	Pre > Post ($p > .0001$) Pre > 2 h Post ($p = .006$)
		D × T	(2,44) = 2.40	0.10	0.01	MID: Pre > Post ($p = .04$) KET: Pre > Post ($p = .003$) Pre > 2 h Post ($p > .0001$) Post: MID > KET ($p = .004$)
	FMT1 μV^2	D	(1,22) = 8.38	0.008**	0.28	MID > KET ($p = .008$)
		T	(2,44) = 7.53	0.002**	0.26	Pre > Post ($p = .006$) Pre > 2 h Post ($p = .02$)
		D × T	(2,44) = 1.93	0.16	0.08	KET: Pre > Post ($p = .03$) Pre > 2 h Post ($p > .0001$) Post: MID > KET ($p = .008$)
	FMT2 μV^2	D	(1,22) = 6.57	0.02*	0.23	MID > KET ($p = .02$)
		T	(2,44) = 22.84	0.0001**	0.51	Pre > Post ($p > .0001$) Pre > 2 h Post ($p > .0001$)
		D × T	(1.6,34.8) = 1.76	0.19	0.07	MID: Pre > Post ($p = .001$) KET: Pre > Post ($p = .001$) Pre > 2 h Post ($p = .001$) Post: MID > KET ($p = .02$)
	FMTT μV^2	D	(1,22) = 9.01	0.007**	0.29	MID > KET ($p = .007$)
		T	(2,44) = 16.51	0.0001**	0.43	Pre > Post ($p > .0001$) Pre > 2 h Post ($p = .001$)
		D × T	(1.5,33.8) = 2.10	0.15	0.09	MID: Pre > Post ($p = .008$) KET: Pre > Post ($p = .004$) Pre > 2 h Post ($p > .0001$) Post: MID > KET ($p = .007$)
	ThetaT PF Cordance	D	(1,22) = 3.66	0.07	0.14	n.d.
		T	(2,44) = 0.92	0.40	0.04	n.d.
		D × T	(1.6, 35.2) = 6.25	0.008**	0.22	KET: Pre > Post ($p = .005$) Post: MID > KET ($p = .003$)
	ThetaT MRF Cordance	D	(1,22) = 3.23	0.09	0.13	n.d.
		T	(2,44) = 2.54	0.09	0.10	n.d.
		D × T	(1.5, 32.2) = 6.53	0.008**	0.23	KET: Pre > Post ($p = .002$) Post: MID > KET ($p = .005$)

(*continued on next page*)

Table 3 (*continued*)

Frequency band	Variable	Main effect	F (df)	p	ηp^2	Pairwise comparisons
	Theta1 ACC Å/m^2	D	(1,22) = 0.04	0.84	0.002	n.d.
		T	(2,44) = 0.35	0.71	0.02	n.d.
		DxTxBA	(4,88) = 2.62	0.04*	0.11	KET, BA25 (sgACC): Pre < 2 h Post (p = .02) Post<2 h Post (p = .03) 2 h Post: KET>MID (p = .01)
	Theta2 ACC Å/m^2	D	(1,22) = 2.42	0.13	0.10	n.d.
		T	(2,44) = 0.92	0.41	0.04	n.d.
		D × T	(2,44) = 0.95	0.39	0.04	n.d.
	ThetaT ACC Å/m^2	D	(1,22) = 0.52	0.48	0.02	n.d.
		T	(2,44) = 0.55	0.58	0.02	n.d.
		D × T	(2,44) = 1.46	0.24	0.06	n.d.
Alpha	Alpha1 μV^2	D	(1,22) = 2.67	0.12	0.11	n.d.
		T	(2,44) = 19.76	0.0001**	0.47	Pre > Post (p = .0001) 2 h Post> Post (p = .006)
		D × T	(1.4,30.7) = 0.32	0.65	0.01	MID: Pre > Post (p = .008) KET: Pre > Post (p = .001) Pre > 2 h Post (p = .007)
	Alpha2 μV^2	D	(1,22) = 2.83	0.11	0.11	n.d.
		T	(2,44) = 11.60	0.0001**	0.35	Pre > Post (p = .0001) 2 h Post> Post (p = .02)
		DxTxR	(2.9,62.8) = 4.13	0.01**	0.16	MID: Pre > Post at PF [p = .0001], F [p = .0001], C [p = .0001], P [p = .0001], O [p = .001] Pre > 2 h Post at PF (p = .02), F (p = .04), and C (p = .04) KET: Pre > Post at PF (p = .006), F(p = .003), C (p = .02), and P (p = .02) Pre > 2 h Post at PF (p = .03), F (p = .02). Post: MID > KET at PF (p = .02) and F (p = .02)
	AlphaT μV^2	D	(1,22) = 3.34	0.08	0.13	n.d.
		T	(2,44) = 17.48	0.0001**	0.44	Pre > Post (p = .0001) 2 h Post> Post (p = .003)
		D × T	(1.5,33.4) = 0.30	0.68	0.01	MID: Pre > Post (p = .0001) KET: Pre > Post (p = .001) Pre > 2 h Post (p = .02)
Beta	Beta μV^2	D	(1,22) = 4.9	0.04*	0.18	MID > KET (p = .04)
		T	(1.4, 30.8) = 2.55	0.11	0.10	n.d.
		DxTxR	(35,76.5) = 4.77	0.003	0.18	KET: Pre > Post at C [p = .003], P [p = .005]) 2 h Post > Post at C [p = .003], P [p = .04] Post: MID > KET at C (p = .03)
Gamma	Gamma μV^2	D	(1,22) = 2.43	0.13	0.10	n.d.
		T	(2,44) = 1.24	0.30	0.05	n.d.
		DxTxR	(8176) = 2.08	0.04*	0.09	KET: Pre < Post at F (p = .02) Pre < 2 h Post at F (p = .01)

