

## ORIGINAL ARTICLE

## Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression

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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.

*Translational Psychiatry* (2014) 4, e469; doi:10.1038/tp.2014.105; published online 14 October 2014

## INTRODUCTION

Over half of patients diagnosed with bipolar disorder (BD) suffer from significant levels of anhedonia,<sup>1</sup> defined as loss of enjoyment in, or desire to engage in, previously pleasurable activities.<sup>2</sup> Notably, anhedonic patients with affective disorders have a poorer treatment prognosis than their non-anhedonic counterparts.<sup>3–5</sup> Indeed, accumulating evidence suggests that standard treatments for depression do little to alleviate anhedonia<sup>6</sup> and may even cause reward and emotional blunting,<sup>7–9</sup> sexual anhedonia<sup>10</sup> and anorgasmia.<sup>11,12</sup> Furthermore, the presence of anhedonia in a major depressive episode (MDE) is a predictor of proximal suicide completion.<sup>13</sup> 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.<sup>15</sup>

Indeed, research suggests that currently depressed MDD and BD patients may possess a substantial deficit in motivational, but not consummatory, reward behaviors.<sup>16,17</sup> 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.<sup>18,19</sup> Furthermore, Sherdell

*et al.*<sup>20</sup> 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.*<sup>21</sup> 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.<sup>22–24</sup> Phasic bursts in dopaminergic neurons in the ventral tegmental area (VTA) have reliably been shown to co-occur with violations in reward expectancy,<sup>25</sup> 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.<sup>26</sup> Functional neuroimaging in humans indicates that structures such as the VTA,<sup>27,28</sup> substantia nigra,<sup>28</sup> amygdala,<sup>28</sup> putamen,<sup>28</sup> caudate,<sup>28</sup> ventral striatum,<sup>29,30</sup> and orbitofrontal cortex<sup>28,31</sup>—all of which receive innervation from or project to dopaminergic nuclei—are recruited during reward anticipation.

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Received 6 February 2014; revised 14 July 2014; accepted 13 August 2014

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.<sup>32</sup> 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<sup>33</sup> and BD<sup>34,35</sup> 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<sup>36</sup>), and found that pramipexole treatment decreased anticipatory anhedonia levels by 25% across the entire sample;<sup>37</sup> 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,<sup>38</sup> 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 conjunction 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<sup>39–43</sup> and BD.<sup>44,45</sup> 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.<sup>46</sup> Ketamine acts directly on the glutamatergic system, which appears to be critical in depression;<sup>47,48</sup> 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.*<sup>49</sup> found that MDD patients with high levels of anhedonia had lower levels of glutamine, but not glutamate, than healthy controls, but only a trend towards lower glutamine 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,<sup>50</sup> particularly in the prefrontal cortex.<sup>51</sup> In addition, ketamine<sup>52,53</sup> and other NMDA antagonists (for example, MK-801<sup>54</sup> and memantine<sup>55</sup>) 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.<sup>56</sup> 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 [<sup>18</sup>F] fluorodeoxyglucose (FDG) positron emission tomography (PET). <sup>18</sup>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.<sup>57</sup> It is important to

note that approximately all glucose entering the central nervous system is transformed into glutamate.<sup>58</sup> Thus, <sup>18</sup>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,<sup>44,45</sup> together with neurobiological correlates of mood improvement derived from <sup>18</sup>FDG-PET.<sup>59</sup> The present study specifically explores the previously unaddressed issue of ketamine's anti-anhedonic effects and its neural correlates in this sample.

