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# Acute changes in cerebral blood flow after single-infusion ketamine in major depression: a pilot study

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## Abstract

**BACKGROUND:** Ketamine provides rapid antidepressant response in those struggling with major depressive disorder (MDD). This study measured acute changes in brain activity over 24 hours after a single infusion of ketamine using arterial spin labeled (ASL) functional magnetic resonance imaging (fMRI) in patients with MDD. ASL is a novel technique that provides quantitative values to measure cerebral blood flow (CBF).

**METHODS:** A single sub-anesthetic dose (0.5 mg/kg) of ketamine was delivered intravenously. Treatment-refractory patients (n=11) were assessed at: Baseline (pre-infusion), and approximately 1hr, 6hrs, and 24hrs post-infusion. Linear mixed-effects models detected changes in CBF with respect to treatment outcome, and results were corrected for false discovery rate (FDR).

**RESULTS:** After ketamine infusion, increased CBF was observed in the thalamus, while decreased CBF was observed in lateral occipital cortex in all patients. Time-by-response interactions were noted in ventral basal ganglia and medial prefrontal cortex, where CBF change differed according to antidepressant response.

**LIMITATIONS:** Modest sample size is a limitation of this pilot study; strict statistical correction and visualization of single-subject data attempted to ameliorate this issue.

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**Contributors:** Authors K.L.N., R.E., and A.M.L. designed the study. Authors A.M.L., M.V., and S.N. collected and managed data collection. Authors S.G. and A.M.L. conducted MRI preprocessing and analysis. Authors S.G. and A.M.L. undertook the statistical analyses. Authors S.G. and A.M.L. wrote the first draft of the manuscript. All authors have contributed to and have approved the final manuscript.

DISCLOSURES

The authors declare no conflicts of interest.

Ethical Statement

This research was conducted with approval and oversight by the UCLA Institutional Review Board.

Supplemental information: None

**CONCLUSION:** In this pilot study, a sub-anesthetic dose of ketamine was associated with acute neurofunctional changes that may be consistent with altered attention, specifically increased thalamus activity coupled with decreased cortical activity. By contrast, antidepressant response to ketamine was associated with changes in reward-system regions, specifically ventral basal ganglia and medial prefrontal cortex. Further work is needed to determine whether these results generalize to larger samples and/or serial ketamine infusions associated with longer-lasting clinical effects.

### Keywords

ketamine; antidepressant; treatment resistant depression; arterial spin labeling; cerebral blood flow; functional magnetic resonance imaging

## INTRODUCTION

Depression is a pervasive health issue, with an estimated 16.2 million U.S. adults having experienced at least one depressive episode (Ahrnsbrak et al., 2017). However, an estimated 12%–20% of those adults were unsuccessful in achieving remission after two or more pharmacotherapies, rendering them treatment resistant (McIntyre et al., 2014; Souery et al., 1999). Seeing as this is a major issue, rapid-acting treatment alternatives like ketamine are a focus of ongoing clinical research.

At high doses, ketamine is used clinically as an anesthetic, first synthesized by chemists Calvin Stevens and Parke Davis consultant in 1962 (Li and Vlisides, 2016; Schwartz et al., 2016). At subanesthetic doses, ketamine has been shown to provide analgesic and psychotomimetic effects (Gorlin et al., 2016; Krystal et al., 1994), as well as rapid antidepressant effects at lower doses (Newport et al., 2015; Zarate et al., 2006).Indeed, multiple clinical trials have shown the efficacy of ketamine's rapid antidepressant response in those with severe depression (Lapidus et al., 2014; McGirr et al., 2015; Wan et al., 2015; Zarate et al., 2006)and acute suicidality (Lee et al., 2015; Price et al., 2009). However, it remains unclear how ketamine affects the brain to induce these antidepressant effects.

Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, inhibiting the binding of glutamate, the major excitatory neurotransmitter of the CNS (Li and Vlisides, 2016). Literature suggests glutamate levels in the brain may be affected in mood disorders (Mathews et al., 2012), also demonstrated in animal models of depression (Koike et al., 2011). Low levels of glutamate-related metabolites have been detected in depressed patients by a large number of neuroimaging studies in the medial prefrontal cortex, anterior cingulate cortex, left dorsal lateral prefrontal cortex, amygdala, and hippocampus (Abdallah et al., 2018; Auer et al., 2000; Block et al., 2009; Hasler et al., 2007; Luykx et al., 2012; Nikolaus Michael et al., 2003; N. Michael et al., 2003; Pfleiderer et al., 2003; Stone et al., 2012; Taylor et al., 2012; Yüksel and Öngür, 2010). This corresponds well with studies implicating the prefrontal cortex, limbic, basal ganglia, and brainstem regions in depression using other neuroimaging modalities (Pandya et al., 2012; Price and Drevets, 2010), including changes in resting brain function and connectivity in these regions (Evans et al., 2018; Leaver et al., 2016). We hypothesize that, while ketamine may have nonspecific effects on resting brain function in all patients, the drug may preferentially influence these brain regions

previously associated with depression in patients who respond to ketamine. Indeed, recent neuroimaging studies suggest that ketamine may influence activity in these brain regions in people with depression (Abdallah et al., 2017b; Sahib et al., 2020), and a compelling study demonstrated decreased activity in medial prefrontal and subgenual anterior cingulate after ketamine in nondepressed controls (Deakin et al., 2008). However, evidence remains sparse.

In this open-label mechanistic pilot study, we investigated the effects of ketamine on resting brain activity via a functional neuroimaging technique, arterial spin-labelled (ASL) MRI, which yields a quantitative measure of cerebral blood flow as a proxy for brain activity. Based on previous clinical trials of ketamine for severe depression, a subanesthetic dose of 0.5 mg/kg was administered intravenously, which optimizes bioavailability in comparison to intranasal or intramuscular methods (Chilukuri et al., 2014; Li and Vlisides, 2016). Our objective was to observe how ketamine treatment affects resting brain activity acutely in the hours after treatment, measured with MRI before, and 1, 6, and 24 hours after infusion. Critically, statistical analyses measured both monotonic and nonmonotonic trajectories of CBF change, while also attempting to dissociate nonspecific effects of ketamine from changes associated with antidepressant response (i.e., CBF change occurring in all patients while controlling for outcome vs. CBF changes correlated with symptom improvement). We anticipate that the results of this exploratory pilot study will inform approaches to larger scale studies of longitudinal effects of ketamine therapy on the depressed brain.

## MATERIALS AND METHODS

### Subjects

Depressed patients (n=11) provided informed written consent and acknowledgment from their treating physician prior to participating in this pilot study. Volunteers were between the ages of 27 and 62 years old, and met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) (American Psychiatric Association, 2000) criteria for non-psychotic major depression. Patients (1) were in a current depressive episode for at least 6 months, (2) had not responded to at least 2 adequate antidepressant trials, (3) had not changed antidepressant usage for the past 1-month, and (4) had no contraindications to a joint trial of ketamine infusion.

### Ketamine Therapy

Participants were administered a single sub-anaesthetic dose (0.5 mg/kg) of ketamine diluted in 60 cc normal saline administered intravenously over 40 minutes (Ibrahim et al., 2012; Niciu et al., 2014; Zarate et al., 2006). Vital signs were monitored every 3 minutes for any detections of blood pressure increase, respiratory rate decrease, or any unusual behavioral or psychological effects. No complications were experienced during ketamine infusion for any of the patients in this study.

### Clinical Assessments

The following assessment scores were documented for each of the pre- and post-infusion time points: Hamilton Depression Rating Scale, 17 item (HAMD-17) (Hamilton, 1980), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979),

and Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) (Rush et al., 2003).