2 h Post = 2 h post-infusion; Å/m^2 = current source density; ACC = anterior cingulate cortex; C = central; BA = Brodmann Area; D = drug condition; F = frontal; KET = ketamine; MID = midazolam; n.d. = no significant differences; O = occipital; P = parietal; PF = prefrontal; Post = post-infusion; Pre = pre-infusion; R = region; T = recording time point. μV^2 = power. * > 0.05; ** > 0.01.

TRD, and examined the relationship of baseline and acute ketamine-induced changes in electrophysiological measures with acute and sustained change in depressive and SI symptoms.

4.1. Regional- and frequency-specific ketamine-induced changes in electrophysiological measures

Within the randomized, double-blind, crossover phase of the study, regional- and frequency-specific ketamine-induced changes in electrophysiological measures were observed. Delta band increases were observed from pre- to post-infusion in the midazolam condition. This is in line with previous work demonstrating increases in delta power during sedation (Hering et al., 1994; Numan et al., 2019) and with lower sub-anesthetic doses (Forsyth et al., 2018). Though previous studies have found decreases in delta power with sub-anesthetic doses of ketamine (de la Salle et al., 2016; Forsyth et al., 2018; Knott et al., 2006; McMillan et al., 2019; Shaw et al., 2015; Vlisides et al., 2018; Vlisides et al., 2017), none were observed in this study sample.

Measures of theta band activity showed differing patterns of changes with both ketamine and midazolam. While functional differences between resting theta1 and theta2 activity have not been elaborated, studies have shown sub-band specific alterations in MDD (Jaworska et al., 2012; Narushima et al., 2010; Pizzagalli et al., 2001). In the current study, midazolam did not alter theta1, but decreased theta2 (prefrontal, frontal, central) and thetaT post-infusion, while ketamine decreased theta1, theta2 (all regions), and thetaT post-infusion. At the immediate post-infusion time point, ketamine also had decreased power to a greater degree than midazolam (all sites for theta1, thetaT, central

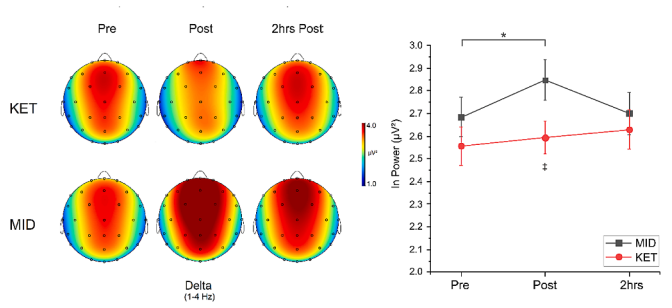

Fig. 2. Average delta power (μV^2) ± S.E. and topographical headmaps at each time point and drug condition. * = time comparison, ‡ = drug condition comparison, $p < .05$.

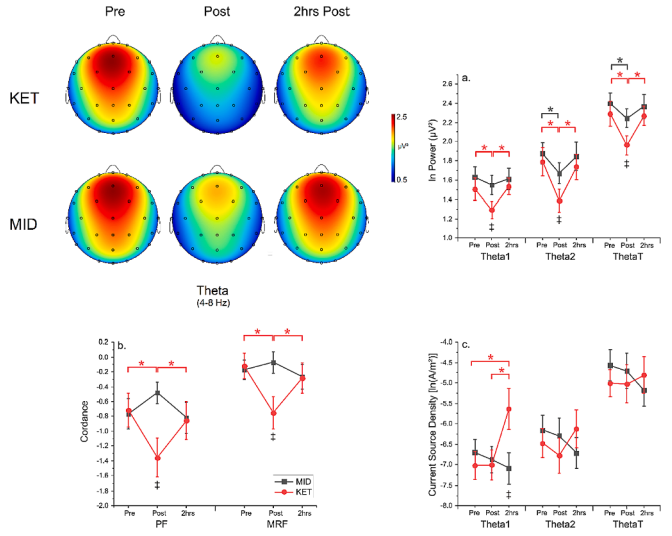

Fig. 3. Average theta power (μV^2) ± S.E. and topographical headmaps at each time point and drug condition. * = time comparison, ‡ = drug condition comparison, p < .05.

