Effects of ketamine on cognition–emotion interaction in the brain

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ABSTRACT

Cognition–emotion interaction in the brain can be investigated by incorporating stimuli with emotional content into cognitive tasks. Emotional stimuli in the context of a working memory (WM) task yield increased activation in WM-related lateral prefrontal regions, whereas cognitive effort enhances deactivation in emotion-related cortical midline regions. N-methyl-D-aspartate glutamate receptors (NMDA-Rs) are critically involved in WM, and NMDA-R antagonists, such as ketamine, accordingly affect WM but also have a profound impact on emotional processing, as underscored by the rapid reduction of depressive symptoms after administration of a single dose of ketamine. The effect of ketamine on both cognitive and emotional processing therefore makes it a useful tool to further explore cognition–emotion interaction in the brain. Twenty-three healthy subjects were administered ketamine to investigate whether its effects on WM performance and brain reactivity depend on emotional content or emotional valence of stimuli. Furthermore, we aimed at investigating how ketamine affects the integration of emotion and WM processes in emotion-related cortical midline regions and WM-related lateral prefrontal regions. Results show that ketamine modulates cognition–emotion interaction in the brain by inducing lateralized and valence-specific effects in emotion-related cortical midline regions, WM-related lateral prefrontal regions and insula. In emotion-related cortical midline regions ketamine abolishes enhancement of deactivation normally observed during cognitive effort, while in the right DLPFC and the left insula the previously described pattern of increased activation due to emotional content is abrogated exclusively for negative stimuli. Our data therefore shows a specific effect of ketamine on cognition–emotion interaction in the brain and indicates that its effect on amelioration of negative biases in MDD patients might be related to less interference of cognitive processing by negative emotional content.

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Introduction

The interplay between cognition and emotion has become a major research interest in the field of cognitive neuroscience over the last two decades (Dolan, 2002; Ledoux, 1998; Pessoa, 2008). While historically, cognition and emotion have been viewed as largely separate domains, recent evidence suggests that they may be in a constant state of interaction depending on ongoing environmental and organismal demands and may jointly contribute to behavior (Pessoa, 2008). Furthermore, many psychiatric disorders such as major depressive disorder (MDD) involve deficits in emotional and cognitive processing (Millan et al., 2012), highlighting the need to understand mechanisms that underlie cognition–emotion interactions in the brain. The investigation of memory processes might be particularly suited to better understand cognition–emotion interaction, as it is well-known from experiences in our everyday life that information and situations associated with emotions are better remembered. While an emotional enhancement effect on episodic memory performance has been demonstrated at the behavioral as well as at the neural level (Moore and Oaksford, 2002; Kensinger and Corkin, 2003; Smith et al., 2005), less is known about the relation between emotion and working memory (WM), which is an essential component of many cognitive operations (Baddeley, 2003). Previous studies demonstrated that the dorsolateral prefrontal cortex (DLPFC) is implicated in numerous cognitive functions relevant to WM, including holding to-be-remembered information on-line (Goldman-Rakic, 1994; Jonides et al., 1993), monitoring and

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manipulating the to-be-remembered information (Petrides, 1994), response selection (Rowe et al., 2000), and implementation of strategies to facilitate memory (Bor et al., 2003, 2004). Activity in the anterior cingulate cortex (ACC) during WM tasks is often described in relation to increased effort, complexity, or attention (Botvinick et al., 2004; Duncan and Owen, 2000). WM studies using stimuli with emotional content reported conflicting results, with either no behavioral impact (Döhnel et al., 2008; Grimm et al., 2012; Perlstein et al., 2002) or impaired reaction times and improved accuracy for negative emotional stimuli (Becerril and Barch, 2011; Kensinger and Corkin, 2003). Also, regarding the question whether emotional content affects brain regions supporting working memory, studies reported reduced as well as increased and unchanged DLPFC activity during emotional WM tasks (Döhnel et al., 2008; Neta and Whalen, 2011; Perlstein et al., 2002).

