

PRIORITY COMMUNICATION

Psilocybin Biases Facial Recognition, Goal-Directed Behavior, and Mood State Toward Positive Relative to Negative Emotions Through Different Serotonergic Subreceptors

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Background: Serotonin (5-HT) 1A and 2A receptors have been associated with dysfunctional emotional processing biases in mood disorders. These receptors further predominantly mediate the subjective and behavioral effects of psilocybin and might be important for its recently suggested antidepressive effects. However, the effect of psilocybin on emotional processing biases and the specific contribution of 5-HT_{2A} receptors across different emotional domains is unknown.

Methods: In a randomized, double-blind study, 17 healthy human subjects received on 4 separate days placebo, psilocybin (215 µg/kg), the preferential 5-HT_{2A} antagonist ketanserin (50 mg), or psilocybin plus ketanserin. Mood states were assessed by self-report ratings, and behavioral and event-related potential measurements were used to quantify facial emotional recognition and goal-directed behavior toward emotional cues.

Results: Psilocybin enhanced positive mood and attenuated recognition of negative facial expression. Furthermore, psilocybin increased goal-directed behavior toward positive compared with negative cues, facilitated positive but inhibited negative sequential emotional effects, and valence-dependently attenuated the P300 component. Ketanserin alone had no effects but blocked the psilocybin-induced mood enhancement and decreased recognition of negative facial expression.

Conclusions: This study shows that psilocybin shifts the emotional bias across various psychological domains and that activation of 5-HT_{2A} receptors is central in mood regulation and emotional face recognition in healthy subjects. These findings may not only have implications for the pathophysiology of dysfunctional emotional biases but may also provide a framework to delineate the mechanisms underlying psilocybin's putative antidepressant effects.

Key Words: Affect, anxiety, depression, emotion, P300, serotonin

Central components in the pathophysiology of mood disorders are biases toward the processing of negative compared with positive emotions across different psychological domains, including perception, attention, and behavior. For example, depressed subjects need more intensely happy facial expression to correctly label happiness (1) and are slower in responding to positive but not to negative words in emotional go/nogo tasks (2,3). A crucial role for serotonin (5-HT) in the regulation of emotional biases is evidenced by genetic and pharmacologic studies, while the differential contribution of 5-HT subreceptors across psychological domains in humans is less well understood (4,5). However, accumulating evidence suggests that serotonin 1A (5-HT_{1A}) and 2A (5-HT_{2A}) receptors are particularly implicated in the pathophysiology of dysfunctional emotional biases, because 5-HT_{1A} and 5-HT_{2A} receptor densities are altered in depressive (6–10), bipolar (11,12), and anxiety disorders (13,14). In line with this view, 5-HT_{1A} receptor

agonists, such as buspirone or pindolol, have been particularly used as add-on treatment to enhance the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs) (7). Also, more recently, preferential 5-HT_{2A} receptor agonists revealed anxiolytic and antidepressive effects in different animal models of mood disorders (15–21). In humans, activation of 5-HT_{2A} receptors has been identified as the primary mechanism underlying the acute subjective effects of classical psychedelics, such as psilocybin (22), which, at low to medium doses, are predominantly characterized by heightened mood and visual disturbances (23–25). Furthermore, psilocybin induces neuronal activity and neuroplastic effects in prefrontal-limbic circuits implicated in mood disorder (24). These findings suggest that psilocybin, whose bioactive metabolite psilocin activates 5-HT_{2A}, 5-HT_{1A}, and serotonin 2C (5-HT_{2C}) receptors (26,27), may not only produce acute mood-enhancing effects but may also induce sustained antidepressant or anxiolytic effects (24). In support of this view, a gradual reduction of depressive symptoms and trait anxiety over 6 months was observed after a single dose of psilocybin in a recent placebo-controlled pilot study in terminal cancer patients (28).

Taken together, these findings suggest that psilocybin might bias emotional processing away from negative information by activating 5-HT_{1A}, 5-HT_{2A}, or both receptors. Assessing this hypothesis might help to unravel the psychopharmacologic mechanism underlying the pathophysiology of dysfunctional emotional biases and the recently proposed antidepressant and anxiolytic potential of psilocybin.

To this end, here we investigated for the first time the effect of psilocybin on emotional processing biases across psychological

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Received Nov 7, 2011; revised Apr 3, 2012; accepted Apr 4, 2012.

domains. We also disentangled the specific contribution of the 5-HT_{2A} receptor by antagonizing it with ketanserin. First, we assessed behaviorally the ability to recognize the emotional state of another person from facial cues, which has been previously shown to be biased toward negative emotions in depressed and anxious subjects (1,29–31) and to be related to serotonergic tone (29–33). Second, response selection and inhibition to emotional cues were quantified by behavioral and event-related electroencephalogram measurements in an emotional go/nogo task (2). These are crucial components of goal-directed behavior in social environments (34) and are regulated by the 5-HT system (35–37). Finally, we evaluated and quantified acute psilocybin-induced mood effects using clinical relevant rating scales.

Methods and Materials

Subjects

Seventeen healthy, right-handed subjects (11 male subjects, 6 female subjects, mean age 26.0 ± 4.36 years, 15 university students/graduates, 1 high school diploma, 1 apprenticeship) were recruited through advertisement from the University of Zürich. All subjects were healthy according to physical examination, including electrocardiography and detailed blood analysis. The Mini-International Neuropsychiatric Interview for DSM-IV (38), the Expert System for Diagnosing Mental Disorders (39), and the Hopkins Symptom Checklist 90-Revised (40) were used to exclude subjects with present or antecedent psychiatric disorders or a history of major psychiatric disorders in first-degree relatives. The absence of drug dependence or present drug abuse was verified by urine drug screening and a self-report drug use questionnaire. Seven subjects reported having previous experiences with psilocybin or other hallucinogens (mean lifetime experiences 2.4 ± 1.1 times) and three subjects with 3,4-methylenedioxymethamphetamine (MDMA) (mean lifetime experiences 3.3 ± 2.5 times). Eight subjects reported to have rarely or sporadically used cannabis (<4 joints per month).

