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Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors

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Abstract

Psilocybin can occasion mystical-type experiences with participant-attributed increases in well-being. However, little research has examined enduring changes in traits. This study administered psilocybin to participants who undertook a program of meditation/spiritual practices. Healthy participants were randomized to three groups (25 each): (1) very low-dose (1 mg/70 kg on sessions 1 and 2) with moderate-level (“standard”) support for spiritual-practice (LD-SS); (2) high-dose (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with standard support (HD-SS); and (3) high-dose (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with high support for spiritual practice (HD-HS). Psilocybin was administered double-blind and instructions to participants/staff minimized expectancy confounds. Psilocybin was administered 1 and 2 months after spiritual-practice initiation. Outcomes at 6 months included rates of spiritual practice and persisting effects of psilocybin. Compared with low-dose, high-dose psilocybin produced greater acute and persisting effects. At 6 months, compared with LD-SS, both high-dose groups showed large significant positive changes on longitudinal measures of interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and community observer ratings. Determinants of enduring effects were psilocybin-occasioned mystical-type experience and rates of meditation/spiritual practices. Psilocybin can occasion enduring trait-level increases in prosocial attitudes/behaviors and in healthy psychological functioning.

Trial Registration

ClinicalTrials.gov Identifier NCT00802282

Keywords

Psilocybin, psychedelic, entheogen, meditation, mystical experience, traits

Introduction

Quantum change experiences refer to sudden, distinctive, benevolent, and often profoundly meaningful experiences that are said to result in personal transformations that affect a broad range of personal emotions, cognitions and behaviors (Miller, 2004; Miller and C’de Baca, 2001). The phenomenon of quantum change is differentiated from the usual process of behavioral change, which occurs in small incremental steps (James, 1902). Such experiences, which have been described in anecdotal reports dating back centuries, have been variously labeled as mystical experiences, conversion experiences, religious experiences, peak experiences, transcendental experiences, transforming moments, or epiphanies (e.g. James, 1902; Maslow, 1968; Miller and C’de Baca, 2001; Stace, 1960). Although numerous cases of such quantum change experiences have been described, they have generally not been examined in prospective experimental studies because such experiences occur at low rates and usually unpredictably (Paloutzian and Park, 2013).

Administration of psilocybin, a classic psychedelic, provides a model for experimental investigation of quantum change experiences. Controlled, double-blind clinical trials in healthy volunteers show that under supportive conditions psilocybin can

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reliably occasion deeply personally meaningful and often spiritually significant experiences (e.g. mystical-type experiences) (Griffiths et al., 2006, 2011; Pahnke, 1963) having many characteristics similar to those described for quantum change experiences (Miller and C'de Baca, 2001). Such psilocybin effects are dose dependent (Griffiths et al., 2011) and have been demonstrated under conditions that provide substantial controls for expectancy bias (Griffiths et al., 2006, 2016). Although participants often attribute enduring positive changes in well-being and worldview to such experiences, there is little evidence from studies in healthy volunteers that psilocybin produces enduring changes on well-validated trait measures of disposition or personality (Darling et al., 2004; Doblin, 1991; Griffiths et al., 2008; 2011; Leary et al., 1963; Pahnke, 1963; Studerus et al., 2011). For example, a previous study in 36 participants who received a high dose of psilocybin showed enduring positive changes in moods, attitudes, and behavior attributed to the psilocybin experience, but no significant changes from screening to 14-month follow-up on various measures of personality, quality of life, faith maturity, and spiritual well-being (Griffiths et al., 2008). A later post-hoc analysis which combined data from that study with data from a similar subsequent study with 18 participants (Griffiths et al., 2011) showed that psilocybin-occasioned mystical-type experiences were associated with increases in the personality trait of openness (MacLean et al., 2011).

Although an older literature on psilocybin-assisted psychotherapy in psychiatric patient populations suggests that administration of psilocybin in a psychotherapeutic context may produce enduring decreases in psychopathology and increases in positive worldview and dispositional characteristics, methodological limitations render those reports inconclusive (Passie, 2004, 2007). However, recent placebo-controlled trials in psychologically distressed cancer patients showed that psilocybin produced decreases in anxiety and depression and increases in quality of life that persisted for at least a month and possibly 6 months or more (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016).

The present study in healthy participants sought to extend understanding of possible enduring effects of quantum change experiences generally and psilocybin-occasioned experiences specifically by manipulating psilocybin dose and the intensity with which participants were encouraged to engage in meditation and other spiritual practices. Acute psilocybin effects, retrospective attributions to the experience, and enduring changes in prosocial attitudes and behaviors, and psychological functioning were assessed. More specifically, the present study used an across-group design to compare these outcomes in three groups of 25 healthy participants: (1) low-dose (active placebo) psilocybin with moderate-level ("standard") support for spiritual practice; (2) high-dose psilocybin with standard support; and (3) high-dose psilocybin with high support.

Materials and methods

Participants

Participants were recruited from the local community through flyers seeking volunteers interested in developing their spiritual lives by participating in a study of the combined effects of meditation and psilocybin, a psychoactive substance found in mushrooms used as sacraments in some cultures. In total, 1305 individuals

were screened by telephone and 184 were further screened in person. Primary reasons for exclusion between phone screen and in-person screening were prior use of psychedelics (312); medical/psychiatric exclusion (288); pre-existing regular meditation or other spiritual practice (261); logistics or lack of interest (220). Eighty-five volunteers were enrolled in the study and 10 did not complete the study. Reasons for non-completion included illness or a disqualifying medical or psychological issue (five volunteers), noncompliance with study procedures for personal or job-related reasons (three volunteers), and missing data on key measures (two volunteers). The 75 study completers (40% male) were medically healthy (as determined by medical history, physical examination, an electrocardiogram, routine medical blood laboratory tests, and urine testing for common drugs of abuse), and psychiatrically healthy. They were without personal or family histories of psychotic disorders or bipolar I or II disorder as determined by structured clinical interviews. Individuals with current alcohol or other drug dependence (including nicotine) were excluded, as were individuals with a past history within the past 5 years of alcohol or drug dependence (excluding nicotine). Twenty-five percent of participants reported past use of a psychedelic, with a mean of 25.1 years since last use. Participants were excluded if they reported any history of either spontaneous or psychedelic-occasioned salient mystical-type experiences. Participants had a mean age of 42 years (range 22 to 69) and a mean weight of 71.5 kg (range 49.2 to 97.5); 89% had college or post-graduate degrees and 87% were full-time employees or students. Although 31% reported practicing seated meditation, the mean frequency of practice was very low (1.1 times per month for the group). Volunteers did not receive monetary compensation for participation. Based on interviews, their motivation for participation was their interest in learning meditation, exploring their spiritual lives, and their curiosity about the effects of psilocybin. The Johns Hopkins IRB approved the study. Written informed consent was obtained from participants.

Study design and overview

The study procedures followed recommendations provided for safe conduct of research administering high doses of a classic psychedelic (Johnson et al., 2008). This study investigated the effects of psilocybin dose and the frequency and intensity of support provided for spiritual practice (i.e. meditation, spiritual awareness practice, journaling) on a battery of attitudinal and behavioral outcome measures in 75 healthy participants. The psilocybin dose manipulation was double-blind.

The duration of each volunteer's participation was approximately 6 to 8 months. After enrollment and before the first of two psilocybin sessions (described below), each participant had several preparation meetings with two study staff trained to serve as session "guides." The two psilocybin sessions were separated by about 1 month. Some measures were assessed during and immediately after sessions, and various longitudinal measures were evaluated immediately after study enrollment (i.e. baseline assessment) and 4 months after the second psilocybin session (i.e. 6-month assessment).

Assignment to the three experimental groups. After screening and study enrollment, each participant was randomized to one of three groups of 25 each: (1) very low-dose psilocybin (1

Table 1. Participant demographics.

Measure	Low-Dose Standard-Support (N=25)	High-Dose Standard-Support (N=25)	High-Dose High-Support (N=25)	Group Comparisons
Gender (Male/Female)	9/16	13/12	8/17	N.S.
Age in years (mean, SEM)	40.2 (2.5)	41.0 (2.7)	45.6 (2.3)	N.S.
Weight in kilograms (mean, SEM)	69.0 (2.2)	72.6 (2.4)	72.9 (2.6)	N.S.
Race/Ethnicity				
White	76%	88%	92%	N.S.
Black/African American	8%	4%	4%	
Asian	16%	8%	4%	
Hispanic	4%	8%	4%	
Education (college or post-graduate degree)	96%	84%	88%	N.S.
Employment				
Full-time job or student	84%	84%	92%	N.S.
Part-time, retired or unemployed	16%	16%	8%	
Life-time Use of Psychedelics				
Percent reporting any past use ¹	32%	28%	20%	N.S.
Current Meditation				
Percent reporting some meditation	24%	36%	32%	N.S.
Times per month for the group (mean, SEM)	1.08 (0.44)	1.36 (0.46)	1.00 (0.37)	N.S.
Mysticism Scale Score (mean, SEM)	175.0 (8.1)	166.3 (13.8)	190.3 (10.0)	N.S.
Judged very likely to do spiritual practices ²	8%	8%	8%	N.S.

N.S. = No significant differences between groups; ANOVA was used for continuous variables; Chi-square was used for categorical variables, with White compared to other racial categories combined and Full-time job or student compared to other employment categories combined.

¹Mean number of years since last use among those who reported using was 25.1 years.

²Judgment made by based on an interview by one of the investigators.

mg/70 kg on sessions 1 and 2—functionally a placebo) with standard support for spiritual practice (LD-SS); (2) high-dose psilocybin (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with standard support for spiritual practice (HD-SS); and (3) high-dose psilocybin (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with high support for spiritual practice (HD-HS). An urn randomization procedure (Stout et al., 1994) was used to balance the three groups as closely as possible on six dichotomous variables (gender, age at study intake, lifetime psychedelic use, baseline lifetime Hood Mysticism Scale score, baseline frequency of meditation, and staff judgment about whether the participant was especially likely to engage in spiritual practices). Table 1 shows that these and other demographic characteristics did not differ across the three experimental groups.

Instructions to participants and guides, and the purpose of a third session. Study instructions and procedures were designed to minimize some of the effects of expectancy. Participants and guides were told that participants would receive psilocybin during each session, that dose levels could range between very low to high, that each participant would receive two or more different dose levels across two or three sessions, and that all participants would have at least one session with a moderately high or high dose of psilocybin. Although the most important comparative data on attitudinal and behavioral change were obtained in the first two sessions and subsequent follow-up, 39 participants were assigned to receive a third session after the

6-month data assessment in which they received 30 mg/70 kg psilocybin. This design feature was used in part to control expectancies through the 6-month follow-up evaluation. Although participants and guides were informed that over two or three sessions all participants would receive one or more high doses of psilocybin, they were not informed which participants or how many participants would be scheduled for a third session, nor were they told that the third session would be a high dose. In fact, all 25 participants in the low-dose psilocybin group (LD-SS) were assigned to receive a third session. An additional 14 participants (eight and six from HD-SS and HD-HS, respectively) were also assigned to receive a third session. Nine of these 14 participants were distributed within the first one-third (25) participants enrolled in the study. The purpose of scheduling a third session in these 14 participants was to obscure the study design from the guides early in the trial and reduce the possibility that guides would have strong expectancies whether or not a participant would have a third session. Data from the third session and data from several exploratory measures are beyond the scope of this report and are not presented.

Guide–participant meetings and support for spiritual practice

The guide–participant meetings served the functions of establishing rapport, providing specific preparation for the psilocybin sessions (see Johnson et al., 2008), and providing instructions and support

for spiritual practices. The primary guides had established personal meditation practices as well as extensive experience supporting psilocybin sessions. An assistant guide was usually present at these meetings. Except for the dialogue-group meetings described below, the same primary and assistant guides were paired with a given participant throughout the study. Guide-participant meetings began and ended with a brief period of meditation.

Standard-Support groups. The frequency of guide-participant meetings differed across the standard vs. high-support conditions. Before the first psilocybin session (in the 1-month period following enrollment) guides and participants in the two standard-support groups (Low-Dose Standard-Support group; High-Dose Standard-Support group) had three 1-hour meetings and one 2-hour meeting (5 total contact hours). After each of the first two psilocybin sessions, participants in the standard-support group met for 1 hour within one or two days (usually one day) and had a 10 minute teleconference with guides about 2 weeks later. Thus, the total guide-participant contact hours for those in the Standard-Support groups from study acceptance to the 6-month follow-up was about 7 hours and 20 minutes.

