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Down the rabbit hole – the psychological and neural mechanisms of psychedelic compounds and their use in treating mental health and medical conditions

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Down the rabbit hole – the psychological and neural mechanisms of psychedelic compounds and their use in treating mental health and medical conditions

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Editorial: Down the rabbit hole – the psychological and neural mechanisms of psychedelic compounds and their use in treating mental health and medical conditions

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Editorial on the Research Topic

Down the rabbit hole – the psychological and neural mechanisms of psychedelic compounds and their use in treating mental health and medical conditions

Psychedelic substances have demonstrated promising therapeutic effects across a wide range of mental health conditions including depression (1–13) anxiety disorders including generalized anxiety (14–16) and social anxiety (17, 18) and autism (19), post-traumatic stress disorder (PTSD) (6, 20–23), and substance use disorders such as tobacco addiction (24) and alcoholism (25–30). These therapeutic effects are hypothesized to work through various mechanisms operating at different levels of analysis. At the cellular and molecular level, these include increased stimulation of the 5-HT2A serotonin receptor, increased cortical glutamatergic transmission, increased neuroplasticity, and decreased inflammation (31). At the network and circuit levels, the proposed mechanisms involve decreased brain modularity, changes in network functional connectivity, and increased neural entropy (32, 33). Psychologically and behaviorally, the effects are thought to involve increased cognitive and psychological flexibility, experiences of psychological insight, heightened emotional acceptance, and peak experiences or mystical-type states (34, 35). By further examining the neurobiological and psychological mechanisms of psychedelic substances, we can gain a deeper understanding of how these substances interact with the brain and influence behavior and help alleviate suffering in various psychopathologies.

This Research Topic aimed to highlight new interdisciplinary research on psychedelic substances, furthering our understanding of their mechanisms of action and their potential impact on clinical populations. By bringing together data from basic research, as well as clinical and interventional studies, this endeavor seeks to advance the field and pave the way for the responsible and evidence-based use of psychedelics in the realm of psychiatry and mental health.

To begin, several articles in the Research Topic examined the role of phenomenology as a putative mechanism underlying the therapeutic effects of psychedelics. For example, mystical experiences (i.e., characterized by transcendence of time and space, positive mood, and ineffability) can be reliably induced by psychedelics and have previously been linked to positive therapeutic outcomes across several studies (36). In this Research Topic, Mosurinjohn et al. contribute to the theoretical knowledge in this area by providing an interdisciplinary discussion and critique. The authors note how the discussion of mystical experiences in psychedelic literature has only been minimally informed by decades of research in relevant fields such as religious studies and anthropology. Specifically, by tracing the origins of mystical experiences in psychedelic research, the authors outline how the field has failed to acknowledge its perennialist and Christian bias. Although mystical experiences as currently defined and measured have been a useful construct for the field, the authors demonstrate that stronger interdisciplinary theoretical and empirical approaches are needed.

Further supporting the role of mystical experiences in positive therapeutic outcomes, Ortiz Bernal et al. examined reactivations (i.e., "flashbacks") after the use of 5-MeO-DMT in a non-clinical sample (N=513). Reactivations constitute a recurrence of specific aspects of the drug-induced experience after the effects of the drug have diminished. Being female, being older at the time of first 5-MeO-DMT dose, having higher educational attainment, and dosing in a structured group setting were all associated with increased probability of reporting a reactivation event. The authors also found that higher mystical experience scores were associated with neutral or positive emotional valence of a reactivation experience. The results suggest that reactivations were commonly reported, but were overwhelmingly perceived as positive or neutral experiences, suggesting they may contribute to therapeutic benefits rather than being adverse effects.

Another alteration in subjective experience that has been linked with psychedelics and may be relevant in long-term outcomes is ayahuasca-induced personal death (APD) experience. During an APD experience, an individual may experience a profoundly convincing sensation of imminent death or being deceased, so realistic that it is indistinguishable from actual death. In their paper delving into reports of ayahuasca users in ceremonies in South America, David et al. examined potential associations between APD experiences and individual characteristics (N=306). Interestingly, no association was found between demographics (age and gender), personality type or psychopathology and these death-like experiences which occurred in 50% of the participants in their sample. Nevertheless, APD experiences were correlated with increased self-reported environmental concern, ability to cope with distressing life events, and the sense of fulfillment in life, suggesting they may contribute to positive outcomes of the psychedelic experience.

Garel et al. also demonstrated how previous environmental stimuli such as exposure to social media, influence the experiences of patients (N=26) undergoing ketamine treatment for treatment-resistant depression (TRD). The authors introduce the concept of "imprinting" to explain time-lagged effects across various hallucinogenic drugs. Findings suggest that higher levels of media exposure prior to treatment reduce mystical/emotional qualities, altering subjective experiences. The study highlights the need to recognize and explore the role of past environmental factors in psychedelic therapy, proposing imprinting as a novel framework to enhance understanding and guide future research efforts.

Indeed, external factors may affect the subjective experience and use of psychedelics, as was explored in Bălăeț et al. during the COVID-19 pandemic. Data was collected between December 2019 and May 2020. Users (N=30,598) who consumed psychedelics and cannabis simultaneously during the pandemic reported decreased mood (over the past month from the time of assessment) compared to users who consumed cannabis without psychedelics or no substances at all. These results shed further light on the contextual and types of substances used to affect mood following psychedelic use.

One somewhat provocative suggestion is that experiencing the subjective perceptual effects related to psychedelics is in and of itself therapeutic. Kaup et al. explored this possibility by developing a virtual reality experience, Psyreal, that mimics the phenomenological components of psychedelic states. In an open-label feasibility study, 13 participants with mild-to-moderate depression underwent a 2-day Psyreal intervention. At the two-week follow-up, the researchers observed a significant decrease in depressive symptoms. Although limited by an open-label study design and small sample size, the results warrant further research on using psychedelic-like experiences induced by virtual reality for the treatment of psychological disorders.

Further substantiating the therapeutic effect of psychedelics on depression, Warner-Schmidt et al. showed that methylone, a rapid-acting entactogen, had a superior antidepressant effect compared to prototypical SSRI fluoxetine in preclinical animal models of antidepressant screening (N=16). Using the forced swim test in adult rats, a single dose of methylone alone reduced immobility by nearly 95% of the animals lasting for 72 hrs post injection compared to SSRI which reduced immobility by 50% lasting for one hour post injection. These results indicate that methylone might have a potential clinical benefit for treatment of depression.

Psychedelics are also beginning to be explored for novel treatment indications, such as attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), and Fibromyalgia. Haijen et al. explored the effects of microdosing of psilocybin on the behavior of individuals with ADHD in a large cohort of online participants (n=233). They found that trait mindfulness (i.e., description and non-judging of inner experience) was increased and neuroticism was decreased after 4 weeks of microdosing compared to baseline. The authors concluded that microdosing may have potential to induce changes in stable traits and suggest that a larger, controlled study would shed light on the therapeutic effects of microdosing on individuals with ADHD.

Ragnhildstveit et al. presented a case study of cannabis-assisted psychotherapy. They report that a female diagnosed with dissociative-PTSD (D-PTSD), a subtype of posttraumatic stress disorder, no longer met criteria for the disorder following the treatment. The patient experienced a common psychedelic phenomenon during the treatment - ego dissolution. This experience involves a profound loss of self-boundaries, merging with the environment. The experience of ego dissolution facilitated acceptance for this patient, which enabled the patient to access buried emotions and memories related to the trauma. Despite the study being limited to N=1, the case supports further study into cannabis-assisted psychotherapy as a tool for D-PTSD treatment.

Bornemann et al. describes a protocol for investigating the effects of psilocybin -assisted psychotherapy in fibromyalgia patients, aiming to understand its neural mechanisms using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). The findings aim to deepen the understanding of psilocybin therapy's neural mechanisms in fibromyalgia, which would benefit future studies on psychedelic therapy.

One paper in this Research Topic looked into the molecular mechanisms that underlie the effects of psychedelics. The study investigated the direct effects of classic psychedelics like LSD, psilocin, DMT, and mescaline on the immune function of human T cells and monocytes *in vitro* (Rudin et al.). Specifically, it examined whether these substances modulated T cell proliferation, cytokine release, and NF-κB induction in monocytes. The results showed no relevant immune-modulatory effects from any of the tested psychedelics on these immune parameters in the cell lines studied. This suggests classic psychedelics do not directly suppress immune function, supporting their potential safe therapeutic use in patients where diminished immunity would be detrimental.

In conclusion, the Research Topic provides an interdisciplinary overview of recent research on the neurobiological and psychological mechanisms of psychedelic substances, highlighting several key findings. Mystical experiences induced by psychedelics are linked to positive therapeutic outcomes but require deeper theoretical examination across disciplines. Contextual factors like prior media exposure and substance combinations significantly influence psychedelic experiences, which should be accounted for in future research and clinical applications. Novel psychedelic substances, as well as non-pharmacological simulations of psychedelic effects, show promise for treating psychiatric conditions like depression. At the same time, psychedelics may also benefit disorders like ADHD, PTSD, and fibromyalgia, though more clinical research is needed. Importantly, *in vitro* studies suggest psychedelics may not have concerning immunosuppressive effects, supporting their safe implementation. Overall, this Research Topic demonstrates the value of an interdisciplinary approach to understanding and responsibly harnessing the complex therapeutic potential of psychedelics in helping individuals to cope and heal from mental illness.

Author contributions

LP: Writing – original draft, Writing – review & editing. JA: Writing – original draft, Writing – review & editing. AK: Writing – original draft, Writing – review & editing. HH: Writing – review & editing. JW: Writing – review & editing.

Conflict of interest

Author AK was employed by company NLC Health Ventures.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Reactivations after 5-methoxy-N,N-dimethyltryptamine use in naturalistic settings: An initial exploratory analysis of the phenomenon's predictors and its emotional valence

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Background: The psychedelic 5-MeO-DMT has shown clinical potential due to its short duration and ability to induce mystical experiences. However, a phenomenon known as "reactivations" (similar to "flashbacks") is a poorly understood and frequently reported phenomenon which appears associated with 5-MeO-DMT use and warranted further investigation.

Aims: This study examined whether differences in age, gender, education, lifetime use, use location, and preparation strategies predict reactivations (primary outcome). Additionally, we explored how reactivations were perceived by survey respondents and whether demographic data predicted emotional valence (secondary outcome) of reported reactivations.

Materials and methods: This study used secondary quantitative data from a survey assessing epidemiological and behavioral associations of 5-MeO-DMT use in non-clinical settings (N = 513). Descriptive statistics, chi-square tests, t-tests, and logistic regressions were utilized to explore aims.

Results: Being female, older at the time of first 5-MeO-DMT dose, having higher educational attainment, and dosing in a structured group setting were associated with increased odds of reporting a reactivation event. Higher mystical experience scores, greater personal wellbeing and having had a non-dual awareness experience that was not substance-induced were associated with higher likelihood of reporting a neutral or positive emotional valence of a reactivation event.

Conclusion: These findings suggest that reactivation phenomena, in this particular sample may most often represent a neutral or positive byproduct

of the acute 5-MeO-DMT experience. More information is needed to best identify individuals most likely to experience a reactivation as a negative event to prevent such potential challenging outcomes.

KEYWORDS

5-methoxy-N, N-dimethyltryptamine, 5-MeO-DMT, reactivation, flashback, wellbeing

Introduction

Recent years have seen renewed interest in the use of psychedelic substances for treating various psychiatric conditions. Psilocybin has been most extensively studied, with small-scale academic studies reporting efficacy for depression and anxiety (1–9), and substance use disorders (10–14). Despite these promising results, a challenge facing the clinical uptake of psilocybin and other agents with protracted acute psychedelic effects is the amount of time and clinical resources a well conducted therapy session entails (15). This may represent a logistical and financial roadblock to making this type of therapy available in an affordable way, especially for underserved populations, highlighting the need to identify alternative options that could elicit a shorter acute psychedelic effect while maintaining comparable long-term therapeutic benefits.

One short-acting psychedelic that has the potential to fill this role is 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). 5-MeO-DMT is a non-selective serotonin agonist with high affinity for the 5-HT1A receptor, and less affinity for the 5-HT2A and 5-HT2C receptor subtypes (16, 17). 5-MeO-DMT is found in numerous plants and in large quantities in the defense secretions of the *Incilius alvarius* toad, endemic to the Sonoran Desert (18–22). 5-MeO-DMT induces a much shorter altered-state experience, on the order of 20–60 min (23, 24), as opposed to ∼6 h for psilocybin, ∼12 h for LSD (25) and ∼8–12 h for mescaline (26). Preliminary evidence indicates that 5-MeO-DMT has the potential to ameliorate mental health disorders and improve wellbeing (21, 27). A recent survey on the epidemiology of 5-MeO-DMT showed that many respondents reported improvements in anxiety, depression, substance misuse and posttraumatic-stress-disorder (15, 27) following 5-MeO-DMT use in naturalistic settings.

Pre-clinical data offer evidence of 5-MeO-DMT's anti-inflammatory, neuro-regenerative and anti-addictive potential through its interaction with Sigma 1 receptors, as well of its effects on glutamate receptors (16, 17, 28), both of which may have relevance in the treatment of mental health disorders. Moreover, despite the significantly reduced period of psychedelic effects compared to most other psychedelic compounds in development, a low to moderate dose of 5-MeO-DMT reliably induced a mystical experience of similar intensity to a high-dose of psilocybin administered in clinical settings (29). This is of therapeutic significance given that the occurrence of mystical experiences has been consistently associated with positive long-term outcomes (5, 14, 30–34). Taken together, these findings point to the potential role of 5-MeO-DMT as a therapeutic tool, and a viable alternative to circumvent the challenges inherent in the clinical use of longer-acting psychedelics.

However, epidemiological data (15), as well as anecdotal reports in online forums and social media groups (35, 36) indicate that the use of 5-MeO-DMT is associated with the frequent occurrence of a complex and not well understood phenomenon that has been termed "reactivation." The term reactivation is similar to the 1960's term "flashback," which is defined as "a reexperiencing of certain elements of the drug induced state *after* the drug's effects have worn off" (37, 38).

Descriptions of flashbacks include perceptual, somatic, or emotional sensations that were first experienced during the acute psychedelic state. These transient after-effects have been described as ranging from delusions to pleasant bodily sensations and perceptual illusions, to feelings of serenity, relaxation, and a sense of being "one with the world" (39).

The DSM-5 includes a similar phenomenon by the name of Hallucinogen Persisting Perceptual Disorder (HPPD) (40), and it distinguishes two subtypes of HPPD: Type 1 and Type 2. Type 1 is characterized by brief, benign, intermittent re-experiences of some aspect of the altered state induced by the psychedelic that may appear days or months after the psychedelic was taken (40). Type 2 is a radically different condition in which the re-experiencing of some aspect of the altered state generates significant distress in terms of individual, familial, social, or occupational areas of functioning on an on-going basis (41).

Flashbacks were a contributing factor to the 1970's political banning of psychedelics (42). As such, the reported incidence of flashback-like reactivation phenomenon associated with 5-MeO-DMT use, and the phenomenon's unknown emotional valence could potentially hinder 5-MeO-DMT's viability as a therapeutic modality.

To help advance future clinical applications of 5-MeO-DMT, and to better understand and characterize reactivations, this study aimed to examine prevalence rates as well as predictors associated with this phenomenon. Additionally, we

conducted an initial exploration of the phenomenon's emotional valence (i.e., whether it was perceived as a positive, neutral, or negative experience).

Demographic variables (i.e., educational attainment, age at first dose, gender) and variables related to the intensity of past drug use (i.e., lifetime use, frequency of dose) used in the present study were chosen based on a review of the literature on the flashback phenomenon from the 1970's, (37–39).

The variables grouped under the header of "preparation" in **Tables 3**, **4** were selected based on the idea that the longer one planned ahead for a 5-MeO-DMT experience, the more mindful and engaged in a process of self-directed positive growth one was, and wanted to see if this may be associated with reactivation experiences. The harm reduction, or as they have been called in the literature "benefit enhancement strategies" (43) of setting an intention, meditating prior to the experience, obtaining drug from a trusted source, and abstaining from using other drugs were also selected as indicators of a deliberate thoughtful process of carefully preparing for the 5-MeO-DMT experience and wanted to explore if use of these strategies was associated with an increased likelihood of reactivation experiences, and their reported emotional valence.

The variables included under the header of "salience of experience" were chosen based on the preliminary idea that higher scores on the Mystical Experiences Questionnaire, as well as higher ratings of personal meaning and life satisfaction as measured by the Persisting Effects Questionnaire items included would be predictive of higher likelihood of reactivation experiences and positive/neutral emotional valence.

The variable assessing a person's tendency toward experiencing non-drug induced altered states (non-dual sober) was included based on the observation by Heaton and Victor (37) that flashbacks may be caused "not by psychedelic drugs but by the tendency of some drug users to mislabel and selectively attend to aspects of naturally occurring altered states of consciousness which are reminiscent of psychedelic drug states." In this study we wanted to explore if someone that tends to experience non-dual states of awareness without using substances, would report a higher likelihood of reactivation experiences. Lastly, the variable that assesses quality of life was included to examine how the incidence of reactivation events may be associated with perceived satisfaction with life.

Materials and methods

Study procedure

This study used secondary data from a survey assessing epidemiological and behavioral associations of 5-MeO-DMT use in non-clinical settings (15). This study was deemed exempt from IRB review from Bowling Green State University. Each respondent was presented with a consent document, a statement regarding the purpose of the study, and eligibility criteria after clicking the link for the secure survey (hosted on surveygizmo.com). No identifying information was collected. Recruitment took place from April 2017 to August 2017. Survey respondents were English-speaking individuals who had used 5-MeO-DMT at least once during their lifetime. All survey participants in the parent study who reported using synthetic 5-MeO-DMT were eligible for this study. Potential respondents came from two different subsamples recruited at the same time:

Subsample 1 ("Structured group") was recruited using an email distribution list of people in the US who used 5-MeO-DMT in a structured ceremonial group context. A detailed description of this subsample is documented elsewhere (27). Briefly, the group used laboratory-tested synthetic 5-MeO-DMT and administered it following procedures that are similar to those used in research studies with psychedelics (i.e., preparation, integration). An administrator of the group's email distribution list sent an email with a recruitment notice for the online survey.

Subsample 2 ("General population") was recruited using online advertisements and consists of individuals from the general population who reported using 5-MeO-DMT in non-structured settings (e.g., their home/apartment, outdoors). A detailed description of this sample is documented elsewhere (15). In brief, survey advertisements were posted on sites such as bluelight.org, erowid.org, and 5meodmt.org.

The present study includes 344 respondents from subsample 1 and 216 respondents from subsample 2. After excluding respondents with missing data, our final analytic sample consisted of a total of 513 respondents (Structured group subsample n = 344; General population subsample n = 169). The full survey and data are available upon request.

Measures

Primary and secondary outcome measures for the current study were prevalence of reactivation events and emotional valence of these events when they occurred. To assess these outcomes, the following questions were administered:

> *-Have you had a spontaneous re-experiencing or re-activation of a past 5-MeO-DMT experience after using the medicine (e.g., a flashback or a feeling as though your 5-MeO-DMT experience is happening again? (No/Yes)*. Those who answered yes, were further asked:
> *-Was it a negative, neutral, or positive experience? (Negative vs. Neutral/Positive).*

Predictors of reactivation and emotional valence included demographic information, preparation steps, use patterns, mystical experience phenomenology, and meaningfulness,

propensity to experience non-dual states, and personal wellbeing. Respondents self-reported their demographic information including age, sex (male, female), age at first 5-MeO-DMT dose, (range: 20–50) and education (High school/Some college vs. bachelor's or higher).

Preparation steps individuals took prior to 5-MeO-DMT administration were assessed with an item asking, *"How far in advance do you typically plan before a 5-MeO-DMT session?"* Originally recorded categorically (I do not plan, a few days, a week, a month, or more) was coded numerically as 0, 3, 7, and 30, respectively, for the regression analyses. The use of a series of benefit enhancement strategies (43) were also assessed, including *setting an intention for the 5-MeO-DMT session, meditating prior to the session, obtaining 5-MeO-DMT from a trusted source, and abstaining from alcohol and other drugs prior to the 5-MeO-DMT session* (No/Yes).

Data regarding 5-MeO-DMT use patterns were originally recorded as categorical variables: Lifetime number of 5-MeO-DMT doses (1–2, 3–4, 5–10, 11+), frequency of dose (only once, about once per year, less than once per month but more than once per year, about once per month) but were transformed to continuous variables for regression analyses by taking the floor of each category. Re-dose frequency (i.e., taking a second dose of 5-MeO-DMT within a single session) was also assessed (No/Yes). An item asking "*When was the last time you used 5-MeO-DMT*?" (Last use), originally recorded as a categorical variable (within the past month, between one and six months ago, between 6 and 12 months ago, more than 12 months ago) was coded as 0 for the category "within the last month" and using the floor option for the rest of the categories, (i.e., 1 for within one and 6 months, 6 for within 6 and 12 months) for regression analyses.

Mystical-type experiences were assessed using the Mystical Experiences Questionnaire (MEQ30), a valid and reliable 30-item self-report measure (44). The MEQ30 is scored using a 6-point Likert scale that ranges from "None, not at all" to "extreme." For this study, we used a total MEQ mean score. Higher scores indicate stronger mystical experience. Internal consistency of the total scale was excellent (Cronbach's alpha = 0.97).

Perceived impact of the 5-MeO-DMT experience on personal wellbeing was assessed with the question "*Do you believe that your first experience with 5-MeO-DMT and your contemplation of that experience have led to change in your current sense of personal wellbeing or life satisfaction?*" This item was scored with a 7-point Likert scale ranging from "Increased very much" to Decreased very much" (range −3 to 3). Meaningfulness of the experience was assessed with the question *"Overall, how personally meaningful was your first experience with 5-MeO-DMT?"* This item was scored with an 8-point Likert scale ranging from "No more than routine, everyday experiences" to "The single most meaningful experience of my life" (range 0–7).

Propensity to experience drug-free altered states of consciousness was assessed with the question: *"Do you have any experiences with non-dual states of consciousness (e.g., transcendental, or unitary states) that were not induced by substance use?"* (No, Yes, Unsure).

Lastly, the Subjective Wellbeing and Life Satisfaction (SWLS) scale was used to measure global cognitive judgment of their life as a whole in relationship to a self-imposed ideal using five items (45). The SWLS is a 5-item instrument that is scored on a 7-point Likert scale that ranges from "Strongly disagree" to "Strongly agree" (range −3 to 3), with higher scores denoting higher levels of wellbeing and life satisfaction. Internal consistency of this scale was good (Cronbach's alpha = 0.86).

Statistical analysis

Data analysis for this project proceeded in five stages. First, descriptive statistics were examined. Second, chi-square tests and *t*-tests were conducted to explore differences in age, gender, education, lifetime use, use location, preparation strategies, etc., between study subsamples ($p < 0.05$ level). Third, the primary outcome variable (reactivation: yes/no) was regressed on each individual predictor variable to assess bivariate relations using logistic regression.

The secondary outcome (emotional valence) was also regressed on each individual predictor variable. Fourth, the interaction term between the predictor and study subsample (structured group vs. general population) was included in each bivariate regression to determine whether the bivariate association was moderated by the context in which 5-MeO-DMT was consumed. Emotional valence was also regressed on each predictor variable and the interaction of that predictor variable and the study sample. Fifth, reactivation and emotional valence were regressed on all 18 predictor variables simultaneously to determine which predictor variables accounted for unique variance in the outcome, while controlling for all other predictor variables in the model. Effect sizes for-significant tests and chi-square results were calculated using the Cohen's *d* statistic and Cramer's *v* statistic, respectively. Given the exploratory nature of this study no adjustments were made for multiple comparisons. Analyses were conducted using Stata 15 (46).

Results

Descriptive statistics

The demographic characteristics of participants are shown in **Table 1**. On average, study participants were 43 years old, about two thirds of the sample were male. Twenty nine percent of participants were between 18 and 29 years old when they

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TABLE 1 Demographic characteristics of study participants.

Characteristic	Total sample $n = 513$ M (SD) or %	Structured group $n = 344$ M (SD) or %	General population $n = 169$ M (SD) or %	P-value t-test/Pearson X^2	Cohen's Cramer's v
Age	43.8 (14.0)	47.8 (13.3)	35.7 (11.86)	<0.001	−0.94
Sex				<0.001	0.3
Male	66.2	54.6	89.7		
Female	33.7	45.3	10.0		
Age at first dose				<0.001	−1.3
18–29	29.2	10.7	66.8		
30–39	24.5	28.4	16.5		
40–49	21.8	26.7	11.8		
50+	24.3	34.0	4.7		
Highest education				<0.001	−0.7
High school or less	8.3	4.3	16.5		
Some college, no degree	21.2	15.1	33.7		
Associate's degree	5.4	4.9	6.5		
Bachelor's degree	34.5	39.2	24.5		
Advanced degree (MA/MS, PhD, MD)	30.4	36.3	18.3		

first tried 5-MeO-DMT and about 65% had a bachelor's or higher educational degree. Effect sizes for variables that were significantly different between subsamples (structured group vs. general population subsamples) are noted on Table 1.

As Shown in Table 2, context of 5-MeO-DMT use (structured group subsample vs. general population subsample) was associated with numerous between-group differences, including differences in the prevalence of reactivation events. In the structured group subsample, 73% of participants reported having a reactivation event. In the general population subsample, 27% of participants reported having a reactivation event. In the structured group subsample, 86% of respondents reported their reactivation event as positive, 10% as neutral and 4% of respondents reported their reactivation event as negative. In the general population subsample 73% indicated their reactivation event had been positive, 20% said it was neutral and 7% reported their reactivation event had been negative.

Reactivation

Results of bivariate and multivariable logistic regression analyses for reactivation are shown on Table 3. In the bivariate analyses, being a female, older age at the time of first 5-MeO-DMT dose, higher educational attainment, and being in the structured group subsample were significantly associated with increased odds of reporting a reactivation event. Interaction tests indicated that age at first dose and time since last use were moderated by study subsample such that being older at first dose and longer time since last use was more strongly associated with higher likelihood of reporting a reactivation in the structured group subsample compared to reporting a reactivation in the general population subsample.

In the multivariable model, females were about twice as likely to report reactivation events (OR = 1.82, CI: 1.11–2.99, $p = 0.016$). Using 5-MeO-DMT in the structured group setting (OR = 2.28, CI: 1.19–4.39, $p = 0.013$), planned ahead time (OR = 1.02, CI: 1.00–1.04, $p = 0.006$) and greater meaningfulness of the 5-MeO-DMT experience (OR = 1.27, CI: 1.04–1.55, $p = 0.015$) were significantly associated with an increased likelihood of reporting a reactivation event, while longer time since the last 5-MeO-DMT use (OR = 0.94, CI: 0.90–0.98, $p = 0.007$) was associated with a decreased likelihood of reporting a reactivation event.

Emotional valence

Table 4 shows bivariate and multivariable results of logistic regression analyses of the emotional valence attributed to the reactivation event. In the bivariate analyses longer time since the last 5-MeO-DMT use was associated with a decreased likelihood of reporting a neutral or positive reactivation event. Higher mystical experience scores, greater personal wellbeing, and having had a non-dual awareness experience that was not substance-induced were significantly associated with higher likelihood of reporting neutral or positive emotional valence of a reactivation event. The interaction tests indicated that current personal wellbeing was moderated by study subsample, such that greater wellbeing was more strongly associated with higher likelihood of reactivations being reported as neutral/positive in the structured group. In the general population there was no association

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TABLE 2 Distribution of variables by group (n = 513).

Independent variables	Structured group n = 344			General population n = 169		
	Mean/%	*SD*	*Range*	*Mean/%*	*SD*	*Range*
Preparation						
Planned time ahead (days)	22.29	11.89	0–30	5.13	8.66	0–30
Set an intention for the experience	0.88	0.32	0–1	0.60	0.49	0–1
Meditated prior to the experience	0.55	0.49	0–1	0.33	0.47	0–1
Obtained drug from a trusted source	0.91	0.27	0–1	0.66	0.47	0–1
Abstained from using other drugs	0.68	0.46	0–1	0.41	0.49	0–1
5-MeO-DMT use patterns						
Lifetime number of doses	3.16	3.05	1–11	5.97	3.87	1–11
Frequency of dose	1.93	0.80	1–4	2.52	0.74	1–11
Re-dose frequency*	0.51	0.50	0–1	0.52	0.50	0–1
Last use (months since last use)	6.28	5.3	0–12	7.52	5.38	0–12
Salience of 5-MeO-DMT experience						
Mystical Experience Questionnaire	4.29	0.90	0–5	3.41	1.25	0.1666–5
PEQ–wellbeing	2.33	1.01	−3–3	1.53	1.19	−3–3
PEQ–meaningfulness	5.79	1.05	0–7	4.56	1.91	0–7
Other						
Non-dual experience while sober						
Yes	0.66	0.47	0–1	0.40	0.49	0–1
Unsure	0.15	0.36	0–1	0.20	0.40	0–1
Satisfaction with life scale	1.11	1.35	−3–3	0.30	1.44	−3–3

*A second dose within single 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) session. PEQ, Persistent Effects Questionnaire. T-test/Pearson X^2 p-$value$ is < 0.001 on all variables except "Re-dose frequency" (0.847), and "Last use" (0.014).

between greater wellbeing and positive/neutral emotional valence.

In the multivariable model older age at first dose (OR = 0.88, CI: 79–0.99, p = 0.041) and longer time since last 5-MeO-DMT use (OR = 0.71, CI: 0.56–0.94, p = 0.008) decreased the likelihood, while being in the structured subsample (OR = 16.14, CI: 1.34–194.32, p = 0.028), a higher score on personal wellbeing (OR = 2.86, CI: 1.49–5.48, p = 0.002) and having had a non-dual experience that was not drug-induced (OR = 9.32, CI: 1.20–72.10, p = 0.032) significantly increased the likelihood of positive or neutral emotional valence of reactivation events. Study group was not associated with emotional valence of reactivation events.

Discussion

To begin to examine the 5-MeO-DMT reactivation phenomenon and how it may compare to the better-known LSD-related flashback and HPPD, in the present study we conducted an initial exploratory analysis of the prevalence, predictors and emotional valence of reactivation phenomena associated with the use of synthetic 5-MeO-DMT in two separate study subsamples. We found a statistically significant difference in the rate of reactivations reported between the study subsamples (73% in the structured group subsample vs. 27% in the general population subsample). Nearly all survey respondents indicated that their reactivation experiences were positive or neutral (96% in the structured group subsample and 93% in the general population subsample). Having taken the substance in the structured group setting, and being a female showed the strongest independent effects on predicting reports of reactivation. To our knowledge, this study is the first to show that context of use and female sex may increase the likelihood of reactivation phenomena associated with synthetic 5-MeO-DMT use.

In several review papers of the LSD-related flashback phenomena this sex difference is not noted (40, 47). Furthermore, Baggott et al. (48) conducted an online survey study to document flashback phenomena in a large sample of users who reported having used LSD, psilocybin, and several other drugs, and although this sex difference was not noted there either, the authors report that almost 90% of the sample were male (compared to 68% in the present study). Therefore, it could be that when survey samples include more females this phenomenon is more apparent. Future studies should focus on exploring this topic specifically among females to better understand this phenomenon of the 5-MeO-DMT experience. The finding that neither number of lifetime doses,

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TABLE 3 Relationships between independent variables and occurrence of reactivation following use of synthetic 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in naturalistic settings (n = 513).

Variables	Bivariate effects			Multivariate effects		
	OR	*95% CI*	*P-value*	*OR*	*95% CI*	*P-value*
Demographics						
Sex (ref = male)	3.16	2.11–4.75	0.000	1.82	1.11–2.99	0.016
Age at first dose (ref = younger age)	1.05	1.03–1.06	0.000	1.00	0.97–1.02	0.967
Education (ref = lower education)	2.47	1.70–3.59	0.000	1.41	0.88–2.83	0.150
Context of use						
Study population (ref = general population)	7.43	4.90–11.24	0.000	2.28	1.19–4.39	0.013
Preparation						
Planned time ahead (days)	1.06	1.04–1.07	0.000	1.02	1.00–1.04	0.006
Set an intention for the experience (ref = no)	2.58	1.67–4.00	0.000	0.77	0.42–1.43	0.419
Meditated prior to the experience (ref = no)	2.21	1.54–3.17	0.000	1.42	0.89–2.28	0.140
Obtained drug from a trusted source (ref = no)	1.93	1.20–3.10	0.005	0.52	0.26–1.00	0.051
Abstained from using other drugs (ref = no)	2.10	1.47–3.02	0.000	1.29	0.80–2.07	0.292
5-MeO-DMT use patterns						
Lifetime number of doses	0.89	0.85–0.94	0.000	0.95	0.88–1.03	0.265
Frequency of dose	0.79	0.63 –0.97	0.030	1.04	0.74–1.46	0.804
Re-dose frequency*	1.16	0.81–1.64	0.404	1.17	0.74–1.87	0.488
Last use (months since last use)	0.93	0.90–0.96	0.000	0.94	0.90–0.98	0.007
Salience of 5-MeO-DMT experience						
Mystical Experience Questionnaire	1.98	1.62–2.42	0.000	1.26	0.97–1.63	0.082
PEQ–wellbeing	1.68	1.45–1.94	0.000	1.02	0.82–1.29	0.800
PEQ–meaningfulness	1.68	1.45–1.94	0.000	1.27	1.04–1.55	0.015
Other						
Non-dual experience while sober						
Yes	2.81	1.83–4.31	0.000	1.63	0.94–2.82	0.081
Unsure	1.94	1.12–3.37	0.017	1.67	0.86–3.24	0.129
Satisfaction with life scale	1.34	1.18–1.52	0.000	1.07	0.91–1.25	0.396

*A second dose within single 5-MeO-DMT session. PEQ, Persistent Effects Questionnaire.

nor frequency of dosing increased the odds of reactivation phenomena is consistent with data from the 1970's on the prevalence of flashbacks (37, 49).

It is notable that nearly all participants who reported a reactivation in the current study perceived it as a positive experience. This observation suggests that the reactivation phenomenon might be conceptualized not as an adverse effect, but rather as neutral or positive byproduct of the acute 5-MeO-DMT experience when administered in certain settings. It is possible that reactivations may even contribute to the antidepressant and anti-anxiety effects that have been published previously (15, 17, 21). Indeed, that the greater length of time an individual planned for their 5-MeO-DMT experience, the greater their report of meaning attributed to their 5-MeO-DMT experience, and the higher the odds of reactivation, could be indicative of an intentional self-directed behavior process facilitated by the use of 5-MeO-DMT.

In this sense, these initial findings would seem to suggest that 5-MeO-DMT reactivations may be considered to be more akin to HPPD Type 1, as opposed to Type 2 (40), but these findings are preliminary and limited by the nature of the study (i.e., selection bias potentially leading to the high rate of positive valence, and the retrospective nature of the cross-sectional survey design). Furthermore, there are anecdotal reports from individuals who do struggle with reactivations for weeks after a high-dose of toad-derived 5-MeO-DMT that have been reported in online forums (i.e., 5-Hive) which would be indicative of HPPD Type 2. Based on the few online anecdotal reports, it seems that people who are more likely to struggle with reactivations longer term are those that receive an unweighted and hence, likely higher than needed dose of 5-MeO-DMT derived from toad secretions. Unfortunately, in this study, we did not have data regarding dosage to examine whether higher doses would show higher odds of reactivations compared to lower or moderate doses.

The differential prevalence rates of reactivation among our study samples seem consistent with findings from early reports of flashback prevalence rates among psychedelic users. These

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TABLE 4 Relationships between independent variables and neutral or positive emotional valence of reactivation experiences (n = 295).

Variables	Bivariate effects			Multivariate effects		
	OR	*95% CI*	*P-value*	*OR*	*95% CI*	*P-value*
Demographics						
Sex (ref = male)	0.77	0.24–2.44	0.673	0.34	0.05–2.05	0.241
Age at first dose of 5-MeO-DMT	0.96	0.91–1.02	0.282	0.88	0.79–0.99	0.041
Education (ref = lower education)	0.92	0.24–3.50	0.908	1.67	0.19–14.07	0.636
Context of use						
Study population (ref = general population)	1.91	0.49–7.35	0.345	16.14	0.1.34–194.32	0.028
Preparation						
Planned time ahead (days)	1.00	0.95–1.04	0.954	0.97	0.89–1.04	0.450
Set an intention for the experience (ref = No)	3.22	0.92–11.22	0.066	3.10	0.45–21.34	0.250
Meditated prior to the experience (ref = No)	1.84	0.57–5.96	0.304	0.72	0.11–4.75	0.742
Obtained drug from trusted source (ref = No)	1.41	0.29–6.73	0.661	1.05	0.13–8.58	0.935
Abstained from using other drugs (ref = No)	2.10	0.66–6.72	0.207	2.03	0.32–12.72	0.449
5-MeO-DMT use patterns						
Lifetime number of doses	1.20	0.91–1.58	0.180	1.17	0.77–1.77	0.441
Frequency of dose	2.26	0.99–5.19	0.053	2.20	0.51–9.36	0.284
Re-dose frequency*	1.62	0.50–5.24	0.417	0.33	0.04–2.53	0.292
Last use (months since last use)	0.87	0.77–0.99	0.041	0.71	0.56–0.94	0.008
Salience of 5-MeO-DMT experience						
Mystical Experience Questionnaire	1.97	1.30–2.97	0.001	1.59	0.85–2.98	0.140
PEQ–wellbeing	2.06	1.40–3.02	0.000	2.86	1.49–5.48	0.002
PEQ–meaningfulness	1.12	0.71–1.75	0.617	0.67	0.34–1.30	0.246
Other						
Non-dual experience while sober						
Yes	4.90	1.43–16.77	0.011	9.32	1.20–72.10	0.032
Unsure	6.39	0.74–55.13	0.092	12.54	0.90–173.52	0.059
Satisfaction with life scale	1.01	0.65–1.58	0.930	0.94	0.55–1.60	0.833

*A second dose within single 5-MeO-DMT session. PEQ, Persistent Effects Questionnaire.

early findings reported a wide range of prevalence rates, from 1 in 4 (50) to 1 in 20 (51), and from 15 to 77% of psychedelic users (52). Strassman highlights a list of methodological concerns regarding criteria for determining these prevalence rates (52).

In the multivariable model for emotional valence, greater personal wellbeing was significantly positively associated with positive or neutral emotional valence of these reactivation events. It could be that, for those that subsequently have a positive reactivation experience, they also had a positive emotional experience during the acute effects of the 5-MeO-DMT (state dependent processing), which in turn contributes to their enhanced sense of wellbeing. However, the opposite could also be true (negative experiences during the acute effects being related to interpretation of negative reactivation should it occur).

The finding that 80% of survey respondents in the structured group also reported improvements in symptoms of depression and anxiety (27), together with the present results provide a theoretical rationale for an overall benign or positive conceptualization of reactivation phenomena among people who consume synthetic 5-MeO-DMT in structured ceremonial settings. This finding further emphasizes the importance of using 5-MeO-DMT in a carefully controlled clinical setting where personal wellbeing and meaning-making are supported and facilitated, and thus positive experiences and outcomes are more likely. Nevertheless, it should be noted that, for the small percentage of those who report their reactivation is a negative experience, this may contribute to anxiety, panic, and other concerning emotional states requiring emergency crisis treatment. More information is needed to understand how to best identify those most likely to experience a reactivation as negative to prevent such challenging outcomes.

Having had a "non-dual" experience (e.g., transcendental, or unitary states) that was not induced by substance use significantly predicted neutral or positive emotional valence of reactivation events. The term "non-dual" derives from Tibetan Buddhism. It refers to a state of awareness that transcends the subject-object dichotomy which underlies internally and externally driven mentation (53). Although such dichotomies are known to be somewhat natural, psychological inflexibility

about them can result in an excessively fragmented experience that leads to ruminative thought patterns which are associated with various mental health disorders (53–55).

In line with this, Davis et al. (56) report that increases in psychological flexibility mediate the relation between mystical and insightful experiences on decreases in depression and anxiety following a psychedelic experience. In terms of the neural correlates of this increase in psychological flexibility, neuroimaging studies have revealed that there is a decoupling of the various structures that make up the "default mode network" (57), a large-scale brain network believed to underlie internally focused mentation. The acute temporary decoupling of the default mode network's structural nodes during the acute psychedelic state, along with global increases in connectivity are hypothesized to be correlated with the experience of "ego dissolution" (1, 58–60), and to result in a less constrained (higher entropy) style of cognition (1, 59). This in turn is believed to map out to psychological flexibility and mediate positive therapeutic outcomes (56, 61).

In terms of electrical activity in the brain, another neural correlate of the experience of non-dual ego dissolution is a significant decrease in *alpha* brain oscillations in the posterior cingulate cortex (62). In line with this, Acosta-Urquidi (63) also found consistent and significant *alpha* oscillations suppression in the cortex of individuals under the acute effects of 5-MeO-DMT in naturalistic settings, which was followed by an *alpha* rebound effect (a return of spectral power in this band as the effects of the drug subsided). This is interesting given that some of the most common precipitating factors of reactivation events are various activities such as falling asleep, meditating, mindfulness practices, relaxation techniques, and being in nature, all of which are known to induce *alpha* oscillations (64, 65). It is possible that reactivations could be experienced when the brain shifts from higher power brain oscillations, like *beta*, to lower power *alpha* oscillations during these types of activities. Moreover, because there is a sharp suppression of these oscillations under the effect of vaporized 5-MeO-DMT, followed by an *alpha* recovery rebound effect, it is possible that the combination of these experiences triggers a memory of the transition from the deep 5-MeO-DMT state back to normal consciousness, which is perceived or felt as a reactivation.

Of note, sex differences in modulation of *alpha* peak oscillations indicate that *alpha* oscillatory activity across time periods changes more in females than in males (66), and overall brain oscillations have been found to be highly influenced by sex differences (67), which could potentially underlie the significantly greater likelihood of reactivations reported by females in the present study. Future high-density EEG studies with 5-MeO-DMT could help elucidate the etiology of reactivations. For example, exploring whether baseline *alpha* power is associated with reactivations could be an intriguing next step.

Although as we have shown here, reactivations need not be construed as negative/adverse effects/events, it is important to note that the prevalence rates described herein are in relation to synthetic 5-MeO-DMT administered *via* vaporization route (i.e., smoked). It is possible that the rapid onset of the 5-MeO-DMT state afforded by this route of administration contributes to the likelihood of reactivation experiences. Indeed, a recent study (68) found lower rates of reactivation among a subsample of individuals who use 5-MeO-DMT *via* intramuscular (IM) injection. 5-MeO-DMT administered *via* IM injection likely produces a more gradual experience that may be physiologically and psychologically easier to integrate and thus less likely to promote reactivation phenomena. However, such findings have not been explored using laboratory assessments and thus further research is needed to determine the likelihood of reactivation following various routes of administration of 5-MeO-DMT in laboratory settings.

Interestingly, if 5-MeO-DMT were to be moved along the FDA pipeline to be tested as a pharmacological treatment for depression, or substance use disorders, it would most likely be administered *via* IM injection or intranasal formulation, not unlike ketamine treatment for depression, (69), which also has a slower onset compared to vaporization, thus potentially decreasing the likelihood that reactivations are experienced. Given that the data presented here indicate that females have a significantly higher likelihood of reporting reactivations, perhaps certain precautions can be taken to reduce the potential for any adverse effects resulting from unanticipated reactivation experiences. This in turn, however, could prime participants to be more likely to experience reactivations given the role that expectancy bias has been noted to have in association with the flashback phenomena (70). In fact, the rate of reactivations being so much higher among those in the structured group subsample could be hypothesized to be a function of expectancy bias, given that those who partake of 5-MeO-DMT in the structured group undergo an orientation session where the possibility of experiencing reactivations post 5-MeO-DMT is addressed, whereas those in the general population sample may have not had such expectancies.

