

# Psilocybin-Induced Decrease in Amygdala Reactivity Correlates with Enhanced Positive Mood in Healthy Volunteers

Rainer Kraehenmann, Katrin H. Preller, Milan Scheidegger, Thomas Pokorny, Oliver G. Bosch, Erich Seifritz, and Franz X. Vollenweider

## ABSTRACT

**BACKGROUND:** The amygdala is a key structure in serotonergic emotion-processing circuits. In healthy volunteers, acute administration of the serotonin 1A/2A/2C receptor agonist psilocybin reduces neural responses to negative stimuli and induces mood changes toward positive states. However, it is little-known whether psilocybin reduces amygdala reactivity to negative stimuli and whether any change in amygdala reactivity is related to mood change.

**METHODS:** This study assessed the effects of acute administration of the hallucinogen psilocybin (.16 mg/kg) versus placebo on amygdala reactivity to negative stimuli in 25 healthy volunteers using blood oxygen level-dependent functional magnetic resonance imaging. Mood changes were assessed using the Positive and Negative Affect Schedule and the state portion of the State-Trait Anxiety Inventory. A double-blind, randomized, cross-over design was used with volunteers counterbalanced to receive psilocybin and placebo in two separate sessions at least 14 days apart.

**RESULTS:** Amygdala reactivity to negative and neutral stimuli was lower after psilocybin administration than after placebo administration. The psilocybin-induced attenuation of right amygdala reactivity in response to negative stimuli was related to the psilocybin-induced increase in positive mood state.

**CONCLUSIONS:** These results demonstrate that acute treatment with psilocybin decreased amygdala reactivity during emotion processing and that this was associated with an increase of positive mood in healthy volunteers. These findings may be relevant to the normalization of amygdala hyperactivity and negative mood states in patients with major depression.

**Keywords:** Amygdala, Depression, Emotion, fMRI, Psilocybin, Serotonin

<http://dx.doi.org/10.1016/j.biopsych.2014.04.010>

The amygdala is a key structure in the serotonergic neuro-circuitry of emotion processing and thus plays a crucial role in the perception and generation of emotions (1,2). Amygdala hyperactivity in response to negative stimuli and a relation between amygdala activity and negative mood states have consistently been found in depressed patients and individuals at risk of major depression (3–5). Amygdala hyperactivity in patients with major depression decreased after treatment with selective serotonin reuptake inhibitors (SSRIs) and this was associated with mood changes toward positive states (6,7). Growing evidence suggests that genetic dysfunctions in serotonergic neurotransmission underlie amygdala hyperactivity in major depression and constitute a vulnerability marker of major depression (8–10). The relevance of serotonin (5-hydroxytryptamine [5-HT]) neurotransmission in the pathogenesis and treatment of major depression is further supported by the finding that depletion of tryptophan, a precursor in the biosynthesis of serotonin, induced depression in vulnerable individuals (11) and that SSRIs have strong antidepressant properties (1). These and other findings (12–14) implicate the amygdala in the pathogenesis of major depression.

The hallucinogen psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is the main psychoactive principle of many species of the genus *Psilocybe*, commonly known as magic mushrooms (15). Psilocybin acts as a selective agonist on 5-HT<sub>1A/2A/2C</sub> receptors (16,17). In line with the notion that modulation of serotonergic neurotransmission may critically alter neural activity within circuits related to emotion processing, it has recently been shown (18–23) that psilocybin may alter neural activity as well as induce sustained neuroplastic adaptations within circuits related to emotion processing. These and previous studies (24–26) suggest that psilocybin has antidepressant properties, as it acutely induces mood changes toward positive states and reduces neural responses to negative stimuli in healthy subjects. This effect might counteract negative mood states and neural hyperactivity in response to negative perceptual input in patients with major depression. In support of this view, a recent clinical trial (27) of the effect of psilocybin in patients with depression and anxiety related to advanced stage cancer found that a single dose of psilocybin significantly decreased anxiety and increased positive mood state for up to 6 months. However, the

SEE COMMENTARY ON PAGE 516

neurobiological mechanisms by which psilocybin influences emotion processing remain poorly understood. In particular, there is sparse evidence (21) whether psilocybin modulates the activity of the amygdala, a region that plays a crucial role in the neural effects of antidepressants (28), during emotion processing and whether any psilocybin-induced effect on amygdala activity during emotion processing is related to changes in mood state.

Thus, in this pharmacologic functional magnetic resonance imaging (fMRI) study, we evaluated the neural effects of psilocybin on brain activity during emotion processing, focusing on the amygdala as a region of interest (ROI). We conducted statistical parametric mapping on fMRI blood oxygen level-dependent (BOLD) responses during an established amygdala reactivity task (8) in healthy volunteers following administration of psilocybin and placebo. In addition, we assessed the effects of psilocybin on mood states using validated self-rating questionnaires. Thus, the present study provides an evaluation of the neural mechanisms underlying the acute effects of psilocybin on emotion processing in relation to mood changes. We hypothesized that a single dose of psilocybin would decrease amygdala reactivity to negative stimuli and increase positive mood state.

## METHODS AND MATERIALS

### Study Design

Twenty-five healthy, right-handed subjects (16 male subjects, mean age  $24.2 \pm 3.42$  years, all students or university-educated persons) with normal or corrected-to-normal vision were recruited through advertisements placed in local universities. Subjects were healthy according to medical history, physical examination, routine blood analysis, electrocardiography, and urine tests for drug abuse and pregnancy. Most subjects had no history of previous hallucinogen use (Table S1 in Supplement 1). Using a randomized, double-blind, placebo-controlled, cross-over design, subjects received either placebo or .16 mg/kg oral psilocybin in two separate imaging sessions at least 14 days apart. Based on our hypothesis, variables related to mood state were of particular interest in this study. Mood state was assessed using the Positive and Negative Affect Schedule (PANAS) (29) and the state portion of the State-Trait Anxiety Inventory (STAI) (30) before and 210 minutes after each drug treatment. The study was approved by the Cantonal Ethics Committee of Zurich. Written informed consent was obtained from all subjects and the study was performed in accordance with the Declaration of Helsinki. See Supplement 1 for further information on screening and experimental procedures.

### Experimental Paradigm

During fMRI, subjects first completed a slightly modified version of the amygdala reactivity task (8,31,32). The task comprised alternating blocks of emotional picture discrimination tasks. The picture discrimination task was interspersed with shape discrimination tasks, which served as baseline tasks and allowed amygdala responses to return to baseline (Supplement 1). It has been shown to reliably and robustly activate the amygdala and its use has been effective in other pharmacologic fMRI studies (31,33–36). Second, subjects

performed a simple motor task, which was used to examine whether the effects of psilocybin were specific to the amygdala and to emotion processing or confounded by global pharmacologic effects on the BOLD signal (see Supplement 1 for details about stimulus material, task design, and implementation of the paradigm).

