Anhedonia—which is defined as diminished pleasure from, or interest in, previously rewarding activities—is one of two cardinal symptoms of a major depressive episode. However, evidence suggests that standard treatments for depression do little to alleviate the symptoms of anhedonia and may cause reward blunting. Indeed, no therapeutics are currently approved for the treatment of anhedonia. Notably, over half of patients diagnosed with bipolar disorder experience significant levels of anhedonia during a depressive episode. Recent research into novel and rapid-acting therapeutics for depression, particularly the noncompetitive N-Methyl-D-aspartate receptor antagonist ketamine, has highlighted the role of the glutamatergic system in the treatment of depression; however, it is unknown whether ketamine specifically improves anhedonic symptoms. The present study used a randomized, placebo-controlled, double-blind crossover design to examine whether a single ketamine infusion could reduce anhedonia levels in 36 patients with treatment-resistant bipolar depression. The study also used positron emission tomography imaging in a subset of patients to explore the neurobiological mechanisms underpinning ketamine’s anti-anhedonic effects. We found that ketamine rapidly reduced the levels of anhedonia. Furthermore, this reduction occurred independently from reductions in general depressive symptoms. Anti-anhedonic effects were specifically related to increased glucose metabolism in the dorsal anterior cingulate cortex and putamen. Our study emphasizes the importance of the glutamatergic system in treatment-refractory bipolar depression, particularly in the treatment of symptoms such as anhedonia.

**INTRODUCTION**

Over half of patients diagnosed with bipolar disorder (BD) suffer from significant levels of anhedonia, as defined as loss of enjoyment in, or desire to engage in, previously pleasurable activities. Notably, anhedonic patients with affective disorders have a poorer treatment prognosis than their non-anhedonic counterparts. Indeed, accumulating evidence suggests that standard treatments for depression do little to alleviate anhedonia and may even cause reward and emotional blunting, sexual anhedonia and anorgasmia. Furthermore, the presence of anhedonia in a major depressive episode (MDE) is a predictor of proximal suicide completion. Critically, no US Food and Drug Administration-approved treatment currently exists specifically for anhedonia.

The Diagnostic and Statistical Manual-5 (ref. 14) identifies anhedonia as one of two cardinal symptoms in the diagnosis of an MDE in both major depressive disorder (MDD) and BD. Anhedonia can be subdivided into consummatory (subjective pleasure, for example, enjoying food) and motivational components (anticipation of and drive towards rewarding stimuli, for example, planning and looking forward to a vacation) that have distinct biological bases.

Indeed, research suggests that currently depressed MDD and BD patients may possess a substantial deficit in motivational, but not consummatory, reward behaviors. Studies using the sweet taste test—a task that mirrors preclinical assessments of consummatory anhedonia in rodents—found that patients with MDD demonstrated the same preference for sucrose water concentrations as healthy volunteers. Furthermore, Sherdell et al. found that MDD patients experienced the same levels of pleasure as healthy volunteers while viewing humorous cartoons in a computer task, but were not willing to exert as much effort to gain access to these stimuli; the results suggest intact consummatory processes, but attenuated motivational ones. In another study, Etain et al. found no evidence for consummatory anhedonia in BD patients. Although research pertaining to BD patients in particular is lacking, overall, the extant evidence suggests that anhedonia in depression is primarily associated with a deficit in non-consummatory reward behaviors. Understanding the neural pathways that mediate anticipatory pleasure is thus a critical step towards successful treatment of anhedonia.

