ANESTHESIOLOGY

Increased Reactivity of the Mesolimbic Reward System after Ketamine Injection in Patients with Treatment-resistant Major Depressive Disorder

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ANESTHESIOLOGY 2019; XXX:00–00

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The antidepressant effect of ketamine is associated with increased activity in the reward circuitry of the brain and a suppression of circuitry that mediates perceptual processing of negative emotions. The duration of ketamine effect on these brain structures remains to be defined.

What This Article Tells Us That Is New

- As expected, ketamine administration led to an improvement in mood and global vigilance. The improvement in mood was accompanied by an increased recruitment of the orbitofrontal cortex, ventral striatum, medial substantial nigra and ventral tegmental area, structures that are part of the reward circuitry.
- Responses in the mesolimbic structures (amygdala, medial substantial nigra and ventral tegmental area, orbitofrontal cortex) to negative stimuli were decreased after ketamine administration.
- The data are consistent with the premise that ketamine induces sustained changes in the mesolimbic neural circuits to reset pathological reward and emotional processing.

ABSTRACT

Background: Ketamine rapidly improves maladaptive mood states in major depressive disorder, and some of the neural substrates underlying this therapeutic effect have been identified. This study aimed to identify functional changes within neural networks that may underlie the impact of ketamine on both reward and emotional processing in patients with treatment-resistant major depression.

Methods: Ten adult patients with a Montgomery–Åsberg Depression Rating Scale score above 25 were enrolled to receive a single intravenous administration of ketamine (0.5 mg/kg). Patients' performance along with related neural network activations were analyzed in a game-like reward task and in an emotional judgment task using functional magnetic resonance imaging 1 day before and 1 and 7 days after ketamine administration.

Results: A significant correlation ($R^2 = 0.46$, $P = 0.03$) between the improvement of depression scores and the enhanced reaction time for positive items was found in the game-like reward task 1 day after ketamine administration. This enhanced sensitivity for rewarded items was accompanied by increased activity of reward-related brain regions, including the orbitofrontal cortex, ventral striatum, and the ventral tegmental area, an effect that persisted up to 1 week after ketamine injection. In the emotional judgment task, it was found that ketamine rapidly modified local brain activities in response to emotionally negative, positive, or neutral stimuli in the amygdala, insula, anterior cingulate cortex, and in the ventral tegmental area.

Conclusions: Single bolus ketamine administration rapidly triggers lasting changes in mesolimbic neural networks to improve pathologic reward and emotional processing in patients with major depressive disorder.

(ANESTHESIOLOGY 2019; XXX:00–00)

Major depressive disorder is a seriously debilitating condition.[1] Anhedonia and impaired recognition of emotional stimuli are major hallmarks of depression and could be involved in the emergence of maladaptive mood states. Anhedonia, the inability to experience pleasure from activities usually found enjoyable, is accompanied by decreased motivation or drive, and functional magnetic resonance imaging together with positron emission tomography studies have revealed altered neural activity in several components of the reward circuitry in patients with major depressive disorder.[2–4] Abnormal perceptual processing of emotional valence, such as attentional bias away from or reduced sensitivity to happy facial expressions, are thought to reflect reduced functional connectivity and feedback between certain cortical and limbic brain structures.[5,6]

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Submitted for publication December 6, 2017. Accepted for publication January 28, 2019. From the Department of Neuroscience, Faculty of Medicine (V.S., J.H., D.W., A.D., S.S., L.V.), Geneva Neuroscience Center (V.S., J.H., D.W., A.D., S.S., L.V.), and Swiss Center for Affective Sciences (V.S., J.H., D.W., S.S.), University of Geneva, Geneva, Switzerland; Department of Mental Health and Psychiatry, Service of Psychiatric Specialties (S.V., G.M., V.B., A.D., J.-M.A., M.K.), and Department of Anesthesiology, Pharmacology, and Intensive Care (L.V.), University Hospitals of Geneva, Geneva, Switzerland; Faculty of Medicine, University of Namur, Namur, Belgium (M.D.).

The clinical effectiveness of currently approved pharmacologic approaches to treat major depressive disorder is seriously hampered by the fact that these drugs may need several weeks to provide therapeutic effects, and that they operate with a relatively low rate of clinical effectiveness along with a high incidence of relapse.[7] In pioneering studies, low subanesthetic concentrations of ketamine rapidly and significantly alleviated depressive symptoms in patients resistant to classic pharmacologic antidepressant medications.[8,9] These initial findings were confirmed by subsequent clinical trials, and recent meta-analyses unanimously support the antidepressant therapeutic potential of ketamine.[10,11]

Identifying the neural substrates involved in the antidepressant effects of ketamine will provide us with important new information about the neurobiology of depression and, ultimately, regarding mood disorder therapeutics. Recent investigations in patients with major depressive disorder revealed no change in whole brain metabolism 2 hours after ketamine injection, whereas *a priori* region of interest analysis showed acute ketamine-induced alterations in the activity levels of several brain structures specifically involved in emotional and reward processing.[12–17] However, we currently do not know whether and to what extent the ketamine-induced changes in network activities persist over time. A related important series of yet-unexplored questions concern the impact of ketamine on both reward and emotional processing in these patients, and how functional changes within neural networks may explain changes in depressive symptoms. The present study aimed to answer these questions by acquiring whole-brain functional magnetic resonance imaging data in 10 treatment-resistant patients with major depressive disorder while they performed a game-like reward task[18] and an emotional judgment task[19] up to 1 week after a single ketamine injection. We hypothesized that ketamine would normalize responses within emotion and reward brain networks, including the amygdala, insula, anterior cingulate cortex, orbitofrontal cortex, ventral striatum, and ventral tegmental area.[20–23]

Materials and Methods

This open uncontrolled pilot study was conducted at the Geneva University Hospitals, Geneva, Switzerland, in accordance with local and national legislation, and the Declaration of Helsinki.[24] The study protocol was approved by the local ethics committee and registered in the clinicaltrials.gov database (NCT01135758). The primary objective of the study protocol was to confirm the robust and rapid antidepressant effects of intravenously administered ketamine (0.5 mg/kg) using the Montgomery–Åsberg Depression Rating Scale as a primary outcome measure at baseline and after distinct time intervals of ketamine injection.[25] A secondary objective of the study protocol, reported specifically in the present manuscript, was to examine changes in regional cerebral blood flow induced by ketamine using functional magnetic resonance imaging. All patients gave written informed consent before any assessment. No *a priori* statistical power calculation was conducted.