Preclinical studies indicate that N-methyl-D-aspartate glutamate receptors (NMDA-Rs) are critically involved in WM (Fellous and Sejnowski, 2003; Lisman et al., 2008; Seamans et al., 2003). In recent years, the NMDA-R antagonist ketamine has been increasingly explored in terms of WM function and associated brain activity. For verbal WM tasks, an effect of ketamine was either not detectable at all or detectable only at higher doses. At the same time, ketamine induced greater task-associated activation in bilateral DLPFC and ACC (Honey et al., 2003, 2004). During spatial WM tasks an impaired performance and reduced task-related activations and connectivity in the lateral prefrontal cortex have been described (Anticevic et al., 2012; Driesen et al., 2013). Regarding the response to emotional stimuli, reduced limbic activity has been demonstrated after ketamine administration (Abel et al., 2003). Furthermore, the notion that NMDA-receptor antagonism is not only relevant to cognitive, but also to emotional processing is supported by the rapid antidepressant effect of ketamine in otherwise treatment-resistant MDD patients (Aan Het Rot et al., 2012; Duman and Aghajanian, 2012; Zarate et al., 2006). Indicators for disturbed cognition–emotion interaction in patients are impaired WM and negative processing bias (Elliott et al., 2011; Matsuo et al., 2007; McClintock et al., 2010; Rose and Ebmeier, 2006), which have been related to aberrant functioning of DLPFC, ACC and insula (Gotlib and Joormann, 2010; Hamilton et al., 2012; Siegle et al., 2007; van Tol et al., 2012). An antidepressant response to ketamine is associated with decreased metabolism in insula, and ventrolateral and dorsolateral prefrontal cortices of the right hemisphere (Carlson et al., 2013). Taken together, these findings suggest that pharmacological manipulation of NMDA-receptors with ketamine combined with functional neuroimaging might be a useful tool for the investigation of cognition–emotion interaction in the brain.

The aim of the present study was therefore to investigate how NMDA-receptor antagonism modulates cognition–emotion interaction, i.e. behavioral and neural effects of emotional content in the context of a verbal working memory task. To assess WM function during ketamine infusion we here used an emotional n-back task that was developed in a previous study to demonstrate that emotional content increases activation in cognition-related lateral prefrontal regions, whereas cognitive effort enhances deactivation in emotion-related cortical midline regions (Grimm et al., 2012). We here asked whether effects of ketamine on WM performance and brain reactivity depend on emotional content or emotional valence. Furthermore, we aimed at investigating how ketamine affects the integration of emotion and WM processes in emotion-related cortical midline regions and WM-related lateral prefrontal regions.

Methods

Ethics statement

The study was approved by the University of Zurich institutional review board, and all subjects gave written informed consent before screening.

Subjects

Healthy subjects ($n = 23$, mean age, 25.5y $\pm$ 5y (SD); 12 males) without any psychiatric, neurological, or medical illness were self-referred from online study advertisements. All subjects underwent a medical examination and psychiatric interview based on the Brief Psychiatric Rating Scale (BPRS; Rhoades and Overall, 1988) and the Hamilton Rating Scale for Depression (HAMD). Only medication-free subjects that were healthy according to the physical examination, electrocardiogram, and blood and urine analyses were included in the study. Exclusion criteria were a history of psychiatric/neurological diseases, drug abuse, concurrent medication, cardiovascular disease, anemia, thyroid disease, any somatic disease affecting drug metabolism and excretion (e.g. renal or liver disease), MR exclusion criteria, pregnancy and left handedness.

Experimental design

All subjects completed two separate fMRI sessions (baseline and pharmacological intervention respectively). In one of the sessions, S-ketamine (Ketanest® S, Pfizer, Zurich, Switzerland) was administered as an intravenous bolus of 0.12 mg/kg approximately 25 min prior to the fMRI task, followed by a continuous infusion of 0.25 mg/kg/h during the entire scanning and task period. Subjects were kept under surveillance for at least 40 min after treatment until psychotomimetic effects subsided.

The other session preceded the ketamine session by three days on average, did not include any pharmacological intervention and thus served as the physiological baseline for statistical comparisons.

Working memory task

Stimuli were German nouns taken from the Berlin Affective Word List (BAWL) (Võ et al., 2009). The stimuli were classified as positive, negative and neutral according to the BAWL norms with positive and negative pictures being matched according to arousal levels in order to adjust for arousal effects. In addition, the words of the three valence conditions were matched for word length (5–8 letters), imageability and frequency (total frequency of appearance per million words). The stimuli were consecutively presented within a 2-back working memory task, which provides an established means of both studying the interface between working memory and emotion and eliciting BOLD-responses in cognition- and emotion-related regions (Grimm et al., 2012; Weigand et al., 2013). Subjects were required to monitor a series of words and to respond whenever a word was presented that was the same as the one presented 2 trials previously. Subjects performed a practice run prior to the experiment followed by 15 blocks of experimental trials. Each block consisted of 15 words of either positive, negative or neutral valence presented for 500 ms with an interstimulus interval (ISI) of 1500 ms. Every block was followed by a fixation trial (10–14 s). During the experiment 75 words per condition were presented. The condition order was randomized across the task. Parallel versions of the task were applied in the two sessions. Stimuli were generated by Presentation® (Neurobehavioral Systems, Inc., Albany, CA, USA) and presented via video goggles (VisuaStim digital, Resonance Technology, Inc., Los Angeles, CA, USA). Participants responded by pushing a fiber-optic light sensitive key press.

