ORIGINAL INVESTIGATION

The NMDA antagonist ketamine and the 5-HT agonist psilocybin produce dissociable effects on structural encoding of emotional face expressions

André Schmidt · Michael Kometer · Rosilla Bachmann · Erich Seifritz · Franz Vollenweider

Abstract

Rationale Both glutamate and serotonin (5-HT) play a key role in the pathophysiology of emotional biases. Recent studies indicate that the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine and the 5-HT receptor agonist psilocybin are implicated in emotion processing. However, as yet, no study has systematically compared their contribution to emotional biases.

Objectives This study used event-related potentials (ERPs) and signal detection theory to compare the effects of the NMDA (via S-ketamine) and 5-HT (via psilocybin) receptor system on non-conscious or conscious emotional face processing biases.

Methods S-ketamine or psilocybin was administered to two groups of healthy subjects in a double-blind within-subject placebo-controlled design. We behaviorally assessed objective thresholds for non-conscious discrimination in all drug conditions. Electrophysiological responses to fearful, happy, and neutral faces were subsequently recorded with the face-specific P100 and N170 ERP.

Results Both S-ketamine and psilocybin impaired the encoding of fearful faces as expressed by a reduced N170 over parieto-occipital brain regions. In contrast, while S-ketamine also impaired the encoding of happy facial expressions, psilocybin had no effect on the N170 in response to happy faces.

Conclusion This study demonstrates that the NMDA and 5-HT receptor systems differentially contribute to the structural encoding of emotional face expressions as expressed by the N170. These findings suggest that the assessment of early visual evoked responses might allow detecting pharmacologically induced changes in emotional processing biases and thus provides a framework to study the pathophysiology of dysfunctional emotional biases.

Keywords Glutamate · Serotonin · Ketamine · Psilocybin · Emotional processing biases · Event-related potential · Visual awareness · Non-conscious · Conscious

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Introduction

Emotional processing including the recognition of other people's feelings from their facial expression is fundamental to social interaction and behavior. The importance of face recognition in the human social functioning is shown by the fact that emotional faces increase neuronal activity relative to neutral faces in specific brain areas. For example, increased brain responses to emotional faces have been observed in visual face-selective areas of the brain, even when emotional faces were masked to prevent visual awareness (Pegna et al. 2008; Smith 2011). Thus, modulation of face-specific responses in the visual cortex by emotional expressions might correspond to a fundamental regulatory role of basic emotional signals associated with social appraisal and cognition (Schultz et al. 2003; Singer et al. 2004).

Emotional face processing can be modulated by serotonin (5-hydroxytryptamine, 5-HT). For example, acute administration of the selective serotonin reuptake inhibitor (SSRI) citalopram facilitated recognition of fear and happy facial expressions in the citalopram treated group relative to

the placebo group (Bhagwagar et al. 2004; Browning et al. 2007; Harmer et al. 2003). In a later study, repeated administration of citalopram in healthy subjects increased the relative processing of positive to negative emotional faces in a manner directly opposite to the negative biases previously described in depression (Harmer et al. 2004). Both findings suggest important neuropsychological evidence of a possible mechanism of action of antidepressant drugs (Nathan et al. 2003). The findings are consistent with other studies examining the neurophysiological mechanisms underlying antidepressant effects on emotional processing. In these studies, acute citalopram administration was shown to inhibit visual evoked electrophysiological responses to unpleasant stimuli, while it facilitates visual responses to pleasant stimuli (Kemp et al. 2003, 2004; Nathan et al. 2003). These studies suggest that this capacity to shift emotional biases—increasing the response to positive and decreasing the response to negative stimuli—seems not only to be characteristic for the action of SSRI on emotional processing but seems also to be highly relevant for the treatment of emotional biases found in depression (Harmer 2008).

In addition, emotional face processing can also be affected by glutamatergic manipulation. Specifically, a functional imaging study in healthy subjects showed that the visual activity in response to fearful faces is abolished under the influence of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (Abel et al. 2003). Taken together, these findings suggest that acute manipulations of the serotonergic and glutamatergic systems by psilocybin and ketamine may change emotional processing biases as indexed by the assessment of visual evoked responses to emotional expressions.

Recent studies used event-related potential (ERP) recording to investigate the time course of non-conscious and conscious emotional face processing (Pegna et al. 2011; Smith 2011). Studies of ERPs generated by faces often focus on key components such as the P100 and the face-sensitive N170. The P100 is an early positive occipital potential, peaking at around 80–120 ms post-stimulus, and reflects rapid extraction of information related to emotion or salience that occurs before more fine-grained perceptual analyses are completed (Vuilleumier and Pourtois 2007). Modulation of the P100 has been shown with fearful (Fichtenholtz et al. 2009; Pourtois and Vuilleumier 2006), angry (Santesso et al. 2008) and positive expressions (Batty and Taylor 2003; Brosch et al. 2008). The N170 is a negative occipitotemporal potential at approximately 170 ms post-stimulus and is associated with structural encoding of facial configurations (Itier and Taylor 2004; Rossion and Jacques 2008). The view that the N170 ERP is not modulated by the emotional content of faces (Ashley et al. 2004; Eimer and Holmes 2002; Krolak-Salmon et al. 2001) has been challenged by other findings (Batty and Taylor 2003; Blau et al. 2007; Jaworska et al. 2010;

Krombholz et al. 2007; Schyns et al. 2007; Sprengelmeyer and Jentzsch 2006; Stekelenburg and de Gelder 2004), even when faces are non-consciously processed (Pegna et al. 2008; Smith 2011). Thus, the N170 reflects not only face sensitivity but also emotion sensitivity during conscious as well as non-conscious face processing. Furthermore, it has been shown that the N170 amplitude correlates with the severity of depressive symptoms (Noll et al. 2012), while both the P100 and N170 amplitudes are significantly differed between healthy volunteers and subjects with bipolar disorder (Degabriele et al. 2011; Sokhadze et al. 2011). These studies together demonstrate the potential of these ERPs to study pharmacological mechanisms underlying emotional biases and their pathophysiology.