High-Support group. Before the first session (in the 1 month period following enrollment) participants and guides in the High-Dose High-Support group had five 2-hour meetings (10 total contact hours). Between the first and second psilocybin sessions (1 month apart) there were three 1-hour participant-guide meetings (3 total contact hours). As with the Standard-Support groups, the first of these meetings was scheduled within a day or two following the session. During the 4-month period after the second psilocybin session, 1-hour participant-guide meetings occurred within a day or two of the session, at weekly intervals for the first 2 weeks, and at twice-monthly intervals for the remainder of the 4 months (10 contact hours). Also during the 4-month period after the second psilocybin session, participants in the High-Support group participated in twice-monthly 90-minute dialogue-group sessions. Approximately eight study participants plus one or two facilitators (study staff) participated in each session. The group membership changed over sessions as individual participants entered and left the group as they progressed through the study. The facilitators provided an opportunity to discuss psilocybin experiences but mainly encouraged dialogue about successes and challenges in implementing and sustaining the regular spiritual practices of meditation, spiritual awareness, and journaling. The total guide-participant contact hours for the High-Support group from study acceptance to the 6-month follow-up was 35 hours.

Spiritual practice support. At the first guide-participant meeting, each participant was given: (1) a copy of the book, *Meditation: A Simple 8-Point Program for Translating Spiritual Ideals into Daily Life* (Easwaran, 1991/1978); (2) a blank journal; and (3) a one-page outline of spiritual practice suggestions. All participants were required to read the book on meditation and integration of spiritual values into daily life. This book was used as a primary teaching resource because its approach provides an easily understood, nonsectarian program for spiritual living that has shown increases in measures of spirituality, well-being, self-efficacy, and health outcomes (Flinders et al., 2007; Oman et al., 2006, 2008a,b). The spiritual practice suggestions had three primary elements: meditation (10 to 30 minutes of sitting meditation daily); daily

awareness practice (use of mantra and one-pointed attention in daily activities); and daily self-reflective journaling of insights, benefits, and challenges of spiritual practice in daily life. Participants were also encouraged to engage in activities they personally judged to facilitate spiritual growth (e.g. being in nature, contemplative movement, artwork, or service activities). At each of the guide-participant meetings, the guide asked about, encouraged, and offered instructions in the participant's implementation of the spiritual practice suggestions.

Psilocybin sessions

Psilocybin doses were prepared in opaque, size 0 gelatin capsules of identical appearance, with lactose as the inactive capsule filler. On each session, a single capsule was administered with 180 mL water. As described in more detail previously (Griffiths et al., 2006), psilocybin sessions were conducted in an aesthetic living-room-like environment with two guides present. Participants were instructed to consume a low-fat breakfast before arriving at the research unit at about 08:15 in the morning. A urine sample was taken to verify abstinence from common drugs of abuse and that female participants were not pregnant. For most of the time during the session, participants were encouraged to lie down on the couch, use an eye mask to block external visual distractions, and use headphones through which a program of classical and world music was played. The same music program was played for all participants in all sessions. Throughout the session, guides were nondirective and supportive and they encouraged participants to focus their attention on their inner experiences.

Measures assessed throughout the session

Ten minutes before and 30, 60, 90, 120, 180, 240, 300, and 360 minutes after capsule administration, blood pressure, heart rate, and monitor ratings were obtained by session guides as described previously (Griffiths et al., 2006). Blood pressure (systolic and diastolic pressure using oscillometric method with the blood-pressure cuff placed on the arm) and heart rate were monitored using a Non-Invasive Patient Monitor Model 507E (Criticare Systems, Inc., Waukesha, WI). At the same time-points the two session guides completed the Monitor Rating Questionnaire, which involved rating or scoring several dimensions of the participant's behavior or mood (Table 2). The dimensions that are expressed as peak scores in Table 2 were rated on a 5-point scale from 0 to 4. Data were the mean of the two monitor ratings at each time-point.

Measures assessed 7 hours after drug administration

When psilocybin effects had subsided, participants completed four questionnaires: *Hallucinogen Rating Scale (HRS)* (Strassman et al., 1994); *5-Dimension Altered States of Consciousness (5D-ASC)* (Dittrich, 1998); *Mysticism Scale* (Experience-specific version rated on a 9-point scale) (Hood et al., 2001, 2009); and the *States of Consciousness Questionnaire (SOCQ)* (Griffiths et al., 2006). Thirty items on the SOCQ comprise the *Mystical Experience Questionnaire (MEQ30)*, which has been shown to be sensitive to mystical-type subjective effects of psilocybin in laboratory studies as well as in survey studies of psilocybin mushroom use (Barrett

Table 2. Cardiovascular measures and guide ratings of volunteer behavior and mood assessed throughout the session.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
<i>Cardiovascular Measures (peak effects)</i>			
Systolic blood pressure (mm Hg)	129.38 (2.37)	145.50 (2.62)***	148.54 (3.33)***
Diastolic blood pressure (mm Hg)	77.44 (1.71)	83.46 (1.68)**	85.22 (1.50)***
Heart rate (beats per minute)	75.74 (1.81)	91.04 (2.70)***	89.96 (2.77)***
<i>Guide Ratings (peak effects, max score=4)</i>			
Overall drug effect	1.17 (0.09)	2.68 (0.14)***	2.82 (0.10)***
Anxiety or Fearfulness	0.31 (0.09)	1.01 (0.17)*	1.43 (0.33)***
Distance from ordinary reality	0.75 (0.11)	2.46 (0.18)***	2.43 (0.11)***
Systematized ideas of reference	0.04 (0.02)	0.14 (0.05)	0.17 (0.06)*
Yawning	0.46 (0.15)	0.76 (0.23)	1.16 (0.24)*
Tearing/Crying	0.19 (0.11)	1.02 (0.17)	2.56 (0.72)***+
Nausea/vomiting	0.06 (0.04)	0.44 (0.15)*	0.5 (0.11)**
Joy/intense happiness	0.46 (0.09)	1.98 (0.20)***	1.8 (0.16)***
Peace/harmony	0.87 (0.13)	2.00 (0.20)***	1.72 (0.13)***
Psychological Discomfort	0.14 (0.06)	0.75 (0.17)**	0.87 (0.17)***
Physical Distress	0.07 (0.03)	0.56 (0.18)**	0.57 (0.13)**

Data are means of the peak response in each of the two psilocybin sessions in each participant. Group means with 1 SEM in parentheses ($n=25$) are shown.

Within a row, asterisks indicate a significant difference from the Low-Dose Standard-Support group (* $p<.05$, ** $p<.01$, *** $p<.001$, Planned comparisons), and + indicates a significant difference between the High-Dose High-Support and High-Dose Standard-Support groups ($p<.05$, Planned comparisons).

et al., 2015; MacLean et al., 2012). A total score (mean of all 30 items) and four factor scores were assessed: (1) Mystical, comprising items assessing internal and external unity, sacredness, and noetic feelings; (2) Positive mood (e.g. joy, peace awe); (3) Transcendence of time and space; (4) Ineffability. A participant was designated as having had a “complete” mystical experience if scores on each of the four factors was $\geq 60\%$ of the maximum possible factor score (Barrett et al., 2015). The MEQ30 is a psychometrically more rigorous derivation of the Pahnke–Richards scale, which has been described previously (Griffiths et al., 2006).

Spiritual practices assessed at the 6-month follow-up

Spiritual practices questionnaire. This questionnaire assessed engagement with the three primary spiritual practices that were the focus of the spiritual practice teachings, the guide–participant meetings, and the dialogue-group meetings. Participants were instructed to complete the questionnaire based on their spiritual practices over the past 4 months (since the second psilocybin session). Participants rated the frequency and duration of their usual meditation practice, the frequency of their daily awareness practice (e.g. mantra repetition during daily activities), and the frequency of their self-reflective journaling.

Persisting effects assessed at the 6-month follow-up

Persisting effects questionnaire. This questionnaire assessed changes in attitudes, moods, behavior, and spiritual experience and has been shown sensitive to the effects of psilocybin 14 months after a psilocybin session (Griffiths et al., 2011). Participants were asked to rate any current persisting effects that they attributed to

the experiences during either or both of the two psilocybin sessions. One hundred forty items were rated on a 6-point scale (0=none, not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong; 5=extreme, more than ever before in your life and stronger than 4). Within the questionnaire, the items were labeled in six categories: Attitudes about life (13 positive and 13 negative items); Attitudes about self (11 positive and 11 negative items); Mood changes (9 positive and 9 negative items); Relationships (9 positive and 9 negative items); Behavioral changes (1 positive and 1 negative item); Spirituality (22 positive and 21 negative items). The positive and negative items were intermixed within each category. For purposes of scoring the resulting 12 scales (positive and negative scales for each of six categories) scores were expressed as the percentage of the maximum possible score.

The questionnaire included three additional questions (see Griffiths et al., 2006 for more specific wording): (1) How personally meaningful was the experience? (rated from 1 to 8, with 1=no more than routine, everyday experiences; 7=among the five most meaningful experiences of my life; and 8=the single most meaningful experience of my life); (2) Indicate the degree to which the experience was spiritually significant to you? (rated from 1 to 6, with 1=not at all; 5=among the five most spiritually significant experiences of my life; 6=the single most spiritually significant experience of my life); (3) Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction? (rated from +3=Increased very much; 0=No change; −3=Decreased very much).

Longitudinal measures assessed at baseline and at the 6-month follow-up

At baseline (immediately after study enrollment) and at the 6-month follow-up, a battery of measures focused on attitudes, dispositions, and behaviors thought to be relevant to changes that

could occur with engagement in psilocybin-facilitated spiritual practice was assessed. These measures included the previously described *Hood Mysticism Scale (Lifetime)* completed with reference to lifetime experience (Hood et al., 2001); *Faith Maturity Scale*, a questionnaire assessing the degree to which a person embodies the priorities, commitments, and perspectives of faith as these have been understood in mainline Protestant traditions (Benson et al., 1993); *Brief RCOPE*, a measure of religious/spiritual coping with stressful life events (Pargament, 1999; Pargament et al., 1998); *Daily Spiritual Experience Scale*, a measure of an individual's perception of and interaction with the transcendent in daily life (Underwood, 2006; Underwood and Teresi, 2002), scored from 5 (Many times a day) to 0 (Never/almost never); *Death Transcendence Scale*, a 26 item questionnaire rated on a 7-point scale that assesses five subscales reflecting attitudes about death (Hood and Morris, 1983; VandeCreek, 1999); *Gratitude Questionnaire (GQ-6)*, a measure of gratefulness and appreciation in daily life (McCullough et al., 2002); *Coherence and Death Acceptance subscales of the Life Attitude Profile - Revised (LAP-R)*, these 15 questions assess a dimension (Coherence subscale) of life meaning reflecting a logically integrated analytical and intuitive understanding of self, others, and life in general and a dimension (Death Acceptance subscale) reflecting death acceptance (Reker, 2007); *Trait Forgiveness Scale*, a measure of trait forgiveness (Berry et al., 2005); *TRIM-18*, a scale assessing forgiveness of interpersonal transgression (McCullough et al., 2006); the 3-item *Forgiveness* subscale of the *BMMRS* (The Fetzer Institute, 1999); *Santification of Strivings* rated life strivings on the dimensions of sacred, spiritual, holy, heavenly, and blessed (Mahoney et al., 2005); *Schwartz Value Scale*, a measure of relative importance of various life values (Schwartz, 1992, 1994); *Inclusion of Others in the Self* scale (IOS), a measure of interpersonal closeness (Aron et al., 1992), mean score of ratings of closest person, closest family member, least close family member, a stranger, and a difficult personal relationship; *ASPIRES* (*Assessment of Spirituality and Religious Sentiments*), a community observer-rated and self-rated questionnaire assessing a construct that reflects an individual's effort to create a broad sense of personal meaning in his or her life, reflected in three factors: Prayer Fulfillment, Universality, and Connectedness (Piedmont, 2010); the *Dispositional Positive Emotions Scale*, a measure assessing seven scales of positive emotion (joy, contentment, pride, love, compassion, amusement, and awe) (Shiota et al., 2006); *Life-Orientation Test-Revised (LOT-R)*, a measure of optimism associated with health outcomes (Scheier et al., 1994); *Satisfaction with Life Scale* (Pavot and Diener, 1993); *Purpose in Life Test (PIL)*, a assessment of meaningfulness in life (Crumbaugh and Maholick, 1964); the *Nonattachment Scale (NAS)*, a questionnaire designed to assess the Buddhist concept of nonattachment (Sahdra et al., 2010); and the revised NEO Personality Inventory (NEO) (Costa and McCrae, 1992).

