

General and emotion-specific neural effects of ketamine during emotional memory formation

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ABSTRACT

Animal studies suggest that N-methyl-D-aspartate receptor (NMDAR) dependent signalling in limbic and prefrontal regions is critically involved in both cognitive and emotional functions. In humans, ketamine-induced transient, and disorder associated chronic NMDAR hypofunction (i.e. in schizophrenia) has been associated with deficient performance in the domains of memory and higher-order emotional functioning, as well as altered neural activity in the underlying limbic-prefrontal circuits. To model the effects of NMDAR hypofunction on the integration of emotion and cognition the present pharmacological fMRI study applied the NMDAR antagonist ketamine (target plasma level=100 ng/ml) to 21 healthy volunteers in a within-subject placebo-controlled crossover design during encoding of neutral, positive and negative pictures. Our results show that irrespective of emotion, ketamine suppressed parahippocampal and medial prefrontal activity. In contrast, ketamine selectively increased amygdala and orbitofrontal activity during successful encoding of negative stimuli. On the network level ketamine generally increased medial prefrontal-parahippocampal coupling while specifically decreasing amygdala-orbitofrontal interplay during encoding of negative stimuli. On the behavioural level, ketamine produced generally decreased memory performance and abolished the emotional enhancement of memory after a wash-out period of 5 days. The present findings suggest that ketamine produces general as well as valence-specific effects during emotional memory formation. The pattern partly overlaps with alterations previously observed in patients with schizophrenia.

Introduction

N-methyl-D-aspartate receptors (NMDAR) are widely distributed throughout the brain, with particular high densities in frontal and limbic regions involved in cognition, including memory processing, and emotion (Fletcher and Henson, 2001; Lepage et al., 1998; Walter et al., 2014; Riedel et al., 2003; Phan et al., 2002; Etkin et al., 2011). Animal studies consistently revealed that experimental application of competitive or non-competitive NMDAR antagonists transiently disrupts memory performance (Puma et al., 1998), with particularly pronounced effects when the drug interfered with the acquisition of novel information (Newcomer et al., 2000). In recent years pharmacological

studies in humans have increasingly employed the non-competitive NMDAR antagonist ketamine as a translational model to explore the behavioural and neural effects of NMDAR-hypofunction (Stone et al., 2009). The observed detrimental effects of ketamine administration on cognitive performance, including memory (Krystal et al., 1994, Newcomer et al., 1999, Hetem et al., 2000), closely resemble those observed in animal models. Results from functional MRI (fMRI) further suggest that ketamine administration in humans influences, and interferes with, the underlying memory-related neural circuitry (Honey et al., 2005; Wong et al., 2016, Grimm et al., 2015).

Recent animal work emphasizes an involvement of NMDAR-dependent signalling in medial prefrontal cortex (mPFC) and amygdala

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during emotional processing and emotion-cognition interactions, including emotional learning (Vieira et al., 2015; Hegoburu et al., 2014; Masneuf et al., 2014). These are in line with studies in humans which revealed emotion-specific disruptions during facial emotion encoding and recognition, as well as altered amygdala and prefrontal functioning following ketamine-induced NMDAR blockade (Ebert et al., 2012; Schmidt et al., 2013; Abel et al., 2003). The potential involvement of the NMDAR in emotion processing is further substantiated by the rapid antidepressant effect of single-dose administrations of ketamine in treatment-resistant depression (Aan Het Rot et al., 2012; Zarate et al., 2006).

In addition to its potential involvement in depression, altered NMDAR-signalling has been suggested to play a critical role in the pathophysiology of schizophrenia (Krystal et al., 2003). Initial observations that NMDAR antagonists, including ketamine, produce psychotomimetic symptoms and cognitive disruptions similar to those observed in schizophrenia patients (Krystal et al., 1994; Corlett et al., 2011) resulted in a NMDAR hypofunction model of schizophrenia (e.g. Jentsch and Roth 1999). Schizophrenia is a complex neuropsychiatric disorder characterized by marked impairments in cognitive and emotional domains (Bleuler, 1950). Neuropsychological studies consistently revealed cognitive (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007), particularly memory (Mesholam-Gately et al., 2009), deficits in patients with schizophrenia. Dysfunctions in the emotional domain have gained increasing attention during the last years, with meta-analytic data suggesting marked impairments in higher-order emotional processing in schizophrenia patients (Marwick and Hall, 2008; McCleery et al., 2015). In contrast, findings regarding disruptions in basic emotional processing remain less clear. Whereas some studies revealed that schizophrenia patients retrospectively report decreased levels of positive and increased levels of negative emotional experience (Cohen and Minor, 2008; Blanchard et al., 1998), immediate emotional experience have been found to be intact (Aleman and Kahn, 2005; Kring and Moran, 2008). These contradictory findings might point to a disintegration of emotion and cognition in schizophrenia, where immediate emotional experiences are intact, however, the impact of emotional experience on memory is disrupted.

Current concepts of emotion-memory interactions hold that memory for emotional information is enhanced relative to neutral information (Dolcos et al., 2004; La Bar and Cabeza, 2006). Neuroimaging studies on encoding of neutral (Kim, 2011) and emotional information (Murty et al., 2010; Hermans et al., 2014) indicate a high overlap between NMDAR-rich regions and the emotional memory networks, with successful encoding being associated with increased activity in hippocampal, fusiform and prefrontal regions (subsequent memory effect, SM), and the enhancement of emotional relative to neutral information being dependent on the hippocampal formation and the amygdala (emotional subsequent memory effect, ESM). A number of studies examined the ESM in schizophrenia patients to specifically probe the disintegration of emotion and cognition (Herbener, 2008). Most ESM studies observed normal emotional experience during encoding in schizophrenia patients (Lakis et al., 2011; Herbener et al., 2007; Hall et al., 2007), however, with regard to the specificity of impairments in the domain of the emotional subsequent memory effect findings remained inconsistent ranging from unspecific impairments (Lakis et al., 2011; Hall et al., 2007) to highly selective impairments for positive information only (Herbener et al., 2007).

Based on accumulating evidence for a critical role of NMDAR-signaling in both cognition and emotion, initial pharmacological fMRI evidence for emotion-specific effects of ketamine-induced transient NMDAR hypofunctioning (Abel et al., 2003; Scheidegger et al., 2016) and findings in schizophrenia patients with a putative NMDAR hypofunctioning it is hypothesized that experimentally induced NMDAR hypofunctioning in healthy subjects might (1) disrupt emotion-cognition interaction during emotional memory formation, and

(2) produce a pattern of general as well as emotion-specific neural effects. To this end, the present randomized within-subject placebo-controlled crossover design combined the application of ketamine versus placebo during emotional memory formation with fMRI. To control for (sub-)acute effects of ketamine on recognition participants underwent a 5-day washout period before the assessment of emotional memory performance. Based on previous findings we expected that ketamine administration would abolish the emotional enhancement of memory and suppress amygdala-hippocampal activity during emotional memory formation mirroring disintegration of emotional experience on memory formation.

