

**Characterization and prediction of acute and sustained response to psychedelic psilocybin
in a mindfulness group retreat**

Lukasz Smigielski, Michael Kometer, Milan Scheidegger, Rainer Krähenmann, Theo Huber,
Franz X. Vollenweider

Neuropsychopharmacology and Brain Imaging, Department of Psychiatry, Psychotherapy and
Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, CH-8032 Zurich,
Switzerland

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Abstract

Meditation and psychedelics have played key roles in humankind's search for self-transcendence and altered consciousness. However, neither their possible synergistic effect, nor related state and trait predictors have been experimentally studied. To elucidate these issues, we administered double-blind the psychedelic drug psilocybin (315 µg/kg PO) or placebo to expert meditators ($n = 39$) during a 5 day mindfulness group retreat. Psilocybin increased meditation depth and incidence of positively experienced self-dissolution, with no concomitant anxiety. Openness, optimism, and emotional reappraisal were predictors of the acute response. Compared with placebo, psilocybin enhanced post-intervention mindfulness and produced larger positive changes in psychosocial functioning at 4 month follow-up, which were mediated by self-dissolution. These findings highlight the interaction of non-pharmacological and pharmacological factors, and the role of emotion/attention regulation in shaping the experiential quality of deep psychedelic states, as well as the experience of selflessness as a modulator of behaviour and attitudes.

Recent years have seen a burgeoning interest in the phenomenology and neurobiology of psychedelic drugs, motivated by growing evidence of their therapeutic potential for some psychiatric disorders^{1, 2}. Classic psychedelics such as psilocybin are partial serotonin-2A-receptor agonists³ that may produce transient, profound changes in self-consciousness, experienced as a dissolution of the ordinary sense of self and a breakdown of the perceived boundaries between self and the world⁴. Empirical research has repeatedly reported that, in a supportive setting at medium-to-high doses (20–30 mg PO), psilocybin can trigger a dissolution of self-boundaries that is associated with feelings of bliss, oneness, and unity with all that exists, and a sense of insight into a timeless “ultimate reality”⁵⁻⁸. These psilocybin-induced alterations of the sense of self resemble the experience of self-transcendence reported by various traditions of Eastern descent^{9, 10}, and can occasionally occur during deep meditative practices, such as Zen and Vipassana^{11, 12}. Such experiences have variously been referred to as different but overlapping concepts known as self/ego dissolution^{13, 14}, self-loss¹⁵, states of selflessness¹⁶⁻¹⁸, mystical-type experiences^{19, 20}, or non-dual awareness²¹. Reaching such states is an ultimate goal of various meditation schools^{11, 17}.

Although the content and intensity of psychedelic experiences depend most critically on the dosage²², the same dose can induce a pleasurable “oceanic” state of self-dissolution or, under certain circumstances, a more distressing response associated with thought disturbances, fear of losing control, anxiety, or panic²³. A number of factors may modulate the subjective experience and contribute to the observed within-individual variance in responses²⁴. These factors are commonly categorized as “set” (e.g., the subject’s expectation, personality traits, and current mood state) and “setting” (e.g., the physical and social environment in which the drug is taken), and are important in shaping the reactions to psychedelics and their subsequent interpretations²⁵⁻²⁸. Considering the role of set and setting in study designs resulted in more positive subjective effects and fewer dysphoric reactions^{7, 29} than in earlier experimental work that ignored these issues^{30, 31}.

A better understanding of the influence of non-pharmacological variables on the outcome of the psychedelic experience appears to be crucial, in consideration of their suggested therapeutic potential. In fact, the intensity and quality of the psychedelic-induced alterations of consciousness, and particularly the transient experience of self-dissolution, seem to mediate the long-term beneficial effects of these compounds in healthy individuals^{32, 33} and psychiatric patients³⁴. When given in a supportive, therapeutic setting, psilocybin reduced symptoms and improved quality of life in terminal cancer patients with depression and anxiety³⁵ and in therapy-resistant patients with major depression³⁶ after administration of just one or two doses. The intensity and form of psychedelic experience, indexed as mystical-type experience or self-loss, were shown to predict a beneficial therapeutic outcome³⁷⁻³⁹. Similarly, many meditation practices aim to reduce self-referential processing^{40, 41} and achieve a temporary dissolution of self-boundaries¹⁷, which is thought to lead to an enduring reduction of self-focus or egocentricity^{16, 42, 43}. Meditation alleviates symptoms of depression, anxiety, and stress and promotes lasting benevolent emotions and prosocial behaviour⁴³ in clinical and non-clinical populations⁴⁴⁻⁴⁶. Despite similarities between meditation- and psychedelic-induced temporary alterations in the sense of self, neither the phenomenological similarities and differences of such multifaceted experiences of self-dissolution, nor the impact of additional putative modulatory factors (e.g., personality traits, emotion regulation), have yet been systematically investigated in a prospective study. It is possible that the phenomenological differences between meditation- and psychedelic-induced self-dissolution may result in different long-term alterations in behaviour and attitudes.

Many traditional meditative practices, and in particular mindfulness-based meditation such as Vipassana, Zen, and their secular forms⁴⁷, aim at maintaining attention to the present moment with a non-judgmental, accepting stance toward the enfolding experiences^{17, 48, 49}. Cultivating mindfulness typically includes two attentional deployment strategies: focused attention and open monitoring⁵⁰. Focused attention is related to a particular object or process,

such as breathing, whereas open monitoring involves a non-judgmental global awareness to one's inner experiences, moment by moment⁵⁰. Observing one's own experience with curiosity is at the core of Zen and Vipassana meditation and involves attention regulation, body awareness, and emotion regulation strategies to achieve increased cognitive and emotional flexibility and states of equanimity^{48, 49, 51}. This, in turn, is thought to reduce self-centered psychological functioning^{17, 43} and to bring forward the dissolution of self-boundaries, which may culminate in profound states of selflessness^{17, 52}. Although meditation can be exercised daily, it is often practiced in intensive meditation retreats, typically lasting 4 to 10 days⁴⁴. Meditation experiences arise along a spectrum of meditation depth⁵³ and are shaped by other factors, such as the extent of previous meditation experience, dispositional (trait) mindfulness, personality traits like openness to new experiences, and absorption^{54, 55}. Profound states of self-dissolution during meditation occur rarely and mostly in long-term meditators¹¹. By contrast, psilocybin can induce a state of self-dissolution at a relatively high rate (up to 60%), particularly at higher doses^{32, 56}.

Taken together, current evidence suggests that both meditation and psilocybin can promote a spectrum of altered states of consciousness, including various forms of self-dissolution, that are modulated by additional dispositional (trait) and state factors. In this prospective, matched-group study, we quantified the effects of meditation alone and meditation combined with psilocybin in expert meditators participating in a well-structured 5 day mindfulness-based meditation retreat. In total, thirty-nine individuals participated in two retreat sessions. On day 4, participants received either placebo ($n = 19$) or psilocybin ($n = 20$) in a double-blind manner.

First, we explored whether state mindfulness, evaluated using the Toronto Mindfulness Scale (TMS), and meditation depth, evaluated using the Meditation Depth Questionnaire (MEDEQ)⁵³, increased across the 5 days of the retreat, and whether psilocybin modulated these outcomes, in addition to direct pre-post trait-like mindfulness. Second, we compared the

spectrum and extent of alterations of consciousness, evaluated using the Altered States of Consciousness Rating Scale (5D-ASC), and mysticism, evaluated using the Mysticism Scale (M-scale). Furthermore, we conducted a multiple regression analysis to explore whether a number of trait and state factors contributed to inter-individual differences in self-dissolution as indexed by the 5D-ASC and M-Scale. Specifically, we hypothesized that the personality traits of openness, extraversion, and neuroticism^{24, 57}, absorption capacity^{22, 55}, optimism toward life²⁴, pre-experience with altered states²⁴, mood and emotion regulation strategies^{22, 24, 49}, trait and state mindfulness, and meditation depth the day before drug intake⁵⁵ would influence self-dissolution. Additionally, we postulated that the high cognitive and emotion regulation capacity of meditation experts^{49, 50, 58-60} would buffer possible distressing aspects of psychedelic experiences, such as negative emotions, anxiety, disorientation, and fear of loss of control and of self-identity (colloquially known as a “bad trip”)⁶¹, which can arise with high doses of psilocybin. Since both the extent of psilocybin-induced alterations of self-consciousness, as indexed by mystical-type experience^{35, 39}, and mindfulness-based meditation retreats lead to persisting positive outcomes in healthy subjects^{44, 62} and patient populations^{34, 35, 39, 44}, we explored whether the intensity of different sub-dimensions of the mystical-type experience predicted persisting changes in behaviour and attitudes at 4 month follow-up. We hypothesized that the combination of psilocybin and mindfulness meditation training would lead to larger changes than meditation alone.

Results

State mindfulness and meditation depth

During the 5 day retreat, participants practiced mindfulness meditation, which can be described as a temporary state of intentional self-regulation of attention to foster greater awareness of one's sensations, emotions, and thoughts with a non-judgmental attitude. On day 4, participants received either a placebo or psilocybin in a double-blind manner.

Daily, at the end of the meditation session, participants rated the intensity of state mindfulness using the TMS. There was no significant interaction between group (placebo/psilocybin) and time (day 1 to 5) for total TMS score (ANOVA $F(4,148) = 1.05, p = 0.38$), and no significant main effect of group ($F(1,148) = 0.41, p = 0.53$), indicating that psilocybin did not significantly increase the state mindfulness. However, there was a main effect of time ($F(4,148) = 4.41, p < 0.01$). Post-hoc tests showed that total TMS score increased from day 1 to day 5 (mean \pm SEM: 29.61 ± 1.18 ; mean \pm SEM: 32.42 ± 1.36 ; $p < 0.05$; Fig. 1A).