Subjects were informed by a written and oral description about the procedures of the study, including that they would receive on each experimental day in a double-blind manner two substances, either placebo + placebo, placebo + psilocybin, ketanserin + placebo, or ketanserin + psilocybin. Furthermore, they were informed about the possible risk of psilocybin administration and the broad spectrum of its consciousness-altering effects that may range from alterations in sensory perception, mood, thought, and the experience of self. To minimize the influence of the individual's expectations, we emphasized that the psychological effect of psilocybin is known to vary largely between and within subjects. The study was approved by the ethics committee of the Canton of Zürich. The use of psilocybin in humans was authorized by the Swiss Federal Office of Public Health, Department of Pharmacology and Narcotics, Bern, Switzerland.

Experimental Design

Using a double-blind, within-subject, placebo-controlled randomized design, subjects received on 4 experimental days, separated from each other by at least 2 weeks, placebo or ketanserin (50 mg) (pretreatment) followed after 1 hour by placebo or psilocybin (215 μ g/kg) (treatment). These specific doses were chosen because they have previously been shown to effectively induce or block the associated changes in conscious states, respectively (41). The time delay between pretreatment and treatment was 1 hour to ensure maximal 5-HT_{2A} receptor occupancy. Experiments started approximately 130 minutes after treatment and self-report ques-

tionnaires were given 360 minutes posttreatment to retrospectively rate their subjective experience since drug intake.

Acute Subjective Drug Effects

The 5-Dimensions Altered States of Consciousness (5D-ASC) questionnaire (42), a self-rating scale with 94 visual analogue items, was used to quantify the subjective psychological effects of psilocybin. Eleven subscales were recently constructed (43). Of primary interest in regard to the current study was the blissful state subscale measuring experiences of pleasure, peace, and love and the anxiety subscale quantifying anxiety associated with derealization and depersonalization. The German version of the Positive and Negative Affect Schedule (PANAS) was used to assess the self-reported positive and negative affect (44,45) and the German version of State-Trait Anxiety Inventory (STAI) was used to quantify state-anxiety (46).

Facial Emotional Recognition

The accuracy of inferring emotional states from the eye region was measured by a German adaptation of the Reading the Mind in the Eyes Test (47). Briefly, 36 black-and-white photographs of the eye region of persons expressing different subtle emotional states (e.g., ashamed) were presented on a computer screen together with four words describing the states of the persons. Participants were instructed to choose the word that described the state of the person most accurately. The total number of correct recognitions was computed for different valence categories (positive, negative, and neutral). Because the previously used valence categorization (48) was based on a small sample of 12 undergraduate women who rated the picture in combination with the target word, pictures and target/distracter words were rerated separately in a study comprising 40 subjects (Supplement 1).

Emotional Go/Nogo Task

In the emotional go/nogo task, emotionally valenced words (positive, negative, neutral) were presented in easy readable font (Universe) in the middle of the computer screen. We used emotional words as stimulus material because they have, in contrast to faces, a stronger impact on cognitive versus perceptual processes (49) and therefore allow better differentiation of the performance in the emotional go/nogo from the facial recognition task. Participants were instructed by text appearing at the beginning of each block to press as rapidly as possible a response button when words of one valence category were presented (go cues) and withhold responses to words of another valence category (nogo cues). The following blocks were presented once in the first half and once in the second half of the experiment in a randomized order: 1) positive go, neutral nogo, 2) positive go, negative nogo, 3) neutral go, positive nogo, 4) neutral go, negative nogo, 5) negative go, positive nogo, and 6) negative go, neutral nogo. Each block contained a pseudorandomized presentation of 30 go trials and 10 nogo trials, resulting in a total of 360 go trials and 120 nogo trials. To enable a parametric assessment of sequential facilitatory and inhibitory processes, the number of go cues preceding nogo cues in the trial order was counterbalanced in all blocks from zero to six according to previous studies (34). In each trial, words were presented for 280 msec followed by a fixation cross, which was used to reduce eye movements. The presentation time of the fixation cross was randomized from 1200 msec to 1400 msec to discourage anticipatory responses. Words were taken from the Berlin Affective Word List Reloaded (50) and were matched for number of letters, syllables, phonemes, frequency of appearance, number of orthographic neighbors, and imageability. Furthermore, negative and positive

words were matched for arousal but differed in valence ratings (Supplement 1).

Electroencephalogram Recording

Electroencephalogram recordings were made using BioSemi ActiveTwo electrode system with 64 scalp electrodes (BioSemi, Amsterdam, The Netherlands). Additional electrodes were attached on the outer canthus of each eye to record the horizontal electrooculogram and infraorbitally and supraorbitally to the left eye to record the vertical electrooculogram. Electrophysiologic signals were digitized at 512 Hz.