### fMRI Analysis

Blood oxygen level-dependent fMRI data analysis was completed using SPM12b (Wellcome Trust Centre for Neuroimaging, London, United Kingdom; <http://www.fil.ion.ucl.ac.uk/spm/>) (see Supplement 1 for details on image acquisition parameters, preprocessing, design matrix, and analysis of the motor task). The amygdala reactivity task was analyzed as follows: using both left and right amygdala masks, we first assessed significant differences of amygdala reactivity between the psilocybin and placebo conditions using a second-level voxel-wise analysis of variance (ANOVA) with drug (psilocybin and placebo) and emotion (negative vs. shapes: contrast 1 0 -1; and neutral vs. shapes: contrast 0 1 -1) as within-subject factors and subject as a random factor, followed by paired *t* tests for planned comparisons between psilocybin and placebo sessions. Amygdala masks were based on anatomically defined ROIs from the Automated Anatomical Labeling atlas (Groupe d'Imagerie Neurofonctionnelle, Caen Cedex, France) (37) implemented in the WFU PickAtlas tool (Wake Forest University Health Sciences, Winston-Salem, North Carolina) (38). For our a priori hypothesis in the amygdala ROI, the significance threshold was set to  $p < .05$ , family-wise error (FWE) corrected for multiple comparisons across the amygdala (small volume correction) (39) at an initial voxel-level threshold of  $p < .001$  and an extent threshold of  $k = 0$  voxels.

Second, BOLD signal responses (parameter estimates in arbitrary units) were extracted from both left and right amygdala ROIs for each emotion condition (negative vs. shapes and neutral vs. shapes) and from each session separately (psilocybin and placebo) using the same anatomical masks as described above. The anatomical ROI extractions from the left and right amygdala were then analyzed using 1) a repeated-measures ANOVA with emotion (negative and neutral), laterality (left and right amygdala), and drug (psilocybin and placebo) as within-subject factors; and 2) Bonferroni-corrected paired *t* tests for planned comparisons between psilocybin and placebo sessions, with significance set at  $p < .05$ . Given previous evidence that hallucinogens may increase baseline brain activity (16,40), we additionally extracted BOLD signal responses from bilateral amygdala ROIs for the control condition during the baseline tasks (shape discrimination) and used paired *t* tests to address the question of whether psilocybin increased amygdala activity during the control condition.

Third, an exploratory whole-brain ANOVA with drug (psilocybin and placebo) and emotion (negative and neutral vs. control shapes) as within-subject factors and subjects as a random factor was carried out to determine whether psilocybin affected nonhypothesized brain regions. The significance threshold was set to  $p < .05$ , FWE-corrected, for multiple comparisons across the entire brain with an extent threshold of  $k = 0$  voxels.

Fourth, given our primary focus of psilocybin's effects on amygdala reactivity and mood state in relation to emotion

processing and given the results of our exploratory whole-brain analysis (showing significant psilocybin-induced decreases in the BOLD signal in visual cortical regions), we conducted Pearson correlations between the activity in the right amygdala during the negative emotional condition (psilocybin-placebo change score) and each of the five mood rating scores (psilocybin-placebo change score for PANAS positive affect, PANAS negative affect, STAI anxiety, and the Altered States of Consciousness questionnaire score for elementary and complex imagery) to account for influences of mood and visual perceptual alterations. To demonstrate the specificity of our findings from the correlation analyses, a multiple regression analysis was conducted with removal with right amygdala BOLD change as the dependent variable and the five rating scores as predictor variables. Predictor variables were mean-centered before the analyses. Residual tests and diagnostic plots were used to detect outliers and to ascertain that regression modeling assumptions were met.

## RESULTS

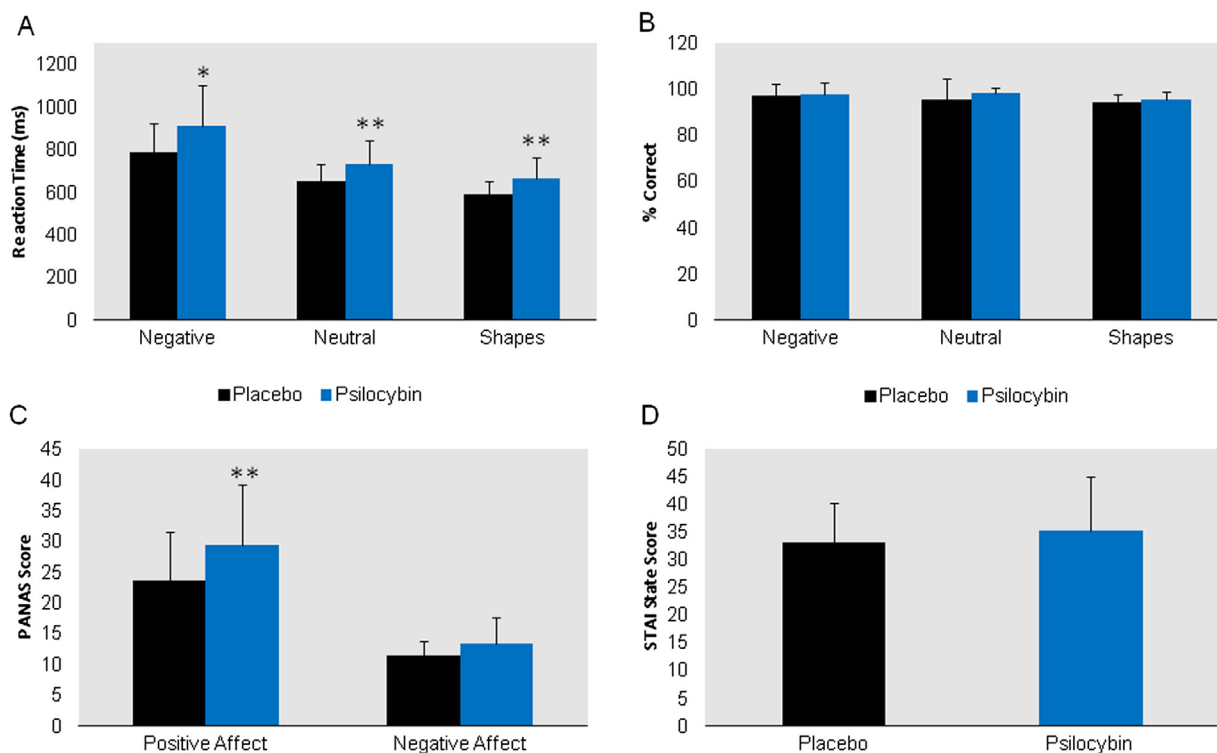
### Mood Ratings

Psilocybin significantly increased positive affect (Bonferroni-corrected  $p = .001$ , Figure 1) but not negative affect (Bonferroni-corrected  $p = .87$ ) or state anxiety (Bonferroni-corrected