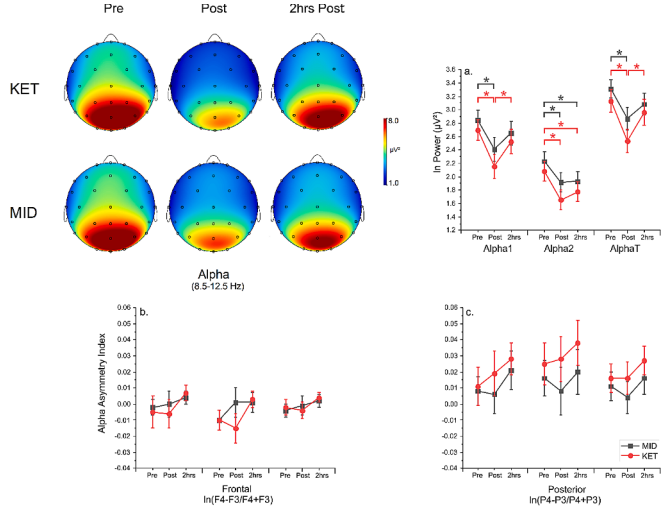

Fig. 4. Average alpha power (μV^2) ± S.E. and topographical headmaps at each time point and drug condition. * = time comparison, ‡ = drug condition comparison, p < .05.

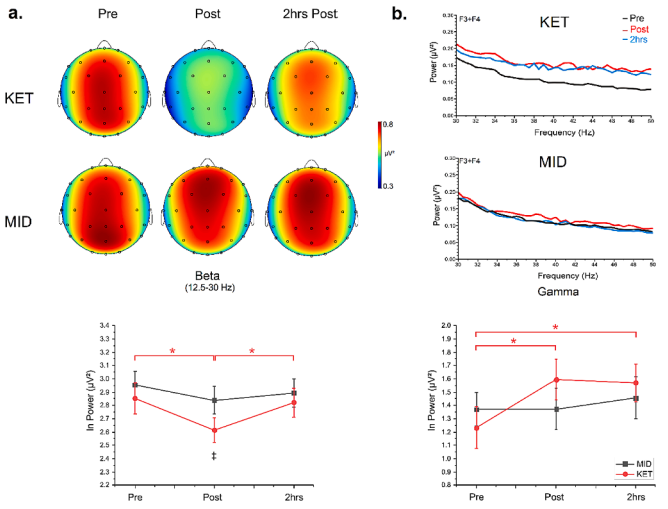

Fig. 5. (*Left*) Average central-parietal beta power (μV^2) and topographical headmaps at each time point and drug condition and (*Right*) Frontal (F3, F4) gamma spectral plots (μV^2) ± S.E. * = time comparison, ‡ = drug condition comparison, p < .05.

