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ARTICLE

Ketamine normalizes subgenual cingulate cortex hyper-activity in depression

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Mounting evidence supports the rapid antidepressant efficacy of the *N*-methyl-D-aspartate receptor antagonist, ketamine, for treating major depressive disorder (MDD); however, its neural mechanism of action remains poorly understood. Subgenual anterior cingulate cortex (sgACC) hyper-activity during rest has been consistently implicated in the pathophysiology of MDD, potentially driven in part by excessive hippocampal gluatmatergic efferents to sgACC. Reduction of sgACC activity has been associated with successful antidepressant treatment. This study aimed to examine whether task-based sgACC activity was higher in patients with MDD compared to controls and to determine whether this activity was altered by single-dose ketamine. In Study 1, patients with MDD ($N = 28$) and healthy controls ($N = 20$) completed task-based functional magnetic resonance imaging using an established incentive-processing task. In Study 2, a second cohort of patients with MDD ($N = 14$) completed the same scanning protocol at baseline and following a 40 min infusion of ketamine (0.5 mg/kg). Task-based activation of sgACC was examined with a seed-driven analysis assessing group differences and changes from pre to post treatment. Patients with MDD showed higher sgACC activation to positive and negative monetary incentives compared to controls, associated with anhedonia and anxiety, respectively. In addition, patients with MDD had higher resting-state functional connectivity between hippocampus and sgACC, associated with sgACC hyper-activation to positive incentives, but not negative incentives. Finally, ketamine reduced sgACC hyper-activation to positive incentives, but not negative incentives. These findings suggest a neural mechanism by which ketamine exerts its antidepressant efficacy, via rapid blunting of aberrant sgACC hyper-reactivity to positive incentives.

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INTRODUCTION

Major depressive disorder (MDD) is one of the world's largest public health issues to date, representing the leading cause of disability worldwide [1]. Despite its widespread prevalence, widely prescribed pharmacological treatments such as selective serotonin re-uptake inhibitors (SSRI) are slow to act and are often only partially effective, rendering a significant proportion of patients unresponsive [2, 3]. The US Food and Drug Administration has recently approved the s-enantiomer of ketamine, 'esketamine' for the treatment of depression in patients with MDD who have failed to respond to prior antidepressants, following growing clinical evidence of the efficacy of ketamine over the past two decades [4–6]. However, while the first report of the antidepressant effect of ketamine was published in 2000, there remains a lack of clarity regarding its effect on neural functioning in patients with MDD.

MDD is associated with widespread neural, cognitive, and behavioral dysfunction. One of the most consistently implicated regions in MDD is the subgenual anterior cingulate cortex (sgACC), putatively corresponding to the infralimbic cortex in rodent models [7], although functional homology has not been widely demonstrated between human and rodent regions. The human sgACC plays an important role in emotion regulation [8], reward anticipation [9], and anhedonia (inability to feel pleasure) [10, 11], core features of MDD. The sgACC is hyper-active in MDD [12] and reducing sgACC hyper-activity has been associated with reduction in depressive symptoms [13]. Evidence from rodent models suggests that aberrant infralimbic cortex hyper-activity might be driven by excessive hippocampal output, leading to depressive symptoms or behaviors [14]. Indeed, chronic mild stress in rats leads to increased hippocampal extracellular glutamate [15] and output particularly to the infralimbic cortex [14, 16]. The hippocampus and sgACC are strongly anatomically connected in humans [17] and several studies in MDD demonstrate hippocampus and sgACC hyper-connectivity [18–20], associated with illness duration and severity [18, 20].

A recent study in non-human primates has demonstrated a critical link between sgACC hyper-activation, core depressive symptoms, and the antidepressant effects of ketamine [11]. Over-activation of the sgACC (Brodmann area 25) via glutamate re-uptake inhibition led to deficits in anticipatory arousal to receipt of a primary reinforcer (food reward) in marmosets—a model analog of anhedonia in MDD [11]. In this model, single-dose ketamine led to an improvement in anticipatory arousal, as well as a normalization of sgACC hyper-activity, whereas SSRI treatment had no effect [11]. In this study, we aimed to determine the responsivity of sgACC to receipt of a secondary reinforcer (money) in humans with MDD and to determine whether the rapid antidepressant effect of ketamine

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may act by altering sgACC activation. We also aimed to replicate previous reports of hippocampal–sgACC hyper-connectivity in patients with MDD, and to determine the relationship between resting connectivity and task-based activation.

