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Modulatory Effects of Ketamine and Lamotrigine on Cognition: Emotion Interaction in the Brain

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Abstract
Introduction: Cognition and emotion are fundamentally integrated in the brain and mutually contribute to behavior. The relation between working memory (WM) and emotion is particularly suited to investigate cognition-emotion interaction since WM is an essential component of many higher cognitive functions. Ketamine affects not only WM but also has a profound impact on emotional processing. Effects of acute ketamine challenge are sensitive to modulation by pretreatment with lamotrigine, which inhibits glutamate release. Accordingly, a combination of these approaches should be particularly suited to investigate cognition-emotion interaction. ***Methods:*** Seventy five healthy subjects were investigated in a double-blind, placebo-controlled, randomized, single-dose, parallel-group study with three treatment conditions. All subjects underwent two scanning sessions (acute/post 24 h). ***Results:*** Compared to placebo, acute ketamine administration induced significant dissociative, psychotomimetic, and cognitive effects, as well as an increase in neural activity during WM for positive stimuli. Inhibition of glutamate release by pretreatment with lamotrigine did not influence ketamine's subjective effects, but significantly attenuated its impact on emotional WM and associated neural activity. There was no effect on these measures 24 h after ketamine administration. ***Conclusion:*** Our results demonstrate differential acute effects of modulated glutamate release and a swift restoration of disturbed neurobehavioral homeostasis in healthy subjects.

Introduction

Historically, cognition and emotion have been viewed as largely separate domains, but their interplay has become a major research interest in both basic and clinical neuroscience [1–3] with converging evidence, suggesting

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that they are fundamentally integrated in the brain and jointly contribute to behavior [4].

Many mental disorders such as major depressive disorder (MDD) or schizophrenia involve deficits in both cognitive and emotional processing [5], thus further highlighting the need to understand mechanisms that underlie cognition-emotion interactions in the brain. The relation between working memory (WM) and emotion seems to be particularly well suited to investigate cognition-emotion interaction, since WM is an essential component of many higher cognitive functions [6]. Daily life frequently requires these cognitive functions to operate in contexts where much of the information being processed has emotional characteristics. However, the impact of emotional information on WM and related neural mechanisms remains poorly understood [7, 8]. Previous quantitative meta-analyses of WM studies regardless of stimulus content [9, 10] reported broadly consistent activation of dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and anterior insula (AI). The DLPFC is implicated in numerous cognitive functions relevant to WM, including holding to-be-remembered information online [11, 12], monitoring and manipulating the to-be-remembered information [13], response selection [14], and implementation of strategies to facilitate memory [15, 16]. Activity in the ACC during WM tasks is often described in relation to increased effort, complexity, or attention [17, 18]. ACC and AI are considered core regions of the salience network [19] and crucial for the integration of emotional and cognitive information [8, 20, 21]. WM studies using stimuli with emotional content reported conflicting behavioral results, with either no impact [22–24] or impaired [25, 26] as well as improved [27, 28] performance for emotional compared to neutral material. However, a recent meta-analysis showed that despite limited evidence for a behavioral impact, at the neural level WM for emotional relative to neutral information is associated with differential recruitment of the salience network and the frontal control network [24], thereby highlighting the importance of combining behavioral and neuroimaging research.

Preclinical studies indicate that N-methyl-D-aspartate glutamate receptors (NMDA-Rs) are critically involved in WM [29–31]. 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, a behavioral effect of ketamine was either not detectable at all or only at higher doses. At the same time, ketamine induced greater task-associated activation in bilateral DLPFC and ACC [32, 33]. During spatial WM tasks, an impaired performance and reduced task-related activations and connectivity in the lateral prefrontal cortex have been described [34, 35]. Importantly, NMDA-R antagonism is relevant not only to cognitive but also to emotional processing as demonstrated by the rapid antidepressant effect of ketamine in otherwise treatment-resistant MDD patients [36, 37]. Indicators for disturbed cognition-emotion interaction in patients are impaired WM and negative processing bias [38, 39], which have been related to aberrant functioning of DLPFC, ACC, and insula [40–42]. Ameliorating symptoms of depression with subanesthetic ketamine has been associated with improved cognitive performance [43, 44]. The specific effect on cognitive function in MDD patients might be related to enhanced prefrontal control after ketamine [40] mediated by rapid synaptogenesis [45]. To the best of our knowledge, only 2 studies investigated effects of acute ketamine administration on cognition-emotion interaction in the brain. Our own previous results show that compared to a baseline condition, ketamine had no impact on verbal WM performance regardless of stimulus content but reduced BOLD reactivity in insula and DLPFC [46]. Becker et al. [47] applied a placebo-controlled crossover design to investigate encoding of neutral, positive, and negative pictures and showed that ketamine decreased memory performance irrespective of emotion and suppressed parahippocampal and medial prefrontal activity. On the other hand, there was a selective increase of amygdala and orbitofrontal activity during successful encoding of negative stimuli.

Direct modulatory approaches might provide complementary insights into ketamine's mechanisms of action and thereby also shed some more light on its effect on cognitive and emotional processing in the brain. Several studies have demonstrated that effects of acute ketamine challenge are sensitive to modulation by pretreatment with lamotrigine, a broad-spectrum anticonvulsant that inhibits voltage-gated ion channels, with downstream effects resulting in inhibition of glutamate release [48]. In a recent systematic review, Veraart et al. [49] reported that until now seven studies were conducted on the effects of lamotrigine prior to ketamine administration. Except one study in MDD patients [50] effects were investigated in healthy subjects [51–56]. Findings are contradictory, with Anand et al. [52] and Deakin et al. [53] reporting that pretreatment with lamotrigine significantly attenuated ketamine-induced psychotomimetic effects and cognitive impairments, while Mathew et al. [50] and Abdallah et al. [51] found no impact of lamotrigine on ketamine's psychotomimetic effects. During acute ketamine admin-

istration, resting-state blood oxygenation level-dependent (BOLD) responses and global brain connectivity were attenuated by lamotrigine pretreatment [51, 53, 54]. The absence of a significant effect of lamotrigine on resting brain perfusion [55, 56] argues against this attenuation as being due to changes in neurovascular responsivity. Rather, it reinforces the interpretation of lamotrigine's attenuation of the ketamine-evoked BOLD signal as being due to reduced glutamate release.