Electroencephalogram Analysis

Electroencephalogram data were high-pass filtered at .5 Hz to attenuate channel drifts. Bad channels were interpolated using spherical splines (51), and eye movements and blinks were removed by applying the extended infomax independent component analysis algorithm (52,53). Electroencephalogram data were low-pass filtered at 30 Hz. All trials (correct and incorrect) were segmented separately for each valence go/nogo combination from -200 to $+1200$ msec relative to stimulus presentation. To avoid remaining artifacts in further analysis, segments with activity exceeding ± 75 μV in any channel, gradients of 50 $\mu\text{V}/\text{second}$, and activity below .5 μV for at least 100 msec were excluded from further analysis before averaging. Event-related potentials were rereferenced to the average reference before N2 and P300 amplitudes were quantified against baseline activity. Peak amplitudes were obtained from the four midline electrodes that revealed highest amplitudes across all drug conditions. The N2 was therefore defined as the most negative peak from 250 to 450 msec at electrode AFz, Fz, FCz, Cz, and the P300 was defined as the most positive peak from 450 to 700 msec at FCz, Cz, CPz, Pz (Figure S1 in Supplement 1).

Results

Acute Subjective Effects

PANAS. Repeated-measures analysis of variance (ANOVA) with pretreatment, treatment, and subscale as within-subject factors revealed that psilocybin significantly increased PANAS scores [$F(1,16) = 16.608, p < .001, \eta_p^2 = .509$]. Importantly, the triple interaction between pretreatment \times treatment \times subscale [$F(1,16) = 21.160, p < .001, \eta_p^2 = .569$] showed that psilocybin significantly increased positive affect subscale after pretreatment with placebo ($p < .00001$) but not ketanserin ($p = 1$) (Figure 1). In contrast, psilocybin did not increase negative affect, either after pretreatment with placebo ($p = 1$) or after pretreatment with ketanserin ($p = 1$).

STAI-State. Repeated-measures ANOVA revealed a significant pretreatment \times treatment interaction [$F(1,16) = 14.708, p < .01, \eta_p^2 = .480$]. Bonferroni-corrected post hoc analyses of this interaction indicated that ketanserin increased STAI scores in placebo-treated ($p < .01$) and psilocybin-treated ($p < .000001$) subjects. In contrast, psilocybin did not change STAI scores after pretreatment with placebo ($p = .515$) (Figure 1).

5D-ASC. Psilocybin significantly increased 5D-ASC scores [$F(1,16) = 78.059, p < 1^{-6}, \eta_p^2 = .823$] and pretreatment with ketanserin reduced this psilocybin-induced increase [$F(1,16) = 87.223, p < 1^{-7}, \eta_p^2 = .845$]. Bonferroni-corrected post hoc analysis on the triple interaction between pretreatment \times treatment \times subscale [$F(10,160) = 9.549, p < 1^{-11}, \eta_p^2 = .374$] indicated that psilocybin increased the blissful state subscale, as well as the experience of unity, insightfulness, complex imagery, elementary imagery, changed meaning of percepts (all $ps < 1^{-9}$), the disembodiment ($p < 1^{-8}$), audio-visual synesthesiae ($p < .00001$), impaired

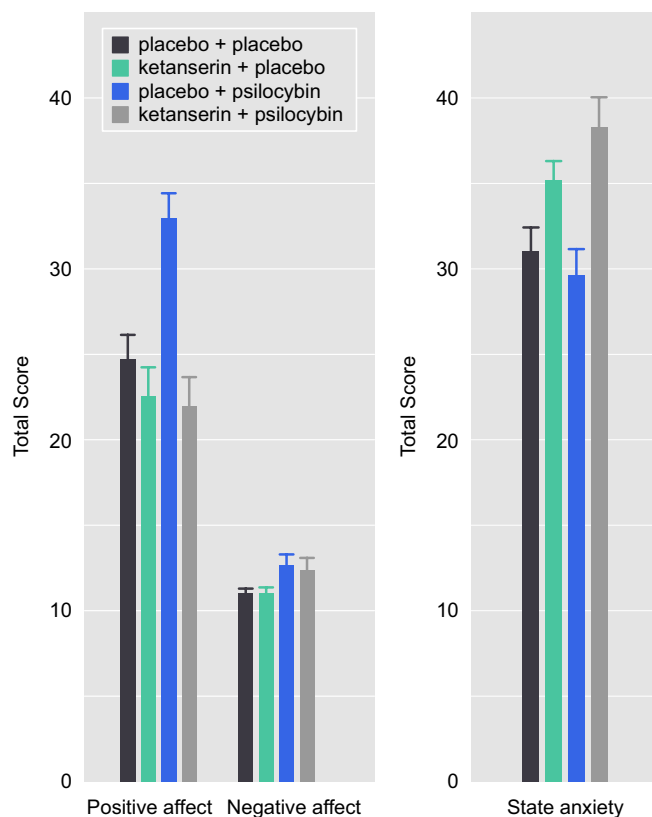


Figure 1. Subjective effects of psilocybin and ketanserin as measured by the Positive and Negative Affect Scale and the State-Trait Anxiety Inventory. Values are the mean and standard errors of total scores.

control and cognition ($p < .001$), spiritual experience ($p < .01$), but not anxiety ($p = 1$), subscales after pretreatment with placebo. Psilocybin did not increase any of these 11 subscales after pretreatment with ketanserin (all $ps = 1$) (Figure 2).