Material and methods

Participants

Healthy, non-smoking, right-handed male volunteers with normal verbal intelligence as assessed by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-b, Lehrl, 2005) were recruited at the University of Bonn, Germany. Prior to study inclusion all participants were thoroughly screened for exclusion criteria. Study-specific exclusion criteria included MRI contraindications, current or previous history of axis I disorders according to the DSM IV criteria (assessed by the MINI, Ackenheim et al., 1999), diagnosis of psychotic disorders among first degree relatives, neurological or cardiovascular disorders, history of illicit drug use, head-injuries, body mass index (BMI) < 19 or > 25, regular use of medication, use of psychoactive substances in the 7 days prior to the experiment (validated via urine sample and enzyme-multiplied immunoassay, nal von minden GmbH, Regensburg, Germany). Participants were instructed to maintain their regular sleep and wake cycles before the experiment, and to abstain from food intake during the 6 h preceding treatment. Participants received monetary compensation for study participation. The study had ethical approval of the local ethics committee at the University of Bonn and was in accordance with the latest revision of the Declaration of Helsinki. All participants provided written informed consent before study inclusion.

From a total of 43 volunteers assessed for study eligibility 29 met the study-specific criteria and were enrolled in the study. Participants data were excluded from all further analyses in case participants failed to attend the second pharmacofMRI assessment (n=2), were not able to adhere to the 5-day post pharmacofMRI memory assessment interval (n=2), misunderstood the instructions (n=1), or showed head-movements > 3mm during fMRI (ketamine, 2; placebo, 1). The final study sample (n=21) had an average age of 25.1 (\pm 3.5) years, 17.5 (\pm 2.8) years of education, and an estimated verbal IQ of 111 (\pm 7.4).

Study protocols

Effect of ketamine on emotional memory formation and subsequent recognition performance were assessed by embedding a pharmacological fMRI (pharmacofMRI) experiment in a double-blind randomized within-subject placebo-controlled crossover design. To control for order effects the order of ketamine and placebo administration was counterbalanced across participants, pharmacofMRI assessments were separated by \geq 7 days and administered at the same time of the day (< 1.5 h difference). Immediately before the start of the pharmacofMRI experiments subjects were screened by an experienced anaesthesiologist (C.N.), the anaesthesiologist also continuously monitored the vital signs of the participants during pharmacofMRI using an MRI-compatible pulse oximeter and a supervised post-scanning period. In line with previous ketamine-induced model psychosis experiments (Schmechtig et al., 2013) participants received either racemic ketamine (Ketamin-Ratiopharm 500, injection solution, Ratiopharm®, Ulm, Germany) or placebo (0.9% saline solution, Ratiopharm®, Ulm, Germany) via identical 1-h application protocols by means of a

computer-controlled infusion pump (Graseby 3500 infusion pump, Smith Medical Int. Ltd, Luton, UK). Ketamine was administered as a 2 mg/ml solution with a constant target plasma level of 100 ng/ml, application protocols were individually adapted to the weight and height of each participant. The infusion protocol adhered a previously validated continuous bolus infusion protocol based on a three compartment model (Domino et al., 1982; Schmechtig et al., 2013) and was implemented using the STANPUMP software (Steven L. Shafer, M.D., Anesthesiology Service (112A), PAVAMC, Palo Alto, CA, USA). Ketamine reaches peak plasma concentrations within a minute when administered intravenously (Domino et al., 1984). Ketamine has a high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood–brain barrier. Initially, it is distributed to highly perfused tissues, including the brain (Hass and Harper, 1992). Terminal elimination half-life ranges from 100–200 min. To evaluate the ketamine blood-levels and confirm treatment, blood samples were drawn from the non-infusion arm before, during, and after infusion of both, placebo and ketamine. Plasma-samples were stored at -80°C and ng/ml, concentrations were analysed by an independent biomedical laboratory (Schotttdorf MVZ GmbH, Augsburg, Germany).

Experimental paradigms started 5 min after the infusion, the present paradigm started 30 min after infusion onset and was preceded by a non-emotional eye movement paradigm (Steffens et al., 2016). To control for potential confounding effects of ketamine on cardiovascular activity, heart rate was recorded from the MRI-compatible pulse oximeter at the start of the experimental paradigm, and +15 and +30 min relative to the start of the experiment. To control for potential confounding effects of treatment on attention, sustained attention was assessed during infusion of both, ketamine and placebo, using a subset of the validated d2 test of attention (Brickenkamp, 2002). To evaluate the psychotomimetic properties of ketamine administration participants completed the Psychotomimetic States Inventory (PSI) (Mason et al., 2008) before during and after infusion of ketamine and placebo. To evaluate the effects of treatment on the ESM effect recognition memory performance was assessed after a 5-day washout period. In order to control for circadian effects on memory performance assessment times were intra-individually matched.

Experimental paradigm

The event-related ESM paradigm was adopted from a previous pharmacofMRI study (Striepens et al., 2012). Briefly, during each fMRI assessment neutral, positive and negative pictorial stimuli from the standardized IAPS database (Lang et al., 2005) were displayed. To control for repetition effects two matched stimuli sets with 30 pictures per condition were used (mean valence (SD): Set A, negative 2.8 (0.6), positive 7.1 (0.5), neutral 5.1 (0.3); Set B, negative 2.8 (0.6), positive 6.9 (0.6), neutral 5.2 (0.5); mean arousal (SD): Set A, negative 5.4 (0.9), POS 5.5 (1.2), neutral 3.6 (0.7); Set B, negative 5.4 (0.9), positive 5.5 (1.2), neutral 3.4 (0.6), all $p > 0.12$, paired t-test comparing valence and arousal ratings between sets) and balanced across treatments. Pictures were presented 3 s for encoding, followed by validated ratings scales for arousal and valence to assess immediate emotional experience during treatment (self-assessment manikin, scales ranging from 1 (minimum) to 9 (maximum), Bradley and Lang, 1994) and a jittered interstimulus interval ranging from 4–6 s. Each rating scale was presented for 3 s and the order of rating scales was balanced across participants. Before treatment application each participant was familiarized with the paradigm during a short training session and was informed about the subsequent memory assessment. Five days after each scanning session subjects were presented the stimuli shown during the previous scanning session randomly intermixed with 20 matched distractors stimuli per condition (distractor sets, mean valence (SD): Set A, negative 2.9 (0.6), positive 7.0 (0.5), neutral 5.2 (0.5); Set B, negative 2.9 (0.5), positive 7.0 (0.6), neutral 5.0 (0.6);

mean arousal (SD): Set A, negative 5.4 (0.8), positive 5.5 (1.3), neutral 3.4 (0.7); Set B, negative 5.4 (0.8), positive 5.5 (1.3), neutral 3.5 (0.8), all $p > 0.37$, paired t-test). During the forced choice recognition memory test outside of the scanner subjects had to indicate via button press whether the stimuli had been shown during the preceding scanning session or not.