However, until now, no study investigated the effects of lamotrigine pretreatment on the ketamine signal in the brain during any type of task, and even behaviorally, only Anand et al. [52] investigated verbal learning and memory. Furthermore, previous studies investigating the impact of lamotrigine pretreatment were conducted during the acute administration of ketamine and it is not yet known whether the inhibition of glutamate release via lamotrigine has longer term consequences. Along that line, previous studies investigating cognitive and emotional processing as well as cognition-emotion interaction were conducted either during or after ketamine administration, but no study has yet investigated both in the same subjects. Longitudinal assessments of participants would however provide additional insights, given that antidepressant effects of ketamine are most pronounced 24 h after administration, thereby indicating sustained adaptive changes in brain dynamics [57, 58].

Consequently, the aim of the present study was to investigate acute and delayed (24 h) effects of a single dose of ketamine on cognition-emotion interaction in the brain. Healthy subjects performed an emotional WM task during ketamine administration, and effects were compared to a placebo group. To investigate whether effects of ketamine on cognition-emotion interaction are modulated by inhibited glutamate release, a third group received lamotrigine prior to ketamine administration.

Methods

Participants

In a double-blind, placebo-controlled, randomized, single-dose, parallel-group study with three treatment conditions (placebo-placebo [PP], placebo-ketamine [PK], lamotrigine-ketamine [LK]), healthy, right-handed male and female subjects aged 18–45 years underwent the fMRI procedures. Exclusion criteria were a history of or current psychiatric conditions, as determined by the SCID-5-CV at screening, a positive drug screen, alcohol or substance dependence within the last 12 months, previous participation in studies that used the EMOBACK task, prescribed psychotropic medication within 28 days prior to screening and nonprescription medication within 48 h prior to treatment visit. Further exclusion criteria were a history of relevant neurological diseases, migraine headaches, relevant medical condition, MRI exclusion criteria, and pregnancy. All participants gave written informed consent to participate in the study, which was approved by the Local Ethics Committee and registered at ClinicalTrials.gov (NCT04156035). The progress of participant exclusion and inclusion is shown in the flow diagram in online supplementary Figure 1 (see www.karger.com/doi/10.1159/000528315 for all online suppl. material).

Experimental Design and Procedure

After written informed consent, subjects meeting all in-/exclusion criteria were randomly assigned at baseline to one of the three treatment groups in a 1:1:1 ratio. Subjects in the first group were pretreated with placebo and were administered a placebo infusion (PP group). Subjects in the second group were pretreated with placebo and were administered a ketamine infusion (PK group), and subjects in the third group were pretreated with lamotrigine and were administered ketamine (LK group). All subjects underwent two scanning sessions on two consecutive days. Prior to the first scanning session, subjects were pretreated with an oral dose of 300 mg lamotrigine (LK) or matching placebo (PP, PK) 2 h before they entered the scanner. During the first scanning session (acute), subjects were intravenously administered ketamine or placebo (ketamine dosage: 0.12 ± 0.003 mg/kg during the first minute followed by a continuous infusion of approximately 0.31 mg/kg/h). Blood samples were taken at 0:30, 1:00, 1:30, 2:55, and 4 h following oral drug administration to determine the plasma levels of lamotrigine, and at 55 min after commencing ketamine infusion to determine ketamine plasma levels. Before the infusion started, all subjects underwent a short resting-state scan that was repeated after the start of the infusion. Next, subjects performed a picture viewing task (reported elsewhere) followed by the EMOBACK task. The scanning session ended with an ASL sequence (reported elsewhere). Total scanning time was approximately 1 h. To investigate the possible delayed effects of a single dose of ketamine on cognition-emotion interaction in the brain, subjects underwent the same scanning procedure without the drug treatment and without the baseline resting-state scan 24 h later.

Materials

Psychometric Assessments

Psychotomimetic and dissociative effects were assessed after each scanning session (acute and delayed timepoints) using the Dissociation-Tension-Scale (DSS [59]) and 5D Altered States of Consciousness Scale (5D-ASC [60]). The DSS is a brief self-report measure of dissociative symptomology and consists of 22 items, which assess dissociative phenomena on a psychological, somatoform, and global scale. Psychological dissociative symptoms include depersonalization, derealization, or hallucinatory experiences. Somatoform dissociative symptoms include immobility and optical or acoustical perceptual changes.

The 5D-ASC assesses altered states of consciousness with 94 items on 5 main dimensions: oceanic boundlessness (OBN), dread of ego dissolution (DED), visionary restructuralization (VRS), auditory alterations, and vigilance reduction (VIR). Participants use a visual analogue scale to report the extent to which the experiences during the infusion differ from their normal waking state.