At the end of each meditation session, participants also rated meditation depth using the MEDEQ. There was a significant interaction between group (placebo/psilocybin) and time (day 1 to day 5) for MEDEQ score (ANOVA $F(4,148) = 4.69, p < 0.001$). Post-hoc tests confirmed the hypothesized increase in meditation depth on day 4 in the psilocybin group was greater than in the placebo group ($p < 0.05$; Fig. 1). We also found a significant main effect of time ($F(4,148) = 14.44, p < 0.00001$), but no main effect of group ($F(1,37) = 2.44, p = 0.13$). Post-hoc tests confirmed that MEDEQ score increased from day 1 to day 5 (mean \pm SEM: 63.0 ± 3.31 and 77.7 ± 3.74 ; $p < 0.001$, Fig. 1B).

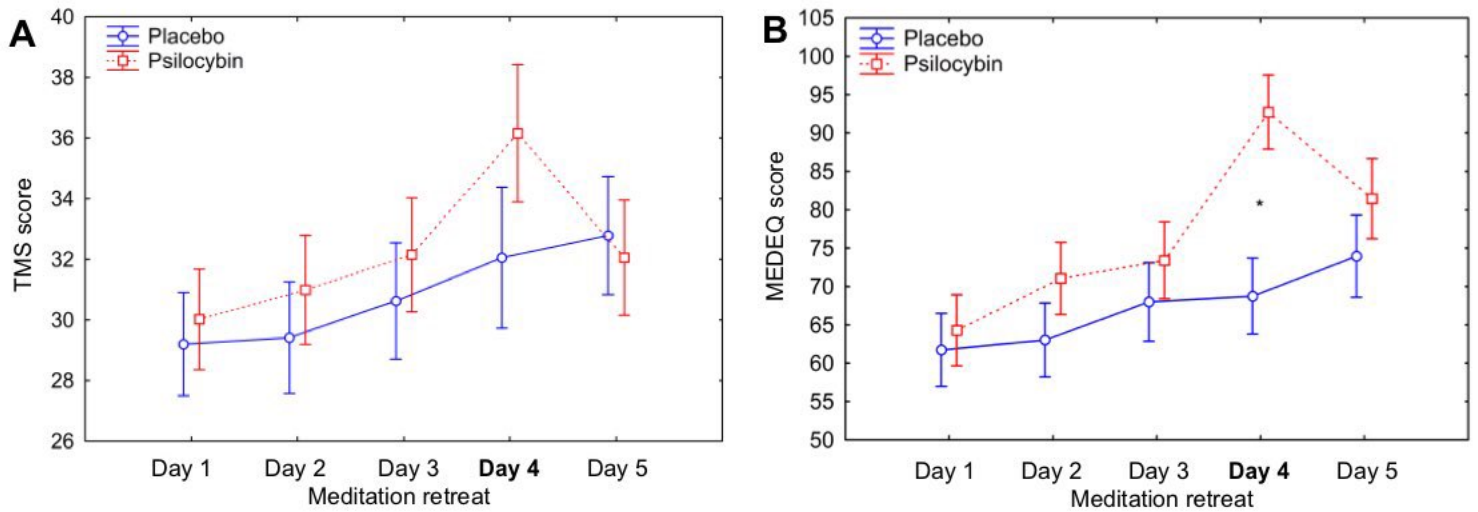


Figure 1. A) Levels of state mindfulness (Toronto Mindfulness Scale total score) and **B)** meditation depth (Meditation Depth Questionnaire total score) over the course of the retreat. Data are mean \pm 1 SEM (standard error of the mean). Asterisk indicates a significant difference between psilocybin and placebo groups on day 4, when the drug was administered (* = $p < 0.05$). Both state mindfulness and meditation depth increased between day 1 and day 5 (mindfulness: mean \pm SEM: 29.61 ± 1.18 and 32.42 ± 1.36 on day 1 and day 5, respectively, $p < 0.05$; meditation depth: mean \pm SEM: 63.0 ± 3.31 and 77.7 ± 3.74 on day 1 and day 5, respectively, $p < 0.001$).

Trait mindfulness

Trait mindfulness was evaluated pre- and post-retreat, on day 0 and day 6, respectively, using the Freiburg Mindfulness Inventory (FMI, short form). There was a significant interaction between group (placebo/psilocybin) and time (pre-retreat, post-retreat) for FMI score (ANOVA $F(1,37) = 4.14$, $p < 0.05$) and a significant main effect of time ($F(1,37) = 22.85$, $p < 0.0001$). Post-hoc tests confirmed that FMI score was higher post-retreat than pre-retreat ($p < 0.001$), and that post-retreat FMI score was higher in the psilocybin group than in the placebo group ($p < 0.001$; Fig. 2).

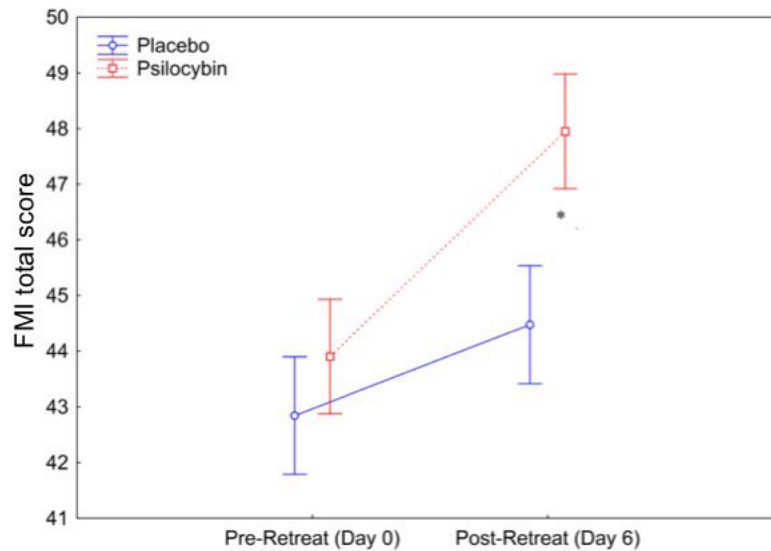


Figure 2. Trait mindfulness (Freiburg Mindfulness Inventory score) pre- and post-retreat. The score was significantly higher in the psilocybin group than in the placebo group on day 6, 2 days after psilocybin administration ($* = p < 0.001$). When collapsed across the two groups (independent of drug treatment), trait mindfulness was significantly higher on day 6 (mean \pm SEM: 46.2 ± 0.73) than on day 0 (mean \pm SEM: 43.3 ± 0.70).

Subjective effects during psilocybin-assisted meditation

After psilocybin or placebo administration at 1030 h on day 4, participants engaged in their usual meditation practice, preserving complete silence. The psychological effects of psilocybin peak at about 60–90 min after drug intake, subside gradually, and are absent 6 hours after drug intake⁶³. To assess the effect of psilocybin on the subjective experience during the meditation session, participants completed the 5D-ASC and the M-scale. 5D-ASC is designed to quantify positive and negative forms of self/ego-dissolution, including perceptual alterations. The M-scale differentiates between extrovertive self-dissolution (framed by perception of unity and an outward merging with surroundings) and introvertive self-dissolution (framed by ego loss, spacelessness, and/or timelessness, denoting an inward unitary experience beyond time and space)^{64, 65}.

There was a significant interaction between group (placebo/psilocybin) and 5D-ASC main scales (Oceanic Boundlessness [OB], Visionary Restructuralization [VR], Vigilance

Reduction [VIR], Anxious Ego Dissolution [AED], Acoustic Alterations [AA]) for 5D-ASC score (ANOVA $F(4,148) = 36.27, p < 0.00001$). Post-hoc tests indicated that the OB ($p < 0.0001$), VR ($p < 0.0001$), and VIR ($p < 0.05$) scores were higher in the psilocybin group than in the placebo group. By contrast, the groups did not differ on the AED and AA scales (SI Table 2).

A subsequent analysis of the subscale scores for the OB, VR, and AED core scales revealed a significant group \times subscale interaction ($F(10,37) = 13.14, p < 0.00001$). Post-hoc tests indicated that scores for the OB-related subscales of unity, spiritual experience, blissfulness, insightfulness, and disembodiment were higher in the psilocybin group than in the placebo group (all $p < 0.01$). Similarly scores for the VR-related subscales of complex imagery, elementary imagery, audiovisual synesthesia, and changed meaning of percepts were higher in the psilocybin group than in the placebo group (all $p < 0.01$). By contrast, scores on the AED-related subscales of impaired control and cognition and anxiety did not differ across the two groups ($p > 0.9$; Fig. 3).

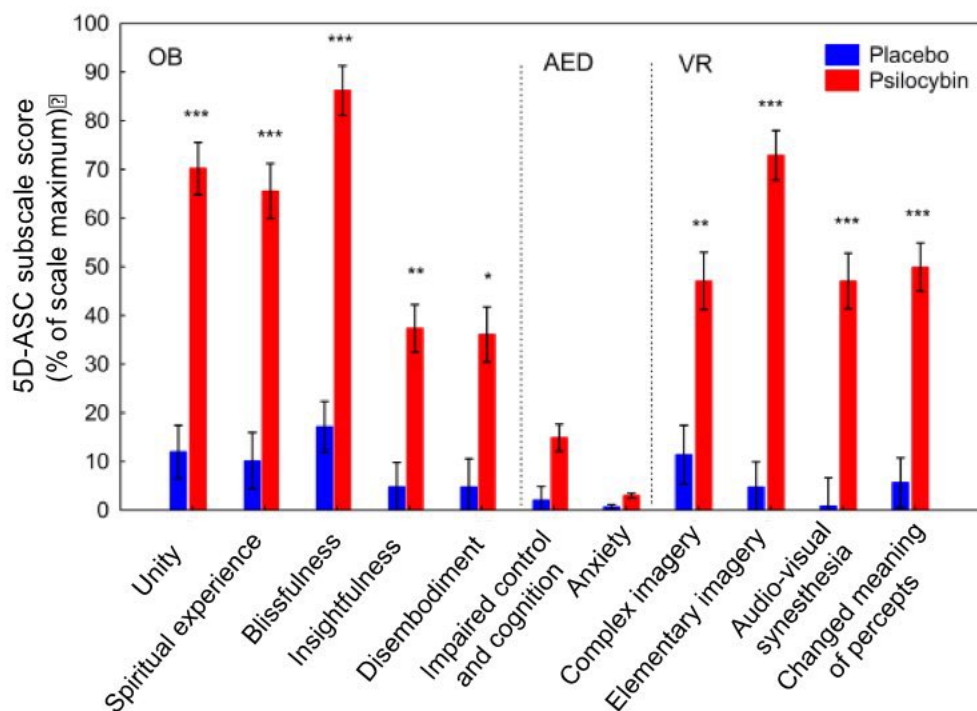


Figure 3. Effects of psilocybin on the subscales of the Altered States of Consciousness Rating Scale (5D-ASC). Scores are expressed as percent of scale maximum. Error bars indicate ± 1 SEM (standard error of the mean). Asterisks indicate significant differences between psilocybin and placebo groups (** $p < 0.0001$, ** $p < 0.001$, * $p < 0.05$). OB, Oceanic Boundlessness; AED, Anxious Ego Dissolution; VR, Visual Restructuralization.