In this study, we assessed these ERPs to compare the effects of the glutamate NMDA receptor antagonist ketamine and the 5-HT receptor agonist psilocybin on visual processing stages during emotional face processing. Notably, both ketamine and psilocybin are suggested to modulate neuronal activity in circuits implicated in emotion regulation and to have implications for the treatment of affective disorders. While it has repeatedly been pointed out that acute ketamine administration ameliorates depressive symptoms in treatment-resistant depression within a few hours persisting for several days (Diazgranados et al. 2010; Zarate et al. 2006), a gradual reduction in trait anxiety at 1 and 3 months, as well as in depressive symptoms at 6 months, was observed after a single dose of psilocybin in terminal cancer and anxiety patients (Grob et al. 2011). Based on these findings, in this paper we hypothesized that manipulations of both the NMDA and 5-HT receptor system using ketamine and psilocybin may inhibit negative face processing and facilitate the processing of positive faces as expressed by modulations of the P100 and N170 ERP. Given that visual responses are modulated by face visibility (Pessoa et al. 2006), we further predicted that both drug effects on the visual ERPs might vary between non-conscious and conscious face processing. Thus, to test our hypothesis, we examined on the one hand whether psilocybin and ketamine affect visual ERP responses to emotional faces in a valence specific manner and on the other hand whether these drug effects depend on visual awareness.

Method

Participants

Healthy subjects were recruited through advertisement from the local universities and were then separated into two groups (S-ketamine group: $N=21$ [male, 12], mean age=26 ± 5.39 years; psilocybin group: $N=21$ [male, 13], mean age=23 ± 2.22 years, all were students). Subjects

were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. Subjects were screened by the DIA-X diagnostic expert system (Wittchen and Pfister 1997), a semi-structured psychiatric interview to exclude those with personal or family (first-degrees relatives) histories of major psychiatric disorders, and by the Symptom Checklist (SCL-90–R) (Derogatis 1994). Furthermore, subjects replied to the Mini-International Neuropsychiatric Interview, a brief, structured psychiatric interview (Sheehan et al. 1998). No subjects had to be excluded using these criteria. We verified the absence of a history of drug dependence by urine drug-screening and a self-made consumption questionnaire. In the S-ketamine group, seven subjects were occasional smokers (<10 cigarettes/day), eight subjects reported a sporadic or rare cannabis use in the past (<3 joints/month), two subjects reported experiences with MDMA (three pills lifetime), two subjects had previous LSD experiences (5 lifetime experiences), and one subject reported having previous experiences with ketamine (one occasions lifetime). In the psilocybin group, eight subjects were occasional smokers (<6 cigarettes/day), eight subjects reported a sporadic or rare cannabis use in the past (<2 joints/month), one subject reported experiences with MDMA (two pills lifetime), two subjects had prior use histories of ingesting psilocybin containing mushrooms (two lifetime experiences), and one subject reported experiences with LSD (two lifetime experiences). All subjects were free of any medication for at least 3 weeks before the experiment.

This study was approved by the Ethics Committee of the University Hospital of Psychiatry in Zurich. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion. The use of psilocybin was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Berne, Switzerland.

Drug administration

In both groups, subjects underwent two sessions (placebo/active drug) in a counterbalanced and double-blind fashion at an interval of at least 2 weeks. Subjects were monitored until all drug effects had worn off and were then released into the custody of a partner. For the S-ketamine/placebo infusion, an in-dwelling catheter was placed in the antecubital vein of the nondominant arm. Once the subject was ready, a bolus injection of 10 mg over 5 min was given. Following a 1-min break, a continuous infusion with 0.006 mg/kg/min was administered over 80 min. To keep S-ketamine's plasma level fairly constant, the dose was reduced every 10 min by 10 % as previously described ((Feng et al. 1995; Vollenweider et al. 1997). In the placebo session, the same procedure was followed and an infusion of

physiological sodium chloride solution and 5 % glucose was given. Psilocybin (115 μg/kg) and lactose placebo were orally administered in gelatin capsules of identical number and appearance as previously described in studies assessing the acute psychological and physiological effects of psilocybin in healthy humans (Hasler et al. 2004; Studerus et al. 2011). Psilocybin was orally given not only to ensure direct comparability with these previous studies and external validity but also to induce stabile psychological effects after 60–90 min post-treatment, lasting for 60–120 min (Hasler et al. 2004). Furthermore, given the putative therapeutic potential of psilocybin (Kometer et al. 2012; Vollenweider and Kometer 2010; Grob et al. 2011), an oral dosing regimen provides a more personable setup than utilizing an intravenous dosing regime for psilocybin.

Psychological assessment

The Altered State of Consciousness (ASC) questionnaire, a visual analog and self-rating scale, was used to assess the subjective psychological effects induced by S-ketamine and psilocybin (Dittrich 1975, 1998). A recent evaluation study of the ASC questionnaires has constructed 11 new lower-order scales (Studerus et al. 2010), which were assessed in this study. After the acute effects of S-ketamine (about 240 min post-treatment) and psilocybin (about 360 min after treatment) had subsided, the ASC questionnaire was given to retrospectively rate their introspective experiences since drug intake.

Stimuli and backward masking procedure

As stimulus material, we took black and white photographs taken from the Ekman–Friesen series (Ekman and Friesen 1976). In order to exclude the hair and non-facial contours and further to match for luminance and contrast, each face was modified using Adobe Photoshop as previously done in other studies (Blau et al. 2007; Pegna et al. 2008; Pourtois et al. 2004). The final facial images subtended a visual angle of 3° horizontally and 4.4° vertically and were displayed in the center of a CRT monitor (refresh rate of 100 Hz). Subjects first underwent a mismatch negativity event-related paradigm for 15 min, which has been published elsewhere (Schmidt et al. 2011). Emotional measures using backward masking paradigms were started 25 min after S-ketamine infusion and 110 min following psilocybin administration during the known plateau (Hasler et al. 2004; Passie et al. 2002).

Backward masking paradigms (*facial affect discrimination and EEG/ERP recording*) were generated by a software dedicated to psychological testing (E-prime; Schneider et al. 2002). Backward masking is a key experimental paradigm for investigating sensory unawareness because this method interferes with the activity in the ventral occipitotemporal cortex, an area which is highly relevant for visual awareness

(Tamietto and de Gelder 2010). The accuracy of stimulus duration was confirmed using an oscilloscope. Figure 1 shows the backward making procedures for the facial discrimination task (A) and for the subsequent EEG/ERP recording (B).

Facial affect discrimination Two discrimination tasks were conducted to establish thresholds for visual awareness in all drug conditions, i.e., to determine the time point, at which subjects can distinguish emotional from neutral expression above chance level. In a first task, subjects had to discriminate fearful from neutral faces, while in a second task they had to discriminate happy from neutral faces. For each discrimination task, target faces consisted of neutral and fearful/happy faces and were presented for 20, 30, 50, 90, or 170 ms (Williams et al. 2004). Target faces were immediately followed by a neutral mask of the same person lasting for 150 ms. Participants performed five blocks of 40 trials (target–mask pairs) for each of both tasks, in which target faces were randomly presented with equal probability. Before the presentation of target–mask pairs, a fixation cross was presented for 1,000 ms. Subjects had to make a forced-choice decision about the valence of the target face (fearful/happy vs. neutral) via button-press.