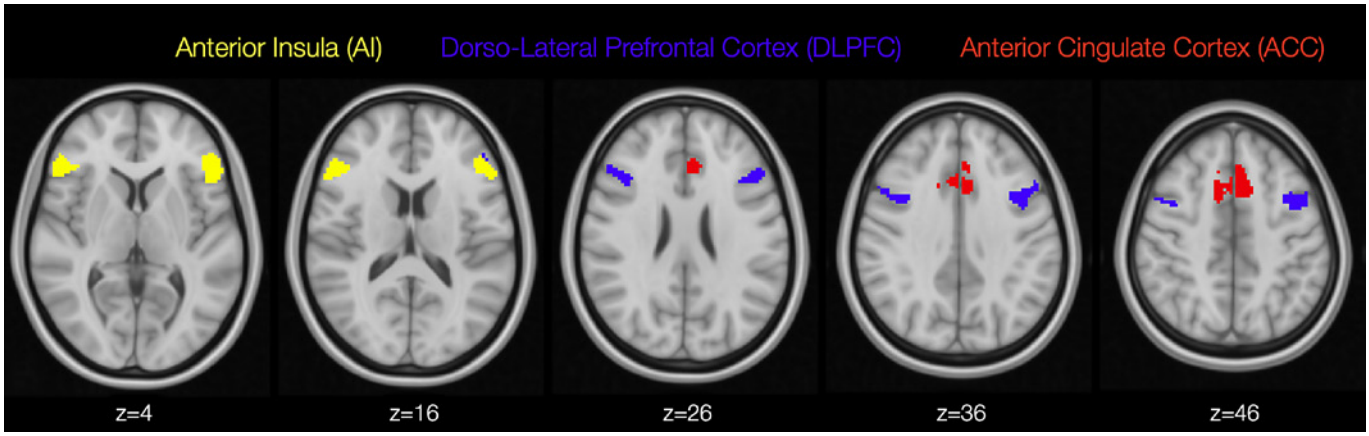

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Fig. 1. ROIs. The three bilateral ROIs used in the data analysis are shown on axial brain slices in the respective plane.

EMOBACK Task

To investigate functional brain activity during cognition-emotion interaction, we applied the EMOBACK task [23, 61], an emotional 2-back task that uses verbal stimuli selected from the Berlin Affective Word List [62]. Subjects were required to monitor a series of words and to respond if the word presented was identical to the one presented two trials previously. The stimuli were categorized as either positive, negative, or neutral and were matched regarding length, imageability, emotional arousal, and frequency of appearance. The stimuli were presented in 15 blocks: five for each valence category (positive, negative, or neutral). Between the blocks, a fixation cross appeared for 10–14 s. Each block contained 15 words presented for 500 ms each with an interstimulus interval of 1500 ms. In total, the task lasted for 12 min and was conducted approximately 20 min after the start of the ketamine infusion. Stimuli were presented using Presentation software (Neurobehavioral Systems Inc., Berkeley, USA). Two different sets of stimuli were matched for the acute and delayed timepoints. The performance during the WM task was calculated as proportion of correct responses and false alarms (accuracy in %, hits-false alarms/targets*100). Furthermore, the reaction time (RT) during the task was assessed. For both measures, an overall score across all conditions was calculated. Additionally, separate scores were calculated for the conditions with positive, negative, and neutral stimuli.

MRI Acquisition and Analysis

Brain images were acquired using a 3 T MRI scanner (PRISMA, Siemens Medical Systems, Erlangen, Germany) with a 64-channel head coil and a T2*- weighted gradient echo-planar imaging sequence (TR = 2 s, TE = 30 ms, flip angle = 80°, voxel size = 3 × 3 × 3 mm, matrix 64 × 64, 36 slices, FOV = 192 × 192 × 143 mm, GRAPPA acceleration factor 2). An anatomical brain image was acquired with a 3D T1-weighted scan (Magnetization Prepared Rapid Acquisition Gradient Echo sequence, TE = 3.03 ms, TR = 2.3 s, 192 slices and FOV = 256 × 256 × 192 mm).

All image preprocessing and first-level analyses were carried out using FEAT (FMRI Expert Analysis Tool) Version 6.0, part of FMRIB's Software Library (FSL, www.fmrib.ox.ac.uk/fsl) (for details see suppl. Methods). Our main analyses focused on the average % BOLD signal change within three prespecified regions of interest (ROIs): bilateral AI, bilateral DLPFC, and bilateral ACC (see Fig. 1). These ROIs were derived from activation maps obtained in a 15-participant prestudy (unpublished data). Activation maps were intersected with substructures of the Harvard-Oxford atlas implemented in FSL to obtain anatomical specificity. These ROIs were used in previous studies [63] on brain function during processing of emotional stimuli.

Three contrasts of interest were defined in the first-level analyses: to investigate WM-related brain activations, a contrast in which all WM conditions were compared to fixation was defined (1. WM > Break). To investigate effects of emotional content, two additional contrasts were defined in which the positive and negative WM conditions were compared to the neutral WM condition (2. Pos > Neu and 3. Neg > Neu).

Statistical Analyses

Univariate ANOVAs with the main factor group (PK, LK, PP) were performed for the psychometric, behavioral, and fMRI data. For reporting, an unadjusted significance level of $\alpha = 0.05$ was assumed. In case of a significant main effect of group, post hoc tests were performed using paired comparisons. For the analysis of ketamine plasma concentration, only the PK and LK groups were compared using an independent *t*-test. Correlation analyses were conducted using Pearson's correlation coefficient. All statistical analyses were conducted using SPSS version 27 (IBM, USA).

Results

Sample

The final sample consisted of 75 male and female participants (age: M = 28.96, SD = 6.58) that were randomly assigned to one of the three treatment conditions in a 1:1:1 ratio: PP (N = 25), PK (N = 25), and placebo-lamotrigine (LK, N = 25).