METHODS AND MATERIALS

Participants and procedures

Study 1 and 2. Subjects in Study 1 and Study 2 were recruited at the Icahn School of Medicine at Mount Sinai and underwent a complete medical and psychiatric assessment. For Study 1, subjects were recruited between September 2016 and August 2018; for Study 2, subjects were recruited between June 2013 and September 2016. Depressed patients meeting Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for a depressive disorder (MDD, persistent depressive disorder, or other specified depressive disorder) according to the Structured Clinical Interview for DSM Axis I Disorders-Patient Edition (SCID-I/P) were deemed eligible to participate in the study. Subjects were excluded if they had substance use disorder in the past 2 years, or a lifetime history of a psychotic disorder, bipolar disorder, a developmental disorder, obsessive-compulsive disorder, an eating disorder, or a personality disorder as their primary presenting problem. Subjects were free of antidepressant or other psychotropic medication at the time of the scans. Healthy control subjects were free of any current or past psychiatric disorder, as determined by the SCID-I/P.

Study 2. Subjects in Study 2 were enrolled in a clinical trial (clinicaltrials.gov ID: NCT01880593) between June 2013 and September 2016, in which they received intravenous ketamine in a prospective, open-label design (for detailed methods, see [21]). Subjects were eligible if they had previously failed to respond to at least two previous antidepressant medications, as determined by the antidepressant treatment history form (ATHF). Subjects were excluded if they had any history of recreational use of ketamine or phencyclidine. Subjects received one intravenous ketamine infusion (0.5 mg/kg over 40 min). Pre- and post-ketamine magnetic resonance imaging (MRI) scans were collected within 14 and 5 days of this single infusion, respectively.

Depression severity was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) [22]. All subjects also completed the self-reported temporal experience of pleasure scale (TEPS) [23] to assess anticipatory anhedonia and the state-trait inventory of cognitive and somatic anxiety (STICSA) [24] to assess trait anxiety. The TEPS yields a total score for anhedonia, as well as sub-scores for anticipatory and consummatory anhedonia, respectively. All subjects provided written informed consent prior to any study procedures using consent forms approved by the Program for the Protection of Human Subjects at Mount Sinai for Study 1 and Study 2.

MRI acquisition and processing

All MRI data was acquired with a Siemens 3T MAGNETOM Skyra scanner and a 32-channel head coil at Mount Sinai's Translational and Molecular Imaging Institute. Scans included an anatomical T1-weighted scan, a functional scan during resting state (10 min, eyes open), and a task-based functional scan with the incentive flanker task (IFT, detailed below).

Study 1. The anatomical T1-weighted images were acquired with a magnetization-prepared 2 rapid gradient-echo sequence, which collects two volumes after each inversion for improved image quality (repetition time (TR) = 4000 ms, echo time (TE) = 1.9, inversion 1/2 time = 633/1860, field of view (FOV) = 186 × 162, voxel resolution = 1 × 1 × 1 mm^3), and the functional scans for both resting state and task performance were collected with a multi-echo (ME) multi-band accelerated echo planar imaging sequence (TR = 882 ms, TE = 11.0, 29.7, 48.4, 67.1, multi-band factor = 5, FOV = 560 × 560, voxel resolution = 3 × 3 × 3 mm^3, flip angle = 45). Both functional scans were preprocessed and denoized for motion and physiological noise using ME-independent component analysis (ME-ICA) [25, 26]. ME functional MRI data was decomposed into independent components, and scaled against TE [25, 26]. Components with high TE dependence are considered BOLD like, whereas components with low TE dependence are considered noise like [25, 26]. Removal of non-BOLD components allows robust data denoizing for motion, physiological, and scanner artifacts [25, 26].

