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

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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

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The amygdala is a key structure in the serotonergic neurocircuitry 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-HT1A/2A/2C 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

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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 ± 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, crossover 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 Neurofonctionelle, 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