Community observer ratings of changes in participants' behavior and attitudes. This previously described measure was shown to be sensitive to enduring effects of psilocybin (Griffiths et al., 2006, 2011, 2016). After acceptance into the study, each participant designated as raters three adults who were expected to have continuing contact with the participant (e.g. family members, friends, or colleagues at work). Ratings were conducted via a structured telephone interview approximately 1

week after the participant had been accepted into the study, 3 to 4 weeks after the last session, and as part of the 6-month follow-up. The interviewer provided no information to the rater about the participant. The structured interview consisted of asking the rater to rate the participant's behavior and attitudes using a 10 point scale (from 1=not at all, to 10=extremely) on 13 items: inner peace; patience; good-natured humor/playfulness; mental flexibility; optimism; anxiety; interpersonal perceptiveness and caring; negative expression of anger; compassion/social concern; expression of positive emotions (e.g. joy, love, appreciation); self-confidence; forgiveness of others; and forgiveness of self. For the first rating assessment, which occurred soon after acceptance into the study, raters were instructed to base their ratings on observations of and conversations with the participant over the past 3 months. On subsequent assessments, raters were told their previous ratings and were instructed to rate the participant based on interactions over the last several weeks. Data from each interview with each rater were calculated as a total score, with anxiety and anger scored negatively. Changes in each participant's behavior and attitudes after drug sessions were expressed as a mean change score (i.e. difference score) from the baseline rating across the raters. At the same assessment times, the community observer who knew the participant best (as judged by the participant at baseline) also completed via telephone interview the 35 item Observer Rated ASPIRES questionnaire, which assesses spirituality and religious sentiments (Piedmont, 2010). Seven of 225 (<6%) scheduled ratings by community observers at 6 months were missed due to failure to return calls or to the rater not having contact with the participant over the rating period.

Data analyses

Pearson Chi-square (SPSS version 22.0.0.0) was used to compare experimental groups on dichotomous variables (demographics and proportion of group endorsing specific responses). Planned comparisons among groups were conducted with z-tests of proportions.

For time-course data during psilocybin sessions, for each participant, peak score during the time-course was defined as the maximum value from pre-capsule to 6 hours post-capsule and time to peak effect was defined as the time to peak score. ANOVA (SAS version 9.2, PROC GLM) with planned comparisons between groups were used to analyze data at each time-point, peak effects, and time to peak effects for Sessions 1 and 2 separately. A similar analysis was conducted using mean peak data from Sessions 1 and 2 combined. Similar analyses were conducted comparing peak effects and time to peak effect between sessions 1 (20 mg/70 kg) and 2 (30 mg/70 kg) collapsing across the two high-dose groups ($n=50$).

A similar approach (ANOVA with planned comparisons between groups) was used to examine demographic data for continuous variables, data obtained 7 hours after psilocybin administration (end of session), and single time-point data from the 6-month follow-up (e.g. spiritual practices and persisting effects attributed to psilocybin).

Longitudinal measures (i.e. those measures assessed immediately after study enrollment and at the 6-month follow-up), were analyzed with a repeated measures regression model with AR(1) covariance structure (SAS version 9.2, PROC MIXED) with planned comparisons between groups. Measures that

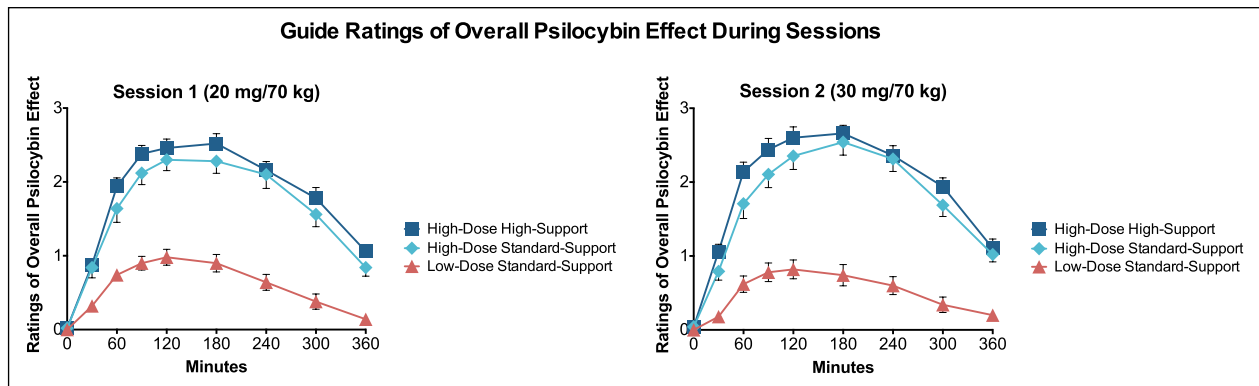


Figure 1. Within-session time-course of guide ratings of overall psilocybin effect during the sessions.

Data points are means; brackets show ± 1 SEM ($n=25$); time 0=before capsule administration). The High-Dose High-Support and the High-Dose Standard-Support groups were significantly different from the Low-Dose Standard-Support group at all post-capsule time-points. The two high-dose groups were not significantly different at any time-points except for 60 and 90 minutes in Session 2.

showed significant differences between groups at baseline were reanalyzed as difference from baseline scores using ANOVA (SAS version 9.2, PROC GLM) with planned comparisons between groups. If difference scores at 6 months were not significantly different between groups, those measures were dropped from further analysis. For the remaining longitudinal measures, planned comparisons between groups at 6 months were conducted. Finally, to determine if there were changes over time within each group, planned comparisons between baseline and 6-month data were examined.

Hierarchical regression analysis was used to explore the relationship of spiritual practices and psilocybin-occasioned mystical experience to various outcome measures. For this analysis, the three spiritual practice measures (minutes per day of meditation; times per day of spiritual awareness practice; times per week of spiritual journaling) were entered together in the first step of the regression model. In the second step, the mean of the Mystical Experience Questionnaire (MEQ30) total scores (completed after both psilocybin sessions) was entered into the regression model. In another analysis, MEQ30 mean total score was entered into the regression model first.

Results

Integrity of blinding procedures

After the psilocybin sessions had been completed, the five study staff members who had served as primary guides for the study completed a questionnaire that asked about their understanding of the study drug and dose conditions. Although all correctly believed that psilocybin had been administered, most made incorrect inferences about the drug or dose conditions, with three of five believing that doses higher than 30 mg/70 kg had been administered, two believing that four or more psilocybin dose levels had been administered; two believing that a drug other than psilocybin was administered (guesses included MDMA, ketamine, and dextromethorphan), and two believing that a true placebo had been administered. Surprisingly, some of these incorrect inferences were contrary to study design parameters that had been described verbally and in the consent form to participants and these primary study guides (e.g.

administration of something other than psilocybin). None correctly understood the study design, although two correctly inferred that two lower dose sessions were followed by a high-dose third session.

Cardiovascular measures and guide ratings assessed throughout the session

Time-course. As expected, inspection of mean group data over time in the low-dose group (LD-LS) for sessions 1 and 2 showed evidence of only modest effects of 1 mg/70 kg psilocybin. In this group, cardiovascular effects generally reached peak at 30 minutes after capsule administration, while guide ratings reached peak at 120 minutes (Figure 1). Also as expected and as illustrated for guide ratings in Figure 1, the two high-dose groups showed similar time-courses and, compared with the low-dose group, effects in the two high-dose groups were larger, with peak cardiovascular effects occurring at 30 to 180 minutes and peak guide ratings occurring at 180 minutes. Analysis of differences in time to peak effects between the first and second sessions (20 vs. 30 mg/70 kg) for the two high-dose groups separately and combined did not show significant differences in time to peak effects for guide ratings. For the cardiovascular measures, only time to peak heart rate showed a significant difference, with peak effects occurring significantly earlier at the high dose (112 ± 13 vs. 163 ± 14 minutes for sessions 1 (20 mg/70 kg) and 2 (30 mg/70 kg) respectively, mean $\pm$ SEM for the two high-dose groups combined).

Peak effects. Analysis of differences in peak effects for guide ratings between the first and second sessions (20 vs. 30 mg/70 kg) for the two high-dose groups separately and combined did not show significant differences. For the cardiovascular measures, peak systolic and diastolic pressures were modestly but significantly higher after the high dose (mean $\pm$ SEM for the two high-dose groups combined: 144 ± 2 vs. 150 ± 2 mm Hg systolic pressure for low and high doses, respectively, and 83 ± 1 vs. 86 ± 1 mm Hg diastolic pressure for low and high doses, respectively).

Given that differences between sessions 1 and 2 were minimal, and to simplify comparison across the three experimental

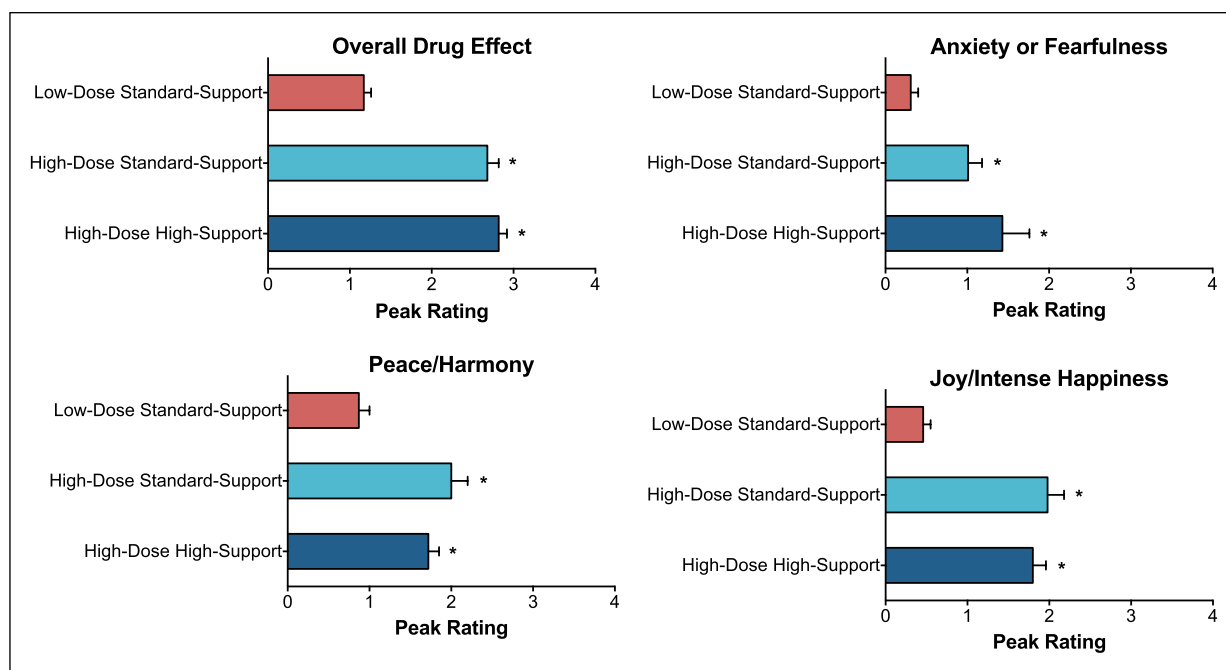


Figure 2. Guide ratings of volunteer behavior and mood assessed throughout the psilocybin sessions (Illustrative results from Table 2).

Data are means of the peak response in each of the two psilocybin sessions in each participant. Bars show group means; brackets show 1 SEM; * indicates a significant difference from Low-Dose Standard-Support (Planned comparisons, $p < .05$); there were no significant differences between the High-Dose High-Support and High-Dose Standard-Support groups.

groups, mean peak cardiovascular effects and guide ratings across the two sessions were used in subsequent analyses. For all three cardiovascular measures and for almost all of the guide ratings, the HD-SS and HD-HS groups were significantly higher than the LD-SS group (Table 2 and Figure 2). The HD-HS group differed from the HD-SS group only on guide ratings of tearing/crying, which were higher in the HD-HS group.