Participants

Ten patients (four men, 38 to 58 yr of age; see table 1 for detailed patients' characteristics) were recruited from the Department of Mental Health and Psychiatry of the University Hospital of Geneva using the following inclusion criteria: (1) *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision diagnostic criteria for recurrent major depressive disorder without psychotic features, (2) the absence of Axis I psychiatric comorbidities except anxiety disorder, (3) no lifetime history of psychotic symptoms nor bipolar disorder, (4) no substance abuse or dependence in the previous 3 months (except nicotine consumption), (5) a score of 25 or higher on the Montgomery–Åsberg Depression Rating Scale (MADRS),[26] (6) unchanged medication (antidepressants, antipsychotics, mood stabilizers) during the last 6 weeks before inclusion, and (7) failure of at least two adequate antidepressant treatments (*i.e.*, 4 weeks at the maximal authorized or tolerated dose). Exclusion criteria included (1) serious and imminent risk of suicide (score at or above 4 on item 10 of the MADRS), and (2) any contraindication to the administration of ketamine or to undergo magnetic resonance imaging scanning. All patients participated in the entire protocol, and there were no missing data.

Experimental Procedure

Upon inclusion to the protocol and receipt of their written informed consent, patients were scheduled for four visits: one for the administration of a single dose of ketamine (DAY 0), and three magnetic resonance imaging sessions performed one day before (DAY−1), one day after (DAY+1), and seven days after (DAY+7) ketamine administration (fig. 1A). This experimental design allowed us to compare baseline (DAY−1) with early (DAY+1) and late (DAY+7) effects of ketamine on brain function.

Ketamine administration occurred at the Clinical Research Center, University Hospital of Geneva, Switzerland. Upon arrival, depression level was assessed in each patient using the clinician-administered MADRS, the Hamilton Depression Rating Scale (HDRS-21),[27] and the Beck Depression Inventory (BDI-II) scales.[28] A clinical monitoring (pulse, blood pressure, digital pulse oximetry, and electrocardiogram) was then set to control physiologic parameters during and shortly after ketamine injection. Ketamine hydrochloride (0.5 mg/kg) was administered by a senior anesthesiologist in a bolus injection over 1 min *via* a dorsal hand vein of the nondominant arm. To control for potential adverse events after ketamine administration, patients were monitored at the clinical research unit for 4 h after the injection. Although all patients displayed

Table 1. Sociodemographic and Clinical Characteristics (N = 10 Patients)

Characteristic	Number of Patients or Median (Range)
Sociodemographic parameters	
Female	6
Age, yr	51 (38–58)
Education, yr	14 (9–18)
Married	4
Currently unemployed	9
Living alone	3
Psychiatric diagnosis (DSM-V code)	
Major depressive disorder, recurrent, severe without psychotic features (296.33)	9
Major depressive disorder, single episode, severe without psychotic features (296.23)	1
Persistent depressive disorder (300.4)	8
Anxiety disorders	9
Social anxiety disorder (300.23)	2
Specific phobia (300.29)	1
Panic disorder (300.01)	4
Generalized anxiety disorder (300.02)	4
Obsessive-compulsive disorder (300.3)	1
Posttraumatic stress disorder (309.81)	1
Unspecified anxiety disorder (300.00)	1
History of illness	
Age of onset, yr	27 (18–51)
Duration of major depressive disorder, yr	21 (4–29)
Number of major depressive episodes	3 (1–5)
Prior suicide attempt	4
Current depressive episode	
Episode duration, months	47 (9–204)
Hospitalization during current episode	6
Psychotropic medication	
Antidepressants	10
Antipsychotics	7
Mood stabilizers	5
Benzodiazepines	10

DSM-V, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.

a transient increase in blood pressure, none needed pharmacologic intervention to reduce this. In line, none of the patients displayed any major adverse events necessitating clinical intervention. Six of the 10 patients displayed transiently altered vigilance lasting less than 15 min. To assess the rapid effect of ketamine on self-reported depression level, the depression scales were further assessed 60 min before and 40, 80, 110, and 230 min after ketamine injection.

The three magnetic resonance imaging sessions were conducted at the Brain and Behavior Laboratory, University of Geneva, Switzerland. The protocol included a three-dimensional T1-weighted whole brain structural image and two event-related functional magnetic resonance imaging scans during which patients performed a reward task and an emotional judgment task (see below). Patients arrived at 9 AM and were screened for changes in their clinical assessment by a psychiatrist. Their depression level was again assessed using the MADRS, HDRS-21, and BDI-II scales. Then, before the first session, they received detailed instructions relative to the magnetic resonance imaging protocol and performed a demo version of the two tasks on a computer outside the magnetic resonance imaging scanner, to familiarize the patients with the tasks and minimize any potential learning effect during the following magnetic resonance imaging sessions. They were next placed into the magnetic resonance imaging scanner and performed the full versions of both tasks.

Experimental Tasks and Behavioral Analysis

Reward Task

The reward task was a game-like task, adapted from the Monetary Incentive Delay task.[18] In this task, patients could win or lose points by rapidly pressing a key when a visual target was shown. Each trial started with the

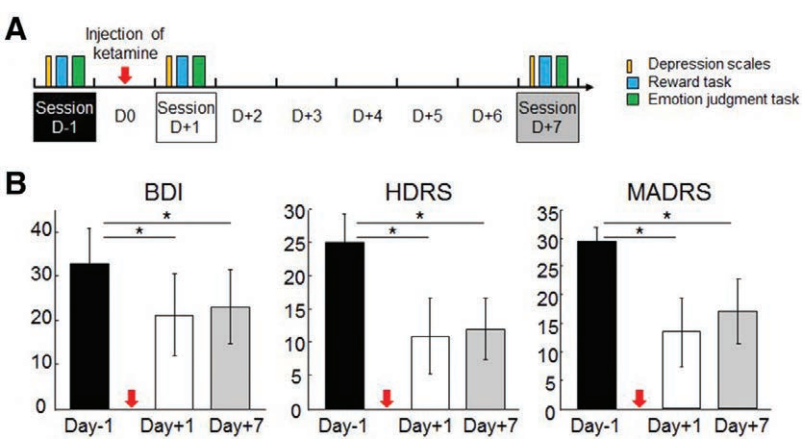

Fig. 1. Overall experimental design and depression scores. (*A*) Experimental design. (*B*) Evolution of the level of depression over the three visits and for different mood scales (mean ± SD). BDI, Beck Depression Inventory; D, day; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

