Original Paper

Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies

Erich Studerus, Michael Kometer, Felix Hasler and Franz X Vollenweider

Journal of Psychopharmacology
25(11) 1434–1452

DOI: 10.1177/0269881110382466
jop.sagepub.com

Abstract

Psilocybin and related hallucinogenic compounds are increasingly used in human research. However, due to limited information about potential subjective side effects, the controlled medical use of these compounds has remained controversial. We therefore analysed acute, short- and long-term subjective effects of psilocybin in healthy humans by pooling raw data from eight double-blind placebo-controlled experimental studies conducted between 1999 and 2008. The analysis included 110 healthy subjects who had received 1–4 oral doses of psilocybin (45–315 μg/kg body weight). Although psilocybin dose-dependently induced profound changes in mood, perception, thought and self-experience, most subjects described the experience as pleasurable, enriching and non-threatening. Acute adverse drug reactions, characterized by strong dysphoria and/or anxiety/panic, occurred only in the two highest dose conditions in a relatively small proportion of subjects. All acute adverse drug reactions were successfully managed by providing interpersonal support and did not need psychopharmacological intervention. Follow-up questionnaires indicated no subsequent drug abuse, persisting perception disorders, prolonged psychosis or other long-term impairment of functioning in any of our subjects. The results suggest that the administration of moderate doses of psilocybin to healthy, high-functioning and well-prepared subjects in the context of a carefully monitored research environment is associated with an acceptable level of risk.

Keywords

5-HT_{2A}-agonists, adverse effects, altered states of consciousness, dose–response relationship, drug abuse, flashbacks, hallucinogens, human research, long-term effects, psilocybin

Introduction

Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) is an indoleamine or serotonin-like hallucinogen and the main psychoactive principle of a group of hallucinogenic fungi of the genus Psilocybe, also often referred to as 'magic mushrooms' (Hofmann, 1968). Psilocybe mushrooms occur throughout the world and their human use in medical and religious rituals dates back for centuries, if not millennia (Guzmán et al., 2000; Stamets, 1996).

Modern psychopharmacological research with psilocybin began with the discovery of the cultic use of Psilocybe mushrooms by Mesoamerican Mazatec Indians in 1955 (Wasson, 1958). Psilocybin and psilocin were identified at Sandoz Laboratories as the psychoactive compounds of Psilocybe mushrooms and synthesized by the renowned Swiss chemist Albert Hofmann et al. (1958), who some 15 years earlier also discovered the chemically related ergoline hallucinogen LSD. Soon after, synthetic psilocybin was marketed by Sandoz under the name Indocybin® for basic psychopharmacological and therapeutic clinical research (Hofmann et al., 1959; Passie, 1995; Passie et al., 2002).

Early clinical studies in the 1960s and 1970s demonstrated that psilocybin produces an altered state of consciousness (ASC) similar to LSD, characterized by marked alterations in perception, mood, and thought, including changes in the experience of time, space, and self that are otherwise rarely experienced except in dreams, religious exaltation, and acute psychoses (Fischer, 1971; Geyer and Vollenweider, 2008; Isbell, 1959; Leuner, 1962; Nichols and Chemel, 2006; Rümmele and Gnirss, 1961; Wolbach et al., 1962).

In these states, perceptual hypersensitivity, illusions, and pseudohallucinations (i.e. hallucinations with intact reality testing and insight) are common (Fischer et al., 1969, 1970; Hill et al., 1969; Leuner, 1962). Intensification of affective responses, enhanced ability for introspection, regression to primitive and childlike thinking, and activation of vivid memory traces with pronounced emotional undertones can

University Hospital of Psychiatry Zürich, Neuropsychopharmacology and Brain Imaging & Heffter Research Center, Zürich, Switzerland.

Corresponding author:
Erich Studerus, University Hospital of Psychiatry Zürich, Neuropsychopharmacology and Brain Imaging & Heffter Research Center, CH-8032 Zürich, Switzerland
Email: erich.studerus@bli.uzh.ch

also occur (Chandler and Hartman, 1960; Leuner, 1971; Sandison and Whitelaw, 1957). Psychophysiological and pharmacological studies revealed that psilocybin had a much shorter duration of action than LSD (4–6 h instead 8–12 h) (Cerletti, 1959). Although – apart from the duration of action – the effects of both drugs were found to be highly similar in a controlled study (Hollister and Hartman, 1962), clinical observations indicated that psilocybin tended to produce less anxiety, fewer panic reactions and affective disturbances, and milder vegetative side effects than LSD (Clark, 1968; David and David, 1961; Heimann, 1962; Leuner, 1968; Nieto, 1962; Passie, 1995). Hence, many hallucinogen researchers valued psilocybin as a useful substitute for the earlier discovered LSD to explore the neural basis of ASC including the basis of hallucinations, religious, spiritual, and psychotic dimension, while for others it was an attractive adjunct in psychodynamic-oriented psychotherapy to bring the unconscious into conscious (Leuner, 1971; Nichols, 2004; Nichols and Chemel, 2006).

Throughout the 1960s, LSD and related drugs became increasingly associated with cultural rebellion, were widely popularized as drugs of abuse, and depicted as dangerous. Consequently, around 1970, LSD and related drugs were scheduled in the most restrictive category in most countries. Accordingly, human research on psychedelics became severely restricted, funding became difficult, and interests in therapeutic use of these drugs faded.

The 1990s witnessed a re-emergence of human hallucinogen research in Europe, particularly with the development of new brain imaging techniques, sophisticated neuropsychological approaches, and neuropharmacological findings that have supported hallucinogens as models of at least some aspects of natural occurring psychosis (for a review, see Geyer and Vollenweider, 2008). Many of these studies conducted in our and other laboratories used psilocybin as a tool to investigate the neural underpinnings of psychotic symptom formation including ego disorders and hallucinations (Gouzoulis-Mayfrank et al., 1999a, 1999b; Hasler et al., 2004; Vollenweider, 1992, 1998; Vollenweider and Geyer, 2001; Vollenweider et al., 1997), or to explore the effect of psilocybin on cognitive and visual processes (Carter et al., 2004, 2005a, 2005b, 2007; Heekeren et al., 2008; Spitzer et al., 1996; Umbricht et al., 2002, 2003), time perception (Wackermann et al., 2008; Wittmann et al., 2007), and on sensory gating and its relation to cognitive alterations (Gouzoulis-Mayfrank et al., 1998a; Vollenweider et al., 2007).

Recent work has also explored the acute and long-term subjective effects of psilocybin in hallucinogen-naïve healthy subjects and found that 14 months after the experiments about two-thirds of participants still rated the experience as among the most personally meaningful and spiritually significant of their lives (Griffiths et al., 2006, 2008). In addition, several recent studies have re-investigated the tolerability and efficacy of psilocybin in the treatment of anxiety-related advanced-stage cancer (Grob et al., 2009) and obsessive-compulsive disorders (Moreno et al., 2006). Other studies have focused on the pharmacokinetics (Hasler et al., 1997), metabolism (Hasler et al., 2002), dose–response effects (Hasler et al., 2004), and receptor mechanism of psilocybin (Ametamey et al., 1998; Hasler et al., 2009; Vollenweider et al., 1998, 1999, 2008). For example, we have shown that the selective 5-HT2A receptor antagonist ketanserin blocks the hallucinogenic effects of psilocybin in human subjects (Vollenweider et al., 1998), providing strong evidence for the link between 5-HT2A receptor activation and hallucinosis (Sanders-Bush et al., 1988). Moreover, a recent animal study found a novel mechanism of functional interaction between 5-HT2A and mGluR2 receptors and suggests that specific mGluR2 agonists may block the effect of hallucinogens such as psilocybin in humans (Gonzalez-Maeso and Sealfon, 2009; Gonzalez-Maeso et al., 2007, 2008). Although molecular and mechanistic studies in animal are pertinent, translational research in human subjects and particularly the establishing of the links between the mechanism of action of hallucinogens and the subjective effects in humans is essential (Vollenweider, 2001).

Although serotonergic hallucinogens such as psilocybin are considered relatively safe physiologically and do not produce dependence (Johnson et al., 2008; Leuner, 1981; Nichols, 2004), there is limited information on the acute tolerability and long-term psychological effects of psilocybin. Moreover, given that many of the early human studies with psilocybin were poorly standardized and lacked adequate control groups or follow-up measures, or often had small and unrepresentative sample sizes, it is difficult to draw inferences with this work, for example on dose–response effects and the incidence of acute and subacute distress and side effects.

The purpose of this paper is to provide further information about the acute, subacute and potential long-term subjective effects of psilocybin administration in healthy human subjects in a controlled experimental setting. The present analysis is based on data of eight double-blind placebo-controlled psilocybin studies that were conducted in our laboratory during the past 10 years. The data report on acute, subacute, and long-term effects of 227 individual psilocybin sessions obtained in 110 subjects using validated instruments to assess various aspects of consciousness, mood, psychological and physical side effects. Whereas parts of the data on the acute effects of psilocybin were previously published (see Table 1), the data on subacute and long-term effects/side effects have not been presented elsewhere before.