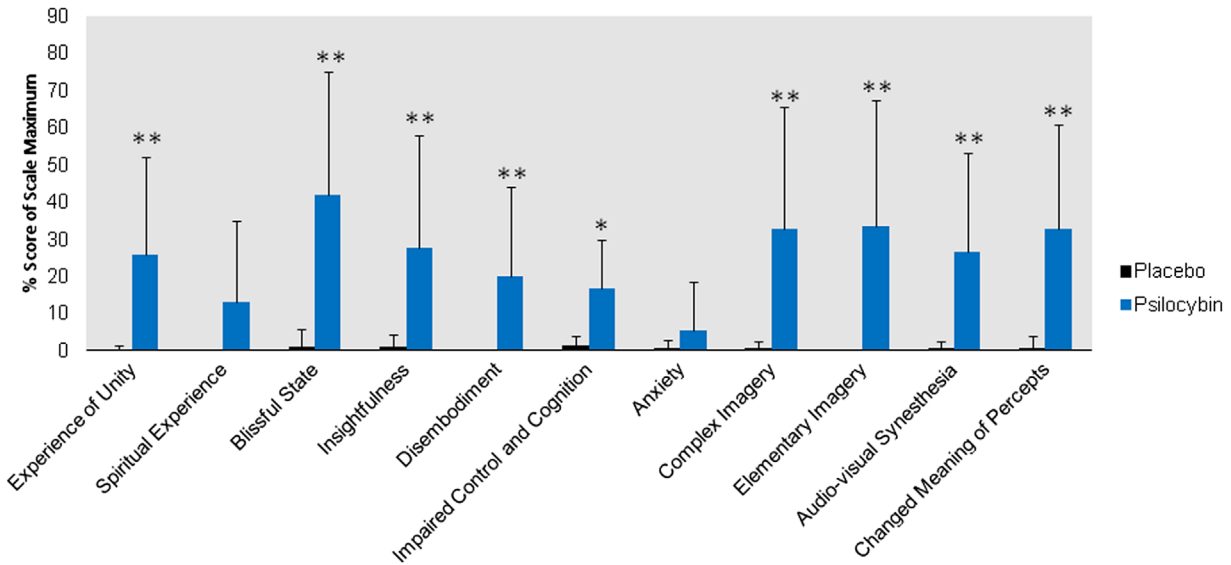
$p = .37$ ). See Supplement 1 for detailed results of the effects of psilocybin on behavioral measures and mood state (Figure 2).

### Effects of Psilocybin on Amygdala and Motor Cortex Reactivity

In the whole-brain voxel-wise fMRI data analysis, there was a significant main effect of drug localized within the right amygdala (peak Montreal Neurological Institute coordinates 27, -4, -19;  $F_{1,72} = 27.25$ ;  $Z = 4.25$ ; FWE-corrected  $p < .001$ ; Table 1) but no drug  $\times$  emotion interaction (all FWE-corrected  $p > .05$ ). Paired  $t$  tests for planned comparisons showed that psilocybin significantly attenuated right amygdala activation to both negative (24, -4, -22;  $Z = 4.38$ ; FWE-corrected  $p = .001$ ) and neutral (27, -7, -19;  $Z = 4.60$ ; FWE-corrected  $p < .001$ ) pictures (Figure 3; Table S2 in Supplement 1). Consistent with these results, the ROI-based analysis revealed a significant main effect of drug ( $F_{1,24} = 19.45$ ;  $p < .001$ ) but no drug  $\times$  emotion interaction ( $F_{1,24} = .29$ ;  $p = .59$ ; Table S3 in Supplement 1). In addition, there was a significant drug  $\times$  side interaction ( $F_{1,24} = 6.24$ ;  $p < .05$ ), and paired  $t$  tests showed that psilocybin, compared with placebo, preferentially reduced activation of the right amygdala to both negative (vs. shapes; psilocybin mean BOLD signal parameter estimates mean  $\pm$  SD:  $.36 \pm .28$ ; placebo:  $.58 \pm .23$ ;  $p < .001$ )



**Figure 1.** Behavioral and subjective effects of placebo and a .16 mg/kg dose of oral psilocybin. Reaction time (A) and accuracy (B) in a modified amygdala reactivity task with negative pictures, neutral pictures and shapes, and mood state assessed using the Positive and Negative Affect Schedule (PANAS) (C) and the state portion of the State-Trait Anxiety Inventory (STAI) (D) after placebo (black) and psilocybin (blue) treatment. Data are expressed as mean plus SD. Asterisks indicate significant differences between psilocybin and placebo treatment (\* $p < .05$ ; \*\* $p < .001$ ).



**Figure 2.** Score for each subscale of the Altered States of Consciousness Scale during placebo and psilocybin treatment. The subscale score was higher during psilocybin treatment (blue) than during placebo treatment (black) for all symptoms except spiritual experience and anxiety. Scores are expressed as percent of scale maximum. Data are expressed as mean plus SD. Asterisks indicate significant differences between psilocybin and placebo treatment (\* $p < .05$ ; \*\* $p < .001$ ).

and neutral (vs. shapes; psilocybin:  $.15 \pm .33$ ; placebo:  $.31 \pm .19$ ;  $p < .001$ ) pictures and to a significantly smaller extent ( $p < .05$ ) reduced activation of the left amygdala to negative (vs. shapes; psilocybin:  $.49 \pm .30$ ; placebo:  $.62 \pm .26$ ;  $p < .05$ ) but not neutral (vs. shapes; psilocybin:  $.19 \pm .34$ ; placebo:  $.29 \pm .19$ ;  $p = .24$ ; Figure 3) pictures.

Paired  $t$  tests showed that activation during the baseline task was not significantly different between placebo and psilocybin sessions in either the right amygdala ( $t = .05$ ,  $p = .96$ ) or left amygdala ( $t = -1.20$ ,  $p = .24$ ; Figure S1 in Supplement 1). Therefore, there was no evidence that psilocybin increased baseline activity in the amygdala. During a separate motor task, we further investigated whether there were global pharmacologic effects of psilocybin on brain activation. The primary motor cortex was activated during both placebo ( $-39, -22, 65$ ;  $Z = 7.03$ ; FWE-corrected  $p < .001$ ) and psilocybin ( $-36, -19, 53$ ;  $Z = 6.70$ ; FWE-corrected  $p < .001$ ) sessions (Figure 4). Importantly, no significant differences were found in primary motor cortex activation between placebo and psilocybin sessions, even at a liberal threshold of  $p < .05$ , uncorrected. Complementary ROI-based analyses of primary motor cortex activation confirmed the lack of difference between placebo and psilocybin sessions ( $t = .36$ ,  $p = .72$ ; Figure 4). The Savage-Dickey Bayes factor  $t$  test supported this; the null hypothesis that there was no effect of psilocybin was six times more probable than the alternative hypothesis.

In sum, the fMRI data showed that psilocybin significantly reduced right amygdala activation to both negative and neutral pictures (vs. shapes) and this was not driven by an increase in activation in the control condition during the baseline task. Moreover, psilocybin had no effect on activation of the primary motor cortex.