Importantly, a gap in the literature exists with regard to characteristics of the reactivation phenomena that warrants further investigation: how long does each transient episode last? In the cases when the emotional valence of reactivations is negative, how disruptive are they and how often do they occur? How long after 5-MeO-DMT use do reactivations tend to occur? What are some of the precipitating triggers individuals may report?

Interestingly, anecdotal reports online do seem to suggest that reactivations tend to occur mainly at night as people are drifting off to sleep, and generally tend to dissipate the longer the time has elapsed from the time they took 5-MeO-DMT. In a broad sense, it appears that reactivations are experienced as transient but intense (Type 1 HPPD) and tend

to subside days or weeks after 5-MeO-DMT use in most cases, as opposed to persisting over longer periods of time as is the case with HPPD Type 2, but much more data is needed in order to ascertain this confidently. Nevertheless, as noted above, there are some anecdotal reports in the popular literature (i.e., Facebook, 5-Hive forum) that document instances of people experiencing anxiety and impaired sleep from continued reactivation experiences months after the experience. Mixed methods research designs that can collect qualitative data regarding reactivation details in upcoming clinical trials will be very valuable to enhance our understanding of the reactivation phenomena and how it may compare to HPPD Type 1 and 2.

Several limitations of this study warrant consideration. First, the cross-sectional nature of this study precludes the ability to infer causality. There was no 5-MeO-DMT dosage information available, and the route of intake (inhalation) likely delivered non-standardized doses across participants. Survey studies are further limited by the retrospective nature of reporting, which is subject to recall bias (71). As noted above, this study is further limited by selection bias. Respondents who have had negative reactivations may be less likely to have wanted to complete the survey, while those who participated in this survey may be inclined to report positive associations due to having a favorable view of the substance, which could explain the high rates of positive valence reported herein. While in the structured group, 5-MeO-DMT was tested for purity, there is no assurance that was done among the general population users, which may account for different rates of reactivation.

Finally, although we used the only empirical epidemiological dataset on patterns of 5-MeO-DMT use available to date and showed that negative experiences of reactivation are highly unlikely, anecdotal reports in popular media (e.g., Facebook, Reddit) have documented examples of individuals who experience persistent, unpleasant reactivations. It is important to clarify that these reports result from the use of *I. alvarius* toad-derived 5-MeO-DMT, rather than synthetically produced 5-MeO-DMT. Importantly, a mixed methods study incorporating qualitative reports about reactivation's precipitating factors and the phenomenology of the felt sense of experience and its emotional valance could help determine if reactivations are more likely to be challenging when consuming toad-derived, compared to synthetically produced, 5-MeO-DMT.

In conclusion, our findings show that the occurrence of reactivation phenomena resulting from synthetic 5-MeO-DMT use is not uncommon. Reactivation experiences are largely perceived as positive or neutral. Rather than being construed as adverse effects, they may well be a contributing factor to long-term therapeutic benefits. Future prospective clinical studies exploring synthetic 5-MeO-DMT as a potential treatment for psychiatric conditions need not be deterred based on the known occurrence of this not-yet well understood phenomena. As clinical research programs with 5-MeO-DMT commence, it will be crucial to collect data that can help further characterize reactivations so they can be harnessed to support personal growth processes of psychological change and wellbeing, and prevent, to the extent possible any potential negative effects from reactivation events.

Data availability statement

The data is available by request. Inquiries can be directed to AKD, davis.5996@osu.edu.

Ethics statement

The studies involving human participants were reviewed and approved by Bowling Green State University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AMOB conceptualized the study and research design, conducted the secondary data analyses, and wrote the manuscript. CLR made a substantial contribution to the conceptualization, research design, interpretation of data, and edited the manuscript. RLL made a substantial contribution to the early conceptualization of the research project as well as to the conceptualization, data collection, and authoring of the primary data set out of which this secondary data analysis derives. AKD made substantial contributions to the conceptualization, methodology, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, project administration, funding acquisition, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author CLR serves as a consultant for Usona Institute, Emory Healthcare, Alfasigma, and Novartis. Authors AKD and RLL were board members at Source Research Foundation and AKD was a lead trainer at Fluence. These organizations were not involved in the design/execution of this study or the interpretation or communication of findings.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Methylone, a rapid acting entactogen with robust anxiolytic and antidepressant-like activity

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Introduction: Selective serotonin reuptake inhibitor (SSRI) antidepressants represent first-line pharmacological treatment for a variety of neuropsychiatric illnesses, including major depressive disorder (MDD), anxiety, and post-traumatic stress disorder (PTSD), which show high rates of comorbidity. SSRIs have a delayed onset of action. Most patients do not show significant effects until 4–8 weeks of continuous treatment, have impairing side effects and as many as 40% of patients do not respond. Methylone (3,4-methylenedioxy-*N*-methylcathinone; MDMC, βk-MDMA, M1) is a rapid-acting entactogen that showed significant benefit in a clinical case series of PTSD patients and was well-tolerated in two Phase 1 studies of healthy volunteers. Based on these early observations in humans, in the current study we tested the hypothesis that methylone has antidepressant-like and anxiolytic effects in preclinical tests.

Methods: For all studies, 6–8-week-old male Sprague Dawley rats ($N = 6–16$) were used. We employed the Forced Swim Test (FST), a classic and widely used screen for antidepressants, to explore the effects of methylone and to probe dose-response relationships, durability of effect, and potential interactions with combined SSRI treatment. We compared the effect of methylone with the prototypical SSRI fluoxetine.

Results: Three doses of fluoxetine (10 mg/kg) given within 24 h before FST testing caused a 50% reduction in immobility compared with controls that lasted less than 24 h. In contrast, a single dose of methylone (5–30 mg/kg) administered 30 min prior to testing produced a rapid, robust, and durable antidepressant-like response in the FST, greater in magnitude than fluoxetine. Immobility was reduced by nearly 95% vs. controls and effects persisted for at least 72 h after a single dose (15 mg/kg). Effects on swimming and climbing behavior in the FST, which reflect serotonergic and noradrenergic activity, respectively, were consistent with studies showing that methylone is less serotoninergic than MDMA. Fluoxetine pretreatment did not change methylone's antidepressant-like effect in the FST, suggesting the possibility that the two may be co-administered. In addition, methylone

(5–30 mg/kg) exhibited anxiolytic effects measured as increased time spent in the center of an open field.

Discussion: Taken together, and consistent with initial clinical findings, our study suggests that methylone may have potential for treating depression and anxiety.

KEYWORDS

empathogen, serotonin, SERT, PTSD, depression, anxiety, MDMA

Introduction

Major depressive disorder (MDD) and anxiety are debilitating diseases with lifetime prevalences of 20.8 and 28.8%, respectively, and a comorbidity rate estimated to be as high as 60% (1). Antidepressants remain a first-line treatment for these and many other central nervous system (CNS) disorders. The development of rapid-acting psychoactive therapeutics offers advantages over traditional slow-acting antidepressants (SAADs). SAADs, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, have a slow onset of action, requiring as long as 4–8 weeks of continuous treatment for potential clinical benefit and have significant side-effects that may hinder compliance with treatment; even when optimally administered, as many as 40% of individuals do not respond (2, 3). Rapid-acting antidepressants (RAADs) offer a number of advantages over SAADs, the first of which is potentially improved efficacy, but also the possibility of improved compliance with a treatment due to rapid onset of action, a shorter-term treatment duration, and durable therapeutic effects that do not require daily dosing (4, 5). Esketamine is the only RAAD that has been FDA-approved as an adjunct therapy for treatment-resistant depression (6)® [package insert]. Titusville, NJ, USA: (Janssen Pharmaceuticals, Inc., 2020), but other drugs in development include psilocybin and 3,4-methylenedioxymethamphetamine (MDMA), which appear to show clinical benefit for the treatment of MDD and post-traumatic stress disorder (PTSD), respectively (4, 7, 8).

Methylone (also known as 3,4-methylenedioxy-*N*-methylcathinone, MDMC, βk-MDMA, and M1) is an entactogen and a beta-ketone analog of MDMA currently in development for the treatment of PTSD. Methylone was synthesized over 25 years ago (9), but the literature describing its properties is relatively sparse, focused largely on *in vitro* studies or binge-dosing regimens that mimic its illicit use. Methylone shares some chemical and pharmacological properties with MDMA, but also has some differences. For example, methylone is a serotonin (5HT), norepinephrine (NE), and dopamine (DA) reuptake inhibitor and releaser like MDMA, but with 3–4× lower potency for inhibition of serotonin uptake (10).

To date, clinical experience with methylone has been described in four studies, which demonstrate that it is well tolerated, produces a milder range of effects compared with MDMA (11, 12), and alleviates symptoms of PTSD in a retrospective clinical case series (13). It is notable that MDD and anxiety show high rates of comorbidity with PTSD (14), and SSRIs are used to treat all three disorders, suggesting that the reported effects of methylone in PTSD (13) may translate to therapeutic benefit in multiple CNS disorders. In fact, a second retrospective clinical case series suggests methylone may have RAAD effects in patients with MDD (15).

Based on the initial clinical reports of methylone's potentially therapeutic activity in PTSD (13) and MDD (15), as well as effects of structurally similar MDMA in clinical (16) and preclinical studies (17, 18), we hypothesized that methylone would show rapid-onset antidepressant and anxiolytic activity in preclinical behavioral tests. To test this, we evaluated the effect of methylone or fluoxetine compared to vehicle treated controls in the forced swim test (FST) and the open field test (OFT) in rats, probing its dose response, duration of activity, and interaction with combined SSRI treatment. Pharmacokinetics in plasma and brain at active doses were also assessed.

Materials and methods

Pharmacokinetics (PK)

Pharmacokinetics studies were carried out at WuXi Apptec, Inc. (Cranbury, NJ, USA) using standard protocols. All animal use and procedures were approved by the WuXi Apptec, Inc., IACUC. Briefly, terminal blood and brain samples were collected from 6 to 8 week old male Sprague Dawley rats (Hilltop Lab Animals, Inc., Scottsdale, PA, USA) at 0.25, 0.5, 1, 2, 4, and 8 h ($N = 3$ per group per time point) for the determination of plasma concentrations of methylone following intraperitoneal (IP) dosing of 5, 10, or 15 mg/kg methylone. Since these were terminal collections, three independent rats per group were used for each time point in a single PK curve from which PK parameters (C_{max}, AUC, etc.) were generated. Samples were collected into K_2EDTA tubes on ice and centrifuged at 3000 × *g* at 4°C for 5 min within 30 min

of collection. Plasma samples were stored at −80°C until analysis by liquid chromatography tandem mass spectrometry (LC-MS/MS). The bioanalytical assay provided a lower limit of quantification (LLOQ) of 1 ng/mL and an upper limit of quantification (ULOQ) of 3000 ng/mL for methylone. The plasma concentration-time data were analyzed using Phoenix WinNonlin (version 8.3) to characterize the PK properties of the analyte. The non-compartmental analysis model and the linear/log trapezoidal method were applied to the calculation of the PK parameters.

Behavioral testing

Animals

Male Sprague Dawley rats (Charles River Laboratories) weighing 180–200 g on arrival, were used for all behavioral studies, which took place at Melior Discovery (Exton, PA, USA). Rats acclimated to their home cages for at least 1 week before testing, were maintained in a controlled environment on a 12 h light/dark cycle, with no more than 2 rats per cage. Animals received *ad libitum* access to standard rodent chow and water and were assigned randomly to treatment groups. All animal use and procedures were in accordance with established protocols approved by the Melior IACUC committee, Melior Standard Operation Procedures (SOP), and Transcend Therapeutics. Distinct cohorts of animals were used for each experiment/Figure presented in this manuscript.

Drug treatments

Methylone HCl (0.5–30 mg/kg; Cayman Chemical) or Fluoxetine HCl (10 mg/kg; Sigma-Aldrich) were formulated in sterile 0.9% saline vehicle before IP administration. Control animals received saline vehicle. Methylone or saline was administered 30 min prior to FST or OFT testing sessions. Fluoxetine or saline were administered 23.5, 5, and 1 h prior to testing, consistent with previous studies (19).

Forced swim test (FST)

All studies were performed and scored by an experimenter blind to treatment group according to standard protocols at Melior Discovery (Exton, PA, USA) and based on published "modified FST" procedures (20). Briefly, rats were placed in a circular plexiglass container (29.2 cm diameter, 49.5 cm height) filled with water to a depth of 30 cm so rats could not support themselves by touching the bottom of the tank. Water was maintained at 22–25°C and was changed for every animal. Day 1 (Training) consisted of a 15 min acclimation trial, and Day 2 (Testing, 24 h later) consisted of the 5 min test. A time sampling procedure was employed where animals were observed every 5 s for the duration of the test session (60 counts or 5 min) and scored for immobility (defined as the failure to struggle), swimming (defined as a circular movement around the tank), or climbing (defined as an upward escape behavior). Data are expressed as the percent time spent immobile, swimming, or climbing for the 5-min testing session (e.g., the number of immobility counts divided by 60). Therefore, to extrapolate these values to time spent immobile in minutes, one can multiply the percent time immobile by 5 min. For example, if an animal shows 80% time spent immobile, this means that 4 min (0.8 × 5) of the 5-min testing session were spent immobile.

Separate vehicle control groups were used for methylone (one injection) and fluoxetine (three injections) since the stress of repeated drug injections can increase immobility time in the FST, accounting for the small difference between those two control groups.

Open field test (OFT)

All studies were performed by an experimenter blind to treatment group and according to standard protocols at Melior Discovery (Exton, PA, USA). The OFT was used to assess both locomotor activity and anxiety-like behavior. The OFT was run in a standard rat OFA chamber (17″ × 17″ × 12″, Med Associates). After habituation to the testing room and drug injection, rats were assessed for 30 min in the OFT using an automated activity monitoring system (MedAssociates). Locomotor activity was measured by recording the total ambulatory distance traveled (cm), reported in 5-min bins for the duration of the 30 min testing period. The center of the open field was defined as a 12″ square, a predefined center setting on the MedAssociates analysis software. Time spent in the center of the open field, an anxiolytic measure, was also recorded for the 30 min testing period.

Statistical analysis

All data are presented as the mean ± SEM. Differences between two groups were determined by unpaired *t*-test, differences between more than two groups were determined by one-way ANOVA and *post hoc* multiple comparison test noted in Figure Legends. When there were two different variables (drug × time), differences were determined by two-way ANOVA and Bonferroni's *post hoc* multiple comparison test unless otherwise noted. A p-value ≤ 0.05 indicated statistical significance. All analyses were completed using Graphpad Prism software version 9.3.1 (San Diego, CA, USA).

Results

Effects of methylone on antidepressant-like activity

We employed the FST, a classic and commonly used preclinical behavioral paradigm to screen drugs for antidepressant-like activity, to test the effect of methylone. Antidepressants consistently reduce immobility time in the

FST, and accompanying increases in climbing or swimming behaviors reflect noradrenergic or serotonergic involvement, respectively (19). Multiple classes of antidepressants, including SSRIs like fluoxetine and more recent RAADs like ketamine, psilocybin, and MDMA have all been reported to reduce immobility in the FST (17, 19, 21–23).

Here, rats received a single injection of methylone (0.5–30 mg/kg, IP) or saline (Vehicle) 30 min before testing in the FST (**Figure 1A**). Results are presented as the percent time spent immobile during the 5-min testing session. A low dose of methylone (5 mg/kg) significantly reduced the percent immobility time to 31.9 ± 4.7% compared to Vehicle controls 63.9 ± 2.7%. Moderate doses of methylone (10–15 mg/kg) robustly reduced immobility to 4.2 ± 1.3% compared with Vehicle controls 63.9 ± 2.7%. [**Figure 1B**, $F_{(7,67)} = 23.32$, $p < 0.0001$]. There was a trend toward less reduction in immobility at the highest doses of methylone (20–30 mg/kg), suggesting a possible U-shaped dose-response curve, although this did not reach statistical significance. As a positive control and comparator, the SSRI fluoxetine (10 mg/kg, IP) or saline (Vehicle) were administered 23.5, 5, and 1 h before testing, based on previous studies (24). The effect of three doses of fluoxetine was comparable in magnitude to a single low (5 mg/kg) dose of methylone in the FST, roughly a 50% change from their respective vehicle control group [**Figure 1C**, $t_{(12)} = 7.149$, $p < 0.0001$]. Climbing behavior was increased only by low to mid doses of methylone (5–10 mg/kg) compared with controls [**Figure 1D**, $F_{(7,67)} = 3.696$, $p < 0.01$] and was unaffected by fluoxetine [**Figure 1E**, $t_{(12)} = 0.2133$, $p = 0.8$, n.s.]. Swimming behavior was significantly increased by mid to high doses of methylone [**Figure 1F**, $F_{(7,67)} = 14.44$, $p < 0.0001$] and, as expected, also by fluoxetine [**Figure 1G**, $t_{(12)} = 5.844$, $p < 0.0001$].

Pharmacokinetic profiles of methylone in plasma and brain were determined at efficacious doses in the FST. Rats were injected with methylone (5, 10, or 15 mg/kg) and terminal blood and brain samples were collected 0.25, 5, 1, 2, 4, and 8 h post-dose. Concentrations of methylone in plasma and brain are plotted in **Figure 2**. Following a single IP administration of methylone at 5, 10, or 15 mg/kg, the peak plasma concentrations (C_{max}) of methylone were 1983, 4507, and 8470 ng/mL, respectively. The C_{max} was achieved 15 min (T_{max}) post-dose. The area under the plasma concentration-time curve from time 0 to the last quantifiable time (AUC_{0-last}) of methylone was 908, 3242, and 7320 h/mL, respectively. The terminal elimination half-life ($T_{1/2}$) of methylone was 0.6–0.8 h and the mean residence time from time 0 to the last quantifiable time (MRT_{0-last}) was 0.7–1.13 h. The brain to plasma AUC ratio was approximately 1.8, demonstrating that methylone effectively crossed the blood-brain barrier. Selected plasma and brain PK parameters are presented in **Table 1**.

In contrast to SAADs like fluoxetine, a feature of RAADs is that they produce more sustainable, longer-lasting effects that do not require daily dosing (22). To test whether this held true for methylone, animals were dosed once with methylone (15 mg/kg, IP) or saline (Vehicle) 30 min prior to testing in the FST and were retested 24 or 72 h later (**Figure 3A**). Methylone produced a durable antidepressant-like response, reducing immobility significantly at all-time points compared to vehicle controls [**Figure 3B**, *Drug*: $F_{(1,36)} = 173.9$ $p < 0.0001$; *Time*: $F_{(2,36)} = 33.82$, $p < 0.0001$; *Drug* × *Time*: $F_{(2,36)} = 8.548$, $p < 0.001$]. Fluoxetine (10 mg/kg, IP) or saline (Vehicle) were given 23.5, 5, and 1 h prior to testing, and rats were also retested 24 and 72 h later. In contrast to the durable effect of methylone, fluoxetine only showed a significant effect on immobility 1 h post-dose [**Figure 3C**, *Drug*: $F_{(1,36)} = 25.85$ $p < 0.0001$; *Time*: $F_{(2,36)} = 11.94$, $p < 0.0001$; *Drug* × *Time*: $F_{(2,36)} = 3.328$, $p < 0.05$]. A small but significant effect of methylone on climbing was observed at 30 min only [**Figure 3D**, *Drug*: $F_{(1,36)} = 15.52$ $p < 0.001$; *Time*: $F_{(2,36)} = 0.3169$, n.s.; *Drug* × *Time*: $F_{(2,36)} = 0.4776$, n.s.] and as expected, fluoxetine had no effect on climbing [**Figure 3E**, *Drug*: $F_{(1,36)} = 15.52$ $p < 0.001$; *Time*: $F_{(2,36)} = 0.3169$, n.s.; *Drug* × *Time*: $F_{(2,36)} = 0.4776$, n.s.]. Methylone had a more robust effect on swimming at this dose, consistent with the previous experiment, significantly increasing swimming at all three time points tested [**Figure 3F**, *Drug*: $F_{(1,36)} = 64.93$ $p < 0.0001$; *Time*: $F_{(2,36)} = 21.12$, $p < 0.0001$; *Drug* × *Time*: $F_{(2,36)} = 3.786$, $p < 0.05$]. Fluoxetine significantly increased swimming compared to vehicle controls, 1 h post-dose, and showed a small but significant increase in swimming 24 h post-dose [**Figure 3G**, *Drug*: $F_{(1,36)} = 24.21$ $p < 0.0001$; *Time*: $F_{(2,36)} = 11.82$, $p = 0.0001$; *Drug* × *Time*: $F_{(2,36)} = 4.249$, $p < 0.05$]. In summary, the antidepressant-like effect of a single dose of methylone lasted at least 72 h, whereas fluoxetine's effect on immobility was only observed 1 h post-dose.

Since large changes in locomotor activity may confound the interpretation of results in the FST, we tested the effects of methylone or fluoxetine on locomotor activity in the OFT. First, we show effects on locomotion for the first 5 min in the OFT, corresponding to the 5-min FST testing session. Rats received fluoxetine (10 mg/kg) or saline (Vehicle) injections 23.5, 5, and 1 h before testing. A separate cohort of rats run in parallel received a single injection of methylone (0.5–30 mg/kg, IP) or saline (Vehicle) 30 min before testing in the OFT (**Figure 4A**). Fluoxetine, which reduces immobility in the FST, also reduced distance traveled in the OFT 1 h post-dose [**Figure 4B**, $t_{(10)} = 2.882$, $p < 0.05$], demonstrating that effects on activity do not always track with FST immobility. Higher doses of methylone (15–30 mg/kg) significantly increased distance traveled in the OFT, but lower doses of methylone (0.5–10 mg/kg), including two effective doses in the FST (**Figure 1B**), did not affect locomotor activity [**Figure 4C**, $F_{(7,72)} = 5.816$, $p < 0.0001$]. Rats were retested 24 h later, a time point at which the antidepressant-like effects of methylone persist (**Figure 3B**).

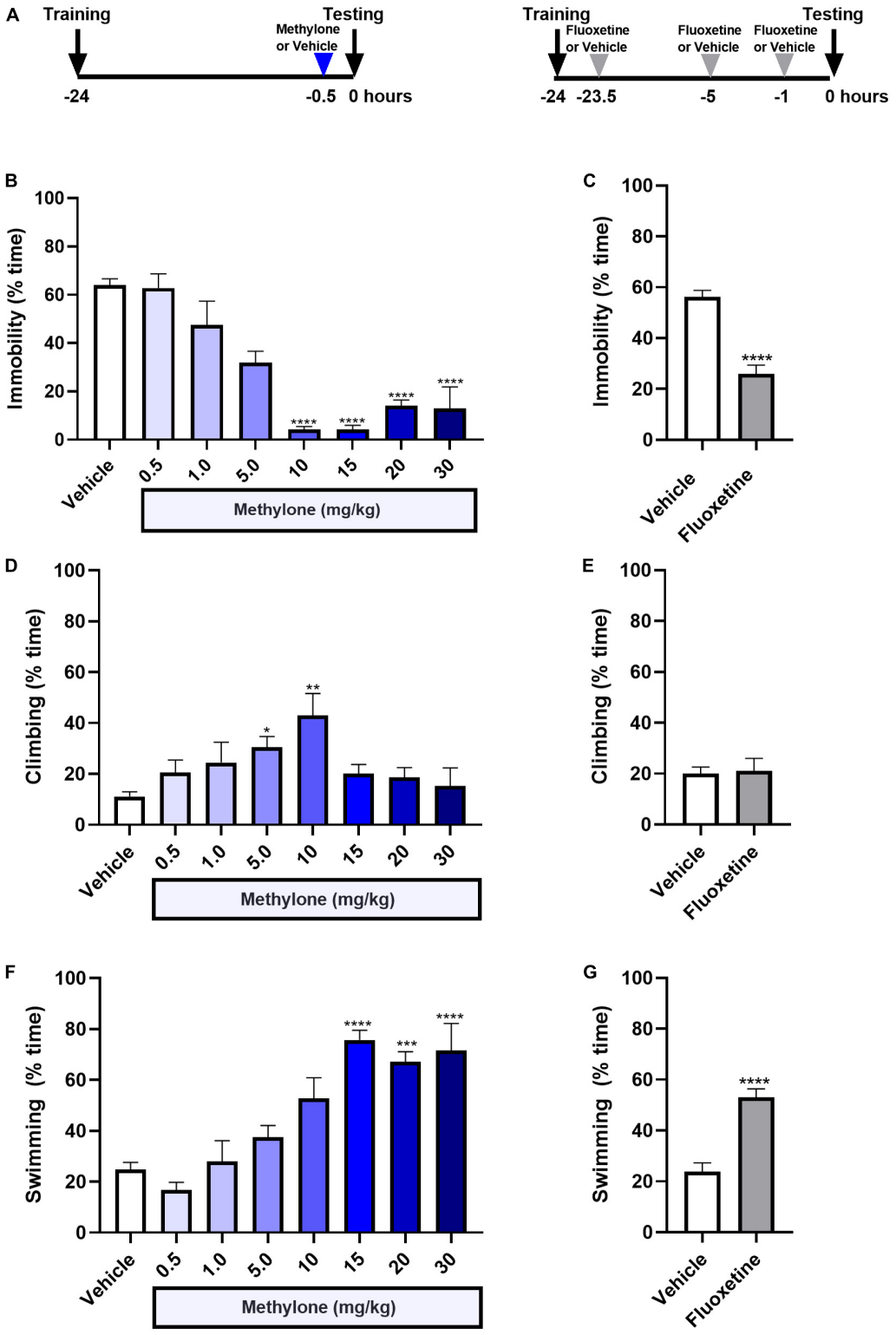

FIGURE 1
Methylone has a rapid-acting and robust antidepressant-like response in the forced swim test. **(A)** Schematic shows experimental design. Methylone (0.5–30 mg/kg, IP) or saline (Vehicle) was administered 30 min prior to testing. Fluoxetine (10 mg/kg, IP) or saline (Vehicle) were administered 23.5, 5, and 1 h prior to testing. Quantification of the percent time spent **(B,C)** immobile, **(D,E)** climbing, or **(F,G)** swimming during the 5-min test session is shown. Data are presented as means ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ vs. Vehicle control group, Bonferroni's *post-hoc* test; $N = 6–16$ per group.

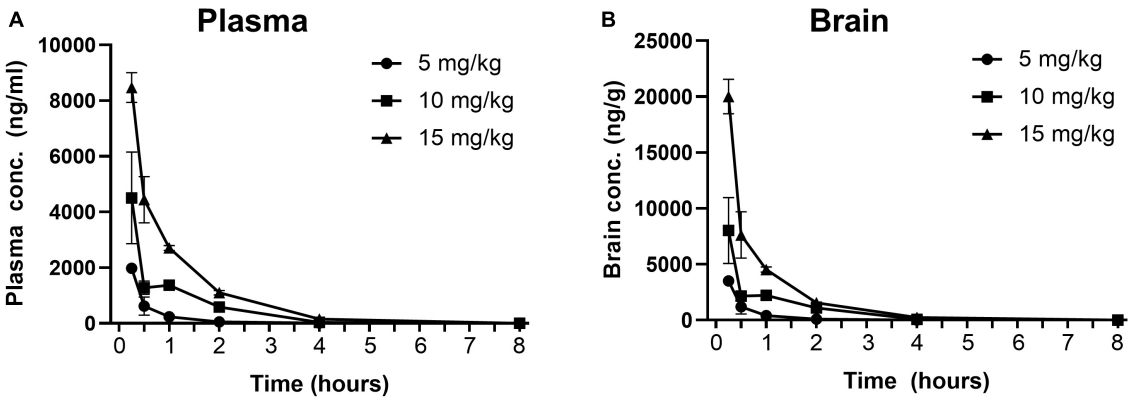

FIGURE 2
Concentration-time profiles of methylone in plasma and brain following a single dose. Methylone (5, 10, 15 mg/kg, IP) was administered and terminal blood and brain samples were collected 0.25, 5, 1, 2, 4, and 8 h post-dose. Concentrations of methylone detected in the **(A)** plasma and **(B)** brain are shown. Data are presented as means ± SEM. $N = 3$ per time point per group.

TABLE 1 **Pharmacokinetic properties of methylone (5, 10, 15 mg/kg, IP) in rat brain and plasma.**

PK parameters of methylone						
PK parameters	5 mg/kg		10 mg/kg		15 mg/kg	
	Mean brain	Mean plasma	Mean brain	Mean plasma	Mean brain	Mean plasma
C_{max} (ng/mL or ng/g)	3513	1983	8021	4507	20013	8470
$T_{1/2}$ (h)	0.691	0.598	0.607	0.674	0.884	0.811
T_{last} (h)	4.00	4.00	4.00	8.00	8.00	8.00
AUC_{0-last} (ng.h/mL or ng.h/g)	1661	908	5576	3242	13201	7320
MRT_{0-last} (h)	0.696	0.666	1.03	1.07	1.01	1.13
AUC ratio (brain: plasma)	1.83	–	1.72	–	1.80	–

Results showed that locomotor activity returned to baseline at this time point for all groups [**Figure 4D**, $F_{(7,44)} = 0.1450$, n.s.]. Therefore, the antidepressant effects of methylone in the FST occur at doses (5–10 mg/kg) and time points (24 h) when there were no detectable changes in locomotor activity. Together, this supports that the antidepressant-like effect of methylone in the FST occurs independent of any changes in locomotion and that methylone has a transient stimulatory effect on distance traveled in the OFT.

The effect of methylone on the distance traveled in the OFT for the duration of a 30-min testing session is also shown, plotted in 5-min time bins, to determine whether methylone affected exploration or habituation to the testing chamber. Fluoxetine reduced distance traveled in the OFT for the first 15 min of the testing session [**Figure 4E**, *Drug*: $F_{(1,10)} = 19.19$, $p < 0.01$; *Time*: $F_{(3.286,32.86)} = 87.29$, $p < 0.0001$; *Time* × *Drug*: $F_{(5,50)} = 2.353$, $p \leq 0.05$; *Subject:* $F_{(10,50)} = 4.020$, $p < 0.001$]. Higher doses of methylone (15–30 mg/kg) increased distance traveled for the duration of the testing session compared to saline-injected controls [**Figure 4F**, *Drug*: $F_{(7,72)} = 6.080$, $p < 0.0001$; *Time*: $F_{(2.995,217.7)} = 200.6$, $p < 0.0001$; *Time* × *Drug*: $F_{(35,360)} = 1.566$, $p < 0.05$; *Subject:* $F_{(72,360)} = 22.50$, $p < 0.001$].

Effect of methylone on anxiety-like behavior

Here we investigated whether methylone also showed anxiolytic effects in a behavioral anxiety test, in addition to its antidepressant-like activity. Results revealed that methylone (5–30 mg/kg) significantly increased time spent in the center compared to controls 30 min after dosing [**Figure 5A**, $F_{(7,71)} = 4.184$, $p < 0.001$], consistent with an anxiolytic-like effect. Data are shown as the percent of vehicle control group, which on average, spent approximately 15 min in the center during the 30 min testing period. Fluoxetine significantly reduced time spent in the center [**Figure 5B**, $t_{(10)} = 3.587$, $p < 0.01$], consistent with an anxiogenic-like effect that has been described previously (25) and consistent with the anxiogenic effect of acute SSRI administration in humans. These results

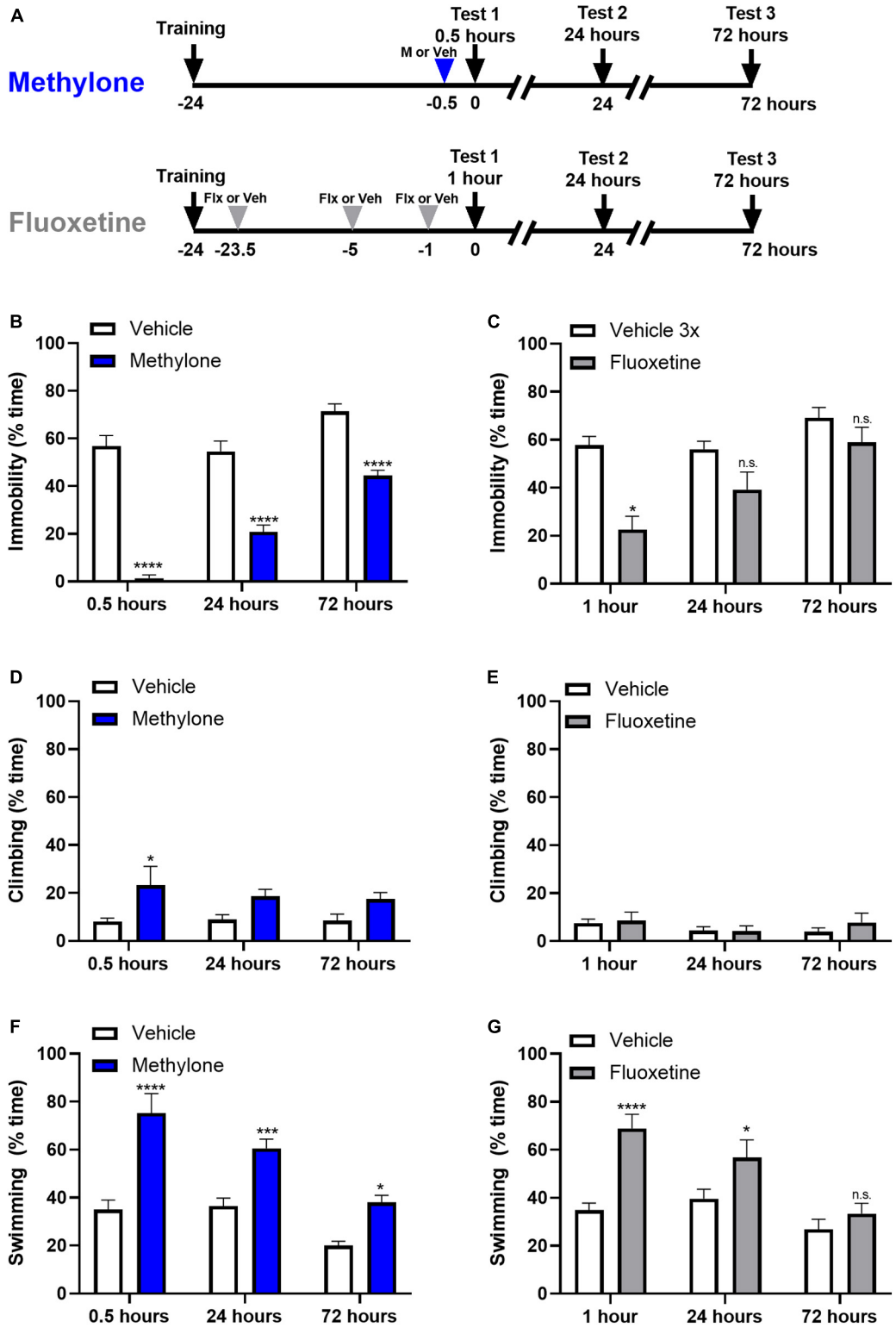

FIGURE 3
The effect of a single dose of methylone is long-lasting. **(A)** Schematic shows experimental design. Methylone (15 mg/kg, IP) or saline (Vehicle) was administered 30 min prior to forced swim testing. Fluoxetine (10 mg/kg, IP) or saline (Vehicle) were administered 23.5, 5, and 1 h prior to testing. Animals were retested 24 or 72 h later. Quantification of the percent time spent **(B,C)** immobile, **(D,E)** climbing, or **(F,G)** swimming during each 5-test session is shown. Data are presented as means ± SEM. *$p < 0.05$, ***$p < 0.001$, ****$p < 0.0001$ vs. Vehicle control group; n.s., not significant, Bonferroni's *post-hoc* test; $N = 6–8$ per group.

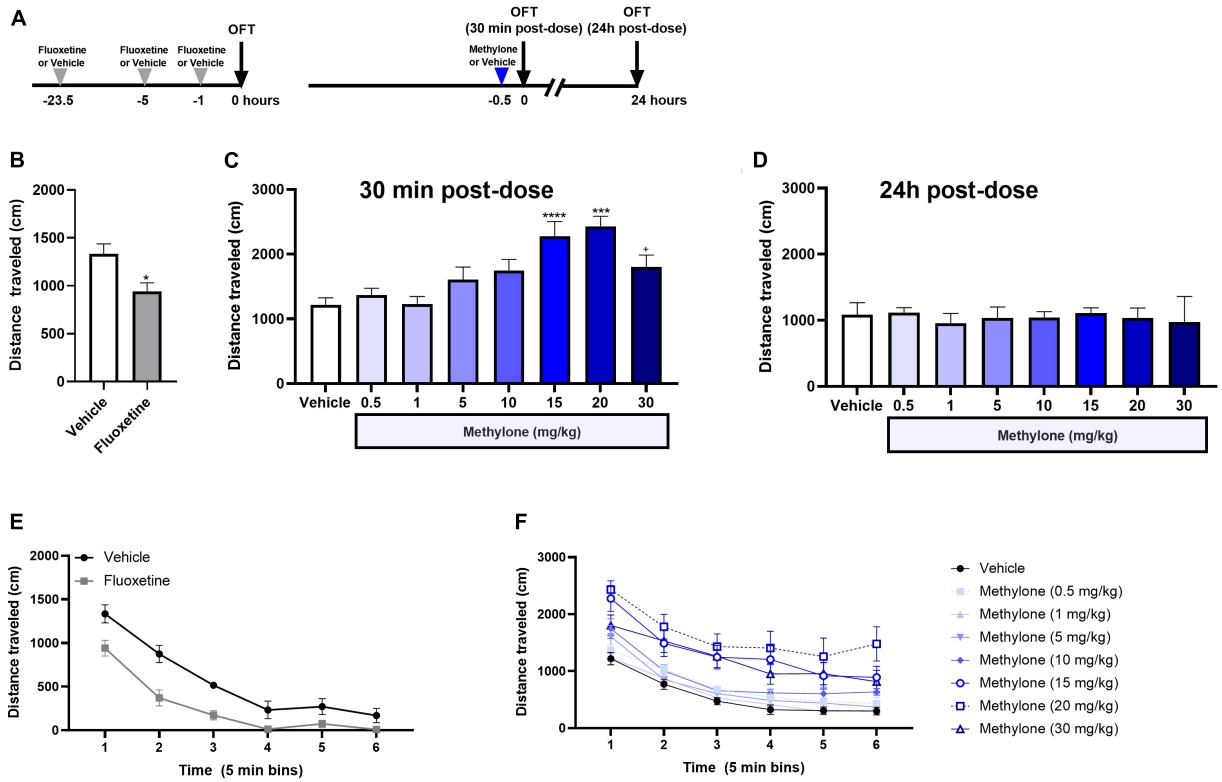

FIGURE 4
Effects of methylone on locomotor activity. **(A)** Schematic showing that the doses and time points tested in the OFT mirrored those used in FST dose response study. **(B)** Fluoxetine (10 mg/kg, IP) or saline (Vehicle) were administered 23.5, 5, and 1 h prior to testing, and the total distance traveled in the OFT is shown for the first 5-min of the test, corresponding to the testing duration in the FST. **(C)** Methylone (0.5–30 mg/kg, IP) or saline (Vehicle) was administered 30 min prior to testing, and the total distance traveled in the OFT is shown for the first 5 min of the test. **(D)** Effects of methylone on distance traveled for the first 5 min in the OFT were measured 24 h post-dose. Total distance traveled is shown for the duration of the 30-min OFT testing session in 5-min time bins after **(E)** fluoxetine or **(F)** methylone treatment. Data are presented as means ± SEM. $^{*}p < 0.05$, $^{***}p < 0.001$, $^{****}p < 0.0001$ vs. Vehicle control group, Bonferroni's *post-hoc* test $N = 6$ for fluoxetine; $N = 7$–13 per group for methylone. $^{+}p = 0.08$.

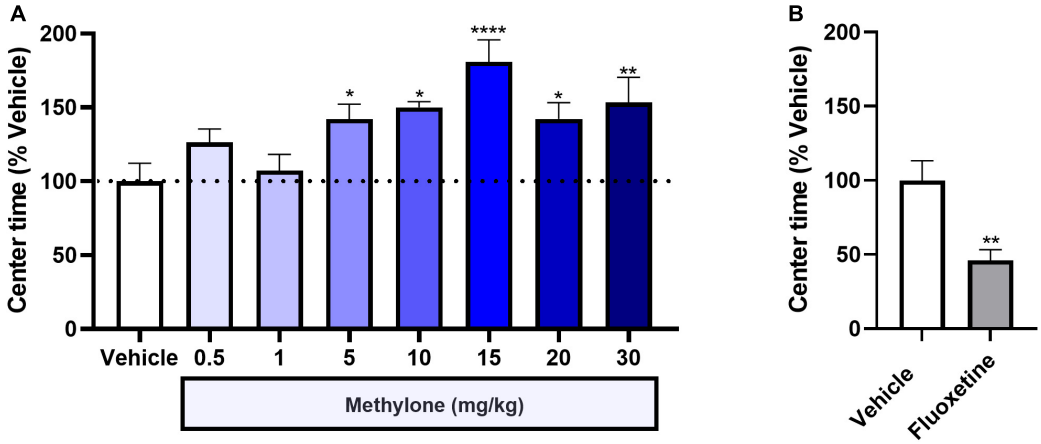

FIGURE 5
Methylone shows anxiolytic activity, increasing the time spent in the center of the open field test. The time spent in the center of the OFT is shown 30-min post-dosing with **(A)** methylone or **(B)** fluoxetine. Data are presented as means ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$, Fisher's LSD *post-hoc* test; $N = 6$ for fluoxetine; $N = 7$–13 per group for methylone.

support the conclusion methylone has an acute anti-anxiety effect in addition to its antidepressant-like activity in the FST.

Combined treatment effects of SSRI and methylone in the forced swim test

Since there is evidence of SSRIs interfering with the efficacy of MDMA in rodents and humans (7, 18, 26), we investigated whether combined treatment with fluoxetine interfered with the behavioral response to methylone in the FST. Fluoxetine (10 mg/kg, IP) or saline were administered 23.5, 5, and 1 h prior to testing, and a low but effective dose of methylone (5 mg/kg, IP) was administered 30 min prior to testing in the FST. Control groups received fluoxetine alone (10 mg/kg, IP), methylone alone (5 mg/kg, IP), or saline vehicle only (**Figure 6A**). A submaximal dose of methylone was chosen to allow for the possibility that fluoxetine might either augment or inhibit the methylone response. Results showed that fluoxetine had no effect on methylone's activity in the FST. Compared to vehicle, all groups demonstrated a comparable reduction in immobility [**Figure 6B**, $F_{(3,26)} = 13.53$, $p < 0.0001$]. Methylone alone significantly increased climbing [**Figure 6C**, $F_{(3,26)} = 3.947$, $p < 0.05$] while fluoxetine and the combined treatment significantly increased swimming [**Figure 6D**, $F_{(3,26)} = 8.677$, $p < 0.001$]. In addition, we tested whether a maximally effective dose of methylone was affected by fluoxetine co-treatment, and found combined treatment with fluoxetine and a higher dose of methylone (15 mg/kg) also did not affect the response to methylone in the FST. Specifically, immobility was significantly reduced by 95% relative to the Vehicle control group (Methylone + Fluoxetine: 3.3 ± 2.4% time immobile vs. Vehicle: 61.6 ± 5.2, $p < 0.0001$), similar to the effect of methylone alone (4.2 ± 1.8% time immobile vs. Vehicle: 63.9 ± 2.7%, **Figure 1B**). In summary, the data demonstrate that combined treatment with fluoxetine had no effect on the response to methylone in the FST.