Study 2. The anatomical T1-weighted MPRAGE images were acquired with the following acquisition parameters: TR = 2400 ms, TE = 2.07 ms, flip angle = 8°, and bandwidth = 240. Functional scans for both resting state and task performance were collected with a multi-band gradient-echo echo planar sequence with 70 axial slices (TR = 1000 ms, TE = 35 ms, multi-band factor = 7, bandwidth = 1860, FOV = 756 × 864, voxel resolution = 2.1 × 2.1 × 2.1, flip angle = 60). Functional data was despiked (3dDespike), outliers removed (3dToutcount), and subject to rigid-body registration (3dvolreg) using a combination of AFNI [27] and FSL [28]. Motion derivatives were used as regressor of no interest in subsequent first-level analyses. Resting-state data was additionally denoized using ICA-based correction, bandpass filtered (0.01–0.1 Hz), and detrended. Functional data was smoothed with a 5 mm kernel. All denoized functional data was coregistered with their respective T1 and normalized to a standard Montreal Neurological Institute template using Advanced Normalization Tools (http://www.picsl.upenn.edu/ANTs) with diffeomorphic symmetric normalization transformation registration.

Incentive flanker task

All subjects completed the IFT (see Fig. 1), a modified version of the monetary incentive delay task, described in detail elsewhere [29, 30], which allows participant engagement due to a cognitive task, as well as measurement of neural activity related to both cue presentation and performance-based feedback. There were three trial types (reward/loss/neutral). Each trial contained an initial monetary cue signaling the value of the current trial (reward/loss/neutral) (2–6 s). This was followed by a flanker task, which consisted of a display of five letters in row and subjects were instructed to respond to the middle letter only by pressing a left button if the middle letter was S or K, and the right button if the middle letter was H or C. Flanker letters could be congruent or incongruent (50/50%) with the middle letter. The response period was titrated based on baseline performance (the mean baseline performance was multiplied by 1.5, with 1700 ms maximum). A correct response was the correct button press within the response period. After a button response, feedback was displayed for 2 s. Across all trial types, feedback following a correct response was a smiling cartoon face with the word: "Correct!," whereas feedback following an incorrect response was a frowning cartoon face with: "Incorrect!." These were considered *positive* and *negative* feedback, respectively, collapsed across trial types. In addition, feedback included monetary value (correct response on reward/loss/neutral = $0.50/$0.00/$0.00; incorrect response on reward/loss/neutral = $0.00/−$0.50/$0.00), and at the end of the session, participants were rewarded with real money based on their performance. One-third of cues were followed by a blank screen for 2 s (instead of the flanker stimuli) to break collinearity between the cue and feedback. Outcome feedback was followed by a blank inter-trial interval for 2–6 s before the next trial. There were 40 of each trial type (reward/loss/neutral), producing a total of 120 trials. Trials were presented in pseudorandom order and equally divided across four runs of ~6 min each.

Data analysis and statistics

Task-based fMRI. Task-based fMRI data was processed in the same way for both cohorts of subjects. First-level general linear