MRI data acquisition

MRI data were acquired at 3 T using a Trio MRI system (Siemens, Erlangen, Germany) equipped with a standard 12 channel head coil. Before treatment application a high-resolution T1-weighted structural MRI image (TR=1570 ms; TE=3.42 ms; inversion time (TI)=800 ms; flip angle=15°; FoV=256 mm; matrix size=256×256; 160 slices; slice thickness=1 mm; sequential slice-order with no inter-slice gap; voxel size=1×1×1) was acquired to exclude subjects with apparent brain pathologies and to optimize off-line normalization of functional time-series. Functional MRI time-series were acquired using a gradient-echo planar image sequence (TR=2500 ms; TE=30 ms; flip angle=90°; FoV=192 mm; matrix size=64×64; 37 slices; slice thickness=3 mm; sequential slice order with interslice gap of 0.3 mm; voxel size=3×3×3.3 mm). In total 550 whole brain images were acquired during each pharmacofMRI session.

Behavioural data analyses

The pattern of ketamine-induced psychotomimetic effects in the present sample were evaluated by means of repeated measures ANOVAS with treatment (ketamine, placebo) and time (before, during, after infusion) as within-subject factors. Dependent variables in this analysis were the scale-specific ln-transformed values from the Psychotomimetic States Inventory (PSI) (Mason et al., 2008) that were assessed before during and after infusion of ketamine and placebo. Post-hoc tests for the PSI scales were Bonferroni adjusted with a $p < 0.01$ considered significant. Effects on heart rate were assessed by means of a repeated measures ANOVA with treatment (placebo, ketamine) and time (recorded at the start of the experiment, after 15 min, after 30 min) and heart rate as dependent variable. Emotional ratings during encoding were analysed using repeated measures ANOVAS with treatment (ketamine, placebo) and valence (negative, neutral, positive) as within-subject factors and arousal or valence ratings as dependent variable. In line with previous studies (e.g. Richardson et al., 2004; Hall et al., 2007) recognition memory was examined using an accuracy measure that accounts for the rate of correctly recognized items (hit rate) as well as the rate of incorrectly identified distractor stimuli (false alarm rate) defined as difference between the hit rate and the false alarm rate. Accuracy measures were separately calculated for each emotional valence (negative, neutral, positive) and each treatment condition (ketamine, placebo). Emotional valence specific effects of ketamine on recognition memory were examined by means of a repeated measures ANOVAS with treatment (ketamine, placebo) and valence (negative, neutral, positive) as within-subject factors and recognition accuracy as dependent variable. In line with previous emotional subsequent memory studies (Rasch et al., 2009) emotional enhancement of memory was further explored by calculating individual differences between the rate of correctly recognized stimuli for each emotional condition (positive, negative) and the neutral condition after each treatment application. Based on our a priori hypothesis that ketamine would abolish the enhancement of emotional relative to neutral information this hypothesis was tested one-sided, with $p < 0.05$ considered significant.

fMRI data analysis

fMRI data were preprocessed and analysed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing was

carried out using standardized protocols (see Becker et al., 2013). Briefly, after discarding the first 5 images, the time-series were motion corrected, co-registered to the T1-image, spatially normalized to the Montreal Neurological Institute (MNI) standard space by means of a two-step procedure implementing segmentation of the T1-image and application of the resulting transformation parameters to the functional time-series SPM8 (resampled at a $3 \times 3 \times 3$ mm resolution), and smoothed using a full width half maximum (FWHM) 8 mm Gaussian kernel. On the first level valence-specific (negative, neutral, positive) regressors were modelled separately for the later successfully remembered and forgotten items. To further control for motor-related activity and movement related artefacts, valence/arousal rating-periods and head motion parameters were included in the design matrix as additional regressors. In line with the design and aim of the present study the second level analysis focused on main and interaction effects of ketamine on: (1) subsequent memory effect (SM): to determine regions involved in memory formation by analysing differences between subsequently remembered vs. subsequently forgotten events ('difference due to memory', Dm, effect); (2) emotional encoding (EE): to determine regions differentially involved in successful encoding of negative, neutral and positive stimuli (to control for effects of ketamine on depth of processing during encoding (Honey et al., 2013) and biasing effects of the hypothesized effects of ketamine on memory performance (Honey et al., 2004) only subsequently remembered items were included in this analysis), (3) emotional subsequent memory (ESM): to determine regions involved in emotion enhanced memory formation by identifying regions that show a larger Dm effect for emotional than neutral events ($Dm_{\text{emotional}} > Dm_{\text{neutral}}$). Given that the mean number of valence-specific forgotten items was rather low in the present sample valence-specific ESM were analysed by comparing the valence-specific subsequently recognized stimuli with all subsequently forgotten stimuli. Based on meta-analyses of studies on successful encoding (Kim, 2011), emotional processing (Phan et al., 2002; Etkin et al., 2011), and emotional memory formation (Murty et al., 2010) fusiform gyrus, amygdala, hippocampal formation, anterior cingulate cortex/medial prefrontal cortex, and the orbitofrontal cortex were defined as a priori regions of interest (ROIs). Bilateral structural masks were defined using a standardized brain atlas (Automated Anatomical Labelling, AAL, Tzourio-Mazoyer et al., 2002), results were thresholded at $p < 0.05$, corrected for multiple comparisons by means of family-wise error (FWE) correction. In addition, ketamine effects on the network level were examined using a generalized form of context-dependent psychophysiological interaction (gPPI) analysis (Mc Laren et al., 2012). Seed-regions for the analysis of functional connectivity were 6-mm spheres centred at the maximum t-value of the ketamine effects as determined by the BOLD level analyses of the emotional encoding (EE) and emotional subsequent memory (ESM) effects. Effects in target regions were examined within the same structural masks as used for the BOLD level analysis and thresholded at $p < 0.05$ FWE-corrected. To further explore treatment effects on BOLD level and functional connectivity parameter estimates were extracted from the underlying contrast maps by means of 6mm spheres centred at the location of the maximum t-value using marsbar (Brett et al., 2002).