There was a significant interaction between group (placebo/psilocybin) and dimension (extrovertive mysticism, introvertive mysticism, interpretation) for M-scale score (ANOVA $F(2,74) = 14.81, p < 0.00001$). Post-hoc tests indicated that, for all three dimensions, the score was higher in the psilocybin group than in the placebo group (all $p < 0.01$; SI Table 2). Extrovertive mysticism comprises the sub-dimensions unity of the world as one and inner subjectivity of all beings; introvertive mysticism comprises the sub-dimensions of ego loss, timelessness/spacelessness, and ineffability of the experience; and interpretation comprises the sub-dimensions positive affect, sacredness, and noetic quality. Subsequent analysis indicated a significant interaction between group (placebo/psilocybin) and sub-dimension score ($F(7,259) = 2.43, p < 0.05$). Post-hoc tests indicated that, for all sub-dimensions, score was higher in the psilocybin group than in the placebo group (Fig. 4).

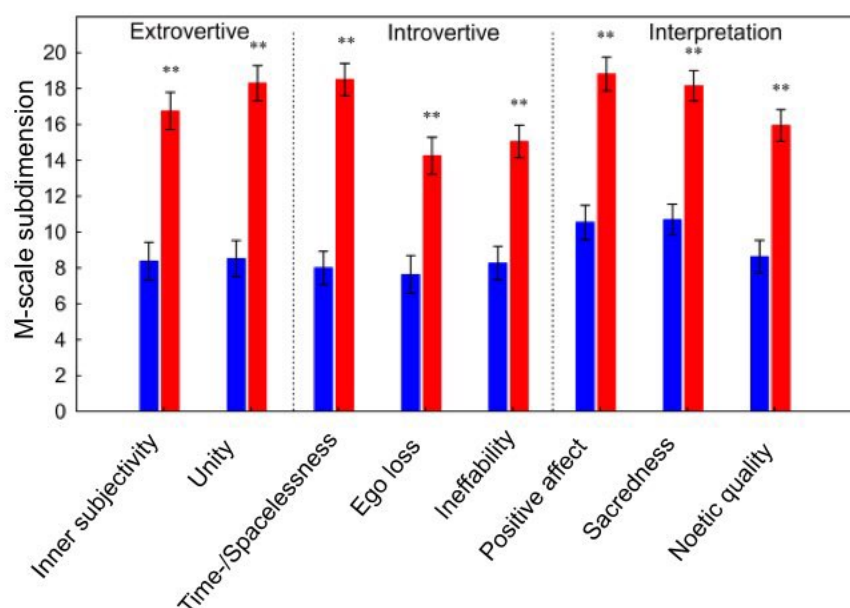


Figure 4. Effect of psilocybin on sub-dimensions of the M-scale. Error bars are ± 1 SEM (standard error of the mean). Asterisks indicate significant differences between psilocybin and placebo groups (** = $p < 0.001$).

Prior to the retreat, participants used the M-scale to rate their strongest lifetime mystical experience. This was then compared with the mystical experience after drug administration during the retreat. There was a significant interaction between group (placebo/psilocybin) and time point (lifetime, retreat) on total M-scale score (ANOVA $F(1,37) = 68.04, p < 0.00001$), and a significant main effect of time point ($F(1,37) = 49.53, p < 0.00001$) and group ($F(1,37) = 23.19, p < 0.0001$; Fig. 5A). Individual M-scale scores revealed that 19 of 20 participants (95%) in the psilocybin group and 3 of 19 participants (16%) in the placebo group met the a priori criteria of 60% of scale maximum for having had a “strong” mystical experience during the retreat (Fig. 5B).

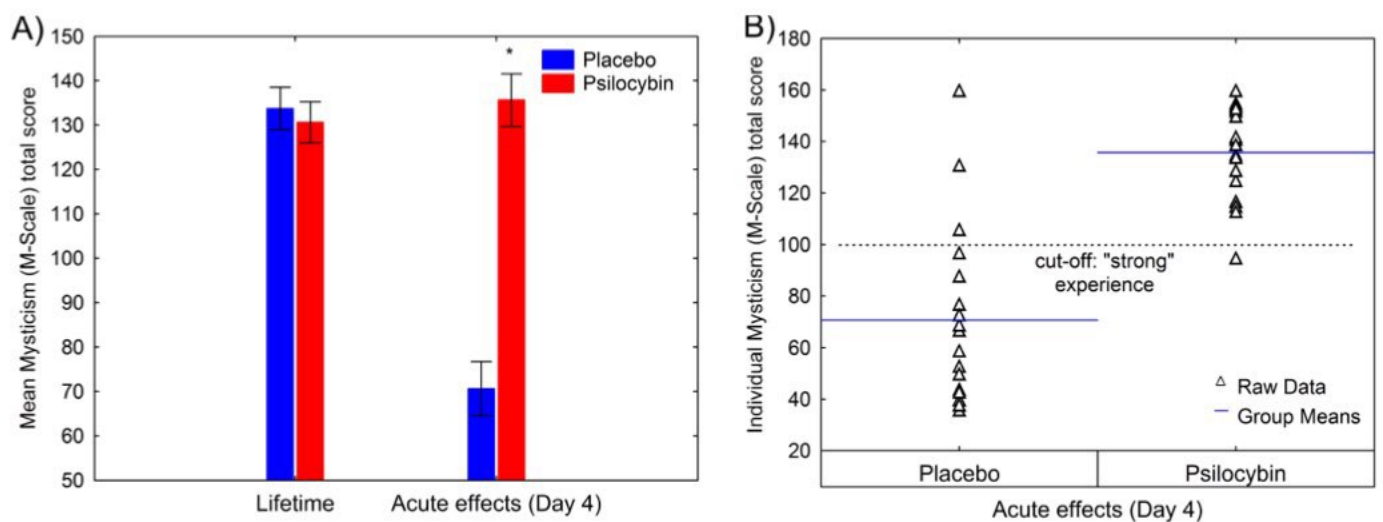


Figure 5. A) M-scale total score for lifetime experience versus acute drug experience for psilocybin and placebo groups. Error bars indicate ± 1 SEM (standard error of the mean). Asterisk indicates a significant difference between psilocybin and placebo groups (* $p < 0.01$). **B)** M-scale total score for each participant. The a priori criterion of 60% of scale maximum for a “strong” mystical-type experience was met by 19 of 20 participants (95%) in the psilocybin group and 3 of 19 participants (15.8%) in the placebo group.

The relations between score on each of the main dimensions of the 5D-ASC scale⁶⁶ and each of the three dimensions of the M-scale⁶⁷ were quantified using Pearson's correlation coefficient. Inspection of the correlation matrix (SI Fig. 2) revealed that score on the OB dimension of the 5D-ASC scale correlated significantly with score on the extrovertive mysticism ($r = 0.47$), introvertive mysticism ($r = 0.59$), and interpretation ($r = 0.59$) dimensions of the M-scale (all $p < 0.01$). No other correlations were significant.

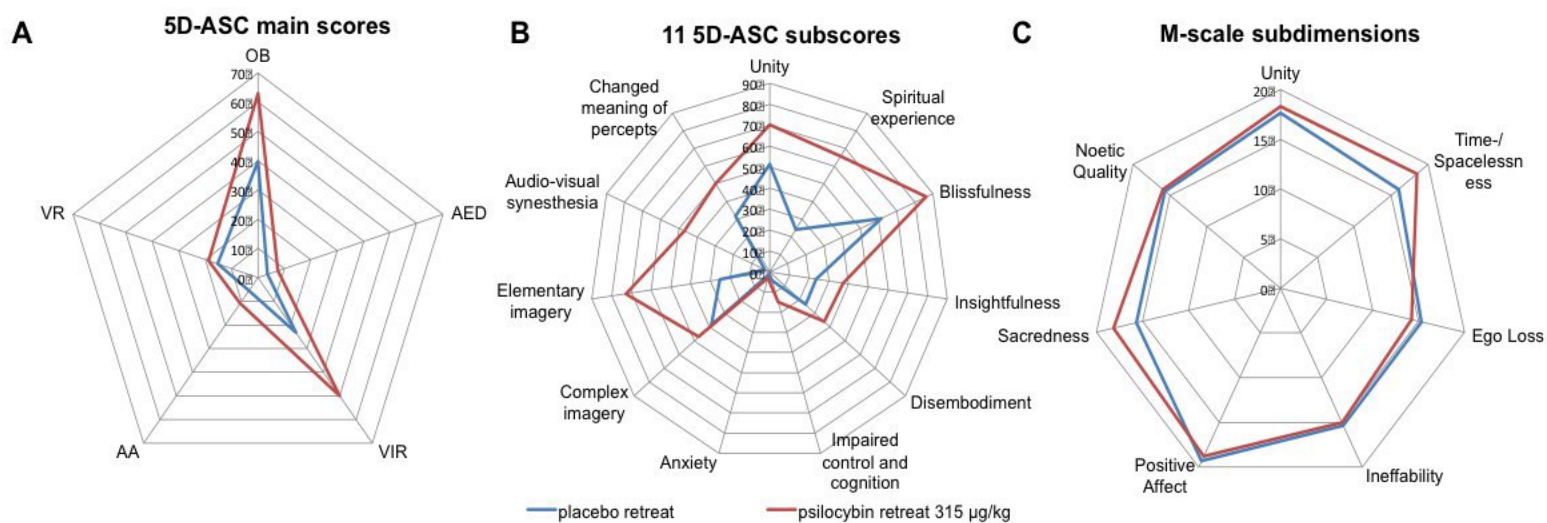


Figure 6. Comparison of subjective effects in participants from the psilocybin group ($n = 19$) with those in the placebo group ($n = 3$), who reached the a priori criteria for a “strong” mystical-type experience. Despite similar M-scale subdimensions (C), there were marked differences in various scale and subscale scores of altered states of consciousness (A-B), particularly in the domain of visual experiences.