Dopaminergic signaling has been consistently correlated with the anticipation, motivation and learning related to pleasurable stimuli, but not to their consumption. Phasic bursts in dopaminergic neurons in the ventral tegmental area (VTA) have reliably been shown to co-occur with violations in reward expectancy, underscoring the evidence for dopaminergic signalling in reward learning. Furthermore, dopamine signalling in the nucleus accumbens, an area of dense dopaminergic projections from the VTA, has been strongly associated with reward motivation in rodents. Functional neuroimaging in humans indicates that structures such as the VTA, substantia nigra, amygdala, putamen, caudate, ventral striatum, and orbitofrontal cortex—all of which receive innervation from or project to dopaminergic nuclei—are recruited during reward anticipation.
Despite the abnormalities in motivational behaviors seen in affective disorders, there is a dearth of robust evidence pertaining to any direct dopaminergic signaling deficit in patients with depression. The strongest indirect evidence for dopaminergic dysfunction in depression comes from pharmacological treatment studies. For instance, the dopamine D2 receptor agonist pramipexole improved levels of depression in both MDD and BD patients after several weeks of daily administration. A study of Parkinson's disease patients with co-occurring depression used the Snaith–Hamilton Pleasure Scale (SHAPS), and found that pramipexole treatment decreased anticipatory anhedonia levels by 25% across the entire sample, however, it is unknown whether this reduction occurred as a function of improvement in mood, Parkinson's symptomatology or hedonic capacity. It is presently unclear whether anhedonic symptoms in depression improve faster with dopaminergic-enhancing medications than with standard treatments. Furthermore, because improvements in self-reported levels of anhedonia are reportedly the last symptom to improve with selective serotonin reuptake inhibitors, there is a critical unmet need for rapid-acting treatments for anhedonia. The fact that standard antidepressants lack any proven anti-anhedonic efficacy, particularly in conjunct with the deleterious side effects associated with these agents, requires novel pharmacotherapeutic approaches.

The noncompetitive N-Methyl-D-aspartate (NMDA) receptor antagonist ketamine has shown remarkable consistency in rapidly ameliorating depressive symptoms in both MDD and BD. However, it is unknown whether ketamine also possesses any specific anti-anhedonic efficacy. Given the likely mechanistic heterogeneity of depression, it is critical to understand the specific targets of treatment response at both the clinical and neural levels, as outlined in the research domain criteria. Ketamine acts directly on the glutamatergic system, which appears to be critical in depression; however, little is known about the specificity of the relationship between commonly occurring symptoms during an MDE (for instance, anhedonia, anxiety) and particular biological phenotypes. In a small sample investigation, Walter et al. found that MDD patients with high levels of anhedonia had lower levels of glutamate, but not glutamine, than healthy controls, but only a trend towards lower levels of anhedonia had lower levels of glutamine, but not glutamate, than MDD patients with low levels of anhedonia, who did not differ from controls. Preclinical evidence suggests that blockade of astrocytic glutamate reuptake in rodents can induce anhedonia-like behaviors, particularly in the prefrontal cortex. In addition, ketamine and memantine have been shown to reverse anhedonic phenotypes in rodents. However, preclinical evidence typically classifies anhedonia as a decrease in consummatory behavior; although anticipatory and consummatory behaviors likely interact, extrapolating from rodent behaviors to clinical patient symptoms is not straightforward. Sub-anesthetic doses of ketamine acutely increase glutamatergic and dopaminergic signaling in the prefrontal cortex of rats. Given the apparent role of dopaminergic and glutamatergic signaling in mediating anhedonia and the reported pharmacological effects in both rodents and humans, ketamine may be ideally suited to specifically ameliorate anticipatory anhedonia in currently depressed patients.

This randomized, double-blind, placebo-controlled, crossover study assessed the anti-anhedonic efficacy of ketamine in treatment-resistant BD patients currently experiencing an MDE. Regional neural metabolism following both placebo and ketamine infusions were also measured in a subsample of these patients using fluorodeoxyglucose (FDG) positron emission tomography (PET). FDG-PET measures glucose metabolism, which is primarily determined by glial uptake of glucose in response to glutamate release from neurons, and principally reflects glutamatergic neurotransmitter release and cycling. It is important to note that approximately all glucose entering the central nervous system is transformed into glutamate. Thus, FDG-PET provides an indirect quantitative measure of cerebral glutamate metabolism throughout the entire brain. The effects of ketamine on general depressive symptoms in the majority of BD subjects presented here (33/36, 92%) were previously reported together with neurobiological correlates of mood improvement derived from FDG-PET. The present study specifically explores the previously unaddressed issue of ketamine's anti-anhedonic effects and its neural correlates in this sample.
stabilizer (either lithium or valproic acid) administered at therapeutic levels during the course of the study, although this was not adequate to alleviate depressive symptoms. Aside from monotherapy with a mood stabilizer, no psychotropic medication or psychotherapy was permitted in the 2 weeks before study randomization (5 weeks for fluoxetine) or during the 4-week study period. Written informed consent was obtained from all participants, and the NIH Combined Neuroscience Institute Review Board approved the study.