presentation of a cue indicating whether this trial could result in more points for successful performance (*vs.* no additional points if unsuccessful; positively cued trials, +1 or +5 points) or in an actual loss for unsuccessful performance (*vs.* no loss if successful; negatively cued trials, −1 or −5 points). The cue was presented for 1,200 ms and then blinked for 1,125 ms (the coin was flipped horizontally at 4 Hz). After a variable delay (mean ± SD: 1,375 ms ± 875 ms), the visual target requiring a rapid key press was briefly shown on the screen. Any response occurring before (anticipated response) or after (late response) target presentation, as well as the absence of a response was considered as an unsuccessful trial. The trial ended with a feedback display indicating whether the trial was won or lost. We could thus distinguish brain activity during the anticipation period (presentation of the cue) and the outcome period (presentation of the feedback). We also compared positively cued trials (+1 and +5; *i.e.*, potential gains) to negatively cued trials (−1 and −5; *i.e.*, potential losses) during the anticipation phase, as well as successful to unsuccessful trials during the feedback period. Each of the four cue types was presented 30 times in random order. To obtain an equal proportion of successful and failed trials as well as to match task difficulty across participants and sessions, the target's presentation time was adjusted based on the participant's current performance: whenever the trial was successful or unsuccessful, 25 ms were subtracted or added to the presentation time of the next trial with identical cue type, respectively. Performance on the task was analyzed using the percentage of correct trials (hits), the percentage of late responses (trials for which the patient responded after the disappearance of the target), and the mean reaction times for correct trials, for each cue type. We used three-way repeated-measures ANOVA in Statistica 11.0 (StataCorp 2009, Stata Statistical Software: Release 11, StataCorp LP, USA), including Session (DAY−1, DAY+1, DAY+7), Cue Valence (positive, negative), and Cue Value (1 point, 5 points) as within-subjects factors. *Post hoc* analyses were performed using planned comparisons corrected for multiple comparisons with the Bonferroni method. Specifically, we tested for differences across sessions (DAY−1 *vs.* DAY+1, DAY−1 *vs.* DAY+7 and DAY+1 *vs.* DAY+7) for high positive cues. These comparison tests directly derive from our main hypothesis about the restoration of adapted emotional response to rewarded stimuli after ketamine injection. Finally, we also wanted to test whether the modification of depression scores was correlated with the modification of behavioral performances. We performed a correlation between the evolution of depression (MADRS score) by ketamine and the evolution of reaction times for positive items.

Emotional Judgment Task

The emotional judgment task was adapted from Sterpenich *et al.*[19] In this task, patients were asked to rate the emotional valence of pictures. Each trial started with the presentation of a fixation cross on a gray screen (1,000 ms), followed by the presentation a picture (3,000 ms). The trial ended with a choice display (2,000 ms), during which the patients were asked to rate the valence of the picture on a four-point scale (from *very negative* to *very positive*), using a rating system inspired by the Self-Assessment Manikin.[29] In each session, a total of 90 different photographs were selected based on the ratings from 12 healthy volunteers and included 30 negative (consisting in aversive scenes), 30 neutral, and 30 positive (consisting of humorous scenes) pictures. The set of stimuli for each emotional category contained a similar proportion of objects, landscapes, animals, and human beings. Moreover, the three sets of stimuli used for the three sessions were matched for emotional ratings. Picture luminance was equalized to obtain the same mean luminance for all pictures. The pictures were presented one at a time and in random order. For subsequent behavioral (and functional magnetic resonance imaging) analyses, each trial was categorized based on each individual's subjective ratings: '−2' ratings were assigned to the negative condition, '−1' and '+1' ratings were grouped into a neutral condition, and '+2' ratings were assigned to a positive condition. The proportion and reaction times of pictures judged emotionally negative, neutral, and positive were analyzed using two-way repeated-measure ANOVAs with Session (DAY−1, DAY+1, DAY+7) and Emotional Valence (negative, neutral, or positive) as within-subject factors.

For both tasks, stimuli were projected by a LCD projector (CP-SX1350, Hitachi, Japan) on a screen (about 19° × 14°) placed inside the scanner bore. Key presses were recorded on an magnetic resonance imaging-compatible response button box (HH-2 × 4-C, Current Designs Inc., USA).

For the analysis of the depression scales, we performed three separate one-way ANOVAs, one for each depression scale measured at three time points (*i.e.*, sessions). *Post hoc* Bonferroni analysis revealed significant differences between sessions.

Magnetic Resonance Imaging Acquisition and Analysis

Magnetic resonance imaging data were acquired on a 3-T Siemens Trio whole-body scanner (Siemens Medical Solutions, Germany) using an eight-channel head coil, at the Brain and Behavior Laboratory, University of Geneva, Switzerland. The protocol included a three-dimensional T1-weighted whole brain structural image (192 contiguous sagittal slices; repetition/echo time/flip angle: 1,900 ms/2.27 ms/9°; field of view: 256 mm; matrix: 256 × 256 × 192; voxel-size: 1 × 1 × 1 mm). This acquisition volume was aligned on the anterior/posterior commissure axis, localized on the mid-sagittal slice of a localizer scan. For each participant, one three-dimensional T1-weighted structural images was normalized using the T1 Montreal Neurological Institute template of SPM8 (Wellcome Department of Imaging Neuroscience, London, United Kingdom;

http://www.fil.ion.ucl.ac.uk/spm, accessed September 15, 2018). Functional images of the two tasks were acquired with a gradient-echo echo-planar imaging sequence (repetition/echo time/flip angle: 2,100 ms/30 ms/80°; field of view: 205 mm, matrix: 64 × 64 × 36, gap 20%: 0.6mm, slice acquisition order: descending) and parallel imaging (GeneRalized Autocalibrating Partial Parallel Acquisition [GRAPPA], acceleration factor = 2). A total of 385 and 290 magnetic resonance imaging volumes in each session were acquired for the reward task and the emotional judgment task, respectively. Each functional image comprised 36 axial slices (voxel-size: 3.2 × 3.2 × 3.2 mm) oriented parallel to the inferior edge of the occipital and temporal lobes, and covering the whole brain.

Functional magnetic resonance imaging data were analyzed using SPM8. Images were realigned to the mean functional image of the corresponding task, then corrected for slice timing, normalized to an EPI template in MNI space (re-sampled voxel-size of 3 mm), and spatially smoothed (8 mm full width at half maximum Gaussian kernel). Statistical analysis were performed using the general linear model implemented in SPM8, with separate regressors for each event-type convolved with a canonical hemodynamic response function.