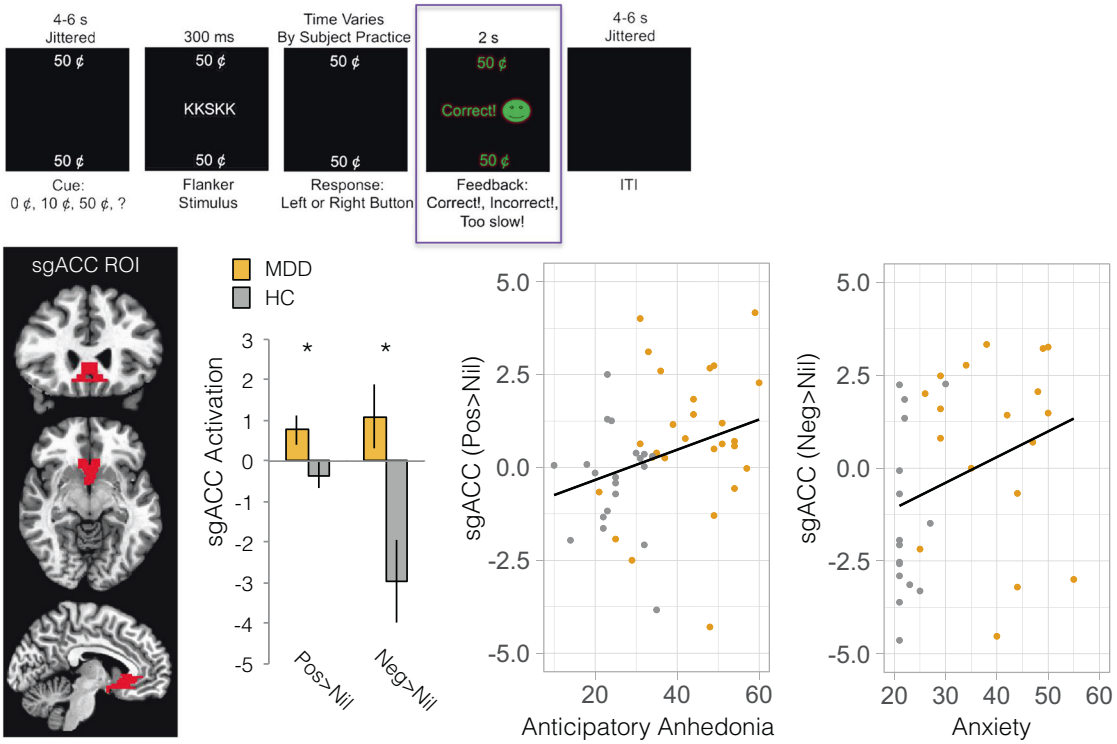

Fig. 1 Linking subgenual anterior cingulate cortex (sgACC) activation with distinct symptoms of depression. Top: Subjects completed the incentive flanker task (IFT) during functional MRI. The task consisted of reward, loss, and neutral trials, which included a cue, followed by a flanker task (congruent/incongruent), followed by feedback (positive/negative). Positive and negative feedback was contrasted against no feedback (Nil). Bottom: Patients with major depressive disorder (MDD) showed higher activity within the sgACC region of interest (ROI) compared to healthy controls (HCs) to both positive ($T_{(45)} = 2.208$, $p = 0.032$) and negative ($T_{(42)} = 3.036$, $p = 0.004$) feedback. Higher sgACC activation to positive was associated with anhedonia ($R = -0.34$, $p = 0.028$), whereas higher activation to negative was associated with higher anxiety ($R = 0.386$, $p = 0.012$) across the full cohort.

models included regressors for cue onset (reward/loss/neutral), flanker onset, and feedback onset (positive/negative), each including duration modulation using AFNI's *dmBLOCK* function and convolved with the hemodynamic response function. Contrasts of interest included gain and loss cues, contrasted against the neutral cue, and positive and negative feedback, contrasted against a blank screen that followed the cue, which represented "no outcome." Activation for each contrast was extracted within the sgACC ROI (based on Brodmann area 25) for each subject and entered into independent-samples *t* test for group difference comparison, controlling for age and sex, and paired-samples *t* test for computing pre/post-ketamine differences. Pearson's correlation was used for examination of relationships between sgACC activation and clinical symptoms.

Resting-state fMRI. Functional connectivity was computed between the sgACC and hippocampus ROI's (automated anatomical labeling atlas) for all subjects using Pearson's correlation and using *Z*-score normalization. Normalized functional connectivity *Z*-values were entered into independent-samples *t* test for group difference comparison, controlling for age and sex, and Pearson's correlation was used for examination of relationships with sgACC task-based activation.

RESULTS

Participants

Participant characteristics are summarized in Table 1. For Study 1, 28 MDD subjects and 20 HC subjects completed the scan.

Table 1. Subject characteristics for Study 1 and Study 2.

	MDD	HC	*p* Value
Study 1			
Female/male	14/14	7/13	
Age (SD)	36.5 (11)	37.8 (9.4)	0.38
MADRS	27.96 (5.5)	1 (1.6)	<0.001
Anhedonia (anticipatory)	26.46 (10.8)	45.0 (6.7)	<0.001
Anhedonia (consummatory)	25.61 (10.3)	39.2 (6.2)	<0.001
Anxiety	23.79 (7.5)	11.15 (2.2)	<0.001
Study 2			
Female/male	9/7		
Age (SD)	44.69 (11.4)		
MADRS (pre-ketamine)	32.13 (5.1)		
MADRS (post-ketamine)	15.29 (7.5)		
Anhedonia (pre-ketamine)	35.69 (6.0)		
Anhedonia (post-ketamine)	28.94 (5.6)		

Subject characteristics are reported for patients with MDD and HCs. Depression severity was measured using the MADRS. Anhedonia was measured using the TEPS and anxiety with the STICSA. For Study 1, scores for the anticipatory and consummatory sub-scales of the TEPS are displayed; For Study 2, the TEPS total score is displayed
MDD major depressive disorder, *HC* healthy controls, *MADRS* Montgomery-Asberg Depression Rating Scale, *TEPS* temporal experience of pleasure scale, *STICSA* state-trait inventory of cognitive and somatic anxiety

For Study 2, MDD subjects received one 40-min ketamine infusion (0.5 mg/kg), with both pre- and post-ketamine MRI data available for 14 MDD subjects.