Predictors of acute subjective experience of meditation

Multiple regression analysis was used to explore if dispositional and state variables before drug intake predicted the acute alterations of consciousness (SI Table 4). Specifically, we tested whether age, personality traits (extraversion, neuroticism, and openness to experience), absorption capacity, optimistic attitude toward life, intensity of previous mystical-

type experience, trait mindfulness (facets of presence and acceptance), emotion regulation strategies (suppression and reappraisal), state mindfulness, and meditation depth influenced score on the OB, AED, and VR main scales of the 5D-ASC questionnaire and on the extrovertive mysticism, introvertive mysticism, and interpretation dimensions of the M-scale. State mindfulness and meditation depth were assessed the day before drug intake, and all other predictor variables were assessed prior to the start of the retreat. Psilocybin intake accounted for the largest proportion of the variance in all six outcome measures, with η^2 ranging from 0.35 to 0.74. Optimistic attitude toward life accounted for a significant proportion of the variance in OB, VR, and the three core dimensions of mysticism ($\eta^2 = 0.16\text{--}0.25$), and openness ($\eta^2 = 0.12\text{--}0.18$) accounted for a significant proportion of the variance in OB and the three core dimensions of mysticism.

Furthermore, we postulated that emotion regulation strategy and mindfulness practice may prevent anxiety and have a beneficial influence on the psychedelic experience. Indeed, reappraisal of emotions counteracted the intensity of AED ($p < 0.0001$, $\eta^2 = 0.21$), and non-judgmental acceptance of thoughts and emotions increased introvertive mysticism ($p < 0.05$ $\eta^2 = 0.14$) and interpretation of mystical experience ($p < 0.05$ $\eta^2 = 0.16$). Finally, as expected meditation depth accounted for a significant proportion of the variance in OB ($p < 0.0001$, $\eta^2 = 0.38$) and interpretation of mystical experience ($p < 0.05$ $\eta^2 = 0.13$), notably both dimensions that depict positive emotions associated with self-dissolution.

Changes in behaviour and attitudes at 4 month follow-up

Four months after the retreat, participants evaluated perceived changes in behaviour and attitudes using the Life Changes Inventory, Revised (LCI-R). LCI-R score was significantly higher in the psilocybin group (mean \pm SEM: 0.75 ± 0.09) than in the placebo group (mean \pm SEM: 0.19 ± 0.05 ; $F(1,37) = 23.41$, $p < 0.0001$), indicating greater change in attitudes and behaviour. There was a significant interaction between group (placebo/psilocybin) and LCI-R scale ($F(8,296) = 9.28$, $p < 0.00001$). Post-hoc tests indicated that scores on the LCI-R scales of

appreciation for life, self-acceptance, quest for meaning/sense of purpose, and appreciation of death were significantly higher in the psilocybin group than in the placebo group (all $p < 0.01$). There was also a trend toward a higher score on the concern for others and spirituality scales, and toward a lower score on the concern with worldly achievements scale (e.g., interest in material things, social status) (all $p < 0.05$ – 0.07 ; Fig. 7).

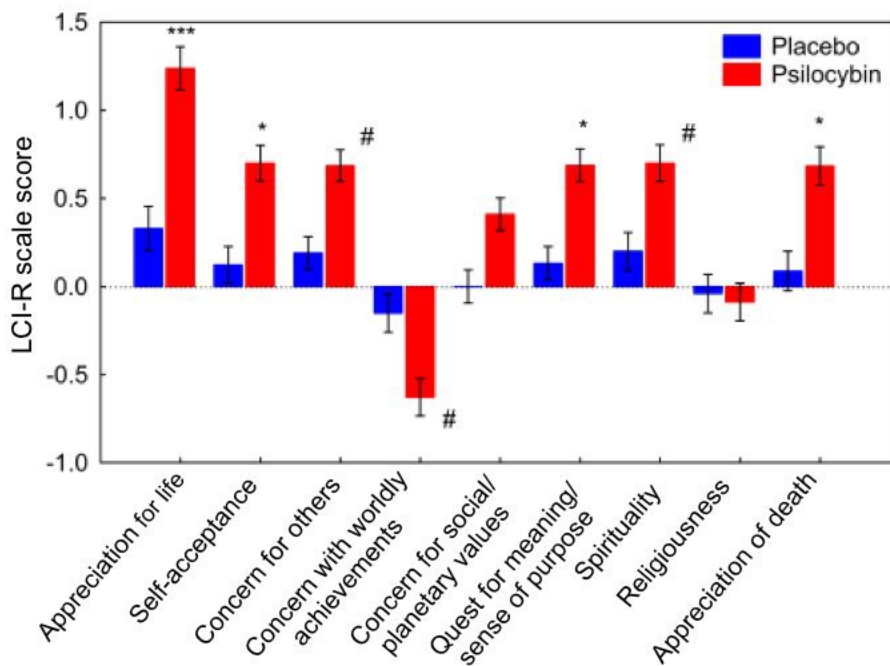


Figure 7. Self-rated changes in attitude and behavior, evaluated using the Life Change Inventory, Revised, at 4 month follow-up. Error bars indicate ± 1 SEM (standard error of the mean). Asterisks indicate significant differences between psilocybin and placebo groups (*** = $p < 0.001$, * = $p < 0.01$, # = $p < 0.05$ – 0.07).

Each participant designated a closely related person with whom he/she had frequent contact since the retreat, to complete a third-person LCI-R with reference to the participant. Completed questionnaires were received from 39 data participants and 37 significant others. Two participants declared that there was no closely related person with whom they had frequent contact at that moment of their life. These community observer LCI-R ratings showed a similar, although less marked, overall pattern of changes with significantly higher scores on

the self-acceptance and quest for meaning/sense of purpose scales in the psilocybin group than in the placebo group (all $p < 0.01$; SI Fig. 3).

Meaningfulness of the study experience

At follow-up, participants were asked how personally meaningful the study experience was. A large proportion of participants in the psilocybin group rated their experience as among either the top ten (50%) or five (35%) most meaningful experiences of their life, whereas the majority of participants in the placebo group rated their experience as meaningful as those experiences occurring once a month (37%), once a year (21%), or every 5 years (26%) (SI Table 3).

Predictors of changes in attitude and behaviours

A multiple regression was used to test the hypothesis that certain features of the mystical-type experience would predict changes in attitudes and behaviours quantified by the LCI-R at 4 month follow-up (SI Table 5). Psilocybin intake ($p < 0.05$, $\eta^2 = 0.15$) and loss of ego boundaries ($p < 0.01$, $\eta^2 = 0.20$) accounted for a significant amount of variance in total LCI-R score. Furthermore, psilocybin intake ($p < 0.001$, $\eta^2 = 0.28$) predicted score on the appreciation of death subscale. Sacredness accounted for a significant amount of variance in score on the appreciation of life scale ($p < 0.00001$, $\eta^2 = 0.48$), and sacredness ($p < 0.05$, $\eta^2 = 0.11$) together with ineffability ($p < 0.01$, $\eta^2 = 0.17$) accounted for a significant amount of variance in score on the quest for meaning/sense of purpose scale. The experience of unity ($p < 0.001$, $\eta^2 = 0.32$) accounted for a significant amount of variance in score on the self-acceptance scale.

Discussion

In deep, mindfulness-based meditation, profound states of self-dissolution occur rarely and unfold along a dimension of increasing meditation depth involving intention, attention and emotion regulation strategies, and a non-judgmental stance to achieve equanimity and insight into the fleeting nature of the self and the change in perception of reality. By contrast, psychedelics such as psilocybin reliably alter the sense of self along a perception-hallucination continuum with increasing emotional arousal to culminate in self/ego dissolution and a profound state of oneness with the external world. Although the experience of self-dissolution and awareness of unity induced by psilocybin appears to resemble the experiential quality of states of awakening in advanced Zen meditation¹² or in spontaneously occurring mystical-type states^{19, 64, 68}, there are no experimental data to support this assumption. Moreover, given the importance of set and setting in shaping the reactions to psychedelics, we hypothesized that mindfulness training may deepen psychedelic-induced experiences and buffer the emotional overload and anxiety that can arise with self-dissolution effect⁶⁹. In the present study, we showed that intensive meditation training gradually increased two aspects of meditation practice, state mindfulness and meditation depth, over the course of the 5 day retreat, and that meditation depth was acutely increased by psilocybin administration (Fig. 1). These findings demonstrate that during acute drug effects, experienced meditators were able to remain engaged in their usual meditation practice and that psilocybin has the capacity to deepen meditative states. Interestingly, dispositional mindfulness measured 1 day after the completion of the retreat was higher among participants who had received psilocybin than among those who had received placebo (Fig. 2). This finding aligns well with the observed increase in mindfulness capacity 24 hours after administration of the psychedelic N,N-dimethyltryptamine in form of ayahuasca to healthy volunteers⁷⁰. Thus, the current findings corroborate the view that psychedelics may enhance mindfulness capacity⁷⁰ and that dispositional mindfulness may

change over time with practice, suggesting putative neuroplasticity-related modulations of this trait^{45, 71, 72}.

