Can we change depressive beliefs? Modulation of belief updating mechanisms by Ketamine in Treatment Resistant Depression

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Abstract

Background: Treatment resistant depression (TRD) is a major public health problem that has encouraged novel treatment strategies involving sub-anesthetic ketamine infusions. While ketamine induces rapid and sustained clinical improvement, its cognitive effects are less well known. Recent theories propose that maladaptive belief updating play a key role in the maintenance of depression. Here, we tested if and how the clinical effects of ketamine were linked to belief updating mechanisms.

Methods: Twenty-six TRD patients performed a belief-updating task before and after ketamine treatment, and were compared to a group of thirty healthy controls. The task involved estimating likelihoods of experiencing adverse life events before and after receiving information about the actual occurrence of events in the general public. A computational reinforcement-learning (RL) model tested how much belief updating was explained by learning from positive (better than thought) and negative (worse than thought) estimation errors, and how these contingencies changed after ketamine.

Results: Following a single ketamine infusion, patients updated their beliefs about the future more after favorable, and less after unfavorable information, controlling for sequential testing effects by comparison to healthy controls. The emergence of optimism biases in belief-updating was underpinned by asymmetric learning from positive rather than negative estimation errors, and formally mediated precocious antidepressant effects after one week of treatment, measured by the Montgomery-Asberg Depression Scale (MADRS).

Discussion: This study was conducted in a naturalistic setting and was not designed as a therapeutic trial. We did not include a placebo group, and patients were not randomly allotted to the ketamine treatment arm. Thus, this concern is partly alleviated by the inclusion of healthy controls who repeated the same assessments at baseline and one week later.

Conclusion: These findings provide novel insights into the cognitive effects and computational mechanisms of ketamine action in TRD. They open the window toward promising perspectives for augmented psychotherapy in mood disorder.

Keywords

Ketamine, Treatment Resistant Depression, Mood disorders, Belief updating, Computational Psychiatry

Introduction

With more than 300 million people affected around the world, Major depressive disorder (MDD) and bipolar depression (BD) are a crucial public health concern (1), which are characterized by a range of negative beliefs such as worthlessness, hopelessness, and pessimism (2,3). Cognitive models of depression propose that such maladaptive beliefs bias one's perception and interpretation of life events, and further produce a negative view of oneself, the world and the future (3). In addition to this cognitive triad, in depressed patients, the excessively negative content of beliefs about the likelihood of life experiences (4) are characterized by a decreased sensitivity to disconfirming information (5). This phenomenon has also been referred to as pervasive pessimism (6), and stands in stark contrast to unrealistic optimism (7,8) that is frequently observed in healthy subjects.

Cognitive studies have shown that beliefs about the likelihood of future events are updated after novel experiences (9,10). In healthy participants, belief updating is often asymmetric (11–13) with more belief updating following desirable than undesirable information. This effect has been termed the good news/bad news bias, and is thought to underlie more general optimism biases (11) that are crucial for maintaining mental and physical health (13–16). Importantly, depressed patients have been shown to lack an optimism bias in belief-updating and to hold persistently negative expectations about the future, despite contradictory evidence (17–19). These characteristics are thought to play an important role in the maintenance of depressive symptoms and potentially in treatment resistance (20–23).

Crucially, about one third of depressed patients do not respond to conventional antidepressant treatments, and thereby suffer from Treatment Resistant Depression (TRD) (24). Over the last decade, ketamine, an ionotropic glutamatergic N-methyl-d-aspartate (NMDA) receptor antagonist, has become an exciting antidepressant therapy for TRD (25). Several meta-analyses of randomized placebo-controlled clinical trials show that ketamine has a rapid antidepressant effect that peaks

within 24 hours (26,27). Despite these promising results, little is known about the cognitive effects of ketamine and their link to clinical improvements (28).

Interestingly, pharmacological studies in healthy participants have shown that ketamine disturbed the belief-updating process by changing the way participants updated their beliefs when faced with new information (29–31). Building on these findings, ketamine has been used in healthy participants to model inference biases that can give rise to psychotic thinking and delusions (31–33). Moreover, another study on MDD has shown that a single ketamine infusion could produce a sustained improvement in depressive beliefs (34). However, it is unknown how ketamine affects the mechanisms of belief updating, which are potentially key to understanding its antidepressant effects.

Against this background, we asked: (a) if TRD patients display a lack of optimism bias in belief updating; (b) if and through what computational mechanisms ketamine restores optimism bias; (c) how this putative effect links to its antidepressant effects. To test these hypotheses, we used a measurement-based care (MBC) approach, which consisted in objectifying clinical assessments and outcomes in patients undergoing ketamine treatment (35). We combined this MBC approach with an assessment of clinical improvement and belief-updating mechanisms before and after ketamine treatment. We mathematically formalized the effects of ketamine (a) on belief updating by using a reinforcement-learning (RL) model (36), and (b) on clinical improvement by using mediation analysis.