Incentive flanker task

Functional MRI data during the IFT (see Fig. 1) were processed and analyzed for 28 MDD subjects (age = 36.5 ± 11, 14 female) and 20 HC subjects (age = 37.8 ± 9.4, 7 female). One MDD subject was excluded due to excessive motion during MRI. Groups did not differ in their performance accuracy (MDD = 85.9 ± 10.4%, HC = 87.7 ± 10.1%, $p = 0.76$), or their baseline reaction times (MDD = 927.6 ± 172.5 ms, HC = 859.3 ± 145.7 ms, $p = 0.16$). Two MDD subjects and one HC subject performed 100% accuracy and therefore received no negative feedback, and thus were not available for analyses including negative feedback.

MDD subjects showed sgACC hyper-activity to receipt of positive and negative feedback, compared to HC (positive, $T_{(45)} = 2.208$, $p = 0.032$; negative, $T_{(42)} = 3.036$, $p = 0.004$; Fig. 1). sgACC hyper-activity to receipt of *positive* feedback was associated with worse anticipatory anhedonia ($R = -0.34$, $p = 0.028$, Fig. 1), and not anxiety ($R = 0.129$, $p = 0.416$; difference in correlations: $Z = -1.9$, $p = 0.05$), across the full sample (controlling for age, sex). This correlation remained significant when also controlling for anxiety ($R = -0.323$, $p = 0.020$). In contrast, sgACC hyper-activity to receipt of *negative* feedback was associated with worse anxiety ($R = 0.386$, $p = 0.012$, Fig. 1), and not with anticipatory anhedonia ($R = -0.282$, $p = 0.07$; difference in correlations: $Z = 2.8$, $p = 0.004$), across the full sample (controlling for age, sex). This remained significant when also controlling for anticipatory anhedonia ($R = -0.290$, $p = 0.033$). sgACC hyper-activity to positive did not correlate with sgACC hyper-activity to negative ($R = 0.167$, $p = 0.29$), suggesting that they may be dissociable. There were no group differences in sgACC activation to gain or loss vs. neutral cue contrasts (p's >0.2).

Resting-state functional MRI

Resting-state functional MRI data were processed and analyzed for the same 28 MDD subjects (age = 36.5 ± 11, 14 female) and 20 HC subjects (age = 37.8 ± 9.4, 7 female). Patients with MDD had increased resting-state functional connectivity between the hippocampus and sgACC, compared to controls ($t_{(44)} = -2.2$, $p = 0.031$, Fig. 2). Hippocampus and sgACC connectivity was positively correlated with sgACC hyper-activation to positive feedback ($R = 0.33$, $p = 0.028$, Fig. 2), but not negative feedback ($R = -0.15$, $p = 0.924$; difference in correlations: $Z = 2.6$, $p = 0.007$) across the full sample.

Effects of ketamine

There was a significant improvement in MDD symptoms following a single-dose intravenous ketamine (MADRS, $T_{(16)} = 10.52$, $p < 0.0001$), as well as improvements in anhedonia ($T_{(16)} = 5.52$, $p < 0.0001$) (see Table 1).

Single-dose ketamine significantly reduced sgACC activation to positive feedback ($t_{(13)} = 3.17$, $p = 0.007$, Fig. 3), but not negative feedback ($t_{(13)} = 1.42$, $p = 0.179$, repeated-measures ANOVA: time × feedback interaction $F_{(1,13)} = 6.09$, $p = 0.028$). Interestingly, higher pre-ketamine sgACC activation to positive feedback was associated with a better improvement in anhedonia after ketamine ($R = -0.437$, $p = 0.045$, Fig. 3). There was no significant change in hippocampus and sgACC connectivity between pre and post ketamine ($p > 0.05$).