The present findings also show that the combination of psilocybin and meditation produced much stronger alterations of consciousness and a profound positively experienced dissolution of the sense of self (OB score) compared with meditation alone, and virtually without loss of cognitive control and anxiety (AED score), despite the relatively high dose of psilocybin that was used. However, this profound experience of self-dissolution was accompanied by marked vivid imagery, ranging from elementary to complex scenery hallucinations (VR score). A comparison of the 5D-ASC results in the psilocybin group in the present study with those obtained in healthy, non-meditating participants who had conducted a simple neuropsychological task under the same psilocybin dose²² revealed that meditation plus psilocybin resulted in substantially higher scores on the spiritual experience (66% vs. 22%), blissful state (86% vs. 48%), and feeling of unity (70% vs. 40%) subscales and lower scores on the AED and VIR scales than psilocybin alone, whereas the auditory and visual alterations did not differ across the two studies²² (SI Fig. 1). These findings support our hypothesis that mindfulness-related trait and state capabilities may foster and positively shape the experiential quality of self-dissolution and buffer psilocybin-induced anxiety and vigilance deficits. Interestingly, a 1–2 month preparatory training in meditation and spiritual practice bolstered the positive effects on self-dissolution in healthy individuals, as tested with similar doses of psilocybin⁷³.

In the present study, three participants in the placebo group met the a priori criteria for a strong mystical-type experience (Fig. 5B). Exploration of the pattern and intensity of the M-scale subscale scores indicated that the mystical-type experience reported by the placebo participants was very similar to that reported by the psilocybin participants. These findings provide the first experimental evidence and corroborate the view⁷⁴ that meditation and psilocybin can occasion phenomenologically overlapping mystical-type experiences. However,

there are also some notable differences between meditation- and psilocybin-induced alterations of consciousness. Whereas the mystical-type experiences in placebo group arose virtually without anxiety, cognitive impairments, audiovisual synesthesia, or vigilance reduction, and with relative few elementary imageries, in the psilocybin group they were associated with vivid visual alterations, pronounced audiovisual synesthesia, moderate cognitive impairments, and vigilance reduction (Fig. 6A, B). Consistent with previous work, such experiences occur in deep meditation unpredictably and at a very low rate^{75, 76}, whereas psilocybin can occasion such positive mystical-type experiences in a supportive clinical setting at relatively high rates (60–70%)^{8, 22, 32, 77}. Psilocybin also produced more intense mystical-type experiences than placebo in the seminal “Good Friday Experiment”, where participants attended a Christian service in a group setting at Harvard University’s Marsh Chapel⁸. In light of these observations, we suggest that the retreat setting in the present study reassured, through the presence of others and social bonding, a safe and supportive environment that may have contributed to the positive outcomes of psilocybin-induced self-dissolution.

Our analysis of putative predictors of the acute psychedelic experience highlights that drug was the most important determinant. This is consistent with the result of a previous pooled analysis of psilocybin experiments²². In accordance with earlier studies^{25, 78, 79}, we also found that the personality trait “openness” (expressing the level of permeability to novel experience) and optimism toward life contributed to the experience of OB, as well as the three core dimensions of mysticism. The significant correlation between OB and these three dimensions further supports this finding. Openness is composed of active imagination, attentiveness to inner feeling, intellectual curiosity, preference for variety, adventurousness, and aesthetic sensitivity, clustering together in one dimension⁸⁰. This personality disposition not only predicted the positive outcome of psychedelic experiences^{24, 62}, but also correlated with the prevalence of spontaneously occurring mystical-type experiences⁸¹, and was associated with the meditation depth⁵⁵. Consistent with previous work²⁴, visionary experience was associated

with the personality trait extroversion, but unlike previous reports it was not correlated with the participant's absorption capacity²². In regard to the core components of mindfulness meditation practice, we found that reappraisal of emotions was negatively related to the AED dimension of altered states of consciousness and introvertive mysticism, which also refers to loss of ego functioning, whereas the mindfulness trait acceptance of thoughts and emotions correlated positively with introvertive mysticism and the interpretation of mystical experience. Furthermore, meditation depth assessed the day before drug administration substantially contributed to the OB dimension of altered states of consciousness and interpretation of mystical experience, both of which depict positive emotions associated with self-dissolution. Relaxation the day before drug administration and age were predictors of positive self-dissolution in a previous study²⁴. In light of these observations, it is conceivable that mindfulness training may help to buffer the emotional distress and anxiety that may arise with the ego dissolution state. This may happen by promoting reappraisals, more flexible selection of interpretation of the experience, and redirection of emotional load. Taken together, this suggests that a better understanding of non-pharmacological variables could help stratify individuals and better predict specific responses to classical psychedelics.

The follow-up results highlight that changes in behaviours were significantly higher in the psilocybin group than in the placebo group for appreciation of life, self-acceptance, quest for meaning and sense of purpose, and appreciation of death (Fig. 7). The pattern of changes was similar although less pronounced than that obtained from an external observer (SI Fig. 3). This adds to the literature reporting transformational processes following psychedelic experiences. Comparable enduring positive changes in attitude and behaviour after one or two doses of psilocybin have been reported to persist at least 14 months⁸² or more⁸³. Interestingly, although our participants were well-functioning individuals who scored high in life satisfaction at baseline, it appears that they could still greatly benefit from the psilocybin-facilitated experience.

Remarkably, despite the long engagement of our study participants in contemplative practices, the present psilocybin experience was valued equivalent to their strongest lifetime mystical-type experience (Fig. 5A). Moreover, most participants in the psilocybin group attributed a high personal meaning to the psilocybin experience: 37% considered it one of the five, and 47% one of the ten most meaningful life experiences. However, this finding is somewhat less pronounced than that of a recent study in non-meditating psilocybin subjects^{32, 82}. A possible explanation for this difference is that we used a smaller dose of psilocybin, and that cultivating profound altered states and achieving enduring happiness and well-being is an intentional part of meditation practice. Thus, these experiences may not have had a great novelty character and importance in our meditation subjects. Our regression analysis into predictors of the long-term behavioural changes showed that the extent of self-dissolution and the drug administered substantially contributed to the global change in attitude and behaviour. Moreover, the experience of unity as an index of reduced self-other boundaries and oneness with the surrounding predicted self-acceptance. This temporary loss of the ordinary ego/self and self-boundaries appears to diminish self-referential processing or ego-centricity and thus to foster an altered perspective toward oneself, others, and the environment. This interpretation is supported by recent findings demonstrating that psilocybin modulates neuronal activity in brain networks that mediate a sense of self^{6, 84}. Furthermore, the sense of sacredness contributed to the change in appreciation of life, and sacredness and ineffability contributed to the change in quest for meaning/sense of purpose, across both groups independent of drug condition. These findings support the view that spiritual experiences, including sense of sacredness and ineffability, contribute to psychological well-being⁸⁵⁻⁸⁷ and act through meaning-making mechanisms^{88, 89}. In line with a recent large survey reporting that peak psychedelic experiences were linked to reduced fear of death⁷⁴, we found that psilocybin alone predicted the change in appreciation of death. This is also consistent with recent studies demonstrating that the extent

of psilocybin-occasioned mystical-type experience mediated the reduction of existential anxiety and depression in terminal cancer patients^{35, 39}.

The present study demonstrated that the combination of psilocybin and mindfulness training increased the incidence and intensity of alterations of consciousness characterized by profound states of self-dissolution and virtually no anxiety. Personality traits and core components of mindfulness-based meditation shaped the different facets of selflessness. The psilocybin-induced dissolution of self, either due to a perception of unity of all things and/or ego loss, mediated beneficial enduring changes in psychosocial functioning. The effect of psilocybin on meditation depth and trait mindfulness may increase the effective positive impact of meditation retreats on psychological outcome. Both meditation depth and higher levels of mindfulness have been linked to a wide range of well-being and mental health markers^{44, 90}. The present results also suggest that the combination of mindfulness training and psychedelic-assisted intervention may offer potential for the further development of psychedelic-assisted applications to improve well-being and health in both therapeutic and non-therapeutic settings.

Materials and methods

Participants

Participants were 39 expert Buddhist meditation practitioners. The study was advertised as an experiment investigating the effect of psilocybin on mindfulness practice embedded in a 5 day meditation retreat. Participants were recruited through flyers in local meditation communities and advertisements in professional Buddhist magazines devoted to meditation. In total, 202 individuals submitted written applications, of which 79 potentially eligible persons were further screened for criteria for participation over the phone. In the next screening stage, 54 were invited to the clinic for a medical check-up and psychological evaluation and 40 were finally qualified for the study. Participants were healthy according to medical history, physical examination, routine blood analysis, electrocardiography, and urine tests for drug abuse and pregnancy. The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland. Written informed consent was obtained from every participant before enrollment, and the study was performed according to the Declaration of Helsinki. See Supplemental Information for further information on screening procedures and participation criteria, and SI Table 1 for detailed sample characteristics.

Substance and dosing

The study was conducted using a double-blind, placebo-controlled, between-subject design. Psilocybin (315 µg/kg of body weight; body weight of subjects, 69.07 ± 12.07 kg; absolute dose, 21.76 ± 3.8 mg) and placebo (lactose) were administered in identical gelatin capsules. The high dose of psilocybin was chosen with reference to previous studies, in which a similar dose induced a significant change in consciousness without producing deep thought disturbances or complete loss of self-control⁴. The use of psilocybin according to the study protocol was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Bern.