## MATERIALS AND METHODS

### Participants

Subjects aged 18–65 were recruited through local and national media. The sample comprised 36 (21F) treatment-refractory individuals with BD I or II without psychotic features who were currently experiencing an MDE (see Table 1). All subjects were inpatients at the National Institutes of Health (NIH), Bethesda, MD, USA. A Montgomery–Åsberg Depression Rating Scale (MADRS)<sup>60</sup> score  $\geq 20$  at the time of screening was an inclusion criterion. All subjects were required to be currently experiencing an MDE lasting at least 4 weeks and to have failed to respond to at least one adequate antidepressant trial before hospital admission, as assessed by the Antidepressant Treatment History Form.<sup>61</sup> Diagnosis was confirmed using the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual-IV Disorders-Patient Version.<sup>62</sup> Primary psychiatric categorization, including comorbid Axis I disorders, was corroborated via evaluation by three clinicians using all available clinical information. During their time as inpatients at the NIH, and before study entry, participants had also not responded to a prospective open-label trial of a mood stabilizer (either lithium or valproic acid) administered at treatment levels (serum lithium, 0.6–1.2 mEq l<sup>-1</sup>; or valproic acid, 50–125 µg ml<sup>-1</sup>).

All patients were in good physical health as determined by medical examination, medical history, chest x-ray, blood laboratory tests, urinary analysis and toxicology. Exclusion criteria, as outlined previously,<sup>44,45</sup> included pregnancy, nursing, serious suicidal ideation, comorbid substance abuse or dependence within the past 3 months, and previous use or treatment with ketamine. The co-occurrence of Axis I anxiety disorders was permitted if this was not the primary cause of illness within the previous 12-month period. All participants continued treatment with a mood

**Table 1.** Demographic information for BD patients and the subgroup that underwent <sup>18</sup>FDG-PET imaging

	All subjects, N = 36		<sup>18</sup> FDG-PET subgroup, N = 21	
	Mean	s.d.	Mean	s.d.
Age	46.69	11.09	45.33	11.89
Age of onset	17.89	7.39	17.50	7.49
Baseline SHAPS	37.19	7.25	36.14	7.92
Baseline MADRS	33.92	5.01	30.05	4.89
BMI	30.09	6.04	29.08	6.34
	N	%	N	%
Bipolar subtype I	20	55	9	43
Caucasian	31	86	18	86
Clinically sig. anhedonia <sup>36</sup>	31	86	17	81
Female	21	58	15	71
Fhx alcohol dependence (1st)	13	36	8	38
Fhx mood disorder	31	86	17	81
Lithium	24	67	16	76

Abbreviations: BD, bipolar disorder; BMI, body mass index; <sup>18</sup>FDG-PET, [<sup>18</sup>F] fluorodeoxyglucose-positron emission tomography; Fhx, family history; MADRS, Montgomery–Åsberg Depression Rating Scale; SHAPS, Snaith–Hamilton Pleasure Scale. Clinically significant (sig.) anhedonia was defined as scoring three or more items on the SHAPS with a value of 3 ('Disagree'), as per the original classification by Snaith *et al.*<sup>36</sup>

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<sup>-1</sup>, 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  $\geq 20$  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 40, 80, 120, 230 min, and days 1, 2, 3, 7, 10 and 14 following each infusion. The primary outcome variable for antidepressant efficacy was the MADRS<sup>44,45</sup> score. However, the main symptom of interest for this report is anhedonia, and levels of anticipatory anhedonia were evaluated using the SHAPS. The SHAPS is 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.<sup>63–65</sup> The SHAPS was scored on a scale of one to four, with higher scores indicating greater anhedonia (range 14–56) 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),<sup>36</sup> where a score  $> 3$  indicated clinically significant anhedonia (see Table 1). Other secondary outcome variables were also assessed and have been reported previously.<sup>44,45</sup>

## Positron emission tomography acquisition and analysis

In addition, 21 of the 36 patients (see Table 1) underwent two resting-state <sup>18</sup>F-DG-PET imaging scans, which began 2 h post infusion and ended (brain emission scan)  $\sim 1.5$  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, Waukesha, WI, USA) in three-dimensional (35 contiguous slices, 4.25 mm plane separation) following an intravenous infusion of 4.5 mCi <sup>18</sup>F-DG over 2 min. According to the method used by Brooks,<sup>66</sup> quantitative images of regional cerebral metabolic rate for glucose metabolism (rCMRGlucose) 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  $\times$  0.9  $\times$  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.<sup>59</sup> 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<sup>67–70</sup> and reward anticipation.<sup>16,31</sup> 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 rCMRGlucose PET images. Mean glucose metabolism rate values, normalized by total gray matter, were then calculated.