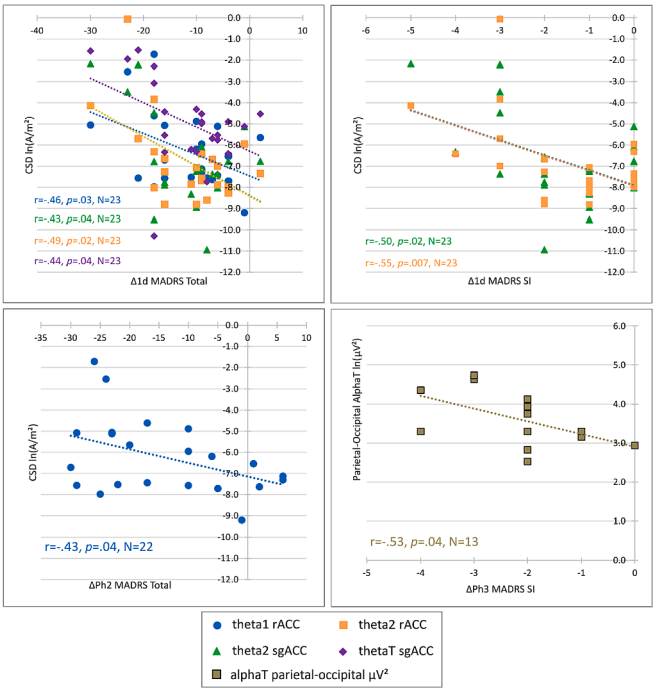

Fig. 6. Scatterplots of significant correlations between baseline current source density (CSD) anterior cingulate cortex (ACC)-localized activity, frontal alpha asymmetry, and alpha total (AlphaT) parieto-occipital power (μV^2) with change in Montgomery-Åsberg Depression Rating Scale (MADRS) and MADRS item 10 (suicidal ideation, SI) at 2 h (Δ 2 h) and one day (Δ 1d) post-infusion, and change from baseline to end of phase 2 (Δ Ph2), and end of phase 3 (Δ Ph3).

and parietal for theta2). As this study did not employ a bolus dose, our finding of decreased theta activity with ketamine is in line with previous work (de la Salle et al., 2016; Knott et al., 2006; Vlisides et al., 2018; Vlisides et al., 2017). Similarly, acute decreases in prefrontal theta cordance were observed with ketamine only; this was also observed in healthy controls receiving a sub-anesthetic infusion without a bolus (Horacek et al., 2010; Sanacora et al., 2014). A similar ketamine-induced decrease was observed in the MRF region. No changes with midazolam were found. This suggests a unique effect of ketamine in

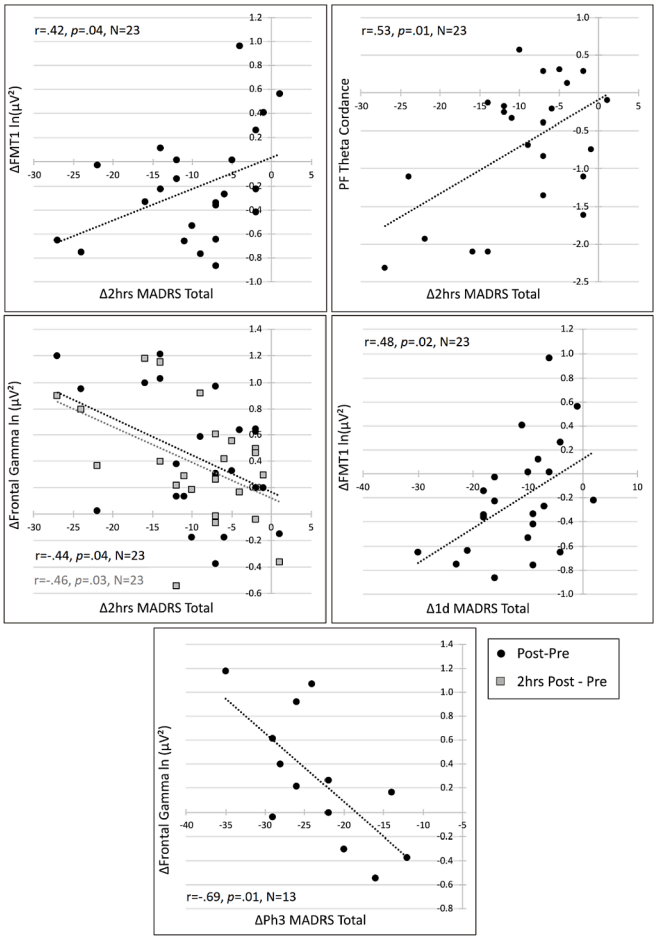

Fig. 7. Scatterplots of significant correlations between change in prefrontal (PF) theta cordance, frontal midline theta1 (FMT1) power (μV^2), and frontal gamma power with change in Montgomery-Åsberg Depression Rating Scale (MADRS) and MADRS item 10 (suicidal ideation, SI) at 2 h (Δ 2 h) and one day (Δ 1d) post-infusion, and change from baseline to end of phase 3 (Δ Ph3).