**Design**

The study was designed as a randomized, double-blind, placebo-controlled, crossover study to assess the antidepressant efficacy of ketamine in patients with treatment-refractory BD. All participants received one intravenous infusion of ketamine hydrochloride, administered at a subanesthetic dose of 0.5 mg kg$^{-1}$, and one infusion of placebo (0.9% saline solution) in a randomized order over a 4-week study period, and with 2 weeks between each infusion. A MADRS score ≥ 20 on the morning of each infusion was required for study continuation. An anesthesiologist administered each infusion over 40 min using a Baxter infusion pump (Deerfield, IL, USA). The two solutions and the appearance of the drug syringe were identical and all study team members were blind to the drug condition.

Clinical ratings were acquired 60 min before the infusion and thereafter at 0.5, 1, 2, 3, 7, 10, and 14 and following each infusion. The primary outcome variable for antidepressant efficacy was the MADRS score. However, the main symptom of interest for this report is anhedonia, and levels of anticipatory anhedonia were evaluated using the SHAPS. The SHAPS has a 14-item, self-administered, user friendly and state-sensitive psychometric scale that overcomes limitations associated with other scales that specifically assess anhedonia, such as length and cultural idiosyncrasies. Importantly, the SHAPS has been validated in a number of independent samples since its publication. The SHAPS was scored on a scale of one to four, with higher scores indicating greater anhedonia (range 14–36), and was administered with reference to either the past 24 h or the time between the present and the previous rating. The presence or absence of anhedonia was judged on the basis of the original scoring guidelines (range 0–14), where a score > 3 indicated clinically significant anhedonia (see Table 1). Other secondary outcome variables were also assessed and have been reported previously.

**Positron emission tomography acquisition and analysis**

In addition, 21 of the 36 patients (see Table 1) underwent two resting-state 18FDG-PET imaging scans, which began 2 h post infusion and ended (brain emission scan) ~1.5 h later. Immediately before both scans, patients completed psychometric rating scales; identical procedures were followed for both scans. PET imaging was performed on a GE Advance PET scanner (GE Medical Systems, Waukega, IL, USA) in three-dimensional mode (35 contiguous slices, 4.25 mm plane separation) following an intravenous infusion of 4.5 mCi 18FDG over 2 min. According to the method used by Brooks, quantitative images of regional cerebral metabolic rate for glucose metabolism (rCMRGlu) were calculated using a cardiac input function derived from a dynamic left ventricular scan collected before both the brain emission scan and venous sampling (reconstructed resolution = 6 mm full-width at half-maximum in all planes). Magnetic resonance imaging (MRI) images were acquired on a 3-Tesla scanner (Signa, GE Medical Systems) using a three-dimensional MPRAGE sequence (echo time = 2.982 ms, repetition time = 7.5 ms, inversion time = 725 ms, voxel size = 0.9 × 0.9 × 1.2 mm) to allow anatomic localization of PET activity. PET analyses comprised both a region of interest approach (ROI) and a whole-brain investigation.

The ROI analysis pipeline used here has been previously described. Briefly, the Analysis of Functional Neuroimages (AFNI; Bethesda, MD, USA) function 3dSkullStrip was used to remove non-brain tissue from the anatomical MRI image. These images were segmented into gray and white matter, and cerebrospinal fluid (separate binary mask images were computed for each component) using the FSL (Oxford, UK) automated segmentation tool. Anatomical images were spatially normalized to the Montreal Neurological Institute 152 template. ROIs (ventral striatum and orbitofrontal cortex) were selected on the basis of extant literature implicating these neuroanatomical structures in depression and reward anticipation. The ventral striatum ROI comprised only the nucleus accumbens and olfactory tubercle. Template-defined ROIs were transferred to the individual anatomical MRIs; to accommodate interindividual anatomical variation, ROI placement was adjusted per subject. ROIs were transferred back to the native MRI space, multiplied by a binary gray matter mask and applied to the rCMRGlu PET images. Mean glucose metabolism rate values, normalized by total gray matter, were then calculated.