For the whole-brain investigation, <sup>18</sup>F-DG-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 rCMRGlucose 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 heterogeneous 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 the strong conceptual overlap between this item and the SHAPS. *Post hoc* Bonferroni-corrected comparisons were conducted for each model 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;<sup>44,45</sup> lack of psychotomimetic 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 score 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)/post-placebo 230) was correlated with difference in mean ROI rCMRGlucose metabolism (post-ketamine – post-placebo). Second, because we previously demonstrated an association between ventral striatum metabolism changes and overall depression score change following ketamine,<sup>59</sup> 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 rCMRGlucose, 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 8) using the SPM *spm\_orth* function within the MATLAB environment, entering a single regressor (SHAPS score orthogonalized to total MADRS score minus item 8). 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

multiple comparisons at  $P < 0.05$ , or at trend level at  $P < 0.1$ , with an initial voxel-level threshold of  $P < 0.05$  uncorrected. In the case of extremely large clusters, the uncorrected threshold was increased so that all surviving clusters were  $< 5000$  contiguous voxels. For clusters surviving correction or trending, the three strongest peaks ( $t$  statistics) are reported along with the corresponding Montreal Neurological Institute coordinates.

## 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 ( $F_{(1,110)} = 24.71$ ,  $P < 0.001$ ) and time ( $F_{(9,194)} = 2.69$ ,  $P = 0.006$ ) were observed, as was a trend towards an interaction between these two variables ( $F_{(9,218)} = 1.90$ ,  $P = 0.053$ ); 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,<sup>1</sup> levels of anhedonia (as measured by the SHAPS) and depressive symptoms (as measured by total MADRS score) were positively correlated ( $r_{(36)} = 0.53$ ,  $P < 0.001$ ) at the first pre-infusion baseline. Critically, the main effect of drug on anhedonia levels was found when levels of depression (MADRS total score minus item 8 at each time point) were entered as a covariate in the model ( $F_{(1,123)} = 7.713$ ,  $P = 0.006$ ), indicating that anhedonia levels in BD respond to ketamine treatment over-and-above its effects on other depressive symptoms. Neither the main effect of time ( $F_{(9,176)} = 1.42$ ,  $P = 0.18$ ) nor the drug-by-time interaction ( $F_{(9,219)} = 1.49$ ,  $P = 0.15$ ) were significant for this model. However, *post-hoc* exploratory simple effects tests (Bonferroni-corrected) revealed that anti-anhedonic effects of ketamine were significant at days 1, 3, 7 and 14 following ketamine infusion (Figure 1b). This suggests that for some BD patients, ketamine may have specific benefits in reducing anhedonia levels, and that these benefits can last up to 2 weeks following a single infusion.

A subsequent model included mood stabilizer as an additional covariate; a trend towards significance, with greater anti-anhedonic response associated with lithium than valproate was observed ( $F_{(1,57)} = 3.57$ ,  $P = 0.06$ ). No interaction effect was noted between drug (ketamine or placebo) and mood stabilizer ( $F_{(1,114)} = 0.08$ ,  $P = 0.78$ ), nor was there a three-way interaction between drug, mood stabilizer and time ( $F_{(9,225)} = 0.41$ ,  $P = 0.93$ ).