EEG/ERP recording During subsequent ERP recording, stimuli were identical to those used during the facial affect discrimination. Target faces comprised neutral, fearful, and happy faces and were immediately followed by a neutral mask of the same person for 150 ms. Each trial began with a fixation cross that lasted for 2,000 ms. According to the results of the discrimination tasks, target faces were 10 ms presented during non-conscious processing and 200 ms during conscious

processing. No subject response (button-press) was required. However, participants were given instructions that pairs of target–mask faces would be presented and that they would be asked questions about the first faces after testing.

Event-related potential recording

EEG recordings were made from 64 scalp electrodes using the ActiveTwo system (Biosemi, the Netherlands). The horizontal electroocculogram (EOG) was recorded from electrodes attached on the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes attached infraorbitally and supraorbitally to the left eye. All electrodes were active silver/silver chloride electrodes and the offset of all electrodes was below 25 mV. Data were recorded at a sampling rate of 512 Hz. The common mode sense active electrode and the driven right leg passive electrode were used as reference and ground electrodes, respectively (see http://www.biosemi.com/faq/cms&drl.htm for more details on this setup).

For ERP analysis, independent component analysis was used to remove artifacts due to eye movements and blinks (Lee et al. 1999). The EEG data were recalculated offline against average reference. Then, epochs with a 200-ms prestimulus baseline and a 500-ms post-stimulus interval were constructed. Epochs with amplitudes that exceeded $\pm 100~\mu V$ at any electrode were excluded from further averaging. After artifact rejection, epochs were averaged for each subject and were digitally filtered with a band-pass filter (1–30 Hz). P100 and N170 ERPs were computed at electrodes P08/P8/P10/O2 (right hemisphere) and PO7/P7/P9/O1 (left hemisphere) as peak positivity/negativity relative to baseline within the 130–200- and 150–250-ms window latency, respectively, as

Fig. 1 Schematic of the backward masking paradigms. During the discrimination threshold tasks (a), a fixation cross was first presented for 1,000 ms, followed by the target face, which lasted for 20, 30, 50, 90, or 170 ms, respectively. Finally, a neutral mask of the same person was presented for 150 ms. After each target–mask pair, subjects were asked to answer via key press. During ERP recording (b), the fixation cross was presented for 2,000 ms. The presentation time for the target faces was 10 ms for non-conscious processing and 200 ms for conscious processing
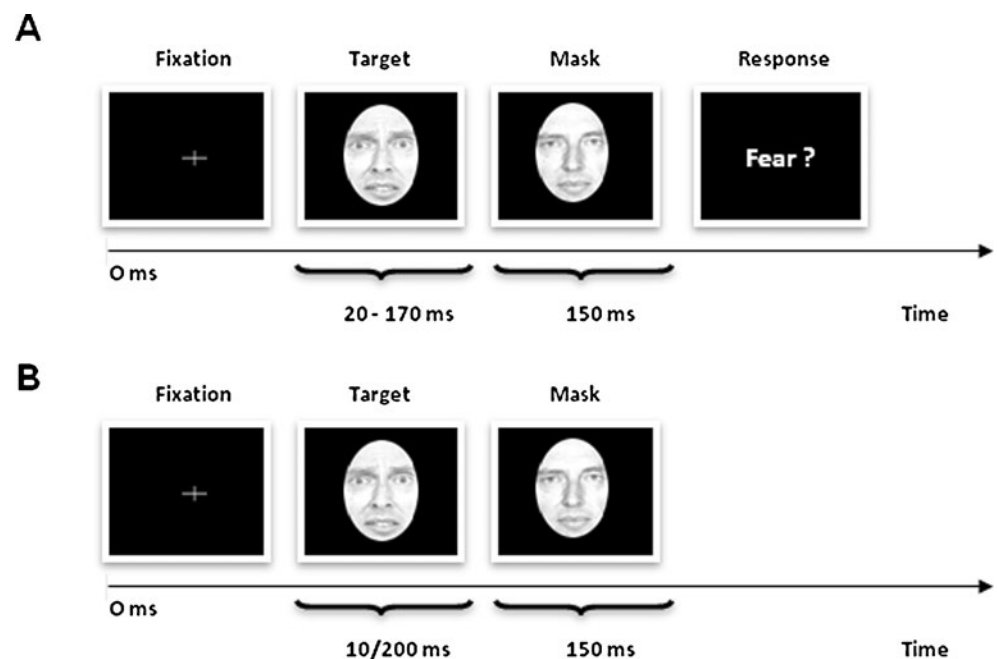
previously described (Frühholz et al. 2011; Jaworska et al. 2010; Wronka and Walentowska 2011).

Statistical analysis

Discrimination performances were analyzed according to signal detection theory, which provides a measure of sensitivity that is independent of subject's response bias (Macmillan and Creelman 1991). This procedure avoid potential limitations of subjective self-report performances, in which subjects report no visual awareness but may nonetheless experience some level of awareness (Bernat et al. 2001). Threshold settings were determined by Student's t tests against chance level (sensitivity indexes of $d'=0$). D's were further subjected to a repeated measurement analysis of variance (ANOVA) with the within-subject factors target duration (20, 30, 50, 90, 170 ms), valence (fearful, happy), and treatment (placebo, drug), as well as with the between-subject factor group (S-ketamine, psilocybin). In a first step, P100 and N170 ERP data were separately analyzed for the S-ketamine and psilocybin group by repeated measurement ANOVAs with the within-subject factors treatment (placebo, S-ketamine, or psilocybin), target duration (non-conscious, conscious), valence (fearful, happy, and neutral), and laterality (right, left). To further compare both drug effects on the specific ERP, in a second step, we computed the change scores between the placebo and both drug conditions (placebo−drug). Change scores were subjected to a repeated-measures ANOVA with the within-subject factors target duration (non-conscious, conscious), valence (fearful, happy, and neutral), and laterality (right, left) and with the between-subject factor group (S-ketamine, psilocybin). Repeated measurement ANOVA on the ASC data with treatment and scale as within-subject factors and group as between-subject factor was used to examine drug-induced psychological effects. Where the ANOVA null hypotheses of equal means were rejected, we used Fisher's least significant difference tests (LSD) for post hoc testing. For further analysis, we computed the average of the d' change score (d' pla−d' drug) over all target durations as indexed by "d' fear" and "d' happy." Given that the activity in face-sensitive areas within the visual cortex increases gradually with subjective rating of recognition success (Bar et al. 2001), we used linear regression analysis to examine the relationship between discrimination success (i.e., d' fear and d' happy) and N170 changes scores.