Results

Ketamine blood levels, psychotomimetic states, pulse and attention

On average participants received 0.45 mg/kg ketamine (± 0.02 , range 0.41–0.50) during the 1 h scanning protocol. Due to technical difficulties detailed ketamine levels could not be obtained from all blood samples. For the $n=16$ samples that allowed detailed analysis of ketamine during infusion, ketamine mean plasma level was 89.76 ± 14.32 ng/ml (range 54.30–114.00 ng/ml). Blood samples drawn 1 h after the ketamine infusion indicated that ketamine plasma levels significantly decreased during the post scanning period ($42.38 \pm$

14.65 ng/ml, $t_{(15)}=9.85$, $p < 0.001$, paired t-test). An additional application check for the entire sample revealed that in all blood samples drawn during placebo infusion ketamine concentration was < 10 ng/ml plasma in all pre-, during- and post-infusion samples. Ketamine concentration was < 10 ng/ml plasma in all pre-ketamine infusion samples and > 10 ng/ml in all samples collected during ketamine infusion. Examination of ln-transformed PSI scores revealed that ketamine increased values on the PSI subscales of Delusional Thinking ($F_{(1,20)}=4.41$, $p=0.049$) and Perceptual Distortion ($F_{(1,20)}=18.15$, $p < 0.001$) across application stages. Increases in interaction with application stage were found for the subscales Delusional Thinking ($F_{(2,40)}=5.12$, $p=0.010$), Perceptual Distortion, ($F_{(2,40)}=5.77$, $p < 0.001$), and Cognitive Disorganization ($F_{(2,40)}=6.22$, $p=0.004$). Compared to placebo, ketamine increased the self-reported psychotomimetic states on these subscales specifically during infusion (Delusional thinking, $t_{(20)}=3.12$, $p=0.005$; Perceptual Distortion, $t_{(20)}=6.06$, $p < 0.001$; Cognitive Disorganization, $t_{(20)}=3.08$, $p=0.006$). Examining the heart rate over the course of the experiment revealed no main effect of assessment time or interaction effects between assessment time and treatment (both $p > 0.22$), however a significant main effect of treatment ($F_{(1,20)}=41.38$, $p < 0.001$) indicating that ketamine significantly increased heart rate (mean placebo, 68.11 ± 7.14 ; ketamine 76.47 ± 10.08). Comparison of attentional performance during placebo and ketamine did not reveal significant differences in the total number of items (placebo, 175.20 ± 16.91 ; ketamine, 173.75 ± 16.72) or errors (placebo, 3.3 ± 2.70 ; ketamine 4.2 ± 7.26 ; both $p > 0.56$, paired t-test) arguing against confounding effects of ketamine on basal attentional performance during encoding.

Effects of ketamine on valence and arousal ratings during encoding

In line with the standardized arousal ratings from the IAPS database, positive and negative stimuli were perceived as more arousing than the neutral stimuli (mean rating neutral 3.46 ± 1.19 , negative 5.41 ± 1.19 , positive 5.04 ± 1.27 , both $p < 0.05$). As expected, valence ratings differed between the emotional categories, with low valence ratings for negative stimuli (2.57 ± 0.42), intermediate ratings for neutral stimuli (5.20 ± 0.34), and highest valence ratings for positive stimuli (6.60 ± 0.70). Repeated-measures ANOVA with treatment (ketamine, placebo) and stimulus valence (negative, neutral, positive) as within-subject variables and arousal ratings during pharmacofMRI as dependent variable yielded a significant main effect of stimulus valence ($F_{(2,40)}=28.38$, $p < 0.01$) and a trend-to-significant treatment \times stimulus valence interaction effect ($F_{(2,40)}=2.79$, $p=0.074$), but no main effect of treatment ($p=0.28$). An exploratory post-hoc test for the treatment \times arousal interaction effect by means of a direct comparison between treatment-specific arousal ratings for the high-arousal conditions (positive, negative) revealed that ketamine increased arousal for positive (placebo 4.85 ± 1.23 , ketamine 5.39 ± 1.38 , $t_{(20)}=-3.142$, $p=0.005$) but not negative stimuli (placebo 5.45 ± 1.10 , ketamine 5.39 ± 1.48 , $t_{(20)}=0.25$, $p=0.81$). A corresponding repeated-measures ANOVA with valence ratings during pharmacofMRI as dependent variable yielded a main effect of stimulus valence ($F_{(2,40)}=336.63$, $p < 0.01$), but neither main nor interaction effect with treatment reached statistical significance (both $p > 0.20$), suggesting that ketamine did not affect the perceived valence of the stimuli during encoding.

Effects of ketamine on subsequent memory performance

Repeated measures ANOVA with accuracy (hit rate – false alarm rate) as dependent variable yielded a significant main effect of treatment ($F_{(1,20)}=5.59$, $p=0.028$) indicating significantly lower accuracy following ketamine independent of valence. Neither the main effect of emotion nor the treatment \times emotion interaction passed the significance threshold (both $p > 0.52$). Given the low false alarm (7–

13%) rates in the present sample, additional analyses separately assessed effects on false alarm and hit rate. Repeated measures ANOVA with false alarm rate at follow-up revealed a significant main effect of emotion ($F_{(2,40)}=7.89$, $p=0.001$), with post-hoc tests indicating that independent of treatment false alarm rates were higher for negative compared to neutral (mean false alarm rate in percent: neutral 7.14 ± 7.38 , negative 11.79 ± 7.95 , $p=0.001$) as well as positive compared to neutral stimuli (positive 10.24 ± 9.58 , $p=0.009$), whereas false alarm rates for positive and negative stimuli did not differ ($p=0.266$). Neither the main effect of treatment nor the treatment \times emotion interaction reached significance (both $p > 0.27$). Repeated measures ANOVA with subsequent recognition performance (hit rate) as dependent variable revealed a main effect of emotion ($F_{(2,40)}=5.95$, $p=0.019$) and treatment ($F_{(1,20)}=6.47$, $p=0.005$). Post-hoc tests confirmed the memory advantage of emotional stimuli as indicated by significantly enhanced recognition performance for emotional stimuli compared to neutral stimuli (mean hit rate in percent: neutral 75.15 ± 13.79 , negative $82.30\% \pm 11.04$, positive 78.96 ± 9.41). Ketamine administration generally decreased recognition performance across emotional conditions (mean hit rate in percent: placebo 81.43 ± 10.51 , ketamine 76.19 ± 11.86). Further exploratory analyses of valence-specific decreased memory performance using paired t-tests revealed preliminary evidence that ketamine significantly decreased recognition of positive stimuli (placebo $81.90\% \pm 10.19$, ketamine $76.03\% \pm 12.27\%$; $t_{(20)}=-2.54$, $p=0.009$), while relatively sparing recognition performance for neutral and negative stimuli (neutral: placebo $77.46\% \pm 12.24$, ketamine 72.85 ± 16.84 ; $t_{(20)}=-1.92$, $p=0.070$; negative: placebo $84.92\% \pm 14.89$; ketamine $79.68\% \pm 12.19$; $t_{(20)}=-1.69$, $p=0.110$).