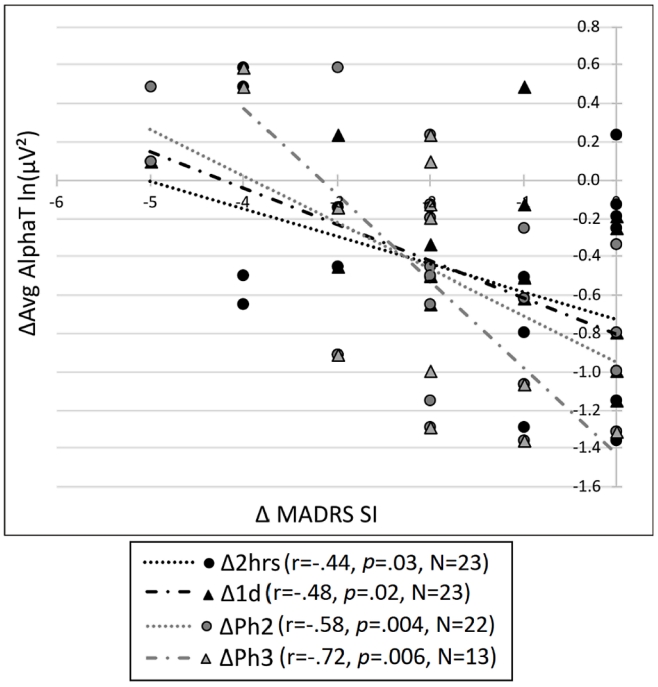

Fig. 8. Scatterplots of significant correlations between change in alpha total (AlphaT) power (μV^2) with change in Montgomery-Åsberg Depression Rating Scale (MADRS) item 10 (suicidal ideation, SI) at 2 h (Δ 2 h) and one day (Δ 1d) post-infusion, and change from baseline to end of phase 2 (Δ Ph2), and end of phase 3 (Δ Ph3).

MDD that is independent of the general decrease in theta cordance observed with power values. sgACC theta1 source-localized CSD activity was found to increase with ketamine 2 h post-infusion, with no significant changes observed with midazolam. Previous studies have found decreases in the sgACC with acute ketamine administration in healthy controls (Deakin et al., 2008; Stone et al., 2015; Wong et al., 2016). However, an increase with ketamine was observed with BOLD signal in the sgACC during an hour-long scanning session, with the activation predicting depression improvements at 24 h and 1 week post-ketamine (though the study did not observe changes in depression symptoms immediately post-infusion, Downey et al., 2016). The authors suggest that the previously reported deactivation of sgACC after ketamine potentially reflects the rapid and pronounced subjective effects evoked by the bolus-infusion method used in the previous study. Additionally, activity within the sgACC activity increased over the whole recording, so it's possible that the decrease in other studies is related to time of measurement.

Alpha power was reduced with both ketamine and midazolam, reflecting an overall decrease in arousal in both drug conditions. This is consistent with our hypothesis, as well as with previous healthy control studies with midazolam (Berchou et al., 1986; Hotz et al., 2000; Kuizenga et al., 2001; Veselis et al., 1991) and sub-anesthetic ketamine (de la Salle et al., 2016; Forsyth et al., 2018; Kochs et al., 1996; McMillan et al., 2019; Muthukumaraswamy et al., 2015; Vlisides et al., 2018; Vlisides et al., 2017). Alpha power during eyes-closed resting conditions is thought to reflect a state of relaxed alertness (Zoon et al., 2013), though it has also been implicated in various cognitive processes, including attention, perception, and working memory, and may prioritize relevant sensory input (Klimesch, 2012; Klimesch, 1999; Van Diepen et al., 2019). In MDD, alpha power is typically increased (Bruder et al., 2008; Grin-Yatsenko et al., 2009; Jaworska et al., 2012), suggesting an overall pattern of cortical hypoactivity. We observed decreases in parietal alpha power which were correlated with greater increases in BPRS-P symptoms, suggesting that the specific positive symptoms induced by ketamine are disrupting alpha oscillations, perhaps representing a decrease in sensory input filtering. Alpha asymmetry was not significantly altered within either drug condition. This is in line with the results of the international Study to Predict Optimized Treatment in Depression (iSPOT-D), which found that frontal alpha asymmetry is a state-invariant prognostic biomarker (van der Vinne et al., 2019).

Beta oscillations have traditionally been associated with the sensorimotor cortex (Kilavik et al., 2013), though recent work has also suggested a role in large-scale neural integration (Donner and Siegel, 2011) and temporal perception (Arnal, 2012). Central-parietal beta power was reduced following acute ketamine infusion, which is consistent with previous human trials (Forsyth et al., 2018; Knott et al., 2006; McMillan et al., 2019; Muthukumaraswamy et al., 2015; Rivolta et al., 2015; Vlisides et al., 2018).

Gamma oscillations resulting from emotional stimuli have been found to be altered in MDD (Bi et al., 2018; Lee et al., 2010; Liu et al., 2014; Liu et al., 2012), possibly reflecting disruptions within glutamatergic excitation-gamma aminobutyric acid (GABA)ergic inhibition (Fee et al., 2017). Ketamine-induced increases in gamma power are thought to occur through pyramidal cell disinhibition downstream of NMDA receptor antagonism, and this increase in gamma may be involved in the reduction of depression symptoms via cortical excitation increase (Gilbert and Zarate, 2020). Consistent with our hypothesis, we observed increases in frontal gamma power both immediately and 2 h post-infusion. Increased resting gamma power is a consistent finding

Table 4
Model parameters (Beta coefficient [B], standard error [S.E.)], t-statistic [t-value] and significance [p value]) for regression analyses.