Study procedures and setting

The 40 participants were randomly allocated to one of two groups (placebo, psilocybin) matched for age, gender, mindfulness level, meditation experience (quantified as lifetime hours of meditation practice), and retreat experience (quantified as number of attended retreats). One participant withdrew after the matching procedure. Two retreats at different times and following the same procedures with 16 (8 placebo/8 psilocybin) and 23 (11 placebo/12 psilocybin) subjects were conducted. During the retreat, the participants engaged in daily, structured meditation sessions in which they sat upright facing the wall, kept their eyes half open, and engaged in meditation practice. On day 4, participants in each group received either placebo or psilocybin, administered in a double-blind manner.

The retreats were held in a meditation center where, for 5 days, the participants lived and practiced meditation under the guidance of an experienced Zen teacher. All individuals followed a structured meditative discipline known in the Zen tradition as *sesshin*. The daily schedule consisted of a 15 hour highly structured program (from 0600 to 2100 h) including typical elements of mindfulness-based Zen practice: 8 × 30 min sitting meditation (*zazen*), 5 × 10 min indoor and 2 × 30 min outdoor walking meditation (*kinhin*), 75 min of mindful physical work (*samu*), interleaved with recitations, short rest breaks, and meals. The participants were instructed to observe silence during the whole retreat. Psilocybin and placebo were administered on the fourth day at 1030 h following a slightly adapted schedule containing additional musical elements and short relaxation periods. Thus, the retreat was conceptually divided into three phases: preparation (days 1-3), psilocybin/placebo administration (proper experience on day 4), and post-experience integration (day 5).

Trait mindfulness was evaluated the day preceding the retreat and the day following the retreat. State mindfulness and meditation depth were evaluated at the end of each day of the retreat (2100 h). Altered states of consciousness and mysticism were evaluated 360 min after drug administration.

Perceived changes in behaviours and attitudes were evaluated at follow-up, 4 months after the retreat. At this time point, participants also answered the question “*How personally meaningful was the experience made during the study?*” (1 - no more than everyday experiences; 2 - similar to meaningful experiences that occur on average once or more a week; 3 - once a month; 4 - once a year; 5 - once every 5 years; 6 - among the ten most meaningful experiences of my life; 7 - among the five most meaningful experiences of my life; 8 - the single most meaningful experience of my life)⁷. Additionally, each participant designated a closely related person with whom he/she had frequent contact since the retreat, such as a family member or close friend, who would likely notice changes in the participant’s behaviour and attitudes. This individual was asked to provide a third-person evaluation of changes (if any) in the participant’s behaviour and attitudes.

Baseline measures

At baseline, the following information was collected to characterize and enable matching of the study sample: socio-demographic data, meditation tradition, hours of formal meditation practice, history of drug use, Multiple Choice Vocabulary Test⁹¹ (verbal fluency intelligence), FMI⁹² long form (dispositional/trait mindfulness, completed with reference to preceding 2 months), Satisfaction with Life Scale⁹³, and Symptom Checklist-90-Revised⁹⁴. The last measure was used as a screening inventory to detect clinical symptoms and indicators of psychological distress, and was completed with reference to the last month.

Personality, absorption (propensity to become absorbed in experiences), dispositional optimism and pessimism, emotion regulation strategies, and the occurrence of primary mystical experiences over the course of a lifetime were also evaluated at baseline and considered in the analysis as possible predictors. Personality was evaluated using the NEO Five-Factor Inventory⁹⁵. This is a concise 60-item measure of five basic personality dimensions: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience. The propensity to become absorbed in experiences was evaluated using the Tellegen Absorption

Scale⁹⁶, which consists of 34 items. Dispositional optimism and pessimism were evaluated using the Life Orientation Test, Revised⁹⁷, which consists of ten items. Emotion regulation strategies were evaluated using the Emotion Regulation Questionnaire⁹⁸, which, by means of ten items, evaluates the habitual use of two emotion regulation strategies: cognitive reappraisal and expressive suppression. The occurrence of primary mystical experiences over the course of a lifetime was evaluated using the M-scale (lifetime version)⁹⁹. This 32-item questionnaire derives from Stace's common criteria of mysticism⁶⁸, and has been extensively used in the field of psychology of religion with well-documented reliability, validity, and cross-cultural generalizability^{100, 101}. The total score, ranging from 32 (least mystical) to 160 (most mystical), as well as three core dimensions and subdimensions were used for analysis¹⁰².

Outcome measures

Trait mindfulness

Trait mindfulness was evaluated the day preceding the retreat and the day following the retreat using the FMI short form¹⁰³. The FMI short form is a 14-item reliable instrument assessing the construct of mindfulness closely following Buddhist conceptualization. Mindfulness was treated as a one-dimensional construct, but separate factors of presence and acceptance were also used to refine the predictor analysis. The FMI was completed with reference to the previous 5 days.

State mindfulness

State mindfulness was evaluated on each day of the retreat using the TMS¹⁰⁴, a 13-item measure particularly well-suited to evaluate the level of mindfulness in those who actively practice it. It conceptualizes the construct as an intentional, reflective style of introspection or self-observation. The TMS was completed at the end of the evening meditation session (2100 h) with reference to the meditation practice of the corresponding day.

Meditation depth

Meditation depth was evaluated on each day of the retreat using the MEDEQ⁵³, which is a 30-item questionnaire designed to capture five aspects of meditation experience: hindrances (e.g., being restless), relaxation (e.g., feeling calm), concentration (e.g., being attentive and detached from emotions and thoughts), transpersonal qualities (e.g., feeling connected, bliss, and grace), and non-dual qualities (e.g., complete rest of thoughts and emotions, experiencing unity of all things). The global MEDEQ score was used for analysis. The instrument was completed at the end of the evening meditation session (2100 h) with reference to the meditation practice of the corresponding day.

Altered states of consciousness

Alteration of consciousness was evaluated 360 min after drug administration using the 5D-ASC⁶⁶. This measure comprises 94 visual-analogue items, each rated as a percentage score of a maximum scale value, and was used to quantify the experiential effects of the drug, compared with the placebo. The instrument is a well-validated tool for measuring etiology-independent altered states of consciousness and has been frequently used in previous studies with psilocybin. The global score, the five original scales, and the 11 empirically derived subscales¹⁰⁵ were quantified. The five original scales are as follows: [OB] Oceanic Boundlessness (derealization and depersonalization, positive affect, altered time perception), [AED] Anxious Ego Dissolution (personal disintegration, loss of self-control, anxiety, thought disturbances), [VR] Visual Restructuralization (visual hallucinations and imagery, synesthesia, changed meaning of percepts), [AA] Auditory Alterations (auditory illusions and hallucinations), and [VIR] Vigilance Reduction (changes in vigilance and alertness). This instrument was completed with reference to drug/placebo experience.

Mystical-type experiences

Mystical-type experiences were evaluated around 360 min after drug administration using the M-scale⁶⁴. This comprises three culture-independent core dimensions depicting eight faces of mystical-type experiences: extrovertive mysticism, comprising the sub-dimensions

unity of the world as one and inner subjectivity of all beings; introvertive mysticism comprising the sub-dimensions ego loss, timelessness/spacelessness, and ineffability of the experience; and interpretation, comprising the sub-dimensions positive affect, sacredness, and noetic quality. The interpretation dimension reflects a first interpretation of the mystical experience. The scale was found to be sensitive to the effects of psilocybin^{7, 32}. The following measures were used for analysis: total score, introvertive mysticism score (characterized by an inward-facing ego loss, time and spacelessness, and ineffability), extrovertive mysticism score (relating to the experience of unity of all things and inner subjectivity), interpretation score (referring to a positive mood, sacredness, and noetic quality)¹⁰², and score on each of the eight original sub-dimensions to allow for comparisons with earlier studies. This instrument was completed with reference to drug/placebo experience.

Changes in behaviour and attitudes

Changes in behaviour and attitudes associated with a possibly transformative event were evaluated at the follow-up time point, 4 months after the retreat, using the LCI-R¹⁰⁶. The LCI-R was originally used in the context of near-death experiences and adapted for the purpose of this study. The instrument consists of 50 items, each rated on a five-point Likert scale ranging from -2 (strongly decreased) to +2 (strongly increased). The items indicate the change in nine clusters (scales), and combine to create one total change score. Two versions of the instrument were used: a self-report version was completed by participants, and a third-person version was completed by the significant others. Both versions were completed with reference to the 4 month period since the completion of the study. All questionnaires were anonymized before analysis.

Statistical analysis

T-tests for independent samples and Pearson chi square tests were used to compare continuous and categorical variables, respectively, between the two groups (psilocybin, placebo) to evaluate matching.

A two-way repeated measures ANOVA with group (psilocybin, placebo) as a between-subject factor and dimension or subscale (when appropriate) as a within-subject factor was used to compare the score from each of the 5D-ASC rating, M-scale, and LCI-R (main scales and subscales of the 5D-ASC, dimensions and subdimensions of the M-scale, and their global/total scores). A two-way repeated measures ANOVA with group (psilocybin, placebo) as a between-subject factor and scale version (lifetime, acute) as a within-subject factor was used to compare the strongest mystical experience across lifespan with the acute psilocybin-induced experience in the study. A two-way repeated measures ANOVA with group (psilocybin, placebo) as a between-subject factor and time (days 1–5) as a within-subject factor was used to assess TMS score and MEDEQ score across the retreat. A two-way repeated measures ANOVA with group (psilocybin, placebo) as a between-subject factor and time (pre-retreat, post-retreat) as a within-subject factor was used to assess FMI score. When significant effects were found, post-hoc pairwise comparisons were performed using Tukey's HSD test.

Pearson's correlation was used to quantify the relation between score on each of the main scales of the 5D-ASC and each of the core dimensions of the M-scale, with p-values reported after correction for multiple comparisons (SI Fig. 2).