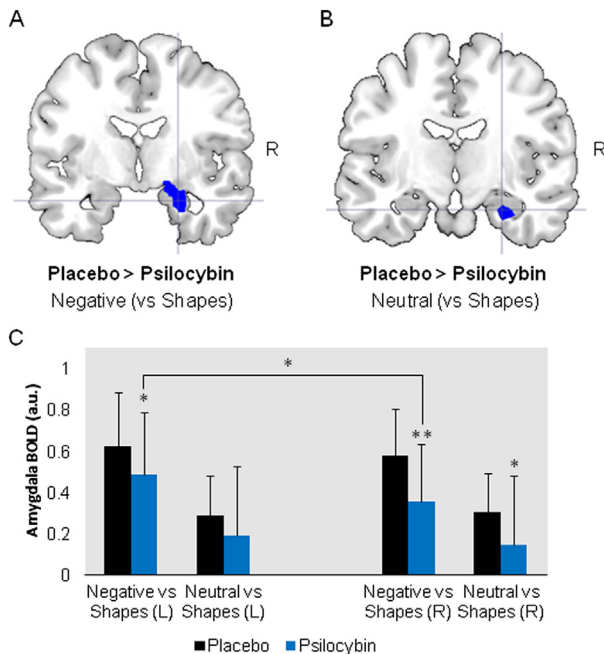
**Table 1. Results of Whole-Brain Repeated-Measures Analysis of Variance for a Main Effect of Drug and Drug-Related Interactions on Blood Oxygen Level-Dependent Signal Intensity in Amygdala Reactivity Task<sup>a</sup>**

Region	Side	Coordinates			Cluster k	Voxel	
		x	y	z		F	Z
<b>Drug Main Effects</b>							
Amygdala <sup>b</sup>	R	27	-4	-19	29	27.25	4.25
Calcarine sulcus	R	24	-58	14	269	53.1	5.18
	L	-21	-64	11	165	49.6	5.01
Lingual gyrus	R	18	-70	-4	372	122	>8
	L	-21	-49	-7	445	84.1	7.35
Superior occipital gyrus	R	27	-82	23	250	137	>8
	L	-15	-85	38	240	89.8	7.52
Middle occipital gyrus	R	27	-88	17	341	131	>8
	L	-30	-79	20	540	97.1	7.72
Inferior occipital gyrus	R	39	-76	-1	199	98	7.75
	L	-39	-79	-10	188	96.5	7.70
Fusiform gyrus	R	33	-51	-10	385	108	>8
	L	-27	-70	-7	356	120	>8
Inferior temporal gyrus	R	48	-40	-19	94	39	5.44
	L	-39	-28	-19	62	31.6	4.97
<b>Drug × Valence Interactions</b>							
No suprathreshold voxels							

L, left; R, right.  
<sup>a</sup>Significance threshold set at  $p < .05$ , family-wise error-corrected for multiple comparisons across the entire brain, at an extent threshold  $k \geq 0$  voxels.

<sup>b</sup>Significance threshold set at  $p < .05$ , family-wise error-corrected for multiple comparisons across the amygdala (small volume correction) at an initial voxel-level threshold of  $p < .001$  and an extent threshold of  $k = 0$  voxels.





**Figure 3.** Effects of psilocybin on amygdala activation. **(A)** Statistical *t* map overlaid on a canonical brain slice (Montreal Neurological Institute coronal *y* plane = -4) showing greater right (R) amygdala activation to negative pictures (vs. shapes) in the placebo session than in the psilocybin session (placebo > psilocybin). **(B)** Statistical *t* map overlaid on a canonical brain slice (Montreal Neurological Institute coronal *y* plane = -10) showing greater right amygdala activation to neutral pictures (vs. shapes) in the placebo session than in the psilocybin session (placebo > psilocybin). The significance threshold was set to  $p < .05$ , family-wise error-corrected for multiple comparisons across the amygdala (small volume correction) at an initial voxel-level threshold of  $p < .001$  and an extent threshold of  $k = 0$  voxels. **(C)** Extracted blood oxygen level-dependent (BOLD) responses (mean parameter estimates, arbitrary units [a.u.]) to negative and neutral pictures (vs. shapes) from the left (L) and right amygdala for each session (placebo and psilocybin), showing attenuation of amygdala reactivity by psilocybin treatment and greater attenuation of right amygdala reactivity than of left amygdala reactivity. Data are expressed as mean plus SD. Asterisks indicate significant differences between psilocybin and placebo treatment (\* $p < .05$ ; \*\* $p < .001$ ).

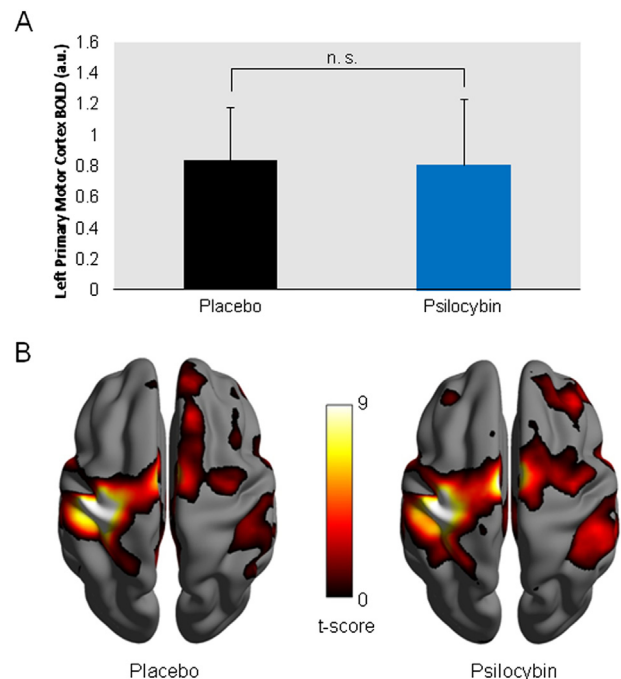
### Whole-Brain Analysis

The voxel-wise whole-brain analysis revealed a main effect of drug in bilateral occipital gyri, lingual gyrus, fusiform gyrus, and temporal gyri (all FWE-corrected  $p < .05$ , Table 1). There was no significant drug  $\times$  emotion interaction (all FWE-corrected  $p > .05$ ). Paired *t* tests showed that psilocybin significantly attenuated activation in these regions in response to both negative and neutral pictures (Table S2 in Supplement 1). No area was activated to a significantly greater degree by psilocybin than by placebo (all FWE-corrected  $p > .05$ ). To further investigate whether the observed decreases of regional activity were either driven by a decrease of BOLD responses to negative stimuli during the emotional picture discrimination task or by an increase of BOLD responses to the control condition (shapes) during the baseline task, we additionally

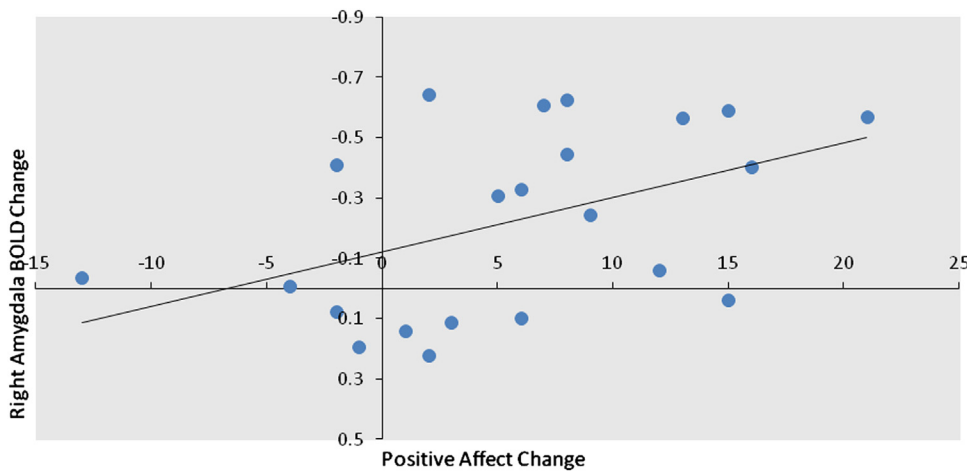
extracted BOLD responses of the negative condition and the control condition for each session (placebo and psilocybin). Paired *t* tests showed that the psilocybin-induced attenuation of regional activity was driven by decreased activation to negative stimuli (all Bonferroni-corrected  $p < .04$ ) but not by increased activation to the control condition during the baseline task (all Bonferroni-corrected  $p > .44$ ; Figure S1 in Supplement 1).