Discussion

The current study shows for the first time that methylone has both antidepressant and anxiolytic effects in rodent tests of antidepressant-like activity and anxiety. Specifically, methylone had a rapid-acting, robust, and long-lasting antidepressant-like effect in the FST. The magnitude of the antidepressant effect observed after a single dose of methylone (i.e., 78–98% reduced immobility relative to Vehicle controls) was greater than many other antidepressants reported in the FST literature, including SSRIs sertraline (50–68%), paroxetine (40%), fluoxetine (56%), tricyclic antidepressant desipramine (55–75%), and RAADs ketamine (25–62%), MDMA (47–78%), and psilocybin (67%) (17, 19, 21–23). Moreover, and like other proposed RAADs such as ketamine, MDMA, and psilocybin, the effect of methylone was rapid-acting, occurring within 30 min of a single dose. In contrast, the effects of SSRIs and TCAs required three doses given between FST training and testing. Importantly, methylone's effect in the FST is not due solely to stimulatory effects on locomotor activity. We further demonstrate an anxiolytic effect of methylone in the OFT. Pharmacokinetic profiling reveals dose-dependent changes in plasma and brain methylone concentrations and a brain-plasma ratio of approximately 1.8, all of which indicate CNS availability and are consistent with previous reports in rodents (27–29). Together, our results show that methylone may have potential to treat disorders such as MDD and anxiety. Future work in rodents and humans will aim to determine whether methylone may also have potential for treating PTSD and other CNS disorders for which conventional antidepressants are efficacious.

Despite having been synthesized over 25 years ago (9), there is a relatively small literature on methylone, and published studies have largely used binge-dosing regimens to mimic the illicit use of the drug. The only prior study of methylone in the FST reported that in mice, 3–4 doses of methylone (25 mg/kg) over a 2-day period increased immobility in the FST 3 days after dosing, consistent with a depression-like phenotype (29). This prior study intended to model the binge-dosing regimen of a drug user, as compared to our study, which aimed to mirror use of the drug at a lower, potentially therapeutic dose, accounting for the discrepancy in the findings. Similarly, while our data show that methylone is also anxiolytic in the OFT, two previous studies have shown anxiogenic effects of methylone using a binge-dosing regimen with dose levels and timing that differ significantly from the current study (30, 31).

There was a steep dose response relationship in immobility, such that the first significant effect was observed at 5 mg/kg and maximal effect at 10 mg/kg. We sought to determine whether pharmacokinetic properties of methylone could help to explain the observed behavioral responses. The plasma concentrations of methylone after 5 and 10 mg/kg doses were approximately 8 and 18 μM, respectively. The IC_{50} value for inhibition of serotonin uptake by methylone has been reported to be 5.75 μM *in vitro* (32). We speculate that at the 5 mg/kg dose, IC_{50} is likely achieved, and that at 10 mg/kg the transporter may become saturated, accounting for the maximal effect on behavior at this dose. However, additional studies, beyond the scope of the current report, are required to confirm this hypothesis.

Methylone is a structurally similar, beta-ketone analog of MDMA, so the similarities and differences between the two compounds should be considered when putting our new data into context. MDMA-assisted psychotherapy significantly alleviates symptoms of PTSD (7), a condition for which antidepressants (sertraline and paroxetine) are the only approved treatments (33). In contrast to methylone, MDMA has been well-studied using both binge-dosing paradigms and lower therapeutic doses in preclinical species. Both drugs produce

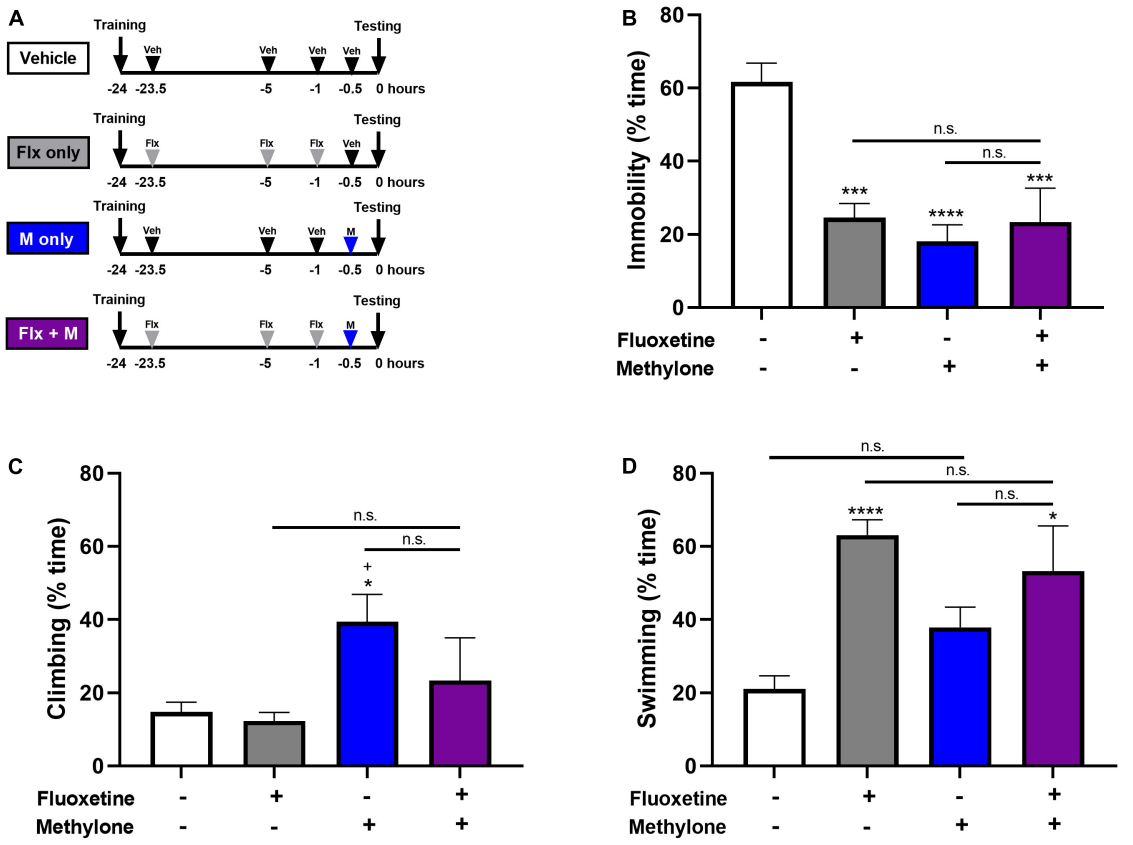

FIGURE 6
(A) Schematic shows experimental design and groups tested. Animals received three doses of fluoxetine (10 mg/kg, IP) 23.5, 5, and 1 h before testing and a single low dose of methylone (5 mg/kg, IP) 30 min before testing in the FST. Controls received fluoxetine only, methylone only, or saline vehicle. Quantification of the time spent **(B)** immobile, **(C)** climbing or, **(D)** swimming are shown. Data are presented as means ± SEM. $^{*}p < 0.05$, $^{***}p < 0.001$, $^{****}p < 0.0001$ vs. Vehicle control group; $^{+}p \leq 0.05$ vs. Fluoxetine alone, n.s., not significant, Bonferroni's *post-hoc* test; $N = 6–8$ animals per group.

antidepressant-like effects in the FST, specifically, MDMA has been shown to reduce immobility by 47–78% and methylone by 78–98% compared to vehicle controls (17, 23). Both are monoamine uptake inhibitors and releasers, but *in vitro* studies show that methylone is a 3–4-fold less potent inhibitor of serotonin uptake than MDMA (10, 28, 32, 34, 35). Serotonergic drugs like MDMA or SSRIs increase FST swimming behavior (19). Therefore, methylone's lesser effect on serotonin can be observed in our FST data: lower doses of methylone increased climbing behavior, which has been linked to noradrenergic activity (19) and only at higher doses was swimming behavior, linked to serotonergic activity (19) increased. MDMA also disrupts vesicular stores of serotonin *via* vesicular monoamine transporter 2 (VMAT2), which contributes to its effects on serotonin release. In contrast, methylone has more than a 10-fold lower potency at VMAT2 than MDMA (32), suggesting methylone is more selective for monoamine transporters and that the psychopharmacology of these drugs occurs at the level of the monoamine transporters. Finally, repeated doses of methylone do not deplete brain serotonin like MDMA (10), suggesting that methylone may be more amenable to repeated clinical dosing at shorter intervals than MDMA, shortening the overall treatment duration.

Another consequence of MDMA's effect on serotonin uptake and release is the potential interference of other drugs that have serotoninergic mechanisms, including SSRIs. Interference between the activities of MDMA and SSRIs when the drugs are co-administered has been reported previously in preclinical studies (36, 37). More recently, an analysis of phase 2 studies of MDMA-assisted psychotherapy showed that antidepressants that target monoamines, like SSRIs, reduce the efficacy of MDMA treatment (38), and exploratory analyses confirm a dampening of MDMA effectiveness by SSRIs (39), suggesting that patients should stop taking SSRIs before starting MDMA to gain the full benefit of the treatment. This is problematic because SSRIs are a first-line treatment for disorders like depression, anxiety, and PTSD, and it can take weeks or months to wean off of an SSRI, delaying treatment and risking serious worsening of patients' symptoms in the interim. Co-treatment with an SSRI had no effect on methylone's

efficacy in the FST. Future studies in rodents and humans will determine whether SSRIs may be coadministered with methylone, as that would be a potential advantage of methylone over MDMA.

Methylone also had anxiolytic activity in a preclinical measure of anxiety, the OFT. A previous study showed there was no effect of MDMA on anxiety at clinically relevant doses, and that higher doses were anxiogenic (40), perhaps due to serotonin depletion (41). The anxiolytic activity of methylone observed here may be attributable to the fact that it does not deplete serotonin (10) and may be a serotonin receptor 1A (5-HTR1A) partial agonist (42), however, not all reports support activity at 5-HTR1A (43). Drugs with 5-HTR1A partial agonist activity, such as buspirone or aripiprazole, have anxiolytic effects and/or augment the efficacy of classical antidepressants, so this remains a direction of future study. Methylone is a monoamine uptake inhibitor and releaser. It acts as a substrate at plasma membrane transporters for dopamine (DAT), norepinephrine (NET), and serotonin (SERT) [reviewed by Baumann et al. (44)]. Overall, published reports suggest that methylone shows higher affinity for and greater effect on monoamine uptake inhibition at DAT and NET compared with SERT (32, 42, 43), distinguishing it from MDMA. In addition, methylone shows weak, if any, affinity for other 5-HT, NE, or DA receptors (43), suggesting that its primary mechanism may be through its actions at DAT, NET, and SERT. Our data provide the first behavioral evidence for the effectiveness of methylone in antidepressant and anxiety tests. Future work will address the underlying mechanism of action.

A limitation of the FST and its reliance on immobility as a primary outcome is that drugs that stimulate locomotion, like methamphetamine, can produce a false-positive result (45). It is notable, however, that there is often a dissociation between locomotor effects and immobility in the FST. For example, our data show that fluoxetine reduces immobility (increases swimming in the FST) but also reduces locomotor activity. Since methylone is a stimulant, reported previously to increase locomotor activity in rodents (46–49), it was important to investigate the effects of methylone on locomotor activity at all the doses used in the FST. Our results support the conclusion that the antidepressant effect of methylone is not driven solely by changes in locomotor activity because (1) lower doses of methylone (5–10 mg/kg) that are effective in the FST had no effect on locomotor activity in the OFT, and (2) 24 h after a higher dose (15 mg/kg), the antidepressant effect of methylone persisted while the locomotor effect resolved.

Antidepressant effects can differ depending on the emotional state of the animals being tested (50). Our studies were performed in naïve animals since the FST does not require repeated or chronic stress to elicit effects of antidepressants. Future studies will explore the effects of methylone in chronically stressed animals, and these experiments will help to extend our current findings and understand methylone's effects in an animal model displaying deficits in emotional behavior.

The translatability of the FST has been questioned, despite its use for over 40 years to screen drugs with antidepressant-like activity (51, 52). However, we believe that it remains a useful screening tool. The translatability of our findings is supported by the reported positive clinical experience with methylone described in a recent retrospective case series of individuals with PTSD (13) and MDD (15). Using an allometric approach to dose scaling (53), rat doses are scaled to a human equivalent dose by dividing the rat dose (mg/kg) by 6.2 and multiplying by an average human bodyweight (estimated at 65 kg). Using this method, our data suggest that the most effective doses in the FST (10–15 mg/kg) correspond to human doses of approximately 100–150 mg. These doses have been evaluated in a phase 1 clinical study and are well tolerated, with no severe adverse events reported and with an effective but "gentler" subjective experience than MDMA (5, 11).

In conclusion, our results suggest that methylone may have a role in treating MDD and anxiety. Future studies in rodents and humans aim to determine whether methylone may also have potential for treating PTSD and other disorders for which antidepressants are effective.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This animal study was reviewed and approved by the Melior Discovery Institutional Animal Care and Use Committee (behavioral studies) and the WuXi AppTec Institutional Animal Care and Use Committee (pharmacokinetic studies).

Author contributions

JW-S, MS, and SO conceived and designed the studies. JW-S analyzed the data and wrote the manuscript with comments from SO, MS, BM, CP, and BK. All authors contributed to the article and approved the submitted version.

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Conflict of interest

BK was a co-founder, advisor, and has equity in Transcend Therapeutics and was also a consultant for Ceruvia Lifesciences. JW-S, MS, BM, and SO were employees and had equity in Transcend Therapeutics. MS, JW-S, and BM were co-inventors on a US Patent Application 17/887,962 filed on August 15, 2022 by Transcend Therapeutics. CP was a consultant to Transcend Therapeutics, Ceruvia Lifesciences, Freedom Biosciences, Biohaven Pharmaceuticals, and Nobilis Therapeutics.

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Classic psychedelics do not affect T cell and monocyte immune responses

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Introduction: Classic psychedelics have been shown to exert therapeutic potential for the treatment of various psychiatric disorders, neuropsychiatric diseases, and neuronal damage. Besides their psychopharmacological activity, psychedelics have been reported to modulate immune functions. There has thus far been a sparse exploration of the direct immune-modulating effect of psychedelics on human immune cells *in vitro*. Since T cells are key mediators of several immune functions, inhibition of their function would increase the risk of infections.

Methods: We investigated the effect of the classic psychedelics lysergic acid diethylamide (LSD), psilocin, *N,N*-dimethyltryptamine (DMT), and mescaline on the proliferation and stimulated cytokine release of primary human T lymphocytes and on the stimulated NF-κB induction of monocytes.

Results: We did not observe any relevant direct immune-modulatory effects of the tested classic psychedelics in either cell line.

Discussion: We concluded that LSD, psilocin, DMT, or mescaline did not directly stimulate the proliferation or cytokine secretion of primary human T lymphocytes or stimulate NF-κB induction of monocytes. Our findings support the future safe use of classic psychedelics in assisted psychotherapy in patients with life-threatening diseases where immune suppression and diminished immune function would be detrimental.

KEYWORDS

psychedelic, LSD, psilocin, DMT, mescaline, T cell, monocyte

1. Introduction

Psychedelics are psychoactive substances that alter cognition and perception predominately through agonistic activity at various serotonin (5-hydroxytryptamine, 5-HT) receptors, whereby 5-HT_{2A} receptor agonism is the main psychoactive/psychedelic trigger (1–3). The so-called "classic psychedelics" comprise tryptamines, such as *N,N*-dimethyltryptamine (DMT), and psilocybin, lysergamides, such as lysergic acid diethylamide (LSD), and phenethylamines, such as mescaline. A growing body of evidence shows that psychedelics have therapeutic potential for the treatment of various psychiatric disorders such as major depression, anxiety, post-traumatic stress disorder (PTSD) as well as depression and anxiety due to terminal illnesses (4–8). Moreover, recent *in vivo* studies in rodents suggest that psychedelics may also exert positive effects on neuropsychiatric diseases and neuronal damage,

such as Alzheimer's Disease and traumatic brain injury (9, 10). Besides their psychopharmacological activity, psychedelics have been shown to be able to modulate immune functions (11, 12). It has been suggested that 5-HT_{2A} and 5-HT_{1A} receptor activation is involved in the immune-modulatory effects of psychedelics. The 5-HT_{2A} and 5-HT_{1A} receptor expression have been detected in many tissues mediating inflammatory conditions, including the brain, gut, and cardiovascular system, as well as platelets, endothelial cells, and smooth muscle cells (13–15). Thus, it has been shown that the 5-HT_2 receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) suppresses tumor necrosis factor-alpha (TNF-α)-induced inflammation in rat aortic smooth muscle cells *via* a protein kinase C (PKC)-mediated pathway (16). PKC activation is a canonical pathway elicited through 5-HT_{2A} receptor stimulation (17).

In healthy volunteers, DMT induced time-dependent modifications in lymphocyte subpopulations after an oral application of 1.0 mg/kg body weight (18). The percentage of $CD3^+$ and $CD4^+$ cells decreased, whereas the percentage of natural killer cells increased, showing maximum changes after 2 h and returning to baseline levels after 24 h (18). Moreover, DMT affected the immunological phenotype in isolated mouse brain microglia. The TLR4 expression on $CD11b^+$ cells and microglial NF-κβ (p65) intensity were significantly lower in cells treated with DMT (19). Similar observations have been reported for the psilocin treatment of isolated mouse brain microglia (19). In lymphocytes isolated from human blood, the 5-HT_{1A} receptor agonist DPAT increased cell proliferation whereas it was inhibited by the 5-HT_{1A} receptor antagonist WAY100.46 (20). It has furthermore been shown that 5-HT_{1A}-mediated cell proliferation of mitogen-activated T and B lymphocytes is associated with an increased translocation of NF-κB into the nucleus (21).

There has thus far been a sparse exploration of the direct immune-modulating effect of classic psychedelics on human immune cells *in vitro*. Since T cells are key mediators of several immune functions, inhibition of their function would increase the risk of infections or even tumor formation (22, 23). Hence, besides the potential future application of classic psychedelics in the treatment of autoimmune diseases, the potential adverse effects of diminished immune function and subsequent risk for infections need to be elucidated. This is of special interest since classic psychedelics have been employed in assisted psychotherapy to treat anxiety in patients with life-threatening diseases (24, 25). Therefore, we investigated the effect of the classic psychedelics LSD, psilocin, DMT, and mescaline on the proliferation and stimulated cytokine release of primary human T lymphocytes and on the stimulated NF-κB induction of monocytes. This study aimed to further elucidate the relationship between classic psychedelics and the immune response of human T lymphocyte subpopulations and monocytes.

2. Materials and methods

2.1. Ethics approval statement

All subjects gave written informed consent for blood collection. The blood samples were obtained in an anonymized and coded form from the central blood donation of the University Hospital in Basel and the Blood Transfusion Center of the University Medical Center Freiburg. No ID number of the samples is visible so any assignment is impossible. The work, therefore, does not fall within the scope of the Swiss Human Research Act.

2.2. Preparation and cultivation of human immunocompetent cells

Human peripheral blood mononuclear cells (PBMCs) were isolated from the blood of adult donors. Venous blood was centrifuged on a LymphoPrep^{TM} gradient (density: 1.077 g/cm^3, 20 min, 500 × g, 20°C; Progen, Heidelberg, Germany). Afterward, cells were washed three times with PBS, and cell viability and concentration were determined using the trypan blue exclusion test. Cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium (Invitrogen, ThermoScientific, Reinach, Switzerland) supplemented with 10% heat-inactivated fetal calf serum (PAA, Cölbe, Germany), 2 mM L-glutamine, 100 U/ml penicillin, and 100 U/ml streptomycin (Invitrogen) at 37°C in a humidified incubator with a 5% CO_2/95% air atmosphere. PBMCs were additionally stimulated with anti-human CD3 (clone HIT3) and anti-human CD28 (clone 28.6) mAb (100 ng/ml; both from eBioscience, ThermoScientific, Reinach, Switzerland).

2.3. Cell division tracking using carboxyfluorescein diacetate succinimidyl ester

Peripheral blood mononuclear cells were harvested and washed twice in cold PBS (Invitrogen) and re-suspended in PBS at a concentration of 5 × 10^6 cells/ml. Carboxyfluorescein diacetate succinimidyl ester (CFSE, 5 mM; Sigma-Aldrich, Merck, Buchs, Switzerland) was diluted 1/1,000 and incubated for 10 min at 37°C. The staining reaction was stopped by washing twice with the complete medium. PBMCs were activated as described above and cultured with psychedelic compounds for 72 h. Cyclosporine A (CsA, 5 μg/ml, Sandimmun^{TM} 50 mg/ml, Novartis, Basel, Switzerland) served as a control substance for proliferation inhibition. Cell division progress was analyzed from three independent experiments with a BD FACSCalibur flow cytometer using BD CellQuest Pro software.

2.4. Quantification of intracellular cytokine production and activation marker

For determination of mediator production and activation marker by PBMCs, cells were activated and treated with psychedelic compounds or CsA for 48 h. PBMCs were then re-stimulated using phorbol-12-myristate-13-acetate (PMA; 50 ng/ml) and ionomycin (500 ng/ml; both from Sigma) and incubated with BD Golgi Plug^{TM} (BD Biosciences, Allschwil, Switzerland) for 4 h. After washing, cells were fixed with 4% paraformaldehyde (PFA; Morphisto, Offenbach am Main, Germany), and staining of intracellular cytokines and markers

was carried out using fluorochrome-conjugated anti-human mAbs (BioLegend, Amsterdam, Netherland, and Beckman Coulter, Zurich, Switzerland). The levels of cytokine production and activation marker expression were determined using flow cytometric analysis of three independent experiments.

2.5. Evaluation of NF-κB expression

The human cell line tagged with an enhanced green fluorescent protein (eGFP) THP-1 NF-κB-eGFP was purchased from Merck (Zug, Switzerland) and is derived from a single-cell clone of THP-1 cells stably transfected with an NF-κB-eGFP reporter construct (26). The parental THP-1 cell line was derived from the peripheral blood of a 1-year-old male suffering from acute monocytic leukemia (27). The cells were cultured in Roswell Park Memorial Institute (RPMI) 1,640 medium (Invitrogen) supplemented with 10% heat-inactivated fetal calf serum (PAA), 2 mM L-glutamine, 100 U/ml penicillin, and 100 U/ml streptomycin (Invitrogen) at 37°C in a humidified incubator with a 5% CO_2/95% air atmosphere. The cells were stimulated with lipopolysaccharide (LPS: 100 ng/ml, Sigma). Incubation was carried out for 24 h in the presence of medium alone, control substances, and psychoactive compounds. The levels of NF-κB expression reflected by eGFP were determined using flow cytometric analysis of four independent experiments.

2.6. Statistical analysis

Data were statistically analyzed using GraphPad Prism (Version 9.3.1, San Diego, CA, USA). The effects of each drug on proliferation rate, cytokine release, and NF-κB induction were evaluated using one-way ANOVA (Brown-Forsythe and Welch ANOVA tests) followed by Dunnett's T3 multiple comparisons test to compare drug effects to stimulated control cells. $^{*}P < 0.05$ was used as the minimum criterion for statistical significance for all experiments.

3. Results

3.1. Psychedelics do not affect primary human T cell proliferation

First, we assessed whether the classic psychedelics LSD, psilocin, mescaline, and DMT inhibit the proliferation of stimulated primary human T cells. The used concentration range of 1–30 μM represents suprapharmacological concentrations of LSD, psilocin, and DMT, when compared to maximal plasma concentrations measured in clinical studies (200 μg LSD oral: 12.1 ± 1.2 nM, 30 mg psilocin oral: 97.9 ± 26.4 nM, 1 mg/min DMT i.v. for 90 min: 236.4 ± 67.5 nM) (28–30). Mescaline plasma concentrations after a 200 mg oral dose were in the range of 4 μM (31). As shown in **Figures 1A–D**, none of the tested psychedelics affected the proliferation rate at concentrations of up to 30 μM. In contrast, the positive control CsA strongly inhibited T cell proliferation. However, the addition of 10 μM of either psychedelic compound to CsA accentuated proliferation inhibition.

3.2. Activation and mediator release of primary human CD8$^+$ T cells by psychedelics

We assessed the activation of stimulated primary human CD8$^+$ T cells by determining CD69 expression as an early marker of lymphocyte activation (32). As depicted in **Figure 2A**, none of the tested psychedelics reduced CD69 expression in stimulated CD8$^+$ T cells. However, CsA did not significantly reduce CD69 expression in stimulated CD8$^+$ T cells. Next, we determined the released interleukin-2 (IL-2), which acts as a growth regulator of T cells *in vitro* and supports the proliferative expansion of cytotoxic T lymphocytes (33). **Figure 2B** shows that none of the tested psychedelics significantly affected IL-2 release in stimulated CD8$^+$ T cells. In contrast, CsA significantly reduced IL-2 release, which was even more pronounced by the addition of 10 μM of either psychedelic compound.

Moreover, we assessed the potential effect of psychedelics on CC-chemokine ligand 4 (MIB1b) release, which has been shown to be up-regulated in patients with type 2 diabetes mellitus and clinical atherosclerosis cardiovascular diseases (34). As shown in **Figure 2C**, none of the tested psychedelics significantly affected the release of CC-chemokine ligand 4 in stimulated CD8$^+$ T cells. However, the positive control CsA significantly reduced the release of CC-chemokine ligand 4, which was not further accentuated by the addition of either psychedelic.

To complement the assessment of stimulated primary human CD8$^+$ T cell activation, we investigated the release of TNF-α. TNF-α release is regulated by various functions, including cell growth modulation, tumorigenesis, inflammation, and autoimmunity (35, 36). **Figure 2D** shows that none of the tested psychedelics had a significant effect on TNF-α release. In contrast, CsA significantly reduced the release of TNF-α, which was not further accentuated by the addition of either psychedelic.

3.3. CD69 activation and mediator release of primary human CD4$^+$ T cells by psychedelics

Next, we investigated the activation of stimulated primary human CD4$^+$ T cells by determining the CD69 expression and the release of various mediators. Similar to the results obtained in stimulated CD8$^+$ T cells, none of the tested psychedelics reduced CD69 expression in stimulated CD4$^+$ T cells (**Figure 3A**).

Moreover, none of the tested psychedelics significantly affected IL-2 release in stimulated CD4$^+$ T cells. In contrast, the included positive control CsA significantly reduced IL-2 release, which was not further accentuated by the addition of either psychedelic compound (**Figure 3B**).

Figure 3C shows that none of the tested psychedelics had a significant effect on TNF-α release up to 10 μM. However, at a concentration of 30 μM, each tested compound reduced TNF-α release below 50%, which was in the same range as the combination of CsA and 10 μM of the respective compounds.

Moreover, we assessed the potential effect of psychedelics on IL-21 release, which is needed to propel central and effector memory CD8 T cell differentiation (37). None of the tested psychedelics significantly affected IL-21 release in stimulated CD4$^+$ T cells. In

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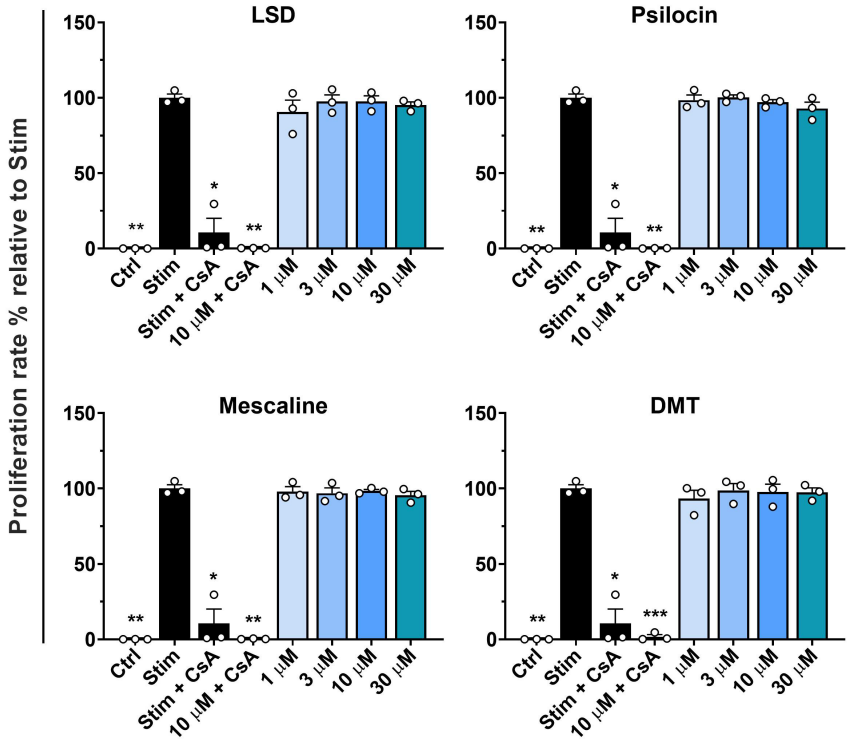

FIGURE 1
Influence of classic psychedelics on the proliferation of primary human T lymphocytes. PBMCs were stimulated with anti-human CD3 and anti-human CD28 mAb (Stim) and incubated in the presence of medium alone (Neg Ctrl), different control substances, and psychedelic compounds for 72 h. Cyclosporine A (CsA) served as a control substance for proliferation inhibition. Data are the mean ± SD from three independent experiments. Data were analyzed by one-way ANOVA followed by Dunnett's T3 multiple comparison test (***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ when compared to stimulated cells without drug treatment).

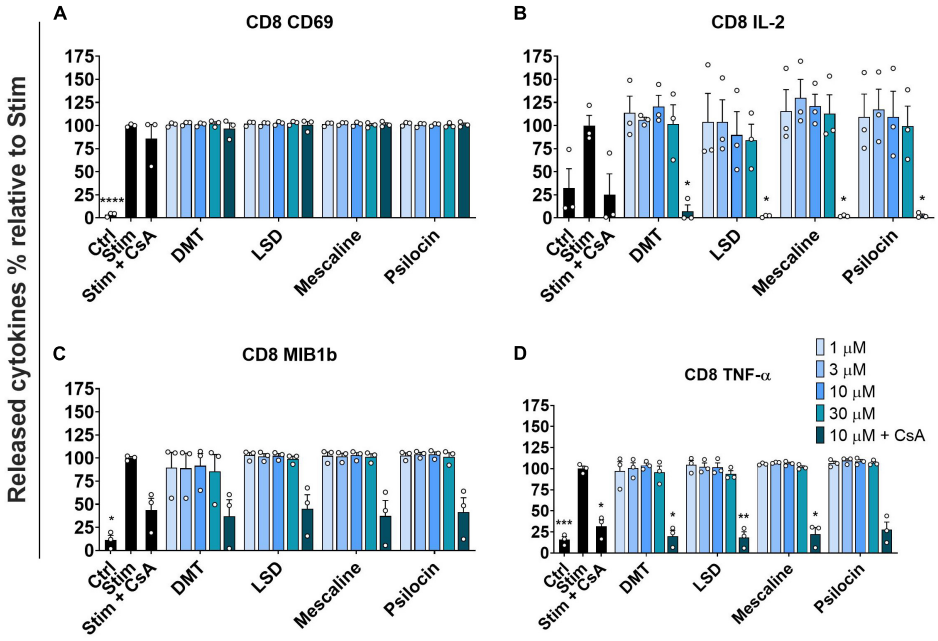

FIGURE 2
Influence of classic psychedelics on **(A)** the activation (CD69) and function/mediator release in form of **(B)** IL-2 release, **(C)** CC-chemokine ligand 4 (MIB1b) release, and **(D)** TNF-α release of primary human $CD8^+$ T cells. PBMCs were stimulated with anti-human CD3 and anti-human CD28 mAb (Stim) and incubated in the presence of medium alone (Neg Ctrl), different control substances, and psychedelic compounds for 48 h. PBMCs were re-stimulated with PMA and ionomycin for 4 h. Cyclosporine A (CsA) served as a control substance for cytokine release inhibition. Data are the mean ± SEM from three independent experiments. Data were analyzed by one-way ANOVA followed by Dunnett's T3 multiple comparison test (****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ when compared to stimulated cells without drug treatment).

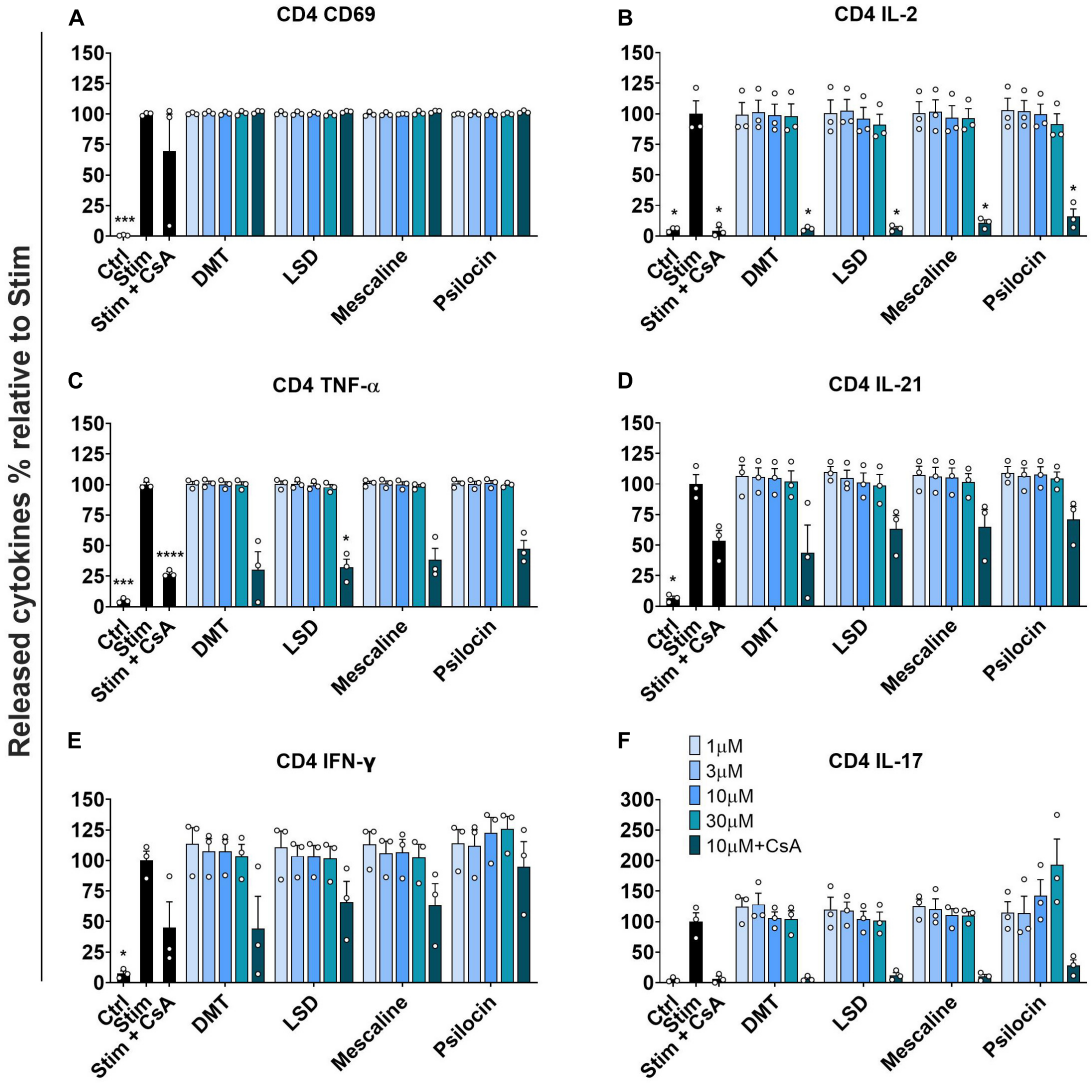

FIGURE 3
Influence of classic psychedelics on **(A)** the activation (CD69) and function/mediator release in form of **(B)** IL-2 release, **(C)** TNF-α release, **(D)** IL-21 release, **(E)** IFN-γ release, and **(F)** IL-17 release of primary human CD4$^+$ T cells. PBMCs were stimulated with anti-human CD3 and anti-human CD28 mAb (Stim) and incubated in the presence of medium alone (Neg Ctrl) and psychedelic compounds for 48 h. PBMCs were re-stimulated with PMA and ionomycin for 4 h. Cyclosporine A (CsA) served as a control substance for cytokine release inhibition. Data are the mean ± SEM from three independent experiments. Data were analyzed by one-way ANOVA followed by Dunnett's T3 multiple comparison test (****$P < 0.0001$, ***$P < 0.001$, *$P < 0.05$ when compared to stimulated cells without drug treatment).

contrast, the included positive control CsA reduced IL-21 release to around 50%, which was not further accentuated by the addition of either psychedelic compound (Figure 3D).

Next, we investigated the effect of psychedelics on the release of interferon-gamma (IFN-γ), which serves as a crucial inducer of immune effector mechanisms between innate immune cells and effector memory T cells (38).

Figure 3E shows that none of the tested psychedelics significantly reduced IFN-γ release in stimulated CD4$^+$ T cells. However, CsA significantly reduced IFN-γ release, which was not further accentuated by the addition of either psychedelic.

Moreover, we assessed the potential effect of psychedelics on IL-17 release, which is associated with various inflammatory autoimmune diseases (39).

As shown in Figure 3F, none of the tested psychedelics significantly affected IL-17 release in stimulated CD4$^+$ T cells. In contrast, CsA significantly reduced the release of IL-17, which was not further accentuated by the addition of either psychedelic.

3.4. Effect of psychedelics on LPS-triggered NF-κB induction of THP1-NF-κB reporter cells

Since we did not observe any relevant immune-modulatory effects of classic psychedelics in the investigated T cell lines, we included the human monocytic THP-1 cell line to monitor the NF-κB signal transduction pathway. Monocytes contribute substantially to pro-inflammatory immune responses in humans, and the transcription factor NF-κB represents a central mediator of inflammation (40, 41). Thus, we assessed the effect of classic psychedelics on the LPS-triggered GFP-NF-κB induction. As shown

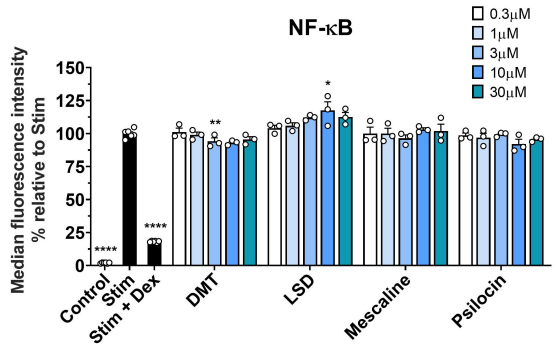

FIGURE 4
Effect of classic psychedelics on the LPS-triggered GFP-NF-κB induction of THP1 NF-κB reporter cells. THP-1 NF-κB-eGFP cells were stimulated with LPS (Stim) and incubated in the presence of medium alone (Ctrl) and classic psychedelics for 24 h. Dexamethasone (Dex) served as a control substance for NF-κB inhibition. Data represent the mean ± SD from four independent experiments. Data were analyzed by one-way ANOVA followed by Dunnett's T3 multiple comparison test (****$P < 0.0001$, **$P < 0.01$, *$P < 0.05$ when compared to stimulated cells without drug treatment).

in Figure 4, none of the tested psychedelics reduced the NF-κB signal compared to the control incubations. However, dexamethasone, which was included as a positive control, significantly reduced the NF-κB signal. Hence, we do not expect LSD, psilocin, DMT, or mescaline to affect the monocytic immune reaction *via* the NF-κB signal transduction pathway in humans.

4. Discussion

The results of the current study indicate that the classic psychedelics LSD, psilocin, DMT, and mescaline do not directly modulate the proliferation or stimulated cytokine release of human T lymphocyte subpopulations. Moreover, classic psychedelics have no effect on the stimulated NF-κB signal in monocytes. Since classic psychedelics are utilized in assisted psychotherapy in patients with life-threatening diseases such as end-stage cancer (4, 42), suppressing effects on lymphocytes or monocytes are unwanted. Immune-suppressive effects of psychedelics would hamper the future treatment of patients with already impaired immune systems. However, worsened immune system function after psychedelic-assisted psychotherapy has not yet been observed. In contrast, the safety of psychedelic treatments has been reported in several studies (24, 43–45), which is in line with the results of the current study.

Nevertheless, studies in PBMCs and animal models have reported potent anti-inflammatory effects due to 5-HT_{2A} or 5-HT_{1A} receptor activation (16, 20, 21, 46, 47). A study investigating the significance of 5-HT in inflammation showed that 5-HT and DOI inhibited TNF-α production in LPS-stimulated PBMCs. Moreover, the inhibitory effect of 5-HT and DOI on TNF-α production was associated with the activation of the 5-HT_{2A} receptor (47). However, all 5-HT and DOI concentrations used in this study (up to 100 μM) that inhibited TNF-α production were much higher than any plasma concentrations detected in humans and could therefore be considered not clinically relevant. In addition, Cloëz-Tayarani and colleagues (47) did not observe any relevant effect of 5-HT or DOI on the production of various interleukins, which is in line with our observations. Yu and colleagues (16) showed that DOI reduces the effects of externally added TNF-α in mouse primary aortic smooth muscle cells, inhibiting various TNF-α-mediated pro-inflammatory markers. Since the effects of DOI on externally added TNF-α were investigated, these findings do not contradict the results of the current study. We analyzed the effect of classic psychedelics on the release of TNF-α from primary $CD4^+$ and $CD8^+$ T cells, which was not affected. However, subsequent effects of TNF-α-mediated pro-inflammatory markers were not part of the current investigation. Studies investigating the association of 5-HT_{1A} receptor activation and immune modulation showed that the potent and selective 5-HT_{1A} receptor agonist DPAT induces lymphocyte proliferation probably by increased translocation of NF-κB into the nucleus (20, 21). However, none of these studies observed immunomodulatory effects of psychedelics, although several psychedelics potently activate the 5-HT_{1A} receptor (48). We, therefore, assume that the in the current study tested psychedelics are, in contrast to DPAT, not potent or selective enough 5-HT_{1A} receptor agonists to induce immune modulation.

In the current study, drug effects were assessed after 24–72 h treatment, whereas a *in vivo* study in healthy volunteers reported peak effects of CD3 and CD4 decrease after 2 h (18). In contrast to the *in vivo* situation, lymphocytes isolated *ex vivo* do not show stable and meaningful cytokine production after such short stimulation periods and therefore cannot be reliably analyzed earlier at the secretion level, since at least 24–48 h are required. Moreover, to assess the cell proliferation parameter, an experimental period of 48–72 h is required to observe meaningful division of the cells *in vitro*. The above-mentioned *in vivo* study (18) analyzed the percentage of certain subpopulations in the blood as well as neuroendocrine factors, whereas in the current study the cytokine secretion by lymphocytes was assessed.

The same study in healthy volunteers showed that both DMT and d-amphetamine significantly decreased peak CD3 and CD4 levels shortly after treatment. Due to the remarkable similarity between the effects of DMT and d-amphetamine, whereof d-amphetamine is no 5-HT_{2A} receptor agonist, the authors concluded that the observed effects were caused by an indirect mechanism rather than specific drug–target interactions with immune cells (18). Hence, they showed that increased cortisol levels due to DMT and d-amphetamine treatment caused decreased peak CD3 and CD4 levels. These results are in line with the observations of the current study, showing that classic psychedelics do not directly affect primary T lymphocytes and monocytes. The mixed stimulant-psychedelic substance 3,4-methylenedioxymethamphetamine (MDMA), which is also used in substance-assisted therapy, similarly acts as a cortisol releaser (49) and also decreases CD4 T-helper cells and the functional responsiveness of lymphocytes to mitogenic stimulation. In addition, MDMA increased natural killer cells and some anti-inflammatory cytokines (transforming growth factor-β and IL-10) but reduced anti-inflammatory IL-2 (50). The activation of the sympathetic nervous system and cortisol release have a known modulatory effect on lymphocytes (51). Similar to the above-mentioned results of Dos Santos and colleagues (18), psilocybin and LSD administrations have been shown to acutely increase cortisol levels in humans (52, 53). It has been suggested that psychoactive substances stimulate stress responses through the 5-HT_{2A} receptor and the associated cortisol release (54). Taken together, this might explain the immune-modulatory effects of classic psychedelics observed in humans or animal models that were attenuated by 5-HT_{2A} receptor inhibition

(18, 52, 55, 56). Hence, classic psychedelics, as well as other cortisol release–stimulating compounds such as d-amphetamine, seem to have indirect anti-inflammatory effects. However, these effects are not elicited by direct stimulation of T lymphocytes or monocytes.