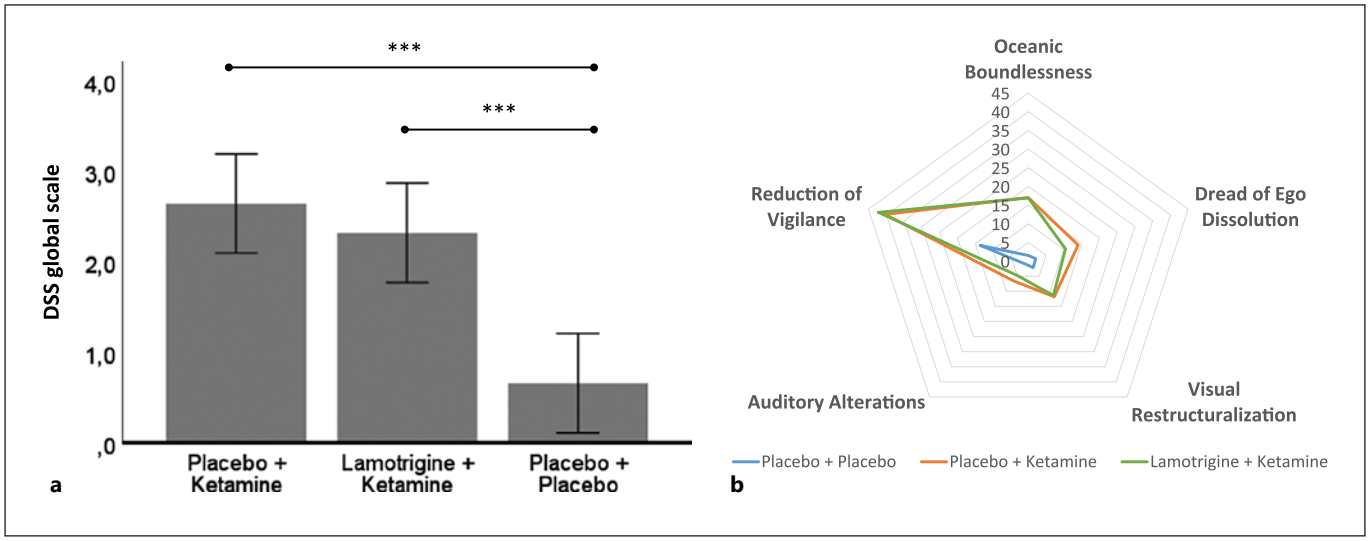

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Fig. 2. Subjective effects in the three treatment groups at the acute timepoint. **a** Dissociative symptoms on the mean DSS global scale: subjects in the PK and LK groups scored significantly higher compared to the PP group. **b** Altered states of consciousness on the five main scales of the 5D-ASC: On all scales, the PK group scored higher compared to the PP group (all $p < 0.05$, see online suppl. Table 1). LK scored higher compared to PP group on the OBN, DED, VRS, and VIR scales (all $p < 0.05$). *** depicts a significance level of $p < 0.001$. Error bars depict a 95% confidence interval. DSS, Dissociation Tension Scale; 5D-ASC, 5D Altered States of Consciousness Scale.

Plasma Concentration

Ketamine plasma concentration (ng/mL) for the PK group was $M = 108.59$, $SD = 27.61$, and for the LK group $M = 94.26$, $SD = 32.45$. Ketamine plasma concentration did not differ significantly between the two groups ($T(48) = 1.68$, $p = 0.099$), i.e., pretreatment with lamotrigine did not significantly attenuate ketamine plasma concentration.

Questionnaire Data

Dissociative Symptoms

At the acute timepoint, a significant difference between groups was observed for the DSS global scale ($F(2, 72) = 15.04$, $p < 0.001$), psychological scale ($F(2, 72) = 11.01$, $p < 0.001$), and somatoform scale ($F(2, 72) = 16.95$, $p < 0.001$). Paired comparisons showed that the PP group had lower scores on all three dimensions compared to the PK and LK groups (all $p < 0.001$). No differences were observed between the PK and LK groups (see Fig. 2a). Furthermore, no significant group differences were observed at the delayed timepoint. Complete descriptive and inference statistics are shown in online supplementary Table 1.

Altered States of Consciousness

At the acute timepoint, a significant difference between groups was observed for all five main scales: OBN ($F(2, 72) = 11.66$, $p < 0.001$), DED ($F(2, 72) = 8.78$, $p < 0.001$), VRS ($F(2, 72) = 7.50$, $p = 0.001$), auditory alterations ($F(2, 72) = 3.50$, $p = 0.035$), and VIR ($F(2, 72) = 15.47$, $p < 0.001$). On all scales, the PK group scored higher compared to the PP group (all $p < 0.05$, see online Suppl. Table 1). LK scored higher compared to PP group on the OBN, DED, VRS, and VIR scales (all $p < 0.05$). No significant differences between PK and LK groups were observed for the five main scales (see Fig. 2b). Also, there were no significant differences between groups at the delayed timepoint.

EMOBACK Performance

For the analysis of the behavioral EMOBACK data, one subject had to be excluded at the acute timepoint because the task instructions were not followed correctly (PK group). One additional subject had to be excluded at the delayed timepoint because the response button did not work (PP group). Analysis of the behavioral EMOBACK data was thus conducted on a final sample of $N = 74$ for the acute timepoint and $N = 73$ for the delayed timepoint. At the acute timepoint, a significant group dif-

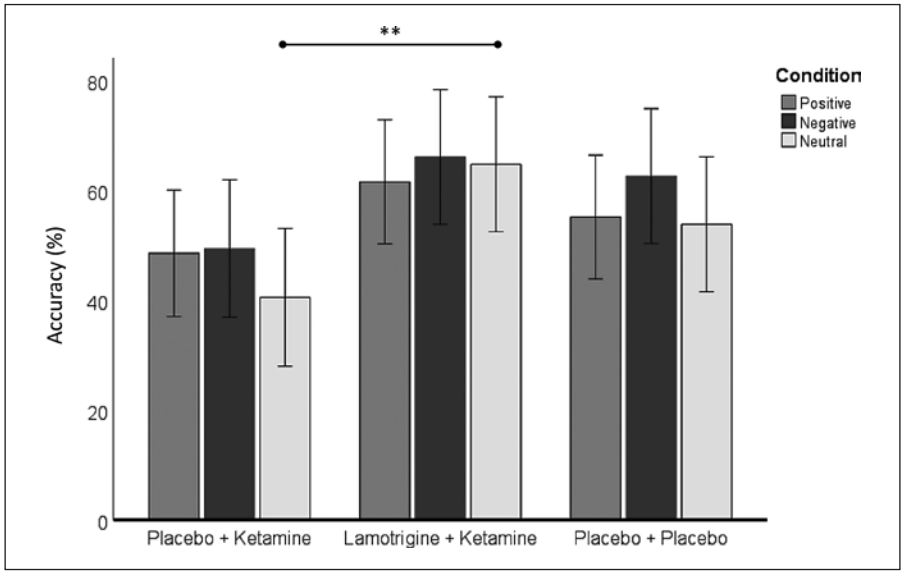

Fig. 3. EMOBACK performance in the three treatment groups at the acute timepoint. Colored bars depict performance (mean accuracy in %) in the different EMOBACK conditions with positive, negative, and neutral stimuli. ** depicts a significance level of $p < 0.01$. Error bars depict a 95% confidence interval.