Results

Facial affect discrimination

Student's t tests against $d'=0$ revealed that for the discrimination of fearful relative to neutral faces (Fig. 2), d' at 20 ms under placebo did not significantly differ from chance level

(S-ketamine group: mean $d'=0.05$, SD=0.31, $p=0.5$; psilocybin group: mean $d'=0.1$, SD=0.35, $p=0.19$), while d' at 30 ms became significantly above chance level (S-ketamine group: mean $d'=0.30$, SD=0.29) ($p<0.0001$; psilocybin group: mean: $d'=0.36$, SD=0.63, $p<0.05$). In contrast, under the influence of both drugs, d's at 30 ms were still not above chance level (S-ketamine group: mean $d'=0.12$, SD=0.67, $p=0.42$; psilocybin group: mean $d'=0.04$, SD=0.7, $p=0.81$), whereas performances at 50 ms reached significance (S-ketamine group: mean $d'=0.36$, SD=0.37, p's<0.001; psilocybin group: mean $d'=0.20$, SD=0.33, $p<0.05$). During the discrimination of happy faces (Fig. 3), d' values for each duration time in all drug conditions significantly varied from chance level.

Independent of threshold setting, repeated-measures ANOVA over both groups revealed that d' significantly increased across target duration [$F(4,160)=195.19$; $p<0.00001$; $\eta_p^2=0.83$]. In general, d' values for happy faces were significantly higher than for fearful faces ($p<0.05$) as indicated by a significant main effect for valence [$F(1,40)=4.15$; $p<0.05$; $\eta_p^2=0.09$]. Furthermore, a significant main effect for treatment was found [$F(1,40)=36.04$; $p<0.00001$; $\eta_p^2=0.47$]. Particularly, a treatment×valence×group interaction [$F(1,40)=4.11$; $p<0.05$; $\eta_p^2=0.09$] revealed that S-ketamine significantly reduced d' for both fearful ($p<0.001$) and happy faces ($p<0.001$) relative to placebo, while psilocybin exclusively reduced d' for fearful ($p<0.001$) but not for happy faces ($p=0.87$).
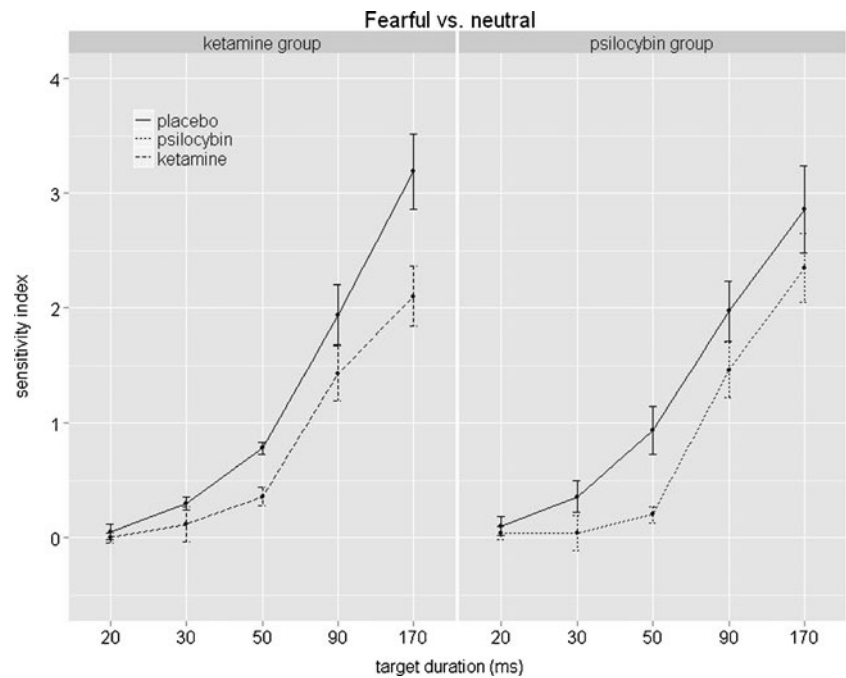
Event-related potential responses

Mean of grand averages over both hemisphere of the P100 and N170 ERP during non-conscious and conscious processing are shown in Fig. 4.

P100 event-related potential

Repeated-measures ANOVA on the P100 amplitudes revealed generally more pronounced P100 amplitudes over right compared to left electrodes in both the S-ketamine [$F(1,20)=18.23$; $p<0.001$; $\eta_p^2=0.48$] and the psilocybin group [$F(1,20)=22.22$; $p<0.001$; $\eta_p^2=0.53$]. However, no treatment effects were observed for the P100 amplitudes in the psilocybin [$F(1,20)=0.099$; $p=0.13$; $\eta_p^2=3.00$] and-ketamine group $F(1,20)=0.011$; $p<0.917$; $\eta_p^2=0.001$]. Comparing the effect of S-ketamine and psilocybin, repeated-measures ANOVA on the change scores for the P100 amplitude showed no main effects and interactions, reflecting an equal influence of S-ketamine and psilocybin on the P100 amplitude.

Fig. 2 Sensitivity indices (d')± SE represented as a function of target duration during fear discrimination. Notably, both S-ketamine and psilocybin significantly reduced d' values for fearful relative to neutral faces


N170 event-related potential

Repeated-measures ANOVA on the S-ketamine data revealed that N170 amplitudes were generally more pronounced over right compared to left electrodes and more pronounced for emotional relative to neutral faces, as indicated by a significant main effect for laterality ($F(1,20)=25.97$; $p<0.0001$; $\eta_p^2=0.56$) and valence ($F(2,40)=5.47$; $p<0.01$; $\eta_p^2=0.21$). Furthermore, a main effect of treatment was found ($F(1,20)=8.73$; $p<0.01$; $\eta^2=0.30$), reflecting the overall N170 reduction under S-ketamine. The treatment × laterality interaction ($F(1,20)=46.70$; $p<0.00001$; $\eta_p^2=0.71$) showed that the treatment effect occurred only over right electrodes ($p<0.000001$) (Fig. 5, left), but not over left electrodes ($p=0.14$). In general, the S-ketamine effect on the N170 amplitude was more pronounced during conscious ($p<0.00001$) (mean difference −1.1 μV) than non-conscious processing ($p<0.001$) (mean difference −0.6 μV), indicated by