5. Conclusion

The classic psychedelics LSD, psilocin, DMT, and mescaline do not directly stimulate the proliferation or cytokine secretion of primary human T lymphocytes or monocytes. However, classic psychedelics, as well as other psychoactive substances, may induce cortisol release potentially through 5-HT_{2A} receptor activation, leading to anti-inflammatory effects in humans and animal models. These findings are of significance for the future safe use of classic psychedelics in assisted psychotherapy in patients with life-threatening diseases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AA performed all experiments and analyzed the data with assistance of CG. DR wrote and revised the manuscript with significant inputs from ML and CG. All authors contributed to the article and approved the submitted version.

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Conflict of interest

ML was a consultant for Mind Medicine Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Navigating intensive altered states of consciousness: How can the set and setting key parameters promote the science of human birth?

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The subjective childbirth experience is crucial from a public health standpoint. There is a correlation between a negative childbirth experience and a poor mental state after birth, with effects that go far beyond the postpartum (PP) period. This paper offers a new approach as to how birthing experiences, and birth in general, can be navigated. The theory of set and setting proves that psychedelic experiences are shaped, first and foremost, by the mindset of an individual entering a psychedelic experience (set) and by the surroundings in which the experience happens (setting). In research on altered states of consciousness during psychedelic experiences, this theory explains how the same substance can lead to a positive and life-changing experience or to a traumatic and frightening experience. Because recent studies suggest that birthing women enter an altered state of consciousness during physiological birth ("birthing consciousness"), I suggest analyzing the typical modern birthing experience in terms of set and setting theory. I argue that the set and setting key parameters can help design, navigate, and explain many psychological and physiological elements of the human birth process. Thus, an operative conclusion that emerges from the theoretical analysis presented in this paper is that framing and characterizing the birth environment and birth preparations in terms of set and setting is a central tool that could be used to promote physiological births as well as subjective positive birthing experiences, which is currently a primary, yet unreached goal, in modern obstetrics and public health.

KEYWORDS

altered states of consciousness (ASC), birth experience, birth medicalization, human birth, intensive inner dynamic, life-altering experiences, sensitive feedback loop, set and setting

1. Introduction

This theoretical paper aims to introduce the critical parameters of "set and setting" from the field of psychedelic research to the field of childbirth research and argue that, if taken seriously, these parameters would significantly advance scientific understanding concerning the birth process and the factors that contribute to or hinder the physiological birth process as well as concerning polar birth experiences.

In spite of the many advances in the field of modern obstetrics, childbirth has become more dangerous to women in the Western world—because of the increase in highly medicalized birth (1, 2). Practices that were originally lifesaving became standard practices. However, these routine procedures do not seem to relate to a reduction in mortality ratios (3). The dangers of highly medicalized birth are both physiological and mental (4). Physiological recovery after natural and less medicated birth is generally far faster and easier than after a highly medicated birth, for example in terms of pelvic floor health (5–7), and according to many studies, the subjective experience of the birthing woman during childbirth affects her postpartum (PP) mental health (8). Acute stress and fear during childbirth hinder the birth process, necessitating medical interventions that have negative physiological and mental health consequences, compared to the physiological birth process with minimum medical intervention (9–11).[1]

Thus it is crucial to understand the factors that shape birth experiences. I propose that a fruitful way to do so would be through comparing physiological birth experiences to psychedelic experiences. There are at least four clear resemblances between the two phenomena.

First, both experiences are, in many cases, associated with altered states of consciousness: the phenomenology of both states is similar, and there is a probability that both have the similar brain mechanism of hypofrontality [see (12–14)]. Altered states of consciousness are typically experienced during activities such as meditation, hypnosis, daydreaming, dreaming, certain drug states, and prolonged running or other extreme sports activities. Dancing, swimming, hiking, swaying in prayer, fasting, or pain stimulations–may also lead to altered states of consciousness experiences in varying degrees (15).

Second, both birth experiences and psychedelic experiences, have an intensive inner dynamic (16, 17) derived from being an altered state of consciousness. This means that there are compound and dynamic emotional and physiological instabilities during childbirth (16). Not all altered states of consciousness always have such an intensive dynamic, for example, a meditative state.

Third, seemingly connected to this intensity, both can be analyzed in terms of surprising causal feedback loops. Causal feedback loops encompass response dynamic: the results of a certain variation, even a minor one, may strengthen, or contradict the initial variation. They introduce complex dynamics by which a shift in one feature may impact a different feature, which then is capable of impact the initial feature. Feedback loops can amplify an event in either a positive or negative direction (18). The birthing experience is created by an highly sensitive feedback loop, because the experience is produced and influences by many factors, that interact and sometimes interrupt one another, such as the mental states of the birthing woman before and during the event of birth, and the communication and interactions with other people in the birth environment (10, 16, 18, 19). Hallucinogens also may lead to these feedback loops (20). In fact, the significant impacts of psychedelics are the result of disruption in the processing of information in brain areas, particularly in the striato–thalamo–cortical feedback loops, with information coming from both internal and external stimuli (21, 22).

Fourth, there are two opposing, extreme subjective experiences possible for both phenomena. Psychedelic substances can generate a tremendously good experience–a "good trip"–but the same substance can sometimes generate the opposite sensation–a "bad trip" (23). A good psychedelic experience may have a persistent positive effect [see (24)]. Similarly, the physiological birth experience sometimes generates a feeling of joy that can be life-altering (e.g., enhancing self-esteem, boosting energy) (10, 11), but it sometimes can be felt as devastating and traumatic (8), even generating post-traumatic stress disorder (PTSD) (10). This effect is unique to birthing and psychedelic experiences. It seems that it is not so dramatically polarized in other altered states of consciousness, such as meditation, hypnosis, or a runner's high (12). For example, I do not believe it is common to experience a traumatic marathon or meditation session. Perhaps this is because these activities can be stopped at will, while normally one cannot stop birthing at will once it is started or stop a psychedelic effect after a mind-altering substance has been taken.

On the face of it, this looks like an enigma: how can the same substance in the case of psychedelics, or the same physiological process in the case of childbirth, produce such extreme and opposing experiences, with such extreme and opposing consequences? For psychedelic experiences, the enigma has been solved through the theory of set and setting parameters that predict and explain how the set and setting surrounding the experience have the power to influence and design the opposing psychedelic experiences (17, 20, 25–29). However, this phenomenon is still an enigma concerning childbirth [see also (10)].

Because of the similarities between birth and psychedelic experiences (illustrated in **Figure 1**), I argue that it would be useful to explore whether set and setting criteria would also help to solve the enigma in the case of childbirth experiences. I also aim to show that analyzing the opposing extreme ends of birth experiences in terms of set and settings would offer empirical support for the hypothesis that almost all set and setting parameters can be controlled. Thus, with the use of set and setting parameters, childbirth could be navigated to be more physiological and more often a positive experience.

In section "2. Birthing consciousness: The unique altered state of consciousness during physiological birth," I elaborate on "birthing consciousness," which is the altered state of consciousness that many women go through during physiological childbirth, and on the extreme polar ends of the birth experience. In section "3. Set and setting as an explanation for the extreme ends of altered states of consciousness experiences," I explain set and setting parameters and how they diminish the enigma of opposing and extreme psychedelic experiences. In section "4. The new hypothesis: The same set and setting key parameters shape both psychedelic and birthing experiences," I offer an analysis of the human birth physiology and experience in terms of set and setting and show how the theory can also solve the enigma concerning opposing birth experiences. In section "5. Discussion: Designing and navigating the childbirth experience rather than controlling it through medicalization," I discuss the difference between "controlling" birth with techno-medical methods and "navigating" birth using set and setting framing, and I suggest a model for empirical research. Section "6. Conclusion: How the science of consciousness can promote the science of birth" is a summary of the paper and its claim that the same set and setting key parameters can help design, shape, and thus also navigate both psychedelic experiences and birthing experiences, concluding with the suggestion that the science of consciousness

1 It is acknowledged that not all birthing persons are *cis* gender women. The terms "women" and "mothers" and female pronouns are used throughout this paper for the sake of simplicity, but the analysis applies to the birthing experiences of all birthing persons.

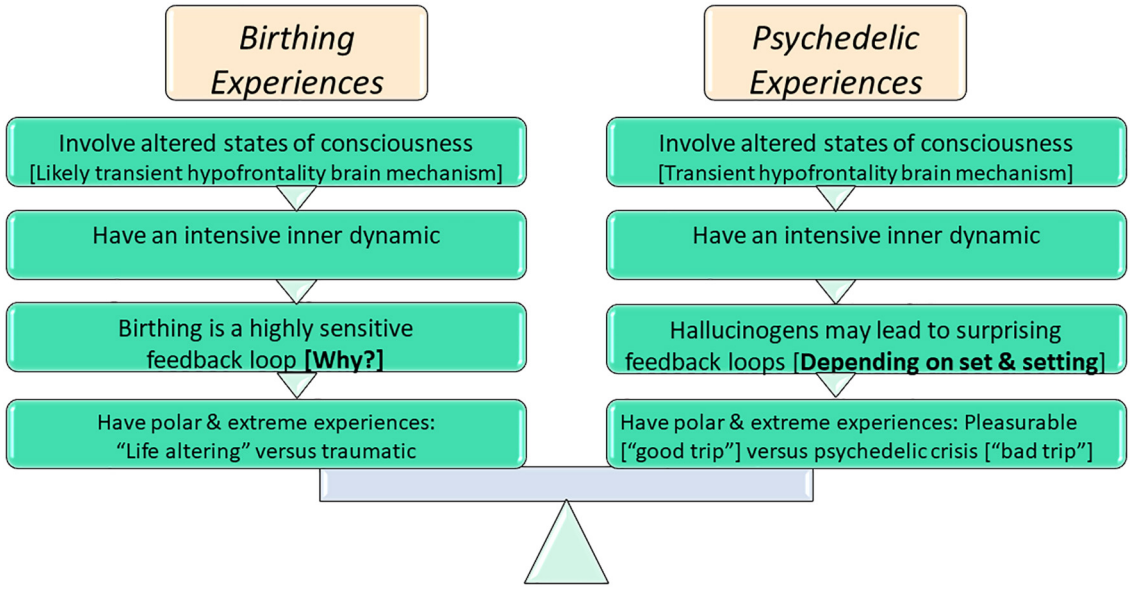

FIGURE 1
Comparing birthing experiences to psychedelic experiences.

in general, and psychedelic research in particular, can promote the science of human birth.

2. Birthing consciousness: The unique altered state of consciousness during physiological birth

Birthing consciousness is an extremely positive altered state that women can experience during physiological childbirth (9, 12, 30). Labor contractions usually start easy, and intensify as labor continue (31). Women who experienced physiological natural childbirth describe a "transcendent" experience (32), with sensations of being in another zone, or another planet (11, 33), which is a less communicative state (13). It appears as a healthful dissociative state (33–35), because as physiological labor continues, although the pain of contractions intensifies, women report being calmer, along with reduced pain perception (36, 37).

I have suggested (12) that this specific altered state of consciousness during birth shares the same brain mechanism as other altered states of consciousness that have similar phenomenological and cognitive features. This brain state is the transient hypofrontality brain mechanism: the downregulation of prefrontal cortex function. I have hypothesized (12, 30) that transient hypofrontality is a key to natural birth, because this specific brain state helps a woman to cope with labor stress and labor pain [see also (9)].

2.1. The polar extremes of childbirth experiences

The birthing experience vastly effect the birthing person, not only in the immediate PP (35), and the method of birth is a significant factor influencing the birthing experience (11, 34, 35, 38). Commonly, the delivery methods used in childbirth are categorized as being one of two types: physiological birth (natural birth) and birth with medical intervention (such as Epidural anesthesia, Pitocin, instrumental delivery, episiotomy, or cesarean birth). However, it is more accurate to view delivery methods as falling on a spectrum—ranging from a birth with no interventions or professional assistance at all (what is called freebirth or unassisted birth) to the most medicalized birth. Having this spectrum perspective allows us to take into account that most Western birthing persons today choose a standard medically managed hospital childbirth, and even the minority of women who choose homebirth choose to be assisted by a childbirth professional (39). Hence, discussing physiological birth as if it were a completely natural birth with no medical intervention or professional assistance is not accurate. Thus, in referring to physiological or natural birth here, I am referring to childbirth that is less medicated and less disturbed, even though the birth may be occurring in a hospital with some minor medical intervention.

Around one-third of women describe their birthing experience as a traumatic, and nearly 85% of women experience varying degrees of mood disorders after childbirth (8). However, other women after birth report they have had an extremely positive birthing (40), and refer to feelings of euphoria, amazement, and awe, particularly after a physiological birth (11, 32, 33, 41). Natural birth is often described by women as a life-changing experience conferring a sense of inspiration, achievement, and empowerment (42, 43). Women have reported intense feelings of achievement, joy, and pride immediately after natural birth (33). These sensations, combined with the endorphins released during natural birth, lead to the PP phenomenon known as the "superwoman syndrome": immediately after giving birth naturally, the birthing woman feels as if she can accomplish anything (41).

Concerning maternal mental health, it was found (8) that a highly medicated birth (instrumental births and emergency cesareans) is linked to mental disorder symptoms— such as somatization, depression, and anxiety [see also (11)].

Olza et al. (14), p. 11) stresses the importance of understanding the altered state of consciousness in physiological childbirth:

> This description of women's experiences during labor and birth and its potential for transformation resembles descriptions of mystical states of consciousness. Classically these states have been achieved through meditation and religious practices (including dancing, praying, and fasting) or through intake of substances with hallucinogenic properties such as psilocybin or LSD, which interact with serotonin receptors. Childbirth has not been mentioned in those classical descriptions. *The experience of spontaneous altered states of consciousness may well be a hallmark of physiological childbirth in humans and therefore its research may offer a unique opportunity to understand consciousness and transcendental growth* [emphasis added] . . . This knowledge is important to include in birth preparation courses and consultations.

Thus, I maintain that the existence of polar extremes of the birth experience, with opposite sensations and consequences, calls for investigation using consciousness studies tools.[2]

3. Set and setting as an explanation for the extreme ends of altered states of consciousness experiences

Since Leary et al. (44) coined the concept "set and setting," it has become a fundamental concept in psychedelic research. The theory of set and setting argues that psychedelic experiences are shaped, first and foremost, by the mindset of an individual entering a psychedelic experience (set) and by the environment in which the event occurs (setting) (20, 45). The current accepted view is that the psychedelic experience depends on the set and setting.[3] The set includes the personality, preparations, expectations, and intentions of the person having the experience, and the setting includes not only the physical location but also the people around and the broader sociocultural context (social setting, cultural setting, and relationship with other people) and the important elements of the freedom to exercise autonomy and access to psychological and physical support (20, 26).

Research began in the 1950s, when the Western world began to discover psychedelic substances. For nearly two decades, scientists studied their effects and during the 1970s, many clinical articles were published. However, studies dealing with the same substance produced contradictory conclusions [(20), pp. 67–93]. In fact, there were two polar perspectives concerning psychedelic substances at that time—the psychedelic perspective and the psychomimetic perspective—which affected the design, results, and interpretations of experiments (27). While the psychomimetic studies concluded, for example, that LSD creates a psychosis-like state, the psychedelic studies concluded that LSD could heal one's mind. While the psychomimetic studies concluded that LSD induces anxiety, impairs cognition, and causes disturbances in perception, the psychedelic studies maintained that it induces euphoria, enhances cognitive abilities, and sharpens perception. While the psychomimetic studies concluded that LSD creates a traumatic experience, the psychedelic studies concluded that it creates a life-altering experience [(20), pp. 23–50, 67–93].

Scientists from each perspective presented research results that supported their claims, so the question arose as to how these claims could be so different. The answer turned out to be set and setting. The effect of psychedelic substances is not uniform, but depends on the individual and the situation (26). In other words, non-pharmacological variables have a vital part in the effects of psychedelic substances (46), thus enabling us to predict, to some extent, individual responses to psychedelic substances and help maximize potential benefits and reduce risks (25). It turned out that there were negative set and setting conditions (rigidity, unfamiliarity, non-acceptance) and positive set and setting conditions (flexibility, familiarity, acceptance). With the proper set and setting conditions, people reported positive and useful altered states of consciousness experiences and even that their lives had been changed for the better (20, 47).

Figure 2 sets out the essential differences between the set and setting of the experiments performed during the 1960s and 1970s, depending on the perspective of the researcher. In the psychedelic experiments, the subjects expected a new and exciting experience, and enjoyed a pleasant and supportive environment. The researchers explained to the subjects that the psychedelic experience could sometimes be frightening and very intense but promised them one-on-one support and instructions on how to deal with the difficulties. In contrast, in the psychomimetic experiments, the subjects were not prepared and did not have support during the experiment. Thus, it is no wonder that their experiences were quite opposite and that the conclusions concerning the effects of the psychedelic substances contradicted one another [for a detailed review, see (27)].

4. The new hypothesis: The same set and setting key parameters shape both psychedelic and birthing experiences

As was discussed in the section "1. Introduction," birthing and psychedelic experiences have similarities that can be explained by the set and setting theory. And, as shown in the previous section, the framing of set and setting also has the power to predict future outcomes of such experiences.

The basics of the set and setting theory contradict one of the most fundamental and rooted premises of modern obstetrics—that birth operates as a purely physiological mechanism. In other words, there are body parts, mostly the womb and the pelvis, that function to achieve the goal of ejecting the fetus out of the birthing body. But the birthing woman also births with her mind, not just with her body (9, 34). Thus, her consciousness and her experiences also function during birth, and the physical and social setting has a crucial effect on these body parts. As long as modern obstetrics maintains its flawed assumption regarding childbirth, it will have no real opportunity to

2 I acknowledge that there are women on the spectrum between the extreme ends of the birth experience who experience fewer intense sensations during childbirth and less significant consequences; however, these women are not the focus of the current paper. Future empirical research can determine the percentages of women with these different experiences.

3 Researchers have demonstrated that set and setting also play a crucial role in shaping the effects of diverse psychoactive drugs such as alcohol, methylphenidate (Ritalin), methamphetamine, cocaine, crack, and heroin.

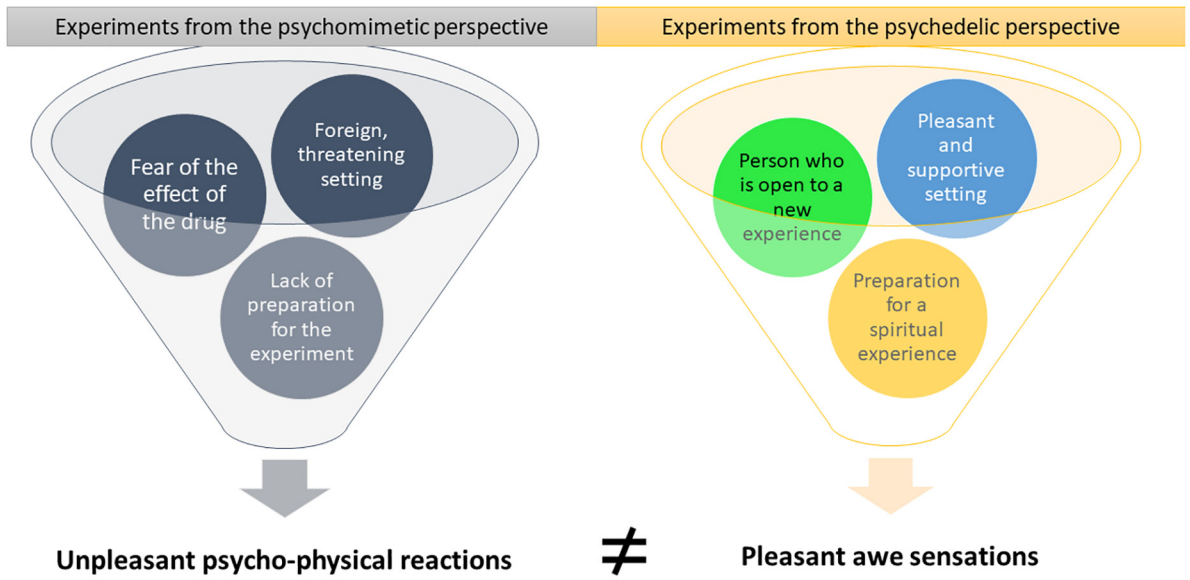

FIGURE 2
Different perspectives lead to different set and setting, thus contradictory results.

seriously acknowledge crucial physical, mental, and social effects on the process of birth (i.e., the set and setting parameters), in spite of increasing bodies of research that empirically validate these kinds of effects. In the following subsections I provide examples of such empirical studies.

4.1. Preparation (set)

In psychedelic research, the term "preparation" refers to the psychological, and perhaps even physiological and environmental, preparation of the person who is about to have the altered state of consciousness experience [(20), pp. 95–128]. This preparation is, of course, also important in the birthing experience. However, there are psycho-physiological, automatic preparations for birth, such as biochemical (31) and brain changes (48). I recently offered a new hypothesis concerning psycho-physiological *automatic preparations* for birth (10). Various researches concerning the maternal brain during pregnancy and after it, reveal remarkable neuroplasticity, and functional and anatomical changes (49–51). While the generally accepted perspective is that these brain changes tend *to prepare the maternal brain for motherhood*, I proposed a complementary perspective, arguing that some of these changes before birth can be *preparations of the maternal brain for childbirth* (48). It seems plausible that the birthing brain is hard wired to experience the unique altered state of consciousness during physiological birth, i.e., birthing consciousness. It seems that the brain is preparing itself for the birthing process, that physiology supports phenomenological characteristics of a focused and calm state (10, 12).

There are also hormonal preparations and activation during birth itself that ameliorate the physiological birth process. Various hormones initiate and maintain the process of birth: oxytocin, endorphins, prolactin, beta-endorphins, and dopamine (31). These biochemistry mechanisms also affect the feelings and reactions of a birthing person (9, 52). For example, beta-endorphins increase pain tolerance (31, 53). The alteration of the pain perception during natural childbirth empowers the possibility for the woman to experience birthing consciousness, with all its psychological and physiological benefits (9).

Thus, it seems that unlike the intentional personal preparation for a psychedelic experience, in the case of preparation for childbirth's special altered state of consciousness, the body and brain of the pregnant woman automatically, adaptively, has 9 months to prepare itself for the birthing hurdle and experience. Of course, there are various social and cultural disturbances to this process, which will be discussed in the following subsections.

4.2. Intentions and expectations (set)

Studies indicate that there are strong connections between the beliefs and perceptions of the birthing woman before the event of birth concerning the birth process and experiences and birth outcomes, in terms of the birth method and the subjective birth experience (54, 55). The practical conclusion of these studies is that enhancing the belief of women, before childbirth, that they can have a physiological birth and that they have the necessary psychological ability (can handle the childbirth pain) and physiological capacity (their body is capable of birth) can decrease fear of childbirth and also reduce the increasing rate of medical obstetric interventions. In another study interviewing midwives concerning their methods of protecting birthing women's perineum during the second stage, the emerging theme was that the fear of the birthing woman correlated with perineal tears (56).

It was empirically validated that the birthing women's beliefs concerning birth–natural process vs. medical procedure–are linked to preferences concerning the birth place–a more natural birthing place and a physiological childbirth vs. a typical hospital birth managed from a medical point of view (57). Interestingly, the beliefs of birthing women regarding birth predicted their preferences better than they predicted their actual birth experience. Research indeed indicates that birth beliefs are crucial in the initial decision-making process

concerning birth options. However, as the authors of this study demonstrated, in the current medicalized obstetric arena, women who want natural childbirth usually must vigorously insist on it (57).

This arena may unintentionally sabotage women's beliefs and plans for more natural childbirth. It also has psychological effects such as anxiety, stress, and nervousness, which raise the probability of dysfunctional childbirth (54, 58). Empirical research shows that elevated levels of epinephrine are caused by fear and anxiety, and during childbirth are linked to less powerful uterine contractions (31, 59). It is probably because fear or anxiety affects the oxytocin system, which has a significant function in promoting contractions (60). Thus, in times of stress or fear, labor does not progress (37, 61), hence leading to more medical interventional childbirth (9, 54, 62).

The feelings of fear, stress, and anxiety have adverse effects also from a biochemical point of view concerning pain, because these sensations hinder anti-nociception (63). The sensation of labor pain itself is not necessarily evaluated negatively by women during physiological birth. For example, Whitburn et al. (64) show that women describe their pain experiences as shifting between two mindsets during the physiological childbirth: a mind that is determined to accept the pain, vs. a mindset of suffering and rejecting the pain.

It is interesting that the intensity of labor pain is not linked to a negative birth experience (9, 64). On the contrary, during physiological childbirth, when no epidural anesthesia is performed, women sometimes experience joy and thrills, not misery (63). These feelings can be comparable to the pain that thrill seekers are facing during an adventure (30, 65). For example, women who delivered in a planned home births described labor pain positively and referred to their desire to accept and master labor pain, signifying they manage their own health and wellbeing (66). A birthing woman may experience greater pain than she has ever experienced before, but it depends on her mindset as to whether she refers to this pain as suffering. Many childbirth educators conclude that when a birthing woman understands the physiological explanation for childbirth pain, she can view the escalating pain as encouraging because it indicated that the birth is progressing (9, 40, 62). Thus, it is not a negligible phenomenon that many birthing women experience the intense labor pain together with feelings of triumph, inspiration, and pride. In these situations, the birth experience can improve wellbeing (11, 32, 33, 35, 41, 63).

For a birthing person who experienced birthing consciousness, withdrawing, and accepting the positive function of labor pain was beneficial. Submitting to the painful natural birth process was motivated by inner power and purposeful decision. In words from set and setting theory, it stemmed from knowledge, self-preparation, and self-intention toward birth.

4.3. Physical environment (setting)

Many recent studies focus on the physical setting of the birth space and how it may impact the process of childbirth and method of delivery. In other words, the physical childbirth environment can support physiological birth or hinder it (67–70). In relation to birthing consciousness, there are aesthetic and physical aspects that tend to activate neocortex regions, such as loud voices, high irradiance lights, and also the knowledge you are constantly being observed by strangers (9, 12, 13). Activity in these areas of the brain is in tension with hypofrontality brain mechanism. Therefore, such conditions prevent the woman to access the state of birthing consciousness (9). Yet, the proper birth arena may encourage birthing consciousness. One example are low irradiance lights in the birth room, that were found to be linked to less emergency medical interventions (70). Another example is removing the standard birth bed from the center of the birth room (68, 69). This aesthetic change explains that horizontal position during birth is linked to more prolonged birth and complications that necessitate emergency medical interventions. Reclining during delivery is also considered more painful, thus frequently leading to epidural anesthesia, which raises the risks of hyper-medicalized childbirth (71).

The birth arena also shapes the behavior of the birthing woman. Women laboring in hospitals tend to behave more passively. But in more homey childbirth setting, such as natural birthing rooms in hospitals or birth centers, women instinctively claim ownership of their surroundings. They tend to behave more actively, for example by changing body positions during birth (72), and it is well known that changing positions during labor promotes physiological birth (73).

The issue of design and aesthetics of the birth space might also be related to the psychological need to feel safe, which, as noted by many [see (13, 36)], is a significant factor in promoting a physiological birth and ensuring psychological comfort. Women describe their deep urgency and desire to be in a sheltered place as contractions intensify and become more painful and how the feeling of safety helps them focus on each contraction. This inherent need is described by birthing women from a social support perspective and an environmental space perspective (74, 75). This need to feel safe and secure to promote the birth process and its connection to physical aspects of the birthing environment was uncovered decades ago in rodent studies. Newton et al. (76, 77) were the first to experimentally demonstrate the environmental regulation of parturition in laboratory mice. Proceeding a series of studies in laboring mice, it was concluded that the labor of mice functions best in a sheltered and undisturbed atmosphere, such as hidden container, as opposed to a glass container. More recently, environmental disturbance during labor in dogs and cows was found to extend parturition (59, 78). In spite of these findings, the typical modern hospital setting includes unfamiliar sounds, voices of strangers, and strong lights and smells. All these aspects are related to catecholamines release in the birthing woman, which can cause neocortical activity and disturb the process of birth [(9, 53), pp. 30–39].

It should be remembered, though, that designing better birthing rooms cannot be counted as a magical solution for supporting natural births; they are merely one factor in the setting and not necessarily the determinative one. The set of the preparations and intentions, e.g., the will, of the women play a crucial role in the outcomes. Another crucial role plays the hospital's birth philosophy, a function of setting. A recent study (79) emphasizes the crucial role of the birth philosophy of medical staff, which reflects the hospital authorities' perspective toward childbirth in creating or denying a birth setting promoting a positive birth experience. Two different childbirth spaces were used. One space was designed from a medicalized birth perspective, where a woman is viewed as a passive agent, and birth is considered a dangerous medical event. The second space was designed from a more physiological birth perspective, where a woman is viewed as an active agent, and childbirth is viewed as a natural process. Interestingly, the different birth spaces' different designs did not help improve birth outcomes because, according to

the researchers, the hospital's medicalization approach also invaded the second space, thus influencing the ambiance and the attitude toward the birthing women.

4.4. Support from and relationship with medical professionals (setting)

One-on-one support decreases the rate and need of various medical interventions (80) and increase the satisfaction of the birthing woman concerning her birth experience (81). Still, while continued support during birth is crucial, and some argue that it should be considered a basic human right (82), in many of typical birthing rooms, hospital systems and procedures rarely prioritize, or support, birthing women's sense of agency and choices (57). As with findings presented in the previous subsection, there is a link between discounting the innate need for care and support during the birth process, with rising rates of hyper-medicalized childbirths (83–85).

Even the historical meanings of the words "obstetrician" and "midwife" reflect the importance of their relationship with the birthing women. *Obstetrician* comes from the Latin phrase *obstetrics*, which plainly means "she who stands before," which refers to "midwife." Moreover, *midwife* is an old German term that simply means "with woman" (86). Many studies have demonstrated that birth outcomes are improved for birthing women who have continuous support during childbirth from a doula or a private midwife, who in both cases use non-pharmacological pain management strategies. These methods promote physiological birth, with less perceived pain, and more positive subjective experiences (87, 88). In fact, there is a well-known saying that "if a doula were a drug, it would be unethical not to use it" (87). However, in the power relationship dynamics in and around the typical birthing room in a Western hospital, it seems there are at least three kinds of power imbalances that most often do not favor the birthing woman (an issue that is crucial to the concept of setting). Dahan and Cohen Shabot (34) show that not only are there power imbalances between the birthing women and the staff in the delivery room, there are also power imbalances within the staff (i.e., doctors vs. midwives) and between the staff and hospital management. For example, in many obstetric systems the tendency is to manage childbirth process from the perspective of avoiding risks for the hospital (such as expensive lawsuits), rather than for the birthing woman. Thus, the hospital management imposed routine practices that tended to underrate the importance of women-centered approach that acknowledge the importance of women's subjective birthing experience (79). This finding is crucial, because the hyper-medicalization approach in most of Western hospitals today appears to conflict, rather than support, many birthing person's sense of agency (57).

Kitzinger (89), a social anthropologist, also described a general negative reduced sense of agency of women throughout childbirth. In most hospitals birthing women are forced to wear a hospital gown. But giving up a person's own wearing sometimes means giving up a person's individuality and choice. Further, in several ways, the birthing woman is supposed to act as a passive patient—to follow instructions, not interfere with the medical staff, and be a "good girl" as if she were a child and not a grown woman (89). Indeed, many women refer to being disempowered during birth in typical modern hospitals (39). Notably, women from developed countries regularly portray their struggle during birth to avoid unnecessary interventions. These birthing persons are often powerless in their effort to refuse medicalized birth, usually because of the hyper-medicalization approach, that is common in many western hospitals, which is translated to medial protocols (9, 39, 90). This finding appears to illustrate the complex relationship between the birthing woman and the medical staff; although they are supposed to support her, they frequently do the opposite. Participants in studies stated:

> "I…thought if the midwives and doctor left me alone I could most certainly birth my baby." [(39), p. 99].

> "I was steamrolled with unnecessary intervention and did not get to speak with a doctor about my options, risks vs. benefits… I feel like the nurses, doctors and hospital only did what was in their best interest, not mine… It was a nightmare." [(90), p. 4].

Reed et al. (90) did an online survey of 748 women, asking what they found to be the most traumatizing during childbirth. The major issues reported were the actions of medical staff and their interaction with them. Women felt that the medical staff prioritized their own agendas on top of the wishes and needs of the birthing woman. Many examples reveal the sometimes-aggressive attempts of the medical staff to convince the birthing woman to agree to unnecessary intervention. Women also described actions that were violent and abusive (90). These themes are all parts of the phenomenon called "obstetric violence"—the ill-mannered and insulting treatment, verbal or physical, of birthing person during the event of birth, which is acknowledged as a worldwide problem [see (91–93)]. For example, medical staff sometimes use threats and twisted-partial facts, usually related to the wellbeing of the fetus, to coerce the birthing person into complying with procedures (90, 94–96). For some women, the actions of the medical staff during the event of the birth triggered memories of sexual assault (90).[4]

A recent review (97) of what is currently known about birth trauma confirmed that it is not directly related to medical pre-existing factors. Three key themes regarding birth trauma, highly relevant to the setting issues here, were identified: support during birth, the birthing person's feeling of knowledge and control, and the quality of care provided by the professionals (97). The attitude of the personnel in the delivery room has a crucial effect on the birthing person from psychological perspective (98). Thus, there is a serious need for childbirth care providers to be trained as to how important a positive relationship with the birthing woman is in terms of physiological and psychological health (90).

4.5. Ability to exercise autonomy (setting)

Dixon et al. (36) notice that the intense absorption present during physiological childbirth reminds the mental state of "flow": despite the dissociation (concerning time and space), along with the sensations of concentration and loss of self-consciousness, a sense of personal control emerges and retained (36). Negative birthing experiences are described as those that suppress birthing person's sense of autonomy and control (99). These sensations and feelings

4 The phenomenon of obstetric violence, although highly relevant to this subject, is beyond the scope of this paper.

usually emerge during emergency, highly medicalized labor. In these cases, women describe experiencing a negative dissociative state (100, 101). However, these negative experiences happen not only during emergency births. As discussed in previous sections, this can include being forced to wear patient gowns, being expected to act passively, and being unable to choose their birthing position. All these issues are linked to adverse emotions of losing choice, control, and autonomy (89).

In particular, the freedom to choose one's birthing position contributes not only to the psychological feeling of control and autonomy but also promotes physiological birth. Reitter et al. (102) were the first to assess dimensions of the pelvis of women (pregnant vs. non-pregnant) in several positions, using MRI. They found that a kneeling squat position strikingly and significantly increases pelvic dimensions: "increase in the transverse diameters of the mid pelvis and the pelvic outlet (0.9e1.9 cm) when women change from the supine dorsal position to a kneeling squat position" (p. 662, e7). They also found that this increase in pelvic dimensions is even more prominent in pregnant women. This means there is great potential in changing positions during birth for easier delivery, because increased pelvic diameters provide an anatomic boost for simpler descent of the fetus during childbirth. Unfortunately, Reed et al. (90) show that in many cases, even birthing women without epidurals are forbidden to move about freely and instead are forced to lie down.

4.6. Cultural factors (setting)

It has been found that prevalent descriptions of childbirth in popular media (e.g., television and film dramas and reality television) perpetuate the medical approach to childbirth, while coverage of more physiological births is generally absent from the media (103). In a sense, the common and accepted image of childbirth in Western culture is a sterile one: from the moment of epidural anesthesia, the birthing woman lies, relaxed, in the delivery room, connected to monitoring devices, free from labor pain. Labor pain is something to fear, something archaic—a thing from before the age of reason and high-tech medicine. Labor pain is introduced in popular mass media as a necessary evil that needs to be gotten rid of, as soon as possible, in contemporary labor in a hospital. After anesthesia is administered, the birthing women is, in a sense, rescued from her own body, thus, she is detached from her body (104). However, although her fear and pain is terminated, so is her own autonomy (105). Moreover, birthing women's bodies are presented in reality shows as incapable of physiological birthing, thus requiring technological help, medical interventions, and surveillance throughout the birth process. These shows represent the birthing women's body as inferior (106). These depictions have real-life effects. For example, students from the University of British Columbia, young adults who had been socialized into a medicalized birth culture, were found to fear vaginal childbirth and prefer an epidural or elective C-section over a physiological birth (107).

This picture of childbirth is inaccurate, however, it does not show what usually happens in the advanced stages of medical birth, such as the association between epidural anesthesia and instrumental and emergency cesarean births (108); the correlation of medical births with a precarious mental state after birth, such as PP depression and post-trauma (8); and potentially more challenging PP physiological recovery, for example in terms of pelvic floor health in cases of buffer incisions (109).

Another example of the effect of cultural factors is the rising use of epidural anesthesia in Western countries. While epidural is highly effective form of pain relief, it does not automatically improve the birthing woman's experience (34). Social support during labor was found to be much more crucial factor than epidural in improving birth experience, although underestimated (110). Birthing women without epidural anesthesia had shorter births, with more chances to have a more natural birth and less interventional birth (111). This is not to suggest that epidurals always have negative effects, but although technological innovations have significantly reduced mortality of birthing women and babies, many technological interventions have become needlessly routine (9, 71). These technological interventions, such as epidurals and electronic fetal monitoring (EFM), convert a typical low-risk birth from a physiologic process into a medical process.

Electronic fetal monitoring is usually used in admission to the hospital with no consideration of the risks in using it continuously during the birth process (9). A continuous use of EFM in low-risk birthing women sometimes starts a chronological sequence of interventions that increase the risk for an unplanned C-section (71, 112). Here is typical example of a cascade of obstetric interventions (113): lying for monitoring sometimes weaken contractions, which require synthetic hormonal induction (Pitocin), which necessitates that the monitoring and lying continues. Pitocin, and lying on the back with no ability to move, lead to intense pain experience. This negative pain experience increases the need for a pain reliever, such as epidural. Unfortunately, epidurals are linked to lengthier births and unproductive pushing, thus increase the risk to instrumental births, such as forceps or vacuum extraction. Instrumental births are linked to perineal cuts (episiotomy). If an instrumental vaginal birth fails, an emergency C-section is necessary to rescue the woman and her child (61, 71, 112, 114, 115). Empirical studies confirms that even a minor intervention increases the risk that a birth will end up being highly medicalized (9, 108).

Another example of the effect of cultural factors are studies that show that ethnocultural differences, such as language, values, or religious beliefs–can affect women's perceptions and beliefs about childbirth, and also influence birth experiences, even when there is no difference in the levels of medical interventions (116).

4.7. The set and setting theory concerning childbirth

The analysis I have offered shows how the same set and setting key parameters that shape psychedelic experiences also shape birthing experiences. And, as stated previously, it is not only that the set and setting theory has explanatory powers to describe the birthing experience retrospectively. The framing of set and setting also has the power to predict future experience outcomes.

Figure 3 shows the set and setting key parameters that enable us to shape and navigate the birth experience, and even birth outcomes, in most cases. It also shows which objective factors we cannot control, i.e., personality, life history, and objective medical condition. Indeed, many personal factors can affect the birth experience and consequences, such as the life history of the birthing woman, previous trauma, current social and psychological state, and her physiological condition and obstetrical status [see, for example (117)].

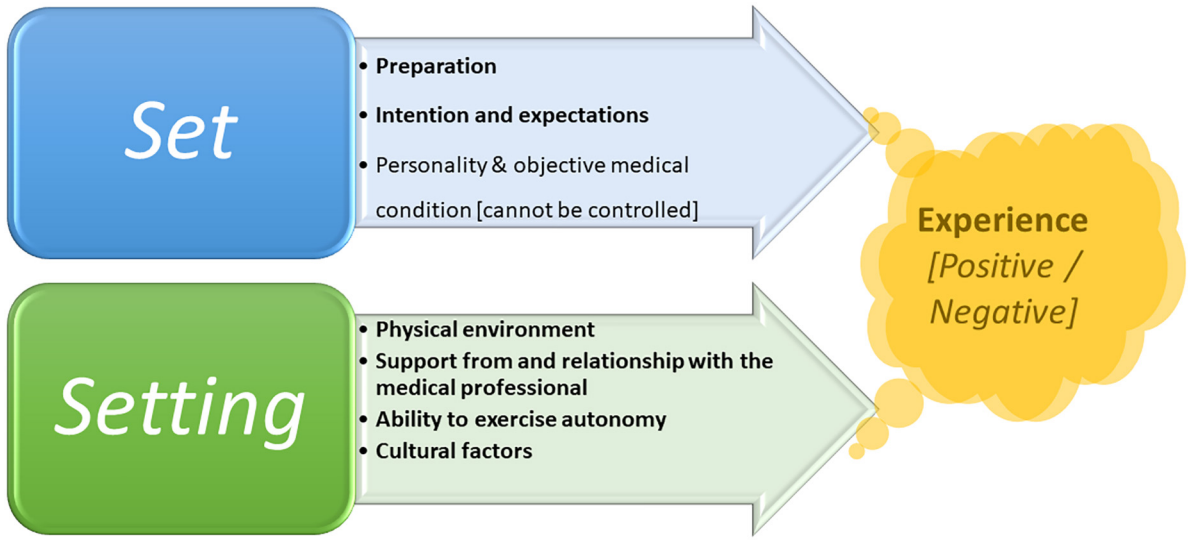

FIGURE 3
Set and setting parameters that shape both psychedelic and birth experiences.

5. Discussion: Designing and navigating the childbirth experience rather than controlling it through medicalization

There seems to be broad agreement with the familiar slogan that "you cannot control birth" (118). Perhaps this is because physiological birth is broadly conceived as a dangerous process that can escalate in an instant toward becoming an emergency medical event. This perspective is usual in typical Western hospital environments (9, 12). Obstetrics has always viewed childbirth as a physical event, focusing on the uterus contractions, the opening of the pelvis, and the fetus's wellbeing: how to finish the event with a healthy mother and child, while preventing many pathological escalations (119, 120). This attitude is not different today [see, for example (121)]. Even in studies of how to minimize PP-PTSD, one of the interventions offered is to instruct women to have realistic expectations concerning birth, to be open-minded about the birth process, to accept that it is unpredictable, and, for example, to exchange their "birth plans" for "birth flow charts" [see for instance (122)]. Women are encouraged to accept in advance that they will not be able to control or manage their birth process and, in general, should hand over power and control to others (i.e., to obstetric and other health care professionals).

In the late 1980s, Newton (123) discussed many social and environmental effects that might promote birth or hinder delivery, and offered that obstetrics should pay attention to and study them, in order to gently control the physiological birth process, navigating it to a safe and healthy place using simple social, psychological, and environmental tools:

> Unfortunately, the psychologic aspects of labor regulation get sparse attention in academic texts. Every day in labor and delivery suites it is noted how labor slows in many women at the time their environment changes from home to hospital and from labor to delivery room. Much more well-controlled research is needed on the environmental regulation of labor. It may be especially important to know which environmental factors inhibit or promote normal human labor. Randomized controlled trials of many aspects of current obstetric procedures that have a psychologic and environmental impact on the laboring woman are especially needed. *I hope that the decade of the 1990s will see this knowledge developed and used to help childbearing women* [emphasis added]. [(123), p. 108].