Given our previous findings that a positive family history of alcohol use disorder (1st degree relative) was associated with an enhanced response to ketamine,<sup>71,72</sup> we examined whether this factor was also associated with the specific anti-anhedonic response demonstrated above; baseline SHAPS score and total depression score were entered as covariates into a subsequent model. There was a significant interaction between drug and family history of alcohol use disorder ( $F_{(1,109)} = 4.12$ ,  $P = 0.045$ ), but no main effect for family history of alcohol use disorder ( $F_{(1,51)} = 0.27$ ,  $P = 0.60$ ), nor an interaction between this variable and time ( $F_{(9,163)} = 0.94$ ,  $P = 0.49$ ), nor a three-way interaction between family history, drug and time ( $F_{(9,205)} = 0.60$ ,  $P = 0.79$ ). The significant interaction between drug and family history of an alcohol use disorder indicated, in comparison with placebo, a specific enhanced anti-anhedonic response to ketamine in those

with ( $F_{(1,116)} = 11.13$ ,  $P = 0.001$ ), in comparison with those without ( $F_{(1,111)} = 1.22$ ,  $P = 0.27$ ), a family history of an alcohol use disorder.

In addition, we explored whether a personal history of alcohol abuse, dependence or illicit substance abuse contributed significantly to the specific anti-anhedonic effect of ketamine. No significant main effects or interactions with drug, time or drug and time were found.

### PET: ROI analyses

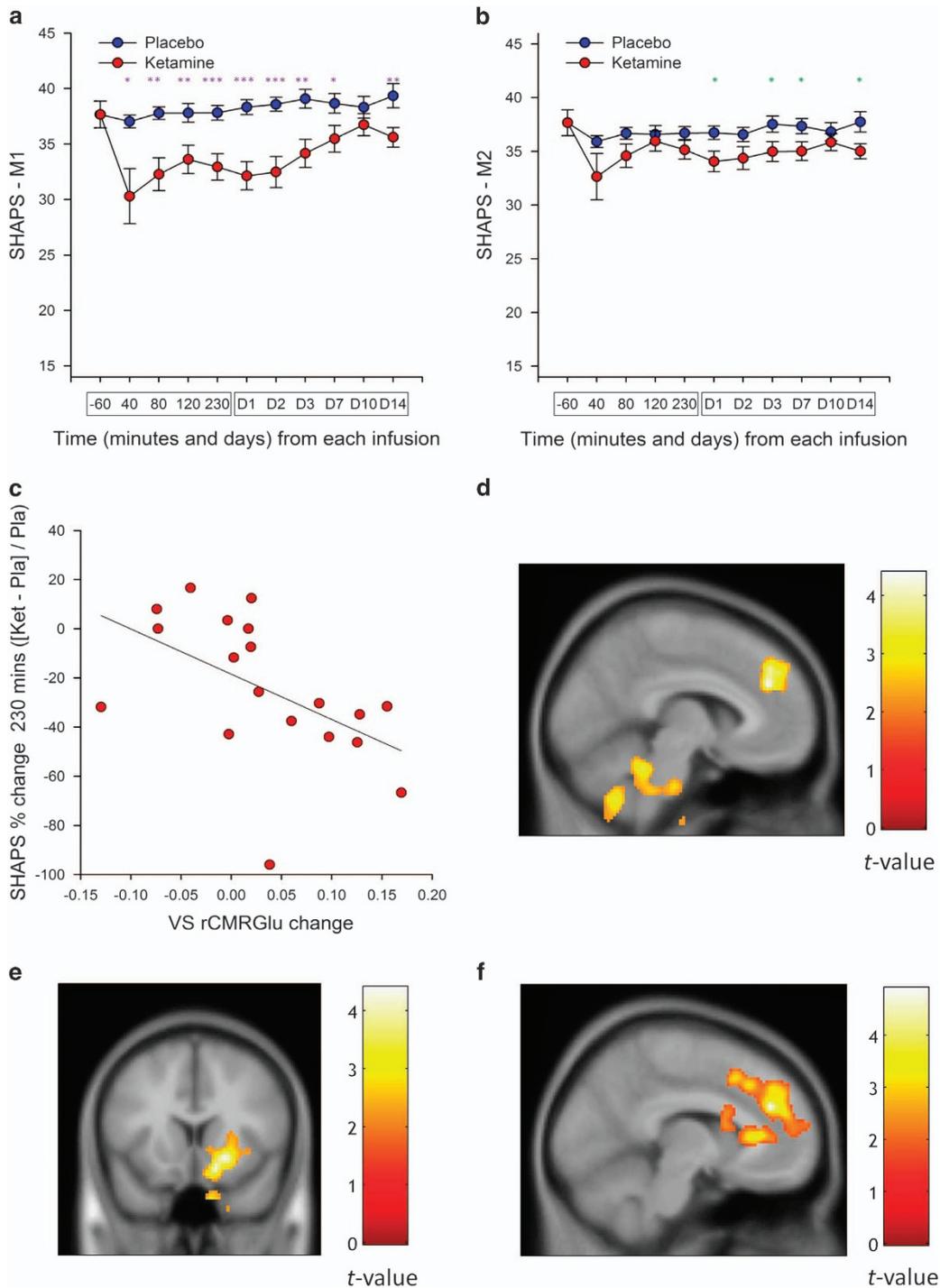
Ketamine-induced change in ventral striatum rCMRGlucose was significantly related to percent change in SHAPS score at 230 min post infusion ( $r_{(19)} = -0.52$ ,  $P = 0.02$ ; Figure 1c). Relative to placebo, individuals with the largest increase in glucose metabolism in the ventral striatum tended to have the highest anti-anhedonic response to ketamine. However, orbitofrontal cortex rCMRGlucose activity was not significantly related to anti-anhedonic response to ketamine ( $r_{(19)} = -0.37$ ,  $P = 0.12$ ). Because we had previously demonstrated a relationship between ventral striatum change in glucose metabolism and improvement in MADRS score following ketamine,<sup>59</sup> 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 rCMRGlucose.