Methods

Study description

Data from eight experimental studies involving psilocybin administration to healthy human subjects carried out between 1999 and 2008 at our research facility were pooled for the present analysis (Table 1). Earlier psilocybin studies were not included because no long-term follow-up measurements were obtained in those experiments. All eight studies were approved by the Ethics Committee of the University Hospital of Psychiatry, Zürich, and the use of psilocybin was authorized by the Swiss Federal Office of Public Health, Department of Pharmacology and Narcotics, Bern. In each study, a double-blind placebo-controlled within-subject design was used. Depending on the study, subjects were tested on 2–5 experimental days, each separated by at least 14 days to avoid carry-over effects. Each volunteer received placebo and 1–4 different oral doses of psilocybin in

Table 1. Psilocybin studies

Study description	Psilocybin dose conditions	Number of subjects receiving at least one dose of psilocybin	Number of administered psilocybin doses				Publication
			Very low dose (45 μg/kg)	Low dose (115–125 μg/kg)	Medium dose (115–260 μg/kg)	High dose (315 μg/kg)	
1) Dose–effect study on acute psychological and physiological effects of psilocybin.	1) 45 μg/kg 2) 115 μg/kg 3) 215 μg/kg 4) 315 μg/kg	8	8	8	8	8	(Hasler et al., 2004)
2) Acute effects of psilocybin on cognitive functions and subjective experience.	1) 115 μg/kg 2) 215 μg/kg 3) 315 μg/kg	16		16	16	16	In progress
3) Effects of psilocybin on brain activity using H2O-PET.	260 μg/kg	12			12		In progress
4) Effects of psilocybin on prepulse inhibition of startle in healthy human volunteers.	1) 115 μg/kg 2) 215 μg/kg 3) 315 μg/kg	20		17	17	18	(Vollenweider et al., 2007)
5) Effects of psilocybin on the rate and rhythmicity of perceptual rivalry alternations.	1) 115 μg/kg 2) 250 μg/kg	12		12	12		(Carter et al., 2004) (Carter et al., 2005b) (Wittmann et al., 2007) (Wackermann et al., 2008)
6) Investigation on the relationship between attention, working memory, and the serotonin 1A and 2A receptors using psilocybin and ketanserin.	1) 215 μg/kg 2) 215 μg/kg after ketanserin pretreatment	10			10		(Carter et al., 2005a) (Carter et al., 2007)
7) Effects of psilocybin on visual processing: An EEG study.	1) 125 μg/kg 2) 250 μg/kg	21		21	18		In progress
8) Serotonin 5-HT2A receptor dynamics in the human brain following psilocybin stimulation: A PET study.	250 μg/kg	11			11		In progress
Total number of subjects		110	8	74	104	42	

a randomized and counterbalanced order. Additionally, in one study subjects also received pre-treatments with the 5-HT_{2A} antagonist ketanserin and placebo. Psilocybin doses ranged from 45–315 μg/kg body weight (absolute doses: 2–28 mg). For a detailed description of the administered psilocybin doses in each study, see Table 1.

Experimental sessions of studies 3 and 7 were conducted at the PET Center of the University Hospital, Zürich, while all other study sessions took place at the University Hospital of Psychiatry, Zürich. All subjects were instructed to have a light breakfast prior to the experiments. Before testing began, blood pressure and heart rate were measured and subsequently monitored at hourly intervals throughout the day. Subjects finished participation of the study approximately 7 h after psilocybin administration and were examined by the principal investigator before being deemed fit for release.

Subjects were asked not to engage in demanding work after the psilocybin session and to contact the research staff if any adverse events occurred. These procedures are generally similar to those subsequently used and recommended by Johnson et al. (2008).

Subjects

Subjects for all studies were recruited through advertisement from the local universities and hospital staff. Participants were informed by a written and oral description of the aim of the studies, the procedures involved, as well as the effects and possible risks of psilocybin administration and were asked to give their written consent as requirement for study participation. They were also informed that they would be reimbursed for their time and that they were free to withdraw from the study at any time. To assure health and to minimize potential risk factors for adverse psilocybin reactions, all subjects underwent the following screening procedures: a structured psychiatric interview, the DIA-X computerized diagnostic expert system (Wittchen and Pfister, 1997), a physical examination including electrocardiogram, and detailed clinical–chemical blood analysis, as well as a psychological assessment with standard psychometric instruments Freiburg Personality Inventory (FPI) (Fahrenberg et al., 1984) and the Symptom Checklist SCL-90 (Derogatis, 1994). Subjects with personal or family (first-degree relatives) histories of schizophrenia, major depression, bipolar disorders, borderline personality disorder, neurological disorders, or regular alcohol or substance abuse were excluded. As the personality trait 'emotional lability' as measured by the FPI was identified to be a predictor for negative experiences during ASC (Dittrich, 1994), scores exceeding the mean value of normative FPI data by two standard deviations (SD) were also used as exclusion criteria. Subjects with high scores in the 'emotional lability' scale of the FPI prove to have many inner problems and conflicts. They often have psychosomatic symptoms; are overly sensitive and anxious; and often feel overwhelmed by events (Fahrenberg et al., 1984).

Substance

In all studies, psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) was obtained through the Swiss Federal Office for Public Health, Bern. Psilocybin capsules (1 mg and 5 mg) were prepared at the Pharmacy of the Cantonal Hospital of Aarau, Switzerland. The psilocybin and lactose placebo were prepared in gelatin capsules of identical appearance.

Psychometric ratings of acute and post-acute effects

All eight studies included in the present analysis used the Altered States of Consciousness Rating Scale (5D-ASC) (Braun, 1997; Dittrich et al., 2006), and six studies also used the short version of the Adjective Mood Rating Scale (AMRS) (Janke and Debus, 1978, 1986) to assess acute and subacute subjective drug effects.

The 5D-ASC questionnaire is a psychometrically improved and extended version of the original APZ questionnaire (Dittrich, 1998). The 5D-ASC is a visual analogue self-rating scale consisting of 94 items, assessing five primary dimensions and one global dimension of ASC. The primary dimensions comprise several item clusters and can be described as follows: (1) Oceanic boundlessness (OB) measures derealization and depersonalization accompanied by changes in affect ranging from heightened mood to euphoria and/or exaltation, and alterations in the sense of time. The corresponding item clusters are *positive experienced derealization*, *positively experienced depersonalization*, *changed sense of time*, *positive mood*, *and mania like experience*. (2) Anxious Ego Dissolution (AED) measures ego disintegration associated with loss of self-control, thought disorder, arousal, and anxiety. The item clusters are *negatively experienced derealization*, *thought disorder*, *paranoia*, *loss of thought control*, *and loss of body control*. (3) Visionary Restructuralization (VR) measures alterations in perception and meaning. The item clusters are *elementary hallucinations and illusions*, *scenery hallucinations*, *synaesthesia*, *changed meaning of percepts*, *facilitated recollection*, *and facilitated imagination*. (4) Auditory Alterations (AA) measures auditory illusions and auditory (pseudo-) hallucinations. (5) Reduction of Vigilance (RV) relates to states of drowsiness, reduced alertness, and impaired cognitive function. The OB, AED, and VR dimensions have been shown to be common to a range of altered states of waking consciousness of varying aetiology and intensity, while the AA and RV dimensions are hypothesized to occur only under certain stimulus conditions (Dittrich, 1998; Dittrich et al., 1985). Items from the OB, AED, and VR dimensions are therefore summed to a global score of ASC (G-ASC). 5D-ASC administration time for measuring peak drug effects varied between studies from 60–270 min after drug intake. In all studies, subjects were instructed to rate their whole experience by the 5D-ASC retrospectively from the moment of drug intake to the respective measuring time point.

The AMRS is a self-rating scale that was developed for the multidimensional assessment of mood states and condition (Janke and Debus, 1986). The AMRS consists of a list of 60 adjectives (e.g. 'anxious', 'tired', 'sociable') that are rated by subjects as to how well they describe their present state. Subjects must choose from four possible answers ('not at all', 'somewhat', 'quite', or 'strongly'). AMRS items can be broken down into 15 mood states and conditions: 'Efficiency–activation', 'Concentration', 'Inactivation', 'Tiredness', 'Drowsiness', 'Extroversion', 'Introversion', 'Self-confidence', 'Heightened mood', 'Emotional excitation', 'Sensitivity', 'Aggression–anger', 'Apprehension–anxiety', 'Depressiveness', and 'Dreaminess'. Depending on the study, the AMRS was administered at one to four time points during the course of an experimental session and between 60 min and 24 h after drug administration (see statistical analysis section for more details on the AMRS administration time points in each study). At each time of assessment, subjects were instructed to rate their present state.

Psychometric rating of subacute side effects

Subacute side effects were assessed in six studies (studies 1, 2, 4, 5, 6, 8) by the List of Complaints (LC) (von Zerssen, 1971).

This self-rating scale consists of a list of 65 common somatic and psychological ailments, which can be summed to a global score of general discomfort. Subjects were asked to rate whether each symptom is present or not at the time of assessment. In all six studies, the LC was administered 24 h after drug intake.

Long-term follow-up

Long-term psilocybin effects were assessed by an investigator-constructed follow-up questionnaire that covered the following areas of content.

1. Ratings of acute drug experiences in retrospect
Subjects were asked the following question: 'How do you rate the acute drug experience during the experiment in retrospect?' For each of six adjectives (pleasant, enriching, frightening, unpleasant, influential, and nothing special), subjects had to choose one of three possible answers (very much, medium, or not).

2. Changes in values and attitudes
Subjects were asked the following questions: 'Did the experiment with psilocybin cause changes in (a) world view, (b) values, (c) awareness of personal problems, (d) the relationship to one's body, (e) relationships to other people, (f) professional relationships, (g) the relationship to the environment/nature, (h) aesthetic experiencing, and (i) in the attitude to ASC?' For each item, subjects had to choose from three possible answers (positive change, negative change, or no change).

3. Changes in drug consumption habits
Subjects were asked whether they had changed their consumption habits of any psychoactive drug after the experiments. For each drug that was consumed either more or less often than before, subjects were asked to give further details on frequency of use, dosages, route of administration, and setting of use. Subjects were also asked whether they considered the described changes as a consequence of their drug experience during the experiments.

4. Spontaneously occurring ASC before and after the experiments and flashbacks
Subjects were asked to describe frequencies, durations, circumstances and symptoms of ASC that spontaneously occurred before and/or after the experiments and whether they interpreted these ASC as a flashback-like re-experiencing of acute drug effects.

5. Negative changes in psychological well-being and/or mental functions
Subjects were asked to report the intensity, duration, and frequency of any experienced negative change in well-being and/or mental functions after the experiments. Sleeping, memory, and concentration problems, as well as mood swings, anxiety and reactivation of old problems were directly listed in the questionnaire, but further symptoms could be described by the subjects if necessary.

Long-term follow-up questionnaires were mailed to the study subjects (including drop-outs) 8–16 months after completion of their last experimental session. All follow-up questionnaires were obtained after subjects had been paid and therefore were more likely to report adverse effects.