The statistical model of the reward task included 16 main regressors of interest: eight regressors with events time-locked to the presentation of the cue (anticipation period) for the four cue types further subdivided into subsequently successful or unsuccessful trials (four cue types × two possible feedbacks), and eight regressors with events time-locked to the presentation of the feedback (outcome period) also subdivided as a function of cue type and feedback. All trials with anticipated responses (keypresses before the target presentation) and trials with no responses, representing less than 1.5% of the total number of responses, were grouped into two regressors (cue onset and feedback onset) of no interest. The contrasts of interest for the reward task were the interactions between positive emotions ([positive cues greater than negative cues] or [positive feedbacks greater than negative feedbacks]) and ketamine sessions ([DAY+1 greater than DAY−1] and [DAY+7 greater than DAY−1]). The reverse contrasts were also presented ([DAY−1 greater than DAY+1] and [DAY−1 greater than DAY+7]). The main effects of emotions and ketamine sessions were not presented here because they are not relevant to the main hypothesis.

The statistical model of the emotional judgment task included three main regressors of interest: the presentation of negative, positive, and neutral pictures. For both models, movement parameters from realignment corrections were entered as additional covariates of no interest to account for residual movement artefacts. The contrasts of interest for the emotional judgment task were the interactions between positive emotions ([positive images greater than negative images]) and ketamine sessions ([DAY+1 greater than DAY−1] and [DAY+7 greater than DAY−1]). The reverse contrasts were also presented ([DAY−1 greater than DAY+1] and [DAY−1 greater than DAY+7]). The main effects of emotions (positive greater than neutral and negative greater than neutral) and ketamine sessions were not presented here because they are not relevant to the aim of the study.

For each task, individual statistical parametric maps were generated from linear contrasts between conditions. These contrast maps then entered second-level random-effect analyses using one-sample *t* tests. Statistical inferences were corrected for multiple comparisons using Gaussian random field theory at the voxel level. For the whole brain analysis, brain activations were detected at a voxel-level of $P \leq 0.001$ (uncorrected) with a cluster size greater than or equal to 5 voxels. If the peak of the regions observed at this threshold did not survive to the correction for multiple comparison for the entire brain ($P < 0.05$ family-wise error correction), we applied the correction for multiple comparison on a smaller volume using the small volume corrections procedure in SPM. Based on the relevant literature,[20–23] we created anatomical masks from automated anatomical labeling[30] for regions specifically involved in reward and emotion processing, including amygdala, insula, anterior cingulate cortex, orbitofrontal cortex, and ventral striatum. Other activated regions for which we had no *a priori* hypothesis are not reported here. In this case, we reported brain activations for regions present at $P < 0.001$ uncorrected and significant at $P < 0.05$ family-wise error correction using the small volume corrections procedure on these selected maks at the voxel level for the peak of the region.

In addition, after the whole-brain analysis, we performed a more specific analysis on a particular region. Because we were interested in changes across the dopaminergic reward system and because reward processing involves midbrain dopaminergic neurons,[31] we performed a region of interest analysis. We extracted directly functional magnetic resonance imaging signal from the medial substantia nigra/ventral tegmental area using a mask generated in a previous study in 19 healthy human volunteers and based on a proton density–weighted sequence.[32] The extracted functional magnetic resonance imaging signal corresponds to the mean of the parameter estimates (beta values) of all voxels of the anatomical region. The extracted data were calculated for each condition, and we analyzed the extracted data using a two-way repeated-measures ANOVA (Emotion by Session) in Statistica.

Finally, we wanted to test whether the modifications of brain activations attributable to ketamine were similar or not after short and long delay. We displayed the contrast of interest (positive *vs.* negative for the different tasks) for the short delay (DAY+1 *vs.* DAY−1), and we masked it inclusively with the similar contrast for long delay (DAY+7 *vs.* DAY−1) to identify the brain regions that were common to both contrasts. The small volume corrections procedure was then performed on the resulting data.

Results

Impact of Ketamine on Depression Scales

In line with previous observations,[10,11] three separate one-way repeated-measures ANOVAs on the HDRS-21, MADRS, and BDI-II scales showed that depression scores, high before ketamine injection (DAY−1), significantly decreased both rapidly (DAY+1) and lastingly (DAY+7) after intravenous ketamine (0.5 mg/kg) administration (main effect of Session, all $P < 0.006$; see fig. 1B). *Post hoc* Bonferroni analyses revealed that these depression scores were significantly lower both at DAY+1 and DAY+7 when compared independently with DAY−1 (DAY+1 *vs.* DAY−1: HDRS-21: $P < 0.001$, MADRS: $P < 0.001$, BDI-II: $P = 0.008$; DAY+7 *vs.* DAY−1: HDRS-21: $P < 0.001$, MADRS: $P < 0.001$, BDI-II: $P = 0.027$). No difference was observed when comparing DAY+1 and DAY+7 (HDRS-21: $P = 1.000$, MADRS: $P = 0.339$, BDI-II: $P = 1.000$).

Effects of Ketamine on the Game-like Reward Task

Behavioral Performance

We first set out to examine whether and how ketamine administration affected behavioral performance in patients with major depressive disorder using the game-like reward task (fig. 2A). As seen in table 2, ketamine injection resulted in a reduction of late responses in our patient population (main effect of Session: $F(2,18) = 4.151$, $P = 0.033$). There was also a main effect of cue type (high *vs.* low), $F(1,9) = 9.094$, $P = 0.015$, no main effect of valence $F(1,9) = 1.308$, $P = 0.282$, and no triple interaction $F(2,18) = 2.34$, $P = 0.13$. However, the interactions between each session after *versus* the session before ketamine (DAY+1 *vs.* DAY−1 and DAY+7 *vs.* DAY−1) and cue type for positive value were significant ([DAY+1 *vs.* DAY−1, cue+5 *vs.* cue+1, $F(1,9) = 6.259$, $P = 0.034$] and ([DAY+7 *vs.* DAY-1, cue+5 *vs.* cue+1, $F(1,9) = 9.704$, $P = 0.012$]). This interaction is explained by a significant decrease in the number of late responses for