Functional Imaging

Measurements were performed on a Philips Achieva 3-T whole-body magnetic resonance unit equipped with an 8-channel head array (Philips Medical Systems, Best, the Netherlands). Functional time series were acquired using a sensitivity-encoded single-shot echo-planar sequence (TE = 35 ms; field of view = 22 cm; acquisition matrix = 80 x 80, interpolated to 128 x 128, voxel size = 2.75 x 2.75 x 4 mm,

and sensitivity-encoded acceleration factor $R = 2.0$) sensitive to blood oxygenation level-dependent (BOLD) contrast (T2* weighting). Using a midsagittal scout image, 32 contiguous axial slices were placed along the anterior–posterior commissure plane covering the entire brain with a repetition time of 2000 ms ($\theta = 82°$). A 3-dimensional T1-weighted anatomical scan was obtained for structural reference.

Psychometric measures

Subjective state and mood were assessed before and after the scanning sessions using the state-trait anxiety inventory (STAI X1) (Spielberger et al., 1970). Subjective psychological effects during ketamine infusion were assessed post hoc using the five-dimensional altered states of consciousness (5D-ASC) self-rating scale (Dittrich, 1998), that was shown to reliably measure ketamine-induced altered states of consciousness (Vollenweider and Kometer, 2010). Approximately 20 min after the scan session, subjects had to indicate the subjective alteration of consciousness compared to their general condition on a visual analog scale.

Statistical analysis

Behavioral data

Accuracy was defined as the ratio of correct responses (correctly pressed and correctly not pressed) to total number of stimuli. Reaction times of the correct responses were analyzed. Accuracy and reaction times were analyzed using two-way repeated measures analyses of variance (ANOVAs) with the factors valence (positive, negative, neutral) and treatment (baseline, ketamine). If ANOVAs revealed significant main or interaction effects, further statistical analyses were conducted using post hoc t-tests. All tests were two-tailed and the significance threshold was set at a probability of $p \leq 0.05$. All statistical analyses were carried out using PASW (Predictive Analysis SoftWare, version 18.0, Chicago: SPSS Inc., Illinois, USA).

fMRI data

fMRI data were analyzed using MATLAB 2012b (The Mathworks Inc., Natick, MA, USA) and SPM8 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). Functional data were realigned to the first volume, corrected for motion artifacts, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and spatially smoothed using a 6 mm FWHM Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. Statistical analysis was performed by modeling the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. A fixed-effect model at a single-subject level was performed to create images of parameter estimates, which were then entered into a second-level random-effects analysis. For the fMRI data group analysis the contrast images from the analysis of the individual participants were analyzed using one-sample t tests. Clusters of activation were identified with a global height threshold of $p < 0.001$, uncorrected and a cluster threshold of greater than 150. fMRI group analyses focused on the effect of emotion on the n-back task during the baseline session and served to replicate BOLD signal changes in WM-related lateral prefrontal regions and emotion-related cortical midline regions reported in our previous paper on the integration of emotion and WM processes (Grimm et al., 2012). Accordingly, we then performed ROI analyses to further investigate signal changes in the baseline and ketamine sessions in these regions. On the basis of

peak voxels obtained in the group analysis (Table 1) and reported in our previous paper (see above), we built spherical (radius = 5–10 mm) ROIs and carried out analyses for pregenual anterior cingulate cortex (PACC; 2, 44, 12), posterior cingulate cortex (PCC; −4, −52, 22), bilateral dorsolateral prefrontal cortex (DLPFC; 42, 30, 28; −46, 26, 30) and bilateral insula (32, 30, 0; −28, 30, −2). For the ROI analyses, effect sizes (% signal changes) for the different conditions were extracted for each subject separately using MarsBaR (Brett et al., 2002). For each event % signal changes were calculated relative to the mean signal intensity of this ROI across the whole experiment. The effect of ketamine on task induced BOLD responses within these ROIs was analyzed using repeated measures ANOVAs with the factors treatment (baseline, ketamine) and condition (fixation, positive, negative, neutral). Individual 5D-ASC and STAI scores as well as n-back reaction times and accuracy were correlated with BOLD signal changes using Pearson correlation analysis.

Results

Behavioral results

Working memory task: There were no significant effects of treatment and condition and no significant interaction effects of these factors on accuracy and reaction times.