### Relation between Amygdala Reactivity, Mood, and Visual Hallucinations

We found a significant relation between (psilocybin-placebo) amygdala reactivity change and (psilocybin-placebo) positive affect change; psilocybin-induced attenuation of amygdala reactivity was significantly correlated with increase of positive mood ( $r = -.46$ ,  $p < .05$ ; Figure 5). None of the other variables were correlated with amygdala reactivity change (all  $p > .1$ ). A multiple regression analysis confirmed the specificity of this relation; positive affect was the only significant predictor variable of right amygdala BOLD change (model:  $F = 5.44$ ,  $p = .03$ , adjusted  $R^2 = .17$ ; positive affect:  $\beta = -.46$ ,  $t = -2.33$ ,  $p = .03$ ).



**Figure 4.** Psilocybin effects on primary motor cortex activation. **(A)** Extracted blood oxygen level-dependent (BOLD) responses (mean parameter estimates, arbitrary units [a.u.]) to the active condition (vs. rest) from the left primary motor cortex for each session (placebo and psilocybin), showing that the BOLD change in the primary motor cortex was similar in the placebo and psilocybin sessions ( $p = .72$ ). Data are expressed as mean plus SD. **(B)** Statistical *t* map overlaid on a canonical brain rendering (dorsal view) showing similar primary motor cortex activation in the placebo and psilocybin sessions. n.s., nonsignificant.



**Figure 5.** Scatter plot ( $n = 22$ ) showing the relation between the change in blood oxygen level-dependent (BOLD) signal in the right amygdala (difference between psilocybin and placebo sessions) and the change in the positive affect subscale of the Positive and Negative Affect Schedule (difference between psilocybin and placebo sessions) following psilocybin administration. The (psilocybin-placebo) increase in positive affect (x axis) was significantly correlated with the (psilocybin-placebo) decrease (y axis) of right amygdala BOLD signal ( $r = -.46, p < .05$ ).

## DISCUSSION

In this study, we found that psilocybin attenuated task-induced activation in the amygdala in response to negative and neutral pictures but had no effect on activation of the primary motor cortex. This psilocybin-induced effect was significantly stronger in the right amygdala than in the left amygdala. Furthermore, psilocybin increased subjective reports of positive mood but did not increase anxiety. Importantly, the effect of psilocybin on amygdala reactivity was most strongly associated with positive mood change. Reduction of amygdala reactivity by psilocybin is consistent with our a priori hypothesis and provides a mechanistic framework to understand psilocybin-induced effects on emotion processing. The current findings support the notion that psilocybin has the potential to normalize limbic hyperactivity in persons with depressed mood state.

We did not find a significant drug by emotion interaction, and planned comparisons showed a reduction of amygdala reactivity in response to both negative and neutral pictures. Therefore, our results do not support a valence-specific effect of psilocybin on amygdala reactivity, i.e., we cannot conclude that psilocybin specifically reduced amygdala reactivity in response to negative pictures. This is in line with previous electrophysiological studies where valence-specific effects of psilocybin on emotion processing have been found but only for positive stimuli, not for neutral stimuli, and only within the first 200 milliseconds after stimulus onset (19–21). For example, Bernasconi *et al.* (21) found a decrease of early (168–189 milliseconds after stimulus onset) electrophysiological responses to negative and neutral faces localized within bilateral parahippocampal/insula and right temporo-occipital regions and a decrease of late (211–242 milliseconds after stimulus onset) electrophysiological responses to positive faces within the same regions. Therefore, our study might have missed valence-specific effects because we used a blocked-design fMRI method, which has good spatial resolution but relatively low temporal resolution compared with electroencephalography (41). Future studies using time-varying stimulus conditions might further clarify this discrepancy.

The observed effects of psilocybin on amygdala reactivity in response to negative and neutral stimuli were lateralized to the

right side. This finding is in accordance with recent evidence that SSRIs preferentially attenuate right amygdala responses to negative stimuli (42,43). The preferential effect of SSRIs on the right amygdala might be attributable to genetic variations in the expression of serotonin transporters, as recent studies have revealed that genetic variations in the availability of serotonin transporters are associated with individual differences in right amygdala activity (8,9). The notion that the right amygdala is particularly relevant to processing negative emotions is further supported by a study in patients undergoing surgery for treatment-resistant partial epilepsies (44), which reported that direct electrical stimulation of the right amygdala induced negative emotions, whereas stimulation of the left amygdala induced either positive or negative emotions. However, findings regarding lateralization of serotonergic effects on amygdala reactivity during emotion processing are still divergent (42–44), and a recent meta-analysis (10) reported similar effect size for the right and left amygdala. Therefore, the relevance of the observed lateralization effect remains inconclusive.

The complementary whole-brain analysis revealed that psilocybin decreased activation in the visual cortex. Transcranial magnetic stimulation studies (45–47) have shown that in the hallucinating brain, the visual cortex is in a state of hyperexcitability, leading to increased BOLD signals in the visual cortex due to internally generated neuronal excitation. It has been shown that a tonic increase of neuronal activity may actually decrease BOLD responses to external, task-related stimuli in the visual cortex (48). Therefore, the psilocybin-induced decrease of activation in the visual cortex might be related to hyperexcitability of neurons in the visual cortex and to visual perceptual alterations. This notion is supported by the recent studies of Kometer *et al.* (49,50), which demonstrated that psilocybin decreased stimulus-induced responses in the visual cortex and the decrease correlated with the intensity of visual hallucinations. However, given that we evaluated a contrast (negative minus shapes—both of which included a visual stimulus) that decreased during psilocybin treatment in areas shown in Table 1 and given that psilocybin-induced decrease of activity in these regions was driven by decreased BOLD responses to negative stimuli but not by increased

BOLD responses to the baseline condition, we cannot conclude that an increase of baseline activity in the visual cortex caused the observed BOLD decreases. Given the abundance of backprojections from the amygdala to the visual cortex that may modulate processing of threat-related signals in the visual cortex (51), we speculate that psilocybin-induced attenuation of amygdala activation might have reduced the activation that normally occurs in the visual cortex in response to threat-related visual stimuli. This notion is supported by an event-related fMRI study in patients with medial temporal lobe sclerosis (52) that showed amygdala lesions may attenuate activation of visual cortex in response to fearful stimuli. However, future connectivity studies are warranted to investigate the effects of psilocybin on emotion processing and amygdala reactivity in relation to distant brain regions. This notion is supported by a recent study of Hornboll *et al.* (53) reporting that ketanserin administration modulated amygdala-frontal coupling in response to fearful faces.