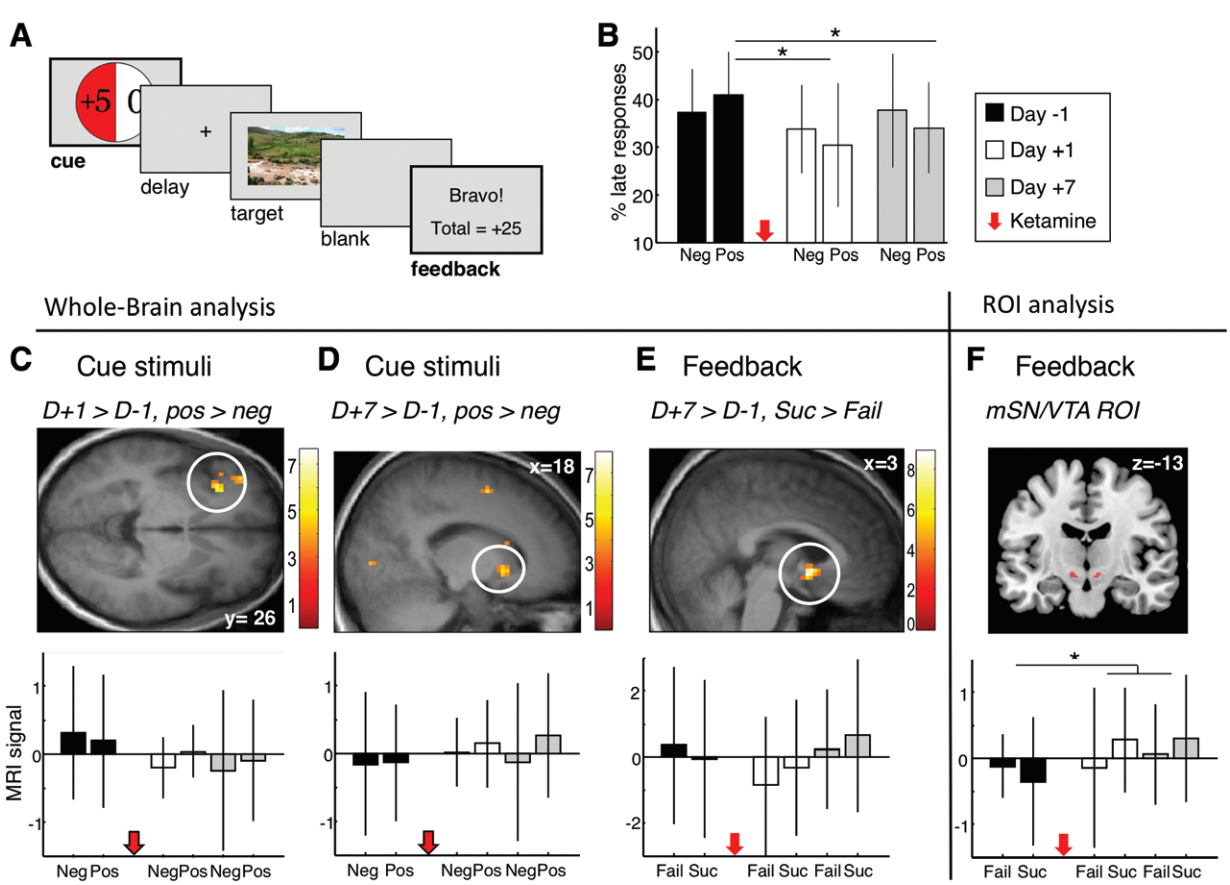

Fig. 2. Reward task. (*A*) Illustration of one trial of the reward task, here a successful highly rewarded trial. (*B*) Percentage of late responses for high positive (+5) and negative cues (–5) across the different sessions (mean ± SD). Insula (*C*) and ventral (*D*) striatum activation for positive *versus* negative cue presentations. (*E*) Ventral striatum and medial substantia nigra/ventral tegmental area (*F*) activation for successful *versus* lost feedback presentations. For display purposes, brain responses are displayed at $P = 0.005$ uncorrected, and projected on the mean structural image, with parameter estimates of activation plotted on the bottom (mean ± SD). MRI, parameter estimates; mSN, medial substantia nigra; Neg, negative; Pos, positive; ROI, region of interest; Suc, success; VTA, ventral tegmental area.

Table 2. Behavioral Results of the Reward Task

	Day−1		Day+1		Day+7	
	Negative Cues	Positive Cues	Negative Cues	Positive Cues	Negative Cues	Positive Cues
Hit, % (SD)	50 (3)	52 (3)	51.(3)	53 (2)	53 (3)	54 (3)
Reaction time for hit, ms (SD)	273 (23)	269 (29)	231 (28)	221 (14)	228 (33)	218 (30)
Late response, % (SD)	39 (2)	39 (3)	36 (3)	33 (4)	37 (3)	36 (3)

highly positively cued trials (*i.e.*, cues +5) when comparing both DAY+1 and DAY+7 session independently with DAY−1 session (*post hoc* pairwise comparison, Bonferroni-corrected for multiple testing, DAY+1 *vs.* DAY−1: $P = 0.042$; DAY+7 *vs.* DAY−1: $P = 0.035$, DAY+1 *vs.* DAY+7: $P = 0.225$; fig. 2B). Besides the effects of ketamine on task performance, two-way repeated measure ANOVA (with Emotion and Session as within-subjects factors) comparing reaction times for these correct responses revealed a main effect of Session, $F(2,18) = 10.7$, $P = 0.001$: patients being faster both at DAY+1 ($P = 0.003$) and DAY+7 ($P = 0.009$) when compared independently with DAY−1, an effect of emotion, $F(3,27) = 3.56$, $P = 0.027$, with no significant Emotion by Session interaction, $F(6,54) = 0.53$, $P = 0.785$. To control for any potential training effects during the paradigm, we also selectively analyzed the second half of each session and found similar results further supporting that our observations are due to ketamine administration itself and not learning effect. Finally, we observed a significant correlation ($R^2 = 0.466$, $P = 0.029$) between the improvement of depression by ketamine after one day (measured by the difference of MADRS scale between DAY−1 and DAY+1) and the improvement of reaction time for positive items (measure by the difference between DAY−1 and DAY+1 reaction times for positive *vs.* negative cues). Taken together, these results indicate that ketamine administration increases global vigilance level along with specifically enhanced sensitivity for rewarded items.

Functional Magnetic Resonance Imaging To identify neural networks implicated in ketamine-induced behavioral changes in the reward paradigm, we performed whole brain analysis using functional magnetic resonance imaging. We first tested whether ketamine changed brain activity when patients expected a potential reward (positively *vs.* negatively cued trials). During this anticipatory phase, we observed rapid ketamine-induced changes in the insula and orbitofrontal cortex when comparing DAY+1 to DAY−1 sessions (fig. 2C; table 3), and in the ventral striatum and orbitofrontal cortex when comparing DAY+7 to DAY−1 (fig. 2D). Parameter estimates indicated that all these regions were more activated for positively than negatively cued trials, selectively after ketamine treatment. To further test whether ketamine-induced rapid modifications in region-specific brain activities persisted over time, we compared brain regions at DAY+1 and DAY+7 using the inclusive masking procedure. Using this approach, we found that, when compared with DAY−1, orbitofrontal cortex and insula were both activated at DAY+1 and DAY+7, suggesting thereby a lasting increase in activity after both short- and long-term delays. The reverse contrast (positive *vs.* negative cues, before *vs.* after ketamine) revealed no significant activation, suggesting that no particular brain regions exhibited decreased activation for rewarded items after ketamine administration.