Unfortunately, Newton's hope was not fulfilled. There is a continually rising rate of medical intervention during childbirth (124), instead of navigating the childbirth process in the environmental and social ways suggested by Newton and confirmed by many others since then. Keeping in mind that studies specify that the increasing C-section childbirth rates in the United States, and the hyper-medicalization attitude, in general, do not contribute women's physiological and psychological health (4, 9, 125), it seems that hyper-medicalization is not the right strategy if the goal is to manage childbirth for the sake of the mother's and the infant's wellbeing.

I believe the central tragedy here is the failure to acknowledge that birth is a complex psycho-physiological, social, biochemical process. Trying to control it by more medical equipment and procedures (such as routine EFM during labor, routine inductions, routine anesthesia), in order to be ready for any possible emergency, probably itself plays a significant role in causing pathological escalation. Many empirical studies on the cascade of interventions during birth demonstrate the path of disturbances to physiological birth: the various mental and environmental variables noted previously that impede childbirth from progressing [see (61, 64, 71, 113, 126, 127)].

It seems reasonable that the broad agreement that birth cannot be predicted or controlled without medicalization is related to the common basic assumption that delivery is dangerous and harrowing and that before the era of modern obstetrics, there was nothing that could be done about it from the perspective of the birthing woman herself, aside from being close to potential helpers around

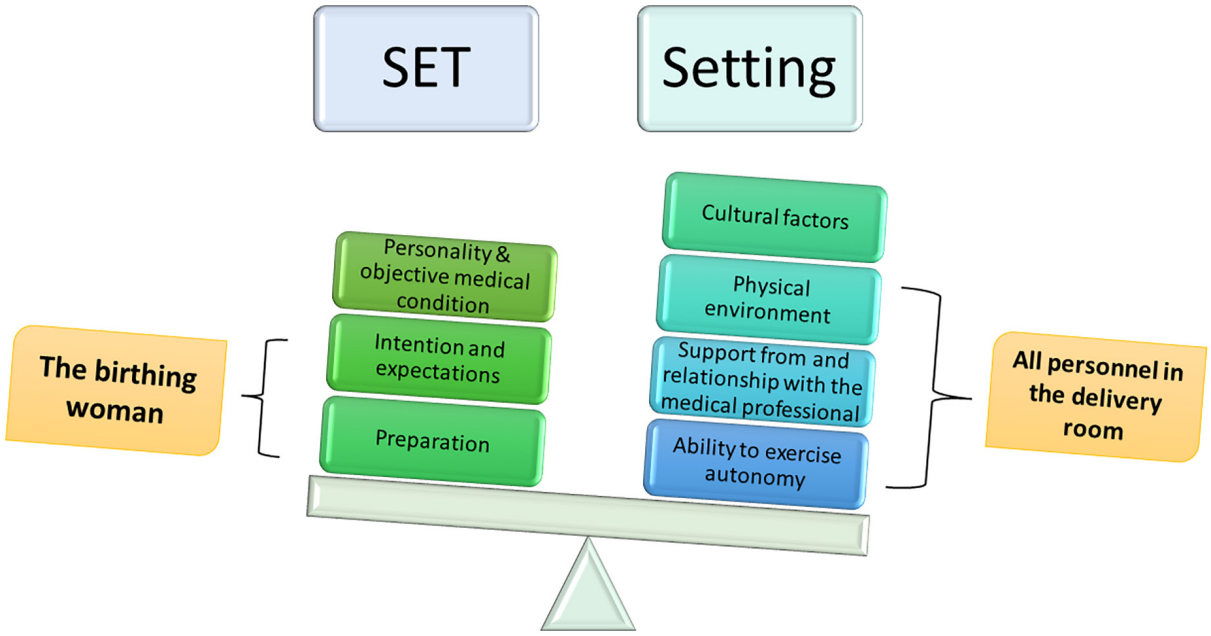

FIGURE 4
How can the science of consciousness promote the science of birth?

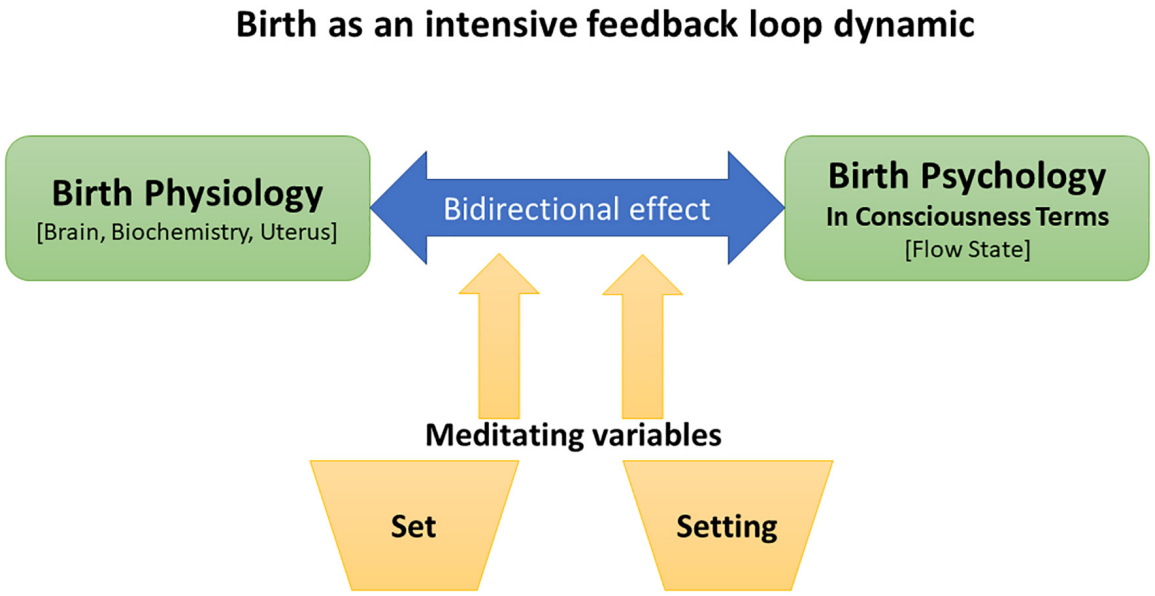

FIGURE 5
The model of physiological birth in terms of set and setting.

the time of birth [see (128)]. The belief that "you cannot control birth" has convinced birthing women to allow medical professionals to take over, because medical professionals believe that the only way to increase control and safety during childbirth is through hyper-medicalization. However, I propose a better way is to help women design and navigate the childbirth experience, using set and setting theory. One can, in most cases, *navigate* birth to a physiological direction if one does not ignore the birthing woman's mental state and the environmental and social settings.

The experience of childbirth does not uniformly emerge in all women in the same way or even in the same women in different births. Far from uniformity, the effects of childbirth are remarkably diverse and sometimes polarized. I suggest that the birth experience depends first and foremost on the set (the psychological variables of personality, preparations, intentions, and expectations of the birthing woman) and the setting (the variables that include the physical, social, and cultural environment in which childbirth occurs).

Thus, for example, the birth experience that takes place in a threatening environment for an anxious woman who is afraid of the pain of birth is likely to provoke unpleasant reactions, anxiety, intense pain, and suffering, to the point of complicating the birth and causing post-traumatic effects. On the other hand, a woman who is aware of

the issue of pain management in childbirth and seeks to maximize the therapeutic and analgesic effects of the hormones that are part of the birth process, with childbirth taking place in a supportive and pleasant environment, could be expected to have a more positive, even empowering, experience.

My hypothesis is that differences in set and setting conditions are what lead to opposite extreme results in the birth experiences of many women, just like differences in set and setting conditions in psychedelic research in the mid-20th century revealed traumatic experiences, on the one hand, and positive and life-changing experiences, on the other. In other words, I suggest a conceptual shift. Instead of thinking in terms of "control" regarding childbirth, it would be better to think in terms of "design and navigation." Instead of trying to control childbirth by hyper-medicalization of it, we should design the birth set and setting to provide optimal conditions for the birth experience and thereby navigate birth. Figure 4 illustrates the set and setting theory in relation to the birth arena.

5.1. The set and setting model concerning physiological childbirth is ripe for empirical investigation

The history of psychedelic research directs us to give more attention to how non-physiological factors shape altered states of consciousness and their effects on the mind and body. During childbirth, the woman responds *immediately* to the set and setting key parameters, because birthing has intensive feedback loop dynamics. Thus, concerning optimal management of the birth process, set and setting are crucial factors we must deal with. If my hypothesis is valid, then the science of consciousness and philosophy of mind can promote the science of birth.

Figure 5 illustrates the hypothesis I offer, concerning a unified model of the psycho-physical event of physiological human birth. This complex dynamic shows the ability of many factors to *enhance* the positive state of consciousness or *suppress* it. The result is an extreme experience: a positive and life-changing experience compared to a negative or even traumatic one. I believe that this model is ripe for empirical inquiry.

6. Conclusion: How the science of consciousness can promote the science of birth

The seeming unpredictability and uncontrollability of the birth process and the possibility for unexpected complications should not encourage fatalism. The set and setting concept may significantly advance scientific understanding of the birth process, particularly what promotes healthy birth and what may hinder it. The history of psychedelics' extreme polar experiences directs us to give more attention as to how non-physiological factors shape altered states of consciousness and their effects on the mind and body. In this paper, I have theoretically demonstrated that a broader understanding of the set and setting key parameters can significantly improve our understanding of human birth.

Moreover, the basics of the set and setting theory challenge one of the fundamental and rooted premises of modern obstetrics: that birth progresses as it does purely from a physiological mechanism. But, as stated, women also give birth with their minds, not just their bodies. Thus, physical and social settings have crucial effects on the birth process, and there are empirical studies that validate these kinds of effects. In examining birth experiences, we must re-examine the implications of the altered states of consciousness in childbirth, which respond immediately and flexibly to set and setting key parameters. For optimal management of the birth process, set and setting are crucial factors.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Cannabis-assisted psychotherapy for complex dissociative posttraumatic stress disorder: A case report

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Background: A dissociative subtype of posttraumatic stress disorder, known as "D-PTSD", has been included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. In addition to meeting criteria for PTSD, patients endorse prominent dissociative symptoms, namely depersonalization and derealization, or detachment from one's self and surroundings. At present, this population is supported by a highly heterogeneous and undeveloped literature. Targeted interventions are therefore lacking, and those indicated for PTSD are limited by poor efficacy, delayed onset of action, and low patient engagement. Here, we introduce cannabis-assisted psychotherapy (CAP) as a novel treatment for D-PTSD, drawing parallels to psychedelic therapy.

Case presentation: A 28-year-old female presented with complex D-PTSD. In a naturalistic setting, she underwent 10 sessions of CAP, scheduled twice monthly over 5 months, coupled with integrative cognitive behavioral therapy. An autonomic and relational approach to CAP was leveraged, specifically psychedelic somatic interactional psychotherapy. Acute effects included oceanic boundlessness, ego dissolution, and emotional breakthrough. From baseline to post-treatment, the patient showed a 98.5% reduction in pathological dissociation, as measured by the Multidimensional Inventory of Dissociation, no longer meeting criteria for D-PTSD. This was accompanied by decreased cognitive distractibility and emotional suffering, as well as increased psychosocial functioning. Anecdotally, the patient has sustained improvements for over 2 years to date.

Conclusions: There is urgency to identify treatments for D-PTSD. The present case, while inherently limited, underscores the potential of CAP as a therapeutic option, leading to robust and sustained improvement. Subjective effects were comparable to those produced by classic and non-classic psychedelics, such as psilocybin and ketamine. Further research is warranted to explore, establish, and optimize CAP in D-PTSD, and to characterize its role in the pharmacological landscape.

KEYWORDS

cannabis, medicinal cannabis, cannabis-assisted psychotherapy, dissociation, posttraumatic stress disorder, trauma, treatment, case report

Introduction

Posttraumatic stress disorder (PTSD) is a chronic and disabling psychiatric condition. It has an estimated lifetime prevalence of 7.7% in the United States (1, 2), with a 12-month prevalence rate of 4.1% (1, 3). While presentations vary, PTSD is characterized by thought intrusion, persistent avoidance, negative mood and cognition, and alterations in arousal and reactivity (4). These symptoms are associated with trauma exposure, including sexual, interpersonal, and organized violence, that may accumulate with repeat events over time (5). This leads to considerable psychosocial and occupational disability, with negative downstream effects on quality of life.

Most recently, a dissociative subtype of PTSD, known as "D-PTSD", has been included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5; (4)]. Apart from meeting criteria for PTSD, these patients endorse prominent dissociative symptoms, namely depersonalization and derealization, or detachment from one's self and surroundings, as well as emotional disengagement (4, 6). Other complaints include memory disturbance, gaps in awareness, and sensory illusions (7, 8). A recent meta-analysis estimated the prevalence of D-PTSD as 38.1% in patients with PTSD (9). The phenotype is further linked to increased role impairment, psychiatric comorbidity, and suicide risk compared to PTSD alone (10, 11).

To date, only two medications are approved by the Food and Drug Administration for PTSD, sertraline and paroxetine, both of which are selective serotonin reuptake inhibitors (SSRIs). Even when optimally delivered, up to 60% of patients do not respond to SSRIs and <30% achieve remission (12–14). This often results in early medication withdrawal. Moreover, the latency period of these slow-acting antidepressants significantly elevates the risk of suicide and self-injurious behavior (15, 16). As such, trauma-focused psychotherapies are designated as first-line treatments for PTSD, including prolonged exposure (PE) and cognitive processing therapy (CPT) (17). However, these interventions are limited by high attrition rates (>45%) and low patient engagement (18). Novel strategies are therefore urgently needed, especially those targeting dissociative symptoms.

Cannabis, colloquially referred to as "marijuana," is derived from the *Sativa* and *Indica* species of the Cannabis plants (19). It contains cannabinoids and several other chemicals acting on cannabinoid type-1 (CB_1) and type-2 (CB_2) receptors in neurons and immune cells (20). This includes Δ^9-tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis known to produce alterations in perception, awareness, and insight; or the "high" commonly reported by users. THC also has analgesic, antiinflammatory, and antioxidant properties (21). In contrast, cannabidiol (CBD) is a non-psychoactive constituent, with anxiolytic, antipsychotic, and anticonvulsive effects (21). Evidence on the clinical benefits of cannabis has thus been growing for a host of indications, ranging from pain to neurologic to sleep disorders (22, 23). There is a particular interest in its application to psychiatric conditions, including PTSD (24). While studies have yet to show robust improvements, their results are confounded by various factors, such as underpowered sample sizes, heterogeneous populations, variant dosing regimens, and anecdotal reporting (25–27). Here, we present the first case, to the best of our knowledge, of cannabis-assisted psychotherapy (CAP) as a treatment for complex D-PTSD, in accordance with CARE (CAse REport) guidelines (28).

Abbreviations: ACE, accept, connect, embody (psychotherapy); CAP, cannabis-assisted psychotherapy; CBD, cannabidiol; CPT, cognitive processing therapy; DMT, dimethyltryptamine; D-PTSD, dissociative posttraumatic stress disorder; DSM-5, diagnostic and statistical manual of mental disorders, fifth edition; MID, multidimensional inventory of dissociation; PE, prolonged exposure; PSIP, psychedelic somatic interactional psychotherapy; PTSD, posttraumatic stress disorder; RD, reduction; SCID-5, structured clinical interview for DSM-5; SSRI, selective serotonin reuptake inhibitors; THC, Δ^9-tetrahydrocannabinol.

Case presentation

A 28-year-old female presented with medical, physical, and sexual polytrauma. At 6 months of age, she was diagnosed with hip dysplasia, resulting in 14 corrective surgeries by age 7. This was compounded by scoliosis and associated chronic pain. The patient was maternally neglected, frequently left without care, adequate food, and supervision. At age 9, she was sexually abused, on multiple occasions, by her mother's boyfriend. This intensified through repeat sexual abuse by a high school partner, persisting until 15 years of age. Overtime, the patient developed a constellation of symptoms, including excessive fear, debilitating anxiety, and negative affect.

According to psychiatric records, she was diagnosed with PTSD plus comorbid anxiety and major depression. The patient first partook in cognitive behavioral therapy (CBT), followed by internal family systems (IFS) therapy and eye movement desensitization and reprocessing (EMDR). These interventions targeted relational trauma, distressing internal experiences, and attachment deficits, respectfully; however, each resulted in poor symptom relief. She was then prescribed various antidepressants, namely sertraline (Zoloft®), escitalopram (Lexapro®), and bupropion (Wellbutrin®). Yet, the patient did not respond to multiple trials of adequate dose and duration. Six years later, she obtained a medical cannabis card to self-manage her chronic pain and PTSD symptoms. This was issued by the Utah Department of Health under the Utah Medical Cannabis Act (House Bill 3001). Despite initial improvement, the patient discontinued use following increased fear and paranoia. Her disease state consequently worsened, leading to agoraphobia and functional disability: "I couldn't leave my house. I couldn't think or clean or make food. I couldn't take care of myself. Everything was too much. Too hard. I was scared all the time, even to use the bathroom at night." She further reported death anxiety with acute panic attacks: "The thought of dying was overwhelming. It constantly interfered with my daily life." This decline in mobility and cognition motivated her to re-consider cannabis use, this time with therapy. The patient's prior experience with cannabis, showing signals of improvement in chronic pain and trauma-related symptoms; the market availability and legality of cannabis in the state of Utah; and the accessibility of specialized, clinician-guided services utilizing cannabis, also influenced her decision to seek CAP.

Diagnostic assessment

Upon intake, the patient underwent the Structured Clinical Interview for DSM-5 (SCID-5) (29), confirming complex PTSD. The Multidimensional Inventory of Dissociation (MID) (30), a 218-item multiscale instrument of dissociative phenomena, was also

administered. Diagnostic impressions revealed a dissociative subtype, with clinically significant symptoms (cut-off score > 100) present in all three criteria: A (general PTSD dissociative symptoms), B (partially dissociated intrusions), and C (fully dissociated actions). Other complaints included absent-mindedness, inattention, and emotional distress. As such, her clinician recommended repeat CAP, leveraging psychedelic somatic interactional psychotherapy (PSIP) (31). This approach involves autonomic and relational processing, activated by legally prescribed cannabis, to target index trauma. In the patient's case, using PSIP to target core dissociation and interpersonal trauma, stemming from early abandonment, abuse, and enmeshment. Her resistance to first-line treatment for PTSD, including CBT and EMDR, further justified PSIP as an alternative to established, evidence-based psychotherapeutic techniques.

Treatment approach

Akin to psychedelic-assisted therapy [reviewed in (32–34)], CAP included preparation, dosing, and integration. The patient received 10 CAP sessions, scheduled twice monthly over 5 months. This frequency was based on treatment response and tolerability (Figure 1). Sessions were followed by integrative CBT, within 1 week of CAP, aimed at decoding experiential phenomena. The "accept, connect, and embody" (ACE) (35) model, predicated on psychological flexibility, was used to facilitate internal and behavioral change. ACE encourages patients to accept challenging experiences, connect to positive material, and deeply attend somatic cues. See Table 1 for details regarding both CAP and CBT regimens. The setting included a private office with warm lighting, mural tapestries, and live plants. All sessions were video recorded for ethical, safety, and integration purposes.

Cannabis-assisted psychotherapy

Sessions were primed with psychoeducation and intention setting. The clinician first discussed D-PTSD and its pathogenesis, explained the course of treatment and possible risks, and taught various grounding and self-regulation techniques. Thereafter, the patient developed a clear and positive motive for CAP, designed to help navigate potentially difficult content. Once primed, sessions began with 10–15 min of "surfacing." Here, thoughts, emotions, and insights from prior CAP sessions were discussed, excluding the first one. This was followed by 10–15 min of "resourcing," aimed at achieving a present state of calm. This involved clinician-guided exercises, such as deep breathing, positive memory recall, and imaginative thinking. Dosing subsequently occurred. Using a battery-operated vape pen, the patient inhaled 6–10 mg of cannabis chemotype II, a mixed ratio of THC and CBD. Subjective effects included oceanic boundlessness and ego dissolution (Table 2). The clinician then initiated PSIP, targeting dissociative symptoms. Through selective inhibition, the patient suppressed voluntary movement and coping strategies, while fully acknowledging and experiencing urges. This induced hypo- and hyper-arousal, presenting as depersonalization and psychomotor agitation, respectively. Muscle contractions, increased body temperature, and physical discomfort followed. To promote somatic processing, the patient endured the state until sensations abated. This resulted in "traumatic discharge," breaking emotional and memory blocks, often terminating in psychocatharsis. Sessions closed with 10–15 min of resourcing, with a return to the present moment (Figure 2). The clinician ended by completing a risk assessment to ensure the patient's safety. Acute psychophysiological changes, albeit their intensity, were generally well tolerated and resolved completely. No adverse events were clinically observed nor self-reported.

Follow-ups occurred 1 day post-CAP *via* telephone. Between sessions, the patient watched the previous recording, journaled insights revealed by the experience, and engaged in CBT. This was considered integration work. Her symptoms partially remitted over the first six sessions, and significantly remitted thereon out. From baseline to post-treatment, following all CAP and CBT sessions, the patient showed a 98.5% reduction (RD) in pathological dissociation ($M_{pre} = 19.7$ vs. $M_{post} = 0.3$), no longer meeting criteria for D-PTSD. This was reflected by robust improvement in 11 clinically significant (cut-off score > 100) dissociative symptoms: derealization ($M_{pre} = 27.5$ vs. $M_{post} = 0$; RD = 100%), depersonalization ($M_{pre} = 19.2$ vs. $M_{post} = 0$; RD = 100%), flashbacks ($M_{pre} = 24.2$ vs. $M_{post} = 0.8$; RD = 96.7%), memory problems ($M_{pre} = 52.5$ vs. $M_{post} = 1.7$; RD = 96.8%), intrusive impulses ($M_{pre} = 20.0$ vs. $M_{post} = 0$; RD = 100%), trance ($M_{pre} = 15.8$ vs. $M_{post} = 0$; RD = 100%), time loss ($M_{pre} = 45.0$ vs. $M_{post} = 0$; RD = 100%), knowledge loss ($M_{pre} = 26.0$ vs. $M_{post} = 0$; RD = 100%), child voices ($M_{pre} = 16.7$ vs. $M_{post} = 0$; RD = 100%), internal voices ($M_{pre} = 33.0$ vs. $M_{post} = 0$; RD = 100%), and persecutory voices ($M_{pre} = 30.0$ vs. $M_{post} = 0$; RD = 100%). See Figure 3. She also exhibited marked decreases in cognitive distractibility ($M_{pre} = 62.5$ vs. $M_{post} = 3.3$; RD = 94.7%) and emotional suffering ($M_{pre} = 47.5$ vs. $M_{post} = 2.5$; RD = 94.7%), as measured by two response sets, the Cognitive Distraction Scale and Emotional Suffering Scale, both included in the MID.

Collectively, this led to anecdotal improvements in daily life activity, personal development, and overall wellbeing: "I've been able to do things I couldn't do before, like be home alone and with my daughters. I can do stuff around the house and be in public spaces. My fear and anxiety are gone. I don't feel like people are trying to hurt me. I feel more connected with myself and the world. I'm learning to accept my past trauma, without blame and judgment. This is something that changed my life." She found interactional psychotherapy most beneficial in processing traumatic and relational memory: "I had all this gunk trapped inside that cannabis activated. Engaging with my therapist during sessions helped me resist, fully express, and clear that gunk – painful events I'd been carrying for a long time. I couldn't have done this alone." The patient also described positive contributions from CBT: "It was extremely helpful to go back and explore my sessions. They were often challenging, but in a good way. Mentally understanding them gave me a lot of clarity and meaning." Since treatment, the patient has engaged in traditional CBT, as needed, to address her complex trauma history. Remarkably, she has sustained improvements for over 2 years to date. This response was qualitatively described at 8-, 16-, and 24-months follow-up.

Discussion

In this case of complex D-PTSD, CAP showed a striking and sustained reduction in pathological dissociation. This

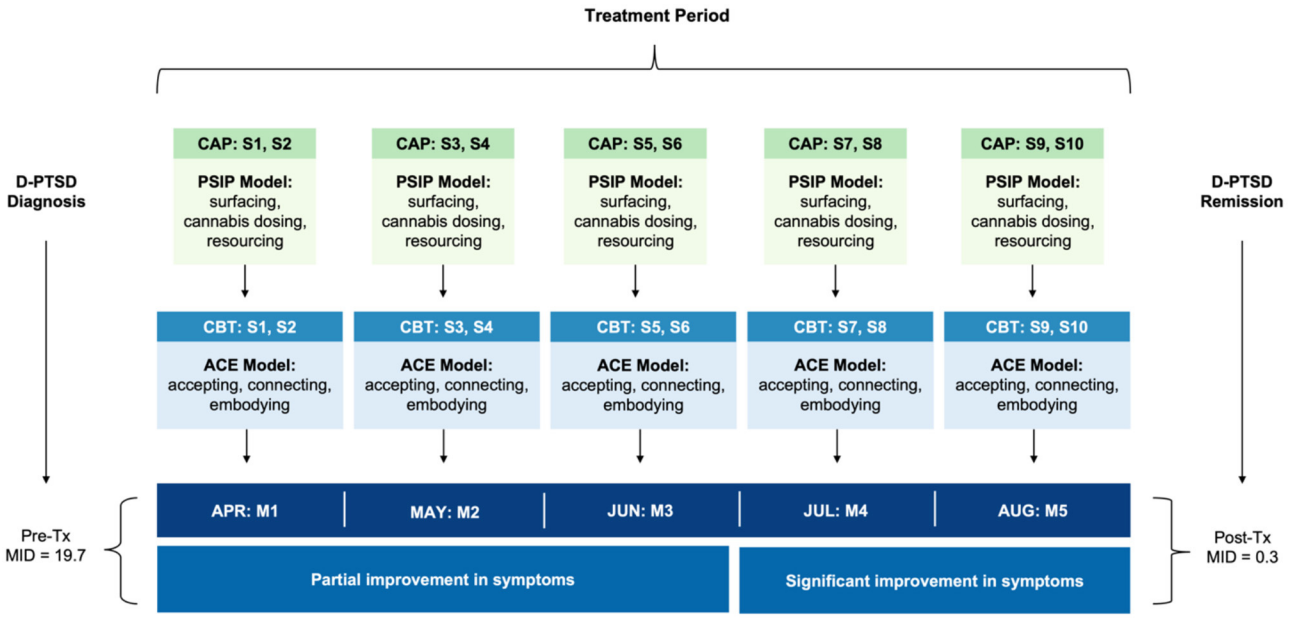

FIGURE 1
Timeline of clinical events. The patient received 10 CAP sessions, scheduled twice monthly, two-to-three weeks apart, as a treatment for complex D-PTSD. An autonomic and relational approach to psychotherapy was leveraged, namely PSIP. Each CAP session was accompanied by CBT, using the ACE model for integration, to decode experiential phenomena. CBT sessions occurred within 1 week of CAP. ACE, accept, connect, and embody (psychotherapy); CAP, cannabis-assisted psychotherapy; CBT, cognitive behavioral therapy; D-PTSD, dissociative posttraumatic stress disorder; M, month; MID, multidimensional inventory of dissociation; PSIP, psychedelic somatic interactional psychotherapy; S, session; Tx, treatment.

TABLE 1 Psychotherapeutic regimens.

Tx	Freq	Min	Schedule	Approach	Emphasis	Components
CAP	10	120	Twice monthly, two-to-three weeks apart, over 5 months	Directive, interactional; PSIP model	Core index trauma	Psychological processing, mind-body grounding, cannabis dosing with therapy
CBT	10	60	Twice monthly, 1 week following CAP, over 5 months	Structured, goal-oriented; ACE model	Treatment integration	Experiential decoding, mindful awareness, meaning-making, insight formation, goal setting

ACE, accept, connect, and embody (psychotherapy); CAP, cannabis-assisted psychotherapy; CBT, cognitive behavioral therapy; Freq, frequency; Min, minute; PSIP, psychedelic somatic interactional psychotherapy; Tx, treatment.

TABLE 2 Subjective effects.

Subjective effects	Definitions	Patient perspective
Oceanic boundlessness	Oneness with the universe accompanied by a sense of awe	"I had these moments of insight that were very profound. Everything would come together all at once: fear, beauty, wonder. Sometimes they would ebb and flow during a session too. It was spiritual in a way. I felt enlightened."
Ego dissolution	Complete loss of subjective self-identity	"Once I started dissociating, I detached from who I was and everything around me. I just dissolved into nothingness. It was dark and very uncomfortable at times."
Emotional breakthrough	Categorical leap in affective experience	"I had my biggest breakthrough after session six. I was able to connect with my younger self and tell her that this [trauma] wasn't her fault. That she did the best she could. It was an emotional purging. After that, I started seeing everything in a new light, and started forgiving and accepting myself and past experiences. That's when my healing truly began."

In response to treatment, the patient reported changes in three facets of mysticism: Oceanic boundlessness, ego dissolution, and emotional breakthrough.

was accompanied by decreased cognitive distractibility and emotional suffering, as well as increased psychosocial functioning. Repeated sessions of CAP, paired with integrative CBT, likely account for the strength and durability of response. Moreover, with gains from CBT for PTSD lasting up to 12 months (36), ad hoc CBT may have prolonged the effects of therapy after treatment, with ongoing development of skills and knowledge overtime.

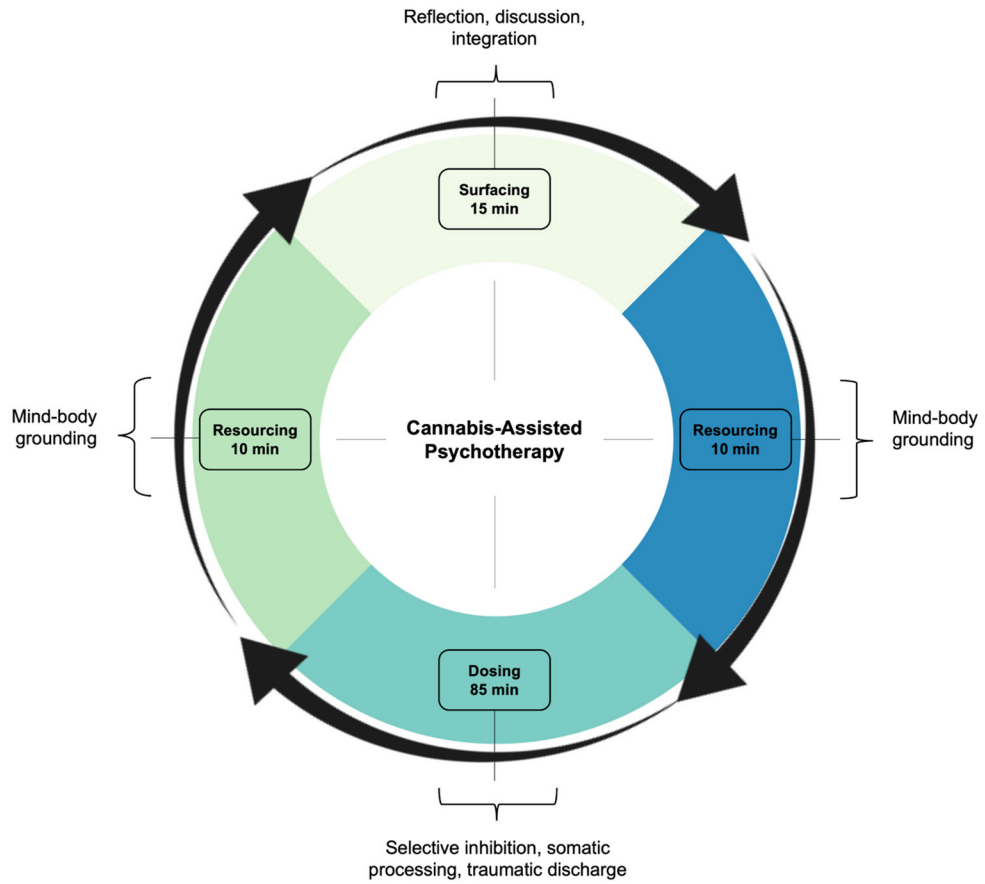

FIGURE 2
Treatment framework. In line with the PSIP model, CAP involved three criteria: surfacing, resourcing, and dosing. Surfacing readied the patient for treatment, integrating experiences from prior sessions, excluding the first one. Resourcing grounded the patient before and after treatment, comprising mindfulness and nervous system regulation. Dosing included cannabis and psychotherapy, as an interactive treatment, targeting dissociative symptoms and interpersonal trauma. CAP, cannabis-assisted psychotherapy; PSIP, psychedelic somatic interactional psychotherapy.

Notably, the patient described acute changes in oceanic boundlessness, ego-dissolution, and emotional breakthrough. These effects are surprising, given the low dose of cannabis used in each session. If cannabis and psychotherapy act synergistically, with therapy augmenting the response to cannabis, then its combined effect may explain the subjective changes. Irrespective, these facets of mysticism have been reported with high dose cannabis and overlap with those produced by classic psychedelics, including lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and psilocybin (37–41). They also reflect properties of ketamine, a dissociative agent, known to reduce self-referential awareness and induce feelings of unity, spirituality, and insight (42, 43). These parallels are intriguing, provided distinct mechanisms of action. Cannabis functions as a partial agonist at cannabinoid CB_1 and CB_2 receptors (20), whereas classic psychedelics generally activate serotonin (5–hydroxytryptamine, 5-HT) receptors, particularly 5-HT_{2A} (44, 45). Ketamine, on the other hand, is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) glutamate receptors, with modulatory effects on neuroplasticity (46).

As psychedelic research on PTSD rapidly expands, the potential of cannabis as a novel pharmacotherapeutic is being questioned (47). This is evidenced by a growing body of literature, systematically reviewed in (27, 48–50). Nabilone, a synthetic cannabinoid that mimics the action of THC, is also being investigated for the condition. The drug shows promise for treating PTSD-related flashbacks and nightmares, with reported improvements in distressing dreams and sleep time (51–54). Notwithstanding, the literature on cannabis in PTSD is highly heterogeneous, stemming from observational and underpowered studies. Its application also remains controversial in humans, with a strong link between trauma and substance dependence (55). The use of adjunctive or combination psychotherapy has neither been explored; and data for D-PTSD is non-existent.

Future research on CAP stands to benefit from the psychedelic "highway," as a feasible path toward clinical utility (56). This is evermore salient, given similarities between cannabis and psychedelics in public, commercial, and federal interests; the latter reflected by rising state and municipal legalization. Drawing parallels may additionally contribute to paradigm shifts in neuropsychiatry and drug development (57); specifically, looking beyond monoaminergic and glutamatergic systems to an endocannabinoid-based model of chronic stress pathology, aimed at neuromodulation. This may otherwise highlight a patient-specific model of trauma response and recovery.

Psychotherapy must also be considered. As a first-line treatment for PTSD, psychotherapy plays a key role in processing traumatic

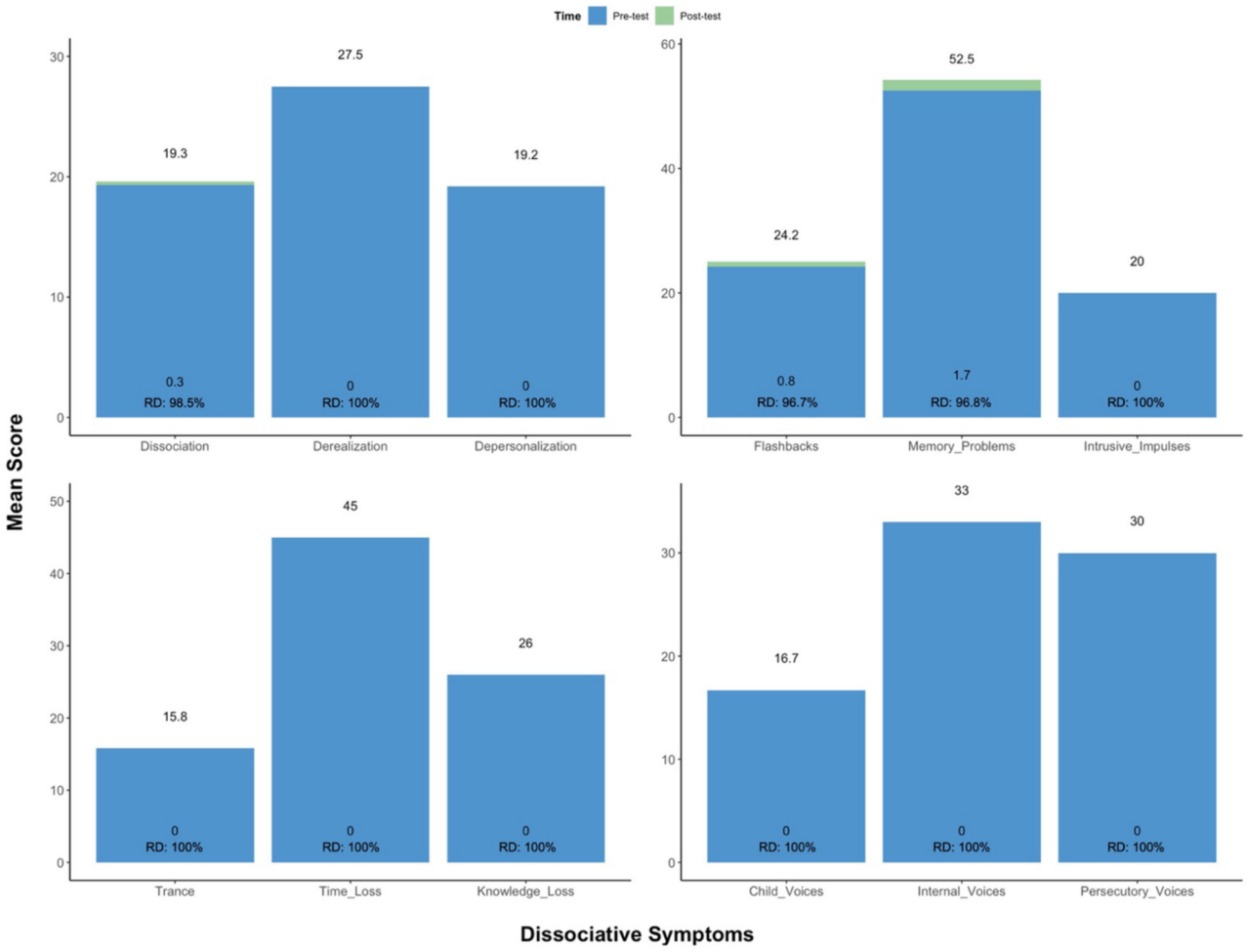

FIGURE 3
Change in scoring on the MID. From baseline to post-treatment, following all CAP and CBT sessions, the patient showed a robust improvement in clinically significant dissociative symptoms, no longer meeting criteria for D-PTSD. CAP, cannabis-assisted psychotherapy; D-PTSD, dissociative posttraumatic stress disorder; MID, multidimensional inventory of dissociation; RD, reduction.

events, often through re-experiencing. It can also target more distressing ailments, such as guilt and shame, not readily addressed by normalizing neurochemical imbalances. In the present study, cannabis was paired with interactional psychotherapy, namely PSIP, to target complex relational trauma that manifested as fear, negative emotions, and detachment. It was additionally used to support inherent, self-correcting processes that arose during CAP. Learning how psychological interventions, like PSIP, maximize altered states of consciousness will be critical in characterizing mechanisms that lead to favorable outcomes. Hence, it is recommended that CAP be understood in the wider landscape of psychedelic-assisted therapy. For instance, understanding whether CAP is preferentially suited for treating D-PTSD, assuming that all assisted forms of psychedelics are available. A recent cross-sectional study, investigating expectations for CAP, showed comparable beliefs to psilocybin-assisted therapy among two samples of cannabis users (58). Participants believed that CAP, when administered at an ideal dose, could elicit mystical and emotional experiences, as well as alter dysfunctional attitudes. However, more data on CAP is patently needed to establish comparisons, specifically for D-PTSD. Finally, the role of "set and setting" should be examined. As with psychedelics (59), one's mindset and external environment, including the therapist, may interact to shape acute and long-term mental health outcomes.

Limitations

This study has inherent limitations. It describes the history, symptoms, diagnosis, treatment, and follow-up of an individual patient, with no randomization, control, or blinding. Cannabis dosing was also subjectively variable, ranging from 6–10 mg per session. Moreover, it is unclear whether cannabis and psychotherapy were interdependent and necessary, the degree to which each produced clinical benefit, and how effective the treatment would have been with fewer or more sessions. Lastly, a directive, interactional approach to psychotherapy was employed, with an emphasis on autonomic and relational processing. This contrasts to other psychotherapeutic techniques, including cognitive, behavioral, and humanistic therapy. It also differs from gold-standard, evidence-based treatments for PTSD, namely CPT and PE, that are cognitive and exposure-based. Hence, it is premature to generalize the findings of this report. Nonetheless, this study represents the first data on

CAP in D-PTSD, within a naturalistic, real-world setting. The results are more robust given the patient's clinical non-response to first- and second-line therapies, the complexity of this population, and its limited evidence base. Larger, well-controlled, and more diverse studies are required to explore potential underlying mechanisms, establish safety profiles and side effects, and assess therapeutic efficacy and effectiveness.

Conclusions

This case highlights the potential of CAP in D-PTSD, with robust and sustained improvement in pathological dissociation. No adverse events were reported. Notably, subjective effects were comparable to those observed in psychedelic therapy, specifically oceanic boundlessness, ego dissolution, and emotional breakthrough. Further data is needed to explore, establish, and optimize CAP in D-PTSD, to determine the contexts and therapeutic frameworks it is best suited for, and to characterize its role in the current pharmacological toolbox.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MK conceptualized the study and drafted the initial manuscript. AR supervised the work, created all figures, and drafted the final manuscript. MS contributed to the literature review and co-drafted the introduction. CM co-drafted the case presentation. AL co-drafted the results. LJ, AM, and RA contributed to the acquisition of data and critically revised the manuscript for intellectual content. PS, RR, and LA provided field expertise, interpretations of data, and substantial manuscript revisions. All authors have read and approved the final manuscript.

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Conflict of interest

AR is the Founding Director of the Integrated Research Literacy Group. RR serves as Chief Clinical Officer of Numinus Wellness, and is an equity holder in the company. LA serves as a Consultant, Speaker and/or Advisory Board Member for Guidepoint, Transcend Therapeutics, Beond, Source Research Foundation, Reason for Hope, and Ampelis.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Psychedelic replications in virtual reality and their potential as a therapeutic instrument: an open-label feasibility study

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Background: Recent research has shown promising results for the therapeutic benefits of psychedelics. One popular view claims that these benefits are mediated by the subjective experiences induced by these substances. Based on this, we designed a virtual reality experience, Psyrreal, that mimics the phenomenological components of psychedelic experiences.

Aims: We aimed to investigate the therapeutic efficacy of Psyrreal and psychedelic VR experiences in treating depressive symptoms as well as explore the effect of Psyrreal on subjective factors which have been suggested to mediate the therapeutic benefits of psychedelics.

Methods: In this open-label feasibility study, thirteen participants with mild-to-moderate depression underwent a 2-day therapeutic intervention implementing Psyrreal. Depressive symptoms were evaluated by the Emotional State Questionnaire (EST-Q2) at the start of the intervention and 2 weeks after. A thematic analysis of semi-structured interviews after Psyrreal was also conducted as an additional assessment of the method.

Results: A 2-day intervention implementing Psyrreal led to significant decreases in depressive symptoms at the 2-week follow-up (n = 10, p = 0.007, Hedges' g = 1.046) measured by the Emotional State Questionnaire (EST-Q2). The analysis of semi-structured interviews suggests that Psyrreal could lead to insight and alterations in the sense of self in some people.

Conclusion: This work proposes a novel method using virtual reality to augment the treatment of psychological disorders as well as to precisely investigate the mediating subjective factors of the therapeutic effects of psychedelic substances. Our preliminary results suggest that VR experiences combined with psychological support show potential in treating depressive symptoms and further research into similar methods is warranted.