Statistical analysis

All statistical analyses were performed using the freely available statistical package R© (version 2.8) (R Development Core Team, 2008). Since all analysed studies used within-subject designs and since there is considerable heterogeneity between studies (for example, differences in setting, study manager, and experimental procedure), our pooled data of acute and subacute psilocybin effects is structured hierarchically with repeated measurements nested within subjects and subjects nested within studies. Since drug dose conditions only partially overlap between studies and some subjects prematurely dropped out, our data set is also unbalanced with respect to drug dose condition. To account for observational heterogeneity and the lack of balance, we used mixed-effects models, which readily handle unbalanced and missing data and allow all observational units to contribute information to the analysis (Pinheiro and Bates, 2000). We used the R add-on package nlme (Pinheiro et al., 2008) to fit mixed-effects models. To minimize a potential bias arising from drop-outs, all available data from drop-outs were included in the statistical analyses on acute, subacute and long-term psilocybin effects.

To investigate the acute effects of drug dose on the five ASC dimensions (OB, AED, VR, AC, and RV), 5D-ASC data assessing peak drug effects were pooled over all eight studies. In studies where the 5D-ASC questionnaire was administered more than once during an experimental session, data from the measuring time points yielding the highest mean total score were used. The marginally differing psilocybin dose conditions 115 and 125 μg/kg, as well as 250 and 260 μg/kg were combined, because *t*-tests between these pairs of dose conditions did not reveal significant differences of subjective drug effects measured by the global and primary dimensions of 5D-ASC. The pooled 5D-ASC data were analysed by linear mixed-effects models with treatment (placebo, 45, 115–125, 215, 250–260, and 315 μg/kg) as a fixed-effects factor and study and subjects within studies as random-effects factors. Random effects were modelled as random intercepts without random slopes. Akaike's Information Criterion (AIC) values were used to decide on appropriate correlation structures of random effects in model specifications. In cases of variance heteroscedasticity, we used a weighting procedure to correct for unequal variances between groups. Statistical assumptions were checked graphically by plotting residuals against predicted values and by normal quantile–quantile plots of residuals and random effects. In each fitted mixed-effects model, the shape of the psilocybin dose–response relationship was evaluated by means of orthogonal polynomial contrasts. In addition, when significant treatment effects were detected, one-tailed Dunnett contrasts were applied using the R add-on package multcomp (Hothorn et al., 2008) in order to find the minimum effective dose. To determine the proportions of subjects experiencing strong subjective drug effects, cumulative distributions of the three aetiology-independent

dimensions (OB, AED, and VR) were inspected for each dose condition. Scale values above 70% of the maximum possible score were considered as strong subjective drug effects.

The analysis of AMRS data was restricted to the placebo and medium-dose psilocybin conditions, because these were the only drug conditions that occurred in all six studies using the AMRS. For the analysis of time-dependent effects of psilocybin, the AMRS administration time, which widely varied across studies, was categorized as follows: $t_1 = 60–95$ min, $t_2 = 160–180$ min, $t_3 = 260–400$ min, and $t_4 = 24$ h after drug intake. Five studies (studies 1, 4, 5, 6, and 8) had used the AMRS during t_1 and t_3. Three studies (studies 3, 4, and 8) administered the AMRS during t_2 and three studies (studies 1, 5, and 8) used the AMRS at t_4. The AMRS subscales were analysed by mixed-effects models using the fixed-effects factors drug (placebo vs. 215–260 µg psilocybin) and time (t_1, t_2, t_3, and t_4) and the hierarchically nested random-effects factors study, subject, and subject within treatment. For the assessment of acute effects of psilocybin, which should occur at t_1 and t_2 and to a lesser degree at t_3 and t_4, the interaction of drug × time was considered as the main source of information. Longer-lasting psilocybin effects were determined by significant main effects of drug in the absence of drug × time interactions. *p*-values were adjusted by Holm's method in order to maintain a type I error rate of $p < 0.05$ over all 30 hypothesis tests arising from the evaluations of the main effect of drug and the drug × time interaction in each of the 15 subscales.

Subacute side effects measured by the LC were analysed on the total scale as well as on the item level. Scores of the total scale were square-root transformed to reduce positive skew and subsequently analysed by a linear mixed-effects model with the within-subject factor treatment (placebo, 115–125, 215, 250, and 315 µg/kg) and the nested random effects factors study and subject. Differences between all possible pairs of drug dose conditions were assessed by specifying Tukey's contrasts and adjusting *p*-values by Holm's method. On the item level, frequency differences of single complaints between three different doses of psilocybin (125, 215, and 315 µg/kg) were analysed by Cochran Q tests using data from studies 1, 2, and 4. In order to analyse single complaints in the largest possible sample, we also used McNemar tests to compare items frequencies on placebo and medium-dose psilocybin (215–250 µg/kg) taking data from six studies (studies 1, 2, 4, 5, 6, and 8).

Since all participants had received psilocybin and no control group was available for comparison on responses to the long-term effects questionnaire, responses were analysed with descriptive statistics only. Data of forced-choice items were analysed by calculating absolute numbers and proportions of responses, whereas data of free-response items were either categorized to calculate sum and percentage scores or summarized in the text.

Results

Sample characteristics and drop-outs

In the studies carried out at our research facility between 1999 and 2008, 227 experimental sessions involving psilocybin administration were conducted. In total, eight very low doses (45 µg/kg body weight), 74 low doses (115–125 µg/kg), 104 medium doses (215–260 µg/kg), and 41 high doses (315 µg/kg) of psilocybin were administered. The number of subjects who received at least one dose of active psilocybin was 110 (59 males and 51 females). Subjects were between the ages of 20 and 47 ($M \pm$ SD: 26.9 ± 5.5 years) and exclusively Caucasians. Of the subjects, 56% were university students and 33% were university graduates; 60% had no prior experience with a classical hallucinogen (LSD, psilocyin, DMT, or mescaline); 20% had consumed it 1–10 times in a lifetime; and 20% had consumed it more than 10 times in a lifetime but maximally six times per year. Of our subjects, 90% had smoked cannabis at least once in a lifetime.

Of the 110 subjects included in the pooled analysis, seven subjects had prematurely dropped out after having received at least one dose of active psilocybin. A review of the study protocols and questionnaire data of these subjects revealed that in two cases, drop-outs were due to technical reasons and unrelated to drug effects (one subject moved to another country and another subject had too many electroencephalograph artefacts). In the remaining five cases, two subjects had an unusually intense reaction to a low dose of psilocybin and were therefore excluded by the study manager due to safety considerations. Another subject experienced a transient hypotonic reaction (systolic and diastolic blood pressure: 86/63 mm/Hg) with dizziness, fainting and vomiting after having received 115 µg/kg of psilocybin and was therefore also excluded from further psilocybin experiments. The remaining two subjects prematurely terminated the study of their own accord after the high-dose psilocybin session. Both subjects reported having had experiences of strong anxiety, fear of loss of ego control, emerging negative memories and thoughts during acute drug effects and were therefore not willing to participate in further psilocybin sessions. All five adverse drug reactions leading to a premature termination of the study were confined to the acute phase of drug effects and were completely resolved by the end of the experimental day.

Acute psychological effects

Dimensions of ASC. Psilocybin significantly increased scores of all 5D-ASC scales (main effects of drug in order of significance: VR ($F_{5,219} = 100.47$, $p < 0.001$), G-ASC ($F_{5,219} = 89.34$, $p < 0.001$), OB ($F_{5,219} = 59.93$, $p < 0.001$), RV ($F_{5,219} = 47.08$, $p < 0.001$), AED ($F_{5,219} = 21.53$, $p < 0.001$), AA ($F_{5,219} = 23.01$, $p < 0.001$)). Dose-dependent effects of psilocybin on the sub-scale level are illustrated in Figure 1. Means and standard deviations of each 5D-ASC item in each dose condition are available online in Supplementary Table 1. One-tailed Dunnett's contrasts detected significant differences between placebo and all drug dose conditions in all 5D-ASC scales, except for the 45 µg/kg dose condition, which was not significantly different from placebo in any of the 5D-ASC scales.

Graphical representations of drug effects by locally weighted scatter plot smoothing curves indicated dose–response relationships that were reasonably well approximated by linear functions in all scales of the 5D-ASC. The notion of linear

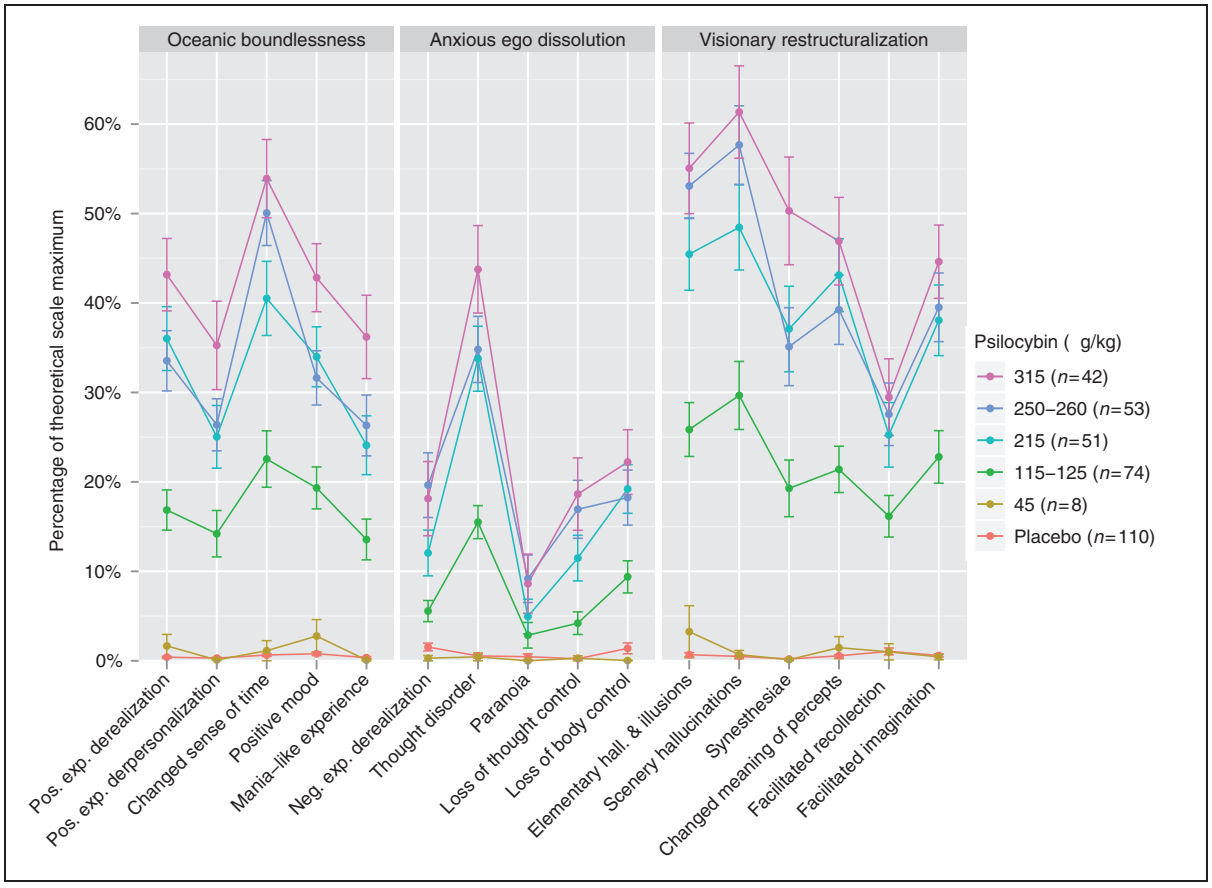

Figure 1. Dose-dependent percentage scores of item clusters from the 'Altered States of Consciousness Rating Scale' (5D-ASC). Error bars represent standard errors. Ratings were obtained during peak drug effects (60–270 min after drug administration).