ference in EMOBACK accuracy was observed for the neutral condition ($F(2, 71) = 3.79$, $p = 0.027$). Post hoc comparisons showed that accuracy was higher in the LK group compared to PK ($M_{PK} = 40.55$, $SD_{PK} = 30.07$, $M_{LK} = 64.80$, $SD_{LK} = 22.89$, $p = 0.008$). No significant group difference was observed for the positive and negative conditions. A marginally significant difference between groups was observed for the overall accuracy score ($F(2, 71) = 2.69$, $p = 0.075$). Post hoc comparisons showed that accuracy was higher in the LK group compared to PK group ($M_{PK} = 46.20$, $SD_{PK} = 26.86$, $M_{LK} = 64.18$, $SD_{LK} = 19.26$, $p = 0.024$). No significant group differences were observed for the RT at the acute timepoint (see online suppl. Table 1). At the delayed timepoint, there were no group differences in accuracy and RT. Accuracy scores at the acute timepoint are shown in Figure 3.

fMRI Results

For the analysis of the fMRI data, one subject had to be excluded because the WM task was not performed as intended. Three additional subjects had to be excluded because the motion limits during scanning were exceeded. Thus, the final sample for the fMRI data analysis was $N = 71$. At the acute timepoint, no significant group differences were observed for the first contrast (WM > break) and the third contrast (Neg > Neu, see online suppl. Table 1). However, the second contrast (Pos > Neu) showed a significant difference between groups for all three investigated bilateral ROIs. Group differences were observed in the ACC ($F(2, 68) = 3.54$, $p = 0.034$), AI ($F(2, 68) = 4.06$, $p = 0.022$), and DLPFC ($F(2, 68) = 3.28$, $p = 0.044$).

For the ACC, paired comparisons showed that PK group had stronger activations compared to LK group ($M_{PK} = 0.21$, $SD_{PK} = 0.26$, $M_{LK} = 0.10$, $SD_{LK} = 0.10$, $p = 0.032$) and compared to PP ($M_{PP} = 0.09$, $SD_{PP} = 0.08$, $p = 0.018$). For the AI, paired comparisons showed that PK group had stronger activations compared to LK ($M_{PK} = 0.22$, $SD_{PK} = 0.16$, $M_{LK} = 0.13$, $SD_{LK} = 0.07$, $p = 0.008$) and PP groups ($M_{PP} = 0.15$, $SD_{PP} = 0.10$, $p = 0.041$). Paired comparisons for the DLPFC showed that PK group had stronger activations compared to LK ($M_{PK} = 0.21$, $SD_{PK} = 0.20$, $M_{LK} = 0.12$, $SD_{LK} = 0.12$, $p = 0.028$) and PP groups ($M_{PP} = 0.12$, $SD_{PP} = 0.09$, $p = 0.031$).

Exploratively, the group analysis for the Pos > Neu contrast was repeated with unilateral ROIs. Effects of group were found for the left ($F(2, 68) = 3.29$, $p = 0.043$) and right ($F(2, 68) = 3.57$, $p = 0.034$) ACC. Paired comparisons for the left ACC showed a stronger activation for the PK group compared to LK ($M_{PK} = 0.19$, $SD_{PK} = 0.22$, $M_{LK} = 0.10$, $SD_{LK} = 0.10$, $p = 0.040$) and PP groups ($M_{PP} = 0.09$, $SD_{PP} = 0.10$, $p = 0.022$), and paired comparisons for the right ACC showed a stronger activation for PK group compared to LK group ($M_{PK} = 0.23$, $SD_{PK} = 0.30$, $M_{LK} = 0.10$, $SD_{LK} = 0.11$, $p = 0.030$) and PP ($M_{PP} = 0.09$, $SD_{PP} = 0.07$, $p = 0.018$). Effects of group were also observed for the left ($F(2, 68) = 3.16$, $p = 0.049$) and right ($F(2, 68) = 3.98$, $p = 0.023$) AI. Paired comparisons for the left AI showed a stronger activation in the PK group compared to LK group ($M_{PK} = 0.20$, $SD_{PK} = 0.16$, $M_{LK} = 0.12$, $SD_{LK} = 0.08$, $p = 0.020$). For the right AI, PK group showed a stronger activation compared to LK ($M_{PK} = 0.23$, $SD_{PK} = 0.17$, $M_{LK} = 0.13$, $SD_{LK} = 0.08$, $p = 0.008$) and PP groups