Fig. 3 Sensitivity indices (d')± SE represented as a function of target duration during the discrimination of happy faces. Notably, S-ketamine but not psilocybin significantly reduced d' values for happy relative to neutral faces
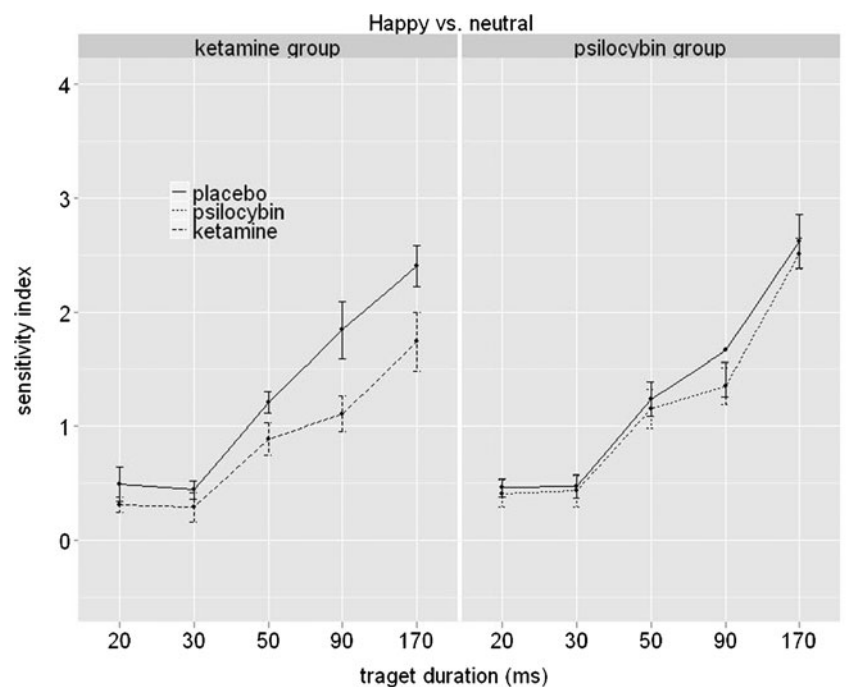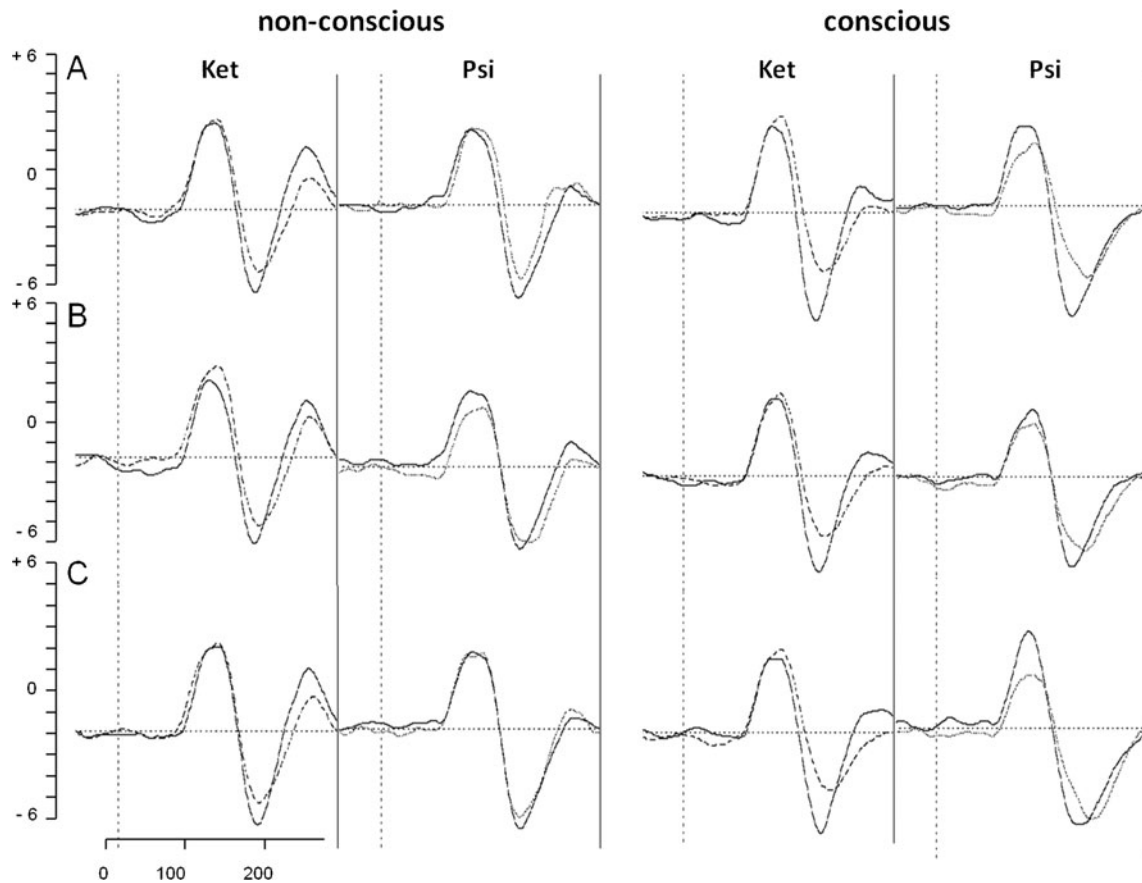
Fig. 4 Mean of grand averages over both hemispheres of the P100 and N170 ERP for fearful (**a**), neutral (**b**), and happy faces (**c**) during non-conscious (*left*) and conscious processing (*right*) following placebo (*solid line*), S-ketamine (*Ket*: *dashed line*), and psilocybin (*Psi*: *dotted line*) administration, respectively

treatment × target duration interaction ($F(1,20)=4.75$; $p<0.05$; $\eta_p^2=0.19$). No treatment × valence interaction was found for S-ketamine on the N170 ($F(1,20)=1.88$; $p=0.1.66$; $\eta_p^2=0.086$).