Facial Emotional Recognition

Error Rate. A repeated-measures ANOVA using pretreatment, treatment, and valence as within-subject factors revealed a main effect of valence [$F(2,32) = 16.857, p < .0001, \eta_p^2 = .513$]. Psilocybin modulated error rates depending on the valence of the facial expression [$F(2,32) = 5.460, p < .01, \eta_p^2 = .254$]. This interaction between treatment and valence was further modulated by pretreatment [$F(2,34) = 3.886, p < .05, \eta_p^2 = .181$] because psilocybin increased error rates for negative faces only after placebo ($p < .05$) but not ketanserin pretreatment ($p = 1$) (Figure 3). Overall, this interaction indicated a relative enhanced performance for positive compared with negative items, particularly in the placebo + psilocybin condition ($p < .00001$) and somewhat in the ketanserin + psilocybin condition ($p < .01$) but not in the placebo + placebo ($p = .44$) and ketanserin + placebo conditions ($p = 1$). A second repeated-measures ANOVA on the valence of the chosen word using pretreatment and treatment as within-subject factors revealed that psilocybin biased to choose higher valenced words [$F(1,16) = 3.667, p = .074, \eta_p^2 = .186$] and ketanserin lower valenced words [$F(1,16) = 4.040, p = .062, \eta_p^2 = .202$] at a trend level.

Emotional Go/Nogo Task: Behavioral Results

Reaction Time. Reaction times (RTs) for correct responses to go-stimuli were subjected to a repeated-measures ANOVA using pretreatment, treatment, and valence as within-subject factors. Re-

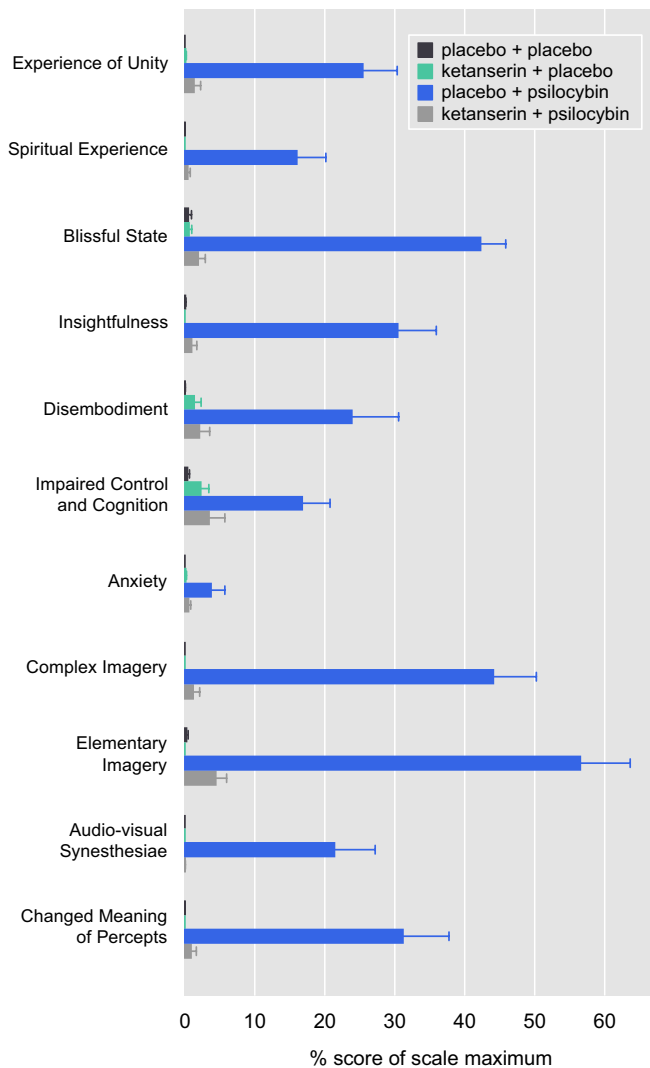


Figure 2. Subjective effects of psilocybin as measured by the 5-Dimensions Altered States of Consciousness scale. Values are the means and standard errors of percentages of the total possible scores of the 11 subscales of the 5-Dimensions Altered States of Consciousness scale.

action times were modulated by word valence [$F(2,32) = 31.312, p < 10^{-7}, \eta_p^2 = .662$]. Psilocybin increased RTs [$F(1,16) = 9.696, p < .01, \eta_p^2 = .378$] as a function of word valence [$F(2,32) = 6.742, p < .01, \eta_p^2 = .296$]. Specifically, psilocybin increased reaction time much more for negative ($p < 10^{-6}$) and neutral ($p < 10^{-7}$) than for positive words ($p < .01$), which indicates a stronger response bias to positive versus negative words in psilocybin ($p < 10^{-6}$) than in placebo condition ($p < .05$) (Figure 4). Pretreatment with ketanserin did not significantly change this psilocybin-induced preferential reaction time for positive words [$F(2,32) = .860, p = .433, \eta_p^2 = .051$].

Error Rate. A repeated-measures ANOVA on error rates with pretreatment, treatment, go/nogo, and valence as within-subject factors showed a main effect of valence [$F(2,32) = 14.949, p < .0001, \eta_p^2 = .480$] and go/nogo condition [$F(1,16) = 25.001, p < .001, \eta_p^2 = .610$]. Psilocybin increased error rates [$F(1,16) = 18.640, p < .001, \eta_p^2 = .5381$] depending on word valence [$F(2,32) = 3.624, p < .05, \eta_p^2 = .185$] but irrespective of go/nogo condition [$F(1,16) = .112, p = .742, \eta_p^2 = .007$]. Specifically, psilocybin signif-

icantly increased error rates only for neutral ($p < .01$) but not for positive ($p = 1$) or negative ($p = 1$) words (Figure 5). Furthermore, error rates were higher for negative compared with positive stimuli after psilocybin ($p < .05$) but not placebo administration ($p = .40$). These valence-specific effects of psilocybin on error rates did not differ between the go and nogo conditions [$F(2,32) = 1.643, p = .209, \eta_p^2 = .093$] and were not altered by ketanserin pretreatment [$F(2,32) = .887, p = .422, \eta_p^2 = .053$].