For the whole-brain investigation, 18FDG-PET images were preprocessed and analyzed using Statistical Parametric Mapping software (SPM; Wellcome Trust Centre for Neuroimaging, London, UK) version 5 within the MATLAB (MathWorks, Natick, MA, USA) environment. Post-placebo and post-ketamine rCMRGlu images were separately co-registered to the anatomical image; the anatomical image was then normalized to Montreal Neurological Institute space and this transformation was applied to the co-registered PET images. A Gaussian smoothing kernel (8 mm full-width at half-maximum) was applied to the PET images. To create difference images for each individual, PET images were first normalized by the global mean (as calculated in SPM) and the post-placebo image was subtracted from the post-ketamine image. A binary mask was applied to all whole-brain investigations to limit the number of multiple comparisons to only intracerebral voxels.

**Statistical analyses**

Symptom rating scale analysis included all available data and was conducted using IBM SPSS (Armonk, NY, USA; version 21). Linear mixed models, using a first-order autoregressive covariance structure and restricted maximum likelihood estimation, were performed to assess the effects of ketamine versus placebo on SHAPS scores over the 4-week period in this crossover design. Fixed main effects of time and drug and their interaction were included along with a random effect for subject. To correct for baseline levels of anhedonia, the SHAPS score at baseline on each infusion day (time point ~ 60) was entered as a covariate into the model. In addition, a linear mixed model with total MADRS score (at each individual time point) entered as a covariate was conducted to evaluate whether ketamine infusion was associated with a change in SHAPS score independent of the effect on other depressive symptoms. MADRS item 8 (inability to feel) was removed from the total MADRS score for this analysis due to its strong conceptual overlap between this item and the SHAPS. Post hoc Bonferroni-corrected comparisons were conducted for both models for all post-baseline time points to determine the specific timing of the anti-anhedonic effects. All significance values were two-tailed, with a significance threshold of $P < 0.05$.

The time point of 230 min was a priori selected for both the ROI and whole-brain analyses on the basis of three factors: previous studies indicating that 230 min is a sensitive time point for detecting antidepressant effects of ketamine, lack of photomimetic effects at this time point; and the proximity to the time of the PET scan. Relationships between glucose metabolism in our ROIs (post-placebo and post-ketamine) and their difference and SHAPS scores were investigated using Pearson product moment correlation coefficients. First, percentage improvement in SHAPS score at 230 min post infusion (post-ketamine 230 – post-placebo 230) was correlated with difference in mean ROI rCMRGlu metabolism (post-ketamine–post-placebo). Second, because we previously demonstrated an association between ventral striatum metabolism changes and overall depression score change following ketamine, we conducted a multiple linear regression analysis to parse the variance associated with anhedonia and total depression score and explore which variable predicted change in ventral striatum metabolism. Finally, as a control analysis, we also assessed whether state-dependent anhedonia levels, as measured by raw SHAPS score, were associated with ROI rCMRGlu, both variables post-ketamine and post-placebo.

Complementing the ROI analysis, the whole-brain investigation comprised the following multiple regression analyses. First, percent improvement on the SHAPS at 230 min (as above) was regressed onto the difference images (post-placebo–post-ketamine). Second, to assess the specificity of the results to anhedonia, and not depressive symptoms per se, we recomputed the whole-brain analyses with percentage change anhedonia scores orthogonalized to the corresponding percentage change in MADRS score (minus item B) using the SPMM$^\text{s,morth}$ function within the MATLAB environment. This single regression model was then orthogonalized to total MADRS score (minus item B). Orthogonalization of one variable against another, in this instance the SHAPS against the MADRS score, results in the removal of shared variance; the output variable represents the residual SHAPS score when the variance associated with the MADRS has been accounted for. Here, we report only those analyses that survived stringent Gaussian random field theory cluster correction for...
RESULTS

Subjects

Patient demographic details are presented in Table 1. One patient was excluded from the PET analyses due to a failure to measure the cardiac input function, and another subject was excluded because there was no SHAPS scale score measurement at 230 min post-ketamine and post-placebo infusions.