Drug effect and mystical-type effect measures assessed 7 hours after psilocybin administration

In an analysis similar to that described above for the peak scores during the session, participant-rated drug effect and mystical-type effect measures after psilocybin sessions did not show significant differences between sessions 1 and 2. Therefore, mean data across the two sessions were used in the analyses below.

Subjective effects questionnaires. Two participant-rated subjective effect questionnaires (HRS and 5D-ASC) completed at the end of the sessions showed a pattern of results across the experimental groups similar to peak effects from the cardiovascular and guide rated measures assessed throughout the session (Table 3). Specifically, the HD-HS and HD-SS groups were consistently higher than the LD-SS group, with no differences between the two high-dose groups. Results from these subjective measures, which were developed for sensitivity to hallucinogens, showed that psilocybin produced the expected range of subjective changes including changes in somatic effects, positive and negative affect, perception, cognition, and volition.

Measures of mystical experience. Also at 7 hours after capsule administration, participants completed two questionnaires (MEQ30 and Mysticism Scale) designed to assess mystical experience (Table 3 and Figure 3). As with the other end-of-day ratings, the HD-HS and HD-SS groups were consistently higher than the LD-SS group. Furthermore, all the subscales from these questionnaires (which are believed to assess various aspects of mystical experience) are numerically higher in the HD-HS group than the HD-SS group and, for three of the four measures on the Mysticism Scale, these differences were significant (Table 3). The proportion of participants who met a priori criteria for having had a “complete” mystical experience on the MEQ30 on session 1 and 2, respectively, were 0% and 4% (LD-SS), 48% and 50% (HD-SS), and 44% and 52% (HD-HS). Overall, 4%, 61%, and 64% of participants in the LD-SS, HD-SS, and HD-HS groups had “complete” mystical experiences at either or both sessions 1 and 2.

Spiritual practices assessed at the 6-month follow-up

Spiritual practices questionnaire. Consistent with the more frequent and intensive support provided in the high spiritual support condition, rates of meditation, spiritual awareness practice, and journal writing in the HD-HS group were about twice the rates in the two standard-support groups, which were quite similar. Likewise, the percentage of participants meditating daily, engaging in spiritual practices daily, or journaling weekly was higher in the HD-HS group. As shown in Table 4 and Figure 4, the HD-HS group was significantly higher than the LD-SS and HD-SS groups on five and four, respectively, of

Table 3. Participant ratings on subjective effects and mystical experience questionnaires completed 7 hours after psilocybin administration.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
<i>Hallucinogen Rating Scale (HRS)</i>			
Intensity (max score=4.25)	1.33 (0.16)	2.92 (0.16)***	2.89 (0.11)***
Somesthesia (max score=4)	0.47 (0.07)	1.48 (0.14)***	1.53 (0.11)***
Affect (max score=4)	0.70 (0.08)	1.82 (0.14)***	1.98 (0.09)***
Perception (max score=4)	0.41 (0.08)	1.78 (0.17)***	1.74 (0.12)***
Cognition (max score=4)	0.52 (0.09)	1.90 (0.19)***	2.02 (0.13)***
Volition (max score=4)	1.16 (0.08)	1.65 (0.09)**	1.59 (0.10)***
<i>5 Dimension Altered States of Consciousness (5D-ASC)</i>			
Oceanic Boundlessness (OBN)(max score=100)	16.54 (3.54)	61.47 (5.56)***	69.50 (3.80)***
Dread of Ego Dissolution (DED)(max score=100)	4.73 (0.91)	20.92 (3.03)**	22.25 (4.42)**
Visionary Restructuralization (VRS)(max score=100)	16.90 (3.46)	57.68 (5.24)***	61.69 (3.44)***
Auditory Alterations (AUA)(max score=100)	4.45 (1.25)	17.04 (2.73)**	19.17 (4.02)**
Vigilance Reduction (VIR)(max score=100)	20.86 (2.53)	32.76 (2.94)**	32.05 (3.52)**
<i>Mystical Experience Questionnaire (MEQ30) ^a</i>			
Mystical (max score=100)	13.9 (3.5)	60.5 (7.3)***	71.8 (3.6)***
Positive mood (max score=100)	30.0 (3.6)	74.5 (4.3)***	79.8 (3.8)***
Transcendence of time and space (max score=100)	22.3 (4.1)	66.6 (5.6)***	70.6 (3.7)***
Ineffability (max score=100)	20.1 (4.1)	74.4 (6.3)***	76.3 (3.9)***
Total (max score=100)	19.4 (3.3)	65.9 (6.0)***	73.6 (3.1)***
<i>Mysticism Scale</i>			
Interpretation (max score=108)	48.82 (4.40)	82.42 (5.63)***	96.08 (2.39)***+
Introvertive (max score=108)	48.00 (3.74)	84.00 (5.13)***	93.20 (2.28)***
Extrovertive (max score=72)	27.44 (3.01)	48.62 (4.28)***	58.86 (2.37)***+
Total (max score=288)	124.26 (10.55)	215.04 (14.52)***	248.14 (6.14)***+

For each participant, ratings were collapsed across the two psilocybin sessions. Data are means with 1 SEM shown in parentheses ($n=25$); data for the 5D-ASC and MEQ30 are expressed as a percentage of the maximum possible score.

Within a row, asterisks indicate a significant difference from the Low-Dose Standard-Support group (* $p<.05$, ** $p<.01$, *** $p<.001$, Planned comparisons), and + indicates a significant difference between the High-Dose High-Support and High-Dose Standard-Support groups ($p<.05$, Planned comparisons).

these measures of engagement with spiritual practice. Moreover, the HD-HS group showed numerically larger effects for all six measures.

Persisting effects assessed at the 6-month follow-up

Table 5 and Figure 5 show participant ratings at the 6-month follow-up of effects that the participants attributed to either or both of the two psilocybin sessions. With regard to positive changes in attitudes, mood, altruism, and behavior as well as increased spirituality, the two high-dose groups were significantly higher than the LD-SS group on all these measures. Table S1 shows that the effect sizes for these comparisons were very large (mean Cohen's $d=1.65$). In addition, the HD-HS group was significantly higher than the HD-SS group on altruistic/positive social effects, positive behavior changes, and increased spirituality. Negative ratings of these same dimensions were very low and did not differ between groups except for negative attitudes about self that showed very small but significant increases in the HD-HS group. Of the eight participants in the HD-HS group that endorsed any increase in negative attitudes about self, all also rated the experience as having increased their sense of personal well-being or life satisfaction at the 6-month follow-up.

Both the high-dose groups also rated the personal meaning, spiritual significance, and change in well-being or life satisfaction attributed to the sessions significantly higher than the LD-SS group (Table 5 and Figure 5). Similar findings were shown for the percentage of each group providing strong endorsements of these same three dimensions. For example, 12%, 76%, and 96% of the LD-SS, HD-SS, and HD-HS groups, respectively, rated the experience(s) among the top five most spiritual experiences of their lives, with 0%, 40%, and 56%, respectively, indicating it to be the single most spiritually significant experience of their life.

Longitudinal measures and community observer ratings assessed at 6 months

Analysis of longitudinal measures. Per the plan in the Data Analysis section, three longitudinal measures were dropped from analysis (Forgiveness subscale of the BMMRS; self-rated ASPIRES; and the Satisfaction with Life Scale) because of significant between-group differences at baseline and no significant difference in change from baseline. The Purpose in Life Test, Nonattachment Scale, and the LOT-R [a measure of optimism] both showed significant increases from baseline to 6 months in the two High-Dose groups. The Openness scale of the NEO showed a significant increase from baseline to 6

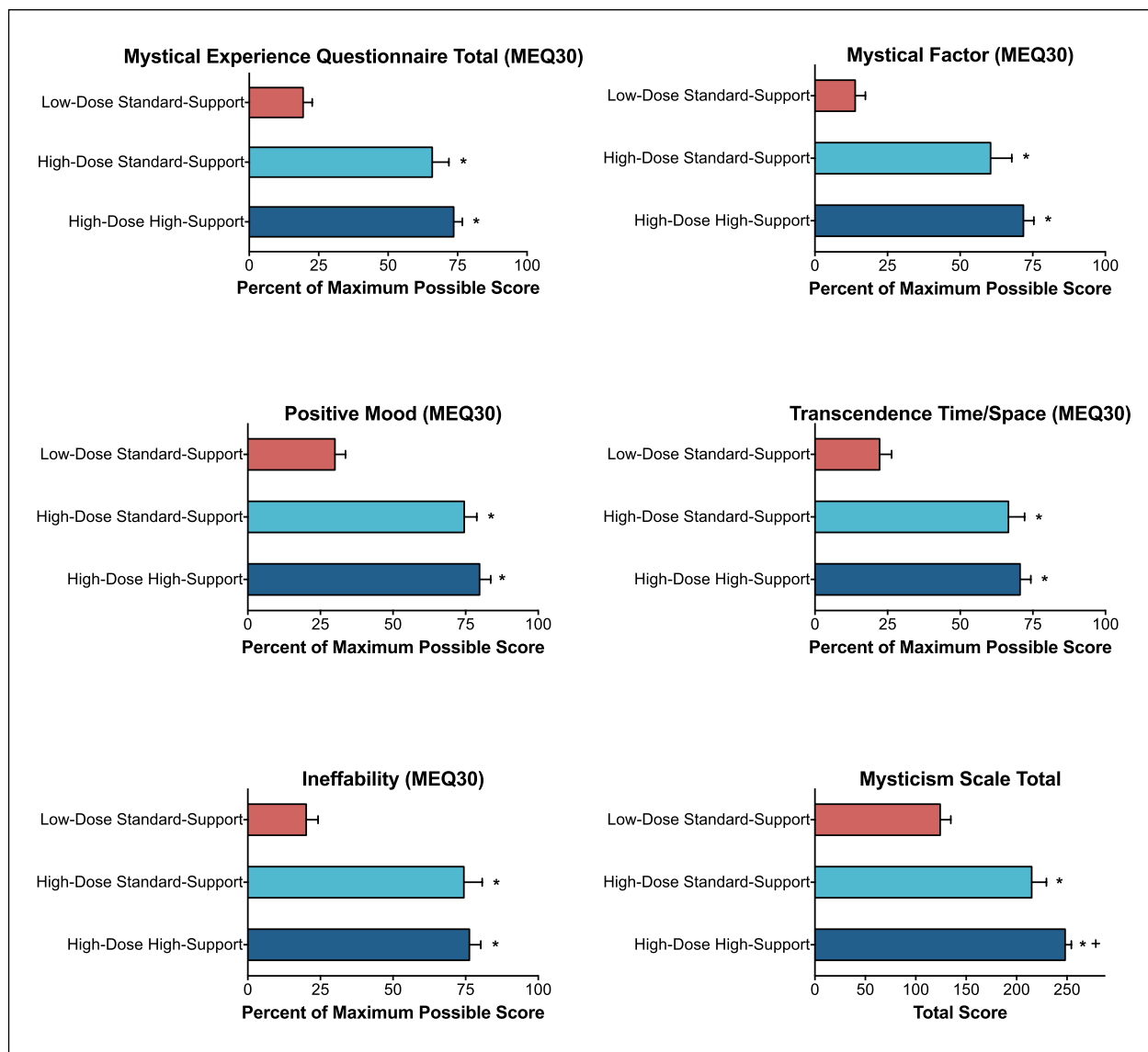


Figure 3. Participant ratings on mystical experience questionnaires completed 7 hours after psilocybin administration (Illustrative results from Table 3).

Data for the Mystical Experience Questionnaire (MEQ30) are percentages of the maximum possible score; data for the Mysticism Scale are total scores. Bars show group means; brackets show 1 SEM; * indicates a significant difference from the Low-Dose Standard-Support group; + indicates a significant difference between the High-Dose High-Support and the High-Dose Standard-Support groups (Planned comparisons, $p < 0.05$).

months in the HD-HS group, but did not show a significant between-group difference at 6 months on Openness or the other four NEO scales. The DPES showed neither a significant increase from baseline to 6 months nor significant between-group differences at 6 months.