In addition to the effects on amygdala reactivity, psilocybin increased positive mood state, as evidenced by a pronounced increase in the PANAS positive affect subscore, but had no effect on negative mood state, as indicated by the PANAS negative affect subscore, or anxiety, as indicated by the STAI state score. Psilocybin is a mixed 5-HT<sub>1A/2A/2C</sub> receptor agonist, and it has consistently been shown that the psychotropic effects of psilocybin are predominantly mediated by activation of 5-HT<sub>2A</sub> receptors (16,17). Therefore, the finding that psilocybin acutely increased positive mood state is consistent with psilocybin-ketanserin blocking studies (19,54) that showed the 5-HT<sub>2A/2C</sub> receptor antagonist ketanserin completely blocked the mood-increasing effects of psilocybin. Notably, we found that the psilocybin-induced increase in positive mood state was related to the psilocybin-induced decrease in right amygdala reactivity. Given the dependence of psilocybin-induced mood changes on 5-HT<sub>2A</sub> receptors, these results indicate that 5-HT<sub>2A</sub> receptor stimulation critically underlies the observed effects of psilocybin on right amygdala reactivity.

Nevertheless, at the synaptic level, the mechanism by which 5-HT receptor stimulation leads to inhibition of the amygdala is not completely understood. Despite strong evidence that activation of 5-HT<sub>2A</sub> receptors is necessary to mediate the hallucinogen action of psilocybin (16,17), psilocin, the bioactive metabolite of psilocybin, also activates 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors (55,56). Serotonergic neurons originate in the brainstem raphe nuclei and release 5-HT at terminal nerve ends within projection areas, such as the amygdala (57–59). In the amygdala, both 5-HT<sub>1A</sub> (60,61) and 5-HT<sub>2A</sub> receptors (62–64) are present in large quantities and are located on gamma-aminobutyric acidergic interneurons that inhibit postsynaptic cell firing (65). Therefore, 5-HT receptor stimulation in the amygdala may indirectly inhibit amygdala reactivity via activation of postsynaptic 5-HT receptors (61,66). Given the critical role of 5-HT<sub>1A/2A</sub> receptors in mood (67–69) and anxiety disorders (70–73) and given the abundance of postsynaptic 5-HT<sub>1A/2A</sub> receptors in the amygdala (59), the observed attenuation of amygdala reactivity might also have resulted from activation of either 5-HT<sub>1A</sub> or 5-HT<sub>2A</sub> postsynaptic receptors. The view that amygdala inhibition is mediated by 5-HT activation is supported by the observation that central 5-HT-deficient mice showed a higher level of

amygdala/hippocampus-dependent fear conditioning than wild-type mice, and this was reversed by cerebral injection of 5-HT (74). Moreover, Catlow *et al.* (75) reported that psilocybin facilitated extinction of conditioned fear responses in the amygdala/hippocampus in mice, thus providing strong evidence of 5-HT<sub>1A/2A</sub>-related inhibition of amygdala/hippocampus reactivity. Finally, a combined positron emission tomography–fMRI study by Fisher *et al.* (76) demonstrated that 5-HT<sub>1A</sub> autoreceptor density in the brainstem region of the dorsal raphe nucleus accounted for 44% of the variability in right amygdala reactivity during emotion processing. In addition, given that psilocybin is also a 5-HT<sub>2C</sub> agonist (56), 5-HT<sub>2C</sub> activation might theoretically have contributed to the acute effects observed here. However, both animal (77) and human (78) studies have reported that acute 5-HT<sub>2C</sub> blockade, rather than 5-HT<sub>2C</sub> activation, may be anxiolytic, although psilocybin did not modulate state anxiety in this study. Therefore, we consider it rather implausible that 5-HT<sub>2C</sub> activation substantially contributed to the effects of psilocybin during emotion processing. In summary, substantial evidence indicates that an increase of serotonergic tone in the amygdala is a crucial mechanism underlying the acute effects of psilocybin. Therefore, it may be worth developing combined 5-HT<sub>1A/2A</sub> agonists that rapidly increase serotonergic neurotransmission in the amygdala, as available treatment options (e.g., SSRIs and buspirone) are inefficient, delayed, or associated with side effects (79,80).

In conclusion, our study investigated the neural substrates underlying the acute effects of psilocybin on emotion processing. We showed that acute treatment with psilocybin caused a marked decrease of amygdala reactivity in healthy volunteers and that this was related to an increase in positive mood state. These findings are in line with previous models of antidepressant action (34,81,82), which pose a decrease of amygdala reactivity as a necessary change associated with treatment response and remission from neuroaffective disturbance. Substantial support for the notion that psilocybin may have rapid antidepressant characteristics also comes from a recent clinical trial showing that in patients with depression and anxiety, a single dose of psilocybin improved mood and decreased anxiety for several months (27). However, despite this and previous evidence (18,22,24–26) of putative antidepressant effects, psilocybin might not show similar actions in patients with depression. Therefore, the effects of psilocybin on mood state and amygdala reactivity in patients with depression remain to be addressed in future clinical studies.

## ACKNOWLEDGMENTS AND DISCLOSURES

The study was supported by grants from the Swiss Neuro-matrix Foundation, Switzerland, and the Heffter Research Institute, United States.

We thank Philipp Stämpfli, Petra Schäfle, Silvia Studer, Anatol Schauwecker, Theodor Huber, Beatrix Römer, Marlise Boss, Bernhard Scheja, and Konstantinos Pipilidis for their excellent support.

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

## ARTICLE INFORMATION

From the Department of Psychiatry, Psychotherapy and Psychosomatics (RK, MS, OGB, ES), University of Zurich, Zurich, Switzerland; Department of Neuropsychopharmacology and Brain Imaging (RK, KHP, MS, TP, FXV), University of Zurich, Zurich, Switzerland; Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Zurich, Switzerland; and Institute for Biomedical Engineering (MS), University of Zurich and Swiss Federal Institute of Technology, Zurich, Switzerland.

Address correspondence to Rainer Kraehenmann, M.D., University of Zürich, Department of Psychiatry, Psychotherapy and Psychosomatics, Neuropsychopharmacology and Brain Imaging, Psychiatric Hospital, Lenggstrasse 31, Zürich, ZH 8032, Switzerland; E-mail: r.kraehenmann@bli.uzh.ch.

Received Dec 2, 2013; revised Apr 14, 2014; accepted Apr 14, 2014.

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.biopsych.2014.04.010>.