Psychometric measures: State anxiety inventory (STAI X1) ratings did not differ significantly from pre- (35.47 ± 9.12) to post-infusion (33.96 ± 9.15). Psychotomimetic effects during ketamine infusion were assessed post-hoc using the altered states of consciousness (5D-ASC) rating scale (Dittrich, 1998). Ketamine treatment increased scores in the scales of oceanic boundlessness ($39.65 \pm 1.39\%$), reduction of vigilance ($37.67 \pm 1.19\%$), anxious ego-dissolution ($18.69 \pm 1.17\%$), visionary restructuralization ($29.56 \pm 1.36\%$), and acoustic alterations ($14.22 \pm 0.8\%$).

Correlation analyses: There were no significant correlations between reaction times and psychotomimetic ketamine effects as measured by 5D-ASC. However, we found a significant negative correlation between reductions in vigilance and behavioral accuracy to positive ($n = 21$; $r = -.537$; $p = .02$) and negative emotional stimuli ($n = 21$; $r = -.475$; $p = .03$). In addition, anxious ego-dissolution was negatively correlated to behavioral accuracy to positive stimuli ($n = 21$; $r = -.477$; $p = .029$).

fMRI Results

Replicating our previous work (Grimm et al., 2012), we first investigated how the integration of emotion and WM processes affects brain activity in emotion-related and WM-related regions and therefore focused on the effects of emotional and neutral words in the context of the 2-back task in the baseline session. Task conditions were associated with BOLD signal changes in bilateral DLPFC, dACC, bilateral insula and medial cortical regions such as PACC, PCC and DMPFC (see Table 1). We then performed ROI analyses to ascertain the effect of the different task conditions on signal increases or decreases in our regions of interest. Confirming our previous results, these analyses revealed that regardless of condition, the 2-back task yielded activations in bilateral DLPFC and insula, but deactivations in cortical midline regions such as PACC and PCC.

Concerning the effect of treatment and the different task conditions, ANOVAs showed a significant main effect of treatment in the right insula ($F(1,22) = 5.522$, $p = .028$) as well as a significant main effect of condition in left ($F(3,20) = 7.166$, $p = .002$) and right ($F(3,20) = 19.400$, $p = .000$) insula, left ($F(3,20) = 25.1954$, $p = .000$) and right ($F(3,20) = 14.600$, $p = .000$) DLPFC, PACC ($F(3,20) = 17.925$, $p = .000$) and PCC ($F(3,20) = 18.204$, $p = .000$). Post hoc comparisons revealed a significant reduction of BOLD reactivity regardless of condition in the right insula (positive: ($t(22) = 2.30$, $p = .031$; negative: ($t(22) =

Table 1
Effect of task conditions during the baseline session.

Region	Side	BA	Emotional vs. neutral
DLPFC	R	9	42 30 28 z: 4.44
	L	9	−46 26 30 z: 3.99
PACC	R/L	32	2 44 12 z: 4.12
PCC	R/L	31	−4 −52 22 z: 5.85
Insula	R	47	32 30 0 z: 4.19
	L	47	−28 30 −2 z: 4.55
dACC	R/L	32	10 22 42 z: 4.86
DMPFC	R/L	8/9	−4 50 38 z: 3.58
STG	R	22	58 −8 6 z: 4.28
	L	22	−58 −12 −10 z: 3.93
MTG	R	21	60 −4 −18 z: 4.99
Parietal cortex	R	40	34 −46 38 z: 5.02
	L	40	−34 −48 42 z: 5.00
Occipital cortex	R	18	32 −88 −4 z: 5.69
	L	18	−24 −86 −4 z: 5.69
Premotor cortex	L	6	−2 12 50 z: 5.40

BA Brodman area, DLPFC dorsolateral prefrontal cortex, PACC pregenual anterior cingulate cortex, dACC dorsal anterior cingulate cortex, DMPFC dorsomedial prefrontal cortex, PCC posterior cingulate cortex, STG superior temporal gyrus, MTG medial temporal gyrus. The global height threshold was set to $p < 0.001$ uncorrected, the extent threshold to $k = 150$ voxels. The values in the table represent maximum z values with peak voxel coordinates in the MNI stereotactic space.

2.71, $p = .013$; neutral: ($t(22) = 2.10, p = .047$) during ketamine administration (see Figs. 1–3).

In both sessions, signal changes during the fixation period were significantly lower than during positive, negative and neutral stimuli ($p < .005$) in bilateral DLPFC, bilateral insula, PACC and PCC.