Table 6 shows the 23 longitudinal measures that demonstrated significant between-group differences at 6 months (Table S2 shows corresponding effect sizes). In the LD-SS group, only one measure (a measure of forgiveness) was significantly different between baseline and 6 months (Table 6, boldface font). In contrast, in the two high dose groups, most of the 23 measures were significantly different between the baseline and 6-month assessment (boldface font). For all 23 measures, the HD-HS group showed numerically larger effects

(in the expected direction) than the HD-SS group (Table 6 and Figure 6), with significant differences on seven measures. Furthermore, the HD-HS group differed significantly on all 23 measures from the LD-SS group and, in contrast, on 14 of 23 measures from the HD-SS group.

Community observer ratings. In addition to the various participant-rated longitudinal measures, it is noteworthy that several observer-rated measures (total score, prayer fulfillment, and universality on the ASPIRES and total change score on the community observer ratings of positive change in behavior and attitudes) generally showed the same pattern of differences across groups with the HD-HS group showing the largest effects (Table 6 and Figure 7).

Table 4. Spiritual practices at 6 months.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
<i>Meditation</i>			
Minutes per day for all days	10.23 (2.24)	9.93 (1.69)	19.33 (0.20)**+++
Percentage of group meditating daily	32%	20%	64%*++
<i>Spiritual awareness practice</i>			
Times per day for all days	2.16 (0.74)	3.05 (0.87)	5.19 (0.97)*
Percentage of group practicing daily	56%	68%	96%**+
<i>Journal writing</i>			
Times per week	1.76 (0.49)	1.78 (0.50)	4.44 (0.52)***+++
Percentage of group journaling daily	12%	16%	40%

Data, which were obtained at the 6-month follow-up, show retrospective ratings for the past 4 months; rate data are means with 1 SEM shown in parentheses ($n=25$); proportion data are the percentage of group ($n=25$) reporting the spiritual practice.

Within a row, asterisks indicate a significant difference from the Low-Dose Standard-Support group (* $p<.05$, ** $p<.01$, *** $p<.001$), and plus symbols indicate a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (+ $p<.05$, ++ $p<.01$, +++ $p<.001$). Significance levels were determined with z-tests for proportions for percentile data and with Planned comparisons for other numerical ratings.

Relationship of spiritual practice and psilocybin-occasioned mystical experience to various outcome measures

Hierarchical regression analysis was used to determine the relationship of spiritual practice and psilocybin-occasioned mystical experience to various outcome measures from Tables 5 and 6 that showed between-group differences at 6 months. For this analysis, the three spiritual practice measures (minutes per day of meditation; times per day of spiritual awareness practice; times per week of spiritual journaling) were entered together in the first step of the regression model. Mean total score from the Mystical Experience Questionnaire (MEQ30) was entered into the regression model in the second step. As shown in Table 7, spiritual practices accounted for a significant proportion of variance (R^2) in 13 of 19 outcome measures, with R^2 ranging from .050 to .293 (mean=.139). As also shown in the table, mystical experience score (MEQ30) accounted for a significant proportion of variance in 18 of 19 measures after accounting for the impact of spiritual practices, with the change in R^2 ranging from .031 to .619, (mean=.266). In contrast to MEQ30 score which was significant for 18 measures even after accounting for the contribution of spiritual practices, the rightmost columns of the table show that, for the overall regression model, meditation, awareness practice, and journaling were significant for six, two and one of the outcome measures, respectively. Not shown in the table, when MEQ30 score was entered as the first step of a regression model, it accounted for a significant proportion of variance in all 19 outcome measures, with R^2 ranging from .123 to .747 (mean=.351).

Open-ended clinical interview at the 6-month follow-up

An open-ended clinical interview at the final follow-up visit was used to obtain spontaneous reports of possible persisting adverse events. There were no reports of bothersome or clinically significant persisting perception phenomena sometimes attributed to psychedelic use. Likewise, there were no reports of any

non-study use of psychedelics since study enrollment. All 75 volunteers appeared to continue to be psychiatrically healthy, high-functioning, productive members of society.

Adverse effects

No serious adverse events attributed to psilocybin administration or the study procedures occurred. A number of adverse events occurred during psilocybin sessions, none of which was deemed to be serious. Consistent with previous research (Griffiths et al., 2006, 2011, 2016), there were transient moderate increases in systolic and/or diastolic blood pressure after psilocybin. In one participant, diastolic blood pressure was elevated (126 mmHg) about an hour after psilocybin administration in the first session. The increase met protocol criteria for administration of sublingual nitroglycerin. The session was completed uneventfully. Although this participant reported that the session experience was positively meaningful and expressed a desire to continue with the study, the participant was discontinued from further participation.

Discussion

The present study with psilocybin extends a large descriptive literature on non-drug and psilocybin-occasioned transformative mystical- and insightful-type experiences (i.e. quantum change experiences, Miller, 2004) by using a prospective experimental design to test for enduring positive changes on well-validated trait measures of prosocial attitudes and behaviors, psychological functioning, and ratings of the participant by community observers. The rigorous double-blind design, which minimized expectancy effects, showed that psilocybin-occasioned mystical experience contributed significantly to the enduring positive changes. The present study results contrast those from previous studies of psilocybin (Darling et al., 2004; Doblin, 1991; Griffiths et al., 2008; 2011; Leary et al., 1963; Pahnke, 1963; Studerus et al., 2011) and the classic psychedelic LSD (McGlothlin et al., 1967; Weil et al., 1965) in healthy volunteers, which have provided little evidence of enduring positive changes on well-validated trait measures of

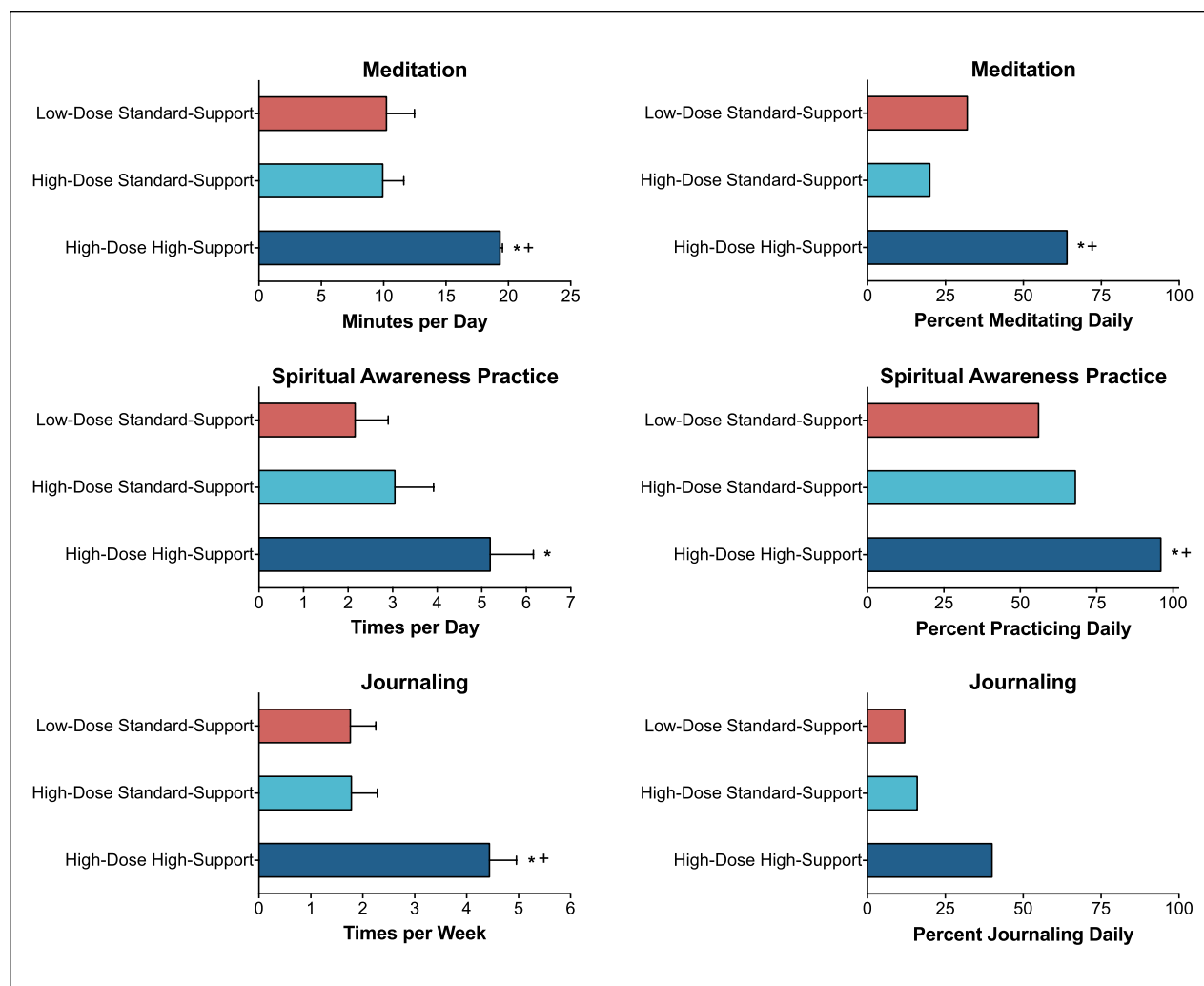


Figure 4. Spiritual practices at 6 months (from Table 4).

Data, which were obtained at the 6-month follow-up, show retrospective ratings for the past 4 months. Bars displaying rate data show means; brackets show 1 SEM ($n=25$). Meditation rate data are minutes per day for all days. Bars displaying proportion data show the percentage of the group ($n=25$) reporting the practice during the indicated time interval. * indicates a significant difference from the Low-Dose Standard-Support group; + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (Planned comparisons, $p<0.05$).

disposition. This difference seems likely due to the experimental context of the present study, which provided encouragement for engagement in a nonsectarian program of meditation and other practices that emphasized the integration of spiritual values in daily life (e.g. prosocial values, self-knowledge through examining the nature of mind, and cultivating a sense of wonder).

Effects of psilocybin dose

Effects of psilocybin dose on session days. The time-course and profile of acute psilocybin effects were consistent with previous studies that have administered these doses of psilocybin to healthy volunteers under similar conditions (Griffiths et al., 2006, 2011). Comparing the low-dose group with each of the two high-dose groups, psilocybin modestly increased blood pressure and heart rate and significantly affected a range of measures assessed by guides during sessions and by participants immediately after

sessions (Tables 2 and 3). The profile of these acute psilocybin effects included perceptual changes (e.g. visual pseudo-hallucinations, illusions, and/or synesthesia), labile moods (e.g. feelings of transcendence, grief, joy, and/or anxiety), and cognitive changes (e.g. sense of meaning, insight, and/or ideas of reference).

In the high-dose conditions, 20 mg/70 kg was administered in session 1 followed by 30 mg/70 kg in session 2. The rationale for administering the doses in the ascending sequence was based on previous research suggesting that ascending doses are more likely to than descending doses to produce long-lasting positive changes in attitudes, behavior, and remembered mystical-type experiences (Griffiths et al., 2011). Peak blood pressure was very modestly higher after the 30 vs. 20 mg/70 kg psilocybin dose but there were no significant differences between these doses on rating by guides during sessions or in participant ratings at the end of the session. It is possible that the fixed sequence of doses contributed to a failure to detect significant differences in acute subjective effects between the two doses.