KEYWORDS

psychedelics, virtual reality, therapy, therapeutic mechanisms of psychedelics, altered states of consciousness (ASC), VR-augmented therapy, depression, depressive disorder

Introduction

"I had profound and visionary encounters with nature, and this was long before I conducted my initial experiments with LSD [lysergic acid diethylamide]. Indeed, my first experiences with LSD were very reminiscent of these early mystical encounters I had had as a child in nature. So, you see that it is even possible to have these experiences without drugs." Albert Hoffman, cited in Grob (1).

The last two decades have seen a massive resurgence of research into psychedelics largely due to their wide range of therapeutic benefits [e.g., addiction (2–5), depression (6–10), end-of-life distress (11–15), suicidality (16–18), obsessive-compulsive disorder (19), migraine (20, 21), phantom-limb pain (22), for reviews see (23–28)]. This has elevated interest in substance-assisted therapies, where psychedelic sessions are included as a part of the therapeutic process. Preliminary results regarding the efficacy of such methods have been promising (24, 25, 27, 29) and have even shown strong effects in patients whose ailment has not responded to conventional methods (11, 12, 15) [see also (6–10)]. However, it is currently unclear how psychedelic substances confer these benefits. One possibility is that the underlying mechanisms are strictly neurochemical (30, 31). The alternative proposal is that subjective experiences hold the key to the success of psychedelic interventions (32, 33). According to the latter view, therapeutic success is caused by the subjective experiences elicited by these substances, such as mystical (8, 34, 35), ego-dissolution (32, 36–38) or insight experiences (5, 32, 34, 39–41). If psychedelic-induced subjective experiences underlie their therapeutic effects, then it should be possible to achieve at least some of the benefits of psychedelic therapy without the substances themselves (42) simply by emulating specific aspects of psychedelic experiences. Furthermore, despite the many benefits of psychedelic therapy, there can also be some disadvantages to administering psychedelic substances (e.g., cost, legality, and contraindication) in certain population groups (43–45) which highlights a necessity for finding more accessible alternatives. We propose a way to study this question by mimicking many of the wildly different subjective psychedelic experiences in virtual reality (VR), replicating the audiovisual phenomena reported during psychedelic, mystical and deep meditative experiences.

The potential of virtual reality as a therapeutic device has become an increasingly researched topic. Different VR interventions have been used in the treatment of anxiety with promising results (46–49), while depression has only been investigated in a couple of studies (46–49). Recent developments in VR technology suggest that it could be possible to induce mystical experiences (50, 51) and imitate parts of the phenomenology of the psychedelic state (52). Also, some recent studies have suggested that using psychedelic phenomenology in VR can lead to similar cognitive (53) and neural (54) effects as seen under psychedelic substances. Thus, these recent works raise the intriguing possibility that perhaps the implementation of such phenomenology in VR could be used to confer similar therapeutic benefits to psychedelic-augmented therapy.

In this work, we have created Psyrreal, a psychedelic-inspired virtual reality experience. While previous studies (50, 52, 55, 56) implementing psychedelic phenomenology in VR used visually relatively simple and unvarying environments, here we have incorporated a much larger set of visual effects and different environments as psychedelic experiences have massive inter-, and intraindividual variance (57, 58). The participant is taken on an immersive journey through many surreal and vastly different virtual environments which aim to convey certain concepts and narratives often reported during psychedelic experiences [e.g., connectedness (59) or ego-dissolution (60)]. Following the example of Carhart-Harris et al. (12), we conducted an open label feasibility study on healthy adults with mild to moderate depressive symptoms to guide further research into similar methods, and investigate the potential therapeutic effects of Psyrreal as well as the specific mechanisms of VR and psychedelic experiences that may confer these benefits. The primary expected outcome of the study was that a VR experience that simulates psychedelic phenomenology could, in combination with an open therapeutic setting, lead to a decrease in depressive symptoms, measured by the Emotional State Questionnaire (61) (EST-Q2). Expected secondary outcomes included increased reported intensity of mystical experiences [measured by the Revised Mystical Experience Questionnaire (29, 62, 63), MEQ30], psychological insight [Psychological Insight Questionnaire (40), PIQ] and ego-dissolution [Ego-Dissolution Inventory (60), EDI].

Materials and methods

Hardware and software

The current version of Psyrreal is a stable release of the virtual reality experience which could already be applied in a therapeutic setting. The experience will run on most modern VR headsets, and HTC Vive Pro Eye was used for development and the experiments. Epic Games Unreal Engine (UE) 4.27 was used as the development platform and the experience was written fully in Blueprint visual scripting language. The final software is distributed as open source upon request[1], with the Creative Commons Attribution-Non-Commercial license.

Psyrreal imitates the audiovisual and narrative phenomenology reported during psychedelic experiences (57, 58, 64–74) (**Figure 1**). Certain elements were also included based on descriptions of pharmacologically induced and spontaneously occurring mystical experiences (29, 72, 75–81), deep meditative states (82–85), and awe-inducing experiences (86–89) as in some cases these offered more details about specific phenomena which also occur in psychedelic states. The phenomenological elements and concepts used in the experience (**Table 1** and **Supplementary material 7**) were selected after careful study of the available literature on psychedelic (57, 58, 64–74), meditative (82–85), awe-inducing (86–89), and mystical (29, 72, 75–81) experiences, written reports (58, 59, 68, 76, 90–92) and visual replications (66, 68, 93) of such experiences.

The participants begin the experience in a virtual "real world" which starts to acquire psychedelic phenomenology and continues to progress through a total of 19 distinct visual levels incorporating and combining various psychedelic effects.

1 Can be requested at the website https://psyrreal.mozellosite.com.

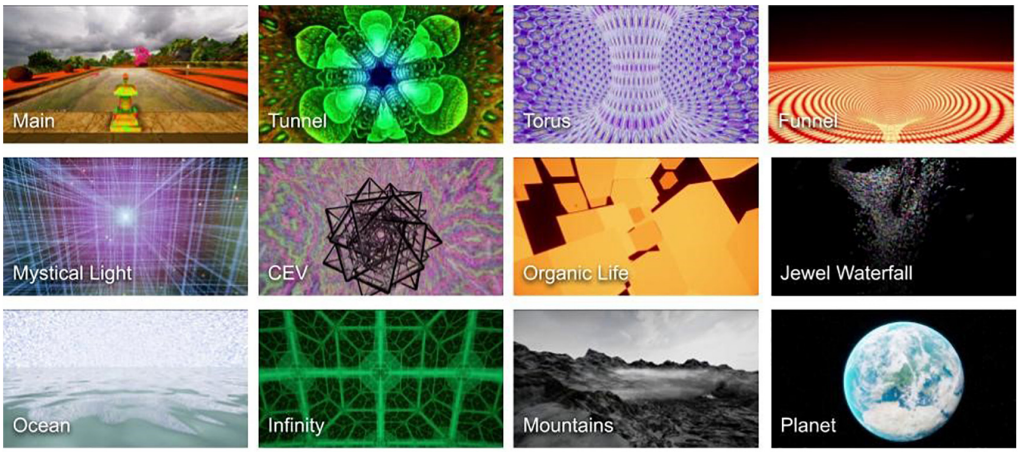

FIGURE 1
Screenshots of some of the environments in Psyrreal shown in sequence to exemplify the diversity of visuals presented to the user during the experience. The experience starts in a temple **(top left)**, progresses through different levels of varying abstraction and intensity, and culminates in outer space **(bottom right)**. See also **Supplementary material 1** for more illustrations of the environments and **Table 1** for more detailed descriptions of the implemented concepts. CEV stands for "closed-eye visuals."

The visuals for the most part consist of abstract shapes and geometric patterns that would allow participants to project their own meaning to the experience. The duration of levels varies from approximately 30 s to 2 min. A specific soundtrack was composed for Psyrreal implementing narrative (e.g., varying intensity) and perceptual (e.g., temporal alterations) aspects of psychedelic phenomenology matching the visual levels. Psyrreal was validated among participants with extensive psychedelic experiences who evaluated its similarity to psychedelic experiences (see **Supplementary material 3** for more details). All participants had prior experiences with lysergic acid diethylamide (LSD) and psilocybin with five (out of seven) participants also having prior experiences with *N,N*-dimethyltryptamine (DMT) or Ayahuasca. Participants in the validation study were recruited *via* social media. Five people rated at least one scene from Psyrreal to be visually very similar (4 on a scale from 0 to 5) to psychedelic experiences. Though the experience is purely audiovisual and did not include any physical stimulation, six people also rated the physical sensations induced by Psyrreal to be very similar to those experienced under the effects of psychedelics.

Therapeutic intervention using Psyrreal

Participants

The sample consisted of 13 participants (8 women, 5 men) of ages 20–58 (M = 33.8, SD = 10.6; further information on the participants can be found in the data files, linked under **Supplementary material**). The study was advertised on an Estonian website that promotes discussion about mental health (peaasi.ee) and recruitment was conducted through self-referral from 20th October 2021 until 8th December 2021. The sample size was determined by practical constraints and concurrent COVID-related restrictions as well as sample sizes of similar feasibility studies [e.g., (12)]. Applicability was decided based on their scores on a self-rated depression screening questionnaire (depressive scale cut-off of ≥12, see below) administered during online registration. The scores of the questionnaire were analyzed and updated with a clinical psychologist on the first day of experiments. Additional criteria for exclusion were: hypersensitivity to motion sickness, a diagnosis of psychotic disorders and schizophrenia, a history of epileptic seizures or psychotic episodes, or a family history of schizophrenia. We also excluded people who were currently undergoing treatment for depression (therapy or medication). Most participants had a previous diagnosis of depression (9 out of 13), but participants who were currently receiving treatment were excluded (see also additional analyses **Supplementary material 2**). All participants had normal or corrected to normal vision. Participants were asked to refrain from consuming alcohol or other substances before the experience to avoid cybersickness and potential confounding.

The study was approved by the ethics committee of the University of Tartu and performed in accordance with relevant guidelines and regulations. Participants gave written informed consent prior to participation. All 13 registered people finished the study. One participant (P6) was excluded from the analyses due to receiving antidepressant therapy at the time of the study and another was excluded due to their updated score of depressive symptoms being below the cut-off, thus leaving the final sample at 11 participants. Note that an estimated effect size of 1.11 (based on a relatively similar approach using VR to treat depression) should be detectable with a sample size of 9 [for a statistical power of 0.8, found with G*Power 3.1 (94)].

Measures

The Emotional State Questionnaire (61) (EST-Q2), a standard self-report tool for depression screening in Estonia (95), was used to evaluate differences in symptoms before the experiment and at a 2-week follow-up. A cut-off of ≥12 (threshold commonly used in clinical practice) was applied to only include participants with symptoms indicative of clinical depression. We also evaluated the response (proportion of participants showing decrease of at least 50% of baseline) and

TABLE 1 Overview of elements and concepts common to psychedelic experiences and examples of their implementation in Psyrreal.

Elements of psychedelic experiences	Implementation in Psyrreal
Visual acuity and color enhancement. One of the first alterations often noticed in psychedelic experiences is an enhancement of visual acuity where the visual field appears clearer and sharper and objects become more well-defined (58, 59, 69, 147). This effect is usually accompanied by an intensification and enhanced saturation of colors (58, 67, 69, 92, 148).	The experience starts in a serene, realistic environment overlooking some mountains, with birds singing and calm water flowing around the user (**Figure 1** "Main"). After a brief period various open eye visual effects start to appear. Colors become brighter and more saturated; elements of drifting and morphing affect different objects as well as the whole perspective; after-images appear behind falling leaves, and flying butterflies. Certain effects on objects, such as increased contrast, edge aura, texture change and drifting, are gaze-activated (**Supplementary Figure 7**). Moving the gaze away from the object decreases the effect strength. As the experience progresses, the affected area can change from object edges to whole objects and to the entire scene (e.g., **Figure 1** "Jewel Waterfall").
After-images. Another visual distortion that is often noticed during the early phases of psychedelic experiences is illusory palinopsia, also called after-images, visual tracers, trails or "ghosting" where moving objects leave behind visual trails (67, 149–151).	
Drifting. Objects, parts or the whole visual field often move and distort in many irregular ways, such as drifting, morphing, melting and breathing (69, 92, 147, 152). These effects can start from a slight oscillation of the outlines of specific objects to seamless drifting of textures and objects changing color or morphing from one to another (153).	
Closed eye visuals (CEVs). While it is common to experience geometric patterns on real stimuli with eyes open, intricate patterns are also often reported with eyes closed. CEVs usually start out with simple geometric forms like lattices, cobwebs, honeycombs and spirals (65). Frequently, CEVs include experiences of infinite, kaleidoscopic tunnels formed of geometric patterns and texture repetition (65, 66, 69, 154).	After about 7 min of gradually increasing distortion of the environment, the experience transitions into scenes of CEVs. These start by rather dim 2D patterns which slowly become more vivid and develop into 3D spaces formed of elaborate geometric patterns akin to reports of "DMT hyperspaces" (e.g., **Figure 1** "Torus"). Many of these environments also stretch infinitely in all directions (e.g., **Figure 1** "Infinity"). The 2D patterns occur recurrently during the rest of the experience, increasing in complexity and acquiring rotating sculptures that generate different mandala-like visuals (**Figure 1** "CEV"). One specific example of such patterned scenes are kaleidoscopic rotating tunnels (**Figure 1** "Tunnel"), which tend to cause feelings of illusory self-motion and can lead to mild nausea or cyber-sickness (which might, unintuitively, benefit the therapeutic process, see Discussion).
DMT hyperspace. A special kind of visionary experience is the so-called "DMT hyperspace" where people are transported into another world (92, 154). These are often high dimensional spaces (59, 148, 154) which contain massive or even infinitely large cathedrals, machines capes or abstract spaces made of geometric patterns (154). The passage into this space, a "DMT breakthrough," is often accompanied by sensations of overwhelming intensity, fast or accelerating movement along geometric tunnels and an ascending or intensifying sound (74, 92, 154–156).	
Visions. With higher doses and during more acute phases of psychedelic experiences, CEVs can become increasingly lucid, hyperdimensional with more complex patterns, and acquire profound meaning (69, 92). Often dreamlike (70, 73) visions arise which can include whole scenes or landscapes, autobiographical memories or imagined realistic situations, as well as mythical or archetypal imagery (57, 58). Such visions are sometimes experienced in a synesthetic fashion, i.e., not just seen or imagined visually, but also "felt" (57, 58, 91).	While many levels consist of abstract shapes and patterns (e.g., **Figure 1** "Organic life"), we also included levels that simulate elements of more coherent visions. "Visions" induce the feeling of being in a completely different environment from the main level. We included views of landscapes and grandiose and vast scenes (e.g., **Figure 1** "Ocean"), involving large cathedrals and a mountain ridge with a floating monastery (**Figure 1** "Mountains"). We also implemented the "Overview" (157–159) and "Ultraview" effects (160) where, respectively, the subject experiences an overview of the Earth (**Figure 1** "Planet") and thereafter the whole Universe.
Mystical experiences. Moderate and higher doses of psychedelics often result in participants having mystical experiences (29, 72, 77, 79). These indescribable and paradoxical experiences are often described to contain a felt union with God, Nature or the Universe, receiving transformative insights and feelings of profound peace and bliss (72, 80, 81). At the core of mystical experiences is losing a sense of individual self (see also ego-dissolution) and "becoming one" with objects of attention or with "everything" (72, 80). Another common mention is that of a bright white or golden light that could be seen or "felt" in a synesthetic nature (72, 82, 161). Mystical experiences also often contain alterations and transcendence of time and space, and feelings of vastness, awe and sacredness (58, 62, 72, 80, 92).	The synesthetic and phenomenologically barren nature of mystical experiences creates a significant hurdle in representing them in the audiovisual medium of VR. Nevertheless, we implemented a recurrently appearing level with a bright white light and calm and sacred music (**Figure 1** "Mystical Light"). We also included a level with spherical particles that circle around the player, giving the impression that the environment is "alive" and interacting with the player. Psyrreal also has a soundtrack with varying tempo and intensity to induce a sense of temporal alteration (see also "Overview of Psyrreal VR").
Ego-dissolution. Psychedelic experiences also bring about alterations of the sense of self which are often discussed under the term ego-dissolution (or "ego-death") (57, 162–166). This is often reported as a dissolution of the embodied self, disintegration of self-related thoughts and felt ownership of thoughts (60, 164, 167), and/or cessation of implicit subject-object distinction as the subject feels as "one" with their surroundings (57, 72).	To emulate ego-dissolution, we included a virtual body representation of the user in certain levels which consists of a sphere that mimics the environment, thus creating a sense of connectedness to the virtual "world." At the culmination of the experience the particles of the universe converge at the position of the subject to then explode outward and fade, disintegrating the virtual self.

remission rate (proportion of participants showing decrease to below 12) based on EST-Q2 scores. The Montgomery—Åsberg Depression Scale (96) (MADRS) was administered by the psychologist before the experiment to validate the depressive symptoms of our sample.

One important facet of subjective experiences that could be instrumental for therapeutic benefits is the insight experience (5, 32, 40, 41). The Psychological Insight Questionnaire (40) (PIQ) was used to capture insights in our sample at the end of the first (control) and second days (**Figure 2**; same for the other following questionnaires). Another aspect of subjective experience that has been suggested to underlie the beneficial effects of psychedelic therapy is ego dissolution (32, 38, 97), measured here by the Ego-Dissolution Inventory (60) (EDI). Mystical experiences have also been proposed as an important mediating factor for the benefits of psychedelic compounds. Here we used The Revised Mystical

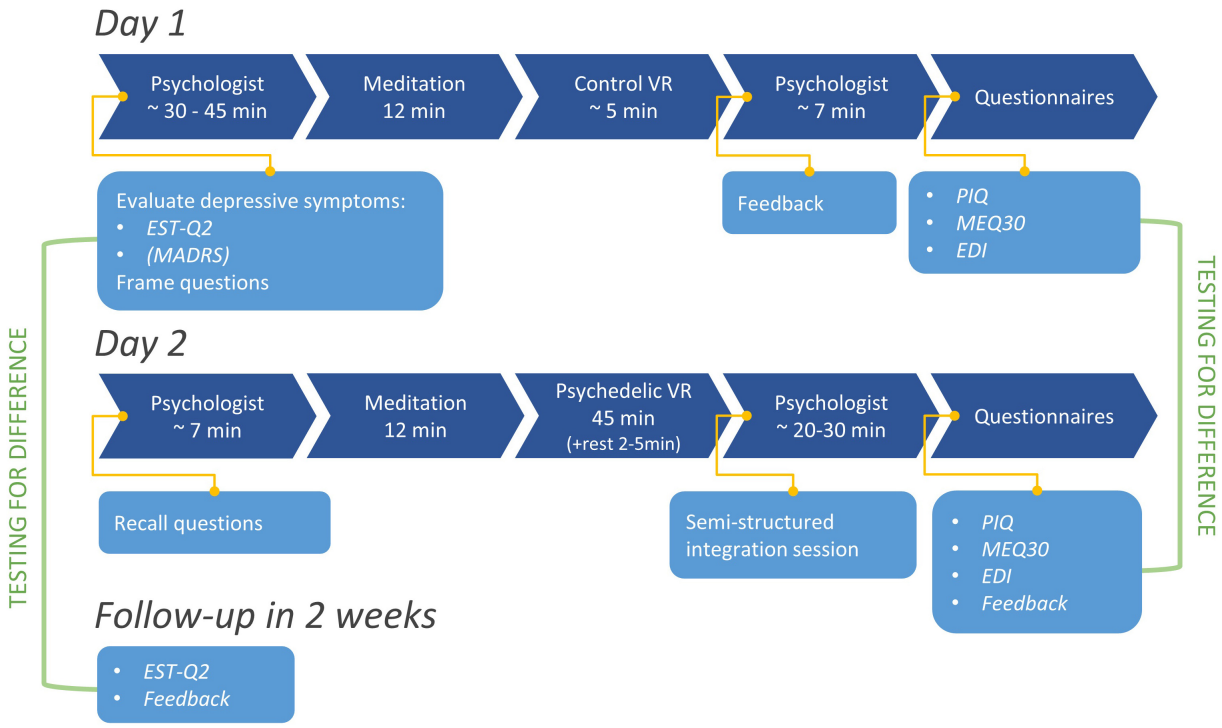

FIGURE 2
An illustration of the procedure of the experiment on day 1 and day 2, as well as measurements conducted on the 2 days of experiments and during the follow-up after 2 weeks. The green lines highlight the comparison groups used for the statistical analyses.

Experience Questionnaire (29, 62, 63) (MEQ30) to measure the intensity of mystical experience.

MEQ30, PIQ, and EDI were administered at the end of the first day and again at the end of the second day. EST-Q2 was administered during registration and 2 weeks after the experiments. More detailed descriptions of the questionnaires can be found in **Supplementary material 5**. Baseline scores were also reevaluated during the first discussion with the clinical psychologist at the start of the first day. A semi-structured interview about the experience was also conducted by the clinical psychologist at the end of the second day. An additional background and feedback questionnaire was administered at the end of the second day of experiments, and a feedback form was sent to the participants 2 weeks after the experiments. All questionnaires were administered in Estonian.

Study procedure

This open-label feasibility study used a one-group, uncontrolled, longitudinal design to investigate the effects of psychedelic phenomenology in VR. Experiments were conducted on two consecutive days (**Figure 2**; see also **Supplementary material 6** for more details on the experimental setting). The first day included a diagnostic and preparative 30–45 min session with a clinical psychologist, discussing the depressive symptomology of the participant based on their scores on the EST-Q2 Depression scale (filled in during the online registration) and guiding the participants to frame questions and think about their worries. Afterward, the participants were instructed on how to use the VR equipment and partook in a demonstrative 15 min VR experience, which consisted of a 10 min guided meditation (in a cave-like environment, **Supplementary Figure 10**; however the participants were instructed to close their eyes for the duration of the meditation) and a further 5 min of being in a non-interactive living-room environment (default Steam VR Home room, **Supplementary Figure 9**). Participants were seated comfortably during both VR experiences on day 1 and 2. Then the participants had another shorter (5–10 min) discussion with a clinical psychologist and filled in the rest of the questionnaires (EDI, PIQ, and MEQ30). The demonstrative VR experience on the first day also served as a control condition for comparisons with EDI, PIQ, and MEQ30 measures. Participants were instructed to answer the questionnaires based on the 5 min spent in the living-room VR environment. EST-Q2 was not administered after the control VR as it is not a suitable measure for short term changes in mood.

The second day had a similar structure starting with a short discussion with the psychologist to evaluate the effects of the first day and to prepare the participant for the VR experience. During this, the participant was also instructed to look around freely during the experience, sit however they felt comfortable, and not to overly focus on their questions but rather to relax and focus on the experience itself. Then, the participant underwent the same guided meditation in VR as the day before which was directly followed by the 45 min long VR experience. The psychologist was waiting in the next room in case of any psychological emergencies, and a technician was present in the room with the participant to monitor the VR system. After the experience, the participant was allowed to rest for as long as they preferred and then had an integrative session (20–30 min) with the psychologist and answered

the questionnaires (EDI, PIQ, and MEQ30). Follow-up EST-Q2 questionnaire was sent to the participants 2 weeks after their participation in the experiment.

The experiments were conducted in the virtual reality laboratory at the Institute of Computer Science of the University of Tartu between 29th October 2021 and 11th December 2021. For more additional details on setting and study procedure see also **Supplementary material 6**.

Statistical analysis

Paired sample *t*-tests were conducted on the before and after scores of the questionnaires (EST-Q2, EDI, PIQ, and MEQ30). All tests were two-tailed with $\alpha = 0.05$. Shapiro–Wilk test confirmed approximately normal distribution for the before-after differences of all datasets. All statistical analyses were conducted with JASP (98) (version 0.16.1.0).

One participant did not fill in the questionnaire at the 2-week follow-up and was therefore excluded from the analyses concerning the EST-Q2 measure. Additionally, two participants implied in their follow-up report that they had sought psychological counseling after the intervention. Because of this, we conducted an additional analysis on all questionnaires, excluding the two participants, yielding similar results which are reported in the **Supplementary material 2**.

Results

Therapeutic intervention

We conducted an open-label feasibility study in adults ($n = 11$) with mild to moderate depressive symptoms. Note that $n = 10$ for the EST-Q2 measure, as one participant did not complete the follow up questionnaire. The experiments took place on two consecutive days with Psyrreal being implemented on the second day (see **Figure 2**). No adverse effects were reported during the administration of the VR experience, even though the participants were encouraged to express any discomfort. In the interviews afterward, four participants (out of 13) mentioned transient nausea during the VR experience.

Baseline EST-Q2 depression subscale results were $M = 15.20$ ($SD = 2.66$) and showed good consistency with the MADRS questionnaire results ($r = 0.66$, $p = 0.010$). There was a significant decrease in EST-Q2 scores at the 2 week follow-up ($M = 11.00$, $SD = 3.74$; paired samples *t*-test, $t_{(9)} = 3.50$, $p = 0.007$, Hedges' $g = 1.046$; **Figure 3A**). The response rate of the treatment was 18% and remission rate was 60%. The difference between the response and remission rate is largely due to the mild-to-moderate symptoms reported by the studied population. The anxiety scale results of the EST-Q2 showed a similar pattern, as scores decreased from baseline $M = 10.10$ ($SD = 4.65$) to $M = 7.60$ ($SD = 4.14$) after 2 weeks [$t_{(9)} = 3.73$, $p = 0.005$, $g = 0.459$; **Figure 3B**].

PIQ score results were $M = 24.74$ ($SD = 22.98$) after the control condition and $M = 29.09$ ($SD = 21.73$) after the experimental condition. Paired samples *t*-test indicated that the change was not statistically significant [$t_{(10)} = 1.256$, $p = 0.238$, $g = 0.161$].

EDI scores increased from $M = 35.76$ ($SD = 21.14$) after the control condition to $M = 39.83$ ($SD = 27.77$) post-experiment, but the change was not statistically significant [$t_{(10)} = 0.829$, $p = 0.426$, $g = 0.136$]. Two participants (P2, P3) did show a large increase (>25 points) in EDI scores.

The MEQ30 average score increased from $M = 39.58$ ($SD = 19.57$) to 42.73 ($\sigma = 18.43$). The change was not statistically significant [$t_{(10)} = 0.673$, $p = 0.520$, $g = 0.137$]. One participant (P3) reported a complete mystical experience (all MEQ30 subscales over 60) on day two. One participant (P7) reported a complete mystical experience on the first day, but not on the second.

While the changes of scores on PIQ, MEQ30 and EDI did not reach statistical significance, the results were highly varied. A thematic analysis (99) was conducted based on the transcripts of the integrative semi-structured interview sessions to investigate the effects of the intervention on individual participants. Extracts from the transcripts that were used in the thematic analysis can be found in **Supplementary material 4**. The analysis revealed certain themes that were often mentioned in the interviews (**Table 2**). All participants reported feeling some positive emotions during the experience with 55% of participants reporting calmness or peace and the same amount of people reporting feelings of joy, pleasure, or fun. Seven participants also reported negative emotions (sadness, fear, and anxiety) with four participants mentioning feeling sadness. A total of 45% of participants reported that they had personally relevant thoughts during the experience, for example, one participant mentioned: "*From this place where I got in touch with this emotion [sadness] these other questions also started to unravel and I understood many of my [behavioural and cognitive] patterns,*" (P12). Six participants mentioned that they did not reach any new understandings, while three did arrive at new beneficial understandings: "*[.] this novel understanding that I can reprogram myself, that this essence of myself doesn't exist—it's very liberating. It gives me, in some sense, a vitality that I'm looking for," (P7).*

Three participants specifically highlighted a physical feeling of insight as illustrated by the following quote from participant seven: "*It was a different kind of insight, like a new insight. Like a physical insight*," (P7). Five people reported changes in perspective: "*[.] Like a shift in perspective - in the beginning, I was looking more at the details, afterward I was looking at the whole*," (P3). Six participants reported alterations in their sense of self with three reporting alterations in the narrative sense of self and four participants reporting alterations in the embodied sense of self. For example: "Did you experience any change or loss of your self-image or sense of self? *Yes, like dissolution, yes. [.] The whole experience was so immersive that you melted into it,*" (P2). A total of 36% of participants reported somatic effects during the experience: *"Specifically the parts with strong motion, these almost physical experiences, those were the most impactful,*" (P12).

Discussion

We created a novel VR experience based on psychedelic and mystical experiences as well as meditative states and implemented it in a therapeutic intervention for people with mild-to-moderate depression.

The results of the study suggest that using VR experiences in a therapeutic setting could be beneficial in treating depressive

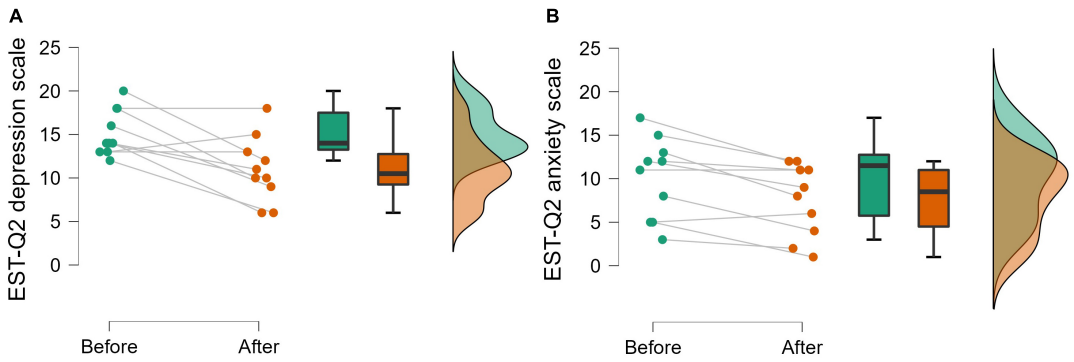

FIGURE 3
A raincloud plot of the EST-Q2 depression scale **(A)** and anxiety scale **(B)** scores as measured before the experiment and 2 weeks after. Depicted are individual scores, as well as boxplots and density distributions of the results (N = 10).

symptoms, with participants showing a significant reduction in depressive symptoms 2 weeks after the experiments. As this was an open-label feasibility study with a relatively small number of participants, strong conclusions about the efficacy of such interventions cannot be made. Nevertheless, as 73% of participants showed a decrease in their depressive symptoms 2 weeks after a short 2-day intervention at a 60% remission rate, further research into such methods is warranted. Additionally, a previous study using a VR experience to treat depression also reported a comparable effect (49), offering preliminary tenability for the potential therapeutic benefits of VR experiences. Anxiety scores also decreased significantly at the follow-up. However, the anxiety scores were generally low beforehand with four participants having a score indicative of an anxiety disorder (≥12). That being said, these results suggest using psychedelic-inspired virtual reality for the treatment of anxiety to also be a promising avenue for research. Additionally, results from the thematic analysis suggest that a psychedelic VR experience, when accompanied by a dedicated therapeutic setting, might be able to induce insight and understanding at least for some people. Three participants reported gaining new and beneficial insights related to their problems and two more mentioned gaining new perspectives during the experience. However, across sample the change in insightfulness rating as measured by PIQ did not reach significance, indicating great interindividual variance.

TABLE 2 Common themes found in the analysis of the semi-structured interviews (n = 11). The colored bar plot indicates the proportion of participants who mentioned that theme in their interviews.

Theme	# of participants
Positive emotions	11
Negative emotions	7
Alterations in sense of self	6
Feelings of joy/pleasure	6
Feelings of calmness/peace	6
Tiredness / Sleepiness	6
No novel insights	6
Thought-provoking	5
Changes in perspective	5
Loss of VR presence	5
Comparison to games/movies	5
Ambiguous tension	5
Somatic effects	4
Ineffability	4
Alterations in embodied sense of self	4
Sadness	4
Fear	4
Cybersickness / Nausea	4
Emotional tension	4
Feeling of insight	3
Intellectual insight / Understanding	3
Alterations in narrative sense of self	3
Technical issues	3
Boredom	3
Physical tension	3

Overall, these results add some tentative support to the hypothesis that subjective experiences mediate the benefits of psychedelics. Psyrreal incorporates a wide range of elements common to psychedelic experiences such as specific audiovisual phenomenology (e.g., visual acuity enhancement and CEVs; see Table 1), different structural elements of these experiences [e.g., overwhelming and oscillating intensity, and progression of the experience (100)], and general experiential themes (e.g., mystical and ego-dissolution experiences; see Table 1). The effects of our intervention on depressive symptoms were similar (albeit weaker) to those seen in psychedelic-assisted therapy (101). While the questionnaires implemented to evaluate the subjective factors which have been found to mediate the therapeutic benefits of psychedelics did not show statistically significant changes, the results of these questionnaires were highly varied in our small sample and prevent us from making strong conclusions. However, the results of the thematic analysis suggest that implementing surreal awe-inducing environments, and intense and variable experiences in VR could facilitate insights or alterations in sense of self at least for some people. Future studies are required to confirm

these speculations and evaluate the mediating factors with a larger sample and a randomized placebo-controlled trial design.

Previous similar studies using VR (50, 51) have found slightly higher results on the MEQ30 questionnaire. Specifically, the scores of the Mystical and Positive Mood subscales were higher for Isness-C (for Isness-D only the Positive Mood subscale was significantly higher) (51). However, these studies also implemented a guiding narration by a "trained drama therapist" which emphasized elements of mystical experiences (50) potentially enhancing the perception of the experience as mystical. While the current version of Psyrreal did not include narration, adding it in the future could further enhance the effect of Psyrreal. The differences on the Positive Mood subscale are likely to be influenced by the symptoms of depression prevalent in our sample and the "amplifying" effect of the experience which allowed some participants to get in touch with their negative emotions.

Possible mechanisms of psychedelic-inspired-VR-augmented therapy

Our augmented therapy intervention combined a therapeutic environment and discussion about one's problems with an engaging VR experience. One potential mechanism how this intervention yields therapeutic benefits could be that the intense and different virtual experience amplifies the therapeutic process and provides an experiential route for the participant to get in touch with their emotions (102–106) as an alternative to cognitive therapies which emphasize the role of explicit verbal discussion and reasoning (107–109). According to current understandings of psychedelic therapy, psychedelic substances in contrast to conventional antidepressants serve to amplify mental content and thus help to address rather than avoid aversive memories and emotions (23, 59, 110). Some participants mentioned that they were able to access feelings that have otherwise stayed out of reach, for example one participant expressed to the psychologist: "*When we met yesterday, [.] I said I could not feel sadness. We could have five more similar sessions and I still wouldn't feel sadness. But thanks to this experience, as short as it was yesterday, suddenly this sadness arose (in me),*" *(P7).*

A related possible mechanism is that the intensity of the experience can require relinquishing control which could result in some degree of relaxation of fixed cognitive constraints. The relaxation of top-down beliefs is suggested to be one of the possible mechanisms behind the therapeutic effects of psychedelics, wherein potentially pathological content can be accessed and overwritten (111). Letting go of control and allowing oneself to experience anything that comes up in a psychedelic experience could allow more difficult content to reach consciousness, shorten the challenging episodes and foster integration and healthy interpretation of difficult content (112, 113). This concept of "letting go" is a central element of psychedelic (59, 113, 114) and other forms of therapy (115, 116), ritual use of psychedelics (117) as well as an important part of meditative practices (84, 118–120) [see also (41)]. Psyrreal mimics the oscillating and overwhelming intensity of psychedelic experiences (68). For example, some sections of Psyrreal purposefully depict high-motion visual scenes without actual physical motion that induce quite strong physical sensations and mild symptoms of cybersickness that can be "let go" (e.g., **Figure 1** "Tunnel"). Hence, this somatoaudiovisual intensity could also function as something that could be accepted or surrendered to. The beneficial effects of "letting go" were also remarked by some participants, for example: *"[.] Then, at one moment, I let go, thinking that it doesn't work like this [focusing on finding answers]. [.] Then it actually started to work, yes. [.] I think that the first half of the experience you kind of get into it or start going along with it and then the answers arrive very clearly somehow,*" (P12). In our study, participants were explicitly instructed to accept and let go of any emotions that might arise during the experience. While Psyrreal does not include any explicitly affective visual stimuli (the music, however, varies in its emotional tone) most participants mentioned experiencing a wide range of emotions with some explicitly reporting "getting in touch" with their emotions (see above). Therefore, we suggest that another potential therapeutic mechanism for this type of therapy could be combining a virtual emotion-eliciting experience with the preparation of "letting go." Somewhat similar ideas have been implemented in VR-augmented exposure therapy where people are exposed to aversive virtual stimuli to facilitate habituation, inhibition or cognitive reappraisal of the psychological reaction (121–123).

While the experience of being in virtual reality in itself might facilitate elements that could beneficially augment the therapeutic process, there could also be added value in implementing specific visual content from reports of subjective psychedelic and mystical experiences. Unusual, infinitely vast, and even surreal stimuli common to such experiences might result in emotions of surprise and awe, where the novel stimulus needs to be accommodated into existing cognitive structures (86). The necessity for accommodating vastly different and novel stimuli would require updating the existing mental framework (86, 124) and thereby lead to a state of plasticity or "insightfulness" (41). This could allow the subject to gain different perspectives, revise pathological beliefs, and come to new insights (105, 124, 125). Such effects have also been discussed in contemporary psychedelic science (111). In fact, awe has been suggested to be a central mediator of the beneficial effects of psychedelics (126) and a potential therapeutic asset for different mental health disorders, including depression (127). Psyrreal contains infinite abstract "worlds" as well as vast landscapes and cathedrals which could induce awe (87). Additionally, virtual environments which break the usual laws of physics might also require accommodation and induce states of relaxed beliefs (105, 128, 129).

Limitations

Despite our efforts, we are far from claiming that Psyrreal is an exact replication of psychedelic experiences. Psychedelic experiences encompass many aspects of consciousness (32, 57, 58) that we tried to replicate within the audiovisually confined medium of virtual reality. Some elements of substance-induced psychedelic experiences are inherently impossible to be implemented in virtual reality (e.g., hyperdimensional spaces, many synesthetic elements). Also, compared to psychedelics, virtual reality has some additional aspects which could contribute to the loss of immersion in the experience. For example, people might lose their immersion due

to interactive elements that fail to meet their expectations or due to the graphics not being realistic enough (130).

The open-label design, small sample size and lack of controls in our reported experiment do not allow us to make strong claims about such interventions yet. We were unable to reliably estimate the effect of the control condition on EST-Q2 scores due to the 2-day design, as such short term changes (or lack thereof) would be unlikely to reflect true effects. Hence, the main comparison in depression scores could only be evaluated at least 2 weeks after the intervention. The design was chosen after careful consideration of how to best optimize resources for the purpose of evaluating preliminary results and feasibility for conducting more expensive future studies – which we now hope to conduct. Therefore, it is also possible that an expectancy bias in the participants, initial discussion with the psychologist, guided meditation or even a brief experience of non-psychedelic virtual reality might be responsible for the decrease of depressive symptoms. This is highlighted by a few participants reporting quite high results on the Psychological Insight Questionnaire and Mystical Experience Questionnaire even on the first day. While the psychologist did not apply usual therapeutic techniques and assumed the role of an observer, simply an opportunity to discuss their problems could already have had a beneficial effect.

While MEQ30 has been validated for psychedelic compounds and it has seen some use in investigating non-pharmacological methods for inducing mystical experiences [e.g., (50, 51, 131–134)], we are not aware of any studies using non-pharmacological methods that have implemented a control/baseline measurement of MEQ30. Our results suggest some potential difficulties in using the MEQ30 with non-pharmacological methods, as multiple participants had confusing results with one participant reporting a complete mystical experience on day one and a further two participants who only very narrowly missed out on the threshold of a complete mystical experience. While it is not impossible that they actually had a real mystical experience on the first day, it is unlikely and they also did not describe their experience as such during their discussion with the psychologist. We speculate that certain inflated scores could be due to the subjective nature of the questionnaire, and/or difficulties in understanding the questions. As the MEQ30 instructions require people to compare a specific experience (in our case, the VR experience) to other previous experiences in their lives, the results are dependent on the intensity of similar experiences they have had in the past, as well as their previous experience with VR. This also relates to difficulties in understanding the questions: people with varying amounts of mystical experiences can have a very different understanding of the questionnaire items which is further exacerbated by the fact that mystical experiences are ineffable and hard to describe (35, 81). It is also possible that a VR experience by itself could incline some participants to report high scores on the MEQ30. Finally, it is possible that the participants scored higher due to not wanting to disappoint the experimenters, as the people conducting the experiment were friendly and supportive to create an environment where participants feel safe and comfortable. Though, due to the open-label design, participants were aware that the measurements on the first day served an introductory and demonstrative purpose.

The guided meditation and short demonstrative VR (used on the first day) could also be conducive to reporting high scores on the MEQ30, PIQ, and EDI. Additionally, the results of these questionnaires were compared between a 5 min long control VR and 45 min long Psyrreal, which limits the comparability of the conditions. The effects of meditation on inducing altered states of consciousness, insight, self-alterations and mystical experiences are well documented (82–84, 132), but even a short experience with VR could have some effect for a couple of reasons. First, for people who have not had much experience with VR, the experience might be something so different that it has a strong effect on them (135). Second, the content of VR might by chance be specifically relevant to the participant, as was the case for one participant (who was excluded from the analysis) who had been pondering whether they should go traveling to the mountains with their ex-spouse. As the demonstrative VR was in a small room with a balcony view onto a mountain range the participant felt it to be very personally meaningful. Third, one of the potential mediators of the beneficial effects of psychedelic experiences as well as a crucial element of mystical experiences (32, 38, 97) — ego-dissolution, might be induced to some degree in any VR experience with an altered image of the body (136, 137). While the EDI did not show a significant change from baseline, half of the participants showed relatively high (a score of over 40) results even after the demo experience on the first day and several participants mentioned alterations in their sense of self during the integrative sessions. Therefore, it can be difficult to disentangle the effects of VR and the specific psychedelic content of our designed experience. Also, blinding procedures for such methods are complicated by a bane common to psychedelic investigation — the active condition is easily distinguishable from the control condition (44, 138, 139). The issues of blinding and confounding are important to be addressed in future studies.

Advantages of virtual reality for studying psychedelic therapy

Although virtual reality is likely a less powerful tool than psychedelic substances (52) [but see (50)], using it to augment therapy could be beneficial for those who suffer from acute side effects of psychedelics or who prefer to avoid consuming these kinds of substances. Virtual reality could also work as a stepping stone before engaging in psychedelic therapy (101) and could be used in countries where psychedelics are not available for medical use. The duration of virtual reality experiences is also less constrained than psychedelic experiences, which (in the case of LSD) can last over 16 h (140). Virtual reality experiences can be stopped at any moment (e.g., in the case of challenging experiences) or paused if the participant would like to immediately discuss something. Virtual reality could also be a powerful tool for investigating the precise therapeutic factors of subjective (e.g., psychedelic) experiences (101) which are often confounded and contain multiple interfering interactions, as it allows to test and separate different elements and concepts that might mediate beneficial effects. In other words, virtual reality allows one to study in a controlled manner which specific subjective experiences (e.g., certain visual experiences, challenging experiences, ego-dissolution) might be beneficial for therapeutic success.

Forms of meditation, audiovisual media, engaging in physical activities (e.g., dancing and hiking) could also be used as therapeutic "amplifiers" (105), but virtual reality offers an especially powerful medium for such a tool. First, it can offer a strong sense of presence and immersion in a specific environment which might be beneficial for the efficacy of such augmentation (101). Second, virtual reality is adaptable and could be tailored to the needs and specific symptomatology of the participant as well as to different disorders (e.g., anxiety and post-traumatic stress disorder). For instance, in Psyrreal it is possible to remove and add specific parts of the experience to customize the virtual reality experience for the specific participant and the circumstances. Third, virtual reality could have some advantages in regard to inducing ego-dissolution (51, 105, 136, 141, 142) which could be one of the mechanisms behind the therapeutic effects of psychedelics (32, 38, 97). Fourth, virtual reality assisted therapeutic interventions have high satisfaction rates (143) and are often preferred by patients. This was also echoed by our participants who subjectively evaluated the potential effectiveness of such an intervention with a mean rating of 8.00 out of 10 ($n = 12$, $SD = 2.30$).