An interaction effect of treatment × condition was found in the left insula ($F(3,20) = 3.206, p = .045$) and right DLPFC ($F(3,20) = 3.009, p = .043$) with post hoc comparisons revealing a significant reduction of BOLD reactivity to negative compared to positive stimuli in the left insula ($t(22) = 2.09, p = .048$) and to negative compared to both positive ($t(22) = 2.35, p = .028$) and neutral ($t(22) = −1.74, p = .096$)

stimuli in right DLPFC during the ketamine but not during the baseline session (see Figs. 2 and 3).

In PCC there was a trend for a significant treatment × condition interaction ($F(3,20) = 2.2661, p = .076$) with increased deactivation to negative compared to positive ($t(22) = 2.17, p = .041$) and neutral stimuli ($t(22) = −3.29, p = .003$) as well as positive compared to neutral stimuli ($t(22) = −2.21, p = .038$) during the ketamine session (see Fig. 1).

There were no associations of signal changes during the different conditions in baseline and ketamine session with psychometric measures. Signal changes in PACC correlated with accuracy of task performance ($r = -0.48, p < 0.05$) and reaction times ($r = 0.44, p < 0.05$) for negative stimuli during the ketamine session.

Discussion

Our findings demonstrate that neither emotional content nor the administration of ketamine had an impact on working memory performance. Results replicated our previous findings regarding the differential involvement of the prefrontal cortex in the emotional working memory task. While emotion lead to an increase of activation in cognition-related lateral prefrontal regions, cognitive effort yielded enhanced deactivation in emotion-related cortical midline regions. During the ketamine session a reduction of BOLD reactivity regardless of valence was found in the right insula, while both the left insula and the right DLPFC showed decreased BOLD reactivity exclusively to negative stimuli. It is interesting to note that while results failed to reach statistical significance, a similar pattern with increased deactivation to negative stimuli during the ketamine session emerged for the PCC. Furthermore, increased deactivation in PACC during the ketamine session was correlated with increased accuracy and faster reaction times for negative stimuli.

Our findings regarding the effect of emotional content on WM performance are in accordance with previous results from our own and other studies that found no impact of emotion on working memory performance (Döhnel et al., 2008; Grimm et al., 2012; Perlstein et al., 2002). Also, the administration of ketamine had no effect on WM accuracy and reaction times. However, we found a significant negative correlation between reduced levels of vigilance and behavioral accuracy for positive and negative stimuli as well as increased levels of anxiety and accuracy for positive stimuli during ketamine infusion. Although ketamine did not change mean performance levels a more subtle effect on behavioral accuracy is not unlikely. While there have been some reports of impaired performance during spatial WM tasks (Anticevic et al., 2012; Driesen et al., 2013), previous studies using verbal stimuli described that subanesthetic ketamine administration had no behavioral effect (Honey et al., 2003, 2004). Impairments of working memory were commonly observed at higher doses of ketamine and were restricted to manipulation of information within working memory suggesting that
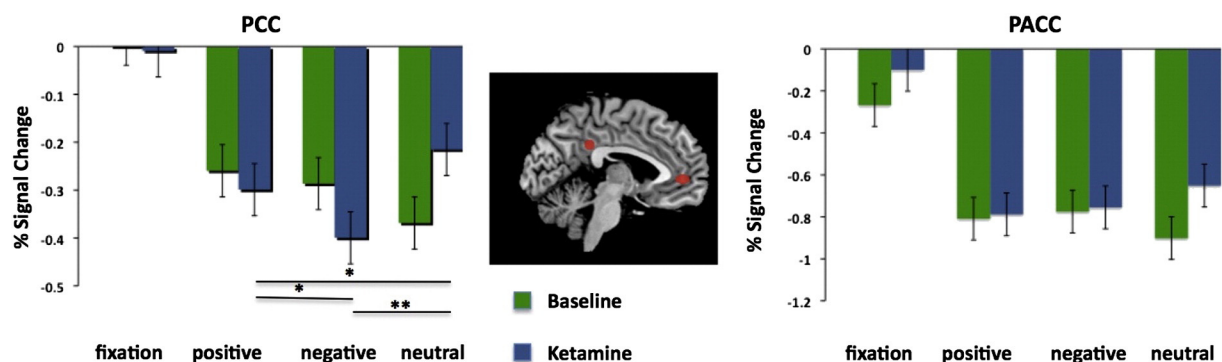

Fig. 1. *Effects of ketamine on cognition–emotion interaction in cortical midline regions.* Signal changes for fixation cross, positive, negative and neutral words during baseline and ketamine sessions. Abbreviations: PCC = posterior cingulate cortex; PACC = pregenual anterior cingulate cortex. Error bars: ±SE. *$p < 0.05$; **$p < 0.01$.