We next assessed whether ketamine also affected neural responses to winning *versus* losing feedbacks presented during the outcome period. When comparing DAY+1 to DAY−1 sessions, we found an activation of the ventral striatum that did not reach significance (*xyz* mm: -6, 11, 4; *z* score: 2.44; pseudo stokes vector correlation = 0.423) and, when comparing DAY+7 with DAY−1 sessions, the same region was significantly more activated, together with the orbitofrontal cortex (pseudo stokes vector correlation = 0.026, fig. 2E). The inclusive masking procedure (DAY+1 *vs.* DAY−1, and DAY+7 *vs.* DAY−1) revealed that this effect was persistent up to one week after injection in the ventral striatum. Again, no significant activation was observed in the reverse contrast (*i.e.*, for winning *vs.* losing before *vs.* after ketamine).

Finally, after the whole brain analysis and to better characterize the impact of ketamine on the dopaminergic system, we specifically focused on the medial substantia nigra/ventral tegmental area as region of interest (analysis, see Materials and Methods). For the anticipation period, extracted functional magnetic resonance imaging data from the substantia nigra/ventral tegmental area showed no effect of Session, $F(2,18) = 2.560$, $P = 0.102$, no effect of Emotion, $F(1,9) = 0.002$, $P = 0.970$, and no significant Emotion by Session interaction, $F(2,18) = 0.132$, $P = 0.877$. For the feedback period, we observed no main effect of Session, $F(2,18) = 1.510$, $P = 0.0248$, and no effect of Emotion, $F(1,9) = 0.640$, $P = 0.444$). However, the substantia nigra/ventral tegmental area was more active when winning than losing after ketamine administration at both posttreatment time points (DAY+1, DAY+7) as compared with baseline (DAY−1) (fig. 2F; Interaction comparing successful *vs.* unsuccessful trials and DAY−1 *vs.* DAY+1 and DAY+7, $F(2,18) = 6.57$, $P = 0.031$). These results suggest that increased reactivity of reward-related regions (orbitofrontal cortex, ventral striatum, and medial substantia nigra/ventral

Table 3. Brain Activations during the Reward Task

Brain Region	*x*	*y*	*z*	*z* score	pSVC
Short-term ketamine-induced activity increases for positive cues (D+1 > D−1, positive > negative)					
Orbitofrontal cortex	21	47	−11	3.87	0.006
Insula	−33	26	−5	3.68	0.041
Short-term ketamine-induced activity decreases for positive cues (D−1 > D+1, positive > negative)					
No significant activation					
Long-term ketamine-induced activity increases for positive cues (D+7 > D−1, positive > negative)					
Ventral striatum (NAcc)	18	14	−5	3.77	0.042
Orbitofrontal cortex	−21	38	−14	3.86	0.007
Long-term ketamine-induced activity decreases for positive cues (D−1 > D+7, positive > negative)					
No significant activation					
Short-term ketamine-induced activity increases for positive feedback (D+1> D−1, feedback successful > failed)					
No significant activation					
Short-term ketamine-induced activity decreases for positive feedback (D−1 > D+1, successful > failed)					
No significant activation					
Long-term ketamine-induced activity increases for positive feedback (D+7 > D−1, successful > failed)					
Ventral striatum (NAcc)	6	8	−8	3.65	0.001
Orbitofrontal cortex	−15	47	−17	3.75	0.011
Long-term ketamine-induced activity decreases for positive feedback (D−1 > D+7, successful > failed)					
No significant activation					

D, day; NAcc, nucleus accumbens; pSVC, pseudo stokes vector correlation.

tegmental area) during this game-like task could then induce a general increase in motivation, which is consistent with the faster reaction times observed after ketamine injection.

Effects of Ketamine in the Emotional Judgment Task

Behavioral Performance

Given the aforementioned effects of ketamine on the reward system, we next set to investigate how this drug influences the perception of aversive emotions (fig. 3A). Using our previously validated emotional judgment task[19] during the three visits, we computed the proportion of pictures rated as negative (−3, −2), neutral (−1, 0, +1), or positive (+2, +3) for each session. We found a main effect of Emotion, $F(2,18) = 61.658$, $P < 0.001$, because patients scored more neutral pictures than positive or negative ones but we showed that ketamine had no significant effect on the emotional rating of the pictures (interaction Emotion by Session $F(4,36) = 2.46$, $P = 0.063$, table 4). However, the treatment had a significant main effect on reaction times across sessions (effect of Session, $F(2,14) = 6.378$, $P = 0.011$) because patients were faster after ketamine injection (DAY−1 *vs.* DAY+1 and DAY+7: $P = 0.11$), but no effect of Emotion on reaction times, $F(2,14) = 1.014$, $P = 0.389$, and no interaction Session × Emotion, $F(4,28) = 1.037$, $P = 0.406$. This pattern of results converges with the results obtained in the reward task to indicate that ketamine increased global vigilance.

Functional Magnetic Resonance Imaging

Using a whole-brain approach, we tested whether ketamine modified local brain activity in response to emotionally negative, positive, or neutral stimuli. We found that ketamine induced changes in activity for negative *versus* positive pictures. Specifically, when comparing DAY+1 to DAY−1 sessions, we found that amygdala and insula response to negative (*vs.* positive) pictures strongly decreased after ketamine injection (fig. 3, B and C; table 5), whereas the reverse contrast showed no significant activation. When comparing DAY+7 with DAY−1 session, we observed that this decrease persisted in the insula and also in the dorsal anterior cingulate cortex. Moreover, the inclusive masking procedure revealed that activity in the posterior insula and dorsal anterior cingulate cortex decreased significantly after both short and long delays (DAY+7 *vs.* DAY−1, and DAY+1 *vs.* DAY−1 contrasts; see Materials and Methods). Here too, the reverse contrast revealed no significant activation. These results indicate that activity in regions typically implicated in the processing of negative emotions was high before ketamine injection and decreased after drug treatment.