Table 5. Participant ratings of effects attributed to psilocybin session experiences at 6 month assessment.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
<i>Attitudes, Moods, Behavior, & Spirituality</i>			
Positive attitudes about life	22.71 (5.11)	61.66 (6.18)***	73.11 (4.14)***
Negative attitudes about life	0.98 (0.37)	1.66 (0.63)	3.02 (1.17)
Positive attitudes about self	23.85 (4.92)	55.35 (6.01)***	68.73 (4.22)***
Negative attitudes about self	0.44 (0.27)	2.04 (0.65)	4.00 (1.54)*
Positive mood changes	21.42 (4.42)	51.47 (5.96)***	65.42 (4.73)***
Negative mood changes	1.07 (0.60)	0.71 (0.28)	1.69 (1.30)
Altruistic/positive social effects	21.24 (4.44)	53.24 (5.85)***	67.02 (4.22)***+
Antisocial/negative social effects	0.8 (0.49)	0.36 (0.36)	1.16 (0.60)
Positive behavior changes	27.20 (4.98)	61.60 (6.76)***	78.40 (5.26)***+
Negative behavior changes	0.8 (0.82)	0.00 (0)	0.00 (0)
Increased spirituality	20.76 (4.95)	58.69 (6.36)***	73.62 (4.00)***+
Decreased spirituality	1.14 (0.44)	0.84 (0.36)	1.26 (0.94)
<i>How personally meaningful was experience?</i>			
Mean (max score=8)	3.80 (0.35)	6.76 (0.31)***	7.20 (0.14)***
% rating top 5 most personally meaningful	12%	84% ***	84% ***
% rating the single most personally meaningful	0%	28%*	36%**
<i>How spiritually significant was the experience?</i>			
Mean (max score=8)	2.60 (0.26)	4.68 (0.34)***	5.52 (0.12)***+
% rating top 5 most spiritually significant	12%	76% ***	96%***+
% rating the single most spiritually significant	0%	40% **	56% ***
<i>Did the experience change your sense of well-being or life satisfaction?</i>			
Mean (max/min score= -3 to +3)	1.08 (0.23)	2.20 (0.23)***	2.60 (0.13)***
% rating moderately or very much (+2 or +3)	20%	72% ***	92%***

Data on attitudes, mood, altruistic/social effects, behavior, and spirituality are means expressed as percentage of maximum possible score, with 1 SEM shown in parentheses ($n=25$); data for the final three questions are either mean raw scores with 1 SEM shown in parentheses or percentages of group ($n=25$).

Within a row, asterisks indicate a significant difference from the Low-Dose Standard-Support group (* $p<.05$, ** $p<.01$, *** $p<.001$), and + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group ($+p<.05$). Significance levels were determined with z-tests for proportions for percentile data and with Planned comparisons for other numerical ratings.

Spiritual practices at 6 months. The study did not provide evidence that psilocybin dose affected engagement with spiritual practices. As expected, compared with the two standard spiritual support conditions, participants in the high spiritual support condition showed greater engagement with the three primary spiritual practices that were taught and encouraged during the guide-participant and dialogue-group meetings (Table 4 and Figure 4). For the last 4 months of the study, participants in the high-support condition reported average rates of meditation (19.3 minutes per day), spiritual awareness practice (5.2 times per day), and journaling (4.4 times per week) that were about double those reported in the standard-support groups. Likewise, the proportion of volunteers meditating daily, doing spiritual practices daily, or journaling daily was generally significantly higher than that in the two standard-support groups. However, the LD-SS and HD-SS groups were not significantly different on any of these six measures, indicating that, under the conditions of the study, psilocybin did not facilitate engagement with these spiritual practices.

Persisting effects attributed to psilocybin assessed at 6 months. Consistent with a previous study (Griffiths et al., 2011), compared with the low-dose group, the high psilocybin dose

groups showed greater increases in persisting positive effects that participants attributed to their psilocybin session experiences (Table 5 and Figure 5). The domains of positive changes were: attitudes about life, attitudes about self, mood, altruism/positive social effects, behavior, and increased spirituality. Also relative to the low-dose group, the two high-dose groups attributed significantly greater personal meaning, spiritual significance, and change in well-being or life satisfaction to the psilocybin experience. Similar significant differences between the low-dose group and two high-dose groups were also shown on the percentage of each group providing strong endorsements of personal meaning, spiritual significance, and change in well-being or life satisfaction (Table 5 and Figure 5).

Longitudinal measures assessed at 6 months. The most intriguing assessments in this study were a series of longitudinal measures, some of which are well-validated trait measures of psychological well-being, prosocial disposition, and spiritual worldview (Table 6). In contrast to prior psilocybin research with healthy volunteers which has generally not demonstrated enduring changes such measures (Griffiths et al., 2008), the present study showed generally large significant effects of psilocybin dose across a range of longitudinal measures (Table 6; Table S2

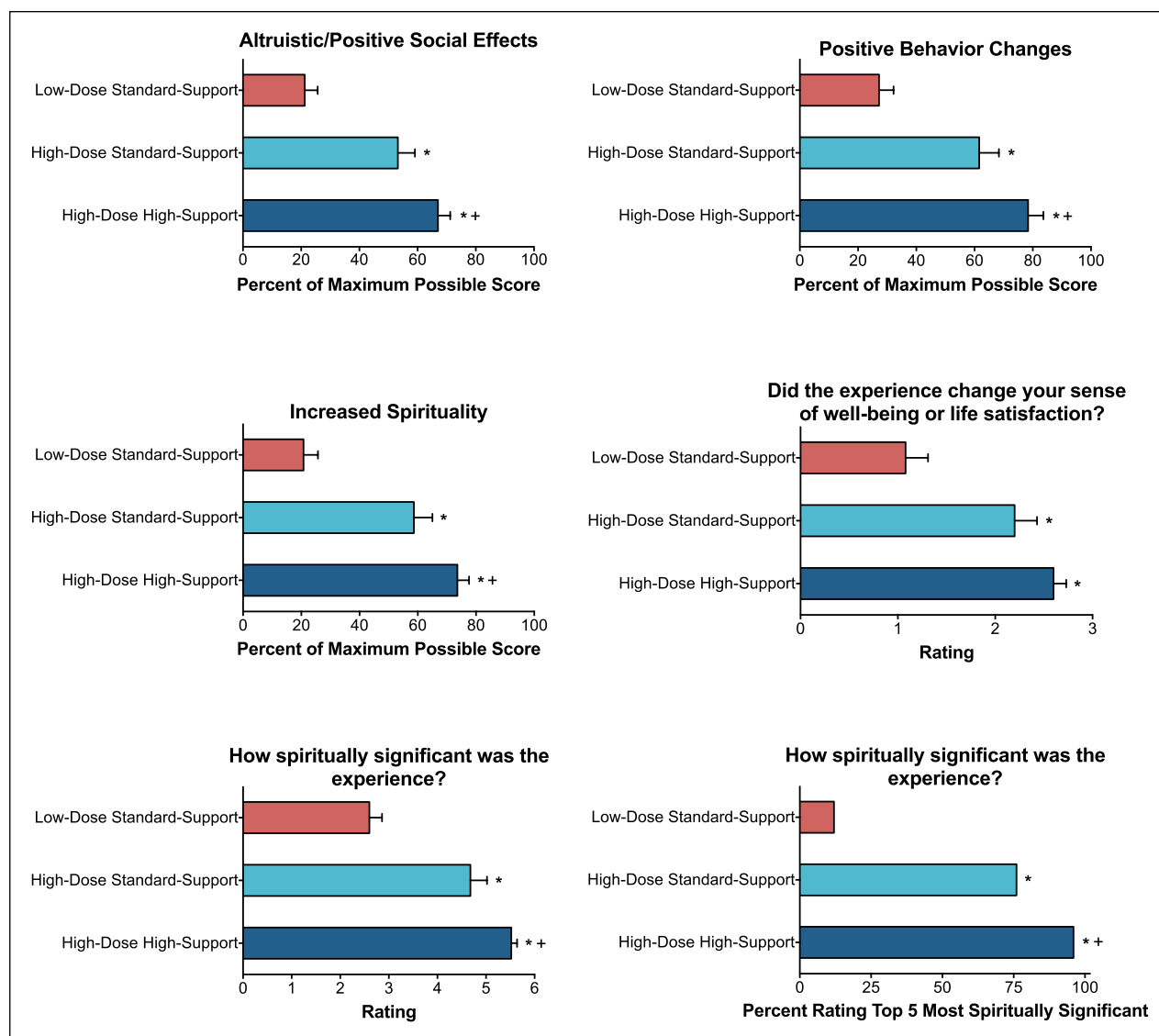


Figure 5. Participant ratings of effects attributed to psilocybin session experiences at the 6-month follow-up (Illustrative results from Table 5). Data on altruistic/social effects, behavior changes, and spirituality are expressed as percentage of maximum possible score (bars show means, brackets show 1 SEM, $n=25$). Data for the questions about spiritual significance and change in well-being or life satisfaction are either raw scores (bars show means, brackets show 1 SEM, $n=25$) or percentages of the group ($n=25$). * indicates a significant difference from the Low-Dose Standard-Support group; + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (Planned comparisons, $p<0.05$).

shows corresponding effect sizes). Specifically, the effect of psilocybin dose is shown by comparing the LD-SS group with the HD-SS group. Of the 23 longitudinal measures in Table 6, the HD-SS group was significantly different from the LD-SS group on 14 measures, all in the expected direction. Furthermore, within-group analysis showed that change from baseline (6-month minus baseline score) were significant on only one of 23 measures in the LD-SS group in contrast to 17 of 23 measures in the HD-SS group.

Contrary to popular beliefs that psychedelic experiences lead to rejection of traditional worldviews (Stevens, 1987), in the current study, the life value of Tradition on the Schwartz Value Scale increased significantly from baseline to 6 months in the HD-HS group and was significantly higher in this group than the LD-SS group at 6 months. This subscale comprises

items assessing respect for tradition, moderation of feelings and action, humility, accepting life's circumstances, and holding religious belief and faith. It is plausible that administering psilocybin in the context of encouraging spiritual practices accounts for this effect, which is consistent with the observation that indigenous sacramental use of psilocybin-containing mushrooms, peyote, ayahuasca and other classic psychedelic-containing substances is often strongly grounded in cultural traditions (Schultes et al., 1998).

In the present study, the personality domain of Openness increased from screening to 6 months in the HD-HS group but not in the HD-SS or LD-SS groups. Further, there were no between-group differences in Openness at 6 months. Further analyses of these data (not presented) did not show significant relationships between several measures of mystical-type

Table 6. Longitudinal measures assessed at 6 months that showed significant between group differences.

Measure	Low-Dose Standard-Support	High-Dose Standard-Support	High-Dose High-Support
<i>Mysticism Scale: (Lifetime)</i>			
Interpretation (max score=108)	75.64 (3.25)	87.58 (5.10)*	99.96 (2.05)***+
Introvertive (max score=108)	60.72 (3.83)	86.96 (5.75)***	95.08 (2.31)***
Extrovertive (max score=172)	40.12 (3.26)	49.22 (4.53)	59.80 (2.90)***+
Total Score (max score=288)	176.48 (9.65)	223.76 (14.78)**	254.84 (5.82)***+
<i>Faith Maturity Scale (FMS)</i>			
Total Score (max score=84)	43.96 (2.36)	52.60 (3.24)*	58.52 (2.15)***
<i>Religious Coping (Brief RCope)</i>			
Positive Religious Coping (max score=21)	2.89 (0.89)	7.28 (1.19)**	7.88 (1.44)**
<i>Daily Spiritual Experience Scale (DSES)</i>			
Total (questions 1-14; max score=70)	28.04 (3.32)	37.88 (3.66)*	41.56 (2.80)**
How close do you feel to God (max score=4)	1.63 (0.16)	2.12 (0.15)*	2.36 (0.15)**
<i>Death Transcendence Scale (26 items)</i>			
Mysticism scale (max score=35)	20.76 (1.83)	26.16 (2.12)*	30.96 (1.25)*
Religious scale (max score=35)	20.72 (1.67)	26.36 (1.86)*	27.67 (1.17)*
Total Score (max score=182)	113.92 (3.33)	125.68 (4.61)*	131.25 (3.53)*
<i>Gratitude Questionnaire (GQ-6)</i>			
Total Score (max score=43)	37.4 (0.82)	39.16 (0.66)	39.52 (0.58)*
<i>Life Attitude Profile (LAP-R)</i>			
Coherence (Life meaning)(max=56)	36.08 (1.74)	38.60 (1.85)	43.40 (1.60)*+
<i>Trait Forgiveness Scale</i>			
Total Score (max score=50)	37.88 (1.32)	37.36 (1.43)	41.08 (0.83)+
<i>Forgiveness of Transgression (TRIM-18)</i>			
Benevolence Motivation (max score=30)	18.63 (1.11)	22.88 (1.36)*	23.80 (0.89)*
Avoidance Motivation (max score=35) ¹	22.38 (1.41)	16.50 (1.67)*	17.20 (1.50)*
<i>Sanctification of Strivings</i>			
Life strivings as sacred/spiritual (max score=5)	2.43 (0.25)	2.76 (0.26)	3.47 (0.20)*+
<i>Schwartz Value Scale</i>			
Tradition (mean centered score)	-1.58 (0.22)	-1.17 (0.24)	-0.79 (0.19)*
<i>Interpersonal Closeness (IOS)</i>			
Mean rating (max score=7)	2.82 (0.20)	3.37 (0.29)	3.70 (0.29)*
<i>Observer-rated spiritual/religious sentiments (ASPIRES)</i>			
Prayer Fulfillment (max score=50)	32.35 (1.51)	39.58 (1.24)***	40.72 (0.94)**
Universality (max score=35)	24.17 (0.96)	27.04 (1.19)	28.08 (0.68)**
Total (max score=115)	76.30 (2.65)	88.42 (2.51)**	89.60 (1.69)**
<i>Observer-rated positive changes in behavior & attitudes</i>			
Total change score	3.24 (0.75)	5.39 (0.93)	9.20 (1.40)***+

Outcome measures are shown in the table if there was one or more significant difference between groups at 6 months; measures showing a between-group difference at baseline were excluded unless the between-group difference was also shown in the planned comparison of change from baseline score (6-month minus baseline score).