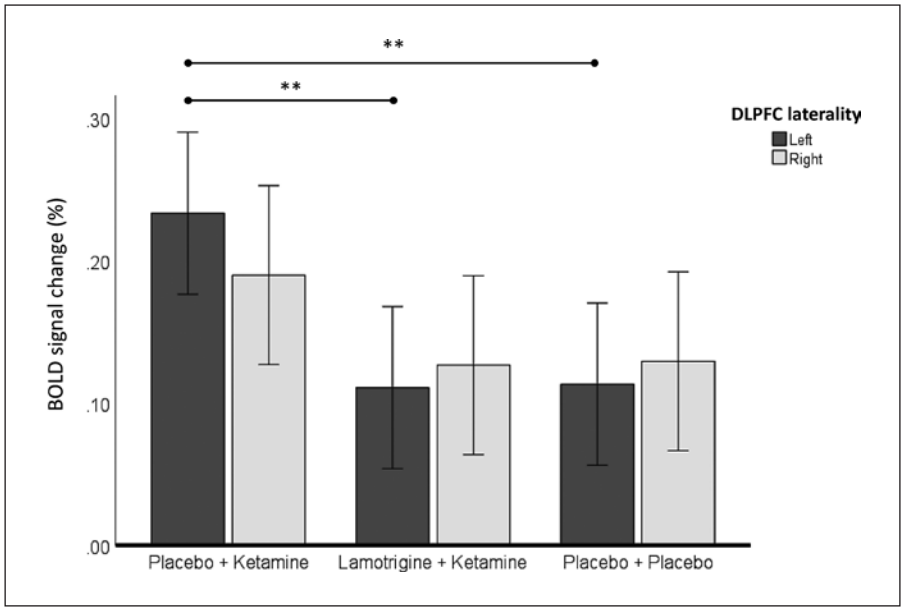

Fig. 4. BOLD signal change in the DLPFC for positive versus neutral stimuli during the EMOBACK task in the three treatment groups at the acute timepoint. Bars depict mean BOLD signal changes (in %) in the left and right DLPFC, respectively. ** depicts a significance level of $p < 0.01$. Error bars depict a 95% confidence interval. DLPFC, dorsolateral prefrontal cortex.

($M_{PP} = 0.16$, $SD_{PP} = 0.12$, $p = 0.049$). For the left DLPFC, a highly significant effect of group was observed ($F(2, 68) = 5.51$, $p = 0.006$), but not for the right DLPFC ($F(2, 68) = 1.29$, $p = 0.282$). Paired comparisons for the left DLPFC showed a stronger activation in the PK group compared to LK ($M_{PK} = 0.23$, $SD_{PK} = 0.19$, $M_{LK} = 0.11$, $SD_{LK} = 0.13$, $p = 0.005$) and PP groups ($M_{PP} = 0.11$, $SD_{PP} = 0.10$, $p = 0.006$). No group differences were observed for the delayed timepoint in the three analyzed ROIs. None of the calculated paired comparisons showed a significant difference between LK and PP groups. The results for the Pos > Neu contrasts for the DLPFC are shown in Figure 4.

Correlation Analyses

Explorative correlation analyses were performed in the PK group to investigate potential relationships between plasma concentration, subjective experience, EMOBACK performance, and brain activation during the ketamine infusion. Ketamine plasma concentration was neither associated with psychotomimetic effects nor with WM performance. Also, there was no association between dissociative effects and WM performance, while the subjective experience of reduced vigilance was negatively linked to overall WM performance ($r = -0.444$, $p = 0.030$), as well as to accuracy in the positive ($r = -0.492$, $p = 0.015$) and neutral ($r = -0.425$, $p = 0.039$) conditions. There was no association between subjective experience and WM-related neural activity. Finally, overall WM accuracy was positively correlated with ACC ($r = 0.460$, $p = 0.027$), AI ($r = 0.586$, $p = 0.003$), and DLPFC ($r = 0.464$, $p = 0.026$) activation. Accuracy in the positive condition showed a positive correlation with ACC ($r = 0.449$, $p = 0.032$), AI ($r = 0.537$, $p = 0.008$), and DLPFC ($r = 0.433$, $p = 0.039$) activation. Accuracy in the negative condition showed a positive correlation with ACC ($r = 0.472$, $p = 0.023$), AI ($r = 0.524$, $p = 0.010$), and DLPFC ($r = 0.513$, $p = 0.012$) activation. Accuracy in the neutral condition showed a positive correlation with AI ($r = 0.497$, $p = 0.016$) activation.

Discussion

To our knowledge, this is the first study to investigate not only acute and delayed effects of a single dose of ketamine on cognition-emotion interaction in the brain but also consequences of modulated glutamate release via lamotrigine pretreatment. Our findings demonstrate differential subjective, cognitive, and neural acute effects, while there was no impact on any of these measures 24 h after ketamine administration. Compared to placebo, acute ketamine administration induced significant dissociative, psychotomimetic, and cognitive effects as well as an increase in neural activity during a WM task probing cognition-emotion interaction. Inhibition of glutamate release by pretreatment with lamotrigine did not influence ketamine's subjective effects, but significantly attenuated its impact on emotional WM and associated neural activity.

Pretreatment with lamotrigine failed to attenuate psychotomimetic and dissociative effects of ketamine, which is consistent with prior reports by Mathew et al. [50] and Abdallah et al. [51] and indicates that the subjective effects of ketamine are not mediated by enhanced glutamate release. Nevertheless, one might also speculate that larger doses of ketamine used in some previous studies [52, 53] may have allowed to detect modulating effects of lamotrigine on the ketamine-induced psychotomimetic symptoms. Also, pretreatment with lamotrigine did not significantly attenuate ketamine plasma concentration, and consistent with prior studies, there were correlations of ketamine plasma levels neither with psychotomimetic symptoms [53, 64] nor with WM performance.