Subdivisions within sgACC

Given that the sgACC ROI encompassed a broad region, we performed an exploratory analysis dividing the sgACC into subdivisions corresponding to the architectonic boundaries of (1) area 25 (posterior medial wall) and (2) prelimbic area 32 (PL32) according to Ongur et al. [31] (see Fig. 4). We found that area PL32 was significantly hyper-active to negative feedback, but not positive feedback ($p = 0.048$, $p = 0.272$), whereas area 25 was trending towards significant hyper-activation to positive feedback, but not negative feedback ($p = 0.054$, $p = 0.478$, Fig. 4). Furthermore, area PL32 hyper-activity to negative feedback (but not positive feedback) was correlated with anxiety (cognitive, $R = 0.359$, $p = 0.017$, Fig. 4) and not anticipatory anhedonia ($R = -0.207$, $p = 0.178$; difference in correlations: $Z = 2.3$, $p = 0.019$), whereas area 25 hyper-activity to positive feedback (but not negative feedback) was correlated with anticipatory anhedonia ($R = -0.346$, $p = 0.017$, Fig. 4) and not anxiety ($R = 0.15$, $p = 0.922$; difference in correlations: $Z = -2.1$, $p = 0.035$). This suggests an anatomical–functional dissociation whereby area PL32 (anterior sgACC) processing of negative feedback is linked with anxiety, while area 25 (posterior sgACC) processing of positive feedback is linked with anticipatory anhedonia.

Hippocampus and sgACC connectivity was correlated with area 25 hyper-activity to positive feedback only ($R = 0.260$, $p = 0.045$) and not with negative or PL32 with either (p's >0.05). An exploratory analysis of hippocampal connectivity with area 25

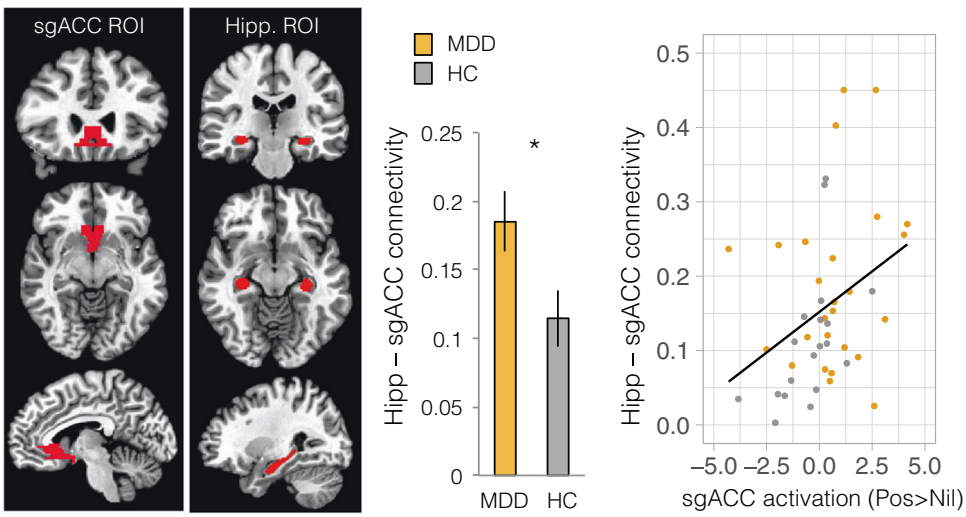

Fig. 2 Hippocampus and subgenual anterior cingulate cortex (sgACC) connectivity in depression. Patients with major depressive disorder (MDD) had increased resting-state functional connectivity between the hippocampus and sgACC, compared to healthy controls (HCs, $t_{(44)} = -2.2$, $p = 0.031$). This connectivity was associated with higher sgACC activation to positive feedback ($R = 0.33$, $p = 0.028$).

and PL32 specifically revealed that connectivity between hippocampus and both area 25 and PL32 were correlated with area 25 hyper-activity to positive feedback ($p = 0.046$, $p = 0.035$), and not negative feedback ($p = 0.105$, $p = 0.308$), and only hippocampal connectivity with PL32 correlated with anxiety ($p = 0.042$). Finally, there was a trend towards ketamine specifically reducing area 25 hyper-activity to positive feedback ($t = 2.045$, $p = 0.062$), but not area PL32 hyper-activity to negative feedback ($p = 0.74$).