Backward-removal regression analyses were run to evaluate predictors of acute effects (global 5D-ASC score, total M-scale score, score on the OB, AED, and VR scales of the 5D-ASC, and score on the extrovertive mysticism, introvertive mysticism, and interpretation dimensions of the M-scale) and follow-up effects (change in attitudes and behaviours). Regression analyses for acute effects included the following predictors: age, neuroticism, extraversion, openness, absorption, optimism, lifetime mystical experience, presence and acceptance facets of mindfulness, suppression and reappraisal types of emotion regulation, mindfulness as state, and meditation depth on the day of pharmacological intervention, as well as group (placebo/psilocybin). Regression analyses for follow-up effects included the following

predictors: score on each of the eight sub-dimensions of the M-scale and group (placebo/psilocybin). The criterion for significance was set at $p < 0.05$.

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Author contributions

L.S. and M.K. designed the experiments. L.S., M.K., M.S., R.K., and T.H. performed the experiment. L.S. and F.X.V. analysed the data and wrote the manuscript. All authors further edited the paper and approved the final version of this manuscript.

Competing interests

The authors declare no competing interests.

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Supplemental Information

SI Table 1. Study population demographics, screening, and baseline measures

	Placebo group <i>n</i> = 19		Psilocybin group <i>n</i> = 20		χ^2	<i>p</i> -value
	N	%	N	%		
Sex					0.041	0.84
Male	11	57.9%	12	60.0%		
Female	8	42.1%	8	40.0%		
Meditation tradition ^a					0.005	0.95
Zen	16	84.2%	17	85.0%		
Vipassana	3	15.8%	3	15.0%		
Previous drug experience ^b						
None	10	52.6%	11	55.0%		
≤3 times, over 20 years ago	6	31.6%	4	20.0%		
≤3 times in the last 20 years	3	15.8%	5	25.0%		
	M	SE	M	SE	<i>t</i>	<i>p</i> -value
Age (years)	50.47	2.15	52.80	1.55	-0.88	0.383
Education (years)	15.42	0.81	14.75	1.04	0.50	0.618
Multiple Choice Vocabulary Test score ^c	124.53	3.66	119.55	3.17	1.03	0.309
Meditation experience						
Hours of meditation ^d	4826.3	1339.8	6155.0	1803.0	-0.59	0.561
Number of retreats ^e	30.58	11.16	31.60	6.60	-0.08	0.937
Freiburg Mindfulness Inventory (long form) score	88.89	1.90	92.50	2.04	-1.29	0.205
Tellegen Absorption Scale score	68.21	5.30	75.45	3.55	-1.15	0.259
NEO Five Factor Inventory score						
Neuroticism	2	0.18	2.02	0.18	-0.09	0.924
Extraversion	3.22	0.17	3.07	0.17	0.63	0.527
Openness	4.3	0.11	4.25	0.13	0.31	0.761
Life Orientation Test, Revised, score						
Optimism	8.37	0.43	8.70	0.54	-0.47	0.638
Meaning in Life Questionnaire score						

Presence of meaning	26.53	1.26	27.05	1.31	0.29	0.775
Search for meaning	22.95	1.78	22.00	1.95	-0.36	0.722
Emotion Regulation Questionnaire score						
Suppression	13.68	0.99	13.65	0.93	-0.11	0.909
Reappraisal	31.58	0.98	31.75	1.12	-0.21	0.831
Satisfaction With Life Scale score	25.16	0.91	26.25	1.26	0.69	0.491
Freiburg Mindfulness Inventory (short form) score						
Presence	19.16	0.49	19.35	0.57	-0.25	0.800
Acceptance	23.68	0.63	24.55	0.71	-0.91	0.367
Lifetime ASC ^f experience score (M-scale)	133.74	4.67	130.65	4.71	0.47	0.645
Symptom Checklist-90-R (Global Severity Index)	0.33	0.04	0.27	0.05	-0.91	0.371

M, mean; SE, standard error. *t*-values are from independent samples *t*-test, two tailed, for continuous variables and Pearson chi square test for categorical variables; *df* = 37.

^aThe only practiced or primary meditation tradition by participants.

^bPrevious experience with consciousness altering drugs (psilocybin, lysergic acid diethylamide (LSD), mescaline, N,N-Dimethyltryptamine (DMT), 3,4-Methylenedioxymethamphetamine (MDMA), ketamine and their derivatives; cannabis, and alcohol were not considered).

^cMeasure of verbal fluency intelligence.

^dTotal lifetime hours of formal meditation practice.

^eNumber of meditation retreats lasting at least 3 consecutive days (lifetime).

^fAltered states of consciousness.

Participants: screening details

The health screening included the Symptom Checklist-90-Revised¹, clinical anamnesis, somatic examination, electrocardiography, and detailed blood analysis. The structured Mini-International Neuropsychiatric Interview² was used to exclude potential axis I and II psychiatric disorders according to the DSM-IV diagnostic guidelines. Exclusion criteria were poor knowledge of German language, major somatic or neurological disorder, present or antecedent psychiatric disorder in the participant or a first-degree relative, alcohol or drug dependence or abuse, current or recent use of medication or drug affecting the nervous system, and pregnancy. Main inclusion criteria were age between 20 and 65 years, no or very limited exposure to hallucinogenic drugs, minimum of 500 hours of lifetime formal meditation practice, Mahayana (Zen) or Theravada (Vipassana) Buddhism as primary meditation background, familiarity with longer periods of meditation in a retreat setting, and for Vipassana practitioners, a previous exposure to Zen-specific elements of meditative discipline. The last criteria ensured that participants would likely comply with the study specific procedures and adapt to physical and emotional rigors of the demanding daily practice. Both Zen and Vipassana practitioners were included due to their resemblance: both are deeply rooted in Buddhist tradition, and both are founded on the cultivation of mindfulness (in Pāli: *sati*)³ and have developed a repertoire of similar mental techniques including sitting and walking meditation practices.

To detect a possible recent use of psychoactive substances, a urine test sensitive to amphetamines, benzodiazepines, tetrahydrocannabinol, cocaine, methadone, and opiate metabolites was performed on the first day of the study. For female participants, an additional urine check was conducted to exclude pregnancy. No test was positive for any of these markers. Forty individuals who met the predefined criteria were enrolled in the study. One person withdrew after randomization, and the remaining 39 took part in the experiment. All volunteers were informed about the study procedures and potential risks related to the use of psilocybin. Board and lodging for subjects during the study was free of charge, and study-related travel costs were compensated. No additional monetary incentive was offered for participation.

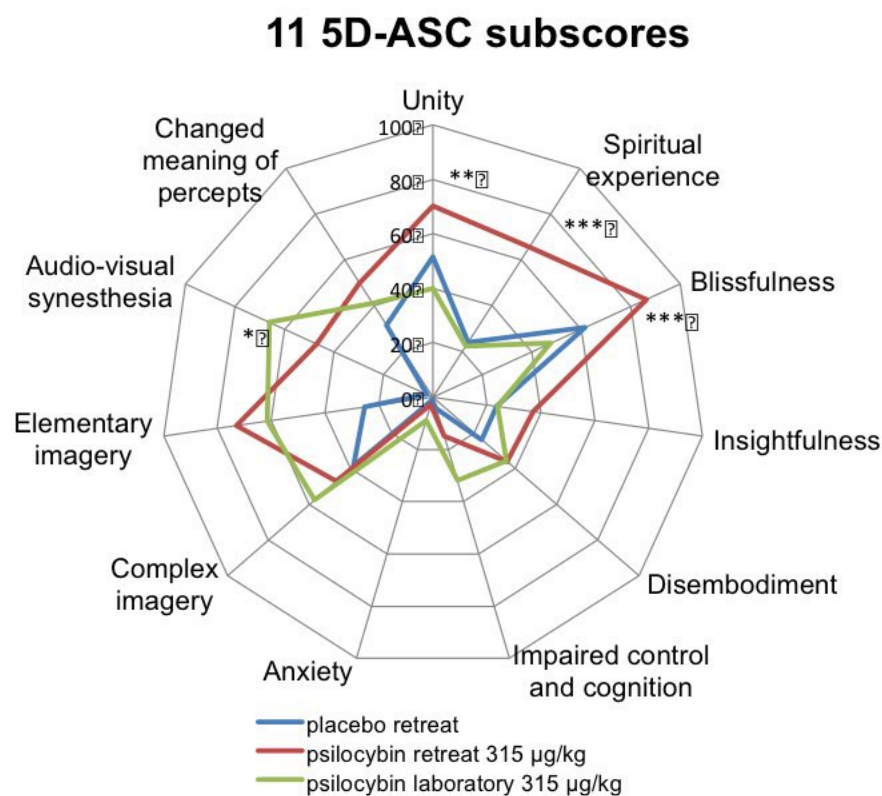
SI Table 2. Subjective effects measured using the Altered States of Consciousness Rating Scale (5D-ASC) and Mysticism Scale (M-scale)

Questionnaire	Scale / dimension	Placebo		Psilocybin	
		Mean (SE)	Range	Mean (SE)	Range
5D-ASC					
	Oceanic Boundlessness	10.94 (3.44)	0–47.81	62.95 (4.82)***	10.41–97.04
	Visionary Restructuralization	5.40 (2.21)	0–31.78	49.96 (4.61)***	5.94–81.67
	Anxious Ego Dissolution	1.74 (0.53)	0–9.53	7.59 (1.36)	0.95–24.90
	Auditory Alterations	1.65 (0.59)	0–9.44	10.88 (2.09)	0.88–33.44
	Vigilance Reduction	4.24 (1.38)	0–19.83	18.57 (2.77)*	6.42–52.75
M-scale					
	Extrovertive	25.37 (3.38)	12–60	52.65 (1.78)**	32–60
	Introvertive	15.42 (1.84)	8–40	30.10 (1.53)**	12–40
	Interpretation	29.84 (2.89)	16–60	52.90 (1.39)**	40–60

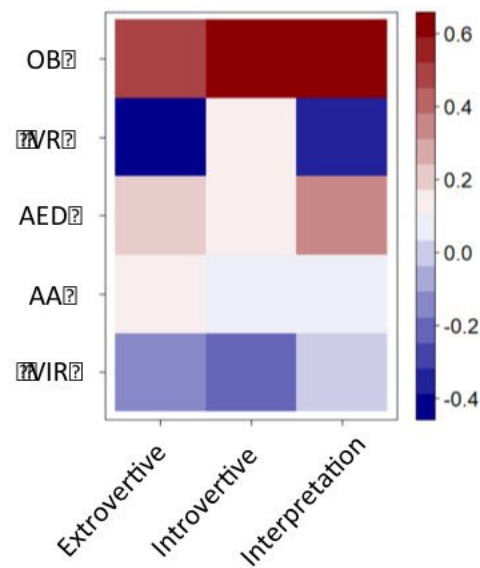
SE, standard error. Asterisks indicate significant differences between psilocybin and placebo groups (*** = $p < 0.0001$, ** = $p < 0.001$, * = $p < 0.05$).