Data are means with 1 SEM shown in parentheses ($n=25$).

Within a row, asterisks indicate a significant difference from the Low-Dose Standard-Support group (* $p<.05$, ** $p<.01$, *** $p<.001$, Planned comparison), and + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (Planned comparisons, $p<.05$).

Within a row, boldface font indicates a significant difference within the group between baseline and 6 months (Planned comparisons, $p>.05$); for all such significant differences, 6-month scores were higher than baseline scores except for Avoidance Motivation in the TRIM-18 which were lower.

¹Lower scores on this scale indicate more forgiveness.

experience and changes in Openness. These findings contrast with the results from a previous analysis that showed that psilocybin-occasioned mystical experience was associated with increases in Openness from screening to 1–2 months and to 14 months after psilocybin (MacLean et al., 2011). Increases in Openness have been shown 2 weeks after administration of LSD in healthy individuals (Lebedev et al., 2016). Another

study showed that increases in Openness predicted greater reduction in post-traumatic stress disorder symptoms among individuals receiving MDMA-assisted psychotherapy (Wagner et al., 2017). The failure to observe significant increases in Openness in the current study may be attributable to engagement in the program of spiritual practices or to some other aspect of the study design.

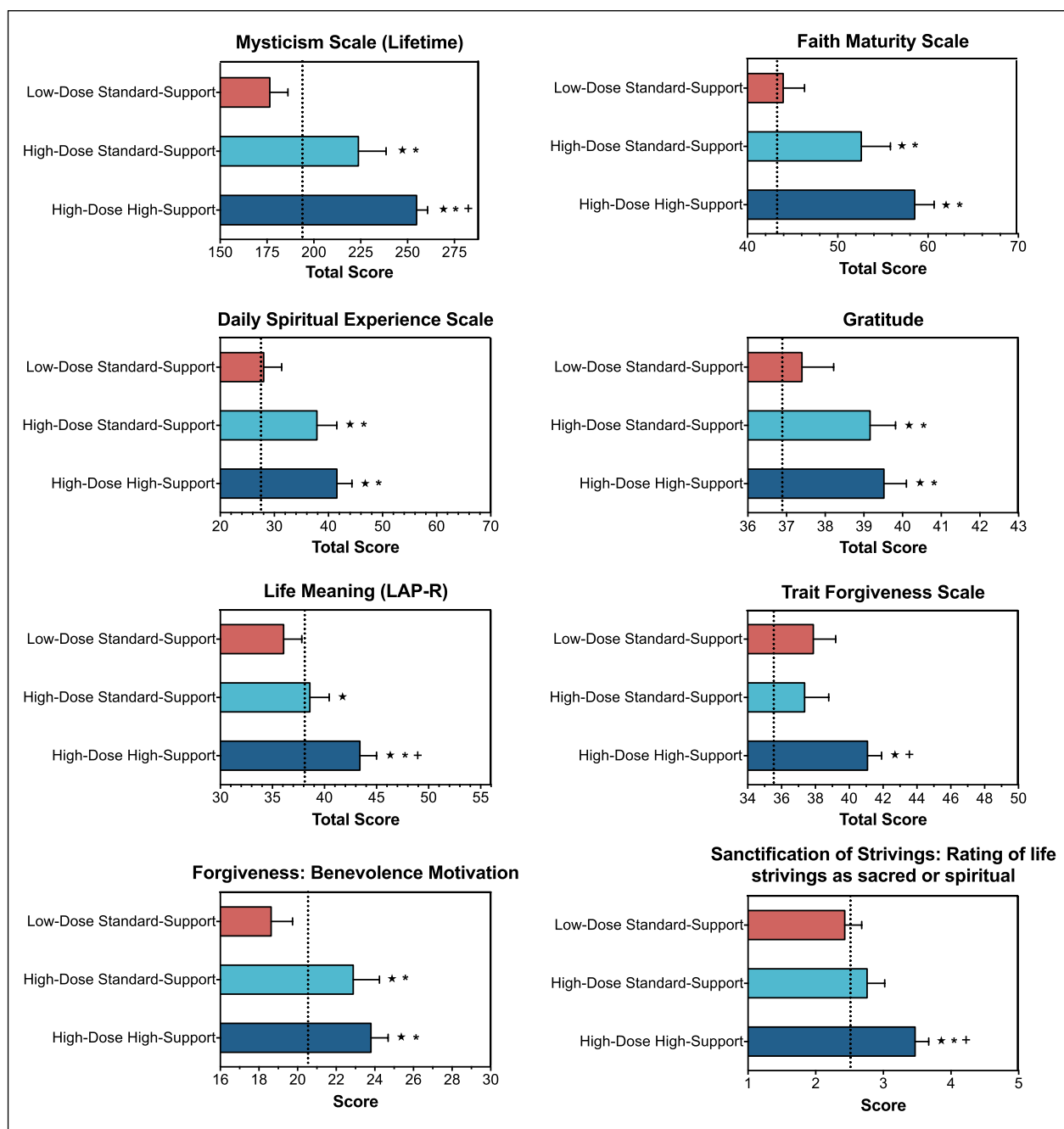


Figure 6. Longitudinal measures assessed at the 6-month follow-up (Illustrative results from Table 6).

Bars show means; brackets show 1 SEM ($n=25$); * indicates a significant difference between baseline and 6 months; * indicates a significant difference from the Low-Dose Standard-Support group; + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (Planned comparisons, $p<0.05$). For comparison, dotted lines show mean scores from previous studies for each measure: Mysticism Scale (college students, Hood et al., 2001; Ralph W. Hood Jr, personal communication); Faith Maturity Scale (university students, Loma Linda University, 2007), Daily Spiritual Experience Scale (general population survey data, Underwood, 2006); Gratitude Questionnaire-6 (adults, McCullough et al., 2002); Life Meaning (college and community sample, Reker, 2007); Trait Forgiveness Scale (college students, Berry et al., 2005); Forgiveness Benevolence Motivation (college students, Tsang et al., 2006); Sanctification of Strivings (adults, Mahoney et al., 2005).

Evidence that high support for spiritual practices increased both the acute and enduring effects of psilocybin

Session day effects. On several measures that were assessed on session days, the effects of the high dose of psilocybin were

greater in the high spiritual practices support group than in the standard-support groups. Guide ratings of tearing/crying during the session and participants scores on the Mysticism Scale (total score and two subscales) were significantly higher in the HD-HS vs. HD-SS groups (Tables 2 and 3). Furthermore, on other participant-rated measures thought to reflect aspects of mystical-type

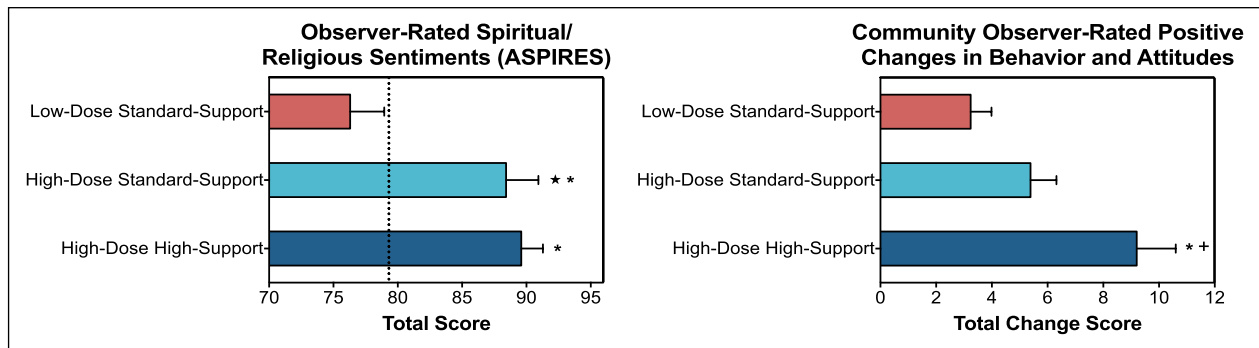


Figure 7. Two observer-rated measures of participant attitudes and behavior assessed at the 6-month follow-up (from Table 6).

Bars show means; brackets show 1 SEM ($n=25$); for both measures, * indicates a significant difference from the Low-Dose Standard-Support group; + indicates a significant difference between the High-Dose High-Support group and the High-Dose Standard-Support group (Planned comparisons, $p<0.05$). For the ASPIRES, which was assessed both at baseline and the 6-month follow-up, ★ indicates a significant difference between baseline and 6 months (Planned comparisons, $p<0.05$). Also for the ASPIRES, dotted line shows mean norm score (Piedmont, 2010).

experience (total scores and subscale scores of the MEQ30, and the Oceanic Boundlessness subscale of the 5D-ASC) the HD-HS group was numerically higher than the HD-SS group. These results contrast with the subjective ratings unrelated to mystical experience (Table 3), for which there were no significant differences or consistent trends between the two high-dose groups. The higher ratings on measures of mystical-type experiences in the HD-HS vs. the HD-SS group likely reflects that, before the first session, the high-support group received about twice as much meeting time with guides, with the majority of this extra time focused on discussion of and support for spiritual practices.

Persisting effects attributed to psilocybin assessed at 6 months. As with measures of mystical experience assessed on psilocybin session days, there was evidence for the HD-HS group showing greater effects than the HD-SS group. Significant differences were shown on altruism/positive social effects, positive behavior change, and increased spirituality, as well as ratings and percentage of strong endorsements of spiritual significance (Table 5, Figure 5). Strikingly, more than half (56%) of participants in the high spiritual support condition rated their experience in one or both psilocybin sessions as the single most spiritually significant experience of their life, with 96% rating it as among the top five most spiritually significant experiences. These results indicate that administering psilocybin in a context of high support for spiritual practices increases both the reported spiritual significance of the experience per se and the attribution to it of increased spirituality.

Longitudinal measures assessed at 6 months. As with measures of mystical experience assessed on session days and persisting positive effects attributed to psilocybin at 6 months, the longitudinal measures provide evidence for greater effects in the HD-HS group than the HD-SS group (Table 6 and Figure 6). Across groups, the HD-HS group showed numerically greater effects than the HD-SS group on 22 of the 23 measures, and showed statistically significant differences on seven of 23 measures. Furthermore, the HD-HS group differed significantly from the LD-SS group on all 23 measures, in contrast to the HD-SS group, which differed from the LD-SS group on 14 of 23 measures. These measures included positive changes in interpersonal closeness, gratitude, life meaning/

purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, sanctification of life strivings, as well as ratings of participants by community observers. The effect sizes for these comparisons were quite large (mean Cohen's $d=1.0$ across all 23 measures, Table S2). Finally, within the HD-HS group, 6-month scores were significantly different from baseline on 20 of 23 measures (compared with 17 significant differences from baseline in the HD-SS group).