Sequential Effects. To assess sequential effects, RTs for correct responses to go-stimuli were subjected to a repeated-measures ANOVA using pretreatment, treatment, valence, and number of repetition as within-subject factors. Reaction times decreased with increasing number of repetition [$F(5,80) = 2.677, p < .05, \eta_p^2 = .143$], which was valence-specific [$F(10,160) = 5.501, p < .00001, \eta_p^2 = .256$]. Subsequent Bonferroni-corrected post hoc analyses showed that RTs to go-stimuli were decreased for the sixth repetition (maximal repetition) of positive ($p < .01$) and neutral ($p < .01$) but not negative go-stimuli ($p = .10$) compared with zero repetition (minimal repetition). Interestingly, psilocybin modulated these sequential emotional effects, which is indicated by the significant triple interaction between treatment \times valence \times number of repetition [$F(10,160) = 2.500, p < .01, \eta_p^2 = .135$]. Specifically, the decrease in RTs between zero and six repeating positive trials reached Bonferroni-corrected significance after treatment with psilocybin ($p < .001$) but not placebo ($p = 1$), while a significant increase of RTs between zero and six repeating negative trials were observed after psilocybin ($p < .01$) but not placebo treatment ($p = 1$) (Figure 6).

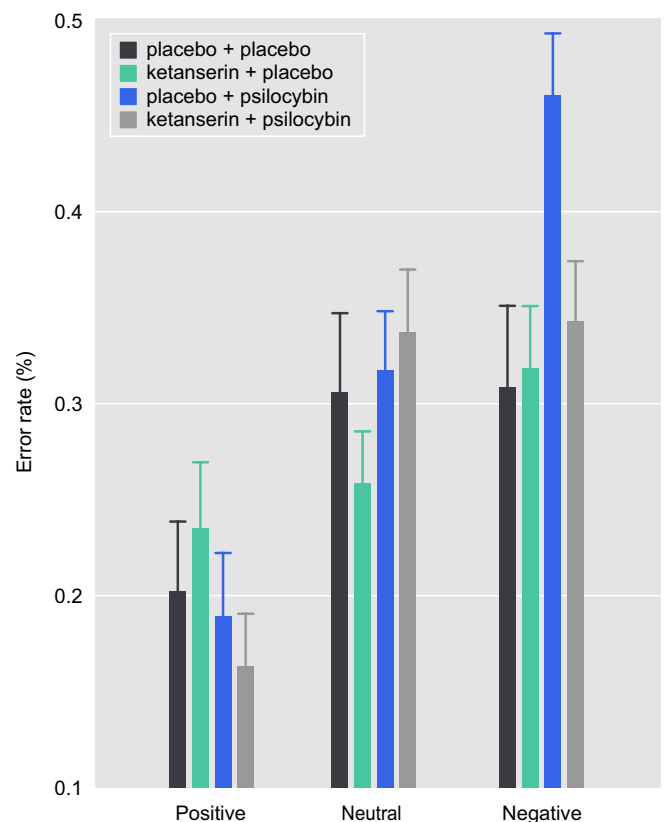


Figure 3. Effect of psilocybin and ketanserin on error rates in recognizing positive, neutral, and negative facial expressions. Values are the means and standard errors.

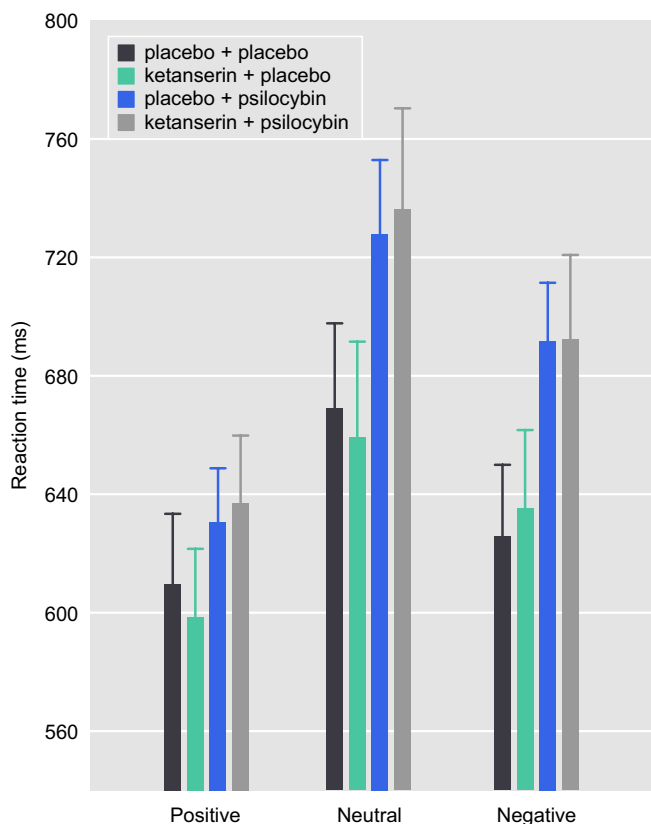


Figure 4. Effect of psilocybin and ketanserin on reaction times toward positive, neutral, and negative cues in the emotional go/nogo task. Values are the means and standard errors.

Emotional Go/Nogo Task: Electrophysiological Results

N2. A repeated-measures ANOVA on the N2 amplitude with pretreatment, treatment, go/nogo, valence, and electrode as within-subject factors revealed higher N2 amplitudes for neutral compared with negative ($p < .05$) and positive ($p < .05$) stimuli [$F(2,32) = 5.036, p < .05, \eta_p^2 = .239$] and higher amplitude for nogo-stimuli compared to go-stimuli [$F(1,16) = 20.073, p < .001, \eta_p^2 = .556$]. Psilocybin attenuated the N2 amplitude [$F(1,16) = 5.230, p < .05, \eta_p^2 = .246$] independent of the word valence [$F(2,32) = 2.538, p = .094, \eta_p^2 = .137$] and the go/nogo condition [$F(1,16) = .701, p = .415, \eta_p^2 = .042$].