Future developments

The current study highlights multiple important directions for further research. First, some participants in our study mentioned that the computer graphics and lack of interactivity led to a loss of immersion in the experience. Next iterations of Psyrreal might benefit from adding a guided narration to make certain implemented concepts (e.g., connectedness or ego-dissolution) clearer, and from incorporating more interactive elements which could be beneficial for increasing immersion in the experience (144). Technical developments in the growing field of virtual reality are likely to hugely enhance designing such therapeutic experiences and could be used to develop more immersive and 'realistic' experiences in the near future. Second, while Psyrreal implements a wide variety of different phenomenological aspects, it could also be interesting to investigate specific components separately to help elucidate the therapeutically beneficial factors of psychedelic experiences. Furthermore, implementing an appropriate control condition is a difficult task for VR methods which could be addressed in future research (i.e., developing suitable "placebo" VR experiences). Third, combining virtual or augmented reality with, for example, sensory deprivation methods or microdosing of psychedelics might also offer intriguing avenues of research (101, 145, 146). Fourth, the results of MEQ30 and EDI highlight some issues in using these questionnaires for VR experiences (see "Limitations"). The development of new questionnaires or adaptation of existing ones for VR could be useful to investigate the effects of similar VR-based methods more reliably.

Conclusion

We developed Psyrreal, a somatoaudiovisual virtual reality experience based on psychedelic and mystical phenomenology to aid the treatment of different psychological disorders and help participants to see things from new perspectives. We observed that using this novel therapeutic tool in an augmented therapy intervention alleviates mild-to-moderate depressive symptoms. The results of the study suggest that psychedelic subjective experiences implemented through virtual reality could have therapeutically beneficial effects (potentially extending beyond depression) and that further research into similar novel tools is warranted. Implementing elements of psychedelic experiences that potentially mediate therapeutic effects in virtual reality can also help to precisely investigate and elucidate the mechanisms underlying psychedelic therapy.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Tartu. The participants provided their written informed consent to participate in this study.

Author contributions

KK, MV, and JA designed the software. KK, MV, JP, and KT conducted the experiments. JA conceived the idea. All authors contributed to the writing of the manuscript, designing the experiments, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1088896/full#supplementary-material

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Corrigendum: Psychedelic replications in virtual reality and their potential as a therapeutic instrument: an open-label feasibility study

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The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Psychedelic-induced mystical experiences: An interdisciplinary discussion and critique

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Contemporary research on serotonergic psychedelic compounds has been rife with references to so-called 'mystical' subjective effects. Several psychometric assessments have been used to assess such effects, and clinical studies have found quantitative associations between 'mystical experiences' and positive mental health outcomes. The nascent study of psychedelic-induced mystical experiences, however, has only minimally intersected with relevant contemporary scholarship from disciplines within the social sciences and humanities, such as religious studies and anthropology. Viewed from the perspective of these disciplines—which feature rich historical and cultural literatures on mysticism, religion, and related topics—'mysticism' as used in psychedelic research is fraught with limitations and intrinsic biases that are seldom acknowledged. Most notably, existing operationalizations of mystical experiences in psychedelic science fail to historicize the concept and therefore fail to acknowledge its perennialist and specifically Christian bias. Here, we trace the historical genesis of the mystical in psychedelic research in order to illuminate such biases, and also offer suggestions toward more nuanced and culturally-sensitive operationalizations of this phenomenon. In addition, we argue for the value of, and outline, complementary 'non-mystical' approaches to understanding putative mystical-type phenomena that may help facilitate empirical investigation and create linkages to existing neuro-psychological constructs. It is our hope that the present paper helps build interdisciplinary bridges that motivate fruitful paths toward stronger theoretical and empirical approaches in the study of psychedelic-induced mystical experiences.

KEYWORDS

psychedelics, mystical experience, mystical experience questionnaire, psilocybin, religious studies

1. Introduction

Psychedelics have re-emerged as compounds of scientific and clinical interest. Preliminary clinical trials with classic psychedelics have indicated the potential for transdiagnostic efficacy spanning the treatment of depression, end-of-life distress, tobacco addiction, alcoholism, and obsessive–compulsive disorder (1–9). Within the current wave of human psychedelic research, the majority of human studies have been with psilocybin (the pro-drug of psilocin, the primary psychoactive compound in so-called 'magic mushrooms'), with additional trials completed and underway with other 'classic' psychedelics such as LSD and DMT. Research with other quasi-psychedelics such as MDMA and ketamine, is further along, with ketamine licensed as a medical intervention and MDMA-assisted therapy on track for this in coming years. In addition,

investigations in healthy subjects have examined psychedelics' potential for improving well-being and enhancing creativity (10–17).

One phenomenon that has garnered a particularly large amount of attention in contemporary psychedelic research is the so-called 'mystical experience' (18–21). Psychometric assessments of mystical experiences have provided quantitative evidence for mystical-type phenomenology in the psychedelic experience, and findings have further indicated that such phenomenology may be central to the therapeutic action of these compounds—potentially mediating or moderating lasting symptom reductions in patients and improvements in well-being in healthy individuals (20, 22–25). The prevalence of constructs pertaining to 'mysticism' in scientific discourse is salient and interesting, given its connotations of spiritual and metaphysical concepts that are typically construed as outside the domain of science (26, 27). Typically, the response to this by researchers in favor of employing the language of 'mysticism' is that their reference to such concepts is independent of metaphysical claims or religious suppositions (27, 28). However, although psychedelic scientists may believe themselves to be avoiding any theological, supernatural, or metaphysical positions (and therefore employing 'mysticism' concepts differently than many study participants, patients, and press), this is often not made explicit. In fact, when defining 'mysticism', papers often explicitly invoke religious or religion-related concepts in the same breath—for instance, Barrett and Griffiths (19) lead their section "What Are Mystical Experiences?" with the following:

> "[Mystical experiences are] those peculiar states of consciousness in which the individual discovers himself to be one continuous process with God, with the Universe, with the Ground of Being, or whatever name he may use by cultural conditioning or personal preference for the ultimate and eternal reality".

When researchers use this label of 'mysticism', and especially when they pair it with theological discourses, God-talk, and reference to religions, they imply that the concept *does* have something to do with theological, supernatural, or metaphysical matters. Of course, other labels for similar psychedelic experiences—like 'ego dissolution' or 'oceanic boundlessness'—carry their own religio-cultural baggage and connotations, and, indeed, all of these could and should also be historicized and critiqued (28). In the present paper, we have chosen to focus on the constructs of mysticism and the so-called mystical experience for three primary reasons: one, the putative ability for psychedelics to induce mystical experiences has received a disproportionate amount of attention both within the academic literature and culture at large; two 'mysticism' is closely linked to alternative concepts such as 'ego dissolution', 'connectedness', 'awe', and 'oceanic boundlessness'; and three, mysticism arguably connotes a metaphysics that is intertwined with religious/theological and supernatural suppositions, and therefore may appear to clash with physicalist/scientific materialistic assumptions implicit in scientific research to a greater degree than alternative similar concepts. Collectively, these characteristics of the mystical experience as construed in psychedelic research render it a central and loaded concept which presents itself as particularly important to critique. It may still be objected that the construct indexed by the Mystical Experience Questionnaire (MEQ) and the constructs indexed by similar measures are so highly inter-correlated that they are essentially measuring the same thing, and thus, the choice of the label we use for them, and which measure we choose to deploy, is simply down to personal preferences. Our point, however, is that the importation of a culturally-loaded concept (like 'mysticism') into scientific practice can perpetuate its associated values and biases if not appropriately examined and critiqued.

We presently define mysticism broadly as the practice of techniques that elicit experiences which are construed as enabling access to metaphysical insight based in self-transcendence and/or extrasensory perception. The term 'mysticism' is derived from the Greek term *mystikos*, referring to the mystery-cults of the ancient Mediterranean world. These mystery cults were centered on secret initiatory rituals that were aimed at leading participants into the awareness of a higher reality (29). It is worth noting that the experiences thereby facilitated were understood to be important and valuable because they revealed insights and esoteric knowledge into the nature of reality, not because participants had experiences they deemed personally meaningful. Indeed, the ancient world and its mystery cults had no comparable notion to our modern Western concept of subjectivity, let alone an interest in cultivating something like personal religious experience (29). Contemporary religious studies thus understands mysticism as highly dependent on the context in which the concept appears. For religion scholars, the interpretive task with mysticism is investigating how, for instance, the mysticism of the ancient cult of Isis meant something different to the mysticism of Medieval Jewish scholars, just as the mysticism we find in the psychedelic discourse today means something different still.

Viewed through a religious studies lens, contemporary conceptions of psychedelic-induced mystical experiences contain inherent perennialist assumptions that are particularly vulnerable to critique, and, furthermore, have more to do with modern Christian notions of mysticism than is typically appreciated (see (27) and (30) for valuable complementary discussions). Our goal in the present paper is to highlight how assessments and conceptualizations of mystical experiences in the context of contemporary psychedelic science have, to date, imported Christian perennialist metaphysical assumptions that thereby limit the scope, nuance, and cross-cultural sensitivity of such investigations. Importantly, we are not advising that psychedelic science jettisons all mention of 'mystical experiences', but, rather, that greater explication of the limitations and biases of past work is required to valuably advance upon and refine existing approaches. In other words, we believe that discussions of mystical experience indeed have a place in psychedelic research, but that this field can do better in acknowledging and interfacing with relevant interdisciplinary critical work.

In the present paper, we provide a comprehensive, critical, and forward-looking discussion of assessments and conceptualizations of 'mystical' experiences in the context of psychedelic research. Our approach is explicitly interdisciplinary, and we seek to create the groundwork for bridges between relevant scholarship in the social sciences and humanities and the scientific investigation of psychedelic-induced 'mystical' experiences. We argue that such bridges are essential to advance this research area's conceptual rigor and contextual inclusivity. In service of this argument, we begin by discussing the historical development of research on psychedelic-induced mystical experiences, highlighting its cultural biases and limitations. Next, we provide an overview of psychometric assessments of mystical experiences and a discussion of their limitations. Finally, we offer suggestions for 'next-generation' assessments and refined

conceptualizations of mystical experiences. These proposed 'next-generation' assessments will draw from interdisciplinary scholarship and can contribute to the mutual enrichment of both scientific-medical and social sciences-humanities approaches to studying psychedelic neurobiology and phenomenology.

2. Historical overview

2.1. Historical reasons for a lack of interdisciplinary dialogue in research on psychedelic-induced mystical experiences

As a result of an interdisciplinary history involving some major overlaps and intentional distancing, contemporary psychedelic science has not benefited from scholarship in social sciences and humanities—disciplines that are responsible for the historical and cultural work focused on 'mystical experience', among other things. The following section highlights the threaded roots of psychedelic science in the study of psychology and religion, and their historical untethering which has ultimately resulted in the contemporary moment.

Despite having shared origins, perhaps best exemplified in the work of one of the founding figures of psychology, William James, whose theoretical interests spanned topics ranging from every day human perception, mystical states, and paranormal séance work, it was during the twentieth century that psychology and religion went their separate ways. In response to the trauma of WWII and influenced by new research in cultural anthropology, the contemporary academic study of religion began shedding its esoteric and theological roots in response to the growth of the 'social sciences.' Whereas theological study takes religion to be *sui generis* and divinely given—thus taking a 'faith' commitment to a particular religious worldview as a premise—religious studies started reconsidering religion as a human-made category that could be analyzed with social scientific methods and the tools of philosophical critique.

During this same period, the field of psychology came to be dominated by psychoanalysis and behaviorism, the latter of which treated the human being as a kind of machine (29), a very different take from its original interest in metaphysical inquiries about the human psyche or soul (in the original Greek). Much like the separation of the study of religion from theology, it was with these developments that "academic psychology distanced itself from its deep historical involvement with [a form of religion called] Western esotericism" (29). Broadly, 'esotericism' refers to the history of practices rejected by both mainstream science and the 'world religions', and which can be roughly captured in the three categories of: magic, alchemy, and astrology. Before this time, esoteric ideas like "mesmerism and somnambulism developed in straight lines towards experimental psychology and psychiatry as practiced in the decades around 1900" (29). With behaviorism, especially (for psychoanalysis retained many esoteric concepts) academic psychology was effectively shorn of *most* untestable metaphysical suppositions.

As such, today's psychology of religion has limited itself to tasks like explaining religion as a form of 'terror management' in the face of mortality (31), in relation to personality traits, as a factor in moral decision-making, in terms of the human development trajectory, as a mental health asset, or as an epiphenomenon of a brain that has evolved to (over)detect agency (32). At the same time, contemporary religious studies has hewed toward the methods of sociology and anthropology, rather than psychology, to emphasize its object as a human social and cultural process (33), rather than a thing 'given' in ontology or a behavior to be understood in terms of neuro-psychological constructs (Though, it must be said that the cognitive science of religion has been forecast as a major growth area among certain quarters of the discipline (34)). For its part, the field of psychedelic studies was curtailed by the Controlled Substance Act of the late 1960s, just as it was beginning to burgeon. So, rather than being able to reconcile with its own esoteric roots, psychedelic science has re-emerged in the 21st century in a state of arrested development. Today, it is still making use of pre-1960s models of mystical experience that developed when psychology and religion were still intertwined with their own esoteric influences, rather than bringing together current religious studies research into its psychologized account of psychedelic experience. Thus dominated by the brain and mind sciences, psychedelic studies miss important tools from religious studies for characterizing non-ordinary experiences that get characterized as 'mystical,' and for working with psychonauts' claims that these experiences afford "insights into the true nature of reality."

2.2. A critical history of the scientific investigation of psychedelic-induced mystical experiences

The systematic investigation of phenomena deemed 'mystical' in the Western context emerged with the work of pioneering psychologist and philosopher William James (35). At the turn of the 20th century, he described a mystical experience as a unitary phenomenon that has four general qualities: ineffability, transiency, passivity, and a noetic quality (i.e., a sense of epistemological authority; (35)). James also introduced the notion that such experiences could be drug-induced—in his case, through the inhalation of nitrous oxide (35). Yet, while James still retains relevance in the study of religion, there were a whole host of other esoteric-science-religion thinkers that were relegated to 'the dustbin of history' in academia, despite achieving some staying power in today's psychedelic research. A notable example is the British novelist and essayist Aldous Huxley. With his 1954 book, 'The Doors of Perception', Huxley was arguably first to widely popularize the concept that psychedelics could induce 'mystical'-type experiences. Like other esoteric thinkers of the day, including Eveylnn Underhill and Mircea Eliade in the study of religion, and Carl Jung in psychology, Huxley had strong leanings towards Eastern and Western mystical traditions—as evidenced, for example, by the themes of his later novels such as 'Time Must Have a Stop' and 'Island', and his involvement in the Vedanta Society of Southern California. He even described his experience with the psychedelic compound mescaline in terms explicitly drawn from such traditions and went so far as to refer to psychedelics as "stimulators of the mystical faculties" (36). And, much like other esoteric thinkers of religion of the time, Huxley viewed mystical experiences in perennialist terms: as a discrete and unmediated (i.e., by conceptual frameworks) experience with phenomenological characteristics that cut across cultural and linguistic divides (37). In the present context, it is important to point out that it is unclear to what extent Huxley's intellectual propensities (i.e., his 'set') played an active role in generating an experience that aligned with his conception of the mystical, and/or in biasing him

towards interpreting an ambiguous experience as such. In addition, given the wide readership of 'Doors of Perception', this mystical framing likely influenced the collective 'set' of the many psychedelic users in the decade following its publication—thereby increasing their likelihood of experiencing putative mystical-like phenomena (and interpreting them as such) in a perpetual cultural feedback loop (38, 39).

Thinkers like James, Huxley, Underhill, Eliade, and Jung were key voices in the conversations regarding the possibility of creating a comparative study of mysticism. Arguably the most influential figure in approaches to the study of psychedelic-induced mystical experiences, however, was the philosopher William Stace. Stace was an English-born philosopher who grew up in a military family and eventually worked in the civil service, which is significant, because it was such Western European travel among the peoples they colonized that propelled speculation about a 'common core' underlying their different religions. This antiquated perspective, known as perennialism (33), dominates the way religion-related phenomena, like 'mystical experience,' are dealt with in psychedelic science today. The concept of 'mysticism' that Stace developed represents an elaborated version of James' model and formed the primary basis of the 'Mystical Consciousness Typology'—the first psychometric assessment of mystical-type effects, introduced by Walter Pahnke in 1963—which itself is the initial predecessor of the MEQ (see Table 1 for the factors that comprised this initial assessment, as well as other assessments of mystical effects). It is critical to note that, given their initial genesis and motivations, measures based on Stace's work import his colonial, perennialist assumptions about 'religion.' As Taves (30) writes, "the theory underlying the 'mysticism construct' reflects a century of debate over the relationship between mystical, religious, psychotic, and drug-induced experiences that was fueled by an effort to identify the distinctive features—the 'common core' that ostensibly unites the religions of the world—and at the same time to defend the claim that religions provide access to ultimate reality."

Stace's work, along with the theories and concepts of the other esoteric thinkers served as motivation for what is now known as the 'Good Friday Experiment', which occurred at Harvard University in the early 1960s under the supervision of the controversial figures Timothy Leary and Richard Alpert (later known as Ram Dass). This is where the first psychometric assessment of so-called 'mystical experiences' appeared. Walter Pahnke, then a doctoral student, decided to test whether psilocybin, when administered to Harvard Divinity School students in a religious setting, can induce mystical experiences similar to those reported by saints and mystics (40). The religious setting in this case was a ritual gathering of people in a church with a Christian leader giving a talk ('sermon'), on the occasion of a significant moment in the Christian liturgical calendar: Good Friday. This occasion is a poignant, sombre, and ultimately hopeful one for Christians because it commemorates the state execution of their key figure, Jesus. They interpret his capital punishment as a religious 'martyrdom' that promises the spiritual 'salvation' of all his followers in the form of an eternal afterlife. We describe the nature of this ritual here because it is an important factor in the set and setting of study participants having a psilocybin experience in a specific ritual container. We attempt to do this description in generic, second order terms precisely because of how easy it is for Westerners to take Christian concepts for granted, as has been done with the 'mysticism' concept in psychedelic research. Note: the distinction we are making here is between the 'etic' and the 'emic' [see, e.g., (46): 'etic' refers to a scholarly reconstruction of a concept (outsider language), whereas 'emic' refers to a folk term (insider language)].

Using the direct precursor to the MEQ—the 'Mystical Consciousness Typology' derived from Stace's work in comparative mysticism—Pahnke's study found that, indeed, psilocybin was able to induce subjective effects that were mystical in character. According to this study, 4 out of 10 experimental subjects reached the 60–70% level of completeness on all components of the questionnaire, indicating a 'complete mystical experience' as defined by Pahnke, whereas no placebo subjects reached this level (40). In addition, all psilocybin-receiving subjects scored significantly higher on all components of the mystical experience questionnaire relative to placebo subjects (40). This study, therefore, provided the first evidence that psilocybin can induce effects indistinguishable from experiences considered traditionally mystical by perennialist theologians and esoteric thinkers of the day. In addition, the experience resulted in lasting positive effects at a 6-month follow-up, as indicated by psilocybin subjects averaging 50% of the maximum score in the 'positive attitudinal/behavioral changes' category of the assessments, compared to 15% in the controls (47). Strikingly, similar scores were also maintained at a

TABLE 1 The factor structure for each of the psychometric assessments used to measure mystical-type experiences as induced by psychedelic drugs.

Factors	Mystical consciousness typology (40)	MEQ-45 (41, 42)	MEQ-30 (43)	Hood mysticism scale (44)	11D-ASC (45)
Factor 1	Internal and external unity	Internal unity	Mystical	Unifying quality	Experience of unity
Factor 2	Positive mood	External unity	Positive mood	Positive affect	Spiritual experience
Factor 3	Transcendence of time and space	Deeply-felt positive mood	Transcendence of time and space	Temporal/spatial quality	Blissful state
Factor 4	Alleged ineffability	Transcendence of time and space	Ineffability	Ineffability	Disembodiment
Factor 5	Paradoxicality	Ineffability and paradoxicality		Noetic quality	
Factor 6	Noetic quality	Sense of sacredness		Religious quality	
Factor 7	Sense of sacredness	Noetic quality		Inner subjective quality	
Factor 8	Transiency			Ego quality	

24–27 year follow up (47). As described by Doblin (47): "the experimental subjects wrote that the experience helped them to resolve career decisions, recognize the arbitrariness of ego boundaries, increase their depth of faith, increase their appreciation of eternal life, deepen their sense of the meaning of Christ, and heighten their sense of joy and beauty." As apparent in this quote, the participants of this study exhibited strong existing ties to Christianity. This relationship to Christianity, and its attendant worldview, values, and conception of what is deemed 'religious' or 'spiritual', constitute a critical part of the 'set' that primed them for the psychedelic experience they would have under the study circumstances ('setting').

Importantly, this set entails a worldview in which mystical experiences are positively valanced, as is spirituality. Thus, we can see that Pahnke's investigation of mysticism was conceptually and experimentally embedded in a larger structure referred to as 'religion,' and since 'religion' is a category (an abstraction), practically speaking, Pahnke's experiment had to take place within a *particular one*. Though Marsh Chapel is nondenominational, it was founded by a Methodist leader. Methodism was an 18th-century charismatic Protestant movement that valued direct personal experience of being sensuously overtaken by their god (in a form called 'the Holy Spirit'), the embodied experience of a 'strange warming of the heart,' and revelations from their god. These kinds of experiences, then, are templated into the earliest 'mystical experience' assessment as markers of 'true' or 'authentic' mysticism.

But then where do experiences of contact with malevolent entities or experiences of going to 'hell' realms or experiences of being violently consumed or entirely fused with a nihilistic universe fit? These are certainly all well described in the trip reports documented in archives such as Erowid, a non-profit psychedelic education and harm-reduction website founded in 1995 which allows individuals to add written trip reports to a public repository. They do not fit in the rubrics of 'mysticism' or 'spirituality' as used in the psychedelic science literature because these concepts are always already defined as positive[1]. This is not a problem in and of itself, but only when the rationale for these assumptions is not laid out clearly. In the case of the definition of spirituality taken up in the psychological disciplines, we can see that it is often informed by data-driven approaches, where researchers ask particular communities what spirituality means to them. For instance, the millennial emerging adults studied by several researchers describe as 'spiritual' their experience of awe, belief, and interconnection (48, 49). This is therefore a particular emic concept of spirituality, which we must be very careful not to accidentally imply can stand for the thing itself, what the term 'really' means, or ought to mean, by failing to contextualize and historicize its cultural specificity. We would obtain a different answer about what types of experiences and things could be considered spiritual if we asked magicians that associated themselves with the controversial esotericist Aleister Crowley (for these esotericists, evil beings, forces, and realms would certainly qualify as spiritual things).

The perennialist and Christian biases of the earlier assessment persisted into the next generation of psychedelic research. This arguably occurred largely via psychedelic researcher Bill Richards, who had worked with Pahnke in the 1960s and who has now been involved in psychedelic research at Johns Hopkins University over the past two decades. Richards played a primary role in developing the MEQ-43, which was directly derived from the Mystical Consciousness Typology used in the original Pahnke study and highly influenced by Stace. This measure was used in a 2006 study at Johns Hopkins University which replicated the main results of the Good Friday Experiment (41). Distinct from the original study, psilocybin was now administered in a warm and supportive environment that featured minimal religious overtones apart from any implicit religious bias on behalf of the subjects themselves or the study's administrators. Subjects were healthy individuals and were not selected for strong religious inclinations. This study found that psilocybin use could elicit mystical-type experiences as indexed by scores on the MEQ-43 and, moreover, that these experiences were rated as highly personally meaningful and as having lasting positive effects on mood and behavior (41, 50). Subsequent studies by this research team have further replicated these findings (19, 43). These latter studies were conducted in the context of refining, validating, and testing the MEQ (see Table 1 below for the factor structure of the different versions of the MEQ, as well as other related measures).

2.3. Christianity as the implicit paradigmatic example in western concepts of 'mysticism' and 'religion'

For the reasons described above, we contend that the concept of 'mysticism' that was originally taken up in psychedelic research is fraught with limitations and intrinsic biases that are seldom acknowledged in the field (see (30) for more discussion). One aspect that warrants additional emphasis is that, since there is frequent reference to 'mysticism' being a function of religions, those of us engaged in psychedelic research must acknowledge the set of assumptions involved in the very concept of 'religion'. Indeed, it is important to recognize that the concept of 'religion' as it is defined in the English language, takes Christianity as its paradigmatic example (see (51) and (33) as entry points to the vast literature on this issue).

The reason that Christianity has been *the* model of religion has a deep history. In the first place it owes to the fact that Christianity became a hegemonic political force in the Western world when the Roman Empire took up its mantle in classical antiquity. Thus, when the medieval and then the modern university system developed in Europe, it was Christian worldviews and values it sought to explain and uphold (33). Following this pattern, North American universities typically grew up around a Christian theological school. Because of the colonial encounters taking place in the 'Age of Discovery' (~ 15th–17th century CE), Christianity was not only the main object of study in universities, but the paradigm case through which scholars understood all other behaviors and artefacts deemed 'religious'. Essentially, whenever European colonizers saw people doing anything that looked like *their* Christian religion, they construed it as a part of those people's religion. Colonizers largely ignored or persecuted what did not look like their own Christian behaviors and artefacts (e.g.,

1 An additional psychometric assessment commonly used in psychedelic research—the five-dimensional altered states of consciousness questionnaire (5D-ASC)—features a factor ('Oceanic Boundlessness') that correlates highly with the MEQ. It also has a factor ('Dread of Ego Dissolution') that loosely pertains to what might be viewed as 'negative' mystical-type experiences. This measure, however, does not explicitly claim to assess mystical-type phenomena and has been less examined in clinical research. Oceanic boundlessness, coming from Freudian depth psychology, has its own religious and cultural biases, some of which overlap with the esoteric roots of the mysticism concept.

bibles, cathedrals, and men in robes holding forth), dismissing other lifeways as "primitive" to the extent that they did not categorically separate out "religion" from the activities of everyday living, and attested instead to perceiving everything as sacred and integrated. It was thus that the 'world religions paradigm' was born, with Christianity at the civilizational top, the other four of the 'big five' (Judaism, Islam, Hinduism, and Buddhism) set underneath it, and the 'primitive' religions of Indigenous peoples at the bottom (e.g., (52)).

In the mid-20th century, academic theology finally splintered under the pressure of the burgeoning disciplines of the social sciences, introducing a new *secular* discipline of religious studies to the academy, in addition to the existing array of academic programs in theology (53). Religious studies, being based on the academic model of Christian theological schools, remained Christian-centric until major anticolonial shifts began taking place in universities over the past 20 years. "Mysticism" is a concept that has been updated in this shift within the discipline of religious studies, but, as we observe, not within others, like the psy disciplines, who sometimes use it. For this reason, the historicization and cultural analysis of religion-related terms (i.e., like 'mysticism') is essential to clarify implicit, deeply rooted biases.

2.4. Section summary

As described, the creation and refinement of psychometric assessments of mystical experience have occurred in the context of colonial, perennialist, and Christian-Protestant perspectives. In order words, they have been motivated by a view of mystical experience as a fundamentally positive, sui generis phenomenon that lies at the heart of diverse traditions, cutting across cultural and linguistic divides. This is particularly through the influence of Walter Stace in the generation of psychometric assessments of mystical experience, as well as the disciplinary disconnect between the psychological sciences and critical work in the humanities and other social sciences. Indeed, it is evident that, although they were initially derived from early scholarship on comparative mysticism, contemporary measures of mystical experiences (e.g., the MEQ) and the research literature in which they are embedded only loosely interface with contemporary scholarship in disciplines that are responsible for historical and cultural work, such as religious studies, philosophy, and anthropology. As a result, research on psychedelically-induced mystical experiences arguably lacks historical and cultural context, as well as awareness of the intrinsic limitations and biases of its current conceptualizations and assessments. More specifically, psychedelic research has only minimally engaged with work indicating the unstable and culturally local nature of concepts such as 'mysticism' and 'religion', or with work indicating that the perennialist project of trying to find a 'common core' of religion is in fact heavily biased by a Euro-American Christian/Protestant framework.

Moreover, it is evident that the beliefs, assumptions, and frameworks articulated by influential thinkers such as Stace and Huxley around the midpoint of the 20th century made a significant impression upon the psychedelic culture at large, thereby likely influencing their 'set' and therefore the nature of their psychedelic experiences. This suggests that a variety of—typically relatively unacknowledged—cultural influences and feedback loops have given rise to the assessments and conceptualization of psychedelic mystical experiences that are now taken to be the status quo. We believe that greater explication and acknowledgement of such influences is essential for creating more refined and culturally-sensitive measures of psychedelically-induced mystical-type phenomena. Next, prior to describing some forward-looking suggestions on how to accomplish this, we briefly comment on a recent discussion of whether 'mystical experience' should be seen as a construct suitable for empirical research at all.

3. Ambivalence towards the mystical in contemporary psychedelic research

Researchers in the emerging field of psychedelic science have voiced some ambivalence towards the inclusion of ostensibly 'non-scientific' language (i.e., such as relating to 'mystical experiences') in psychedelic research. Notably, Sanders and Zijlmans (26) recently called for the field of psychedelic science to "move past mysticism" entirely. For them, the risks and difficulties of using a "framework associated with supernatural or nonempirical belief systems" are too great, and the only solution is to 'demystify' our model of the psychedelic state (26). We contend that this perspective is a direct consequence of the contemporary siloing, discussed above, of scientific research on psychedelic-induced mystical experiences from existing research on mystical/spiritual/religious type phenomena—whether in the humanities (30), or even within other subfields in psychology and neuroscience (54–57). We agree with the two responses to the above-mentioned article (58, 59), which collectively highlight that mystical experiences are, in principle, valid and operationalizable objects of scientific inquiry with a rich history as such (within and outside of psychedelic research), and that their empirical investigation is fundamentally independent of the metaphysical claims derived therefrom (also see (60)). We further point out that the tendency for mystical experiences to be interpreted as having metaphysical or spiritual significance is itself an interesting and valid topic of empirical investigation. This is exemplified, for example, by a recent study which found that psychedelic use can lead to changes in metaphysical beliefs, with a bias away from physicalism towards greater endorsement of panpsychism and mind–body dualism (61).

We emphasize here that, although we have critiqued and drew attention to the limitations of existing conceptualizations and assessments of mystical experience, we are not arguing for a wholesale removal of the term 'mystical' and related concepts and frameworks from psychedelic science. Rather, we believe that if they are used, then greater attention should be paid to the implicit assumptions and biases inherent in their current usage, and that alternative and more refined and culturally-sensitive assessments should be devised which afford a broader operationalization of such phenomena that is aligned with relevant interdisciplinary scholarship.

The above points notwithstanding, we agree with Sanders and Zijlmans that over-reliance on recourse to 'mystical-type' effects as a means of measuring this particular aspect of psychedelic subjective effects has its limitations. The creation of a statistically validated and reliable psychometric assessment does not necessarily entail the ontological status of its purported referent as a discrete, *unified* phenomenon. Rather—as also touched upon by Sanders and Zijlmans—in the absence of a clear and robust causal mapping

between the purported referent and (neuro)biology, the assessment simply serves as a heuristic tool to assess a set of ostensibly interrelated and temporally co-occurring set of effects—which may very well be better captured by a different set of abstractions. As an additional example, a similar state of affairs is the case for the personality construct of 'absorption' (62). Absorption has a multi-decade history of investigation and has been found to reliably correlate with a variety of traits and behaviors, including sensitivity to psychedelic drug effects (63). Yet, ongoing debate exists as to whether absorption should be understood as a single trait or as a heterogenous bundle of tendencies and predispositions that often co-occur (62, 63). In other words, the construct of 'absorption' as measured by the Tellegen Absorption Scale—in a similar fashion to the construct of 'mystical experience' as measured by the MEQ—appears to have strong reliability and heuristic utility, but unclear construct validity. In both cases, exploring alternative conceptualizations through targeted construct validation research is required to ascertain whether they are indeed assessing a discrete and unified psycho-neurobiological phenomenon. As described in Section 4.1 below, we believe that complementary attempts at conceptualizing the subjective phenomena that occur in so-called mystical experiences in terms of existing psychological or neurobiological constructs may make such experiences less of a 'black box' and more amenable to rigorous empirical investigation and construct validation.

4. Advancing theoretical perspectives and empirical approaches to psychedelic-induced mystical experience

So far, we have offered a historical/cultural critique of conceptualizations and psychometric assessments of mystical experiences in the context of psychedelic research. In this final section, we offer some forward-looking suggestions on ways in which this area can be fruitfully advanced. In particular, we suggest two complementary approaches to overcoming previous limitations. The first is to seek to decompose the complex phenomenon of 'mystical experience' into empirically-supported constructs drawn from psychology and neuroscience, thereby 'demystifying' it, absolving it of its ostensible *sui generis* status, and situating it within existing research literature. We emphasize that this is not meant to deny the existence of something called a 'mystical experience', but, rather, to offer an alternative lens on the experience that may have pragmatic utility in the context of scientific research. Second, we draw on the work of religious studies scholar Ann Taves to highlight the value of cross-cultural sensitivity, item-level validation, and narrative reports for coming to more refined and nuanced assessments of mystical experiences.

4.1. Decomposing the mystical experience into psychological and neural constructs

It is important to acknowledge that, at a fundamental level, so-called 'mystical experiences' are complex subjective experiences that are comprised of changes spanning cognition, emotion, perception, and sense of self. Chief among these are changes to one's sense of self or ego, which feature predominantly in experiences of unity, which have been construed as the hallmark of mystical experiences as assessed in psychedelic research. In addition, given that psychometric ratings of such experiences are continuous rather than discrete, and given that factor analyses have revealed the statistical dissociability of their component parts, it is likely that several distinct neuro-psychological functions are at play which can differ in their relative degree of occurrence at any given moment, or in a given instance of such an experience. An important question with regard to rigorously characterizing these experiences, therefore, is: of what distinct neuro-psychological constructs are they comprised?

Towards this end, Girn and Christoff (64) separated psychedelic alterations of self-experience—which are, as mentioned, putatively central to mystical-type effects—into the two categories of 'bodily self-experience' and 'mental self-experience'. Within each of these categories, they list constructs from cognitive psychology/neuroscience that psychedelics putatively alter in the context of mystical-type experiences and more generally (Figure 1). Critically, each of these proposed components have their basis in well-characterized research literatures that are independent of psychedelics (see (64); Table 1). Accordingly, this proposed taxonomy was explicitly aimed at conceptualizing these alterations in generic, second-order terms that can bridge contemporary cognitive neuroscience and research on psychedelics.

As highlighted by Girn and Christoff, this conceptualization of psychedelic effects affords a view of psychedelics as valuable experimental tools to study the usually seamlessly integrated components of selfhood, in a manner analogous to the way sensory mismatch paradigms have been used to identify the neural bases of certain types of bodily self-experience [e.g., (65)]. Given the centrality of self-related changes in mystical-type experiences, this lens could be applied to empirically 'demystify' mystical-type phenomena and facilitate deeper understanding of their neuro-psychological basis.

This taxonomy dovetails nicely with the distinction between the 'narrative' and 'minimal' self, which was initially developed in work in the philosophy of mind (66), and then ported to cognitive neuroscience (67, 68) and, more recently, used to describe psychedelic effects (69). The minimal self represents the bare sense of inhabiting a first-person perspective—the sense of 'I am' (66). It is viewed as a fundamental property of selfhood that is predicated on interoceptive and viscerosomatic inputs which combine to give a sense of existing from a particular spatial location (i.e., in 'this' body). Scaffolded on this, is the narrative self (also referred to as the autobiographical self). This higher-order aspect of selfhood represents our conceptually-based identity which consists of traits, self-beliefs, and personal characteristics, and which is embedded within a temporally extended narrative linking memories of the past to an imagined future (66, 68). Unitive mystical-type experiences seem to imply a dissolution of either one or both of these types of self, however this has not been directly investigated. Employing the taxonomy of Girn and Christoff and/or this distinction between two primary forms of self has strong potential to advance our empirical understanding of mystical experiences.

In 2016, Matthew Nour and colleagues proposed and validated a novel assessment of psychedelic effects, referred to as the Ego Dissolution Inventory (70). This assessment seeks to measure experiences induced by psychedelics in which boundaries between self and world were blurred or dissolved entirely, without invoking the

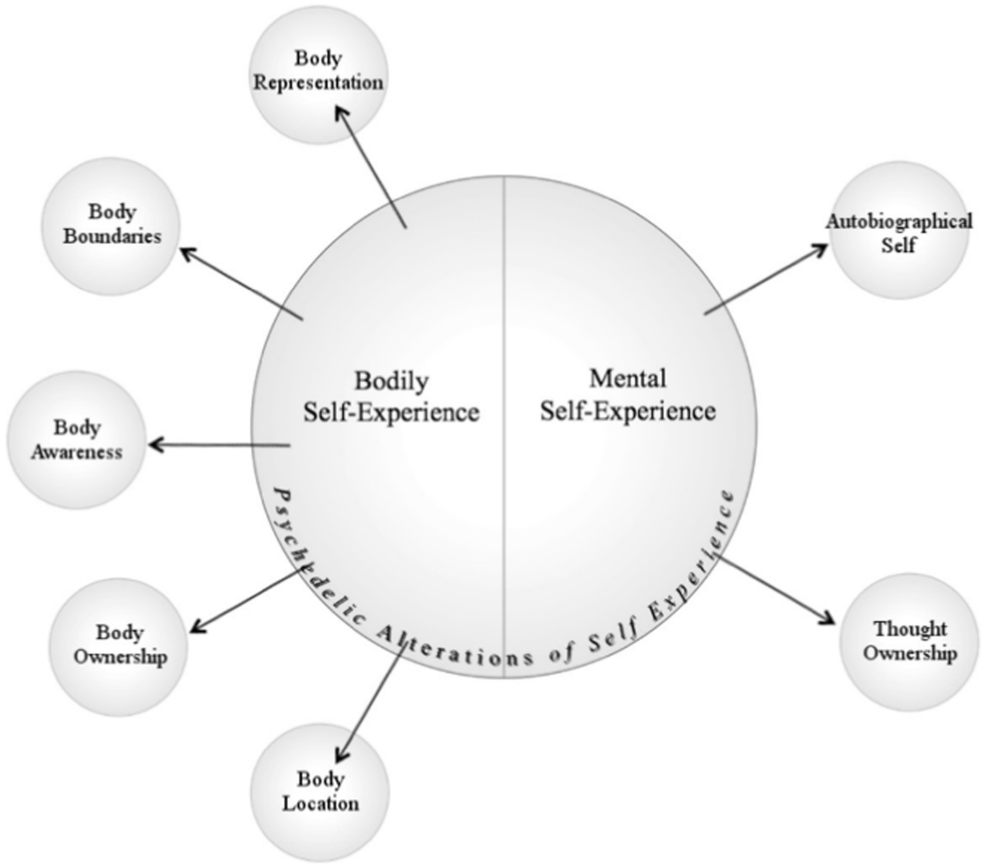

FIGURE 1
Components of self-experience altered by psychedelics. Adapted from (64).

language of mystical experiences. In this way, it represents an alternative metric to assess a putatively core component of mystical experience, without necessarily carrying limitations and connotations of the preceding mysticism-focused instruments. However, this measure is still notably limited in that it does not feature explicit linkages to existing psychological constructs of the self and is thereby relatively siloed from research literatures that have significant potential to enrich its understanding.

Providing a complement to quantitative assessments of psychedelic effects, studies have also analyzed patient responses to questions in structured interviews. A relevant common theme reported by patients in these studies is that of 'connectedness'—a concept also intimately connected to the unitive aspect of mystical experiences as assessed by existing measures (71, 72). Investigations with the psychedelic brew ayahuasca revealed experiences of connectedness to be of a tripartite character—separable into connection with self, connection with others, and connection with spirit or nature (73–75). This aligns strongly with the reports of patients who received psilocybin-assisted therapy for treatment-resistant depression, who reported moving from feelings of disconnection from self, other, and world to feelings of connection in these three domains (71). As a result of the centrality of feelings of connectedness, a novel scale called the 'Watts Connectedness Scale' (WCS) was recently developed (76). This scale captures elements of post-acute psychedelic experience that are highly related to the acute effects targeted by the MEQ, but does so in non-mystical language. Given that his scale was developed based on clinical findings with a goal of isolating therapeutically-relevant outcomes, it is arguably in itself not ideal for gaining deeper empirical understanding of acute experiences. However, it again points to the ways in which mystical experiences may be valuably reconstrued.

It is important to point out that scores on the MEQ, the 'Oceanic Boundlessness' subscale of the 5D-ASC, and the ego-dissolution inventory are highly positively correlated. Psychometrically, it may be arguable that each of these measures differ in label alone and, in reality, index the same underlying construct. However, it is critical to highlight that different labels give rise to distinct connotations and semantic associations that can impact their interpretation and their perceived relatedness to other concepts and constructs. As described above, the language of the MEQ gives rise to associations with religion, thereby implicitly linking the measured phenomenon with related discourses and bodies of work. In contrast, the labels of 'oceanic boundlessness' and 'ego-dissolution' may give rise to associations with Freudian concepts, which in turn also facilitates linkages to distinct literatures. In the present work, we are highlighting concerns specific to the use of the language of 'mysticism', but do not discount concerns related to other conceptualizations.

With concepts like 'ego dissolution', 'connectedness', and a taxonomy of alterations of self-experience in hand, we can ask more fine-grained questions about psychedelic experiences: are positive and

negative ego-dissolution experiences related to different patterns of changes in the sub-types of mental and bodily self-experience? Can we experimentally manipulate these patterns by altering the 'set and setting' or incorporating behavioral paradigms? Can novel molecules be designed to have and not have certain effects? The consequences of investigating (or not investigating) these questions are particularly relevant insofar as 'mystical experience' or 'ego dissolution' is cited as a primary mechanism in psychedelic-assisted psychotherapy.

At the same time, we must take this decomposition of 'mystical' type experience even further by asking: how do some of these models reify problematic mind/body dualism, given that many non-Cartesian worldviews show us that there is no possibility of an autobiographical memory without a body, and there is no bodily experience without a mental representation and interpretation? Are there yet more ways to break down this model of mental and bodily self-experience that do not assume Western European models of consciousness so prevalent throughout neuroscientific and psychedelic discourse? In fact, this is where we would do well to heuristically try out models of self, self-other relationship, etc. from worldviews that are not dominant in the academy, especially from the holistic and process-based models found in many of the Indigenous cultures from which psychedelic substances and practices are being appropriated. These models are worthwhile candidates for use in psychedelic research, with their metaphysical assumptions and cultural locatedness, just as Hood, Stace, and Pahnke's models were with theirs.

For instance, anthropologist Colin Scott (77) writes:

> In Cree, there is no word corresponding to our term "nature." There is a word pimaatisiiwin (life), which includes human as well as animal "persons." The word for "person," iiyiyuu, can itself be glossed as "he lives." Humans, animals, spirits, and several geophysical agents are perceived to have qualities of personhood. All persons engage in a reciprocally communicative reality. Human persons are not set over and against a material context of inert nature, but rather are one species of person in a network of reciprocating persons. These reciprocative interactions constitute the events of experience.

Though we cannot explore the question in depth within the remit of this paper, we can ask: how does ego-dissolution or unitive experience function for people who already inhabit a worldview where everything is experienced as having a person-like animacy and as being already united in a whole comprised not of discrete nouns, but by the *process of living*?