There was a profound effect of lamotrigine pretreatment on ketamine-induced impairment of WM performance. The strongest impact of lamotrigine pretreatment on WM accuracy was observed for neutral stimuli. Accordingly, detrimental effects of ketamine on accuracy were most pronounced for neutral stimuli, while emotional content seemed to boost performance, even though differences between emotional and neutral stimuli did not reach the level of statistical significance. Prior reports on effects of ketamine on WM described no impact for verbal WM tasks [33, 46], but impaired spatial WM performance [34, 35]. Since these studies did not probe for effects of glutamate modulation and only compared WM during ketamine administration to either a placebo or a baseline condition, the impact of ketamine on WM performance might only have been detectable at higher doses in verbal tasks [32] or during more complex spatial tasks [34, 35]. One might speculate that our direct modulatory approach using lamotrigine allowed us to detect subtle effects of ketamine on behavioral accuracy even at a rather low dose and during a comparatively easy verbal WM task. This idea is supported by the fact that there were no significant differences in WM accuracy between the ketamine and placebo group, which is consistent with our previous findings [46]. While prior work clearly established that NMDA-R antagonism is relevant to not only WM [32–35] but also to emotional processing as demonstrated by the rapid antidepressant effect of ketamine in otherwise treatment-resistant MDD patients [36, 37], its role in cognition-emotion interaction remains less clear. Recent animal work emphasized an involvement of NMDA-R-dependent signaling in prefrontal cortex during emotion-cognition interaction [65, 66]), while a reduction of MDD symptom severity with subanesthetic ketamine has been associated with improved cognitive performance [43, 44]. Lamotrigine pretreatment enabled us to ascertain that effects of ketamine on WM performance were mainly driven by neutral stimuli. While there is evidence that processing of emotional stimuli may interfere with cognitive processing, because emotional content draws more attention [8], it might also enhance cognitive performance particularly under demanding conditions as might be posed by the ketamine administration [67]. Emotional stimuli are proposed to have stronger perceptual representations [68], which might lead to prioritized attentional processing in the salience network and in frontal control regions [19, 69]. Preferential allocation of perceptual and executive processing resources to task-relevant emotional stimuli might thereby improve behavioral performance. In the case of neutral stimuli, failure to compensate for disrupted processing by allocating additional processing resources due to stimulus content consequently exposed ketamine-induced impairments. Inhibition of glutamate release by pretreatment with lamotrigine significantly attenuated ketamine's impact on WM performance for neutral stimuli, so that it was comparable to that of the placebo condition. Our findings thereby strongly indicate that effects of ketamine on WM performance are mediated by enhanced glutamate release. It is unlikely that WM impairments in the ketamine group are due to rather unspecific ketamine effects on attention, as reaction times did not differ between groups. This being said, our exploratory analysis in the ketamine group showed that the subjective experience of reduced vigilance was negatively linked to WM accuracy. This association was also observed regarding WM accuracy for positive stimuli, which was not impaired compared to the lamotrigine and placebo groups, though, thereby also arguing against a straightforward correspondence between ketamine's effect on (subjective) vigilance and WM performance.

The here observed neural acute effects of ketamine allowed for new insights into cognition-emotion interaction. Based on previous quantitative meta-analyses of studies of n-back task variants reporting DLPFC, ACC, and AI as key regions with broadly consistent activation [9, 10], we here focused our analysis regarding ketamine's effect on cognition-emotion interaction in the brain on these areas. The key role of these regions for cognition-emotion interaction is further emphasized by a recent meta-analysis, showing that WM for emotional relative to neutral information is associated with their differential recruitment [24]. Lastly, aberrant functioning of these areas in MDD patients is associated with indicators for disturbed cognition-emotion interaction such as impaired WM and negative processing bias [38, 39, 41, 42, 70]. Our

results show that if the content of stimuli is not taken into account, there was no effect of ketamine on WM-evoked BOLD responses in these regions. However, contrasting WM for positive and neutral stimuli showed increased BOLD responses to ketamine compared to placebo in DLPFC, ACC, and AI. Early animal studies demonstrated that subanesthetic ketamine administration increased the rate of glucose utilization in frontal and cingulate regions [71]. Consistent with these findings, studies in healthy volunteers have reported increases in cerebral glucose metabolism and cerebral blood perfusion in similar frontal, cingulate, and insula areas [72–74], while prior fMRI studies reported significant effects of ketamine on resting state activity in ACC and DLPFC [53, 75, 76], thereby suggesting that ketamine increases activation of control regions within the brain. However, these previous results did not offer insights as to whether increased activation after ketamine in these regions reflects an impairment or an enhancement of function due to either diminished or augmented glutamatergic signaling [77].

The use of an emotional WM task and the administration of lamotrigine enabled us to disentangle this question. Lamotrigine attenuated the BOLD signal increase elicited by ketamine infusion, which is in accordance with prior reports investigating BOLD responses at rest [51, 53, 54]. Since it has previously been shown that lamotrigine has no significant effect on resting brain perfusion [55, 56], it seems unlikely that the attenuation of BOLD responses can be explained by an altered neurovascular responsivity to ketamine. Our findings rather reinforce the notion that the ketamine-induced change in BOLD signal is due to an increase in glutamate release, given that lamotrigine inhibits the release of glutamate. Lamotrigine pretreatment thereby antagonizes most of the BOLD signal responses to ketamine [53, 54]. Increased DLPFC and ACC activity in positive compared to neutral stimuli might accordingly reflect the above-mentioned increased allocation of cognitive processing resources to task-relevant emotional stimuli, which enhances performance and hence compensates for ketamine-induced disruption. This idea is also supported by the association between increased activation and improved WM accuracy for emotional, but not for neutral stimuli in the PK group. Pretreatment with lamotrigine prevents the disruption of DLPFC/ACC activity and accordingly of WM performance; therefore, a compensation of WM deficits via increased neural activity is not required and both activity and WM performance approximate that of the placebo group. Increased ketamine-induced DLPFC and ACC activation has been reported by previous studies using verbal WM tasks [32, 33, 46]. Activity in the ACC during WM tasks is often described in relation to increased effort, complexity, or attention [17, 18]. Simmons et al. [78] reported strong ACC activation when processing ambiguous emotional stimuli, which might imply that demanding cognitive and emotional processing recruits this area. Along that line, Lee et al. [79] proposed that the antidepressant effects of ketamine administration are mediated by targeting neural circuits that subserve cognitive processing relevant to executive function and cognitive emotional processing. Effects of ketamine on frontal brain functions have also been linked to its psychotomimetic effects [34, 53]. However, there was no association between subjective experience and WM-related ACC and DLPFC activity.