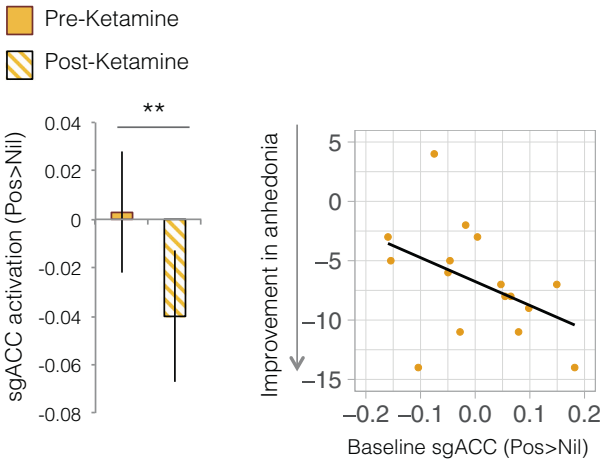

Fig. 3 The influence of ketamine on subgenual anterior cingulate cortex (sgACC) activation. Ketamine reduced sgACC activation to positive feedback in patients MDD ($t_{(13)} = 3.17$, $p = 0.007$). Greater pre-ketamine sgACC activation was associated with greater improvement in anhedonia (TEPS total score) after single-dose ketamine ($R = -0.437$, $p = 0.045$).

DISCUSSION

These data are consistent with previous studies in animal models demonstrating excessive stress-related glutamatergic signalling in projections from hippocampus to sgACC, sgACC hyper-activity, and links with anhedonic behaviors [12–14]. We demonstrate a double dissociation whereby sgACC hyper-activation to positive feedback is associated with anhedonia, whereas hyper-activation to negative feedback is associated with anxiety. In addition, we show that ketamine blunts sgACC hyper-activation to positive feedback, but not negative feedback in patients with MDD. Finally, we highlight a potential anatomical distinction within sgACC, whereby posterior area 25 is more related to positive processing and anhedonia, whereas anterior PL32 is more associated with negative processing and anxiety.

This translational finding mirrors a recent study in marmosets also demonstrating that single-dose ketamine led to normalization of sgACC hyper-activity and an improvement in an autonomic measure of anhedonia (anticipatory arousal) [11]. The current findings coincide with previous reports of increased resting sgACC activity in MDD [12, 13] and extends this work by implicating hyper-activity during valence processing in a task-based setting additionally. We further highlight the potential functional heterogeneity within the sgACC region, suggesting that anhedonia and anxiety may be separately related to area 25 and PL32 as defined by Ongur et al. [31], respectively. This is in line with evidence of phasic reward value encoding in more posterior, ventral subgenual regions in non-human primates [32]. It is important to note that while this work utilizes definition of PL32 as defined by Ongur et al. [31], other work provides alternative subdivisions of sgACC, including, for example, a larger region of area 25 in macaques, which is largely separated from area 32 by area 24 [33]. Therefore, refining and comprehensively characterizing the