dose–response relations was also supported by the results of orthogonal polynomial contrasts, which showed highly significant effects for the linear trends in all 5D-ASC scales. Furthermore, when dose was treated as a continuous variable in the linear mixed-effects models, regression slopes for doses were significantly different from zero in all 5D-ASC scales.

Cumulative distributions of the three aetiology-independent dimensions of ASC for each of four doses of psilocybin and placebo are displayed in Figure 2. As can be seen from the plot, the cumulative distributions for all psilocybin doses were relatively smooth over the whole ranges of the response variables, indicating widely varying individual responses. The proportions of subjects experiencing strong drug effects (scores >70% of the maximum possible score) were clearly dose dependent. In the highest dose condition, 22% of subjects reached or exceeded the cut-off value for strong OB, whereas only 5.7%, 7.8%, and 0% of subjects experienced such a strong effect in the 250–260, 215, and 115–125 µg/kg psilocybin dose conditions, respectively. Experiences of pronounced AED occurred in relatively few subjects and were only observed in the two highest dose conditions. Specifically, 7.3% and 5.7% of subjects reached or exceeded the cut-off-value for AED in the 315 and 250–260 µg/kg condition, respectively. Finally, the number of subjects exhibiting high to very high VR scores amounted to 19.6%, 7.5%, 7.8%, and 1.3% in the 315, 250–260, 215, and 115–125 µg/kg dose conditions, respectively.

Adjective Mood Rating Scale (AMRS). Psilocybin-induced changes in affective mood states and conditions over four different time periods are summarized in Figure 3. Mixed-effects models fitted for each of the 15 AMRS subscales revealed significant drug × time interactions for emotional excitation ($F_{3,284} = 12.54$, $p < 0.001$), dreaminess ($F_{3,284} = 11.62$, $p < 0.001$), heightened mood ($F_{3,284} = 9.23$, $p < 0.001$), dazed state ($F_{3,284} = 6.59$, $p = 0.005$), sensitivity ($F_{3,284} = 5.64$, $p = 0.015$), concentration ($F_{3,284} = 4.98$, $p = 0.032$), and tiredness ($F_{3,284} = 4.74$, $p = 0.041$). Interaction plots indicated that all significant interaction effects, except for tiredness, were produced by stronger drug effects on early measuring time points relative to later time points and hence represent acute drug effects. The interaction effect for tiredness was produced by stronger drug effects on later measuring time points relative to earlier time points and hence represents a psilocybin after effect. Significant main effects of drug in the absence of significant drug × time interactions were detected for introversion ($F_{3,284} = 60.96$, $p < 0.001$), inactivation ($F_{3,284} = 50.82$, $p < 0.001$), efficiency–activation

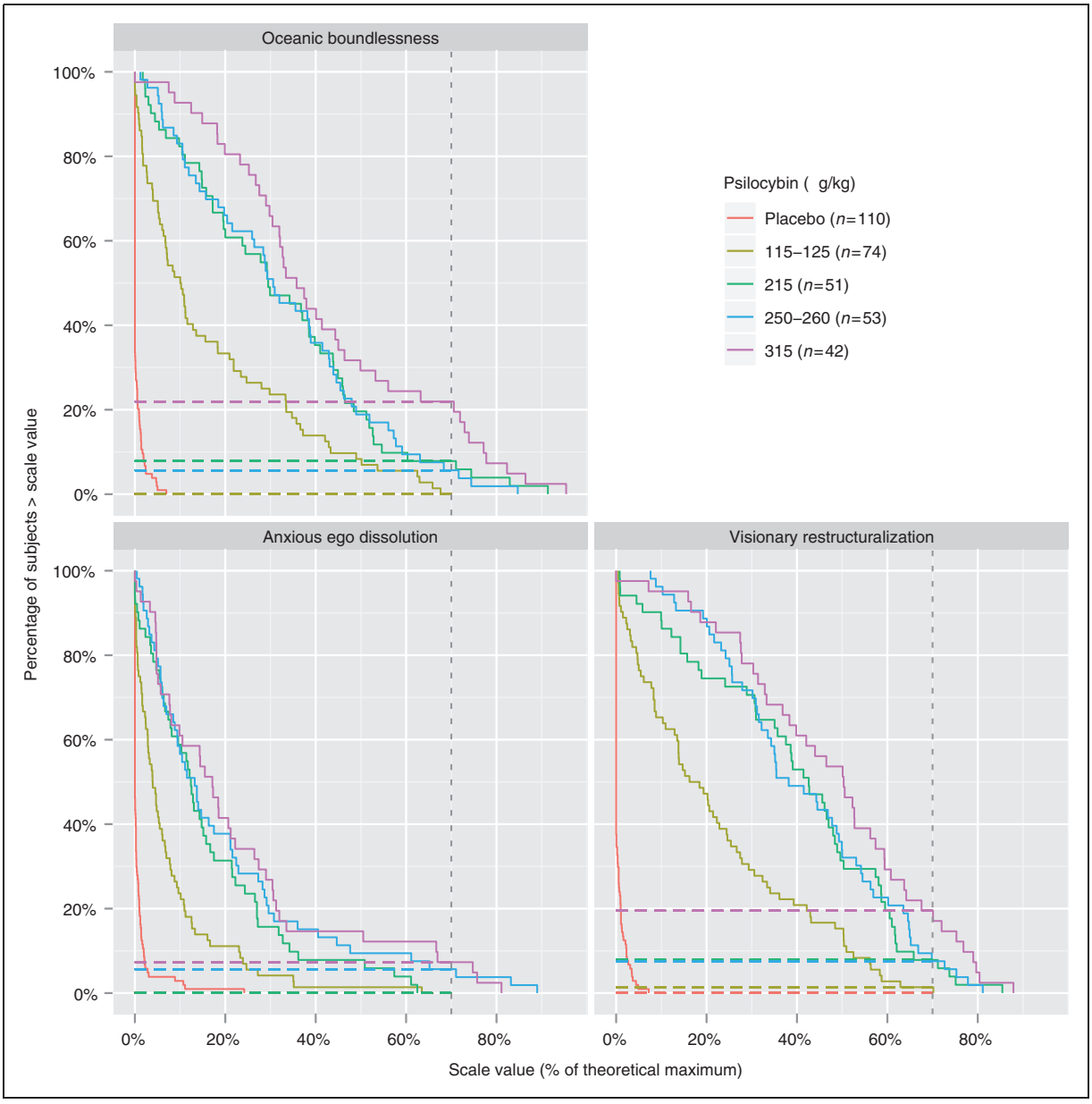

Figure 2. Cumulative distributions of the three aetiology independent dimensions of the 'Altered States of Consciousness Rating Scale' (5D-ASC) for each of four psilocybin doses and placebo. Dashed reference lines mark strong subjective drug effects (70% of theoretical scale maxima).

($F_{3,284} = 38.92$, $p < 0.001$), extroversion ($F_{3,284} = 12.40$, $p = 0.014$), and apprehension–anxiety ($F_{3,288} = 12.36$, $p < 0.001$). Since these drug effects were independent of measurement time, they represent longer-lasting psilocybin effects.

Short-term side effects

Global scores of the LC measured 24 h after drug intake were dependent on drug condition ($F_{5,159} = 9.64$, $p < 0.001$). All pair-wise comparisons between placebo and active psilocybin conditions were statistically significant except for the very low-dose psilocybin condition. No comparison between any of two active psilocybin dose conditions was statistically significant. Single complaints registered 24 h after psilocybin administrations are summarized in Table 2. Item-level comparisons between three different psilocybin doses and placebo by Cochran Q tests revealed significant differences for the items fatigue, headaches, lack of energy, difficulty concentrating, 'gone feeling', lack of appetite, and heavy or tired legs. Item-level comparisons of the LC responses in the largest possible sample (i.e. medium-dose psilocybin vs. placebo) by McNemar tests indicated increased fatigue, exhaustion, lack of energy, difficulty concentrating, and 'gone feeling' after psilocybin administration. However, if a Holm correction for multiple comparisons is applied, only the items fatigue, headaches and lack of energy in the dose-effect