## REFERENCES

- DeRubeis RJ, Siegle GJ, Hollon SD (2008): Cognitive therapy versus medication for depression: Treatment outcomes and neural mechanisms. *Nat Rev Neurosci* 9:788–796.
- Phelps EA, LeDoux JE (2005): Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron* 48:175–187.
- Ramel W, Goldin PR, Eyer LT, Brown GG, Gotlib IH, McQuaid JR (2007): Amygdala reactivity and mood-congruent memory in individuals at risk for depressive relapse. *Biol Psychiatry* 61:231–239.
- Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS (2002): Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 51:693–707.
- Stuhmann A, Dohm K, Kugel H, Zwanzger P, Redlich R, Grotegerd D, et al. (2013): Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: Associations with anhedonia. *J Psychiatry Neurosci* 38:249–258.
- Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. (2004): Attenuation of the neural response to sad faces in major depression by antidepressant treatment: A prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry* 61:877–889.
- Victor TA, Furey ML, Fromm SJ, Ohman A, Drevets WC (2010): Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. *Arch Gen Psychiatry* 67:1128–1138.
- Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, et al. (2002): Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297:400–403.
- Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, et al. (2005): A susceptibility gene for affective disorders and the response of the human amygdala. *Arch Gen Psychiatry* 62:146–152.
- Murphy SE, Norbury R, Godlewska BR, Cowen PJ, Mannie ZM, Harmer CJ, Munafò MR (2013): The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: A meta-analysis. *Mol Psychiatry* 18:512–520.
- Wong ML, Licinio J (2001): Research and treatment approaches to depression. *Nat Rev Neurosci* 2:343–351.
- Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH (2012): Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of base line activation and neural response data. *Am J Psychiatry* 169:693–703.
- Drevets WC (2003): Neuroimaging abnormalities in the amygdala in mood disorders. *Ann N Y Acad Sci* 985:420–444.
- Hahn A, Lanzenberger R, Wadsak W, Spindelegger C, Moser U, Mien L, et al. (2010): Escitalopram enhances the association of serotonin-1A autoreceptors to heteroreceptors in anxiety disorders. *J Neurosci* 30:14482–14489.
- Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX (2004): Acute psychological and physiological effects of psilocybin in healthy humans: A double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berl)* 172:145–156.
- Nichols DE (2004): Hallucinogens. *Pharmacol Ther* 101:131–181.
- González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, et al. (2007): Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 53:439–452.
- Vollenweider FX, Kometer M (2010): The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nat Rev Neurosci* 11:642–651.
- Komater M, Schmidt A, Bachmann R, Studerus E, Seifritz E, Vollenweider FX (2012): Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biol Psychiatry* 72:898–906.
- Schmidt A, Kometer M, Bachmann R, Seifritz E, Vollenweider F (2013): The NMDA antagonist ketamine and the 5-HT agonist psilocybin produce dissociable effects on structural encoding of emotional face expressions. *Psychopharmacology (Berl)* 225:227–239.
- Bernasconi F, Schmidt A, Pokorny T, Kometer M, Seifritz E, Vollenweider FX (2013): Spatiotemporal brain dynamics of emotional face processing modulations induced by the serotonin 1A/2A receptor agonist psilocybin [published online ahead of print July 16]. *Cereb Cortex*.
- Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, et al. (2012): Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci U S A* 109:2138–2143.
- Carhart-Harris RL, Leech R, Williams TM, Erritzoe D, Abbasi N, Bargiotas T, et al. (2012): Implications for psychedelic-assisted psychotherapy: Functional magnetic resonance imaging study with psilocybin. *Br J Psychiatry* 200:238–244.
- Sercl M, Kovarik J, Jaros O (1961): [Clinical experiences with psilocybin (CY 39 Sandoz)]. *Psychiatr Neurol (Basel)* 142:137–146.
- Riedlinger TJ, Riedlinger JE (1994): Psychedelic and entactogenic drugs in the treatment of depression. *J Psychoactive Drugs* 26:41–55.
- Leuner H (1966): [Psychotherapy with the aid of hallucinogenic drugs] [German]. *Arzneimittelforschung* 16:253–255.
- Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR (2011): Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry* 68:71–78.
- Dannlowski U, Ohrmann P, Bauer J, Kugel H, Baune BT, Hohoff C, et al. (2007): Serotonergic genes modulate amygdala activity in major depression. *Genes Brain Behav* 6:672–676.
- Watson M, Clark LA, Tellegen A (1988): Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol* 54:1063–1070.
- Spielberger CD, Gorsuch RL (1983): Manual for the State-Trait Anxiety Inventory (Form Y) ("Self-Evaluation Questionnaire"). Palo Alto, CA: Consulting Psychologists Press.
- Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR (2002): The amygdala response to emotional stimuli: A comparison of faces and scenes. *Neuroimage* 17:317–323.
- Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003): Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry* 53:494–501.
- Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, et al. (2005): Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci* 25:11489–11493.
- Patin A, Hurlmann R (2011): Modulating amygdala responses to emotion: Evidence from pharmacological fMRI. *Neuropsychologia* 49:706–717.