After the whole-brain approach, and using the same region of interest procedure as for the reward task described

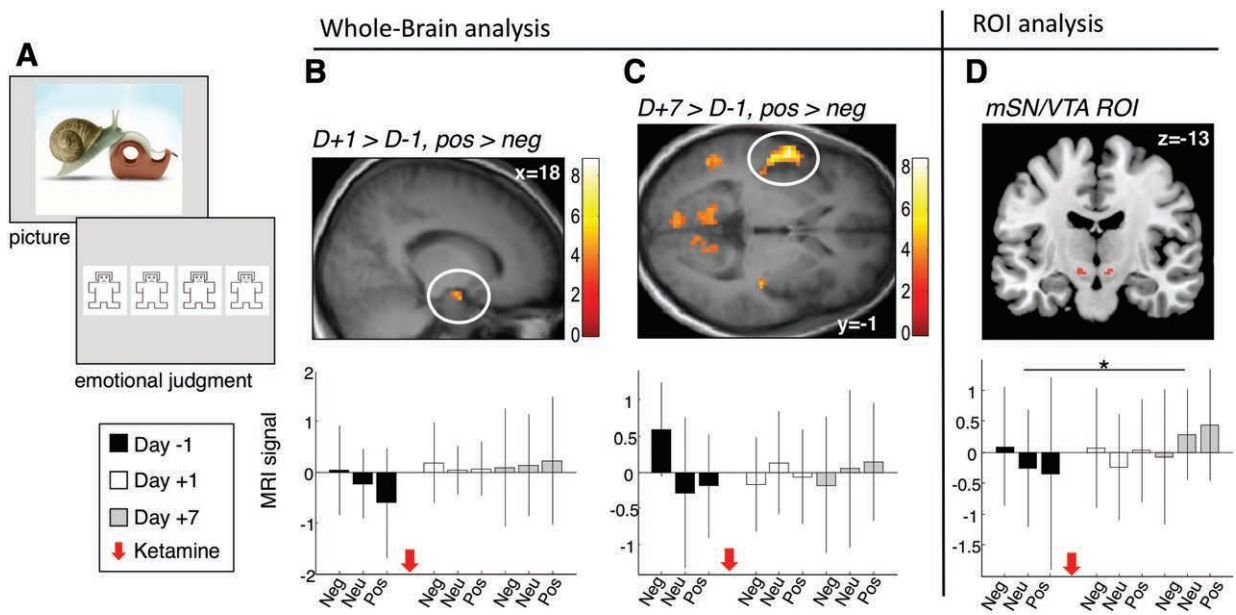

Fig. 3. Emotional judgment task. (*A*) Illustration of one trial of the emotional judgment task, here a positive (*i.e.* humorous) trial. (*B*) Amygdala, (*C*) insula, and medial substantia nigra/ventral tegmental area increased activity for positive pictures. For display purposes, brain responses are displayed at $P = 0.005$ uncorrected, and projected on the mean structural image, with parameter estimates of activation plotted on the bottom (mean ± SD). mSN, medial subtantia nigra; Neg, negative; Neu, neutral; Pos, positive; ROI, region of interest; VTA, ventral tegmental area.

Table 4. Behavioral Results of the Emotion Judgment Task

	Day-1			Day+1			Day+7		
	Negative	**Neutral**	**Positive**	**Negative**	**Neutral**	**Positive**	**Negative**	**Neutral**	**Positive**
Emotional ratings, % of pictures (SD)	23 (2)	64 (4)	13 (3)	24 (2)	60 (6)	16 (5)	21 (3)	72 (4)	8 (3)
Mean reaction time, ms (SD)	701 (47)	799 (44)	870 (101)	612 (58)	657 (61)	671 (83)	576 (47)	650 (48)	567 (41)

above, we found a striking pattern of activation of the medial substantia nigra/ventral tegmental area, with no effect of Session, $F(2,18) = 0.615$, $P = 0.552$, no effect of Emotion, $F(2,18) = 0.358$, $P = 0.704$, but a significant interaction between Session and Emotion $F(4,36) = 3.031$, $P = 0.030$ (fig. 3D). Specifically, the medial substantia nigra/ventral tegmental area was more active for negative than positive pictures before treatment (*i.e.*, at DAY−1), whereas it became more active for positive than negative pictures at DAY+7 (negative *vs.* positive DAY−1 *vs.* DAY+7: $P < 0.001$).

Discussion

Combining behavioral tests with functional magnetic resonance imaging in treatment-resistant patients with major depressive disorder, we assessed the rapid (*i.e.*, after one day, DAY+1) and lasting (*i.e.*, after 7 days, DAY+7) effects of a single bolus ketamine administration on brain responses during reward and emotional processing. Our findings support previous data suggesting that ketamine reduces depression scores in treatment-resistant major depressive disorder.[10,11] We also show here that ketamine rapidly modified behavior and restored brain reactivity in patients with major depressive disorder when they were provided with rewarding stimuli and when they actively processed emotional pictures, with effects persisting at least for one week after drug injection.

Ketamine and Reward Processing

Because dysfunctional reward processing is an important hallmark of the pathophysiology of major depressive disorder,[2] we implemented a monetary incentive delay task to evaluate the impact of ketamine on reward function in patients with major depressive disorder. This paradigm has

Table 5. Brain Activations during the Emotional Judgment Task

Brain Region	*x*	*y*	*Z*	*z* score	pSVC
Short-term ketamine-induced activity increases for positive pictures (D+1 > D−1, positive > negative)					
Amygdala	18	−1	−20	3.26	0.028
Insula	−39	8	−11	4.42	0.002
Dorsal ACC	3	−1	34	3.50	0.026
Short-term ketamine-induced activity decreases for positive pictures (D−1 > D+1, positive > negative)					
No significant activation					
Long-term ketamine-induced activity increases for positive pictures (D+7 > D−1, positive > negative)					
Posterior Insula	−57	−1	−2	4.33	0.005
Dorsal ACC	−3	−4	34	3.94	0.024
Long-term ketamine-induced activity decreases for positive pictures (D−1 > D+7, positive > negative)					
No significant activation					

ACC, anterior cingulate cortex; D, day; pSVC, pseudo stokes vector correlation.

been previously applied across a wide range of psychiatric disorders and, in combination with functional magnetic resonance imaging, allows to specifically identify the neural structures implicated in reward anticipation as well as in the feedback response to the anticipated reward.[4,18,33–35] Using this task, we found that the ketamine-induced mood improvement in the patients was accompanied by a rapid and lasting increase in global vigilance (*i.e.*, decreased reaction times) as well as by better performance for trials associated with a potential gain, suggesting increased motivation or sensitivity to rewards. Indeed, given that reaction times, including movement initiation and execution, are deeply influenced by motivational factors,[36] and that the trials are specifically designed to minimize expectancy and habituation,[18] these findings indicate that ketamine administration rapidly reverses impaired reward processing in patients with major depressive disorder. Our behavioral observations are also in line with previous studies demonstrating that depressed individuals show impaired vigilance and poorer memory for positive material[37,38] while failing to behaviorally respond faster to monetary reward.[34,39]