Materials and methods

Participants

The study was conducted at the Pitié-Salpêtrière hospital mood center in a unit devoted to MBC approaches to TRD. It was conducted in accordance with the Declaration of Helsinki and approved by local authorities. Participants gave informed consent prior to participating in the experiment. In

total, 26 patients with TRD (mean age= 31.6 ± 9.7 years; 14/12 male/female), and 30 healthy control participants (mean age= 33.7 ± 1.9 years; 18/12 male/female) were enrolled in the study (Table 1).

Table 1: Demographics

	Healthy controls (n=30)	TRD patients (n=26)
Gender, male : female	18 : 12	16 : 10
Years of age	33.7 ± 1.9 (22 – 59)	52.5 ± 1.9 (34 – 67)*
Years of higher education	5.1 ± 0.4 (0 – 7)	3.9 ± 0.4 (0 – 5)*
Total MADRS score	0.2 ± 0.4	37.1 ± 1.4

*mean $\pm$ sem (range), * $p < 0.05$, two-sampled two-tailed t-test. TRD (treatment resistant depression) patients were significantly older ($t(2,54) = 6.25$, $p =$), and had fewer years of higher education ($t(2,54) = -2.4$, $p = 0.02$) compared to healthy controls. Both groups were comparable in male: female participant distribution ($X^2 = 0.03$; $p = 0.86$). Higher education was calculated in years of study after high school.*

Healthy participants were recruited in the Paris area. Patients were recruited at the Psychiatry department of the Pitié-Salpêtrière hospital, and were clinically evaluated by a psychiatrist specialized in TRD during a clinical interview to assess inclusion and exclusion criteria. Patient inclusion criteria included: age between 18 and 70 years, MDD or Bipolar depression according to the DSM-5 criteria Montgomery-Asberg Depression Rating Scale (MADRS) score > 20 , TRD (defined by a failure to respond to at least two antidepressant treatments), and moderate to high treatment resistance as defined by the Maudsley Staging Method (MSM, score > 7) (37,38).

Exclusion criteria for all participants included: any other psychiatric disorder, neurological and neurosurgical comorbidities, substance abuse or addictive disorders in the last 12 months, and recreational ketamine consumption during lifetime. All participants were able to understand and perform the belief-updating task.

Study design

We used an observational protocol with a mixed-effects design that nested two factors: group and testing timepoints. TRD patients were tested at three different timepoints: 24 hours before a first ketamine infusion (T0, baseline), 4 hours after a first ketamine infusion (T1, early treatment

response), and 4 hours after a third ketamine infusion (T2) that was administered one-week after T1 (**Figure 1**). At each testing timepoint, patients performed a belief-updating task, and clinical improvement in depressive symptoms was assessed with the MADRS (39). Remission and responsiveness at T1 and T2 relative to baseline (T0) were calculated based on the following criteria: for remission, $>50\%$ improvement and MADRS score ≤ 10 , and for treatment responsiveness, $>50\%$ improvement and MADRS score > 10 . Healthy controls were tested on the belief updating task at two time points, separated by one-week.

Figure 1. Study design. Patients were administered a total of three doses of ketamine (0.5 mg/kg) by intravenous infusion, over the course of a week. Depression (MADRS) and belief updating (Belief Updating Task) were assessed at three timepoints: 24 hours before (T0), 4 hours after (T1) the first infusion, and 4 hours after (T2) the third ketamine infusion that was one week after the first infusion. At each timepoint (T0, T1 and T2), testing lasted for a total duration of one hour.

Ketamine treatment administration

Ketamine treatment was administered open-labelled, not at the discretion of the investigator. After overnight fasting, subanesthetic doses of ketamine (ketamine-ratiopharm, 500 mg/10 mL, Ratiopharm) were infused for 40 minutes (0.5 mg/kg) intravenously following a previously reported procedure (40). In total, all patients received three infusions during a week, with a delay of 48 hours between the first two infusions, and a delay of 72 hours between the last two infusions. After each infusion, patients were discharged home following a 4-hour recovery period.

Belief updating task

All participants performed a belief-updating task adapted from decision neuroscience (17,17,18,36,41) (**Figure 2**). The task involved two sessions of 40 trials. In session 1, an adverse life event was presented on a computer screen, and participants rated their lifetime risk of experiencing this event in the future (i.e. initial estimate – E1), their confidence (C1) in E1, and how likely was someone with a similar socio-economic background to experience this event (i.e. estimated base rate – eBR). At the end of each trial, they were presented with information about the occurrence of that event in the general population (i.e. actual base rate – BR), and rated their confidence (C2) in BR. In the second session, the same 40 adverse life events were presented again, on a trial-by-trial basis, together with their respective base rates. On each trial, participants re-estimated their lifetime risk (E2), and confidence (C3) in E2. Patients were explicitly told to provide E2 that were different from E1.