Repeated-measures ANOVA on the psilocybin data revealed significant main effects for laterality ($F(1,20)=39.43$; $p<0.00001$; $\eta_p^2=0.66$) and treatment ($F(1,20)=14.21$;

Fig. 5 Mean N170 amplitudes ± SE over right electrodes for fearful, neutral, and happy faces under S-ketamine (*red line*), psilocybin (*blue*), and placebo (*green*). Note: Significant differences between treatment conditions at *$p<0.01$ and at **$p<0.00001$
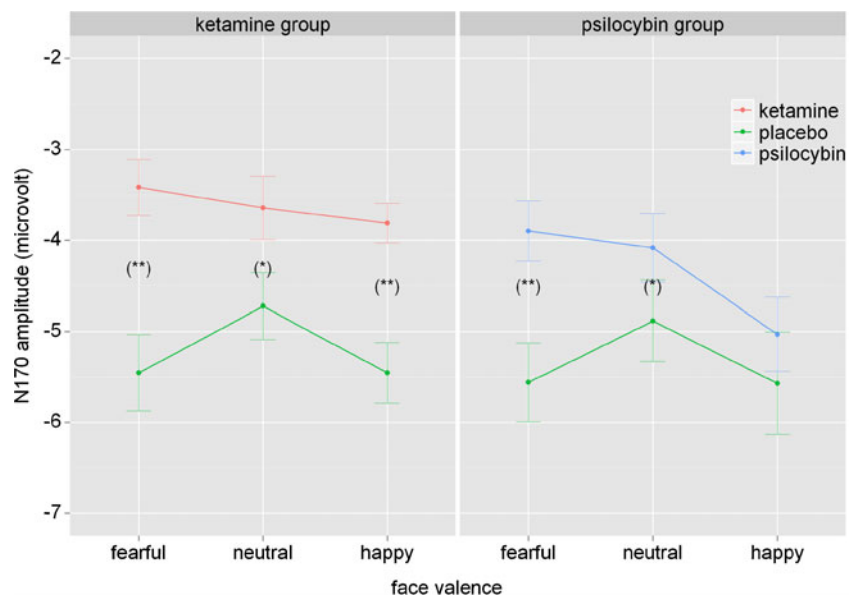
$p < 0.01$; $\eta_p^2 = 0.42$), reflecting the more pronounced response over right relative to left electrodes ($p < 0.00001$) and the general N170 reduction induced by psilocybin ($p < 0.01$). This treatment effect was found only over right electrodes ($F(1,20) = 6.61$; $p < 0.05$; $\eta_p^2 = 0.25$). The main effect of valence indicated the more pronounced N170 amplitude for emotional compared to neutral faces ($F(2,40) = 9.79$; $p < 0.001$; $\eta_p^2 = 0.33$). Furthermore, the laterality × treatment × target duration interaction ($F(1,20) = 4.52$; $p < 0.05$; $\eta_p^2 = 0.18$) revealed that the N170 effect over right electrodes was more pronounced during conscious ($p < 0.000001$) (mean difference −1.38 μV) than non-conscious processing ($p < 0.01$) (mean difference −0.71 μV). Finally, as shown by a significant treatment × valence interaction ($F(2,40) = 5.92$; $p < 0.01$; $\eta_p^2 = 0.23$), psilocybin significantly reduced the N170 amplitudes in response to fearful ($p < 0.000001$) and neutral faces ($p < 0.01$), but not to happy faces ($p = 0.1$) (Fig. 5, right).

Comparing the S-ketamine and psilocybin effects on the N170, repeated-measures ANOVA on the change scores revealed significant main effects for target duration ($F(1, 40) = 6.53$; $p < 0.05$; $\eta_p^2 = 0.14$) ($F(1,40) = 6.53$; $p < 0.05$; $\eta_p^2 = 0.14$), laterality ($F(1,40) = 34.29$; $p < 0.00001$; $\eta_p^2 = 0.46$), and valence ($F(2,80) = 5.15$; $p < 0.01$; $\eta_p^2 = 0.11$). LSD post hoc testing revealed that in general both drug effects were more pronounced over right than left electrodes ($p < 0.00001$) and more pronounced during conscious than non-conscious processing ($p < 0.05$). Most intriguingly in regard to the contribution of glutamate and serotonin to emotional processing, a laterality × valence × group interaction was found ($F(2,80) = 4.02$; $p < 0.05$; $\eta_p^2 = 0.09$). Particularly, although S-ketamine and psilocybin equally modulated the N170 amplitudes in response to fearful ($p = 0.78$) and neutral faces ($p = 0.82$) over right electrodes, happy faces were differentially modulated by S-ketamine and psilocybin ($p < 0.05$) (Fig. 6).

Finally, we asked whether the drug-induced changes in the behavioral performances (d' fear and d' happy) might be explained through the drug effects on the N170 over right electrodes using linear regression analysis. For both groups, we found no significant relations between d' fear and N170 change score for fearful faces (psilocybin group: $F = 0.28$, $p = 0.757$; S-ketamine group: $F = 2.23$, $p = 0.136$), as well as between d' happy and N170 change score for happy faces (psilocybin group: $F = 1.25$, $p = 0.311$; S-ketamine group: $F = 0.974$, $p = 0.397$).

Psychological assessment

Both S-ketamine and psilocybin produced similar alterations on the global ASC scores (Fig. 7). Repeated-measures ANOVA on the ASC data showed significant main effects for treatment ($F(1,40) = 80.99$; $p < 0.00001$; $\eta_p^2 = 0.67$) and scale ($F(11,440) = 9.73$; $p < 0.000001$; $\eta_p^2 = 0.20$). A triple treatment × scale × group interaction indicated significant differences between both drug effects on specific scales [$F(11, 440) = 5.35$; $p < 0.00001$; $\eta_p^2 = 0.12$]. Post hoc testing showed that S-ketamine increased all scales relative to placebo (p's < 0.01), expect for anxiety ($p = 0.09$), while psilocybin increased all scales (p's < 0.01), expect for auditory alterations ($p = 0.42$) and anxiety ($p = 0.36$). Moreover, LSD post hoc analysis showed that S-ketamine produced significantly higher scores than psilocybin for disembodiment ($p < 0.000001$), auditory alterations ($p < 0.05$), and for impaired control and cognition ($p < 0.05$). Otherwise, psilocybin produced more pronounced visual illusions and elementary hallucinations than S-ketamine as indexed by the elementary imagery score ($p < 0.01$).