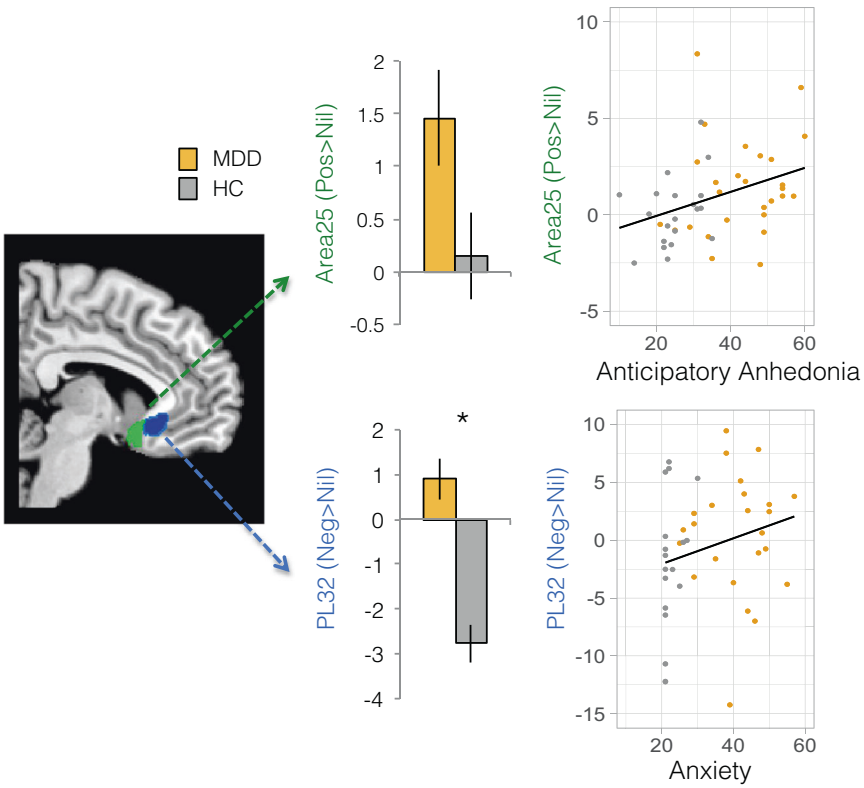

Fig. 4 Putative subdivisions within subgenual anterior cingulate cortex (sgACC) relate to distinct symptomology. The sgACC was divided based on architectonic boundaries of area 25 (posterior medial wall) and prelimbic area 32 (PL32). Exploratory analysis revealed area 25 was hyper-activate to positive feedback only ($p = 0.054$, $p = 0.478$), which was correlated with anhedonia ($R = -0.346$, $p = 0.017$), whereas PL32 was significantly hyper-active to negative feedback only ($p = 0.048$, $p = 0.272$), and correlated with anxiety ($R = 0.359$, $p = 0.017$).

specific valence-processing functions of subdivisions within sgACC will be critical for tackling the heterogeneity of MDD.

This work additionally underscores the functional role of hippocampal projections to area 25, which have been previously shown to be hyper-active in rodents following chronic mild stress [14–16], and related to MDD illness duration and severity in humans [18, 20]. A recent study has also demonstrated that interactions between anterior hippocampus to area 25 are critical for normal harm avoidance behaviors [34], a common indication of anxiety-like behaviors in humans with depression, as well as often co-morbid anxiety disorders [35, 36].

Previous findings of effects of ketamine on neural activity have been mixed. One study of acute ketamine administration in a small sample of healthy male subjects resulted in reduced sgACC resting functional connectivity with hippocampus, thalamus, and brainstem [37]. Another study of single-dose ketamine showed no change in whole brain metabolism as measured by positron-emission tomography, but showed both increases and decreases in regional resting metabolism throughout the cortex, with clinical improvement associated with reduced parahipp/temporoparietal metabolism [38]. Similar to the current findings, another previous study demonstrated that ketamine decreased ventromedial prefrontal/sgACC activity in healthy male subjects [39]. However, the same group also showed the opposite effect in patients with MDD [40]. In the latter study, patients with MDD were given slow, single-dose ketamine (non-bolus), which acutely increased sgACC resting activity as measured using pharmacological MRI, although it showed no antidepressant effect [40]. This suggests that the effect of ketamine on neural activity may depend on the antidepressant efficacy, in which a clinical effect is associated with reduced sgACC activation. Since the methodology between these two studies were quite different (pharmacological MRI versus task-based functional MRI), further studies are required to explain these inconsistencies.

Interestingly, the current findings revealed altered sgACC activation to valenced feedback rather than cue. Outcome anticipation (cue) rather than outcome receipt (feedback) is typically related to sgACC hyper-activation in primate work [11]. However, this inconsistency may be due to differences in rewards used in humans and primate studies: in humans, money is used as a secondary reinforcer rather than the primary food reinforcers typically used in primate studies [11]. Since money is a secondary reinforcer [41, 42], receipt could be considered a cue-like event rather than a consummatory event.

There were several limitations of this study. First, the two studies were performed on two cohorts of patients, with differing gender make-up, so follow-up replication studies in the same subjects will be required. Second, the MRI scan pre and post ketamine did not happen on the same day as the infusion. This was to mitigate against any psychotomimetic effects of ketamine and to better characterize longer-term changes in mood. While there was a relatively long lag between the ketamine infusion and the post-ketamine scan (up to 14 days), previous studies have suggested that even single-dose ketamine can have longer-term effects on mood symptoms [43]. Further studies should explore the effects of multiple doses of ketamine on neural activity as well as examine short and longer-term effects of the drug.

The current work demonstrates that sgACC hyper-activity in depression is not just confined to resting state, but is observed during task too. We further dissect putative subregions within sgACC and indicate a more posterior area 25-like region associated with positive incentive processing and anhedonia, versus a more anterior PL32-like region associated more with negative processing and anxiety. Furthermore, this work suggests that ketamine acts rapidly to normalize the area 25 hyper-activity to positive incentives, potentially indicating an antidepressant mechanism.

FUNDING AND DISCLOSURE

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ADDITIONAL INFORMATION

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