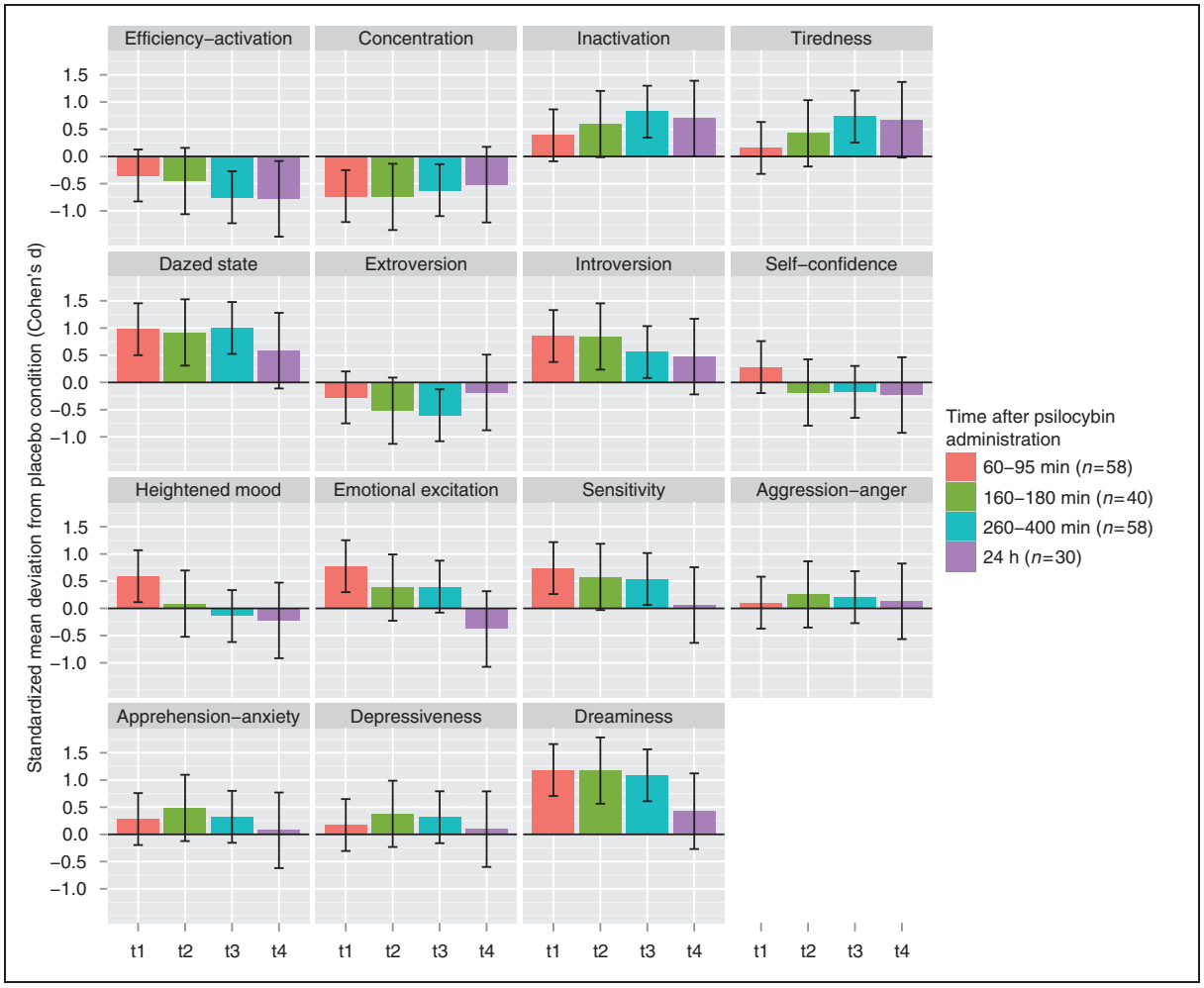

Figure 3. Time-dependent effects of medium-dose psilocybin (215–260 µg/kg) on mood states and condition measured by the 'Adjective Mood Rating Scale' (AMRS). Paired differences between placebo and psilocybin conditions for each time and variable combination were divided by their standard deviations in order to express psilocybin effects in units of Cohen's *d* effect size. By convention, Cohen's *d* of 0.2, 0.5, and 0.8 are termed small, medium, and large effect sizes, respectively. Error bars denote Bonferroni-corrected 95% confidence intervals of mean differences. Thus, mean differences between placebo and psilocybin are significant, where error bars do not include zero.

comparison remain statistically significant. Serious complications, such as fear of death, shortness of breath, feelings of suffocation, vomiting and fainting, which were also covered by the questionnaire, were not reported by any of the subjects.

Long-term follow-up

Long-term follow-up questionnaires were completed by 90 of 110 subjects (82%). Some 20 subjects were either unavailable due to address change or unresponsive. Chi-square and Welch's *t*-tests indicated that those subjects who completed the follow-up questionnaire were not statistically different from subjects who did not with respect to age, gender, education, 5D-ASC, and LC scores. Subjects completed follow-up assessments between 8 and 16 months after their last experimental day ($M \pm$SD: 330 ± 90 days).

Retrospective ratings of acute drug effects and changes in values and attitudes. Retrospective ratings of acute drug effects are summarized in Table 3, whereas changes in values and attitudes are shown in Table 4.

Changes in drug consumption habits. Changes in consumption habits of the most often used psychotropic substances are summarized in Table 5. Most subjects reported unchanged consumption habits for all drugs. Those subjects who did report changes more often described decreased consumption. Even for psilocybin itself, more subjects reported to have consumed it less often (5.6%) than more often (3.3%). Of the three subjects who described increased psilocybin consumption, two subjects reported to consume it twice a year and one three times per year. Except for alcohol, nicotine, and cannabis, no drug was used more often than once per month on average. From the 29 subjects who reported

Table 2. List of complaints, 24 h after drug intake

	Dose effect relation ($n = 40$)						Medium dose comparison ($n = 72$)			
Complaints	Placebo	115 µg/kg	215 µg/kg	315 µg/kg	p-value[a]	Signif.	Placebo	215–250 µg/kg	p-value[b]	Signif.
Fatigue	12.5% (5)	40.0% (16)	35.0% (14)	60.0% (24)	<0.001	***	19.4% (14)	40.3% (29)	0.009	**
Exhaustion	7.5% (3)	22.5% (9)	22.5% (9)	22.5% (9)	0.090		9.7% (7)	27.8% (20)	0.009	**
Headaches, head pressure or face pain	2.5% (1)	12.5% (5)	22.5% (9)	37.5% (15)	<0.001	***	8.3% (6)	19.4% (14)	0.099	
Lack of energy	0.0% (0)	15.0% (6)	7.5% (3)	22.5% (9)	0.002	**	4.2% (3)	16.7% (12)	0.027	*
Excessive sleep requirement	2.5% (1)	10.0% (4)	10.0% (4)	15.0% (6)	0.177		6.9% (5)	12.5% (9)	0.386	
Difficulty concentrating	5.0% (2)	7.5% (3)	7.5% (3)	17.5% (7)	0.015	*	4.2% (3)	13.9% (10)	0.046	*
Gone feeling	2.5% (1)	10.0% (4)	5.0% (2)	22.5% (9)	0.005	**	2.8% (2)	12.5% (9)	0.023	*
Fast exhaustibility	2.5% (1)	12.5% (5)	10.0% (4)	17.5% (7)	0.064		4.2% (3)	8.3% (6)	0.371	
Brooding	5.0% (2)	5.0% (2)	0.0% (0)	12.5% (5)	0.106		4.2% (3)	12.5% (9)	0.114	
Lack of appetite	0.0% (0)	7.5% (3)	5.0% (2)	17.5% (7)	0.015	*	1.4% (1)	9.7% (7)	0.077	
Neck or shoulder pain	7.5% (3)	7.5% (3)	2.5% (1)	5.0% (2)	0.629		4.2% (3)	8.3% (6)	0.450	
Irritability	5.0% (2)	10.0% (4)	5.0% (2)	7.5% (3)	0.768		2.8% (2)	5.6% (4)	0.683	
Sexually stimulating fantasies	5.0% (2)	2.5% (1)	5.0% (2)	5.0% (2)	0.801		6.9% (5)	5.6% (4)	1.000	
Strong thirst	2.5% (1)	5.0% (2)	5.0% (2)	0.0% (0)	0.468		1.4% (1)	9.7% (7)	0.077	
Heavy or tired legs	2.5% (1)	0.0% (0)	2.5% (1)	12.5% (5)	0.008	**	2.8% (2)	4.2% (3)	1.000	
Sleeplessness	2.5% (1)	0.0% (0)	7.5% (3)	5.0% (2)	0.290		1.4% (1)	6.9% (5)	0.221	
Bloated feeling	5.0% (2)	0.0% (0)	5.0% (2)	2.5% (1)	0.300		2.8% (2)	5.6% (4)	0.617	
Backache	2.5% (1)	5.0% (2)	2.5% (1)	2.5% (1)	0.896		2.8% (2)	5.6% (4)	0.683	
Worries about professional or private affairs	0.0% (0)	5.0% (2)	2.5% (1)	5.0% (2)	0.532		4.2% (3)	4.2% (3)	1.000	
Dark thoughts	5.0% (2)	5.0% (2)	2.5% (1)	2.5% (1)	0.801		4.2% (3)	2.8% (2)	1.000	
Inner tension	2.5% (1)	7.5% (3)	0.0% (0)	7.5% (3)	0.234		1.4% (1)	2.8% (2)	1.000	
Abdominal pain or stomach ache	2.5% (1)	2.5% (1)	2.5% (1)	7.5% (3)	0.392		1.4% (1)	2.8% (2)	1.000	
Intolerances to certain smells	0.0% (0)	2.5% (1)	2.5% (1)	5.0% (2)	0.494		1.4% (1)	5.6% (4)	0.371	
Nausea	0.0% (0)	7.5% (3)	5.0% (2)	2.5% (1)	0.232		0.0% (0)	4.2% (3)	0.248	
Uneasiness	2.5% (1)	2.5% (1)	2.5% (1)	5.0% (2)	0.875		1.4% (1)	2.8% (2)	1.000	
Tendency of crying	2.5% (1)	0.0% (0)	2.5% (1)	0.0% (0)	0.572		1.4% (1)	5.6% (4)	0.371	
Joint aches	2.5% (1)	2.5% (1)	2.5% (1)	0.0% (0)	0.733		1.4% (1)	4.2% (3)	0.617	
Cold feet	2.5% (1)	0.0% (0)	2.5% (1)	2.5% (1)	0.801		1.4% (1)	4.2% (3)	0.617	
Freezing	0.0% (0)	2.5% (1)	5.0% (2)	0.0% (0)	0.300		1.4% (1)	4.2% (3)	0.617	
Ravenous appetite	5.0% (2)	2.5% (1)	2.5% (1)	0.0% (0)	0.494		2.8% (2)	1.4% (1)	1.000	
Throat pain or irritated throat	5.0% (2)	0.0% (0)	0.0% (0)	7.5% (3)	0.101		2.8% (2)	0.0% (0)	0.480	
Easy rubescence	2.5% (1)	7.5% (3)	0.0% (0)	0.0% (0)	0.066		2.8% (2)	0.0% (0)	0.480	
Lump in throat or throat tightness	2.5% (1)	2.5% (1)	2.5% (1)	0.0% (0)	0.733		1.4% (1)	1.4% (1)	1.000	
Diarrhoea	2.5% (1)	0.0% (0)	0.0% (0)	7.5% (3)	0.112		1.4% (1)	0.0% (0)	1.000	
Restless legs	5.0% (2)	2.5% (1)	0.0% (0)	0.0% (0)	0.300		2.8% (2)	0.0% (0)	0.480	
Cold intolerance	0.0% (0)	2.5% (1)	2.5% (1)	0.0% (0)	0.392		0.0% (0)	4.2% (3)	0.248	
Vertigo	2.5% (1)	0.0% (0)	0.0% (0)	2.5% (1)	0.392		2.8% (2)	1.4% (1)	1.000	
Forgetfulness	0.0% (0)	0.0% (0)	2.5% (1)	5.0% (2)	0.194		0.0% (0)	2.8% (2)	0.480	
Difficulty swallowing	2.5% (1)	0.0% (0)	0.0% (0)	5.0% (2)	0.300		1.4% (1)	0.0% (0)	1.000	
Frequent urges to urinate	2.5% (1)	0.0% (0)	2.5% (1)	0.0% (0)	0.572		1.4% (1)	1.4% (1)	1.000	
Strong perspiration	2.5% (1)	2.5% (1)	0.0% (0)	0.0% (0)	0.572		1.4% (1)	1.4% (1)	1.000	