Discussion

In this paper, we present a suitable approach to compare glutamatergic and serotonergic effects on emotional face processing. Specifically, according to the firstly assessed discrimination thresholds, we used event-related potential recording to investigate the effect of the NMDA receptor antagonist S-ketamine and the 5-HT receptor agonist psilocybin either on conscious or non-conscious emotional face processing. Our study provide three major results: Firstly, the structural encoding of facial configurations as expressed by the N170 ERP is impaired by S-ketamine and psilocybin, while the fast extraction of visual emotion-related information (i.e., P100 ERP) is not affected by both drugs. Secondly, the N170 ERP is differentially modulated by S-ketamine and psilocybin. Although both drugs reduce the N170 ERP responses to fearful faces, the structural encoding of happy faces is only impaired by S-ketamine. Finally, both drug effects on the N170 ERP are more pronounced during conscious than non-conscious processing. In the following, we discuss our results and consider their potential implications.

On the behavioral level, regardless of threshold setting, S-ketamine and psilocybin differentially affected facial discrimination performances. Particularly, the subjective ability to discriminate fearful from neutral face identities was impaired following both S-ketamine and psilocybin administration. In contrast, the discrimination performance of happy relative to neutral faces was only affected by S-ketamine but not by psilocybin, suggesting that the effect of psilocybin is valence specific on the behavioral level.

On the electrophysiological level, the N170 amplitude was more pronounced for emotional relative to neutral faces in both groups without any drug intake (i.e., under placebo),

Fig. 6 Mean change scores of N170 ERP±SE as a function of face valence over right parieto-occipital electrodes. Notably, the N170 ERP reduction for fearful and neutral faces was comparable among both drugs, but the N170 ERP for happy faces was significantly more reduced after S-ketamine (*circle*) than psilocybin exposure (*triangle*). *$p<0.05$ indicates a significant difference between the effect of S-ketamine and psilocybin on happy faces
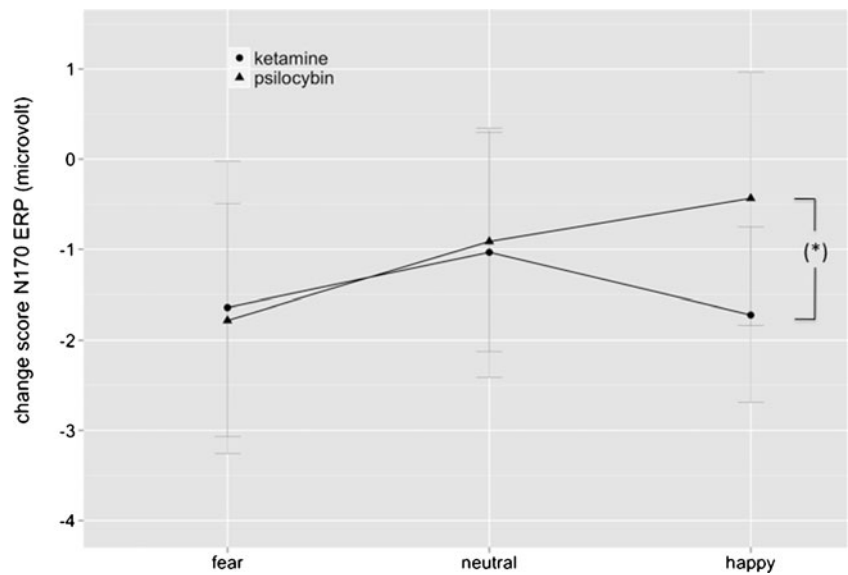
reflecting an emotional face processing bias as previously reported (Blau et al. 2007; Jaworska et al. 2010; Krombholz et al. 2007; Pegna et al. 2008; Schyns et al. 2007; Smith 2011). Psilocybin impaired the structural encoding of fearful faces as expressed by reduced N170 responses to fearful faces, while no psilocybin-induced N170 alteration in response to happy faces was found in this study. Thus, psilocybin shifted the negative N170 processing bias seen under placebo. These findings differ from previous studies reporting that the SSRI citalopram does not acutely modulate the N170 ERP in response to emotional faces in healthy subjects (Kerestes et al. 2009; Labuschagne et al. 2010), whereas later ERPs such as the N250 or the LPP, which have been

associated with "expression decoding," are modulated by citalopram (Kerestes et al. 2009; Labuschagne et al. 2010). Beyond methodological differences across these studies such as the use of the reference electrodes, the differential effect of psilocybin and citalopram on the N170 ERP may be due to the different pharmacological effects of psilocybin and citalopram on the 5-HT system. While citalopram overall increases 5-HT brain levels (Elliott et al. 2011; Nutt et al. 1999), psilocin, the active metabolite of psilocybin, is an agonists at 5-HT receptors which binds with high affinity specifically at 5-HT1, HT2, and 5-HT6 receptors (Nichols 2004). That the different pharmacological profiles of psilocybin and citalopram on the 5-HT system may be most

Fig. 7 Effects of S-ketamine (*dashed line*) and psilocybin (*dotted line*) on the ASC scales. Mean scores and ±SE (both $n=21$). Note: *$p<0.05$, **$p<0.01$, and ***$p<0.000001$ indicate significant differences between drugs. Symptoms scores were expressed as percent of scale maximum
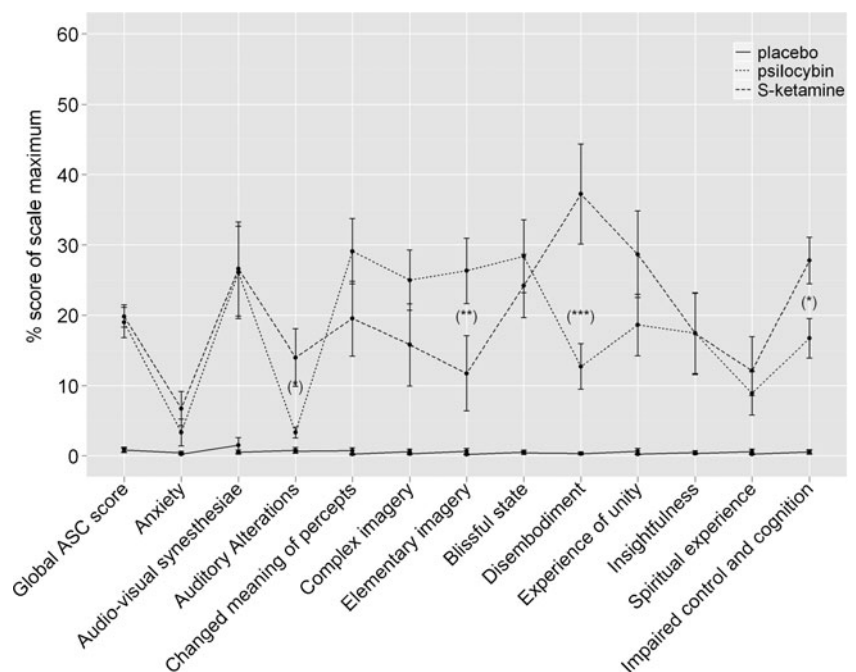
critical in mediating their N170 effects on emotional face processing is further supported by the finding that decreasing brain 5-HT levels by acute tryptophan depletion (ATD) did not affect the N170 during face processing as well (Jaworska et al. 2010). Along this line, the P100 ERP is also differently altered by psilocybin and ATD. Particularly, while ATD enhances the P100 for sad versus joyful faces (Jaworska et al. 2010), in this study no P100 alteration to facial expressions was found under psilocybin. Thus, the sensitivity of the P100 and N170 ERP may differentially depend on 5-HT brain levels and the activation of a set of different 5-HT receptors subtypes.