Behavioral response

Main effects of drug (F(1,119) = 24.71, P < 0.001) and time (F(9,194) = 2.69, P = 0.006) were observed, as was a trend towards an interaction between these two variables (F(9,186) = 1.90, P = 0.053); this indicates that ketamine caused a greater reduction in levels of anhedonia across time than placebo. (Figure 1a).

Bonferroni-corrected post-hoc comparisons demonstrated that ketamine, compared with placebo, significantly decreased levels of anhedonia at multiple times throughout the 14-day period following a single ketamine infusion (Figure 1a).

Consistent with previous reports, levels of anhedonia (as measured by the SHAPS) and depressive symptoms (as measured by total MADRS score) were positively correlated (r(20) = 0.06, P = 0.81; r(19) = 0.03, P = 0.91; r(19) = 0.10, P = 0.68) nor post-ketamine (r(20) = 0.06, P = 0.81; r(20) = 0.06, P = 0.81).

PET: ROI analyses

Ketamine-induced change in ventral striatum rCMRGlu was significantly related to percent change in SHAPS score at 230 min post infusion (t(19) = −0.52, P = 0.02; Figure 1c). Relative to placebo, individuals with the largest increase in glucose metabolism in the ventral striatum tended to have the highest anti-anhedonic response to ketamine. However, orbitofrontal cortex rCMRGlu activity was not significantly related to anti-anhedonic response to ketamine (t(19) = −0.37, P = 0.12). Because we had previously demonstrated a relationship between ventral striatum change in glucose metabolism and improvement in MADRS score following ketamine, we tested whether this relationship was specific to anhedonia. Multiple regression, including both SHAPS and MADRS (minus item 8), indicated that change in MADRS (t = −2.18, P = 0.045), but not SHAPS (t = −0.05, P = 0.96), significantly predicted change in ventral striatum rCMRGlu.

Examining each session separately, we found no significant correlations between absolute SHAPS scores and ventral striatum or orbitofrontal cortex rCMRGlu, respectively, neither post placebo (t(19) = 0.03, P = 0.91; t(19) = 0.10, P = 0.68) nor post ketamine (t(20) = 0.06, P = 0.81; t(20) = 0.06, P = 0.81).

PET: Whole-brain analyses

Due to the presence of a large cluster, the statistical threshold was raised to 0.025 uncorrected, as opposed to 0.05, for the initial difference image contrast only. Whole-brain analyses revealed a significant relationship between percent improvement (decrease) in SHAPS scores and rCMRGlu increases in the dorsal anterior cingulate cortex (dACC; x = −6, y = 40, z = 43; t(17) = 4.39, P corr = 0.016; Figure 1d). Furthermore, we found a significant increase in cerebellum (x = −40, y = −48, z = −58; t(17) = 1.94, P corr = 0.0019; Table 2), and a trend towards an increase in striatal, rCMRGlu (x = 14, y = 4, z = 10; t(17) = 4.28, P corr = 0.051; Figure 1e), in relation to the percent amelioration in SHAPS scores. Importantly, the striatal cluster extended from the caudate to the putamen and into the ventral striatum (Table 2), corroborating our ROI analysis. The inverse contrast (the relationship between decreases in rCMRGlu and change in SHAPS score) did not yield any whole-brain corrected results.