## Image Acquisition

MR images were obtained using a 3T Siemens Allegra MRI scanner across 4 timepoints: at baseline prior to ketamine infusion and approximately 1hr, 6hrs and 24hrs after the end of infusion. Timepoints were chosen to capture well-established robust antidepressant response occurring 24 hours after infusion, as well as more modest response demonstrated to occur within hours of infusion in some studies (Ibrahim et al., 2011; Zarate et al., 2006). T1-weighted anatomical (MPRAGE) and fMRI continuous ASL (fMRI-ASL) scans were acquired at each scanning time point. The following continuous ASL sequence was used: 60 volumes (30 label, 30 control), 4×4×7.5 $mm^3$ resolution, 18 axial slices, repetition time 4000 ms, echo time 16 ms, label time 2100 ms, post label delay 1000 ms, and 95% duty cycle. Structural imagines were T1-weighted echo-planar navigated multiecho MRPAGE: echo/repetition times 1.74, 3.6, 5.46, 7.32/2530ms, inversion time 1260ms, flip angle 7 °, field of view 256 × 256 $mm^2$, 192 sagittal slices, 1.3×1×1 $mm^3$ resolution. Subjects were asked to close their eyes and rest while ASL data was acquired. Due to technical issues during image acquisition, ASL-fMRI data were not collected for one baseline scan and four follow-up scans (across 3 subjects); adjusted sample sizes are displayed in Table 1. Data for remaining timepoints were retained for analysis, and mixed effects statistical models were applied to compensate for missing datapoints (below).

## Image Preprocessing

Image preprocessing was completed in ASLtoolbox using MATLAB (*The Mathworks, Inc.*), and FSL (*FMRIB, Functional MRI of the Brain)*. ASL offers a quantitative measure of CBF directly measured with MRI in units mL/100g/min, which can be interpreted as reflecting metabolic needs (i.e., activity) of neurons and related cells. The quantitative nature of ASL offers an advantage over the more typical blood-oxygenation-level-dependent (BOLD) signal, where inferences regarding neuronal activity are made through relative contrast of T2* images reflecting blood oxygenation in BOLD rather than direct measurements of CBF in ASL (Detre and Wang, 2002). ASL images were corrected for motion in FSL prior to CBF quantification using ASLtoolbox (simple subtraction) to create CBF and pseudo-BOLD images (Wang et al., 2008). After voxelwise CBF was quantified for each series of ASL images with ASLtoolbox, an additional quality control step identified and removed volumes within each ASL series with non-neurobiological global CBF (gCBF). For each 30-volume ASL series, gCBF was calculated for each volume by averaging CBF values across all voxels within a mask (pseudo-BOLD > 100) (Wang et al., 2008). Per convention (Wang et al., 2008), gCBF calculations include gray- and white-matter tissue. Volumes with gCBF < 20 or >90 mL/100g/min were removed from the ASL series. Remaining volumes for each series were averaged using FSL to yield a single mean CBF image per study session and subject for subsequent statistical analyses (i.e., 1 averaged CBF image for each patient's baseline scan, 1 CBF image for each patient's ~1hr post-infusion scan, etc.). During this quality control process, one volume was removed for 8 ASL series, and two volumes were removed for one ASL series prior to averaging. For all other series, no volumes were removed prior to averaging.

Pseudo-BOLD images derived from fMRI-ASL data with the ASLtoolbox were used for anatomical registration and creation of masks. Intrasession alignment was performed between pseudo-BOLD (and CBF) images to their respective MPRAGE images, followed by intersession alignment to each patient's baseline MPRAGE image. Non-linear MNI transformation was then applied to each image. Each normalized CBF image (i.e. baseline, 1hr, 6hr, and 24hr) was smoothed (6 $mm^3$ FWHM) prior to statistical analyses. A group mask was created using SPM's grey matter (GM) template and averaged pseudo-BOLD images for statistical analyses and calculation of global CBF. Global CBF was calculated by averaging voxelwise CBF within this mask for each of the CBF images. All fMRI-ASL images were inspected for the presence of susceptibility or other artifacts, or low global CBF values (< 20 mL/100g/min). No CBF images were removed during these quality control checks.

## Statistical Analysis

All statistical analyses were performed in R (https://www.r-project.org) using lmer (Bates, Douglas et al., 2015) and oro.nifti (Whitcher et al., 2011) packages. First, linear mixed effects models were used to analyze CBF (dependent variable) focusing on the main effect of time (baseline, ~1hr, ~6hrs, ~24hrs). In one model, time was a numerical variable to examine monotonic increases (or decreases) in CBF over time. In a second model, time was a categorical factor to examine nonmonotonic changes in CBF over time (e.g., if CBF peaked after 1 hour but returned to baseline levels at 24 hours). In both models, nuisance regressors were modeled as such: subjects were the random factor while the independent variables age, gCBF, and ketamine response (% change in mean depression score 24 hours post-infusion) were fixed factors to control any variability in the magnitude of change in CBF over time related to these factors. Age has known correlations with CBF (Moeller et al., 1996; Zhang et al., 2018), and was therefore included as a nuisance variable. However, biological sex is not currently known to influence CBF or ketamine response, and was therefore not included in our statistical models for this pilot study. Future studies better powered to address biological sex are warranted. For multiple voxelwise comparisons, a false discovery rate (FDR) correction $q < 0.05$ was applied across all voxels (using R software).