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

### PET: 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 rCMRGlucose increases in the dorsal anterior cingulate cortex (dACC; [ $x = -6$ ,  $y = 40$ ,  $z = 43$ ];  $t_{(17)} = 4.39$ ,  $P_{\text{corr}} = 0.016$ ; Figure 1d). Furthermore, we found a significant increase in cerebellum ( $[x = -40$ ,  $y = -48$ ,  $z = -58$ ];  $t_{(17)} = 3.94$ ,  $P_{\text{corr}} = 0.019$ ; Table 2), and a trend towards an increase in striatal, rCMRGlucose ( $[x = 14$ ,  $y = 4$ ,  $z = 10$ ];  $t_{(17)} = 4.28$ ,  $P_{\text{corr}} = 0.051$ ; 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 rCMRGlucose 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 rCMRGlucose 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 ( $[x = -8$ ,  $y = 40$ ,  $z = 28$ ];  $t_{(17)} = 4.89$ ,  $P_{\text{corr}} = 0.027$ ; 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 ( $[x = 34$ ,  $y = -28$ ,  $z = -20$ ];  $t_{(17)} = 3.74$ ,  $P_{\text{corr}} = 0.065$ ) that extended into the claustrum and the putamen, but not the ventral striatum. Finally, we assessed whether change in rCMRGlucose 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 Bonferonni-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 **(d)** dorsal anterior cingulate cortex (dACC), cerebellum, **(e)** 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.

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

Region	MNI coordinate			t-value	Uncorrected threshold	$P_{\text{FWE-Corr}}$	$P_{\text{FDR-Corr}}$	Extent
	X	Y	Z					
<i>Ketamine-Placebo vs SHAPS improvement</i>								
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				
Head of caudate	14	4	10	4.28		0.051	0.030	1936
Putamen	20	14	-8	4.20				
VS/posteromedial OFC	14	14	-14	4.17				
Cerebellum lobule VIIb	-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				
<i>Ketamine-Placebo vs SHAPS orthogonalized to MADRS improvement</i>								
dACC	-8	40	28	4.89	$P < 0.05$	0.027	0.042	4686
Pregenua/callosal cingulate	-6	34	8	3.62				
DLPFC	30	40	36	3.18				
Fusiform gyrus	34	-28	-20	3.74		0.065	0.052	3896
Clastrum	34	8	-6	3.51				
Putamen	22	14	-6	3.48				