A total of 120 adverse life events were used: 60 events and base rates were taken from previously published work in healthy and depressed patients (17,18), and 60 new events and base rates were created for this study. Base rates ranged between 10% and 70%. To ensure that the range of possible overestimation was equal to the range of possible underestimation, participants estimated their beliefs anywhere within the range of 5% and 95%.

Figure 2. Belief updating task. Screenshots show successive events for two example trials, one for good (top) and one for bad (bottom) news. The task was self-paced and individual response times were recorded. The task design comprised two sessions. During the first session, participants were presented on each trial with an adverse life event and were asked to estimate their own as well as other people's likelihood of experiencing that event in the future (first estimate and estimated base rate, respectively). They also rated their confidence in each estimate. At the end of each trial, the average likelihood of that event occurring in the general population (base rate) was displayed, and participants rated their confidence in that base rate. During the second session, each trial started with the presentation of the actual base rate associated with an event, and participants re-estimated their likelihood of experiencing this event in the future (second estimate) as well as how confident they were in their second estimate. Belief updating was measured by the difference between the first and the second estimate (before and after knowing the base rate), and as a function of the estimation error sign, reflected by the difference between the first estimate and the base rate. If the estimation error was positive, the trial was categorized as good news, and if it was negative, as bad news.

Participants used the numerical buttons on the computer keyboard to enter their responses, and pressed the space key to confirm each response. All responses were self-paced and participants were required to respond to go to the next rating and trial. All subjects completed a practice session of three trials before beginning the main experiment. The task was identical at all testing timepoints, except for the fact that a different set of adverse life events was used in each testing session. To this

aim, the 120 life events were randomly divided into 3 lists of 40 different adverse life events, with one list for each timepoint (T0, T1, T2). The order of the lists was counterbalanced across participants (Latin square design).

Statistical analysis

All statistical tests were conducted with the Statistics and Machine Learning Toolbox (MATLAB 2015a, from MathWorks), and the Mediation Toolbox (<https://github.com/canlab/CanlabScripts>).

Statistical analysis of global clinical improvement

Two-tailed signed Wilcoxon rank tests were used to assess statistically significant effects of treatment on depressive symptoms measured by the MADRS scores between baseline (T0), 4 hours after the first ketamine infusion (T1), and 4 hours after the third infusion one week after the first infusion (T2). Median MADRS scores and detailed statistics are listed in Table 2.

Table 2: Clinical characteristics of TRD patients (N=26)

Years of current episode (mean $\pm$ sem)	5.7 $\pm$ 0.8
Age at onset of illness (mean $\pm$ sem)	31.0 $\pm$ 2.3
Unipolar : bipolar depression	20 : 6
Total MADRS score (mean $\pm$ sem)	37.1 $\pm$ 1.4
Total MSM score (mean $\pm$ sem)	9.4 $\pm$ 0.4
Disease severity, MADRS category	
Severe depression n (%)	20 (77%)
Moderate depression n (%)	6 (23%)
Resistance severity, MSM category	
Severe resistance n (%)	12 (46%)
Moderate resistance n (%)	14 (54%)
Treatments (% of 26)	
SSRIs	69%
SNRIs	19%
Tricyclic	8%
Antipsychotic	12%
Mood stabilizer	46%
Benzodiazepine	54%
Anticipated treatment outcome (mean % ratings $\pm$ sem)	
Drug efficiency expectancy	53.1 $\pm$ 5.6
Response expectancy	33.6 $\pm$ 4.9
Remission expectancy	33.8 $\pm$ 5.1

MSM – Maudsley Staging Method, MADRS - Montgomery-Asberg Depression Rating Scale, SSRI – Selective Serotonin Reuptake Inhibitors, SNRIs – Serotonin and Noradrenalin Reuptake Inhibitors, SEM – Standard Errors of the Mean. Years of current episode defined the duration of the current depressive episode. Age at onset of illness defined the age (years) at diagnosis with MDD. Disease severity was defined according to MADRS score: moderate (20 to 34), severe (35 to 60). Resistance severity was defined according to MSM score: moderate (7 to 10), severe (11 to 15)

Testing effects of ketamine on belief updating biases:

To answer our first question as to whether biases in absolute belief updating were altered by ketamine treatment in TRD patients compared to healthy controls, we conducted a linear regression using a mixed-effects model following equation 1:

$$(1) |UPD| \sim 1 + \text{Group} + \text{Time} + \text{EE}_{\text{valence}} + |EE| + \text{Group} * \text{Time} + \text{Time} * \text{EE}_{\text{valence}} + \text{Group} * \text{EE}_{\text{valence}} + \text{Group} * \text{Time} * \text{EE}_{\text{valence}} + (1 | \text{Subject})$$