Because our ROI results indicated that metabolic increases in the ventral striatum appear to be driven by change in total depression score but not levels of anhedonia, we conducted a subsequent whole-brain analysis. In this model, change in SHAPS score was orthogonalized to change in MADRS score, both at 230 min, and this orthogonalized change in SHAPS score was regressed onto the rCMRGlu difference image. This regression revealed that the specific changes in anhedonia levels following ketamine—which were not related to general changes in depressive symptoms—were in fact associated with increased dACC metabolism (x = −8, y = 40, z = 28; t(17) = 4.89, P corr = 0.0027; Figure 1f) that extended into the pregenual cingulate/callosal region and the right dorsolateral prefrontal cortex. In addition, a trend was noted towards significantly increased metabolism in the fusiform gyrus (x = 34, y = −28, z = −20; t(17) = 3.74, P corr = 0.0065) that extended into the claustrum and the putamen, but not the ventral striatum. Finally, we assessed whether change in rCMRGlu was associated with longer-term SHAPS response by correlating the difference in dACC (peak voxel; ketamine-placebo)
Figure 1. Anti-anhedonic effect of ketamine and corresponding regression analyses with cerebral glucose metabolism. (a) Snaith–Hamilton Pleasure Scale (SHAPS) estimated scores from linear mixed model 1 (M1) indicating a significant reduction in anhedonia levels following ketamine (red) compared with placebo (blue). (b) Model 2 (M2) is the same as model 1 (M1) but has total depression score (as assessed by the Montgomery–Åsberg Depression Rating Scale (MADRS) minus item 8) entered as a covariate and still reveals a main effect of drug, thus underscoring the unique anti-anhedonic effect of ketamine administration. Asterisks indicate Bonferroni-corrected comparisons at $P < 0.05$ for both A and B. (c) Region of interest analysis with ventral striatum (VS) demonstrating a significant association between anti-anhedonic response to ketamine and increased glucose metabolism in the VS. Changes in anhedonia levels no longer significantly predicted VS change when change in overall depressive symptoms were controlled for. (d, e) Whole-brain corrected relationship between the anti-anhedonic effects of ketamine and dorsal anterior cingulate cortex (dACC), cerebellum, right putamen, VS and medial posterior orbitofrontal cortex increases in glucose metabolism. (f) Whole-brain corrected relationship between SHAPS score orthogonalized against MADRS score indicating that a significant increase in dACC metabolism was associated specifically with anti-anhedonic response to ketamine independent of overall change in depressive symptoms. Error bars represent standard errors. PET images are presented (d and e, $P < 0.025$ uncorrected; f, $P < 0.05$ uncorrected) such that only clusters surviving family-wise error correction are shown. Color bars indicate positive $t$-values associated with increasing glucose metabolism. ket, ketamine; pla, placebo; rCMRGlu, regional cerebral metabolic rate for glucose metabolism.
metabolism with change in SHAPS scores at day 14. There was no significant relationship between change in dACC glucose metabolism and the magnitude of the change in SHAPS score at day 14 ($r_{(18)} = 0.11, P = 0.66$).

**DISCUSSION**

Several notable findings emerged from this study investigating the effects of the rapid-acting antidepressant ketamine on anhedonia in currently depressed treatment-resistant BD patients. Foremost among these findings is that ketamine, compared with placebo, rapidly reduced the levels of anhedonia in these patients; this reduction occurred within 40 min of a single ketamine infusion and lasted up to 14 days. Furthermore, we found that anti-anhedonic effects of ketamine remained significant even when controlling for level of depressive symptoms, suggesting that ketamine has a unique role in ameliorating anhedonia levels independent of other depressive symptoms. This study also used $^{18}$FDG-PET to examine a subgroup of these patients and quantify the rCMRGlux correlates of change in anhedonia levels associated with ketamine treatment. Our PET results demonstrated that the neurobiology of this specific anti-anhedonic effect was mediated in part by increases in glucose metabolism in the dACC, and tentatively the putamen, but not the ventral striatum as originally hypothesized.

These results are particularly important from a public health perspective. No approved treatments for anhedonia currently exist despite its prevalence across multiple psychiatric disorders. Thus, ketamine’s rapid effects (within 1 h) on anhedonia levels are a crucial clinical finding. Currently available standard treatments for depression, such as selective serotonin reuptake inhibitors, have few positive effects on levels of anhedonia in MDD patients and, indeed, have occasionally deleterious effects; $^{6,11,13}$ no research to date has assessed the effects of mood stabilizers on levels of anhedonia in individuals with BD. Our results lend credence to the notion that similar compounds (for example, other NMDA receptor antagonists) should be explored for their clinical relevance in treating this debilitating symptom of depression. The results further suggest that more typically anhedonic subtypes of depression (both MDD and BD)—for instance, melancholic depression—may be particularly suited to treatment with ketamine and its analogs.