Abbreviations: dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex;  $^{18}\text{F}$ FDG-PET, [ $^{18}\text{F}$ ] fluorodeoxyglucose-positron emission tomography; MADRS, Montgomery-Åsberg Depression Rating Scale; SHAPS, Snaith-Hamilton Pleasure Scale; SMG, superior medial gyrus. Increases in glucose metabolism associated with decreases in anhedonia levels. All cluster  $P$ -values are corrected for multiple comparisons using Gaussian random field theory as implemented in SPMS. 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).

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  $^{18}\text{F}$ FDG-PET to examine a subgroup of these patients and quantify the rCMRglu 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;<sup>6-11,73</sup> 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<sup>59</sup> that improvement in total depression score on the MADRS was associated with increased ventral striatum rCMRglu 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,<sup>74</sup> 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;  $^{18}\text{F}$ 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-

making.<sup>75–78</sup> Shidara and Richmond<sup>75</sup> 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.<sup>79</sup> 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;<sup>80,81</sup> 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.*<sup>28</sup> 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.*<sup>82</sup> found that anhedonia levels, as measured by the Fawcett–Clark Pleasure Scale,<sup>83</sup> were positively correlated with activity in the right putamen during an emotional face-processing task that required MDD patients to compare sad and neutral faces; this result was not observed with depression or anxiety scales, though it should be noted that the Fawcett–Clark Pleasure Scale indiscriminately measures both consummatory and anticipatory anhedonia. Taken together, the results of the imaging portion of this study indicate that decreased anticipatory anhedonia is associated with increased glucose metabolism in the dACC and putamen, and that this in turn may reflect increased motivation towards or ability to anticipate pleasurable experiences.

Another interesting finding was that, after the ketamine infusion, individuals taking lithium experienced greater anti-anhedonic effects than those receiving valproate when the antidepressant effect was controlled for. This result could be interpreted in two ways: either valproate caused a deficit in the anti-anhedonic effect of ketamine, or lithium enhanced the anti-anhedonic effect of ketamine. A recent preclinical report by Liu *et al.*<sup>84</sup> found that a single subanesthetic dose of ketamine in conjunction with lithium resulted in enhanced plasticity and antidepressant-like effects (increased struggling time in the forced swim test) in rodents compared with a single dose of ketamine plus vehicle. In light of this result, we suggest that lithium may enhance the anti-anhedonic effects of ketamine in individuals with BD. Future studies in patients both taking and not taking mood stabilizers will need to be conducted to correctly evaluate this possibility.

Ketamine acts primarily by blocking the glutamatergic NMDA receptor. It may also upregulate  $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor throughput.<sup>85</sup> Although glutamate is the major excitatory neurotransmitter, its role in anhedonia has yet to be fully explored. Preliminary evidence suggests that glutamate may have an integral role in both anhedonia and depression.<sup>47,50</sup> Ketamine is also a partial agonist of the dopamine D2 receptor<sup>86,87</sup> and has been found to increase dopamine levels in the striatum, including the caudate and the putamen.<sup>88</sup> Intriguingly, Meyer *et al.*<sup>89</sup> found that MDD patients with co-occurring motor retardation symptoms exhibited lower extracellular dopamine in the putamen compared with healthy volunteers. Taken together, these findings suggest that the 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.*<sup>42</sup>).

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.

## CONFLICT 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.

## ACKNOWLEDGMENTS

The authors thank Wayne Drevets MD and Maura Furey PhD for helpful discussions related to the manuscript, Ioline Henter, MA for outstanding editorial assistance and the 7SE research unit and staff for their support. Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; grant number 04-M-0222), by a National Alliance for Research on Schizophrenia and Depression Award to CAZ, and by a Wellcome Trust-NIH PhD studentship (WT095465) to NL.

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