Effects of ketamine on emotional enhancement of memory

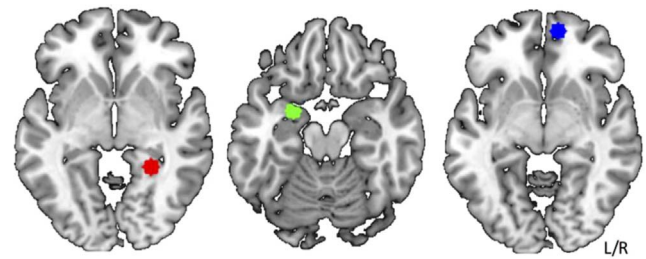
Relative to neutral stimuli, recognition memory was significantly enhanced for both, negative and positive stimuli following the placebo administration. Relative to neutral pictures, subjects recognized on average 7.46% (± 13.07) more negative, and 4.44% (± 10.61) more positive pictures after placebo (negative, $t_{(20)}=2.38$, $p=0.031$; positive, $t_{(20)}=2.22$, $p=0.038$, paired t-tests). Following ketamine administration, subjects recognized significantly more negative than neutral pictures ($6.83\% \pm 14.54\%$, $t_{(20)}=4.40$, $p=0.036$), however ketamine abolished the emotional enhancement for positive stimuli (3.17% , $\pm 13.56\%$, $t_{(20)}=1.23$, $p=0.23$). However, a direct comparison of the ESM during ketamine versus placebo using repeated measure ANOVA failed to reveal significant interaction effects, possibly due to the high interindividual variance in the strengths of the emotional memory effect following both placebo as well as ketamine application.

fMRI findings

Subsequent memory analysis (SM)

In line with previous studies and meta-analytic data (Kim, 2011), encoding of subsequently successful recognized stimuli was associated with higher activity in the hippocampal formation ($T=4.92$, $P_{FWE} < 0.05$, maximum t-value at $-26/-42/-10$, left parahippocampal gyrus, $k=4$) and the bilateral fusiform gyrus (left, $T=4.54$, maximum t-value at $-24/-50/-14$, $k=22$; right, $T=4.41$, maximum t-value at $32/-44/-18$, $k=3$, $P_{FWE} < 0.05$). No interaction effects with treatment were observed for the combined valence conditions including negative, neutral and positive stimuli against an unspecific effect of ketamine on the subsequent memory networks. To explore associations between neural activity during encoding and subsequent memory performance, parameter estimates were extracted from the regions showing higher activity during successful memory formation and correlated with subsequent memory performance. Neither during ketamine nor placebo significant associations were observed ($p > 0.05$).

(a) Location of the valence-specific effects during encoding



(b) Direction of the valence-specific effects during encoding

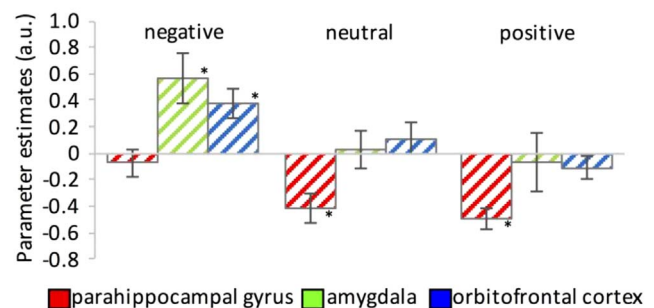


Fig. 1. Title Emotion-specific effects of ketamine during encoding. **Description** During encoding of negative, neutral and positive stimuli ketamine produced valence-specific effects in the parahippocampal region, the amygdala and the orbitofrontal cortex. (a) Location of the interaction effects, (b) extracted parameter estimates showing the direction of the valence-specific effects during encoding. Results were obtained using small-volume correction within a priori defined structural regions of interest using a peak-level threshold of $p < 0.05$ FWE-corrected.

Differential effects on emotional encoding (EE)

Examination of the main effect of treatment on successful encoded items revealed significant main effects in the right parahippocampal gyrus ($T=5.73$, $P_{FWE} < 0.05$, maximum t-value at $22/-44/-6$, $k=3$) and the bilateral mPFC ($T=6.01$, maximum t-value at $8/52/40$, $k=2$; $T=5.78$, maximum t-value at $0/58/28$, $k=6$, $P_{FWE} < 0.05$), indicating that ketamine decreased encoding-related activity in these regions irrespective of emotion. Analyses of differential effects of ketamine during successful encoding of negative, neutral and positive stimuli revealed emotion \times treatment interaction effects in the right parahippocampal gyrus ($T=3.89$, $P_{FWE} < 0.05$, maximum t-value at $26/-44/-4$, $k=5$), left amygdala ($T=3.76$, $P_{FWE} < 0.05$, maximum t-value at $-24/0/-18$, $k=11$), and right medial orbitofrontal cortex ($T=4.67$, $P_{FWE} < 0.05$, maximum t-value at $10/56/-6$, $k=19$) (Fig. 1a). Extraction of individual parameter estimates revealed that ketamine significantly decreased parahippocampal activity during successful encoding of neutral and positive (neutral, $t=3.84$; positive, $t=6.11$, both $p \leq 0.001$, paired t-test), but not negative stimuli ($t=0.72$, $p=0.48$). In contrast, ketamine increased left amygdala and right orbitofrontal activity during successful encoding of negative ($t=-3.01$, $p=0.007$; $t=-3.27$, $p=0.004$), but not positive or neutral stimuli (neutral, $t=-0.18$; $t=-0.93$, positive, $t=0.30$; $t=1.14$ all $p > 0.27$) (Fig. 1b).

Emotional subsequent memory analysis (SEM)

Examining the emotional enhancement of memory revealed that ketamine modulated the ESM for negative events in the left amygdala ($T=4.73$, $P_{FWE} < 0.05$, maximum t-value located at $-18/0/-14$, $k=14$). Extraction of parameter estimates revealed that this region displayed comparable activity for negative and neutral stimuli during placebo ($t=-1.08$, $p=0.29$), with ketamine producing differential encoding-related activity for negative and neutral stimuli ($t=3.89$, $p=0.001$, paired t-test). This modulatory effect was specifically driven by increased amygdala reactivity to negative stimuli during ketamine (NEG, $t=-2.36$, $p=0.03$; NEU, $t=0.85$, $p=0.41$; paired t-test, Fig. 2). In contrast no modulatory effects were found for the positive ESM.