The model fitted average absolute belief updates ($|UPD|$) by nested effects of estimation error valence ($\text{EE}_{\text{valence}}$, coded 1 for good news, -1 for bad news), group (coded 1 for healthy controls, -1 for TRD patients), treatment time point (coded -1 for T0 at baseline, 1 for T1 4 hours after the first infusion), absolute estimation error magnitude ($|EE|$) and the interactions group by time, time by EE valence, group by EE valence, and group by time by EE valence. The intercept nested by participant number was included in the model as a random effect covariate to control for inter-individual differences in the degree of belief updating. All analyzes were controlled by age, and years of higher education.

Mediation analysis

Our next analysis tested whether the emergence of a good news/bad news bias in belief updating after ketamine treatment mediated global clinical improvement. To this aim, a mediation analysis (42) tested the null hypothesis that the two joint effects—ketamine effect on belief updating bias (path a) and belief updating bias on MADRS score (path b)—were uncorrelated, by jointly testing three effects expressed by the following serial regression equations:

$$(2) \text{ path c: } y = cx + e_y$$

$$(3) \text{ path a: } m = ax + e_m$$

$$(4) \text{ path b: } y = bm + c'x + e'_y$$

The variables x , y , and m correspond to data vectors containing each patient's MADRS scores at baseline and one week after the first ketamine infusion (y), testing time (x , coded -1 for before, 1 for

after ketamine), and two scores per patient for averaged, normalized (for effects of EE magnitude) belief update biases at baseline and one week after the first ketamine infusion (m). The variables e_y , e_m , and e'_y denote residual variance for each of the three regression analyses, respectively.

We conducted a single-level mediation that assessed the product of path a, and path b coefficients: $a * b = c - c'$, with c' corresponding to the effect of ketamine on depression symptoms after controlling for effects of belief updating bias (the mediator variable).

A bootstrap test was used to infer significant mediation effects, which is an appropriate non-parametric test to examine the non-normally distributed product of path a and b regression coefficients. This involved calculating a distribution of individual coefficients [a , b , c and c'] based on 10,000 random samples, with the replacement of observed coefficients. Then, bilateral p-values were calculated, based on the confidence intervals of the bootstrapped coefficients distribution.

Computational modeling of belief updating

To gain insights into the cognitive mechanisms underlying the effects of ketamine on belief updating, we used a computational model that has previously been reported to best explain optimistically biased belief updating (31, 38).

The model relies on a generic reinforcement learning (RL) algorithm that assumes belief updating to be proportional to the size of estimation errors, which are themselves weighted by the personal relevance of the life events presented during the task (PR) and the learning rate (LR), following equation 5.

$$(5) \text{ Belief update} = \text{LR} * \text{EE} * \text{PR}$$

The personal relevance (PR) factor controls for a participant's tendency to update beliefs about personally relevant life events more than beliefs about non-relevant events.

The learning rate (LR) determined how much beliefs were updated as a function of the size of estimation errors. In line with previous work, and in order to test for the good news/bad news bias

in belief-updating, learning rates were estimated separately for good and bad news trials (31, 40), following equations 6 and 7.

$$(6) LR_{\text{good}} = \text{Alpha} + \text{Asymmetry}$$

$$(7) LR_{\text{bad}} = \text{Alpha} - \text{Asymmetry}$$

The LR has two free parameters: alpha and asymmetry. The alpha parameter accounts for the tendency to learn from estimation errors independently of their valence. The asymmetry parameter indicates how much updating is biased by the valence (good/bad) of the estimation error.

The model was implemented, and compared to competing RL model versions using the VBA toolbox (45), and following the model comparison procedure (46). More specifically, to obtain optimal free parameter values for each patient, the toolbox fitted four possible variations of the RL model by switching the two free parameters on and off in a 2x2 design (alpha=on & A=on; A=on & alpha=off; alpha=on & A=off; alpha=off & A=off). Bayesian model comparison selected the most veridical model (i.e. the one fitting the observed data the best). Two criteria were considered for model selection: the estimated model frequency in the sample and the exceedance probability, which corresponded to the probability of the model to be above chance in the sample (46).

Paired, two-tailed t-tests against 0 and 1 tested whether the asymmetry and alpha parameters were respectively significant, at all testing timepoints and in both groups. Two patients were removed from the statistical analysis of model output parameters, because their asymmetry (Patient_ID=9, A=0.29) and alpha parameters (Patient_ID=12, alpha=1.6) at baseline (T0) were three standard deviations above the sample mean (T0 TRD patients: A=0.03±0.01; alpha =0.64±0.06) suggesting they were outliers.