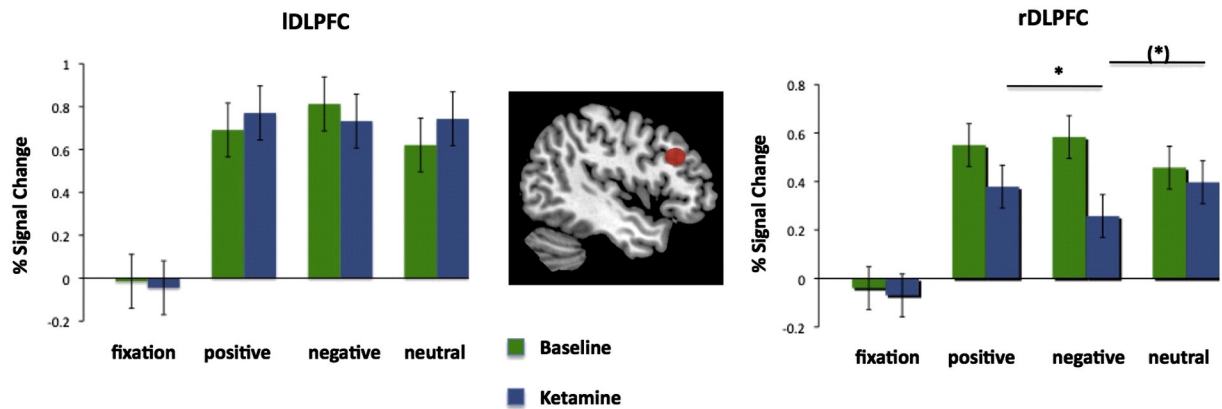**Fig. 2.** *Effects of ketamine on cognition–emotion interaction in lateral prefrontal regions.* Signal changes for fixation cross, positive, negative and neutral words during baseline and ketamine sessions. Abbreviations: lDLPFC = left dorsolateral prefrontal cortex; rDLPFC = right dorsolateral prefrontal cortex. Error bars: ±SE. $^{*}p < 0.05$; $(^{*})p < 0.1$.

ketamine specifically affects higher order control of executive function rather than more basic maintenance processes (Honey et al., 2003). While ketamine poly-drug users display predominantly verbal and visual memory impairments (Liang et al., 2013), significant improvements in simple and complex working memory were found in MDD patients after six ketamine infusions (Shiroma et al., 2014). This is in support of the notion that frequent and high dose ketamine use might be associated with cognitive impairments while ameliorating symptoms of depression with subanesthetic ketamine might even be associated with improved cognitive performance.

Regarding the integration of emotion and WM processes in the brain, our results firstly replicated our previous finding by showing that emotional content increases activation in cognition-related lateral prefrontal regions, whereas cognitive effort enhances deactivation in emotion-related cortical midline regions (Grimm et al., 2012). These cortical midline regions are part of the default-mode network (Fox et al., 2005; Raichle et al., 2001) and characterized by deactivations during various emotional–cognitive tasks that require subjects to attend to external stimuli (Fox et al., 2005; Grimm et al., 2009; Gusnard and Raichle, 2001; Northoff and Bermpohl, 2004). Secondly, we found distinct effects of ketamine in these regions. In emotion-related posterior cortical midline regions (PCC), ketamine was associated with emotion- and valence-specific differences in deactivation, which was significantly increased in emotional compared to neutral stimuli and in negative compared to positive stimuli. Thereby, ketamine abolished enhancement of deactivation normally observed during cognitive effort. While we did not find the exact same pattern in anterior cortical midline regions (PACC), we here also observed a reduction of deactivation for

neutral stimuli, while there were no changes for negative and positive stimuli. However, ketamine-induced changes in BOLD reactivity in this region failed to reach statistical significance. The differential effects of ketamine on PACC and PCC might be explained by our previous finding of decreased connectivity between anterior and posterior cortical midline regions after ketamine administration (Scheidegger et al., 2012). Faster reaction times and increased accuracy for negative stimuli were correlated with neural activity in PACC. BOLD reactivity in the anterior cingulate cortex during WM tasks is often described in relation to increased effort, complexity, or attention (Botvinick et al., 2004; Duncan and Owen, 2000). The association between WM performance and valence-specific increases in NBRs for negative words during the ketamine session could thereby indicate that more deactivation in PACC is necessary to successfully perform the WM task.