Numbers in parenthesis indicate absolute frequencies. Complaints are ordered by row sums of absolute frequencies. Complaints with an absolute frequency <4 over all drug conditions are not shown in the table. [a]Cochran Q-tests. [b]McNemar tests.

changes, seven subjects (24%) considered the change as a direct consequence of their hallucinogen experience. One of these seven reported decreased substance consumption, another reported increased, and five reported both increased and decreased.

Spontaneous alterations of consciousness and flashbacks. Nine subjects (10%) reported spontaneously occurring ASC before and eight (9%) after the experiments. Three of these subjects reported experiencing spontaneous ASC both before and after the experiments. Spontaneous

Table 3. Ratings of acute drug effects at follow-up

Adjective	Number of subjects	
Pleasant		
Very	49%	(43)
Medium	43%	(38)
No	8%	(7)
Enriching		
Very	61%	(53)
Medium	29%	(25)
No	10%	(9)
Frightening		
Very	5%	(4)
Medium	28%	(24)
No	68%	(59)
Unpleasant		
Very	10%	(9)
Medium	24%	(21)
No	66%	(57)
Influential		
Very	22%	(19)
Medium	45%	(39)
No	33%	(29)
Nothing special		
Very	4%	(3)
Medium	11%	(9)
No	85%	(70)

Numbers after percents indicate absolute frequencies.

Table 4. Changes in attitudes

Change	Number of subjects	
Changes in world view		
Positive	18%	(16)
Unchanged	81%	(72)
Negative	1%	(1)
Changes in values		
Positive	18%	(16)
Unchanged	77%	(68)
Negative	5%	(4)
Changes in awareness of personal problems		
Positive	29%	(25)
Unchanged	66%	(57)
Negative	5%	(4)
Change in the relationship to one's body		
Positive	30%	(26)
Unchanged	67%	(59)
Negative	3%	(3)
Change in relationships to other people		
Positive	25%	(22)
Unchanged	68%	(59)
Negative	7%	(6)
Change in professional relationships		
Positive	6%	(5)
Unchanged	89%	(75)
Negative	5%	(4)
Change in the relationship to the environment/nature		
Positive	38%	(33)
Unchanged	58%	(51)
Negative	5%	(4)
Change in aesthetic experiencing		
Positive	37%	(32)
Unchanged	62%	(53)
Negative	1%	(1)
Change in the attitude to altered states of consciousness		
Positive	56%	(49)
Unchanged	41%	(36)
Negative	3%	(3)

Numbers after percents indicate absolute frequencies.

ASC before the experiments included out-of-body-experiences during meditation and sleep, trance-like states while deeply concentrating, euphoric experiences in nature, perceptual alterations in very dark or bright environments, lucid dreams, hearing voices under high fever, and hypnagogic hallucinations. All these alterations lasted a few seconds to no more than 1 h, occurred a few times in a lifetime to no more than once per month, and were limited to specific triggers. They were not experienced as threatening and they did not interfere with subjects' everyday lives. Thus, they cannot be interpreted as psychopathological symptoms.

Spontaneous ASC after the experiments could not be distinguished from those before with respect to frequency, duration and intensity. Except for one subject who reported irritability, depressive feelings, anxiety/panic, and dizziness/nausea, and who will be discussed in more detail below, all spontaneous ASC that occurred after the experiments were described as non-threatening and without impairment in social, occupational, or other important areas of functioning. They were controllable and limited to specific triggers, such as listening to music, meditating, falling asleep (hypnagogic states), deeply concentrating, or being in a calm and sensory deprived environment. In all subjects, spontaneous ASC after the experiments were described as lasting a few seconds to no more than half an hour, and occurring infrequently.

Although three subjects reported minor visual alterations, they mostly appeared after the triggers mentioned above. Moreover, the descriptions of these alterations were vague and not suggestive of the typical symptoms of Hallucinogen Persisting Perception Disorder (HPPD) mentioned in DSM-IV (geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of colour, intensified colours, trails of images of moving objects, after-images of moving objects, macropsia, and micropsia). Only one subject explicitly mentioned the occurrence of visual illusions beyond the acute effects of the drug, but they appeared only 5–7 times, lasted no more than a few seconds at a time, and did

Table 5. Changes in drug consumption habits

Drug	Less often	More often
Alcohol	6.7% (6)	3.3% (3)
Nicotine	4.4% (4)	2.2% (2)
Cannabis	8.9% (8)	3.3% (3)
MDMA	4.4% (4)	3.3% (3)
Psilocybin	5.6% (5)	3.3% (3)
Cocaine	4.4% (4)	1.1% (1)
Amphetamine	2.2% (2)	0% (0)

Numbers after percents indicate absolute frequencies.

not occur after the third day after the drug session. When asked whether they interpreted their spontaneous ASC as a flashback-like re-experiencing of drug effects, five subjects (5.5% of those who completed the follow-up questionnaire and 56% of those who reported spontaneous ASC after the experiments) answered affirmatively. However, since we have also obtained detailed descriptions of these events, including frequency, duration, intensity, and accompanying symptoms and emotions, there was a clear indication that these five subjects had used the term flashback in a very broad sense, denoting vague states of intense remembering of drug effects rather than the criteria described for HPPD in DSM-IV.

Negative changes in psychological well-being and/or mental functions. Eleven subjects (12%) reported in the follow-up questionnaire that they had experienced negative changes in psychological well-being and/or mental functions after the psilocybin experiment. However, four of these 11 reported that the changes were unrelated to the psilocybin sessions and so they will not be discussed here.

Among the remaining seven subjects (8%), only one reported that his symptoms were alarming and severe enough for him to contact us and to seek professional help. This was the same subject who mentioned irritability, anxiety and depressive feelings in the items regarding spontaneous ASC described above. This subject was a 23-year-old medical student who presented himself as psychologically stable and with an unremarkable medical history at screening. There was also no indication of above average emotional lability according to the FPI questionnaire. During the acute effects of the high psilocybin dose (315 µg/kg), the subject experienced a strong sense of unity, but also intense feelings of loneliness and fear of losing control of his thoughts and body. At 150 min after drug intake, he reached an AED score of 76% of the theoretical scale maximum, which is the fourth highest score that we measured in the 227 psilocybin sessions of the present analysis. After providing strong personal support and reassurance by the study manager, the subject had calmed down considerably by the second 5D-ASC measuring time point (300 min after drug intake), reaching only 4% of the maximum possible score in the AED scale. Nevertheless, the subject was monitored carefully and not released until 8 h after drug intake when all acute psilocybin effects had fully worn off. However, since the subject felt uncomfortable over the next couple of weeks, several appointments were made with the principal investigator. In these meetings, the subject reported emotional instability, anxiety, and depressive feelings, which he attributed to suppressed memories, thoughts, and feelings that he had been confronted with during the psilocybin session. Since the subject was strongly motivated to work through these issues psychologically, he was referred to an experienced psychotherapist. After a few sessions of psychotherapy, the subject had completely stabilized and has not relapsed with the symptoms subsequently.

Among the remaining six subjects who also reported negative changes in well-being and/or mental functions, the following symptoms were described (with number of subjects in parenthesis): Concentration problems (2), mood swings (2), reactivation of old problems (1), memory problems (1), and being pensive and introverted (1). In all these subjects, symptoms were described to be of low intensity and frequency, non-interfering with everyday life, and only occurring in the first few weeks subsequent to the experiments.

Discussion

Acute psychological effects

The present work analysed acute, short- and long-term effects of psilocybin in healthy human subjects by pooling raw data from a large body of well-controlled experimental studies. Consistent with other recent, smaller-scaled studies (Griffiths et al., 2006; Moreno et al., 2006), the present analysis has shown that psilocybin dose-dependently induces an ASC, which is characterized by marked alterations in all mental functions, including perception, mood, volition, cognition and self-experience. The most prominent features of the psilocybin-induced ASC were alterations in VR, followed by positively (OB) and negatively (AED) experienced alterations of self-awareness and loosening of ego boundaries. The changes in visual perception ranged from increased visual imagery with closed eyes, optical illusions, elementary hallucinations and synaesthesia to picture-like scenery hallucinations. However, the experienced hallucinations were almost always recognized as unreal and therefore are more accurately described as pseudo- or non-psychotic hallucinations. Drug effects accounting for the substantial increase in the OB scale ranged from pleasurable experiences of depersonalization, derealization and a changed sense of time to phenomena reminiscent of mystical-type experiences. The modest increase in the AED scale was primarily due to unpleasant disturbances of cognitive functions and somatesthesia, and much less so to suspiciousness or paranoid ideation. Reality testing usually remained intact, and most subjects sustained critical distance ('it is as if') to their own subjective experience. The AA scale was only moderately affected by psilocybin, since true auditory hallucinations, such as hearing voices, rarely occurred, and auditory alterations mostly concerned occasional intensification of music and sounds or misperceptions of real auditory stimuli. Psilocybin also dose-dependently increased the RV scale. This observation may come as a surprise, since lack of sedation and clouding of consciousness is usually considered as one of the most prominent characteristics of classical hallucinogens. In fact, according to the classification scheme of Leuner (Gouzoulis-Mayfrank et al., 1999b; Leuner, 1981), hallucinogens of the first order (e.g. LSD, psilocybin, DMT,

and mescaline) are differentiated from hallucinogens of the second order (e.g. ketamine, N_2O, and scopolamine) by this very feature. However, it should be noted that the effect of psilocybin on RV was relatively small and reflects the psilocybin-induced state of dreaminess, contemplativeness, and reduction of attentiveness, rather than true sedation or clouding of consciousness.