A linear mixed effects regression analysis was fitted to the modeled belief updating in order to test the contrast of interest consisting in a significant three-way interaction time by group by estimation error valence analogous to equation 7. Lastly, the emergence of biases in the learning rates after a week of ketamine treatment (T2) relative to baseline (T0) ($LR_{\text{good new}(T2)} - LR_{\text{bad news}(T2)} - (LR_{\text{good}}$

$\text{new}(T_0) - \text{LR}_{\text{bad news}(T_0)})$ was correlated to the emergence of belief update bias at one-week relative to baseline ($\text{UDB}_{(T_2)} - \text{UDB}_{(T_0)}$) using Pearson's correlations. An analogous correlation analysis was conducted in healthy controls.

Results

Clinical improvement

In line with previous work, ketamine treatment induced a rapid clinical improvement. As shown in table 3, MADRS scores decreased significantly 4 hours after a single ketamine infusion ($z = 3.27$, $p = 0.001$), and remained significantly lower than baseline scores one week later ($z = 4.1$, $p = 4.06 \times 10^{-5}$). In total, one out of 26 patients went into remission, and 5 out of 26 patients showed treatment responsiveness one week after ketamine treatment (19%).

Table 3: Improvement in depression measured by the MADRS before and after ketamine treatment in N=26 TRD patients

	Median (IQR)			Statistics	
	T0	T1	T2	T0 > T1	T0 > T2
Total MADRS	37 (9)	33 (10)	27 (16)	$P = 0.001$, $z = 3.3$	$P = 4.1 \times 10^{-5}$, $z = 4.1$
Sadness	4.5 (1)	4 (2)	3 (2)	$P = 0.02$, $z = 2.2$	$P = 2.7 \times 10^{-4}$, $z = 3.6$
Neurovegetative	4 (1)	3 (1)	2 (2)	$P = 7 \times 10^{-4}$, $z = 3.4$	$P = 1.1 \times 10^{-4}$, $z = 3.8$
Detachment	4 (2)	4 (1)	3.5 (1)	$P = 0.08$, $z = 1.7$	$P = 0.003$, $z = 2.9$
Negative thoughts	3.5 (1)	3 (2)	3 (1)	$P = 0.004$, $z = 2.8$	$P = 8.2 \times 10^{-4}$, $z = 3.3$

MADRS – Montgomery-Asberg Depression Rating Scale; IQR – Interquartile Range; T0 – baseline measurement 24h before the first ketamine infusion; T1 – 4h after first ketamine infusion; T2 4h after third ketamine infusion one week after T1; Statistics report paired Wilcoxon rank tests.

Ketamine induced optimism biases in belief updating

We first replicated previous work showing that MDD patients lack of the good/bad news bias in belief updating (17,18). As shown in **Figure 3A**, 24 hours before a first ketamine infusion, TRD patients updated beliefs following good and bad news to a similar magnitude ($t(25) = 1.7$, $p = 0.1$, 95% CI [-0.7; -7.5], paired two-tailed t-test). Second, we performed a linear mixed-effects regression analysis directly comparing absolute belief updating across testing timepoints (T0 vs T1) and participant group (TRD patients vs healthy controls), and controlling for estimation error

magnitude and news valence. We found a significant main effect of testing time ($\beta = -1.02$, $t(215) = -3.06$, $p = 0.002$, 95% CI $[-1.68 ; -0.36]$), indicating that all participants updated less their beliefs with sequential testing sessions from baseline (T0) to T1. We also found a significant main effect of valence ($\beta = 2.8$, $t(215) = 8.7$, $p = 8.8e-016$, 95% CI $[2.2 ; 3.5]$) and absolute estimation error magnitude ($\beta = 0.18$, $t(215) = 3.4$, $p = 0.0008$, 95% CI $[0.07 ; 0.29]$). Participants updated more after good than after bad news, and after estimation errors. Importantly, and in line with our main hypothesis, a significant three-way interaction group by testing time by estimation error valence ($\beta = -0.81$, $t(215) = -2.5$, $p = 0.014$, 95% CI $[-1.5 ; -0.16]$) indicated that patients updated their beliefs more after good than after bad news following a single ketamine infusion relative to baseline and in contrast to healthy controls (**Figure 3A**). We controlled the analyzes by age and years of higher education, without finding any significant difference.

Figure 3. Behavioral results. **A**) Optimistic biases during belief updating in 26 patients with TRD (52 ± 2 years, 14/12 male/female) and in 30 healthy controls (age 33 ± 2 years, 18/12 male/female). Line graphs show average belief updating after favorable (good) and unfavorable (bad) news. Error bars correspond to the standard error of the mean (sem). **B**) The scatterplot shows in N=26 TRD patients the correlation between symptoms of depression (average MADRS score) and good new/bad news updating bias (controlled for the size of the absolute estimation error, EE) at one week after a first ketamine infusion. Each point corresponds to one patient. Pearson's correlation coefficient $r = -0.47$, $p = 0.02$.