35. Hariri AR, Mattay VS, Tessitore A, Fera F, Smith WG, Weinberger DR (2002): Dextroamphetamine modulates the response of the human amygdala. *Neuropsychopharmacology* 27:1036–1040.
36. Muñoz KE, Meyer-Lindenberg A, Hariri AR, Mervis CB, Mattay VS, Morris CA, Berman KF (2010): Abnormalities in neural processing of emotional stimuli in Williams syndrome vary according to social vs. non-social content. *Neuroimage* 50:340–346.
37. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15:273–289.
38. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003): An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19:1233–1239.
39. Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996): A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* 4:58–73.
40. Aghajanian GK, Marek GJ (1999): Serotonin, via 5-HT<sub>2A</sub> receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. *Brain Res* 825:161–171.
41. Dale AM, Halgren E (2001): Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr Opin Neurobiol* 11: 202–208.
42. Wager TD, Phan KL, Liberzon I, Taylor SF (2003): Valence, gender, and lateralization of functional brain anatomy in emotion: A meta-analysis of findings from neuroimaging. *Neuroimage* 19:513–531.
43. Sergerie K, Chochol C, Armony JL (2008): The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev* 32:811–830.
44. Baas D, Aleman A, Kahn RS (2004): Lateralization of amygdala activation: A systematic review of functional neuroimaging studies. *Brain Res Brain Res Rev* 45:96–103.
45. Oliveri M, Calvo G (2003): Increased visual cortical excitability in ecstasy users: A transcranial magnetic stimulation study. *J Neurol Neurosurg Psychiatry* 74:1136–1138.
46. Merabet LB, Kobayashi M, Barton J, Pascual-Leone A (2003): Suppression of complex visual hallucinatory experiences by occipital transcranial magnetic stimulation: A case report. *Neurocase* 9:436–440.
47. Boroojerdi B, Bushara KO, Corwell B, Immisch I, Battaglia F, Muellbacher W, Cohen LG (2000): Enhanced excitability of the human visual cortex induced by short-term light deprivation. *Cereb Cortex* 10:529–534.
48. Fyftche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S (1998): The anatomy of conscious vision: An fMRI study of visual hallucinations. *Nat Neurosci* 1:738–742.
49. Komater M, Cahn BR, Andel D, Carter OL, Vollenweider FX (2011): The 5-HT<sub>2A/1A</sub> agonist psilocybin disrupts modal object completion associated with visual hallucinations. *Biol Psychiatry* 69:399–406.
50. Komater M, Schmidt A, Jäncke L, Vollenweider FX (2013): Activation of serotonin 2A receptors underlies the psilocybin-induced effects on  $\alpha$  oscillations, N170 visual-evoked potentials, and visual hallucinations. *J Neurosci* 33:10544–10551.
51. Amaral DG, Behnia H, Kelly JL (2003): Topographic organization of projections from the amygdala to the visual cortex in the macaque monkey. *Neuroscience* 118:1099–1120.
52. Vuilleumier P, Richardson MP, Armony JL, Driver J, Dolan RJ (2004): Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat Neurosci* 7:1271–1278.
53. Hornboll B, Macoveanu J, Rowe J, Elliott R, Paulson OB, Siebner HR, Knudsen GM (2013): Acute serotonin 2A receptor blocking alters the processing of fearful faces in the orbitofrontal cortex and amygdala. *J Psychopharmacol* 27:903–914.
54. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, Vogel H, Hell D (1998): Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9:3897–3902.
55. Blair JB, Kurrasch-Orbaugh D, Marona-Lewicka D, Cumbay MG, Watts VJ, Barker EL, Nichols DE (2000): Effect of ring fluorination on the pharmacology of hallucinogenic tryptamines. *J Med Chem* 43: 4701–4710.
56. Sard H, Kumaran G, Morency C, Roth BL, Toth BA, He P, Shuster L (2005): SAR of psilocybin analogs: Discovery of a selective 5-HT<sub>2C</sub> agonist. *Bioorg Med Chem Lett* 15:4555–4559.
57. Michelsen KA, Prickaerts J, Steinbusch, Harry WM (2008): The dorsal raphe nucleus and serotonin: Implications for neuroplasticity linked to major depression and Alzheimer's disease. *Prog Brain Res* 172: 233–264.
58. Zhang G, Ásgeirsdóttir HN, Cohen SJ, Munchow AH, Barrera MP, Stackman RW (2013): Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6J mice. *Neuropharmacology* 64:403–413.
59. Savli M, Bauer A, Mitterhauser M, Ding Y, Hahn A, Kroll T, *et al.* (2012): Normative database of the serotonergic system in healthy subjects using multi-tracer PET. *Neuroimage* 63:447–459.
60. Rammes G, Eder M, Dodt HU, Kochs E, Ziegglängsberger W (2001): Long-term depression in the basolateral amygdala of the mouse involves the activation of interneurons. *Neuroscience* 107:85–97.
61. Vicente MA, Zangrossi H (2014): Involvement of 5-HT<sub>2C</sub> and 5-HT<sub>1A</sub> receptors of the basolateral nucleus of the amygdala in the anxiolytic effect of chronic antidepressant treatment. *Neuropharmacology* 79: 127–135.
62. Rainnie DG (1999): Serotonergic modulation of neurotransmission in the rat basolateral amygdala. *J Neurophysiol* 82:69–85.
63. Stutzmann GE, LeDoux JE (1999): GABAergic antagonists block the inhibitory effects of serotonin in the lateral amygdala: A mechanism for modulation of sensory inputs related to fear conditioning. *J Neurosci* 19:RC8.
64. Shen RY, Andrade R (1998): 5-Hydroxytryptamine<sub>2</sub> receptor facilitates GABAergic neurotransmission in rat hippocampus. *J Pharmacol Exp Ther* 285:805–812.
65. Piñeyro G, Blier P (1999): Autoregulation of serotonin neurons: Role in antidepressant drug action. *Pharmacol Rev* 51:533–591.
66. Fink KB, Göthert M (2007): 5-HT receptor regulation of neurotransmitter release. *Pharmacol Rev* 59:360–417.
67. Meltzer CC, Price JC, Mathis CA, Butters MA, Ziolko SK, Moses-Kolko E, *et al.* (2004): Serotonin 1A receptor binding and treatment response in late-life depression. *Neuropsychopharmacology* 29:2258–2265.
68. Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, *et al.* (1999): PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 46:1375–1387.
69. Drevets WC, Frank E, Price JC, Kupfer DJ, Greer PJ, Mathis C (2000): Serotonin type-1A receptor imaging in depression. *Nucl Med Biol* 27: 499–507.
70. Lanzenberger R, Wadsak W, Spindelegger C, Mitterhauser M, Akimova E, Mien L, *et al.* (2010): Cortisol plasma levels in social anxiety disorder patients correlate with serotonin-1A receptor binding in limbic brain regions. *Int J Neuropsychopharmacol* 13:1129–1143.
71. Sladky R, Höflich A, Küblböck M, Kraus C, Baldinger P, Moser E, *et al.* (2013): Disrupted effective connectivity between the amygdala and orbitofrontal cortex in social anxiety disorder during emotion discrimination revealed by dynamic causal modeling for fMRI [published online ahead of print October 9]. *Cereb Cortex*.
72. Hahn A, Stein P, Windischberger C, Weissenbacher A, Spindelegger C, Moser E, *et al.* (2011): Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *Neuroimage* 56:881–889.
73. Spindelegger C, Lanzenberger R, Wadsak W, Mien LK, Stein P, Mitterhauser M, *et al.* (2009): Influence of escitalopram treatment on 5-HT<sub>1A</sub> receptor binding in limbic regions in patients with anxiety disorders. *Mol Psychiatry* 14:1040–1050.
74. Dai J, Han H, Tian M, Cao J, Xiu J, Song N, *et al.* (2008): Enhanced contextual fear memory in central serotonin-deficient mice. *Proc Natl Acad Sci U S A* 105:11981–11986.
75. Catlow BJ, Song S, Paredes DA, Kirstein CL, Sanchez-Ramos J (2013): Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. *Exp Brain Res* 228:481–491.
76. Fisher PM, Meltzer CC, Ziolko SK, Price JC, Moses-Kolko EL, Berga SL, Hariri AR (2006): Capacity for 5-HT<sub>1A</sub>-mediated autoregulation predicts amygdala reactivity. *Nat Neurosci* 9:1362–1363.

77. Griebel G, Perrault G, Sanger DJ (1997): A comparative study of the effects of selective and non-selective 5-HT<sub>2</sub> receptor subtype antagonists in rat and mouse models of anxiety. *Neuropharmacology* 36: 793–802.
78. Millan MJ (2003): The neurobiology and control of anxious states. *Prog Neurobiol* 70:83–244.
79. Li X, Frye MA, Shelton RC (2012): Review of pharmacological treatment in mood disorders and future directions for drug development. *Neuropsychopharmacology* 37:77–101.
80. Blier P, Ward NM (2003): Is there a role for 5-HT<sub>1A</sub> agonists in the treatment of depression? *Biol Psychiatry* 53:193–203.
81. Outhred T, Hawkshead BE, Wager TD, Das P, Malhi GS, Kemp AH (2013): Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: Implications for differential treatment efficacy. *Neurosci Biobehav Rev* 37:1786–1800.
82. Pringle A, Browning M, Cowen PJ, Harmer CJ (2011): A cognitive neuropsychological model of antidepressant drug action. *Prog Neuropsychopharmacol Biol Psychiatry* 35:1586–1592.