Time by response interactions were also analyzed using linear mixed effects models, where time was modeled as a numerical or categorical variable as above, and response was defined as % change in mean depression score at 24 hours post-infusion (a numerical variable). Thus, all available data were used to estimate effects of response (i.e., 10 patients and 39 MRI total scans, Table 1). Again, subject was a random factor and time, age, gCBF, and ketamine response fixed. Similarly, multiple voxelwise comparisons were corrected at FDR $q < 0.05$.

In clusters exhibiting significant time-by-response interactions, additional pairwise analyses were applied post hoc to assess the direction of CBF change across the range of antidepressant response. Time by response interactions were calculated for 3 timepoint pairs: baseline vs. 1hr, baseline vs. 6hrs, and baseline vs. 24hrs post infusion. Linear mixed models

included age, gCBF, and subject as nuisance factors and multiple comparisons (Bonferroni) correction was applied ($\alpha = 0.05/3 = 0.017$).

## RESULTS

### Demographic information and clinical assessments

With a sample size of 11, the average age of the participants was 47.7 with a spread of 11.9 (Table 1). For this study, depression scores decreased significantly 24 hours after infusion, and improved by at least 50% for 5 of the 10 patients to qualify as responders (Table 1).

### Global CBF

There was no significant effect of time on monotonic or nonmonotonic change in global CBF (i.e., numerical time $x^2 = 1.44$ $p = 0.69$; categorical time $x^2 = 1.15$ $p = 0.28$). Change in global CBF also did not differ with respect to antidepressant response; no significant time by response interactions were noted (numerical time $x^2 = 2.90$ $p = 0.09$; categorical time $x^2 = 3.75$ $p = 0.29$).

### Regional CBF changes after ketamine infusion

Monotonic increases or decreases in CBF were detected across all subjects (i.e., time modeled as numerical factor controlling for antidepressant response). These changes are shown in Figure 1, panel A. Increased CBF was observed in the thalamus while decreases were shown in the lateral occipital cortex, $p_{FDR} < 0.05$. Significant nonmonotonic changes in CBF (i.e., time as categorical factor) were not noted, $p_{FDR} > 0.05$.

### Time by response interactions

Significant time by antidepressant response interactions were detected in several depression relevant brain regions when considering nonmonotonic changes (i.e., time as categorical), including ventral basal ganglia overlapping the pallidum and ventral striatum, and in medial prefrontal cortex (Figure 1B). Post hoc region of interest (ROI) tests assessed the direction of CBF change across antidepressant response in these regions. In ventral basal ganglia, significant negative relationships ($p_{Bonf} < 0.05$) were noted between change in depression score (baseline vs. 24h post infusion) and change in CBF from baseline to 1h (beta(SE) = −35.86(8.05), t = −4.46, p = 0.0008) and from baseline to 24h post infusion (beta(SE) = −20.86(4.56), t=−4.57, p=0.002). Here, nonresponders tended to exhibit decreased CBF after ketamine infusion. Positive associations were also noted in medial prefrontal cortex for CBF change from baseline to 6h post infusion ($p_{Bonf} < 0.05$), where responders tended to have decreased CBF after 6 hours (beta(SE) = 67.70(13.49), t=5.02, p=0.0002). Significant interactions were not apparent for monotonic CBF changes in voxelwise analyses, $p_{FDR} > 0.05$.