Optimism bias in belief updating correlated negatively with depression at one week and mediated the effect of ketamine on clinical improvement.

Next, we asked whether sustained effects of ketamine on both belief-updating biases and depression symptoms were associated. As shown in **Figure 3B**, patients who displayed stronger optimism biases in belief updating were also those who displayed fewer depressive symptoms as assessed by the MADRS one week after the first infusion (Pearson's correlation coefficient $r = -0.47$, $p = 0.02$, **Figure 3B**). To further explore how optimistic biases contributed to global clinical improvement, a mediation analysis found a significant path a regression that replicated the main effect of ketamine on belief-updating biases in TRD patients ($\beta = 0.12$, $t = 2.5$, $p = 0.016$). Optimistically biased belief updating also predicted lower MADRS scores, controlling for the main effect of ketamine on belief-updating biases (path b regression: $\beta = -9.3$, $t = -2.5$, $p = 0.003$). Finally, the direct effect of ketamine on MADRS scores was significantly reduced when controlling for belief-updating biases (path c' : $\beta = -3.8$, $t = -2.8$, $p = 0.01$ after controlling for the mediator; path c total effect: $\beta = -4.9$, $t = -3.8$, $p = 0.002$), indicating a partial mediation effect (path $a*b$: $\beta = -1.2$, $t = -1.5$, $p = 0.02$). These results provide formal evidence that the emergence of optimistic bias in belief updating was strongly associated to the sustained improvement in depression observed after one week of ketamine treatment.

Computational-modeling provided evidence that the emergence of optimism biases after ketamine was due to asymmetric learning.

To gain insights into the cognitive mechanism of optimistically biased belief-updating after ketamine, we fitted a generic RL model to observed belief-updating behavior before and after ketamine treatment (43). The RL model predicted asymmetric learning from positive rather than negative EE, and controlled for confounding variables such as personal relevance of events and estimation error magnitude. This RL model fitted the observed belief updating behavior the best, and surprisingly at each testing timepoint in both TRD patients (T0 : $E_f = 0.975$, $p_{xp} = 0.99$ T1 : $E_f = 0.9712$, $p_{xp} = 1$; T2 : $E_f = 0.92$, $p_{xp} = 0.99$) and healthy controls (T0 : $E_f = 0.9747$, $p_{xp} = 1$; T1 :

$E_f = 0.9749$, $p_{xp} = 1$). The average asymmetry parameter ($T0 : A = 0.02 \pm 0.01$, $\alpha = 0.6 \pm 0.04$), which, when positive, reflected how much participants learnt from positive rather than negative estimation errors, was significantly greater than zero at baseline (TRD patients $T0 : t(24) = 2.1$, $p = 0.04$), and remained significantly greater than zero after ketamine ($T1 : A = 0.07 \pm 0.01$, $\alpha = 0.5 \pm 0.05$, $t(25) = 4.7$, $p = 7.8 \times 10^{-5}$; $T2 : A = 0.07 \pm 0.02$, $\alpha = 0.6 \pm 0.06$, $t(25) = 3.7$, $p = 9.7 \times 10^{-4}$). Likewise, in healthy controls, the asymmetry parameter was significantly greater than zero across all testing times ($T0 : A = 0.05 \pm 0.01$, $\alpha = 0.5 \pm 0.05$, $t(29) = 4.3$, $p = 1.7 \times 10^{-4}$; $T1 : A = 0.05 \pm 0.01$, $\alpha = 0.5 \pm 0.05$, $t(29) = 3.7$, $p = 8.7 \times 10^{-4}$). The average alpha parameters for both groups were significantly smaller than 1, indicating that belief updating was not solely driven by the estimation error magnitude in both TRD patients ($T0 : t(24) = -8.7$, $p = 6.05 \times 10^{-9}$; $T1 : t(25) = -8.7$, $p = 4 \times 10^{-9}$; $T2 : t(25) = -6.3$, $p = 1.3 \times 10^{-6}$) and healthy controls ($T0 : t(29) = -10.7$, $p = 1.2 \times 10^{-11}$; $T1 : t(29) = -9.8$, $p = 9.5 \times 10^{-11}$).