Ketamine effects on the ESM effect for negative stimuli

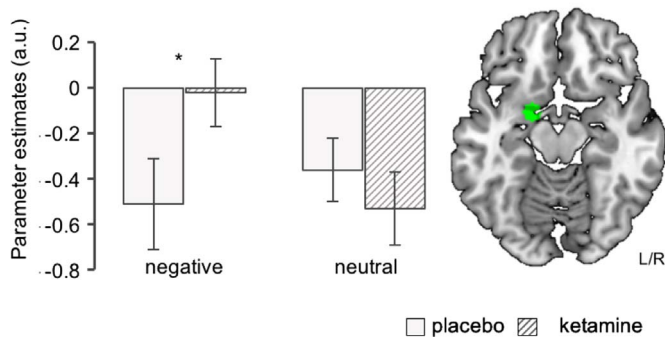


Fig. 2. Title Ketamine effects on the emotional enhancement of memory networks. **Description** Ketamine specifically increased the reactivity of the left amygdala during encoding of negative stimuli. Results were obtained using small-volume correction within a priori defined structural regions of interest using a peak-level threshold of $p < 0.05$ FWE-corrected.

Associations between ketamine-induced increased amygdala activity during encoding of negative stimuli and subsequent memory for negative stimuli were further explored using correlational analyses. Neither during ketamine nor placebo significant associations were observed ($p > 0.05$).

Effects on the network level

Functional connectivity analyses of the regions showing differential effects under ketamine versus placebo during emotional encoding (EE) revealed a significant main effect of ketamine on left mPFC-right hippocampus connectivity (seed centred at 0/58/28; $t=5.15$, $P_{FWE} < 0.05$, maximum t -value located at 16/-32/-4, $k=2$), indicating that ketamine increased coupling between these regions regardless of emotion. A significant valence \times treatment effect was found on left amygdala coupling (seed centred at -24/0/-18) with the ipsilateral frontal orbital cortex ($T=3.58$, $P_{FWE} < 0.05$, maximum t -value located at -26/46/-8, $k=1$). Extraction of parameter estimates from this region revealed that ketamine specifically reduced coupling between this regions for negative ($t=2.12$, $p=0.046$), but not for neutral or positive stimuli (NEU, $t=-0.22$; POS, $t=-1.29$, both $p > 0.22$; paired t -tests, Fig. 3). No significant effects on the interplay of other regions determined by the BOLD level analyses were found.

Associations between effects of ketamine on arousal for positive stimuli and neural activity

To further explore the neural basis of the observed increased arousal ratings for positive stimuli during ketamine a SPM-based multiple regression was performed using individual change-scores for arousal ratings for positive stimuli (ketamine > placebo) as variable to predict neural activity changes in the corresponding activity contrast (all positive stimuli during ketamine > all positive stimuli during placebo). Due to the exploratory nature of the analysis a whole-brain analysis was performed using a cluster-based threshold of $p < 0.05$ (FWE-corrected on the cluster level, using an initial cluster defining threshold of $p < 0.001$ as recommended by Woo et al., 2014, and a cluster extent of > 150 voxel). This analysis revealed a positive association between ketamine-induced changes in positive arousal ratings and corresponding neural activity in the left amygdala ($T=6.04$, $P_{FWE} < 0.05$, maximum t -value located at -18/-2/-16, $k=172$). Extraction of parameter estimates demonstrated that a higher increase in arousal for positive stimuli was accompanied by a higher increase in the left amygdala reactivity to positive stimuli (Fig. 4). Examining the corresponding associations for the negative and neutral condition did not reveal significant associations, indicating valence-specific effects of ketamine on amygdala activity.

Ketamine effects on amygdala-orbitofrontal cortex coupling

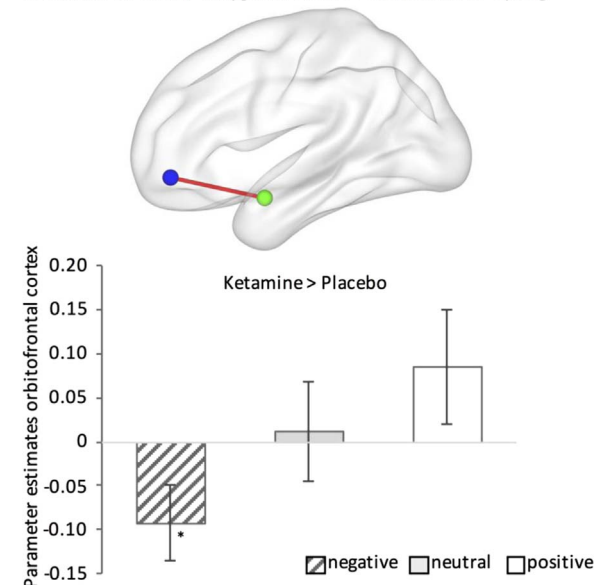


Fig. 3. Title Emotion-specific effects of ketamine on amygdala functional connectivity. **Description** Ketamine specifically decreased coupling of the amygdala with the orbitofrontal region during encoding of negative stimuli. Results were obtained using small-volume correction within a priori defined structural regions of interest using a peak-level threshold of $p < 0.05$ FWE-corrected.

Arousal for positive stimuli and associated amygdala activity

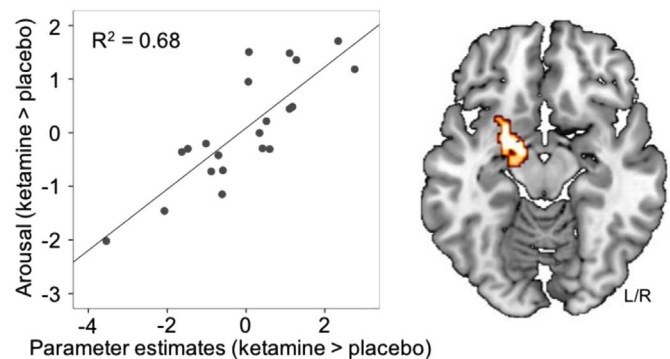


Fig. 4. Title Associations between arousal ratings for positive stimuli and amygdala reactivity. **Description** An exploratory whole-brain analysis revealed associations between the strengths of ketamine-induced changes in arousal for positive stimuli and increased activity in the left amygdala. Results were obtained using a whole-brain cluster corrected threshold using FWE-cluster correction with $p < 0.05$ and a cluster extent of 150 voxels.