In cognition-related lateral prefrontal regions (DLPFC) we found lateralized and valence-specific effects of ketamine. In right DLPFC, ketamine induced a reduction of BOLD reactivity to negative stimuli, while in left DLPFC there were no statistically significant effects. At least for the processing of negative stimuli in right DLPFC one could thereby also propose that ketamine abolishes the previously described pattern of increased activation due to emotional content. Our findings of ketamine-induced reduction of right DLPFC reactivity to negative stimuli in healthy subjects are in accordance with recent studies showing that a reduction in signaling via NMDA-receptors after ketamine administration reduced task-related activations and connectivity in the lateral prefrontal cortex (Anticevic et al., 2012; Driesen et al., 2013). However, these studies used non-verbal stimuli in the context of a WM task and, contrary to our findings, reported impaired WM performance. Similarly,
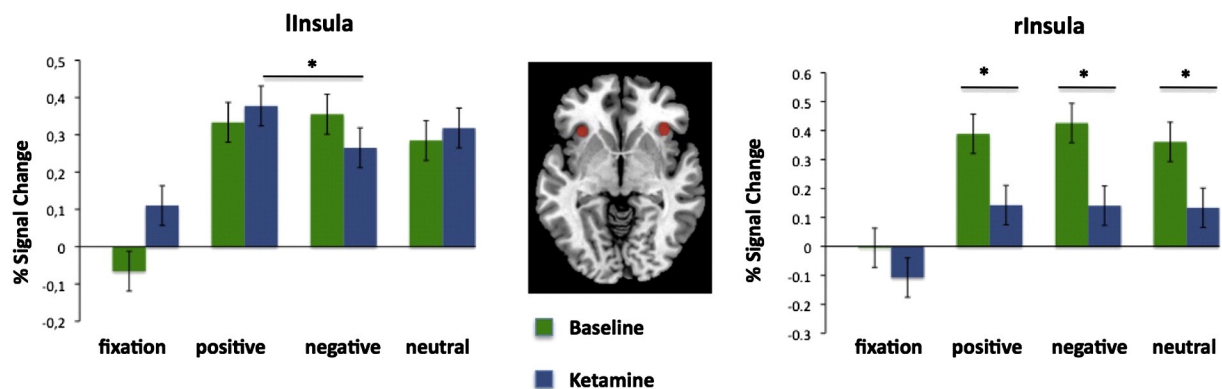

Fig. 3. *Effects of ketamine, emotional content and emotional valence.* Signal changes for fixation cross, positive, negative and neutral words during baseline and ketamine sessions. Abbreviations: lInsula = left insula; rInsula = right insula. Error bars: ±SE. $^{*}p < 0.05$.

studies using verbal WM tasks described that ketamine had no behavioral effect, but induced greater task-associated activation in bilateral DLPFC (Honey et al., 2003, 2004). Another study examined two levels of cognitive load in an fMRI task during ketamine infusion and did not find any significant impairment in task performance relative to placebo, but an interaction of task demand with ketamine was observed in the anterior cingulate, prefrontal, and striatal regions (Fu et al., 2005). This is consistent with a study in which ketamine was associated with increased prefrontal activation when task demands were low, but had little effect on activation when demands were high (Honey et al., 2004). These results were interpreted in terms of ketamine shifting an inverted U-shaped curve denoting the relationship between activity and task demand (Honey et al., 2004). However, unlike in our study, stimuli had no emotional content and therefore might have elicited distinct activation patterns. While failing to reach statistical significance, this assumption is also supported by the finding that for non-emotional, i.e. neutral stimuli, ketamine induced greater activation in left DLPFC and attenuated activity to a much lesser degree in right DLPFC.

Ketamine induced a reduction in BOLD reactivity exclusively to negative stimuli in right DLPFC without impairing behavioral performance, which might reflect that the WM task is less disturbed by negative emotional content. This finding seems particularly relevant in the context of two influential hypotheses in the field of basic and clinical neuroscience. Firstly, the valence hypothesis states that the right prefrontal cortex is dominant in the processing of negative emotions (R. Davidson and Irwin, 1999). Secondly, the imbalance hypothesis of MDD postulates prefrontal asymmetry with relative hyperactivity in the right DLPFC. Correspondingly, fMRI studies during emotional stimulation have also reported hyperactivity of the right DLPFC that is correlated with the severity of depressive symptoms (Grimm et al., 2008; Lawrence et al., 2004). In association with a rapid antidepressant response to ketamine, reduced glucose metabolism in the DLPFC of the right (but not left) hemisphere was found in treatment-resistant MDD patients using positron emission tomography (PET) (Carlson et al., 2013). Reduced right DLPFC metabolism following ketamine treatment in MDD, and reduced DLPFC reactivity to negative stimuli in healthy subjects that we report here might indicate less interference of cognitive processing by negative emotional content and serve as an explanatory model for the amelioration of negative biases in MDD patients. However, changes in neural activity induced by ketamine may differ between depressed and healthy populations. Future studies should therefore use the emotional WM task to investigate MDD patients and thereby shed some more light on the involvement of glutamatergic neurotransmission in cognition–emotion interaction in the brain and particularly in distinct symptoms of MDD such as the negative emotional bias.