A linear mixed-effects model, analogous to the one fitted to the observed belief updates, replicated a significant time by group by valence three-way interaction on the modeled belief updates ($\beta = -0.47$, $t(207) = -2.1$, $p = 0.03$, 95% CI $[-0.91 - -0.03]$). As shown in **Figure 4A**, this interaction was driven by a significant difference in modeled belief-updating biases between TRD patients and healthy controls at baseline ($T0$ TRD patients vs healthy controls: $t(1,52) = -2.3$, $p = 0.02$, two-sampled, two-tailed t-test), and by a more biased modeled belief-updating after ketamine treatment relative to baseline in TRD patients ($T1$ vs $T0 : t(23) = 2.6$, $p = 0.01$, paired, two-tailed t-test). A similar pattern was observed for learning rates (**Figure 4B**). Learning rates trended toward a stronger bias in healthy controls compared to TRD patients at baseline ($T0$ TRD patients vs healthy controls: $t(1,52) = -1.6$, $p = 0.1$, two-sampled, two-tailed t-test), and were significantly more biased 4 hours after a single ketamine infusion in TRD patients ($T0$ vs $T1 : t(23) = -2.2$, $p = 0.03$, paired, two-tailed t-test).

A

B

Figure 4. Model-based results. A) Biased learning rates and modeled belief updating biases (good – bad news) in TRD patients (N=24) at baseline (T0) and 4 hours after a single ketamine infusion T1) and healthy controls (N=30) at the 1st assessment (T0) and one week later at the 2nd assessment (T1). Errors bars correspond to the standard error of the mean (sem). + $p < 0.05$ one-tailed, * $p < 0.05$ two-tailed t-test. **B)** Emergence of asymmetric learning correlates with the emergence of belief updating biases in TRD patients (right panel, N=26), but not in healthy controls (left panel, N=30). Scatterplots display correlations between changes in the learning rates biases (LR good – bad news trials) and in observed belief updating biases (absolute UPD good – bad news trials/ |EE|) from baseline to one week (T2 – T0) in healthy controls and TRD patients. Each dot corresponds to one participant. r – Pearson’s correlation coefficient.

Lastly, we tested if the emergence of learning rate biases predicted the emergence of belief-updating biases, and how specific this association was to TRD patients treated with ketamine. Asymmetric learning rates at four hours and one week after treatment relative to baseline both correlated significantly to biased belief updating at four hours ($r = 0.41$ $p = 0.03$) and one week after ketamine relative to baseline ($r = 0.47$, $p = 0.02$, **Figure 4B**). The correlation between biased learning rate differences between the 1st and 2nd assessment and biased belief-updating differences between the 1st and 2nd assessment was non-significant in healthy controls ($r = 0.19$, $p = 0.25$, **Figure**

4B). These results indicate that the precocious (four hours after a single ketamine treatment) and sustained (one week after treatment) belief-updating biases were specifically underpinned by asymmetric learning from positive and negative EE in TRD patients.

Discussion

The main goals of this study were to assess if and how ketamine affected belief updating in TRD patients, and how this cognitive effect linked to its clinical antidepressant effects. Consistent with previous work (26,27), ketamine induced a rapid and sustained decrease in depressive symptoms. On the cognitive level, TRD patients did not show optimism biases in belief updating at baseline. However, as soon as four hours after the first ketamine infusion, they updated their beliefs about future adverse life events more after good than after bad news. The optimism bias in belief updating correlated to the reduction in MADRS scores after one week of treatment. Computational analyses showed that this effect was underpinned by asymmetric learning from positive rather than negative estimation errors. Mediation analysis provided formal evidence that the emergence of optimism biases mediated the effect of ketamine on clinical improvement of depression.

Major depression is associated with negative expectations and decreased sensitivity to expectation violation (2,17,20,22,47,48). Our finding of an attenuated optimistic bias in belief-updating prior to ketamine treatment in TRD patients is in line with several studies that have used similar belief-updating tasks in MDD patients (17,18). Importantly, our study is the first to show an absence of optimistic bias in TRD patients. More specifically, we found that TRD patients' sensitivity to negative estimation errors decreased after ketamine treatment, while their sensitivity to positive estimation errors remained stable across testing timepoints. This finding stands at odds with results reported by Korn et al. (17) and Kube et al. (48), who showed that MDD was associated with less sensitivity to positive disconfirmation. Several factors may explain these discrepancies including the task itself, its cognitive demands, as well as its content and the clinical heterogeneity of depressed patients. However, Garret et al. (18) have reported that depressed patients were more

sensitive to bad news than good news, and updated their beliefs more after a negative estimation error. Importantly, this previous work has also shown that the lack of optimism bias correlated to depression severity (17,18). Here, we provide further and novel evidence that this correlation was reversed following ketamine treatment. Notably, patients who displayed less severe depressive symptoms after treatment were also those who were more optimistically biased when they updated beliefs.