P300. A repeated-measures ANOVA using pretreatment, treatment, go/nogo, valence, and electrode as within-subject factors revealed higher P300 amplitudes for positive ($p < 10^{-6}$) and negative ($p < 10^{-7}$) compared with neutral stimuli [$F(2,32) = 29.740, p < 10^{-7}, \eta_p^2 = .650$] and higher amplitudes for nogo-stimuli than for go-stimuli [$F(1,16) = 117.689, p < 10^{-8}, \eta_p^2 = .880$]. Psilocybin decreased the P300 amplitude [$F(1,16) = 15.323, p < .01, \eta_p^2 = .483$] depending on pretreatment condition [$F(1,16) = 4.646, p < .05, \eta_p^2 = .225$]. Bonferroni-corrected post hoc tests showed that psilocybin decreased the P300 amplitude only after pretreatment with placebo ($p < .01$) but not ketanserin pretreatment ($p = 1$). Importantly, the psilocybin-induced decrease was dependent on the word valence [$F(2,32) = 3.94, p < .05, \eta_p^2 = .198$] because the decrease was most pronounced for neutral ($p < 10^{-13}, -.97 \mu V$) followed by negative ($p < 10^{-12}, -.85 \mu V$) and positive ($p < 10^{-10}, -.71 \mu V$) words. The significant triple interaction between pretreatment \times treatment \times valence [$F(2,32) = 4.164, p < .05, \eta_p^2 = .207$] revealed the complex nature of the drug effects on the emotional

processing. Specifically, during placebo + placebo condition, Bonferroni-corrected post hoc tests indicated higher P300 amplitudes for negative compared with neutral words ($p < .001$). In contrast in the placebo + psilocybin condition, the positive stimuli evoked higher P300 amplitudes compared with neutral stimuli ($p < .05$). The strongest effects were seen in the ketanserin + psilocybin condition because P300 amplitudes were much higher for positive ($p < .00001$) and negative stimuli ($p < .00001$) compared with neutral stimuli (Figure 7).

Discussion

Our data show that psilocybin biases emotional processing toward positive relative to negative information, an effect that is consistent across different psychological domains. Specifically, psilocybin first enhanced positive mood states; second, decreased recognition of negative facial expression; and third, increased behavior toward positive relative to negative cues. In contrast to these generalized effects of the serotonergic agonist psilocybin, a more specific role for 5-HT_{2A} receptors in elevating mood and attenuating the recognition of negative facial expression is indicated by the finding that the preferential 5-HT_{2A} antagonist ketanserin blocked these psilocybin-induced effects.

Mood States

Psilocybin predominantly enhanced positive mood states, as evidenced by the marked increase in the positive affect but not negative affect subscale scores of the PANAS questionnaire, as well as by the increase in blissful but not anxiety subscale scores of the 5D-ASC questionnaire. These strong effects of psilocybin on mood

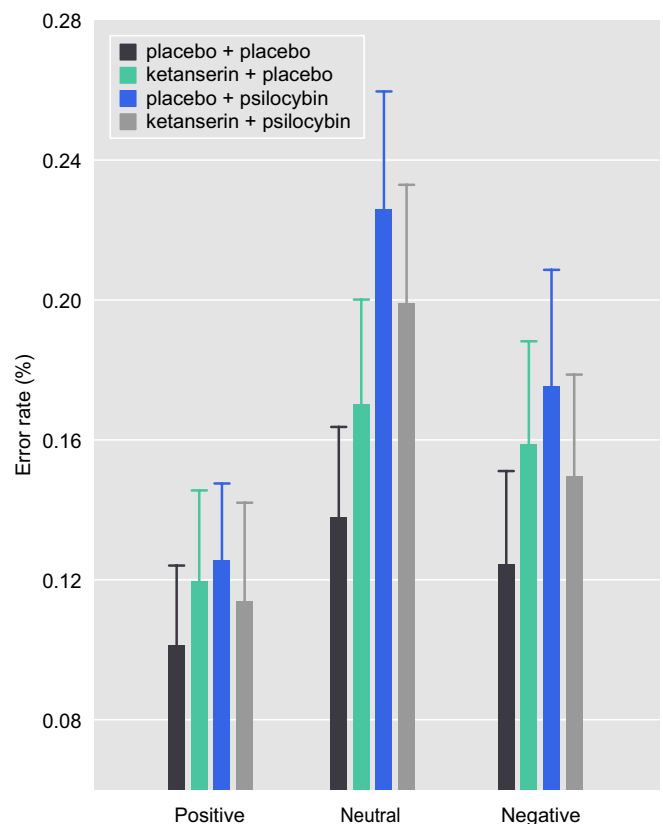


Figure 5. Effect of psilocybin and ketanserin on error rates in responding toward positive, neutral, and negative cues in the emotional go/nogo task. Values are the means and standard errors.