## DISCUSSION

In this pilot study, we demonstrate that ketamine influences brain function measured with ASL-fMRI. In the hours after a single administration of ketamine, resting brain function increased in thalamus and decreased in lateral occipital cortex in all patients, regardless

of antidepressant response to ketamine. CBF changes in ventral basal ganglia and medial prefrontal cortex were correlated with antidepressant response, suggesting that ketamine's effects on fronto-striatal regions may associate with clinical outcome, corroborating recent functional connectivity studies (Abdallah et al., 2017b, 2017a). Our study targets CBF change in a small sample of depressed patients at three 3 timepoints in the 24 hours after a single dose of ketamine, offering novel insight into the rapid effects of ketamine on brain function. Future studies with larger sample sizes and using multiple administrations of this drug are needed to assess the mechanisms of the rapid and long-term antidepressant actions of ketamine.

### Ketamine and altered attention

Ketamine is likely to affect brain function even in those patients who did not experience relief from depressive symptoms. Indeed, a number of studies have reported changes in brain function in participants without depression (Deakin et al., 2008; Scheidegger et al., 2012; Stone et al., 2012). Therefore, dissociating the "nonspecific" effects of ketamine on brain activity from those associated with antidepressant response may aid researchers attempting to understand the antidepressant mechanisms of this promising treatment. In our study, all patients exhibited increased CBF in the thalamus and medial occipital cortex, and decreased CBF in lateral occipital regions. This supports previous studies, which also demonstrated changes after ketamine in thalamus and visual cortex function in both depressed and nondepressed volunteers (Abdallah et al., 2017b; Deakin et al., 2008; Evans et al., 2018; Sahib et al., 2020). These effects could be interpreted in several different ways. In high doses, ketamine is used as an anesthetic to render a patient unconscious; therefore, lower doses of ketamine may influence perceptual awareness and attention (Sousa, 2013) and brain regions associated with awareness and attention (Scheidegger et al., 2012). Subanesthetic ketamine can also be associated with visual disturbances not related to psychotomimetic effects (e.g., double vision; (Wan et al., 2015)); visual cortex CBF changes may reflect general effects of ketamine on basic visual perception. Note that volunteers were instructed to keep their eyes closed during this study, which may explain discrepancies between the direction of brainactivity change in this study vs. others where volunteers had eyes open (Abdallah et al., 2017b; Evans et al., 2018; Sahib et al., 2020). It is also possible that these so-called nonspecific effects of ketamine play a role in antidepressant or placebo response, though they appear to occur in responders, nonresponders, and controls without depression. Future studies designed to target the interactions between these "nonspecific" effects in attentional/perceptual systems and antidepressant effects in limbic/default-mode systems may be illuminating.

### Rapid antidepressant response to ketamine correlates with fronto-striatal function

The purpose of this study was to get a better understanding of the antidepressant mechanisms of ketamine through observation of its effects on resting cerebral blood flow with ASL-fMRI. Previous functional neuroimaging studies have noted changes in basal ganglia, dorsal anterior cingulate cortex, and default mode networks in depressed patients undergoing ketamine infusion (Abdallah et al., 2018, 2017b, 2017a; Sahib et al., 2020). In our study, CBF changes in the pallidum, ventral striatum, and medial prefrontal cortex were correlated with changes in depressive symptoms, suggesting that fronto-striatal

networks associated with the reward and default-mode systems may be involved in acute antidepressant response to single infusions of ketamine. Though our study was open-label, our results are consistent with studies that included a placebo control (Reed et al., 2019) and offer additional novel insight into acute changes in brain function occurring in the first hours after infusion. Confirmation of these ASL-fMRI results with larger sample size, placebo- or active-comparator, and/or long-term follow-up is needed to determine the relationship between ketamine's effects on fronto-striatal function and sustained antidepressant response.

## Limitations

Limitations of this pilot study are as follows: sample size, variation in the sample such as age and gender, limited number of ketamine infusions, and dosage. Lack of placebo or active control must also be considered. However, CBF changes occurring in all patients (i.e., in thalamus and visual cortex) are less likely to be influenced by the placebo effect because they occurred even in those volunteers whose symptoms did not improve with treatment. Furthermore, given the clear superiority of ketamine over placebo in reducing depressive symptoms (Singh et al., 2016; Zarate et al., 2006), frontostriatal changes correlated with antidepressant response may be more related to true antidepressant response, rather than the placebo effect. Volunteers were also treatment refractory, and current/past medication use may have influenced response to ketamine, though we are not aware of studies reporting such effects. For future studies, a larger sample size with placebo or active comparator, comprehensive mediation histories, and more variability in age and gender may be informative. Scanning time points taken more or less frequently may provide additional insight into the effect of ketamine in the brain, particularly with respect to response maintenance. Results obtained after multiple ketamine infusions or increased/decreased dosage may improve the efficacy of ketamine and its antidepressant affects, which may also impact ketamine's effects on brain function.