Cumulative distributions of the 5D-ASC major scales revealed widely varying individual responses. For instance, whereas one subject experienced strong effects on the low dose condition (63% of the possible maximum of the global scale), two subjects noticed almost no effects on the highest dose condition (below 5% of the possible maximum). The high inter-subject and moderate inter-study variability of the pooled analysis supports the view that psilocybin effects are poorly predicted by drug dose alone and that other pharmacological variables, such as plasma levels of the active metabolite psilocin, as well as non-pharmacological variables – notably expectations, personality structure, interpersonal support, and environment – likely play a very important role (Dittrich, 1994; Johnson et al., 2008; Metzner et al., 1965; Rinkel et al., 1961). The significance of such potential non-pharmacological predictors will be analysed and presented in a separate publication.

Dose-response relationships for all major scales of the 5D-ASC were approximately linear. Since no ceiling effect has been observed within the administered dose range (45–315 μg/kg body weight), it is conceivable that psilocybin doses exceeding 315 μg/kg would have produced even stronger subjective drug effects. This view is supported by a recent study of Griffiths et al. (2006), in which subjective drug effects were measured by the APZ questionnaire in 36 healthy volunteers who had received 429 μg/kg psilocybin. By estimating 5D-ASC from APZ scores through linear equations (Bodmer, 1999), we have found higher OB and VR scores in the study of Griffiths et al. than in the highest dose condition of our studies. Furthermore, in the study of Griffiths et al., 61% of subjects fulfilled Pahnke's criteria for having a 'complete' mystical experience (Pahnke, 1969), which seems to be a considerably larger proportion than we have observed in the highest dose condition. Although we have used a different methodology and therefore cannot directly compare results, we have found that only 22% of subjects in the high-dose condition exceeded the cut-off value of the OB scale suggestive of deep mystical or transcendent experiences. However, it should it be noted that, in addition to the higher drug doses in the study of Griffiths et al., several other factors might have contributed to these differences. First, the investigation of transformative peak experiences has not been the primary goal of our research programme. Hence, our studies have not been designed in a way that the occurrence of such profound experiences is most likely. Whereas volunteers in the study of Griffiths et al. were instructed to focus explicitly on the phenomenology of the drug experience and were left essentially undisturbed during their whole psilocybin session, subjects of our studies were engaged in performing tasks for a considerable amount of time. Second, none of the subjects in the study of Griffiths et al. had previous experience with a hallucinogenic drug, whereas in our studies about 40% of subjects had previous experience with a classical hallucinogen (LSD, psilocybin, DMT or mescaline) and almost 90% had smoked cannabis at least once in a lifetime. Third, the subjects in Griffiths et al.'s study were middle-aged (46 years on average) and spiritually active, whereas our subjects were predominantly students, considerably younger (27 years on average), and not selected for being spiritual.

Despite extremely careful preparation, selection, and interpersonal support of subjects, there also seems to have occurred more acute adverse reactions in the study of Griffiths et al. than in our studies. Griffiths et al. report that 31% of subjects experienced significant fear and 17% had transient ideas of reference/paranoia, whereas in our studies only 7% of subjects in the highest-dose condition fulfilled the criteria for strong AED, which is suggestive of acute psychotic reactions. Although these adverse reactions were confined to the acute phase and were readily managed by providing interpersonal support without psychopharmacological intervention in all cases of both research groups, they provide a cautionary note on high-dose psilocybin studies. Clearly, careful selection of subjects and environment and thorough preparation and monitoring of subjects is extremely critical in high-dose psilocybin sessions.

The results of our analysis of the time course of subjective effects measured by the AMRS indicate that the effects follow differential time courses, which are not necessarily paralleled by psilocin plasma levels (Hasler et al., 1997). Whereas the effects of psilocybin on emotional excitation, sensitivity, heightened mood, and concentration reached their maximum in an early phase (60–180 min after drug intake), the effects on dreaminess, dazed state, inactivation, and introversion were more pronounced in a later phase (260–400 min). The results are consistent with a study of Heimann (1961), in which expressive phenomena, such as changes in facial expression, voice, and posture, were analysed by use of video recording in 12 healthy volunteers who had received 0.06–0.19 μg/kg psilocybin on two experimental days. Heimann observed that subjects were more active, emotional, vivid, extroverted, and cognitively impaired in the early phase of the psilocybin session relative to the later phase, and that derealization and depersonalization phenomena began to dominate over visual alterations about 90–120 min after drug intake. During this later phase, subjects also increasingly turned inwards and appeared to be in a state of absent-mindedness with markedly reduced facial expression.

Short-term side effects

Our pooled analysis further revealed that the administration of psilocybin caused only few subacute side effects, as measured by the LC questionnaire 24 h after drug intake. Furthermore, those complaints that were reported significantly more often after psilocybin than after placebo concerned relatively mild conditions. Except for headaches, all significantly affected items described symptoms of tiredness and exhaustion. Serious complications were not reported in any of the subjects. The reported after effects of the LC questionnaire closely match the changes seen in the AMRS questionnaires 24 h after drug intake, namely a moderate increase of tiredness and reduction of activation. The results of our

analysis therefore suggest that psilocybin is usually well tolerated and that normal functioning is almost completely restored within 24 h after drug administration. These findings are in line with an investigation of Hollister (1961), which measured after effects of the administration of 36–205 µg/kg psilocybin to 17 subjects in 27 separate trials and also found occasional headaches and fatigue as being the most frequent complaints. Furthermore, our results are consistent with extensive tests in animals and humans, which found that psilocybin may be considered to be physiologically well tolerated (for a review, see Passie et al., 2002).

Long-term follow-up

Retrospective ratings of acute drug effects. At the time of the long-term follow-up 8–16 months after the last experimental session, the majority of subjects were still positively impressed by the psilocybin experience. When subjects were asked to rate the acute psilocybin effects by six descriptive items, 'enriching' was considered as most applicable. Over 60% of subjects rated the experience as very enriching and over 90% as enriching to at least a medium degree. Interestingly, several of our subjects rated the psilocybin experience as very enriching even though they had experienced significant distress during the acute phase. For instance, among the 16 subjects who had an AED score of more than 50% of the maximum possible score, four subjects (25%) did not respond to the follow-up questionnaire, nine subjects (75% from those who responded) rated the experience as very enriching, two (17%) as medium enriching, and only one subject (8%) as not enriching. The positive long-term resolution of acute distressful experiences by the majority the subjects might be partially explained by the strong support provided by our monitors, with whom subjects were able to talk freely about disturbing thoughts, feelings, and memories that had arisen during the session. A significant number of our subjects reported not only enriching but also influential drug experiences. Our results are therefore in support of a recent follow-up study by Griffiths et al. (2008), in which psilocybin was found to facilitate experiences having enduring personal meaning and spiritual significance.

Changes in values and attitudes. Anecdotal reports and preliminary evidence from small-scaled experimental studies suggest that hallucinogenic drugs, when used under carefully controlled and supportive conditions, sometimes can lead to sustained positive changes in personality, attitudes, and values, particularly in those subjects who have experienced profound personal insights and transcendent or mystical-type experiences. Among the most often reported subjective changes in attitude and personality are more self-understanding, more tolerance of others, less egocentricity, a less materialistic and aggressive orientation, and more appreciation of music, art, and nature (McGlothlin and Arnold, 1971). Subjective changes in attitudes reported in the long-term follow-up questionnaire of the present study are consistent with results of earlier follow-up studies (Doblin, 1991; Griffiths et al., 2008; McGlothlin et al., 1967). We have found the highest percentages of subjects reporting positive changes in items measuring the attitude to ASC (56% of subjects), the relationship to the environment/nature (38%), and aesthetic experiencing (37%). The observation that aesthetic experiencing (e.g. enhanced appreciation of art and music) was amongst the most often reported positive changes is particularly interesting in light of an earlier placebo-controlled study by McGlothlin et al. (1967), which measured long-lasting effects of three high-dose LSD sessions in 24 healthy volunteers. In this study, greater appreciation of music (67% of subjects) and art (46%) were the most frequently reported subjective changes 6 months after the LSD experiments. Furthermore, these subjective evaluations were supported by certain behavioural changes, such as increase in number of records bought, time spent in museums, and number of musical events attended.

Given the positive changes in attitudes and values reported by a relatively large proportion of subjects, it would be tempting to conclude that hallucinogenic drugs hold a large and presently unused potential for increasing life satisfaction and personal growth and for assisting psychotherapy. However, our results should be considered as exploratory in nature, because possible changes have not been measured by validated questionnaires and no attempt has been made to correlate subjective changes with behavioural measures or information provided by close relatives and friends. Therefore, we cannot rule out the possibility that the reported changes are biased towards preconceived opinions and expectations of subjects. Caution is especially warranted since it has been demonstrated that positive changes in personality, attitudes, and values are often attributed to the hallucinogen experience in subjects who have shown a previous interest in hallucinogenic drugs, but not in subjects whose hallucinogen intake was initiated by their psychotherapist (McGlothlin and Arnold, 1971).