Our model-based findings provide insights into the cognitive mechanisms of belief updating in TRD patients. Notably, computational RL modeling revealed an asymmetric learning mechanism that predicted more learning from positive rather than negative estimation errors. Furthermore, we found that patients who showed stronger optimism bias after ketamine treatment compared to baseline also displayed more asymmetric learning rates after ketamine treatment compared to baseline. This correlation was non-significant in healthy controls.

This finding may potentially be explained by an indirect and more tardily-evolving mechanism of action of ketamine, involving the recruitment of dopaminergic pathways in the brain (49). Ketamine increases glutamate levels, but it has also been shown to target the dopamine system by disinhibiting GABAergic neurons in the thalamus. This effect provokes an endogenous dopamine release following the glutamate surge (50). Deficits in reward processing play a central role in major depression, and are underpinned by impaired dopaminergic signaling within the brain's reward system (51).

In line with this interpretation and on a clinical level, we found that improvement in the detachment subscore of the MADRS, which includes a group of symptoms close to anhedonia, evolved more tardily after ketamine treatment compared to other depressive symptoms. Moreover, the relapse in dopamine could be reflected on the behavioral level by an increase in patients' sensitivity to positive feedback during learning and through it induce optimism biases in belief updating (52). Indeed, related work using the same belief-updating task in healthy controls has shown that the administration of soluble precursors of dopamine such as levodopa enhanced the optimism bias in

belief updating (41). An interesting direction for future studies therefore involves investigating more directly how the effects of ketamine on anhedonia link to reward learning and reward learning-related brain activation in TRD patients.

Although we observe a rapid improvement in depression, the clinical response rate following ketamine appears quite low relative to previous, open-labelled studies (26,27). This could be partly related to the timing of assessments, which were completed 4 hours after the first and third infusion. The existing literature is fairly consistent in showing that the peak responder rate is mostly observed at 24-hours following a single infusion (27,53), and the timing of assessments we used might be too close to infusions. Otherwise, we included particularly patients with high level of severity (mean MADRS: 37.1 ± 1.4) and treatment resistance (mean MSM: 9.4 ± 0.4). Among our patients, 77% had severe depression according to MADRS criteria (score > 34), and the average duration of the current episode was 5.7 years (± 0.8), which is a long duration. Even more striking, 46% had a severe treatment resistance and 54% a moderate treatment resistance according to MSM criteria (score > 11 , and score > 7 , respectively). The degree of severity and resistance to treatment could explain the level of clinical response after only three ketamine's infusions. We used a validated experimental task (11,54,55), previously used in MDD (17,18) and in a large number of cognitive science studies involving situations of test-retest (41,56,57). Although it has never been psychometrically evaluated, its wide use in previous studies builds confidence in its validity in being able to detect changes in belief updating. Moreover, this task has a high level of replicability among researchers due to its easy use, that may promote the replication of the results of this study and strengthen the scientific validity of the results.

This study was conducted in a naturalistic MBC setting and was not designed as a therapeutic trial (35). The depressed participants are older and less educated, which could be a confound for the primary analyses. Against this confound, we controlled all the analyzes by age and years of higher education, without finding any significant difference. We both treatment resistant major depressive disorder (MDD) and bipolar disorder (BD), without distinguishing between them in the analyzes

due to the small sample size. However, these two types of TRD could involve different neurocognitive mechanisms.

We did not include a placebo group, and patients were not randomly allotted to the ketamine treatment arm. Thus, this concern is partly alleviated by the inclusion of healthy controls who repeated the same assessments at baseline and one week later. Unlike the patient group, our group controls only performed the experimental task twice due to organizational limitations. Without ketamine infusions, we did not expect changes in beliefs updating mechanisms 24 hours apart. In order to limit mood-related biases, we controlled for the presence of depressed mood at T1 and then the potential for the appearance of depressed mood in control subjects at T2 using MADRS. At T1, the controlled subjects did not present any depressive symptoms: 6 control subjects have 1 point on the 6-points Likert for item related to sleep. There was no difference between MADRS scores at T1 and T2 in these subjects.

Ketamine was added as a strategy to achieve stronger and more sustained antidepressant responses, and patients received ketamine in addition to their ongoing antidepressant treatment. Future work is needed to address how different antidepressant treatment strategies respectively modulate belief-updating processes and alleviate depressive symptoms (58). A direct comparison between the fast-acting effect of ketamine and the delayed antidepressant effect of conventional monoaminergic antidepressants can provide insights into the neurocognitive processes through which different antidepressant treatment strategies produce clinical improvement (59).

Conclusion

In conclusion, our results converge towards the findings that ketamine improved TRD, and that this improvement was strongly associated with changes in belief-updating processes underpinned by increased asymmetric learning from positive rather than negative estimation errors. These findings shed light on the possible mechanisms underlying ketamine's rapid antidepressant effects, and open the window toward the use of ketamine-augmented psychotherapy (KAP) protocols.

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