These behavioral changes attributable to ketamine administration were paralleled by an increased recruitment of the orbitofrontal cortex and the ventral striatum both during reward anticipation and feedback. These brain structures are key components of reward processing,[40,41] and have been shown to display blunted activation patterns in major depressive disorder.[3,4,42] Because these regions are typically activated in healthy volunteers during the processing of positively cued trials, our current results suggest that ketamine leads to (at least partial) recovery of brain reward function in patients with major depressive disorder. To further tackle the role of ketamine on the reward system in major depressive disorder, we also focused on the medial substantia nigra/ventral tegmental area region that gives rise to the dopaminergic projections of the mesocorticolimbic pathway.[31] Optogenetic inhibition of dopamine-releasing neurons in this region have been shown to induce depression-related behavior in rodents,[43] whereas deep brain stimulation of several components of the mesocorticolimbic pathway has been reported to improve depressive symptoms in pharmacologic treatment-resistant patients with major depressive disorder.[44,45] The fact that ketamine rapidly and persistently increased medial substantia nigra/ventral tegmental area activity during positively cued trials in our study population therefore further supports a role of this drug in normalizing reward processing in major depressive disorder. Although our study does not allow us to draw conclusions on the molecular mechanisms behind these effects, experimental evidence indicates that ketamine can increase striatal dopamine release.[46,47] Such a ketamine-induced increase in dopamine could explain increased neural reactivity to rewards in patients with major depressive disorder, as we observed here, which in turn may be responsible for ketamine's therapeutic effects.

Ketamine and Emotional Processing

We also evaluated the impact of ketamine on the processing of positive and negative emotional stimuli and found that ketamine did not induce a detectable shift in the proportion of negatively, neutrally, or positively rated pictures. Although we do not have a clear explanation for this, it has previously been reported that behavioral biases toward sad faces seem to persist even after recovery from depression.[48] An alternative explanation would be that the sensibility of the test, offering merely four distinct possibilities of ratings, might be too low to detect changes in emotional perception. We did, however, find a significant improvement in reaction times after ketamine injection. These results are

in line with our observations from the monetary incentive delay task, and further indicate ketamine-induced increases in global vigilance. Most importantly, we found that amygdala, insula, and medial substantia nigra/ventral tegmental area activity in response to negative (*vs.* positive) emotional stimuli decreased after ketamine injection when compared with preinjection levels. It is known that, compared with healthy controls, patients with major depressive disorder have increased responses in these brain regions when exposed to sad facial stimuli and decreased responses to happy facial stimuli (reviewed in Groenewold *et al.*[6] and Stuhrmann *et al.*[49]). Our results show that ketamine may actually act against this overreactivity to aversive stimuli across limbic and mesolimbic regions, particularly specific of this pathology.[50,51] Our investigations also provide a useful replication of a recent functional magnetic resonance imaging study where treatment-resistant patients with major depressive disorder showed reduced responses in the caudate and insula when compared with healthy volunteers in a positive/negative emotion perception task, whereas ketamine administration restored activity in the caudate.[16] Importantly, our data give additional important information to these previous works by identifying the impact of ketamine in patients with major depressive disorder on neuronal substrates involved in the active processing of both positive emotions and rewards. Here we tested these distinct facets of affective function using two dedicated tasks within the same patients. We relate that ketamine-induced modulation across mesolimbic regions (substantia nigra/ventral tegmental area, ventral striatum, orbitofrontal cortex) to improvement in motivated behavior, which may actively contribute to establishing and maintaining changes in mood. Indeed, our findings also demonstrate that these effects persist at least up to one week after ketamine injection suggesting, thereby, a lasting reorganization of neural networks by a single bolus of this drug.

Limitations

Our study has some limitations. First, the number of patients included in this study could be considered as relatively low. It is nevertheless important to note that patients were selected based on strict inclusion criteria allowing us to investigate a rather homogenous patient population with major depressive disorder. In line with this argument, we found robust responses to ketamine both from the clinical and from the imaging perspective. A second potential limitation is the lack of healthy volunteers as a control population. Although including these healthy controls would have provided us with additional information, this study focused on the question of ketamine-induced changes in neural networks in patients with major depressive disorder. Therefore, we believe that considering the patients as their own control, before ketamine injection, is an appropriate approach. Moreover, because of the absence of control group, we cannot rule out the effect of time and habituation to the tasks and also to the depression scale questionnaires. The comparison between different conditions within each session minimizes this effect. Habituation would also lead to a linear increase or decrease of behavior and brain activity across time, but we clearly see a cut-off before and after the injection of ketamine and only few modifications between DAY+1 and DAY+7 sessions. A third limitation of our study is the lack of placebo control. Nevertheless, ketamine has been shown to exert a robust antidepressant effects when compared with placebo in all placebo-controlled trials in the field. Moreover, in our study, we systematically compared positive and negative emotions at each visit. The fact that we found changes in the positive but not in the negative emotions over time also argues against a potential placebo effect (*i.e.*, we would expect changes in both positive and negative emotions in case of placebo effect). A fourth issue that could be considered as a potential limitation when comparing the results of our study with those of pioneering observations is that we have administered ketamine intravenously as a bolus dose over one minute, whereas most studies applied this drug through a period of 40 min of infusion. Although we cannot exclude that pharmacokinetic or pharmacodynamics differences between these two administration protocols can give rise to different drug effects, the impact of our one-minute-long ketamine administration on clinical depression scales appears to be comparable with previous studies in this field. Defining the most efficient administration modalities leading to the best clinical response is an important part of the current research agenda in this domain.[17] Importantly, this rapid administration did not induce serious side effects necessitating clinical intervention. A fifth important issue that needs to be addressed in the future is the potential for sex-specific differences in responsiveness to ketamine. Indeed, recent meta-analysis suggests that males were a predictor of antidepressant response at 7 days after ketamine injection.[11] Although no such differences appeared between male and female participants regarding the antidepressant and network effects of ketamine, our pilot study, including a limited number of patients, was not designed to test for potential sex-specific effects. Finally, an important remaining question is whether the functional changes induced by ketamine in reward and emotional processing networks persist longer than the one-week period investigated in our study.

In conclusion, our results provide novel mechanistic insights into how ketamine improves mood in patients with major depressive disorder. The rapid and lasting action of this drug on mesolimbic neural networks to reset pathologic reward and emotional processing points toward a potent role of ketamine in the modulation of neuronal plasticity.

Research Support

Supported by the National Center of Competence in Research (NCCR) Affective Sciences financed by the Swiss

National Science Foundation (Geneva, Switzerland; grant No. 51NF40-104897) and hosted by the University of Geneva (Geneva, Switzerland), and the Swiss National Science Foundation (grant No. 135554; to Dr. Kosel).

Competing Interests

The authors declare no competing interests.

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