Explorative comparison of setting effects

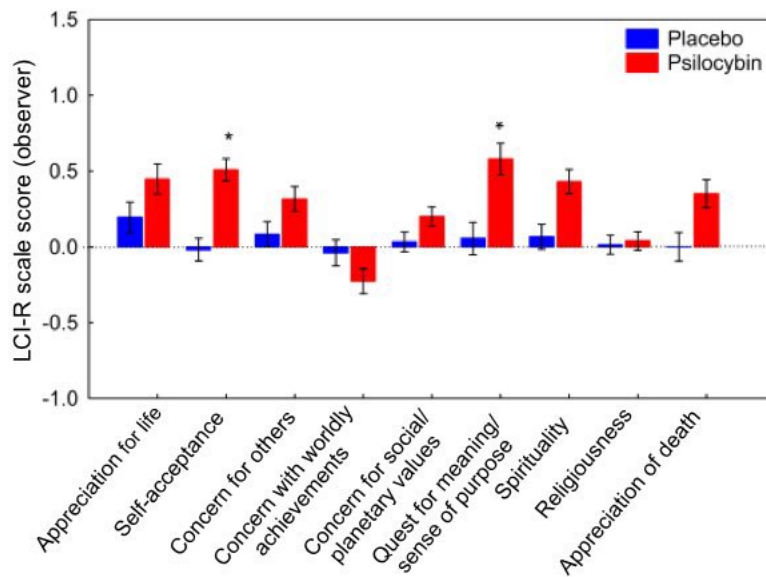
To further explore the putative synergistic effects of psilocybin and meditation, the score on each of the 11 5D-ASC subscales was compared between the psilocybin group in the present study ($n = 20$) and participants from a previous study on the effect of psilocybin in non-meditators who completed four simple neuropsychological tasks in a laboratory setting ($n = 20$)⁴. An explorative analysis of covariance with group (psilocybin retreat/psilocybin laboratory) as a between-subjects factor, 5D-ASC subscale score as a within-subject factor, and age as a covariate revealed a significant group \times subscale interaction ($F(10,350) = 2.09$, $p < 0.05$) with no main effect of age ($F(35,1) = 0.42$, $p = 0.52$). Post-hoc tests indicated that the scores for the unity, spiritual experiences, and blissfulness were higher for the psilocybin retreat group than for the psilocybin laboratory group, while the score for the audio-visual synesthesia was lower for the first group than for the second group (SI Fig. 1).



SI Figure 1. Radar chart comparing the score for each subscale of altered states of consciousness in the psilocybin retreat group ($n = 20$) and non-meditators who took the same dose of psilocybin ($n = 20$) in laboratory setting from our database⁴ (* = $p < 0.05$, ** = $p < 0.01$, *** $p < 0.001$). For further comparison, the scores of the three placebo subjects who met the a priori criteria for a strong mystical-type experience are also shown.



SI Figure 2. Correlations between scores on each dimension of the Altered States of Consciousness Rating Scale (5D-ASC) and M-scale. Score on the Oceanic Boundlessness (OB) scale of the 5D-ASC correlated significantly with the score on the extrovertive mysticism ($r = 0.47$), introvertive mysticism ($r = 0.59$), and interpretation ($r = 0.59$) dimensions of the M-scale (all $p < 0.01$). No other correlations were significant. VR, Visual Restructuralization; AED, Anxious Ego Dissolution; AA, Auditory Alterations; VIR, Vigilance Reduction.



SI Figure 3. Changes in attitude and behavior, evaluated by a significant other using the Life Changes Inventory, Revised, at 4 month follow-up. Bars are means and error bars indicate SEM (standard error of the mean). Asterisks indicate significant differences between psilocybin and placebo groups: * = $p < 0.01$.

SI Table 3. Meaningfulness of study experience

<i>How personally meaningful was the experience made during the study?</i>	Placebo group		Psilocybin group	
	<i>n</i> = 19	%	<i>n</i> = 20	%
1. No more than everyday experiences	1	5.3%	0	0%
2. Similar to meaningful experiences that occur on average once or more a week	1	5.3%	0	0%
3. Similar to meaningful experiences that occur on average once or more a month	7	36.8%	0	0%
4. Similar to meaningful experiences that occur on average once a year	4	21.1%	1	5%
5. Similar to meaningful experiences that occur on average once every 5 years	5	26.3%	2	10%
6. Among the ten most meaningful experiences of my life	1	5.3%	10	50%
7. Among the five most meaningful experiences of my life	0	0%	7	35%
8. The single most meaningful experience of my life	0	0%	0	0%

Percentage (%) and number (*n*) of participants rating the question on personal meaning of the overall retreat experience.

SI Table 4. Predictors of psychological responses evaluated using main scales of the 5D-ASC and main dimensions of the M-scale

	Oceanic Boundlessness				Anxious Ego Dissolution				Visual Restructuralization				Extrovertive Mysticism				Introvertive Mysticism				Interpretation										
Whole model	<i>R²adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <		<i>R²adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <		<i>R²adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <		<i>R²adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <		<i>R²adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <		<i>R²adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <		
	0.82	5,33	36.54	0.00001		0.41	2,36	14.27	0.0001		0.75	3,35	39.35	0.00001		0.69	4,34	22.63	0.00001		0.65	6,32	12.92	0.00001		0.80	8,30	20.16	0.00001		
Multiple Regression backward removal																															
	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η²</i>	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η²</i>	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η²</i>	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η²</i>	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η²</i>	<i>β</i>	<i>df</i>	<i>F</i>	<i>P</i> <	<i>η²</i>	
Predictor																															
Age																											0.26	1	10.76	0.01	0.26
Neuroticism																															
Extraversion											0.25	1	9.13	0.01	0.21																
Openness	0.19	1	7.12	0.01	0.18											0.21	1	4.84	0.05	0.12	0.22	1	4.82	0.05	0.13	0.20	1	6.62	0.05	0.18	
Absorption	0.18	1	4.41	0.05	0.12																										
Optimism	0.24	1	10.71	0.01	0.25						0.27	1	10.27	0.01	0.23	0.24	1	6.65	0.01	0.16	0.27	1	7.25	0.01	0.18	0.26	1	11.17	0.01	0.27	
Lifetime mysticism																0.31	1	11.56	0.01	0.25	0.29	1	7.84	0.01	0.20	0.22	1	5.94	0.05	0.17	
Mindfulness: Presence																										-0.19	1	4.19	0.05	0.12	
Mindfulness: Acceptance																					0.27	1	5.00	0.05	0.14	0.22	1	5.85	0.05	0.16	
Emotion Regulation: S																															
Emotion Regulation: R						-0.39	1	9.58	0.01	0.21											-0.30	1	6.29	0.05	0.16						
State Mindfulness*																															
Meditation Depth*	0.42	1	20.27	0.0001	0.38																					0.21	1	4.58	0.05	0.13	
Group placebo-psilocybin	0.68	1	84.18	0.00001	0.72	0.55	1	19.46	0.0001	0.35	0.81	1	98.73	0.00001	0.74	0.78	1	74.74	0.00001	0.69	0.69	1	48.76	0.00001	0.60	0.63	1	55.27	0.00001	0.65	

Note: *df*, degrees of freedom; *R²adj*, *R²* adjusted; *η²*, partial eta squared; *, drug session; R, Reappraisal; S, Suppression.

SI Table 5. M-scale dimensions as predictors of behavioral changes evaluated using the Life Changes Inventory, Revised

	LCI-R total score				LCI-R Appreciation for life				LCI-R Self-acceptance				LCI-R Quest for meaning				Appreciation of death								
Whole model	<i>R</i> ² <i>adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>R</i> ² <i>adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>R</i> ² <i>adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>R</i> ² <i>adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>R</i> ² <i>adj</i>	<i>df</i>	<i>F</i>	<i>p</i> <					
	0.48	2,36	18.70	0.00001	0.47	1,37	34.45	0.00001	0.30	1,37	17.64	0.001	0.49	2,36	19.58	0.00001	0.26	1,37	14.64	0.001					
Multiple Regression																									
backward removal																									
	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η</i> ²	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η</i> ²	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η</i> ²	<i>β</i>	<i>df</i>	<i>F</i>	<i>p</i> <	<i>η</i> ²					
Predictors																									
(M-Scale dimensions)																									
Inner subjectivity																									
Unity											0.57	1	17.64	0.001	0.32										
Time/Spacelessness																									
Ego loss	0.43	1	8.97	0.01	0.20																				
Ineffability																0.44	1	7.48	0.01	0.17					
Positive affect																									
Sacredness						0.69	1	34.45	0.00001	0.48											0.34	1	4.49	0.05	0.11
Noetic quality																									
Group placebo-psilocybin	0.37	1	6.44	0.05	0.15																0.53	1	14.64	0.001	0.28

Note: *df*, degree of freedom; *R*²*adj*, *R*² adjusted; η^2 , partial eta squared.

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