D.V.	Model	R^2	*F(df)*	*p*	I.V.	β (S.E.)	t	*p*
Δ 2 h MADRS	EEG	0.28	(1,22) = 8.03	0.01	Δ post PF theta cordance	4.49 (1.58)	2.83	0.010
Δ 1d MADRS	MADRS	0.45	(1,22) = 17.03	0.0001	Δ 2 h MADRS	0.69 (0.17)	4.13	0.0001
	EEG + MADRS	0.55	(1,22) = 12.41	0.0001	Δ 2 h MADRS + Baseline sgACC theta2	0.59 (0.16)	3.69	0.0010
						−1.21 (0.55)	−2.18	.04
Δ Ph2 MADRS	EEG	0.23	(1,21) = 5.83	0.03	Baseline rACC theta1	−3.08 (1.27)	−2.42	0.03
Δ Ph3 MADRS	EEG	0.37	(1.12) = 6.22	0.03	Δ 2 h frontal gamma	−6.29 (2.52)	−2.49	0.03
MADRS SI								
Δ 2 h MADRS SI	EEG	0.20	(1,22) = 5.13	0.03	Δ post avg. AlphaT	−1.36 (0.60)	−2.27	0.03
	MADRS	0.45	(1,22) = 17.03	0.0001	Baseline MADRS SI	−0.76 (0.22)	−3.42	0.003
Δ 1d MADRS SI	EEG	0.26	(1,22) = 7.46	0.007	Baseline rACC theta2	−0.37 (0.14)	−2.73	0.01
	EEG	0.49	(1,22) = 9.46	0.001	Δ post avg. AlphaT+	−1.19 (0.40)−	−2.95	0.0080
					Baseline rACC theta2	0.36 (0.12)	−3.16	.005
	MADRS	0.49	(1,22) = 20.45	0.0001	Δ 2 h MADRS SI	0.57 (0.13)	4.52	0.0001
	EEG + MADRS	0.62	(2,22) = 15.99	0.0001	Δ 2 h MADRS SI + rACC theta2 baseline	0.50 (0.12)−	4.29	0.00010
						0.26 (0.1)	−2.52	.02
Δ Ph2 MADRS SI	MADRS	0.55	(1,21) = 24.17	0.0001	Δ 2 h MADRS SI	0.59 (0.12)	4.92	0.0001
Δ Ph3 MADRS SI	EEG	0.34	(1,21) = 10.36	0.004	Δ post avg. AlphaT	−1.03 (2.9)−	−3.57	0.0050
						0.67 (0.29)	−2.28	.04
	MADRS	0.65	(1,12) = 20.57	0.001	Baseline MADRS SI	−0.78 (0.17)	−4.54	0.001

Δ post = change from pre to post-infusion; Δ 2 h = change from pre to 2 h post-infusion; Δ 1d = change from pre to one day post-infusion; Δ Ph2 change from baseline to end of phase 2; Δ Ph3 change from baseline to end of phase 3; ACC = anterior cingulate cortex; alphaT = alpha total power; MADRS = Montgomery-Åsberg Depression Rating Scale; PF = prefrontal; r = rostral; sg = subgenual; SI = suicidal ideation.

with acute sub-anesthetic ketamine administration in healthy controls (de la Salle et al., 2016; Forsyth et al., 2018; McMillan et al., 2019; Muthukumaraswamy et al., 2015; Rivolta et al., 2015; Sanacora et al., 2014; Vlisides et al., 2018; Vlisides et al., 2017) and has recently been observed using magnetoencephalography (MEG) in MDD patients as a delayed effect with increases 6-9 h post-infusion (Nugent et al., 2019). Our findings of acute increases in gamma power both immediately and 2 h post-infusion are the first to demonstrate this increase in treatment-resistant MDD patients, and complement findings of sustained gamma increases beyond the acute physiological and dissociative effects of ketamine.

4.2. Relationships between baseline and ketamine-induced changes in EEG measures and ketamine-induced changes in depressive/suicidal symptoms

Findings with baseline and change in theta oscillations have been observed with traditional medications for depression, though conflicting results have been found (Baskaran et al., 2018; Iosifescu et al., 2009; Knott et al., 2000; Knott et al., 1996; Spronk et al., 2011; Tenke et al., 2011). With ketamine, the findings of McMillan et al. (2020) were increase in frontal theta power, with an observation of a trend towards increased frontal theta power relating to a larger decrease in MADRS score at one day post-infusion. In the current study, we found decreases in measures of theta oscillations, as well as a relationship between decreases in theta and decreases in depressive symptoms. Cao et al. (2019) found that treatment responders exhibited decreases in prefrontal theta cordance 4 h post-ketamine infusion, while we observed an immediate decrease in theta cordance which was related to decreases in depressive symptoms at 2 h, though no differences in cordance values at 2 h. Given the differing recording time points, it is difficult to parse apart the time course of change in theta cordance and more work is required.