## Conclusions

Despite the limitations of this pilot study, these results nevertheless constitute a novel contribution to the ketamine MRI literature by measuring quantitative CBF at four timepoints in the 24 hours after a single infusion of ketamine to treat depression. Consistent with previous studies in depression and nondepressed controls (Abdallah et al., 2017b; Evans et al., 2018; Sahib et al., 2020), ketamine associated with acute CBF change in the thalamus and visual cortex in all patients regardless of antidepressant outcome in our study. Despite our relatively small sample size, these effects survived strict statistical correction and appeared to be robust across all subjects when single-subject data were visualized (i.e., Figure 1A right panels). CBF change in medial frontal cortex and basal ganglia associated with antidepressant response 24 hours after ketamine infusion. These results were also consistent with previous studies (Abdallah et al., 2018, 2017b, 2017a) and survived strict statistical corrections; however, these results in particular should be interpreted with caution given our sample size and lack of an active or placebo comparator. Future studies are needed with larger sample sizes targeting multiple infusions of ketamine, and perhaps using PET-fMRI to simultaneously measure the molecular and brain-network consequences of this promising treatment for depression.

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## Highlights

- Ketamine's effects on cerebral blood flow were measured over 24 hours
- Blood flow in thalamus and visual cortex changed after ketamine
- Ketamine's antidepressant response associated with fronto-striatal change
- These promising pilot results require further study