Discussing the effect of S-ketamine on the visual ERPs, the only work with reference to our result is a previous fMRI study, which explored the functional network following ketamine administration during emotional face processing (Abel et al. 2003). The key finding of this study was that the amygdala and fusiform gyrus (FG) activity in response to fearful faces under placebo was abolished following ketamine administration. The authors suggested that this ketamine-induced effect on limbic and visual regions is associated with the emotional blunting and depersonalization phenomena that are evident in ketamine states (Krystal et al. 1994; Vollenweider et al. 1997). Such an interpretation is consistent with the present finding that S-ketamine reduced the N170 ERP not only in response to fearful but also to neutral and happy faces, reflecting an overall emotional blunting of visually induced neural responses.

According to several source localization studies (Deffke et al. 2007; Rossion et al. 2003; Sadeh et al. 2010), the generators of the N170 ERP have been localized to the FG, which encodes the structural configuration of facial features. The significance of structural information encoding in visual perception is shown by a functional relationship between object discrimination performance and FG activity. In particular, a previous study found that FG activity increases gradually with subjective rating of recognition success (Bar et al. 2001). An identical relationship was also suggested following citalopram administration in healthy subjects (Harmer et al. 2003). It has been proposed that the enhanced fear detection in healthy subjects treated with citalopram (Harmer et al. 2003) may be partly due to an increased activity in the FG (Del-Ben et al. 2005). Albeit not statistically underpinned, we observed that both drug effects on the subjective discrimination performances correspond approximately to the electrophysiological changes on the N170 following drug administration (cf. Figs. 2, 3, and 5). These findings suggest that the relationship between discrimination success and FG activity/N170 amplitude might remain following manipulation of the 5-HT and NMDAR system. However, the lack of a statistical significance warrants further investigations to strengthen this relationship.

Neurofunctionally, increased visual evoked responses to relevant emotional expressions are likely mediated via rich interconnections between the FG and the amygdala (Amaral et al. 2003; Freese and Amaral 2005), the coupling of which is additionally strengthened during attentive viewing of affective faces (Fairhall and Ishai 2007; Herrington et al. 2011). Furthermore, emotional face processing also involves prefrontal areas, which are functionally connected with the FG and the amygdala (Dima et al. 2011). Critically, both S-ketamine and psilocybin were found to deactivate limbic and to increase prefrontal neural activity during resting states in healthy subjects (Vollenweider and Kometer 2010). Thus, it is arguable that the psilocybin- and S-ketamine-induced N170 effects in response to fearful faces may be due to functional alterations in the amygdala-prefrontal network. However, why psilocybin and S-ketamine had dissociable effects on happy face processing is difficult to derive from the present data. A possible explanation could be that S-ketamine and psilocybin differentially modulate circuitries responsible for the processing of positive expressions because the processing of positive information such as happy faces also involves reward-related areas (Adolphs 2003; Ishai 2007; Singer et al. 2004) relative to the processing of negative information and further because the N170 showed priming effects as a function of reward (Marini et al. 2011). However, this is highly speculative at the present time.

Another key finding of this study was further that the psilocybin- and S-ketamine-induced N170 effect was more pronounced during conscious than non-conscious visual processing independent of the face expression. This finding fits with the assumption that the N170 is associated with perceptual consciousness of the face (Rossion and Jacques 2008) and that FG responses are modulated by the level of target visibility (Pessoa et al. 2006; Pessoa and Padmala 2005). Furthermore, numerous studies have described an increase of the N170 ERP with selective attention (Gazzaley et al. 2005; Wronka and Walentowska 2011), suggesting top-down attentional control. In particular, the visual cortex receives top-down modulation from frontal and parietal areas in relation to visual attention (Bressler et al. 2008) in the time range of the N170 ERP (Rose et al. 2005). In this view, several studies reported that psilocybin attenuates attentional performances (Carter et al. 2005; Gouzoulis-Mayfrank et al. 2002; Quednow et al. 2011). A recent study examining the influence of psilocybin on the spatiotemporal dynamics of object completion and found a dose-dependent reduction of the N170 ERP response (Kometer et al. 2011). The authors suggested that this reduction might reflect a psilocybin-induced failure to allocate attention. Similarly, previous evidence revealed that ketamine produce cognitive deficits including impairments of attention (Morgan et al. 2004; Newcomer et al. 1999). Therefore, we suggest that the

more pronounced effects of psilocybin and S-ketamine on the N170 during conscious relative to non-conscious processing indicate a drug-induced reduction of attentional resources. One point of contention, however, may be that there is some evidence of conscious perception of happy faces with 20 ms in this study. This means that we cannot infer from the discrimination threshold task that 10 ms is truly non-conscious for the processing of happy faces. However, recent ERP studies confirmed presentation times below 20 ms for non-conscious processing of happy faces (Balconi and Lucchiari 2008; Pegna et al. 2011; Smith 2011). Therefore, it is conceivable to assume that presentation times of 10 ms as used in our ERP experiment are really non-conscious also for the processing of happy faces.

Summarized, this study demonstrated that the NMDA and 5-HT receptor systems differentially contribute to the structural encoding of emotional face expressions as expressed by the N170 event-related potential. Our findings confirm the emotion sensitivity of the N170 ERP during conscious and non-conscious face processing as recently reported (Pegna et al. 2008; Smith 2011) and further suggest that the assessment of early visual evoked responses might allow detecting pharmacologically induced change in emotional processing biases and provides thus a suitable framework to study pathophysiological mechanisms underlying dysfunctional emotional biases.

Conflict of interest None of the authors have any financial, personal, or organizational conflicts of interest to report in relation to this manuscript.

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