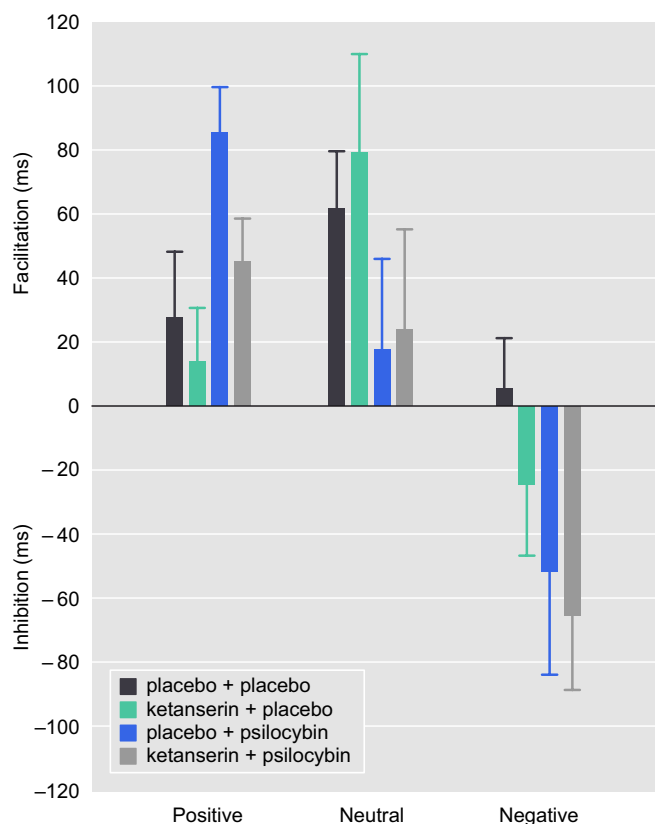


Figure 6. Effect of psilocybin and ketanserin on sequential emotional reaction time effects in the emotional go/nogo task. Depicted are differences in reaction times (means and standard errors) between the conditions with minimal (zero repetition) and maximal repetitions (six repetitions) of positive, neutral, and negative cues.

contrasts with the usually lacking acute mood effects of drugs that modulate the serotonergic tone such as acute tryptophan depletion (30,35,54) or SSRI administration (31,32,55). This apparent disparity suggests that a specific activation of certain 5-HT subreceptors is necessary to acutely enhance mood. Indeed, the finding that

the preferential 5-HT_{2A} antagonist ketanserin blocked the mood-enhancing effects of psilocybin suggests that 5-HT_{2A} receptors are implicated in regulating positive mood states. Moreover, we argue that the additional stimulation of 5-HT_{1A} or 5-HT_{2C} receptors by psilocybin is rather unlikely to contribute to the mood effects of psilocybin, because ketanserin has nearly no affinity to 5-HT_{1A} receptors and about fiftyfold higher affinity to 5-HT_{2A} compared with 5-HT_{2C} receptors (National Institute of Mental Health Psychoactive Drug Screening Program: <http://pdsp.med.unc.edu>). Furthermore, the serotonin 2B/5-HT_{2C} agonist meta-chlorophenylpiperazine induces anxiety rather than positive mood states (56). Finally, it is unlikely that expectation of receiving psilocybin considerably contributed to the mood effects, because various drug combinations were administered in a double-blind procedure and subjects were instructed that the psychological effects of psilocybin vary largely between and within subjects.

Facial Emotional Recognition

Serotonin 2A receptors appear also to be crucially involved in the recognition of negative facial expressions, because ketanserin blocked psilocybin-induced attenuation in recognizing negative emotional states from the eye region of human faces. This finding is in line with the central role of serotonin in emotional facial recognition as previously established by pharmacologic (29–33) and genetic studies (57) but extends this notion by showing that specific activation of 5-HT_{2A} receptors likely biases facial recognition away from negative emotion. This mechanism might also contribute to the attenuated recognition of negative facial expression as previously observed after a single dose of MDMA (33) and after chronic administration of SSRIs (29,58), because MDMA has a moderate affinity at 5-HT_{2A} receptors (59) and chronic SSRI administration changes 5-HT_{2A} receptor density (60,61).

Goal-Directed Behavior

In the emotional go/nogo task, psilocybin enhanced the response bias toward positive relative to neutral and negative emotional stimuli, which was evidenced at the behavioral level by the psilocybin-induced increase in reaction times to negative and neutral compared with positive stimuli. In addition, this response bias was modulated by the sequential context of the stimuli across all drug conditions, an effect that was augmented by psilocybin ad-