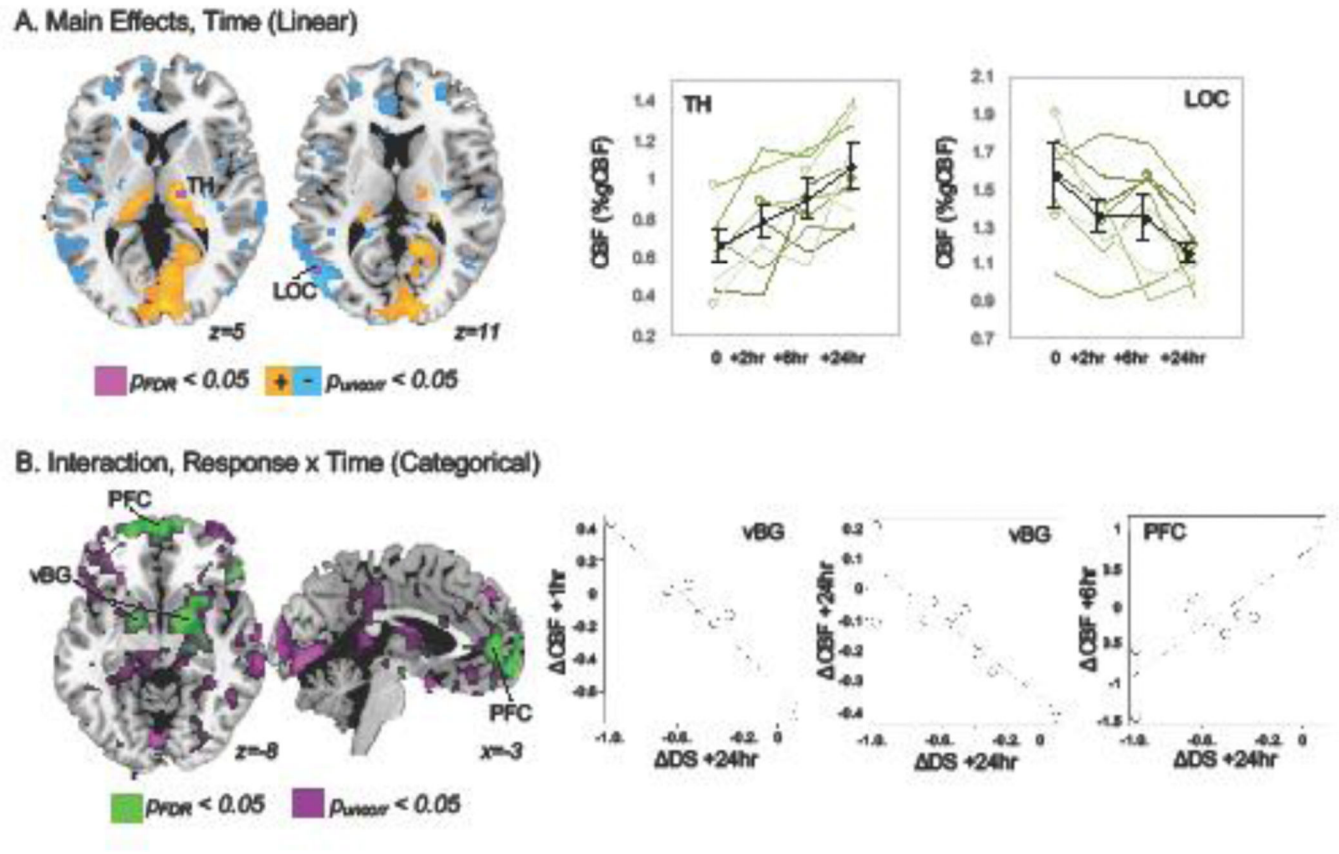


**Figure 1.**

**A.** Monotonic changes in CBF were noted after ketamine infusion in patients with depression. A cluster in the thalamus (TH) exhibited significant increased CBF over time, while a cluster in lateral occipital cortex (LOC) showed significant decreases, pFDR < 0.05 (green). At more permissive thresholds (puncorr < 0.05, orange/blue), decreased CBF was also noted in anterior cingulate and dorsomedial prefrontal cortex, and increased CBF was noted in medial visual cortex. Mean CBF (% global CBF) is plotted for TH and LOC clusters in the top-right panels for all patients in black and for each individual subject in shades of green to demonstrate consistency of these changes across subjects. Subjects with missing data are plotted with open circles. **B.** Non-monotonic changes in CBF differed according to antidepressant response in time-by-response interactions. Bilateral ventral basal ganglia (vBG, including pallidum and ventral striatum) and medial prefrontal regions (PFC) exhibited significant interactions, pFDR <0.05 (green). Scatter plots display relationships between change in (delta, Δ) in CBF and change in depression symptoms (averaged across three inventories) meeting statistical criterion in post hoc analyses (pBonf < 0.05).

**Table 1.**

Patient Characteristics

| **Demographics** | **Depressed** | | | |
|---|---|---|---|---|
| Sample Size | n = 11 | | | |
| Age, Mean (SD) | 47.7 (11.90) | | | |
| Sex, Females : Males | 3:8 | | | |
| | **Baseline** | **Post-1hr** | **Post-6hr** | **Post-24hr** |
| HDRS-17, Mean (SD) | 22.44 (3.68) | 13.33 (9.39) | 9.80 (8.48) | 9.00 (7.67) |
| MADRS, Mean (SD) | 34.89 (3.44) | 21.11 (13.52) | 15.30 (12.54) | 16.00 (13.58) |
| QIDS-SR, Mean (SD) | 17.78 (7.60) | 13.44 (7.60) | 10.80 (8.50) | 10.40 (6.69) |
| Corrected Sample Size | n = 10 | n = 9 | n = 10 | n = 10 |

Abbreviations: HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptoms.

**Table 2.**

MNI Coordinates

| | | | Peak Coordinate MNI | | |
|---|---|---|---|---|---|
| **Statistical Test** | **Brain Region** | **Volume** | **X** | **Y** | **Z** |
| Time, numerical | Right Thalamus | 232 | 16 | −18 | 4 |
| | Left Lateral Occipital Cortex | 168 | −52 | −66 | 12 |
| Time, categorical | n/a | | | | |
| Response*Time, numerical | n/a | | | | |
| Response*Time, categorical | Medial Prefrontal & Anterior Cingulate Cortex | 8578 | 44 | 79 | 17 |
| | Right Ventral Striatum | 9176 | 42 | 57 | 27 |