Relationship of spiritual practices and psilocybin-occasioned mystical experience to outcome measures

Prior research suggests an important role of psilocybin-occasioned mystical experience in the observed enduring positive changes in psychological well-being, prosocial disposition, and spiritual worldview (Garcia-Romeu et al., 2014; Griffiths et al., 2008, 2016; Ross et al., 2016). In the present study, hierarchical regression analysis was used to examine the relationship of mystical experience and specific spiritual practices to the various outcome measures that showed between-group differences at 6 months (Table 7). The measure of mystical experience used for this analysis was the mean total score on the Mystical Experience Questionnaires (MEQ30) that were completed immediately following the two psilocybin sessions (4 and 5 months before the 6-month follow-up). Spiritual practices were assessed at the 6-month assessment with a questionnaire in which participants retrospectively rated over the past 4 months the three spiritual practices that were taught and encouraged during the study (minutes per day of meditation; times per day of spiritual awareness practice; times per week of spiritual journaling). When mystical experience alone was entered into a regression model, it accounted for a significant proportion of variance in all 19 outcome measures studied. In a separate hierarchical regression analysis, when the three spiritual practices were entered first into the regression model, they accounted for a significant proportion of the variance in 13 of 19 outcome measures studied. However, when mystical experience was subsequently entered into the model, it accounted for a significant proportion of variance in 18 of 19 measures after accounting for the impact of spiritual practices. For the overall regression model, meditation was significant on six measures (Faith Maturity Scale, Daily Spiritual Experience Scale,

Table 7. Hierarchical regression analysis of the relationship of spiritual practices and mystical experience to the outcome measures.

Outcome Measure	Spiritual Practices* entered first						Change in model adding post-session mystical experience score (MEQ30)						Beta (standardized coefficient)						t		p	
	R ²	F	d	f	p		R ²	F	d	f	p		Meditation	Awareness	Journaling	MEQ**	Meditation	Awareness	Journaling	MEQ		Meditation
Mysticism Scale: (Lifetime) – total score	0.113	2.97	3	70	0.038	0.560	118.34	1	69	0.000	0.268	1.052	1.790	14.342	-1.09	0.06	0.34	10.88	0.282	0.949	0.736	
Faith Maturity Scale	0.231	7.01	3	70	0.000	0.264	36.00	1	69	0.000	0.077	0.301	0.512	4.100	2.54	1.10	0.53	6.00	0.013	0.276	0.600	
Positive Religious Coping	0.201	5.87	3	70	0.001	0.066	6.19	1	69	0.015	0.041	0.160	0.272	2.183	1.22	0.95	1.84	2.49	0.227	0.344	0.070	
Daily Spiritual Experience Scale – total score	0.293	9.52	3	69	0.000	0.254	38.12	1	68	0.000	0.087	0.340	0.578	4.679	3.43	2.08	-0.04	6.17	0.001	0.042	0.966	
Death Transcendence Scale – total score	0.058	1.44	3	70	0.239	0.285	29.93	1	69	0.000	0.124	0.486	0.826	6.616	-0.37	-0.52	0.70	5.47	0.712	0.606	0.489	
Gratitude Questionnaire	0.050	1.24	3	70	0.302	0.166	14.62	1	69	0.000	0.023	0.089	0.151	1.208	1.98	-0.31	-1.75	3.82	0.052	0.761	0.085	
Coherence (Life meaning and purpose)	0.084	2.11	3	69	0.107	0.329	38.06	1	68	0.000	0.052	0.204	0.347	2.811	1.64	-1.08	0.38	6.17	0.105	0.282	0.708	
Trait Forgiveness Scale	0.083	2.10	3	70	0.108	0.100	8.43	1	69	0.005	0.043	0.167	0.284	2.277	1.79	0.12	-0.09	2.90	0.078	0.901	0.927	
Forgiveness – benevolence motivations	0.116	2.96	3	68	0.038	0.196	19.04	1	67	0.000	0.038	0.148	0.250	2.041	2.24	0.43	-0.63	4.36	0.029	0.673	0.533	
Forgiveness – avoidance motivations	0.120	3.10	3	68	0.032	0.081	6.77	1	67	0.011	0.054	0.211	0.357	2.914	-2.77	-0.31	0.91	-2.60	0.007	0.761	0.367	
Sanctification of Strivings	0.173	4.86	3	70	0.004	0.131	12.99	1	69	0.001	0.008	0.031	0.053	0.422	1.32	0.94	1.10	3.60	0.191	0.351	0.275	
Schwartz Value Scale – Tradition	0.060	1.49	3	70	0.224	0.091	7.37	1	69	0.008	0.008	0.030	0.051	0.411	0.06	0.66	0.46	2.72	0.954	0.515	0.644	
Interpersonal closeness	0.079	2.01	3	70	0.121	0.065	5.26	1	69	0.025	0.010	0.037	0.064	0.509	0.98	0.95	0.10	2.29	0.332	0.348	0.923	
Observer-rated spiritual/religious sentiments	0.141	3.73	3	68	0.015	0.291	34.36	1	67	0.000	0.076	0.281	0.485	3.868	2.68	0.50	-1.38	5.86	0.009	0.617	0.173	
Observer-rated positive behavior and attitude change score	0.248	7.71	3	70	0.000	0.031	2.97	1	69	0.089	0.037	0.146	0.249	1.995	0.85	2.00	2.11	1.72	0.400	0.049	0.039	
Positive attitudes about life, self, mood, altruism, behavior, and spirituality**	0.170	4.44	3	65	0.007	0.542	120.35	1	64	0.000	0.001	0.005	0.008	0.069	0.85	0.77	0.75	10.97	0.397	0.445	0.458	
Personal meaning of session experiences	0.132	3.50	3	69	0.020	0.551	118.26	1	68	0.000	0.009	0.036	0.059	0.472	-2.17	0.56	0.71	10.88	0.033	0.578	0.482	
Spiritual significance of session experiences	0.132	3.49	3	69	0.020	0.619	169.17	1	68	0.000	0.007	0.027	0.045	0.359	-0.90	0.69	0.36	13.01	0.372	0.490	0.719	
Change in well-being/life satisfaction	0.166	4.57	3	69	0.006	0.436	74.53	1	68	0.000	0.006	0.023	0.038	0.303	-0.73	1.26	1.08	8.63	0.471	0.214	0.284	

The first 15 measures are total scores from measures shown in Table 6 and the last four measures are from Table 5; bold font indicates probability < .05.

*Spiritual Practices were: Meditation (minutes per day), Spiritual Awareness Practice (times per day), and Journaling (times per week).

**MEQ: Mean total score of the Mystical Experience Questionnaire (MEQ30).

***This participant-rated measure is a composite total score of the 6 subscales in Table 5 that assessed positive effects attributed to psilocybin session experiences.

Forgiveness-benevolence motivations, Forgiveness-avoidance motivations, Observer-rated spiritual and religious sentiments, and Participant retrospective rating of the personal meaning of the session experiences); spiritual awareness practices were significant on two measures (Daily Spiritual Experience Scale, and Observer-rated changes in behavior and attitudes); and journaling was significant on one measure (Observer-rated changes in behavior and attitudes).

Overall, these results suggest that both mystical experience and spiritual practices contribute to positive outcomes, with mystical experience making a substantially greater contribution. The fact that the measure of mystical experience preceded the assessment of outcome measures by 4–5 months strengthens the interpretation that mystical experience and/or its neurophysiological or other correlates are likely determinants of the enduring positive attitudinal, dispositional, and behavioral effects of psilocybin when administered under spiritually supported conditions.

It is interesting that a previous study with a relatively high dose (200 µg) of LSD, a different classic psychedelic, produced only moderate increases in total mystical experience scores (MEQ30), with only 12.5% of participants meeting criteria for a complete mystical experience (Liechti et al., 2017). Whether this lower rate of mystical experience reflects pharmacodynamic differences between psilocybin and LSD, the use of a relatively lower dose of LSD than psilocybin, and/or differences between the studies in set, setting, or participant characteristics is unknown (Barrett and Griffiths, 2017). Future research should directly compare LSD and psilocybin within subjects, ideally using procedures to minimize expectancy effects.

There was little evidence that the standard-support intervention alone affected longitudinal measures at 6 months. Of the 23 longitudinal measures (Table 6), only one measure in the LD-SS group showed a significant difference from baseline (immediately after study enrollment) to 6 months. Furthermore, across the longitudinal measures shown in Figures 6 and 7, the LD-SS group tended to be similar or lower than comparison data (e.g. norms) from previous studies. The absence of robust effects of the standard-support intervention contrasts with previous studies that showed a more intensive 8- or 9-session program using a similar intervention resulted in a variety of positive changes in spirituality, well-being, self-efficacy, and mental health outcomes (Flinders et al., 2007; Hedberg et al., 2006; Oman et al., 2006, 2008a,b). The lack of greater efficacy for the standard-support intervention in the present study was likely due to the minimal level of teaching and support provided to the LD-SS group.

Experimental design strengths and limitations

Strengths of the present study include the double-blind design, the use of a very low (possibly inactive) psilocybin dose as a control, and instructions to participants and guides, all serving to obscure the actual dose conditions and thereby minimizing participant and guide expectancy effects. This strategy has been used in previous psilocybin research (Griffiths et al., 2016). In the present study, the effects of very low dose of psilocybin (1 mg/70 kg) were compared with the high-dose conditions. The low dose was below a dose (3.15 mg/70 kg) that did not produce statistically significant effects in a previous study (Hasler et al., 2004). Participants and guides did report some psilocybin-like effects

after the very low dose (e.g. Tables 2, 3, and 5), as might be expected under conditions in which participants (most of whom were psychedelic-naïve) had been told they would receive psilocybin. For instance, three of 25 (12%) of participants in the low-dose condition rated their psilocybin session experiences to be among the five most spiritually significant of their lives. Although the low-dose condition served as an important comparison to the high-dose conditions, in absence of a true placebo-dose condition, it is not possible to determine if the very low dose was pharmacologically active.

The integrity of blinding the guides to the study conditions was assessed with a post-study questionnaire that asked guides about their understanding of study drug and dose conditions. The finding that most guides made incorrect inferences about drug or dose conditions suggests substantial success of the blinding conditions. Guides were not required to make guesses about drug conditions after each session because we did not want to make this a focus of interest for guides. However, the absence of such guide ratings on each session precludes drawing a stronger conclusion about the success of blinding guides to study conditions.

The experimental design of the present study can be viewed as representing 3 of 4 cells of a balanced 2×2 design with dose (low dose vs. high dose) and spiritual support (standard support vs. high support) as factors. The fourth cell of a completely balanced design would be the low-dose high-support condition. Addition of that group would have permitted evaluation of the effects of high support independent of psilocybin. Although we considered the benefits of the balanced 2×2 design, we decided against it because of substantially increased study costs and because of concern that participants in this group, who receive only a low dose of psilocybin, might be less likely to comply with the more intensive schedule of participant–guide and dialogue-group meetings required in the high-support condition.

Additional limitations of the present study were the homogeneity of the participant population (predominately White, college educated, and employed) and the absence of brain-based or physiological measures of change or task-based measures such as assessment of implicit bias, emotion regulation, or social behavior. Finally, because the high-support condition involved group discussion of both spiritual practices and psilocybin experiences, the effect of group discussion of spiritual practice alone cannot be determined.

Conclusion

Although previous research shows that psilocybin, under appropriate conditions, can reliably occasion mystical-type experiences to which participants frequently attribute enduring positive changes in well-being and worldview, there has been little evidence from studies in healthy volunteers that psilocybin produces enduring changes on well-validated trait measures of disposition or personality. In the present study, psilocybin was administered in the context of undertaking a nonsectarian program of meditation and other spiritual practices that emphasized integration of spiritual values in daily life. The study showed robust interactive positive effects of psilocybin dose and added support for spiritual practices on a wide range of longitudinal measures at 6 months including interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily

spiritual experiences, religious faith and coping, and rating of participants by community observers. Analyses suggest that the determinants of these effects were the intensity of the psilocybin-occasioned mystical experience and the rates of engagement with meditation and other spiritual practices. Most broadly, as a model system for studying so-called quantum change experiences, which have been described for centuries but which have eluded rigorous prospective experimental analysis, further investigation of psilocybin-occasioned experiences may have broad implications for the development of drug and non-drug interventions in both therapeutic and nontherapeutic applications in order to engender enduring positive trait-level changes in attitudes and behavior and in healthy psychological functioning.

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Declaration of conflicting interests

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Supplemental Material

Supplementary material is available for this article online.

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