Associations between effects on heart rate and BOLD activity

Given ketamine increased the heart rate we used an additional exploratory analysis to examine whether the individual changes in heart rate were associated with altered neural activity on the whole brain level using a sensitive uncorrected threshold of $p < 0.001$ ($k > 5$). A positive associations was found with activity in the right postcentral gyrus (56/-16/12, $k=11$) and the right superior temporal gyrus (56/-2/-2, $k=6$) across valence conditions. Importantly these regions did not overlap with the regions of interest used to determine effects during emotional encoding.

Discussion

The present experiment did not reveal strong evidence for altered emotional experience during ketamine administration. In line with previous behavioural studies (Krystal et al., 1994, Newcomer et al., 1999, Hetem et al., 2000) ketamine produced generally decreased

subsequent memory performance, and an exploratory analysis revealed preliminary evidence of less severe memory impairments and intact emotional enhancement for negative information. Irrespective of emotional valence ketamine suppressed para-hippocampal and mPFC activity in the context of increased mPFC-hippocampal coupling during successful encoding. Analysis of valence-specific effects of ketamine revealed suppressed parahippocampal activity during encoding of neutral and positive stimuli, as well as increased amygdala and orbitofrontal activity during encoding of negative ones. Specifically examining the neural effects of emotion-facilitated memory further revealed that ketamine specifically increased amygdala reactivity to negative stimuli.

Valence-unspecific effects of ketamine

Despite a lack of pronounced effects of ketamine on emotional experience during encoding, ketamine administration produced robust effects on emotional encoding related neural activity, both on a general processing, as well as a valence-specific level. More specifically, ketamine-administration was accompanied by a valence-independent suppression of right parahippocampal and bilateral mPFC activity during successful emotional encoding. The hippocampal formation contributes fundamentally to successful memory encoding (Kim et al., 2011), with intact parahippocampal gyrus functioning being specifically related to successful delayed recall of non-verbal visual material (Köhler et al., 1999), and persisting activity in this region being predictive of long-term encoding success (Schon et al., 2004). In line with the consistently observed impaired memory performance in schizophrenia patients (Mesholam-Gately et al., 2009), previous neuroimaging studies in schizophrenia patients and at-risk populations repeatedly revealed decreased encoding-related activity in the hippocampal formation. In particular decreased parahippocampal activity during encoding of neutral visual and verbal stimuli has been associated with the strengths of memory impairments in schizophrenia patients as well as their first degree relatives and, thus, has been suggested to represent a potential intermediate biological phenotype related to an increased risk for schizophrenia (Rasetti et al., 2014; Thermenos et al., 2007; Di Giorgio et al., 2013).

The mPFC plays a critical role in both emotional experience as well as emotion regulation, including effortful as well as automatic emotion regulation via down-regulation of limbic regions, in particular the amygdala (Buhle et al., 2014; Etkin et al., 2011, Kober et al., 2008). Meta-analytic data indicates that the mPFC is not per se engaged in successful encoding of neutral or emotional material (Kim et al., 2011; Murty et al., 2010) and previous studies employing cognitive paradigms with neutral stimuli mostly observed modulatory effects of ketamine in prefrontal regions with stronger engagement in cognitive processes, particularly dorsolateral regions (Honey et al., 2004; 2005; Anticevic et al., 2012), suggesting that the observed emotion-independent decrease might rather be associated to emotional than cognitive processing. Schizophrenia patients show marked impairments in functional domains that strongly rely on the mPFC, including emotion perception and regulation (Savla et al., 2013; O'Driscoll et al., 2014) and concomitantly attenuated activity in this region (Taylor et al., 2012; Zilverstand et al., 2016). During ketamine administration the generally decreased activity in the mPFC was accompanied by increased coupling of the mPFC with the hippocampus. In addition to its critical involvement in memory processing, the hippocampus strongly interacts with the amygdala during emotion processing (Murty et al., 2010; Kim et al., 2011, Fusar-Poli et al., 2009) and both regions share functional connections with the mPFC (Amft et al., 2015) suggesting that ketamine-induced decreased emotion-regulation in the mPFC might be accompanied by stronger engagement of the hippocampus in emotional processing and in turn disrupts successful memory formation. In addition, hippocampal-mPFC interactions have been suggested crucial for integrating new memory into pre-existing knowl-

edge networks (Preston and Eichenbaum, 2013; van Kesteren et al., 2012), with increased coupling associated to encoding success (Schlichting and Preston, 2015). Thus, increased coupling might represent an (unsuccessful) attempt to compensate for suppressed parahippocampal engagement in memory formation during ketamine administration, by means of integrating the new information with pre-existing knowledge representations.

Valence-specific effects of ketamine

In addition to valence-independent effects, ketamine produced a pattern of valence-specific effects in the right parahippocampus, left amygdala and right orbitofrontal cortex. In line with the pronounced impaired recognition performance for neutral and positive material, parahippocampal activity was specifically suppressed during ketamine for these emotions, yet normal during encoding of negative material. In contrast, ketamine produced increased activity in the amygdala and orbitofrontal cortex specifically during encoding of negative material. Previous studies on emotional encoding in healthy individuals revealed increased amygdala activity for emotional, particularly negative stimuli (Canli et al., 2000; Fusar-Poli et al., 2009), that has been associated with enhanced long-term recognition memory (Hamann et al., 1999; Herbener et al., 2007). In healthy subjects amygdala reactivity to negative emotional material shows an inverse relationship to prefrontal activity, including the mPFC and superior orbital regions, thought to reflect prefrontal top-down emotion regulation of the amygdala (Buhle et al., 2014; Etkin et al., 2011, Kober et al., 2008; Diekhof et al., 2011), suggesting that the interaction of valence-independent suppression of mPFC regulatory functioning during ketamine with valence-dependent amygdala reactivity, i.e. enhanced activity for negative materials, might underlie the observed pattern. The selectively increased amygdala and orbitofrontal cortex activity during ketamine for negative material was furthermore accompanied by reduced functional connectivity between the left amygdala and the ipsilateral superior orbitofrontal cortex. Similar hypoconnectivity has been previously observed in the context of pathologically exaggerated amygdala reactivity for negative material and has been suggested to mirror reduced emotion regulation (Hahn et al., 2011). In concordance with the observed pattern during ketamine-induced NMDAR-hypofunctioning, studies on emotional processing in schizophrenia patients repeatedly observed valence-dependent hyperactivity of the amygdala in schizophrenia patients (Marwick and Hall, 2008; Pankow et al., 2013). Notably, in the present sample ketamine produced predominately positive symptoms of schizophrenia, while in schizophrenia patients stronger positive symptomatology has been associated with exaggerated amygdala reactivity to negative pictorial stimuli (Taylor et al., 2002; Fahim et al., 2005).