In the anterior insula we found both lateralized and valence-specific effects of ketamine with decreased BOLD responses exclusively to negative stimuli in the left insula, while in the right insula, BOLD responses were decreased regardless of emotional content and stimulus valence. The anterior insula has been implicated in the detection of salient stimuli, integration of exteroceptive and interoceptive signals, and the generation and mediation of feeling states as a response to environmental stimuli and affective states (Bartels and Zeki, 2004; Craig, 2009; Critchley et al., 2004; Menon and Uddin, 2010). Stimuli that activate the right anterior insula are generally arousing to the body, whereas the left insula is activated mainly by positive and affiliative emotional feelings (Craig, 2009). Several previous studies described insula dysfunction in MDD (Horn et al., 2010; Kurth et al., 2010; Mayberg, 2003; van Tol et al., 2012; Wiebking et al., 2010) and an antidepressant response to ketamine is associated with decreased metabolism in the right insula (Carlson et al., 2013), which echoes findings of decreased insula activity in MDD subjects following successful treatment with paroxetine (Kennedy et al., 2001). Our finding of decreased right insula activation during ketamine might suggest diminished salience of stimuli. Ketamine has been shown to produce blunting of emotional states and reduced responses to emotional stimuli (Abel et al., 2003).

However, as right insula reactivity was also reduced to neutral stimuli, it seems rather unlikely that this reflects diminished subjective intensity of emotional experience due to reduced salience of solely emotional stimuli. Alternatively, ketamine induces alterations in subjective state with symptoms of disembodiment, experience of unity and vivid imagery (Vollenweider and Kometer, 2010), resulting from a mismatch between interoceptive and exteroceptive information processing that could be reflected in diminished insula reactivity. The reduced left insula reactivity exclusive to negative stimuli might indicate reduced subjective intensity of negative stimuli which in turn promotes positive emotional feelings (Craig, 2009). Notably, the valence-specific reduction of left insula reactivity to negative stimuli during ketamine infusion parallels a previous report of decreased response to negative versus neutral stimuli in the left insular cortex in depressed patients treated with venlafaxine (R. J. Davidson et al., 2003).

There are several limitations to this study. The rather small sample size of this investigation has to be considered when interpreting the results. We only included a 2-back task and did not test the effects of increasing cognitive load. While load is often varied up to 3-back (Neta and Whalen, 2011; Owen et al., 2005), some authors have questioned the validity of results when the ability to successfully perform the task decreases (Callicott et al., 1999). Nevertheless, we cannot exclude the possibility that findings might be confounded due to a ceiling effect. All subjects were aware they were being administered ketamine and of ketamine's effects, which might have influenced their behavior. The choice of an adequate placebo control is an unresolved issue in studies using ketamine. Saline does not provoke similar psychotomimetic effects and is therefore indicative of the experimental condition. However, our data shows that apart from the expected psychotomimetic effect, there was no impact of ketamine on WM performance which makes it rather unlikely that the reported results are due to behavioral ketamine effects. While our study therefore served to establish the proof of concept that pharmacological manipulation of NMDA-receptors with ketamine during an emotional WM task is well suited to better understand cognition–emotion interaction in the brain, future studies might nevertheless consider including a placebo condition as well as investigating MDD patients. Also, it could be argued that changes in neural activity seen during ketamine infusion may be more likely to reflect neurophysiological changes associated with psychotomimetic phenomena, however, our data revealed no association of BOLD reactivity in cognition-related lateral prefrontal regions and emotion-related cortical midline regions with psychotomimetic effects.

To conclude, the current study shows for the first time that effects of ketamine on WM-related brain reactivity depend on emotional content and emotional valence. Ketamine modulates cognition–emotion interaction in the brain by inducing lateralized and valence-specific effects in emotion-related cortical midline regions, WM-related lateral prefrontal regions and insula. In emotion-related cortical midline regions ketamine abolishes enhancement of deactivation normally observed during cognitive effort, while in the right DLPFC and the left insula the previously described pattern of increased activation due to emotional content is abrogated exclusively for negative stimuli. Results therefore show a specific effect of ketamine on cognition–emotion interaction in the brain and indicate that its effect on the amelioration of negative biases in MDD patients might be related to less interference of cognitive processing by negative emotional content. However, these implications remain speculative at this point, since the effects were found in healthy subjects and no placebo control was used.

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