Given our previous finding$^{59}$ that improvement in total depression score on the MADRS was associated with increased ventral striatum rCMRGlux following ketamine, we hypothesized that this region would also be strongly related to anhedonia and its amelioration. Unexpectedly, we found that ventral striatal glucose metabolism was not associated with relative changes in anhedonia levels after controlling for levels of depression. Possible reasons for this result include the severity of illness in these treatment-resistant BD subjects, the underlying biology of the ventral striatum or the distinct symptom assessed by the SHAPS in comparison with the MADRS. Alleviating depressive symptoms is intensely relieving, and thus also rewarding, for treatment-refractory patients. Intriguingly, opioid receptors in the medial accumbens shell are believed to be solely responsible for ‘liking’ or consummatory pleasure behaviors,$^{74}$ whereas motivational hedonic behaviors are thought to arise from a wide array of receptors within the accumbens—the primary structure in the ventral striatum—as well as other neural structures; $^{18}$FDG-PET cannot currently differentiate these structures. Tentatively, we hypothesize that patients showing the greatest antidepressant response to ketamine, as measured by the MADRS, may be experiencing high levels of pleasure, a construct not assessed by the SHAPS. Further investigations are needed to disentangle specific symptoms from the systems level antidepressant mechanisms of action of ketamine in humans.

However, our study did find that individuals with the largest increase in glucose metabolism (post-ketamine–post-placebo) in the dACC and the putamen had the greatest clinical reduction in anhedonia levels; notably, this was true with and without controlling for total depression score. Findings from both human and animal studies indicate that both the dACC and putamen are highly involved in reward processing, learning and decision-

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**Table 2.** $^{18}$FDG-PET imaging results

| Region                          | MNI coordinate | t-value | Uncorrected threshold | $P_{FWE-Corr}$ | $P_{FDR-Corr}$ | Extent |
|--------------------------------|----------------|---------|-----------------------|----------------|----------------|--------|
| **Ketamine–Placebo vs SHAPS improvement** |                |         |                       |                |                |        |
| dACC                           | −6 40 30       | 4.39    | $P < 0.025$           | 0.014          | 0.016          | 2494   |
| dACC                           | 4 30 32        | 4.20    |                       |                |                |        |
| SMG                            | −2 50 42       | 3.82    |                       | 0.051          | 0.030          | 1934   |
| Head of caudate                | 14 4 10        | 4.24    |                       |                |                |        |
| Putamen                        | 20 14 −8       | 4.20    |                       |                |                |        |
| VS/posteromedial OFC           | 14 14 −14      | 4.17    |                       |                |                |        |
| Cerebellum lobule V1b          | −40 −48 −58    | 3.94    |                       | 0.019          | 0.016          | 2370   |
| Cerebellum lobule III          | −4 −46 −26     | 3.66    |                       |                |                |        |
| Cerebellum lobule VIIIa        | −12 −68 −44    | 3.53    |                       |                |                |        |
| **Ketamine–Placebo vs SHAPS orthogonalized to MADRS improvement** |                |         |                       |                |                |        |
| dACC                           | −8 40 28       | 4.89    | $P < 0.05$           | 0.027          | 0.042          | 4686   |
| Pregenual/callosal cingulate   | −6 34 8        | 3.62    |                       |                |                |        |
| DLIFC                          | 30 40 36       | 3.18    |                       |                |                |        |
| Fusiform gyrus                 | 34 −28 −20     | 3.74    |                       | 0.065          | 0.052          | 3896   |
| Claustrum                      | 34 8 −6        | 3.51    |                       |                |                |        |
| Putamen                        | 22 14 −6       | 3.48    |                       |                |                |        |