Correlations were observed with source-localized baseline ACC activity at both early (one day post-infusion) and sustained response time points (end of Phase 2). As well, early and sustained responders had higher levels of theta as compared to non-responders. Increased resting activity in the rACC has been consistently shown to be related to response to many treatments with antidepressant effects (pharmacotherapy, transcranial magnetic stimulation, sleep deprivation, (Fu et al., 2013; Pizzagalli, 2011), and rACC theta activity is related to metabolism (Pizzagalli et al., 2003). Changes within the sgACC have been associated with treatment response to CBT and pharmacotherapy (Kennedy et al., 2007). In the current study, increases in sgACC theta1 activity were found 2 h post-infusion; however, there was no relationship to decrease in depressive symptoms. It is possible that further increases may have been observed with a later recording (one day post-infusion, end of phase 2) which may then have elucidated a relationship with decrease in symptoms.

Regarding gamma power changes, Nugent et al. (2019) observed that baseline gamma levels within widespread regions (including the central executive, salience, and default mode networks) were found to moderate the relationship between change in gamma power post-ketamine (~6–9 h) and antidepressant response; those with lower baseline levels exhibited greater increases in gamma and greater decreases in depressive symptoms (from −60 to 40 mins post-infusion), and the opposite finding for those with higher baseline levels and larger increases in gamma power. We did not observe a baseline influence in our analysis, which may be related to the difference in recording timepoint (immediately and 2 h post-infusion vs. 6–9 h post-infusion) as well as the time of recording for baseline values (first recording, same day as infusion vs. 1–2 days pre-infusion). One possible interpretation is that baseline influences the sustained vs. immediate increase in gamma power. Additionally, our study utilized a scalp-level region (frontal) vs. activity within larger-scale networks. In the current study, patients with greater acute change in gamma power exhibited greater early decrease in depressive symptoms. While the early treatment response rate was low, certain patients did exhibit large decreases in symptoms. Within the sustained treatment responders (i.e. those entering into Phase 3), patients with greater increases in gamma 2 h post-infusion had greater sustained decreases in depressive symptoms, and this increase was predictive of symptom decrease.

Higher baseline alpha power has been found to be associated with positive response to pharmacotherapy (Bruder et al., 2008; Tenke et al., 2011). In our study, higher baseline parieto-occipital power was related to greater sustained (Phase 3) decrease in SI, possibly reflecting an association with vigilance regulation in MDD (Hegerl et al., 2012; Olbrich et al., 2016). In addition, greater ketamine-induced decreases in SI were related to smaller decreases in alpha power. This was observed at early (2 h and one day post-infusion) as well as sustained (Phase 2 and 3) time points. These findings may indicate that stable alpha power (i.e. less subject to alterations with ketamine or other pharmacotherapies) is related to greater decreases in SI. A recent study examining EEG changes in female MDD patients (suicide attempters, ideators, and non-suicidal) found a significant relationship between higher alpha power in ideators

vs. non-suicidal, (Benschop et al., 2019), suggesting a relationship between alpha power and SI. Greater decreases in SI symptoms one day post-infusion were also related to higher baseline theta2 sgACC and rACC activity.

4.3. Theta and gamma measures were most predictive of early and sustained decrease in depressive symptoms

Certain EEG measures were particularly predictive of the decrease in total MADRS and SI. Using only EEG measures, change in PF cordance was predictive of depressive symptom change at 2 h, and baseline theta2 sgACC was predictive of depressive symptom change at one day post-infusion. Sustained decrease in depressive symptoms were predicted by baseline rACC theta1 (Ph2) and increase in frontal gamma power (Ph3). With the addition of baseline MADRS and early changes in MADRS scores, only the model prediction change at one day post-infusion was altered to include both change at 2 h post-infusion in addition to baseline theta2 sgACC. These findings are particularly salient, as they suggest that baseline and early change in depressive symptoms alone are not as useful as baseline and early changes in EEG alone or in combination with early decreases in depressive symptoms with ketamine. This has been shown previously with various pharmacotherapies (Bares et al., 2017; Bares et al., 2015; de la Salle et al., 2020; Jaworska et al., 2019), and adds to the growing body of research suggesting that antidepressant treatment response outcomes may be optimally predicted by the combination of measures (Taliaz et al., 2021) that have been found to be predictive, including clinical (Szegedi et al., 2009; Wagner et al., 2017), brain-derived neurotrophic factor (BDNF) serum and plasma levels (Polyakova et al., 2015), and genetic polymorphisms (Kato and Serretti, 2010), among others. In many previous EEG-prediction studies, theta cordance and theta ACC power have shown the strongest relation to successful treatment prediction with varying treatments and study designs (Widge et al., 2019). The current study adds to and extends this finding, in that many of the strongest predictors of both early and sustained response to ketamine involved the theta band.