Our finding of increased AI activation during ketamine might reflect increased salience of emotional stimuli. AI has strong functional connections to the ACC, with both structures representing core regions of the salience network [19], which is crucial for the integration of emotional and cognitive information [8, 20, 21]. An essential function of the salience network and the AI, in particular, is to identify salient stimuli and to then initiate further attentional, WM, and higher order cognitive processes [21]. High cognitive demand has been shown to activate AI and ACC [80, 81] and AI typically also activates along with DLPFC during WM [82]. Preferential processing of emotional stimuli in the salience network [19, 69] has been related to improved WM performance [28, 83]. Consistently, our results show an association between WM accuracy for both negative and positive stimuli with BOLD responses in ACC and AI. However, we also found that accuracy in the neutral condition was associated with AI activation. One might therefore argue that ketamine increases salience for both emotional and neutral stimuli. While ketamine-induced impairments on WM accuracy were most pronounced for neutral stimuli, increased salience attribution and associated AI activity might partially compensate for these disruptive effects and lead to improved WM performance. Alternatively, ketamine induces alterations in a subjective state resulting from a mismatch between interoceptive and exteroceptive information processing that could be reflected in enhanced AI reactivity [84]. However, there was no association between subjective experience and AI activity. As for ACC and DLPFC, lamotrigine attenuated the ketamine-induced BOLD signal increase in AI.

Furthermore, there were some lateralization effects with stronger BOLD responses in positive compared to neutral stimuli in the ketamine compared to the placebo

condition and an attenuation of BOLD responses by lamotrigine pretreatment in left DLPFC and right AI. Our findings regarding DLPFC lateralization might be considered in the context of two influential hypotheses in the field of basic and clinical neuroscience. First, the valence hypothesis states that the left prefrontal cortex is dominant in the processing of positive emotions [85]. Second, the imbalance hypothesis of MDD postulates prefrontal asymmetry with relative hypoactivity in the left DLPFC. Correspondingly, fMRI studies during emotional stimulation have also reported hypoactivity of the left DLPFC that is correlated with the severity of depressive symptoms [86, 87]. Increased left DLPFC reactivity to positive stimuli might indicate an enhancement of cognitive processing by emotional content. This idea is also supported by the association between WM accuracy for emotional stimuli with BOLD responses in left DLPFC and may serve as an explanatory model for the amelioration of negative biases in MDD patients. Regarding AI, it has been proposed that stimuli that activate the right AI are generally arousing to the body, whereas the left AI is activated mainly by positive emotional feelings [20].

To the best of our knowledge, this is the first study investigating acute and delayed effect of both ketamine administration and lamotrigine pretreatment in the same subjects. It has been hypothesized that ketamine might induce sustained adaptive changes in brain dynamics, given that its antidepressant effects are most pronounced 24 h after administration [57, 58]. However, our results show that there were no subjective, cognitive, and neural effects of ketamine 24 h after its administration, thereby arguing against a longer-term impact in healthy subjects. Also, the inhibition of glutamate release via lamotrigine had no sustained consequences on any of the obtained measures. While it remains to be seen whether the hypothesized sustained changes might occur in MDD patients, our data indicate a swift restoration of disturbed neurobehavioral homeostasis after pharmacological modulation of glutamate-responsive cerebral circuits in healthy subjects.

There are several limitations to this study. 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 [9, 88], some authors have questioned the validity of results when the ability to successfully perform the task decreases [89]. Even though we cannot exclude the possibility that findings might be confounded due to a ceiling effect, we previously showed that an emotional 2-back task is well suited both to probe cognition-emotion interaction and to demonstrate effects of acute ketamine administration [23, 46]. Also, previous studies described strongest effects of ketamine soon after beginning of the infusion [53, 76], while here imaging occurred approximately after 25 min of continuing ketamine infusion. This, however, reflects the steady state of the brain well after the intense immediate action of ketamine and our data clearly demonstrate profound effects of ketamine on subjective, cognitive, and neural measures. While 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, our data revealed no association of BOLD reactivity and WM performance with psychotomimetic effects. Because of the relatively small sample size in the treatment groups, we did not apply statistical correction for multiple testing across brain regions. Thus, results should be interpreted with appropriate caution.

To conclude, we here provide first evidence of differential consequences of modulated glutamate release. The acute effects of ketamine on emotional WM and associated neural activity were profoundly attenuated by an inhibition of glutamate release via pretreatment with lamotrigine, which however did not impact the subjective experience. There were no sustained effects of the pharmacological modulation of glutamate signaling with both ketamine and lamotrigine, which indicates a swift restoration of disturbed neurobehavioral homeostasis in healthy subjects.

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Statement of Ethics

All participants gave written informed consent to participate in the study, which was approved by the Independent Ethics Committee, Landesamt für Gesundheit und Soziales, and the Federal Institute for Drugs and Medical Devices (BfArM; 4043918). The study is registered at ClinicalTrials.gov (NCT04156035). This research was conducted in accordance with the declaration of Helsinki.

Conflict of Interest Statement

Simone Grimm has served as a consultant to and received research support from Boehringer Ingelheim Pharma. Christian Beckmann and Maarten Mennes are employees of SBGneuro contracted to perform the blinded analysis. Andreas Wunder is an

employee of Boehringer Ingelheim International GmbH. Christian Keicher and Rita Hertrampf are employees of Charité Research Organisation. The authors declare no conflict of interest.

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Author Contributions

All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted. Matti Gärtner, Simone Grimm, Anne Weigand, Andreas Wunder, Rita Hertrampf, and Christian Keicher were involved in the conceptualization/design of the study. Matti Gärtner, Simone Grimm, Andreas Wunder, David Weigner, Marvin Meiering, and Luisa Carstens were involved in the interpretation of the study data. Matti Gärtner, Simone Grimm, Anne Weigand, Christian Beckmann, Maarten Mennes, Rita Hertrampf, Christian Keicher, David Weigner, Marvin Meiering, and Luisa Carstens were involved in the acquisition/analysis of the study data.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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