Abbreviations: dACC, dorsal anterior cingulate cortex; DLIFC, dorsolateral prefrontal cortex; 18FDG-PET, $^{18}$F fluorodeoxyglucose-positron emission tomography; MADRS, Montgomery–Åsberg Depression Rating Scale; SHAPS, Snith–Hamilton Pleasure Scale; SMG, superior medial gyrus; OFC, orbitofrontal cortex; rCMRGlux, relative cerebral metabolic rate of glucose; rCMRGlux, regional cerebral metabolic rate of glucose; MNI, Montreal Neurological Institute; SPM, Statistical Parametric Mapping; PWE-Corr, P value corrected for multiple comparisons using the family-wise error (FWE) correction; P FDR-Corr, P value corrected for multiple comparisons using the false discovery rate (FDR) correction. The three most significant sub-peaks are given for each cluster. Montreal Neurological Institute (MNI) coordinates indicate the distance (in millimeters) from the stereotaxic origin (anterior commissure), with x representing the lateral distance from the origin (positive numbers to the right), y representing the anterior–posterior dimension (positive numbers anterior) and z representing the dorsal–ventral dimension (positive numbers dorsal).
making. 75–78 Shidara and Richmond79 demonstrated that reward expectancy, or motivation, was highly correlated with single neuron signals in the monkey ACC (area 24c), a proximal region to the dACC rCMRGlu changes found here. Intriguingly, the dACC has also been strongly linked with the anticipation of rewarding events in humans. 79 The dACC rCMRGlu increases seen in the present study may reflect changes in the motivation and anticipation of, or ability to anticipate, pleasurable events; this is reflected in items of the SHAPS (I would enjoy a...). Deficits in the ability to imagine future events, particularly positive ones, have been reliably identified in MDD patients experiencing an MDE. 80–81 thus, attenuation of depressive symptoms may be accompanied by an improved ability to anticipate pleasure. In a functional MRI study in humans, O’Doherty et al. 82 found that anticipating a primary reward (glucose) elicited heightened activity in the right putamen (as found here) compared with anticipating a punishment (salt water). Keedwell et al. 82 found that anhedonia levels, as measured by the Fawcett–Clark Pleasure Scale, 83 were positively correlated with activity in the right putamen during an emotional face-processing task that required MDD patients to compare sad

volunteers. Taken together, these findings suggest that the dACC rCMRGlu changes found here. Intriguingly, Moyer et al. 85 found that MDD patients with co-occurring motor retardation symptoms exhibited lower

glutamatergic system and its downstream modulation of dopaminergic activity may be one potential route of the anti-anhedonic efficacy of ketamine. The present work has several limitations that should be noted. First, the lack of a baseline PET image meant that we could not exclude carryover effects in this crossover design. Second, the experiential difference between receiving ketamine and saline can be dramatic, and subjects likely realized what infusion they were receiving in each session, potentially invalidating the placebo arm of this study (however, see the recent article by Murrough et al. 84). Third, all participants continued to receive either lithium or valproate, which may have masked or enhanced the effect of ketamine. It is unknown whether the rapid-acting anti-anhedonic effects of ketamine would also occur in unmedicated BD patients. Finally, we do not know how applicable these findings may be to MDD patients. Thus, we recommend that future studies attempting to replicate and extend the promising findings presented here incorporate additional PET or functional imaging scans to evaluate changes from baseline; study medication-free patients; and examine both MDD and BD patients. Furthermore, exploring the precise underlying reward processing improvements found here, for example, via cognitive testing, is essential to our ability to appropriately characterize the anti-anhedonic effects of ketamine. Due to the prevalence of anhedonia in psychiatric and neurological illnesses, particularly in schizophrenia, Parkinson’s disease, drug addiction and both mood and anxiety disorders, anhedonia has been suggested as a tractable endophenotype. As outlined in the research domain criteria, identifying symptom-based etiologies and their treatment may help to clarify specific biological mechanisms mediating mental illnesses, aid to rectify classification and diagnostic issues currently inherent in psychiatry and provide sustainable stepping stones toward treatment improvements in mental health.

In sum, this study demonstrated that ketamine exerts rapid-acting anti-anhedonic effects in treatment-refractory BD patients. These anti-anhedonic effects remained even when the variance associated with depression score changes was removed, suggesting that ketamine ameliorates anhedonia independent of its already considerable antidepressant effects. Furthermore, these anti-anhedonic effects appeared to be mediated by increased glucose metabolism in the dACC and putamen. Our results underscore the putative utility of NMDA receptor antagonists to treat all facets of depression.

CONFICT OF INTEREST

A patent application for the use of ketamine in depression has been submitted listing CAZ among the inventors; he has assigned his rights on the patent to the US government, but will share a percentage of any royalties that may be received by the government. The remaining authors declare no conflict of interest.

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