The medial orbitofrontal cortex mirrored the valence-specific increased reactivity to negative stimuli observed in the amygdala. The medial orbitofrontal cortex shares extensive reciprocal connections with the amygdala (Barbas et al., 2007), and both are central to emotional processing, particularly in evaluating salience aspects of the environment that guide emotional learning and promote adaptive behaviour (Adolphs et al., 1995; Rolls, 1996; Schoenbaum et al., 2011). Moreover, the connectivity of both, the amygdala as well as the orbitofrontal cortex includes reciprocal connections with the hippocampal formation, including the parahippocampus, and these pathways have been suggested to fundamentally contribute to the impact of emotional salience on learning (Cavada et al., 2000). Salience signalling and salience driven-learning have been strongly associated with dopaminergic signalling (Abraham et al., 2016) and both the amygdala and the orbitofrontal cortex receive extensive mesocortical and mesolimbic dopaminergic inputs (Meador-Woodruff et al., 1997). Although ketamine at doses similar to the one used in the present study seem not to directly affect striatal dopaminergic functioning (Aalto et al., 2002) glutamate-mediated effects on dopaminergic functioning might have contributed to the present findings. The salience processing

networks, particularly the amygdala and to a lesser extent the orbitofrontal cortex, have been proposed to show hyper-reactivity during psychotic states at early stages of schizophrenia as a consequence of reduced cortico-accumbens glutamate activity that in turn fails to provide a tonic dopaminergic down-regulation of the phasic dopamine system leading to an exaggerated response to potentially significant stimuli (Grace et al., 2000; Aleman and Kahn, 2005). The role of dopamine in gating amygdala responsivity is further supported by findings on positive associations between measures of amygdala dopamine and higher functional activity in response to aversive stimuli in healthy individuals (Kienast et al., 2008) as well as recent animal models of schizophrenia that revealed disrupted, particularly exaggerated amygdala, dopamine salience signaling that have been proposed to underlie enhanced salience signaling in schizophrenia patients (Hernandez et al., 2015).

Effects of ketamine on arousal for positive stimuli

Findings from an exploratory post hoc analysis examining valence-specific effects of ketamine on arousal revealed preliminary evidence that ketamine increases the perceived arousal for positive stimuli during encoding and that the strengths of this effect was associated with higher reactivity of the left amygdala to positive stimuli. Across species, the amygdala has been associated with arousal processing (Pelletier et al., 2005; McGaugh, 2004). In humans, the association has been demonstrated for negative as well as positive stimuli (Costa et al., 2010; Garavan et al., 2001) and activity in the amygdala has been shown to increase with higher experienced emotional intensity of positive stimuli (Bonnet et al., 2013; Phan et al., 2003). Previous studies have shown an important role of the amygdala in reward and appetitive processing (Wassum and Izquierdo, 2015), and in vivo optical stimulation of glutamatergic signaling from the amygdala to the nucleus accumbens increases reward responses via dopamine dependent receptor mechanisms promoting appetitive behavior (Stuber et al., 2011). Overall, this suggests that ketamine-induced modulation of glutamate-mediated appetitive processing might have contributed to the increased arousal selectively observed for positive stimuli.

Despite increasing arousal for positive stimuli during encoding, ketamine impaired the subsequent recognition performance for positive stimuli. This observation stands in contrast to the well-validated enhancement of memory by arousal via amygdala activity, but might be explained in terms of valence-specific effects of ketamine on encoding-related parahippocampal activity. Indeed, arousal-induced memory enhancement relies on the modulatory influence of the amygdala on memory storage processes in other brain regions, particularly the parahippocampus (Kilpatrick and Cahill, 2003). Ketamine suppressed emotional memory enhancement and encoding-related parahippocampal activity for positive stimuli, whereas memory enhancement and parahippocampal activity were preserved for negative stimuli. This might indicate that ketamine-induced suppression of parahippocampal activity during positive stimuli led to a failure of the amygdalar signal to modulate memory formation in this region.

Potential relevance for schizophrenia

The observed normal emotional experience during encoding and overall impairments in subsequent memory performance following ketamine administration observed in the present study replicate a pattern previously observed in schizophrenia patients. Although ketamine produced a trend for increased arousal ratings for positive stimuli, the lack of effects on arousal for negative/neutral stimuli, as well as the absence of ketamine effects on perceived valence largely resemble previous observations on intact-in-the-moment emotional experience in schizophrenia patients (Herbener, 2008; Horan et al., 2006). Impaired memory encoding of new information is one of the

most consistently reported cognitive impairments during ketamine administration (Morgan and Curran, 2006), observed on recall as well as recognition tasks (Honey et al., 2005), and represents an enduring core cognitive deficit in schizophrenia (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009). Additional exploratory analysis revealed preliminary evidence that ketamine produces a valence-dependent pattern of impairments on longer-term recognition memory performance, with less severe impairments on negative stimuli in the context of intact emotional enhancement for negative information. Two previous studies examining the emotional subsequent memory effect in schizophrenia patients after longer consolidation intervals (< 24 h) reported – in addition to generally impaired memory performance in the schizophrenia patients – greater rates of forgetting of both, positive and neutral stimuli than negative stimuli in a sample of long-hospitalized schizophrenia patients (Calev and Edelist, 1993), and a lack of emotional memory enhancement of positive, but intact enhancement of negative stimuli in a sample of stable-medicated schizophrenia patients (Herbener et al., 2007). However, given the preliminary nature of the emotion-specific behavioural effects of ketamine conclusions in this regard need to be drawn with caution.

Limitations

Some limitations of the present experiment need to be carefully considered. (1) Ketamine increased the heart rate which might have affected the BOLD response. Although the fMRI paradigm included a low-level baseline that might partly control for confounding effects, a regional- and valence-specific pattern of neural effects was observed and an additional exploratory analysis did not reveal strong associations between changes in heart rate and BOLD activity, we cannot completely rule out potential confounding effects of cardiovascular effects of ketamine on the present results, (2) although the psychotomimetic effects of ketamine validate the ketamine model psychosis approach we cannot completely rule out that the subjective effects of ketamine might have interfered with blinding of the participants, (3) ketamine acts primarily as a non-competitive antagonist of the NMDAR, and this action accounts for most of the analgesic, amnesic and psychotomimetic effects of ketamine (Kohrs and Durieux, 1998). However, ketamine interacts with multiple binding sites, including dopaminergic D2 receptor sites, muscarinic and opioid receptors, although the later might only show relevant effects at higher doses (Hirota et al., 1999).

Conclusion

Together, our findings indicate general as well as valence-specific neural effects of ketamine during successful encoding in memory and emotion processing core regions in the context of normal emotional experience during encoding and generally decreased subsequent memory performance after a wash-out period of 5-days. Preliminary evidence suggests that subsequent recognition performance and emotional enhancement for negative material might be less disrupted by ketamine administration during encoding.

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