Changes in drug consumption habits. Changes in drug use patterns that were reported in the follow-up questionnaires of the present study were generally benign and well within expected ranges. Our results therefore indicate that a carefully monitored administration of 1–4 doses of psilocybin to healthy volunteers within an experimental setting does not increase the risk for subsequent abuse of psilocybin or other illicit drugs. Our results are consistent with the widely accepted view that classical hallucinogens have a very low abuse potential. Classical hallucinogens are not typically considered as drugs of addiction, because they neither produce compulsive drug-seeking behaviour nor physical withdrawal symptoms (O'Brian, 2005). They also cannot be considered as reinforcing substances because they fail to engender reliable self-administration behaviour in laboratory animals (Deneau et al., 1969; Fantegrossi et al., 2008). The view that classical hallucinogens lack addictive qualities is further supported by epidemiological evidence. Recent general population survey data on lifetime prevalence of use of hallucinogenic mushrooms in 12 EU Member States indicate that among young people aged 15–24 years old, lifetime use of hallucinogenic mushrooms ranges from less than 1% to 8% (Hillebrand et al., 2006). Although psilocybin has, after

cannabis, one of the highest lifetime prevalence rates of all illicit drugs, the proportion of recent (last 12 months) or current (last month) users is much lower for the use of psilocybin than it is for cannabis and ecstasy. This observation suggests that the use of hallucinogenic mushrooms, like LSD, tends to be occasional, or discontinued after some time. Regular use of classical hallucinogens is unlikely, because tolerance to the effects rapidly develops after three to four daily doses (O'Brian, 2005). Furthermore, the intake of classical hallucinogens, especially in higher doses, is unattractive to many recreational drug users because it does not consistently produce any of the pleasurable effects of addictive drugs, such as escape, euphoria, anxiety relief, increase of self-esteem, etc. Although our experiments have shown that psilocybin can evoke highly valued and in some cases even mystical-type experiences, subjects occasionally are also confronted with frightening and unpleasant thoughts, memories, and emotions. Moreover, as we have measured by the LC and AMRS questionnaires, most subjects describe the psilocybin effects as tiring. This effect is further reflected by the observation that after 3–5 h the 'coming down' from the psilocybin effects, even if it has been a pleasant experience, is usually welcomed, and that most subjects are glad to regain their normal state of consciousness. Subjects often reported they were 'saturated' by new impressions and expressed the need to psychologically integrate their experience before they would consider repeating it.

Our findings are in line with a 10-year follow-up study by McGlothlin and Arnold (1971), which examined 247 subjects who had received LSD in either an experimental or therapeutic setting. As in our study, most subjects reported to have discontinued or reduced their frequency of hallucinogenic drug use. The most often reported reasons for discontinuation were concerns about possible harm or illegality followed by a loss of interest. McGlothlin and Arnold therefore speculated that in many subjects, hallucinogenic drugs lose their appeal over time simply because the uniqueness of the new modes of perception and thought that occur with them often being the primary incentive to take them in the first place is lost after repeated ingestion.

Spontaneous alterations of consciousness and flashbacks. Among the most often reported long-term sequelae of hallucinogenic drug use is a sudden and unexpected reoccurrence of all or certain aspects of the hallucinogenic effects, long after the drug should have worn off. The phenomenon has been first described by Sandison (1954) and is often referred to as 'flashback'. However, since its first description in the scientific literature (Horowitz, 1969), the term 'flashback' has been defined in so many ways that much confusion exists about its characteristics, prevalence, and aetiology (Halpern and Pope, 2003). The present study avoided methodological inconsistencies of earlier follow-up studies and contributes to a better understanding of flashback phenomena after psilocybin administration by using operational criteria consistent with those of DSM-IV ('Hallucinogen Persisting Perception Disorder' (HPPD), 292.89) and ICD-10 ('Flashbacks', F16.70).

Detailed questions about possible flashback phenomena and spontaneous ASC in the follow-up questionnaire of the present study indicated that none of our subjects fulfilled diagnostic criteria for HPPD in DSM-IV or flashbacks in ICD-10. Furthermore, none of our subjects described visual phenomena reminiscent of the typical symptoms of HPPD mentioned under criterion A of HPPD in DSM-IV (292.89).

Our results support the view that HPPD and other troubling perceptual abnormalities rarely occur in a therapeutic or research context, where subjects are carefully screened and monitored and judicious doses of pharmaceutical quality drugs are given (Halpern and Pope, 2003; Strassman, 1984). The clinical relevance of flashback phenomena has been a matter of controversial debate for several decades. Whereas some researchers report virtually no such phenomena in series of hundreds or thousands of cases (Cohen, 1960; McGlothlin and Arnold, 1971), others report incidence rates as high 33% (Moskowitz, 1971) and 77% (Holsten, 1976) among individuals who have taken LSD. A recent review by Halpern and Pope (2003: 116), which analysed 20 quantitative studies reporting flashback phenomena, concludes that 'the data do not permit us to estimate, even crudely, the prevalence of ''strict'' HPPD'. Halpern and Pope (2003) point out that most of these studies were published before operational diagnostic criteria for HPPD had been established and therefore used a wide variety of methodologies. They further criticize that confounding factors such as recent drug intake, polydrug abuse, pre-existing psychiatric disorders, and comorbidity often have been very poorly controlled in the studies.

It should also be noted that the scientific basis for the classification of HPPD in DSM-IV appears to be formed almost exclusively by the research of Abraham and his colleagues (1982, 1983, 1988, 1996, 2001). Since the majority of Abraham's work was focused solely on LSD use, we cannot safely infer that the diagnosis of HPPD has equal implications for all classical hallucinogenic drugs. Interestingly, very few case reports have appeared on flashback phenomena experienced by individuals who have used psilocybin, DMT or mescaline exclusively. In fact, Hermle et al. (2008) report in a recent review that there exists only one case report (Espiard et al., 2005) where HPPD occurred after hallucinogenic mushroom use.

Prolonged adverse reactions. The present study supports the notion that prolonged adverse reactions, such as persisting psychosis or depression, are exceedingly rare when psilocybin is administered to well-adjusted subjects in a controlled experimental setting (Abraham and Aldridge, 1993; El-Mallakh et al., 2008; Strassman, 1984). We have found no incidences of prolonged psychotic reactions or precipitations of schizophrenia-spectrum disorders in the 110 subjects studied. However, one of our subjects experienced symptoms of emotional instability, anxiety, and depression, which lasted several weeks and were severe enough for him to seek professional help. A few subjects described occasional mood swings, reactivation of old problems, excessive pensiveness and introversion, and memory and concentration problems in the first few weeks after the drug session. Although these adverse after

effects were generally benign and in all cases resolved after a few weeks, they underline the importance of careful debriefing and follow-up of subjects – especially in the first few days and weeks after drug administration.

Limitations

It is important to note that the high degree of safety and tolerability of psilocybin reported in the present study cannot be generalized to situations in which psilocybin is used recreationally or administered under less controlled conditions. It is likely that the careful selection, preparation, and monitoring of subjects as well as the administration of predominantly moderate drug doses have largely contributed to the relatively low occurrence of adverse events in our studies. Our sample might be unrepresentative not only due to exclusion of subjects showing potential risk factors (high emotional lability, history of drug abuse, psychiatric illness, and hereditary risk factors) at screening, but also due to the use of a recruitment method that is prone to self-selection bias. The subjects who volunteered for our studies had prior knowledge that experiments would involve psilocybin administration. Hence, it is likely that individuals who had a positive attitude towards hallucinogenic drugs and who had a personal interest in experiencing drug-induced ASC were more likely to participate in our experiments. McGlothlin and Arnold (1971) have shown that subjects who are interested in hallucinogenic drug use are susceptible to naturally occurring ASC, seek to encourage them through both drug and non-drug methods, and have a certain type of personality structure. Indeed, although our subjects were not selected for previous drug experience, 40% had used a classical hallucinogen at least once in a lifetime prior to the experiments, which is a larger proportion than in the general population. Although previous experience, positive expectancy, and personality characteristics might have biased subjective drug effects, it may also have contributed to the low occurrence of adverse events. Subjects who expect positive psilocybin effects tend to experience more positive psilocybin effects, whereas anxiety and preoccupation before drug administration not only increases the likelihood of unpleasant experiences, but also the number of somatic complaints (Metzner et al., 1965). Moreover, emotional lability and rigid conventionality – personality traits that tend to be below average in our sample – are positively correlated with AED in ASC (Dittrich, 1994). Since safety and tolerability considerations, in our opinion, are more important than methodological rigor, we have not sought to maximize the representativeness of our sample by excluding subjects who had some experience with hallucinogenic drugs – unless they used them on a regular basis. In fact, subjects with a few past experiences were considered ideal because they probably would not have volunteered if they had had significant adverse reactions. This policy has also been proposed by Gouzoulis-Mayfrank et al. (1998b).

Apart from the lack of representativeness, our investigation has further limitations. First, cut-off values used to measure the proportion of subjects experiencing very strong subjective drug effects – although similar to specifications used by Pahnke (1969) – are relatively arbitrary, since they neither have been defined a priori nor validated on clear-cut criteria. Second, we have used an investigator-constructed follow-up questionnaire whose reliability and validity is not known.

Conclusion

Taken together, our experimental data from 227 psilocybin administrations have demonstrated safety and tolerability not only acutely, but also in the long run. We found no indication for subsequent drug abuse, persisting perception disorders, prolonged psychosis or other long-term impairments of functioning in any of our subjects. Acute adverse reactions (so called 'bad' or 'horror trips') occurring in a small proportion of subjects in the two highest dose conditions, as well as transient emotional instability lasting a few days or weeks in a small number of subjects, remain the biggest concerns in psilocybin administration. However, given that all of these adverse reactions resolved by providing strong interpersonal support and appeared to be positively integrated at the long-term follow-up, 8–16 months after the drug experiments, we conclude that psilocybin administration to healthy, high-functioning, and well-prepared subjects in a responsible clinical or research setting is generally well tolerated, and that future studies using this important research tool are justified.

Acknowledgements

The authors would like to thank Dr Alex Gamma, Dr Mark Geyer, Dr George Greer, and Dr Boris Quednow for critical comments on the manuscript.

Funding

This work was generously supported by the Heffter Research Institute, Santa Fe, USA, (ES, FH) and the Swiss Neuromatrix Foundation, Switzerland (MK, FXV).

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