4.4. Alpha measures were most predictive of early and sustained decrease in suicidal ideation symptoms

Using only EEG measures, decrease in SI at 2 h post was predicted by Δ post alphaT power, and by baseline rACC theta2 with Δ post alphaT power at one day post-infusion. Sustained decrease in SI (Phase 3) was most predicted by Δ post alphaT. However, with the addition of baseline and early change in MADRS SI, the EEG variables were replaced by the SI symptoms for most models; with the exception of Δ 1d post-infusion, which resulted in a model combining change in SI symptoms at 2 h with baseline rACC theta2. Baseline and early change in electrophysiological measures were not as reliable predictors as baseline and early change in SI symptoms. This is consistent with the current state of prediction of SI and attempts, with a meta-analysis of longitudinal research concluding that current predictors are only slightly better than chance (Franklin et al., 2017), as well as a lack of research for short-term risk prediction (Glenn and Nock, 2014). Prediction of decreases in SI with ketamine or other antidepressant treatments may prove to be even more complex than the prediction of decreases in overall depressive symptoms, though neuroimaging-based predictors are currently being investigated, with some recent positive findings (Benschop et al., 2019; Just et al., 2017).

4.5. Limitations

Despites the strengths and novelties of this study, there are several limitations that warrant discussion. Regarding the clinical component of the study, as discussed in Phillips et al. (2019), there are limitations regarding the effectiveness of midazolam as a blinding agent (lack of dissociative side effects) and the open-label nature of the sustained treatment phases.

Regarding electrophysiological limitations, as the patients maintained their concomitant medication regimens throughout the trial, there may have been an influence on the baseline EEG activity. However, these were stable dosages (>6 weeks) with no change throughout the trial. Only acute EEG recordings were performed, therefore sustained changes in electrophysiological measures (i.e. one day post-infusion, end of Ph2/3) could not be examined. As well, no separate baseline session/time point was held. Additionally, the resting EEG recordings were 3 min in length, which does not allow for the assessment of vigilance. This may influence midline theta band activity (and consequently theta cordance and ACC-localized activity) and has also been shown to differ in antidepressant treatment responders, who display higher baseline brain arousal levels and greater decreases in vigilance with treatment (Schmidt et al., 2017). As well, despite having excellent temporal resolution, EEG has inherent spatial resolution limitations, which is particularly important for our source-localized ACC data. Finally, while EEG has been found to be useful in the prediction of treatment response, more work is required in order to improve its clinical reliability, due in part to under-powered studies and depression heterogeneity (Widge et al., 2019).

The overall sample size did not allow for a dichotomous analysis of responders vs. non-responders at each time point, or the calculation of prediction measures such as sensitivity, specificity, positive and negative predictive values, or the identification of cut-off scores for future studies to form a priori hypotheses. While we did examine responders vs. non-responders at one day post-infusion and end of phase 2 in an exploratory manner, they must be interpreted with caution, though they are in line with previous findings with other antidepressant treatments. Despite the relatively small sample, it is a starting point for future larger trials seeking to determine electrophysiological-based predictors of the antidepressant response to ketamine.

5. Conclusion

This study examined acute ketamine-induces changes in electrophysiological measures and their relationship to early and sustained treatment response to sub-anesthetic ketamine in TRD. To our knowledge, it is the first study to examine acute ketamine-induced changes in relation to repeated ketamine infusions. Overall, this study found regional- and frequency-specific ketamine-induced changes in electrophysiological measures which were related to and predictive of decreases in depressive symptoms and SI. Early and sustained treatment responders also differed at baseline in surface level and source-localized theta. As certain patients may not immediately respond to ketamine, being able to predict sustained response is of great importance, as probable non-responders may benefit from an alternative treatment regime offered prior to engaging in multiple sessions with ketamine.

Ethical statement

All participants provided informed consent for both the clinical trial and add-on EEG arm. The study was approved by the Research Ethics Boards of the Royal Ottawa Health Care Group. This study was conducted in accordance with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans.

Disclosures

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Drs. Phillips, Knott, and de la Salle report no financial interests or potential conflicts of interest.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110507.

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