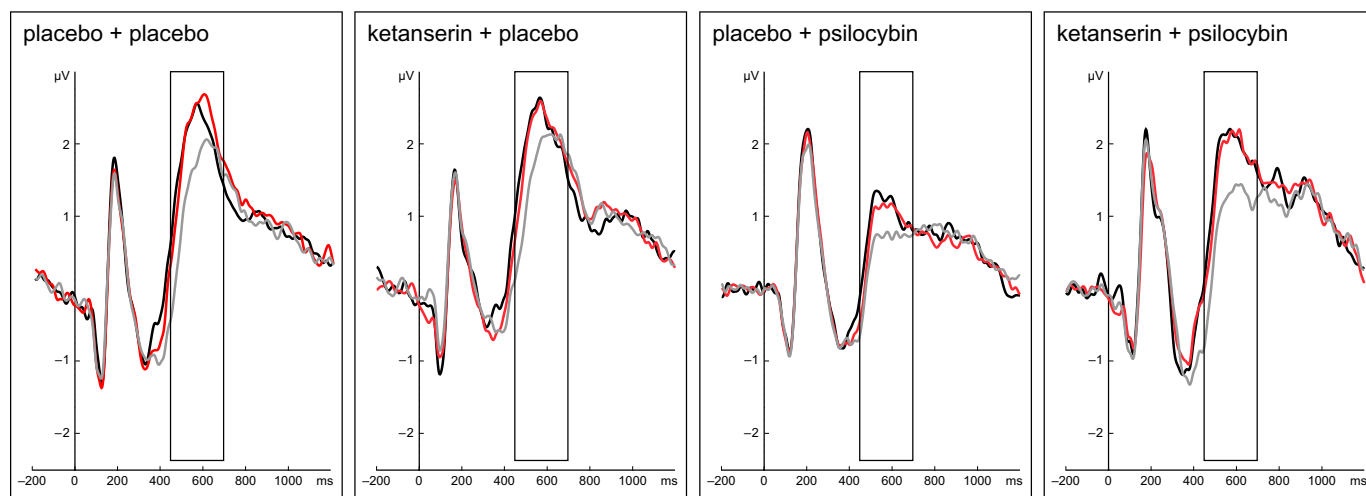


Figure 7. Effect of psilocybin and ketanserin on the group-averaged event-related potential waveforms in response to positive (black traces), negative (red traces), and neutral stimuli (gray traces) averaged from FCz, Cz, CPz, and Pz electrode sites, where P300 amplitude was most pronounced. The box indicates the time range of the P300 component.

ministration. That is, across all drug conditions, sequential repetition of positive and neutral stimuli facilitated processing (62,63), as indicated by decreased reaction times to positive and neutral stimuli. Interestingly, this sequential facilitatory effect was lacking after negative stimuli, a finding that has not yet been reported in emotional go/nogo tasks but was previously observed in semantic (64,65) and negative affective priming tasks (66–68). Given that this lacking facilitation has been interpreted as an inhibition of negative concepts within the attentional (66) or memory system (65) and that psilocybin prolonged reaction time for repeated negative stimuli but decreased it for repeated positive stimuli, psilocybin may also increase inhibition of negative relative to positive concepts in the attentional or memory system.

Support for such a psilocybin-induced shift in the attentional system was revealed by the effect of psilocybin on event-related potentials. The event-related potentials analysis indicated that across all drug conditions, the word valence affected early and late response selection, inhibition, and attention processes as indexed by the decreased N2 and enhanced P3 component for emotional relative to neutral stimuli (69,70). Most importantly, while psilocybin and ketanserin did not modulate these valence-specific effects during the N2 time range, psilocybin strongly decreased the P300 component in all valence conditions and particularly for negative and neutral stimuli. Because this valence-dependent P300 decrease was equally present in both the go and nogo conditions, it is conceivable that this psilocybin-induced change in emotional processing is neither specific for response selection (go) nor specific for inhibition (nogo) but rather reflects a more general process underlying the P300. For instance, the P300 amplitude is strongly modulated by the amount of attentional resource allocation (71), and several behavioral studies previously showed that psilocybin attenuates attentional performance (41,72,73). This suggests, on the one hand, that the strong psilocybin-induced decrease of the P300 seen across all valence conditions might reflect an important electrophysiological index of the previously reported psilocybin-induced attentional deficits. On the other hand, the small valence-dependent decrease suggests that psilocybin may attenuate the allocation of attentional resources to neutral and negative stimuli more strongly than to positive stimuli, which results in a relative positive attentional bias.

Contrary to the crucial contribution of 5-HT_{2A} receptors in modulating mood states and emotional face recognition, the psilocybin-induced relative bias toward the processing of positive emotions in the go/nogo task were not blocked by pretreatment with ketanserin. Thus, the psilocybin-induced emotional bias might rather be due to a stimulation of 5-HT_{1A} or 5-HT_{2C} receptors than 5-HT_{2A} receptors. However, the strong valence-independent reduction of the P300 seen after psilocybin administration was partially reversed by ketanserin, indicating an involvement of 5-HT_{2A} receptors in the valence-independent attentional performance.

Implication for Mood Disorders

In the present study, psilocybin produced behavioral and electrophysiological effects that were opposite to the dysfunctional emotional processing bias seen in depressed subjects in emotional facial recognition (1,29–31), goal-directed behavior (2,3,70), and mood states. For example, in the emotional go/nogo task, psilocybin increased RTs and decreased P300 amplitudes, particularly for negative and neutral stimuli, while depressed subjects were delayed in responding to positive cues (2,3) and displayed increased P300 component for negative stimuli (70). Thus, it appears that psilocybin may have the potential to acutely shift dysfunctional emotional biases in depression. Such an acute shift might, in con-

junction with the reported effect of psilocybin on neuroplastic factors (24), lead to sustained adaptations and may therefore account for the discussed antidepressant potential of psilocybin-like compounds (24,28). Hence, further studies using different and multiple doses of psilocybin are indicated to explore whether the effect of psilocybin on emotional biases are dose-dependent and whether psilocybin may shift the negative emotional biases seen in depression.

Furthermore, here we identify 5-HT_{2A} receptor activity as a potential crucial pharmacologic target in the treatment of negative mood states and negative emotional facial recognition bias. In line with this finding, negative mood is associated with pessimistic attitudes (74) and medication-free major depression patients with high pessimistic attitudes have increased 5-HT_{2A} receptor binding in the prefrontal cortex compared with healthy control subjects (8–10). Furthermore, chronic administration of SSRIs not only shifts negative mood states and negative bias in facial recognition in depressed patients (29,58) but also seems to normalize alterations in 5-HT_{2A} receptor densities in depressed subjects (60,61). In summary, the present study indicates that the assessment of the effects of psilocybin provides a valuable framework to identify neuropsychopharmacologic mechanisms underlying dysfunctional emotional biases and the putative antidepressant effects of psilocybin and related compounds.

This work was generously supported by the Swiss Neuromatrix Foundation.

We thank George Greer for critical comments on the manuscript and Theodor Huber, Beatrix Römer, Marlis Boss, and Barbara Rauscher for conducting the physical health checkup. We express our appreciation to Petra Schäfle for her assistance in recruiting and measuring.

All authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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