In the next section we explore an ongoing attempt at producing cross-culturally relevant psychometric scales for psychedelic experience, and possible future directions for doing so.

4.2. Cultural sensitivity and the need for psychometric meta-data

In 2020 the religion scholar Ann Taves made a vital contribution to dealing with 'mysticism' in psychedelic science and research on other non-ordinary states of consciousness (30). Recognizing that the existing tools (described above) named their factors after descriptions of non-ordinary experience worded in the insider terms of particular religious communities, or the metaphysics of prominent esoteric thinkers, she sought to redescribe them in generic, scholarly terms. She thus developed the Inventory of Non-Ordinary Experiences (INOE), whose goal was to test the possibility for creating generic psychometric items that can be recognized across cultures, including religious cultures, national cultures, linguistic cultures, and so on. To be clear, Taves is not making the neo-perennialist case that these words or concepts are at the basis of all non-ordinary experiences, but, rather, seeking words that are interoperable between cultures as an attempt to build linguistic bridges to facilitate understanding.

As a starting point, Taves and her team created a list of approximately 75 items, many of which were extracted from existing measures, including the above-mentioned mysticism scales, the Appraisals of Anomalous Experience Interview [AANEX; (78)], which is a measure of psychological responses to anomalies associated with psychosis, and the Survey of Anomalous Experiences [SAE; (79)], which is a questionnaire querying how people attribute unusual experiences (specifically 'parapsychological') to paranormal agents. In order to generate generic factors—that is, factors which describe experiences independent of particular culturally-based valenced appraisals—questions related to the occurrence of a particular experience were distinct from questions pertaining to the experience's origin, long-term effects, context, balance, frequency, and significance. In addition, Taves and colleagues' approach depended heavily on item-level validation *via* the collection of psychometric meta-data. In this context, 'psychometric meta-data' refers to responses to questions *about* the questionnaire items. For each item, participants were asked to paraphrase the item in their own words, provide details on how they would respond, and give an actual or hypothetical example of the experience referred to by that item (30). This meta-data provided valuable information on whether each item was understood consistently—or understood at all—and enabled iterative refinement of the wording used. Notably, this validation approach was conducted with independent samples in the United States and India, in English and Hindi, respectively. This revealed significant differences in interpretations of items across cultures and the need for distinct wordings to convey similar concepts. Moreover, this validation procedure revealed that many of the items, including those drawn from widely-used mysticism scales, were inconsistently interpreted across participants and required multiple iterations of refinement to more uniformly convey the intended meaning (30). This suggests that participants may be routinely responding to such items in idiosyncratic ways, highlighting significant limitations in their application and interpretation. More refined assessments of mystical experiences, therefore, would do well to collect psychometric data to best ensure uniformity in item interpretation and alignment with the intended phenomena of interest for the target demographic in question.

Furthermore, the collection of qualitative meta-data such as described above underscores the value of narrative reports. Such reports are essential in order to gauge idiosyncratic appraisals and construals of similar types of experiences, and how these may vary across cultures and influence responses to quantitative psychometric instruments. We suggest that, in the context of mystical experiences, narrative self-report measures should not only be included, but should also be structured so that respondents are encouraged to make fine-grained distinctions between alterations in different aspects of sense of self, and describe the sensorial, emotional, and cognitive experiences of these alterations. This could be supported or complemented by microphenomenological interviewing (69, 80),

where a researcher guides the recall of an experience and the participant's reflection on different aspects of it.

Structured narrative reports such as these have potential to facilitate the refinement of psychedelic assessments that separate out different components of the experience, yielding further fine-grained data. For instance, 'ego-dissolution,' as described above, has gained increasing traction as a more secular, second order concept underlying the 'mystical' one, but it is perhaps only one among others. Narrative reports may suggest querying aspects of psychedelic experience that have previously been ignored by existing scales, given their focus on either a religious type of mysticism or a psychopathological type of psychosis. Conducting this type of qualitative research requires cooperation between psychedelic scientists and humanists and social scientists who are aware of the cultural history of ideas like 'mysticism,' or 'spirituality,' or even 'ego,' and have a sophisticated theoretical model of religion that views it as provisional human concept that can be used to analyze cultural processes, not a sui generis reality that is 'out there.'

Psychedelic scientists and humanists should also explore more ways of relating 'naturalistic' psychedelic experiences to the experiences of trial participants in clinical settings, using a mix of quantitative and qualitative methods. Some recent contributions from medical anthropologist Olivia Marcus (81–83) and multidisciplinary scholar David Yaden (21, 84) offer excellent models for this type of work. Marcus' long-term fieldwork at a psychedelic retreat center in the Peruvian Amazon investigates what she calls 'therapeutic pluralism' in the treatment of mental health conditions. Her research tracks the dialog among shamans, mental health practitioners, and their clients with respect to their ayahuasca use. At the same time, with a team of clinicians and research scientists, she has also used her ethnographic findings to inform clinical tools, namely, a protocol for outcome evaluation of ayahuasca-assisted addiction treatment. Similarly, Yaden has used his combined knowledge of non-ordinary consciousness from religious studies and from psychology to show how the study of rituals in different religions can inform research and clinical contexts. The point of such work is neither to affirm that any particular religion got things 'right,' nor to 'explain away' religion as a neuro-cognitive epiphenomenon, but rather to make comparisons between psychedelic experiences and other non-ordinary states. Making these comparisons can do two crucial things: (1) give us clues about the specificity of what psychedelic *molecules* are doing; and (2) build more robust models of what psychedelic *experiences* are doing. There is no way to do this work but in research collaborations between experts in comparative religion, anthropology, sociology, philosophy, and psychology, cognitive science, and neuroscience.

5. General discussion and conclusions

5.1. Moving forward with 'mysticism' in mind

The foregoing sections have demonstrated the need for a number of different lines of research between psychedelic science and humanities stemming from the 'mysticism' concept. There is the need to historicize the language of 'mysticism' and other religion-relevant concepts (like 'spirituality,' 'sacred,' 'divine,' etc.) as they emerge from religious, Indigenous, underground psychonaut communities, and scientific networks. There is also a need for an ongoing historicizing of the psychedelic present by critically analyzing the current discourse among all psychedelic stakeholders, and to track relationships between the unlikely bedfellows in the contemporary psychedelics space. That is, we need philosophical and anthropological research which is dedicated to dialoguing with the scientists and clinicians actively using these concepts both in their scholarly research and 'behind the scenes' of conference presentations and publications. These dialogues should query their strategies, motivations, and beliefs about the types of 'mystical' (etc.) experiences possible in scientific and clinical studies and beyond. There is also tightly focused psychometric work to be done in refining psychedelic assessments that can help provide a more accurate representation of people's non-ordinary experiences.

These efforts will set the stage for future work on potential pathways to bridge psychedelic science and humanities scholarship, creating the grounds for consilience between these still-disparate domains and contributing to the cultural containers that will allow more thoughtful public consumption and understanding. Consilient psychedelic theory will benefit the public discussions that are underway in the current psychedelic moment, including issues of decriminalization and legalization, accessibility and corporatization, medicalization and cognitive liberty, and the lines between cross-cultural learning and colonial appropriation.

5.2. Conclusion

In this paper we have argued that research on psychedelic-induced mystical experiences exhibits a number of limitations and biases which are a result of a lack of intersection between psychedelic science and contemporary scholarship on mysticism and other religion-related concepts from religious studies and cognate disciplines. This scholarship shows the mysticism concept to be fraught with metaphysical assumptions and cultural biases which have not been sufficiently recognized or reckoned with in the psychedelic science literature. Our core contention has been that, if 'mysticism' is used, then researchers must begin to do this reckoning and/or pursue alternative 'non-mystical' conceptualizations of psychedelic effects, still with attention to operationalizing these alternative concepts in culturally sensitive and properly historicized ways. In sum, we have sought to display how interdisciplinary psychedelic scholarship can offer a more nuanced, cross-contextually relevant, and empirically rigorous approach to studying psychedelic experiences.

Author contributions

SM and MG conceived and of the idea and wrote the first draft. LR provided edits and suggestions, and assisted with draft finalization. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Associations between the use of psychedelics and other recreational drugs with mental health and resilience during the COVID-19 pandemic

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The large-scale disruption to peoples' daily lives during the COVID-19 pandemic provides a context for examining whether use of substances such as psychedelics in a naturalistic (outside of a controlled environment) setting, is associated with better mental wellbeing and resilience relative to those who use other drugs, or who do not use drugs at all. We interrogate data from the Great British Intelligence Test and identify that 7.8% out of N=30,598 unique respondents used recreational drugs inclusive of psychedelics, cannabis, cocaine, and MDMA during the COVID-19 pandemic. Recruitment materials did not mention drug use would be surveyed, thereby enabling us to model the relationship with mood and resilience in people who had not specifically self-selected themselves for a 'drug' study. We report that people form clusters, characterized by different real-world patterns of drug use, and the majority of psychedelics users also use cannabis. However, a subset of cannabis users do not use psychedelics, enabling a subtractive comparison. Those who primarily used psychedelics and cannabis during the COVID-19 pandemic had worse mood self-assessment and resilience scores compared to those who never used drugs or primarily used cannabis. This pattern was also evident for other recreational drug use clusters, except for those who primarily used MDMA and cannabis, who had better mood but were of too low incidence to have confidence in this estimate. These findings cast light on the significant differences in mental wellbeing between users of different drugs and the non-user population during a global-crisis and call for future research to explore the pharmacological, contextual and cultural variables associated with these differences, their generalisability and causal links with greater precision.

KEYWORDS

COVID-19, psychedelics, cannabis, mental health, resilience

1. Introduction

The large-scale disruption of peoples' lives during pandemic provides a unique context for studying the population variables that underpin individual differences in mental health vulnerability and resilience. Sociodemographic characteristics, dimensions of personality, and lifestyle choices such as exercise, meditation and social media use have all received substantial

attention as predictors of mental health and/or resilience and have been extensively modeled in large datasets (1–7). Notably, early predictions were made about a prospective increase in drug use in order to cope with pandemic-induced stress (8–10). However, naturalistic drug use (drug use outside of controlled settings, regardless of underlying reasoning) has been largely overlooked in the majority of large-scale studies surveying the general population. Instead, the effects of drug use have mostly been quantified in studies specifically looking at vulnerable groups, such as people with existing substance use problems (11), or adolescents (12). Consequently, it remains unclear whether members of the broader general population who used drugs during the COVID-19 pandemic were more or less resilient during the global crisis than those who have not used drugs in their lifetime, and whether this varied depending on which drugs they used.

Indeed, investigating the relationship between naturalistic drug use, mental health and resilience in the general population is well-justified; with a recent survey showing that 1 in 11 individuals aged 16–59 in the UK declared drug use within the past year (13), it is likely to be a significant modulator of psychological wellbeing. Cannabis, cocaine, and MDMA/ecstasy are the most common choices in the UK (13), and a recent review of epidemiological data suggests increased global use of psychedelics (14). However, as the current literature provides conflicting evidence, the direction of this modulation is difficult to predict. On the one hand, concerns have been raised about a negative association between drug use and mental health outcomes independently of the COVID-19 pandemic (15–17). On the other hand, a raft of other studies have argued that certain drugs could be used to counter mental health problems (18–20). A pre-pandemic review (21) discusses cannabis, the most widely used recreational drug across the world, as a good example where two competing views dominate the narrative: either it is considered a contributor to poor mental health, or a therapeutic agent. 3, 4-Methylenedioxymethamphetamine (MDMA) is another prime example, where despite past studies illustrating an association between its use and the incidence of mental health problems (22), the recent narrative has been shifted in the light of clinical trials recommending its use for treating post-traumatic stress disorder (20).

In particular, psychedelics have recently received a tremendous increase in positive attention relative to other drugs, with therapeutic effects noted in clinical studies conducted with patients suffering from depression (18), anxiety (19), alcoholism (23), tobacco addiction (24) and obsessive–compulsive disorder (25). Furthermore, these positive effects have also been found to extend to instances where individuals chose to use psychedelics in naturalistic settings (26–29). They have been studied not only at full doses, but also reported by users at microdoses, which are sub-threshold doses that allegedly do not entail a psychoactive manifestation but have been argued to carry benefits pertaining to wellbeing and cognitive performance (30). However, some recent prospective studies have largely attributed these perceived benefits to a placebo effect (31, 32). Despite this recent interest, the relationship between naturalistic drug use and mental health in the general population remains unclear.

A major contributor to the complexity of the problem is that a significant proportion of individuals who consume drugs are polydrug users – they tend to consume more than one drug (33). Therefore, modeling the effects of specific drugs in isolation does not reflect naturalistic behavior. Nor does analysis of drug use under controlled conditions necessarily reflect their effects in different, naturalistic settings. Moreover, there has been little research into whether the use of drugs engenders greater mental health resilience or vulnerability when dealing with real-life stressors. Understanding this complexity requires sampling the general population to capture data from individuals who use drugs in naturalistic settings on a large enough scale to analyse psychological wellbeing changes in response to environmental stressors whilst accounting for different real-world patterns of use.

The aim of the present study was to test the hypothesis that naturalistic use of psychedelics during the COVID-19 pandemic would be associated with better mental health and resilience than for users of other drugs, or non-drug users. For this purpose we analysed data from the Great British Intelligence Test, which surveyed tens of thousands of individuals longitudinally at 6-monthly timepoints between 2020 and 2023. We did not specifically advertise that the study would contain drug-use related questions, thus mitigating recruitment bias caused by self-selection characteristic to other studies of this kind. In particular, we analyse data collected at two timepoints: during December 2020 when national-level restrictions were enforced, and during June 2021 when restrictions were lifted for the first time in the UK. At both of these timepoints participants were presented with questionnaires assessing their personality, compulsivity, lifestyle, mental health and resilience. Without prior advertisement of the study content, participants were surveyed on whether they used certain 'recreational drugs' during the COVID-19 pandemic. We first use clustering analysis to categorize people according to their patterns of drug use choices. Then we compare these clusters in terms of mood and resilience. Lastly, subtractive analyses are applied to test whether individuals who use psychedelics in combination with other drugs had better mood self-assessment and resilience scores during the pandemic relative to those who use other drugs or are not drug users.

2. Methods

2.1. Recruitment and study design

Participants were recruited as part of the Great British Intelligence Test in two waves facilitated by advertisement through the BBC main page website. The first wave was between December 2019 and January 2020, and the second wave in May 2020. In May 2020 the recruitment phase was supplemented with a bespoke pandemic resilience questionnaire titled The Pandemic General Impact Scale (PD-GIS) (2), select items from the Patient Health Questionnaire [PHQ, (34)] and GAD-7 (35), a reduced version of the Big5 questionnaire (36) and a compulsivity questionnaire (37) to assess the impact that the onset of the pandemic and the first couple of months of lockdown in the UK had on the participants.

This study was run in accordance with the Helsinki Declaration of 1975, as revised in 2008. All procedures were approved by the Imperial College Research Ethics Committee (17IC4009). All participants provided informed consent prior to completing the survey.

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2.2. Mental health assessment

We based our mood assessment on items from the extensively validated self-assessment scales: the Patient Health Questionnaire (PHQ) and the complete Generalized Anxiety Disorder Assessment (GAD-7) (34, 35). We selected 5 items from the PHQ questionnaire and the 7 items from the GAD-7 scale (See Supplementary material Part I for full questionnaire items). To capture mood over a longer period of time, we asked the participants to answer these questions pertaining to their mood in the month prior to the assessment (rather than 2 weeks as per the original scales). Additionally, we modified the scoring in order to capture a higher degree of granularity in their overall mood. Specifically, participants were asked to report symptoms over the preceding month from the time of assessment scored on a continuous scale from 0 to 6, as follows: '0-Never', '1-Almost never', '2-Once or twice a week', '3-Several times a week', '4-Daily', '5-Hourly', '6-More often'.

2.3. Personality and compulsivity assessment

Personality traits were quantified using an abbreviated scale comprising 18 (see Supplementary material Part I) out of the 44 items of the extensively validated Big-5 (36). Each item was a short phrase answered on a 5-point rating scale from −2 (strongly disagree) to 2 (strongly agree). Aspects of personality measured by this questionnaire classically reflect five factors: extraversion, agreeableness, conscientiousness, neuroticism and openness to experience. Compulsivity was quantified using a previously validated 15 item questionnaire (37). Each item was a short phrase answered on a 5-point rating scale from −2 (strongly disagree) to 2 (strongly agree). The two factors measured by the compulsivity questionnaire were perfectionism and reward drive.

2.4. Impact of the pandemic assessment

In May 2020 during our second stage of recruitment for the Great British Intelligence Test we were motivated by the pandemic context to develop in collaboration with psychiatrists, psychologists and neuroscientists a bespoke scale to quantify the self-perceived negative and positive impacts of the COVID-19 pandemic on daily life, as well as outlook, on multiple levels of psycho-socio-economic investigation. The Pandemic General Impact Scale (2) (PD-GIS) aimed to quantify self-reported feelings and behavior toward aspects of daily living that were specific to COVID-19 rather than general mental health, quality of life, optimism or resilience metrics. The seven factors of this questionnaire pertain to: disrupted lifestyle, health concerns, optimism, conflict at home, improved environment, more time for loved ones, a more relaxed lifestyle.

The scale quantifies three key aspects: (1) Aspects of positive impact. (2) Aspects of negative impact. (3) Outlook across 47 questions that map onto a 7-factor structure (see Supplementary material Part II). Each item is answered on a 5-point scale ranging from −2 (strongly disagree) to 2 (strongly agree).

2.5. Classifying drug use

In December 2020 and January 2021 participants were given the option to answer questions about their recreational drug use. These questions referred to recreational drugs that are illegal in the UK as opposed to the use of alcohol or tobacco. Based on whether they chose to answer this section or not, participants were split in to a number of drug use categories:

a. Unknown/unwilling to disclose: this category encompasses participants that did not wish to disclose whether they have used drugs in the past.
b. Non-drug users: this category encompasses those participants who reported they have never used a recreational drug in their lives.
c. Drug users: this category encompasses those participants who reported they have used a recreational drug in their lives. This group was further split based on their exact drug use history.

2.6. Statistical analysis

2.6.1. Gaussian mixture modeling

Gaussian Mixture Modeling (GMM) was used to determine the clusters of people by their self-reported drug use in a data-driven way. The clusters of different shapes and sizes, where each cluster is represented by a Gaussian distribution, can be accommodated by GMM, which is a flexible clustering modeling method. A probability score of belonging to a certain cluster is assigned by this algorithm to each datapoint (individual) characterised by N features (drugs they used during the pandemic). Then, the cluster with the highest probability defining that datapoint is assigned as the dominant cluster. In the present study, an individual drug user represented the datapoint, and uses of different drugs during the pandemic coded in binary terms, as well as whether the individuals were users before not during the pandemic, or not at all during their lifetime, were the features.

A 5-fold cross-validation method was used on a 80% train 20% test split (38) of the total data to identify the ideal number of clusters that could be modeled with the highest accuracy. The optimal number for the data was identified as 10 clusters (highest accuracy score), and the trained model was used to assign cluster probabilities and dominant cluster labels to all data points. The clusters were used as groups in the statistical analysis of mood and resilience.

2.6.2. Factor structure of PD-GIS, little big-5, the compulsivity scale

Confirmatory factor analysis (CFA) was run in python using the factor analyzer package (39). The following factor structure was previously reported in publications as 7-factors for PD-GIS, and 2-factors for the compulsivity scale (37). For the reduced big-5 we employed an exploratory factor analysis with varimax rotation. The full set of questions, factor loadings and feature correlations are provided in the Supplementary material Part I.

2.6.3. Mood self-assessment composite score

A factor analysis with one factor was run on the standardized mood self-assessment scores containing all questions asked. The first

component identified this way was kept as the mood self-assessment composite score. This was done with the factor-analyser package in Python (39).

2.6.4. Statistical differences between clusters

Chi-2 statistics were run to analyse demographic differences between clusters at different timepoints (See Supplementary material Part III). Differences between clusters were tested with 2-way ANOVA for group effects, dimension of mood/resilience effects, and their interactions; and subsequently where effects were identified cluster differences were tested with Tukey post-hoc tests. Ordinary Least Squares Regression (OLS) regression was used to model data whilst accounting for sociodemographic, lifestyle (inclusive of tobacco and alcohol use) and personality factors. All statistical analysis was performed using the statsmodels python package (40).

2.6.5. Inferring effect size differences in mood/resilience based on belonging to a certain cluster

A linear regression with binary cluster labels as predictors was fitted to predict the standardized mood self-assessment/resilience scores after controlling for timepoint, sociodemographics, personality and lifestyle (inclusive of tobacco and alcohol use) variables. The model was then run through a type 2 ANOVA to infer the significance of each predictor contribution. The beta coefficients (SD units) are plotted alongside significance levels inferred via this latter analysis.

3. Results

Out of the $N = 243{,}875$ recruited participants who completed the Great British Intelligence Test between December 2019 and May 2020 (2), by December 2020, $N = 95{,}441$ provided their emails and gave permission to be recontacted for research purposes. These participants were recontacted in December 2020 and June 2021. At those subsequent timepoints the questionnaire delivered to participants was extended to include questions related to recreational drug use, which were not part of either the recruitment materials or follow up emails. A total of $N = 22{,}633$ participants responded in December 2020 and $N = 17{,}231$. Out of these, $N = 22{,}304$ and $N = 16{,}903$ participants completed all questionnaires of interest at the December 2020 and June 2021 timepoints respectively, totalling $N = 30{,}598$ unique respondents and $N = 8{,}609$ returning respondents. The original cohort sociodemographic characteristics are presented in Supplementary Figure S7.

3.1. Clustering recreational drug users by choice of drug

10 clusters were identified as optimal when performing a 5-fold cross validation on the data with a 80% train set and 20% test set split. The Gaussian Mixture Model was applied to all data at this model order, to identify the loading of each feature onto each cluster and the probability of belonging to each of the clusters for each participant. The cluster with the highest probability was assigned as the dominant cluster for each participant (Figure 1). In Supplementary material Part III we illustrate that these clusters also vary significantly in their sociodemographics, lifestyle (inclusive of tobacco and alcohol use) and personality.

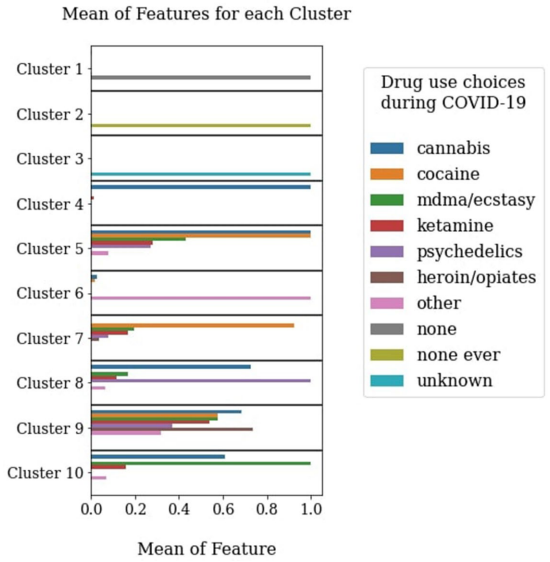

FIGURE 1
Data-driven clusters based on choices of recreational drug use during the COVID-19 pandemic. The *y* axis represents the feature loadings onto different clusters. The different clusters have been interpreted as follows: Cluster 1 (N=6,161) – Drug use history but no pandemic use, Cluster 2 (N=22,653) – Never used drugs, Cluster 3 (N=7,593) – Unknown/Unwilling to disclose use, Cluster 4 (N=1,538) – Cannabis users, Cluster 5 (N=317) – Cannabis and cocaine users, Cluster 6 (N=248) – users of 'other' drugs not covered in the list, Cluster 7 (N=301) – Cocaine users, Cluster 8 (N=216) – Psychedelics and cannabis users, Cluster 9 (N=34) – Extreme polydrug users, Cluster 10 (N=90) – MDMA/ecstasy and cannabis users.

In Figure 2, we present a breakdown of all of the recreational drugs participants within each of the clusters reported using at different timepoints. We find that only for the under sampled cluster, Cluster 9, proportions of drugs use prevalence become notably shifted over time. More participants in Cluster 9 reported using cocaine, MDMA/ecstasy, ketamine and 'other' drugs by June 2021 than by December 2020.

Cannabis was by far the most prevalent recreational drug, being represented in multiple clusters. This was closely followed by cocaine, which had a cluster of people who primarily used only this drug, as well as a cluster paired with cannabis. The cluster representative for psychedelics users also had a strong cannabis use co-incidence, with over two thirds of members of this cluster having reported using it since the pandemic began. Notably, there was only a small proportion of the respondents (N=46) who reported using psychedelics and no other drugs (Figure 2).

3.2. Mental health and resilience differences between clusters

We used a 2-way ANOVA to test for significant differences in mood self-assessment and resilience (Figure 3). On mood self-assessment scores we found a significant effect of cluster ($F_{(9,485,680)} = 35.15$, $p < 0.001$) and an interaction between cluster and variable ($F_{(108,485,680)} = 1.95$, $p < 0.001$). By applying Tukey post-hoc tests, prior to correction for multiple comparisons, we found that some of these effects were driven by group differences between the psychedelics

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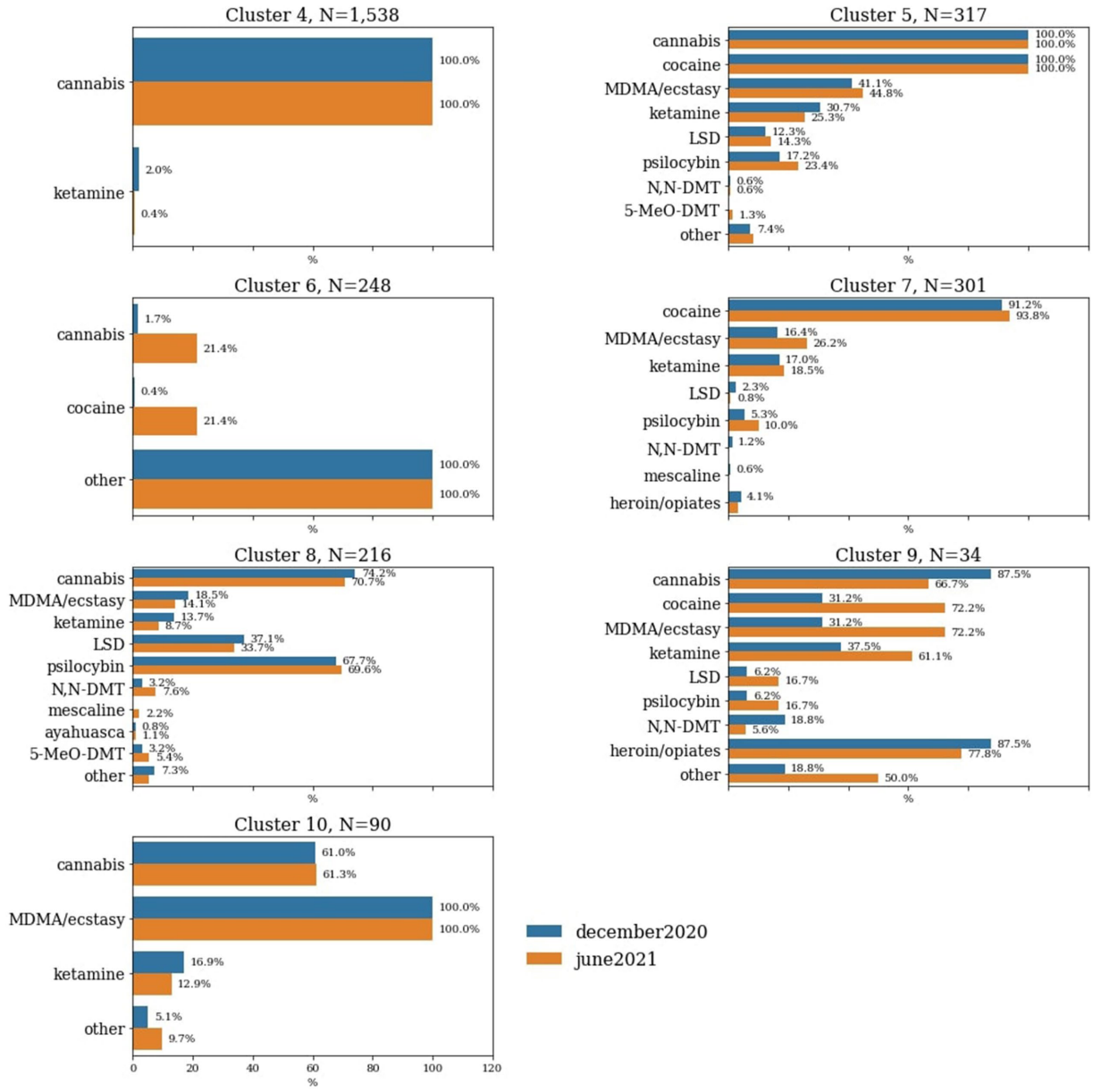

FIGURE 2
Percentage of choices of recreational drugs used during the pandemic within each of the clusters that represent active users. Only the clusters characterised by drug use features are represented in this figure. Percentages of individuals within specific clusters who have used certain drugs during the pandemic are illustrated based on the timepoint of assessment.

and cannabis cluster and other groups. In particular, differences between psychedelics and cannabis users vs. MDMA/ecstasy and cannabis users on anxiety, differences between psychedelics and cannabis users and cannabis only users/those who never used drugs/those unwilling to disclose their drug use on irritability, psychedelics and cannabis users vs. those with drug use history but no pandemic use/those who never used drugs/those unwilling to disclose their use on apathy, and psychedelics and cannabis users vs. MDMA/ecstasy and cannabis users on their overall mood scores. However, we note that none of these survived correction for multiple comparisons. Full *post-hoc* analysis can be found in Supplementary material Part III.

On resilience scores we also found a significant effect of cluster ($F_{(9,261,051)} = 9.32$, $p < 0.001$) and an interaction between cluster and variable ($F_{(54,261,051)} = 4.77$, $p < 0.001$). However, we did not see differences pertaining to the resilience of psychedelics and cannabis/MDMA and cannabis users driving any main cluster effects (full post-hoc analysis can be found in Supplementary material Part III).

First, using linear modeling, we adjusted every single mood self-assessment and resilience factor score to timepoint, demographics, lifestyle (inclusive of use of tobacco and alcohol) and personality. Specifically, for use of tobacco and alcohol, we adjust to the number of alcohol units consumed in a week and the number of cigarettes smoked in a day. Use of tobacco and alcohol was evident in each of the data-driven clusters we present (see Supplementary material Part III for group level differences), therefore justifying the need to account for the confounding effects of using these substances in conjunction

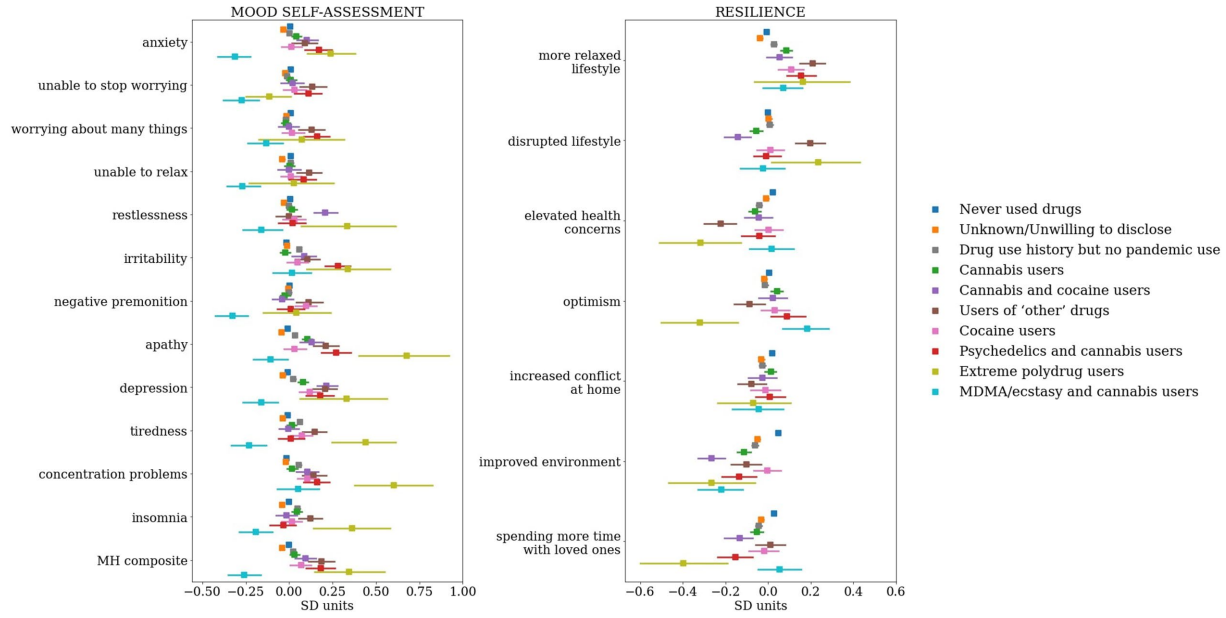

FIGURE 3
Group differences in individual mood self-assessment items and resilience latent factors. The answers received to mood questions were turned to scores, then using a linear regression model adjusted to timepoint, sociodemographic, lifestyle and personality factors. The resulting residuals were then standardized (*z*-scored). The latent factors derived from the PD-GIS questionnaire (2) have been adjusted to using a linear regression model with timepoint, sociodemographic, lifestyle and personality factors as predictors. The resulting residuals were then standardized (*z*-scored) and plotted. On both panels, points represent the cluster mean, error bars represent standard error of mean (SEM). The left panel illustrates group differences in individual dimensions of mood, whereas the right panel illustrates group differences in individual dimensions of resilience.

with other recreational drugs. We then run a linear regression on the adjusted smood self-assessment and resilience scores with the cluster labels as binary predictors (except the cluster indicating participants who never used drugs in their lifetime, which acted as a reference) in order to identify effect size differences in the reports of each cluster relative to those who never used drugs. We use Sawilowsky's updated version of Cohen's notion of effect sizes (0.1 SD = very small, 0.2 SD = small, 0.5 SD = medium, 0.8 SD = large, 1.2 SD = very large and 2.0 SD = huge) for interpreting the magnitude of the effects observed in our data (41, 42). We identify a range of effects in the small to medium range of different drugs/associations of drugs on mood, as well as resilience. Most notably, for mood dimensions, the MDMA and cannabis users and the participants unwilling to disclose their use were the only clusters displaying an association with better mood (lower mood-self assessment scores) relative to those who never used drugs (Figure 4).

For the MDMA and cannabis users we observe significantly less anxiety (effect size −0.32SD, $F_{(1,37,373)} = 8.97$, $p < 0.001$), inability to stop worrying (effect size −0.28SD, $F_{(1,37,378)} = 7.07$, $p = 0.01$), inability to relax (effect size −0.28SD, $F_{(1,37,374)} = 6.85$, $p = 0.01$), and negative premonition (effect size −0.33SD, $F_{(1,37,379)} = 9.57$, $p < 0.001$), tiredness (effect size −0.23SD, $F_{(1,37,379)} = 4.5$, $p = 0.03$), and overall better mood (effect size −0.26SD, $F_{(1,37,360)} = 5.87$, $p = 0.02$). We observe an opposite pattern for psychedelics and cannabis users, with significantly higher anxiety (effect size 0.17SD, $F_{(1,37,373)} = 5.59$, $p = 0.02$), worrying about too many things (effect size 0.15SD, $F_{(1,37,379)} = 4.45$, $p = 0.03$), higher irritability (effect size 0.3SD, $F_{(1,37,379)} = 17.41$, $p < 0.001$), apathy (effect size 0.28SD, $F_{(1,37,370)} = 15.53$, $p < 0.001$), depression (effect size 0.19SD, $F_{(1,37,379)} = 6.97$, $p = 0.01$), concentration problems (effect size 0.18SD, $F_{(1,37,379)} = 6.22$, $p = 0.01$) and overall mood problems (effect size 0.18SD, $F_{(1,37,360)} = 6.57$, $p = 0.01$).

Relative to individuals who never used drugs in their lifetime we observe less agreement to statements suggesting the pandemic led to an improved environment in both psychedelics and cannabis (effect size −0.18SD, $F_{(1,37,293)} = 6.07$, $p = 0.01$) and MDMA and cannabis users (effect size −0.27SD, $F_{(1,37,293)=}5.75$, $p = 0.02$). Psychedelics and cannabis users also reported a more relaxed lifestyle (effect size 0.19SD, $F_{(1,37,293)} = 7.05$, $p = 0.01$) and spending less time with loved ones (effect size −0.18SD, $F_{(1,37,293)} = 5.82$, $p = 0.02$).

To investigate the magnitude of the effect size differences of the clusters of psychedelics and cannabis, and MDMA and cannabis users respectively, relative to the cluster composed of cannabis users only, we repeated the analysis illustrated above with all other clusters as predictors apart from the cannabis users only cluster (Figure 5).

To a large extent the effects on mood dimensions relative to cannabis users were similar to the effects we observe relative to non-users. MDMA and cannabis users, relative to cannabis only users, had significantly lower levels of anxiety (effect size −0.36SD, $F_{(1,37,373)} = 10.57$, $p < 0.01$), inability to stop worrying (effect size −0.28SD, $F_{(1,37,378)} = 6.73$, $p = 0.01$), inability to relax (effect size −0.27SD, $F_{(1,37,374)} = 6.17$, $p = 0.01$), negative premonition (effect size −0.28SD, $F_{(1,37,379)} = 7.61$, $p = 0.01$), apathy (effect size −0.21SD, $F_{(1,37,370)} = 3.86$, $p = 0.049$), depression (effect size −0.3SD, $F_{(1,37,379)} = 4.76$, $p = 0.03$), tiredness (effect size −0.25SD, $F_{(1,37,379)} = 5.08$,$p = 0.02$), insomnia (effect size −0.24SD, $F_{(1,37,378)} = 4.65$, $p = 0.03$) and overall mood problems (effect size −0.29SD, $F_{(1,37,360)} = 6.98$, $p = 0.01$). Psychedelics users, on the other hand, had significantly higher levels, relative to cannabis only users, of worrying about too many different

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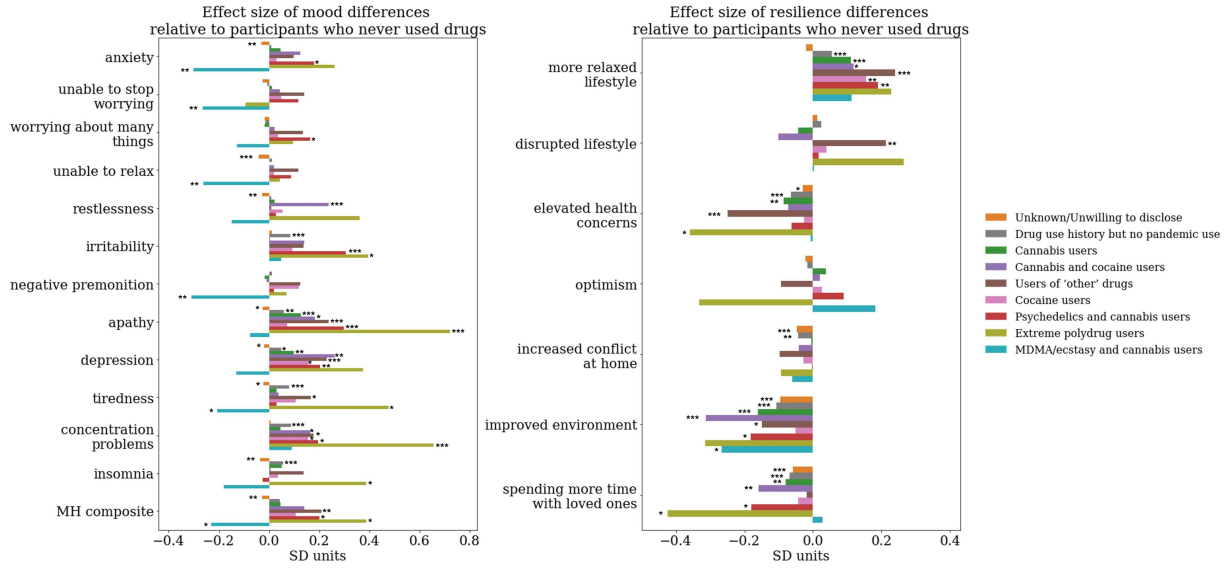

FIGURE 4
Effect size difference relative to the cluster representing participants who never used any drug whilst accounting for the effect of timepoint, sociodemographic, lifestyle and personality factors. A linear regression model was run on the adjusted MH scores/resilience latent factors with each binary dummy-variable representing cluster labels as predictors. The cluster of participants who reported never having used drugs has been kept as the reference. The y axis represents the beta coefficients resulting from the regression associated with the effect size of each of the groups, whereas the significance star annotations represents the statistical significance of this effect size derived from running an ANOVA on the linear regression model. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

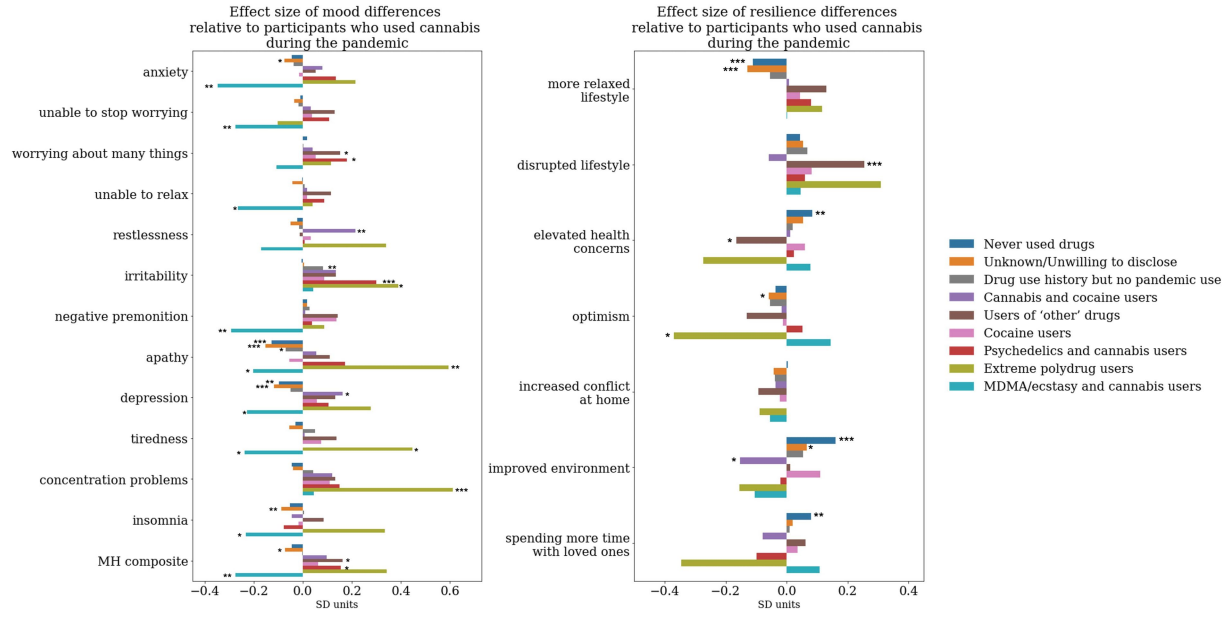

FIGURE 5
Effect size difference relative to the cluster representing participants who took cannabis during the pandemic whilst accounting for the effect of timepoint, sociodemographic, lifestyle and personality factors. A linear regression model has been run on the adjusted MH scores/resilience latent factors with each binary dummy-variable representing cluster labels as predictors. The cluster of participants who reported using cannabis during the pandemic has been kept as the reference. The y axis represents the beta coefficients resulting from the regression associated with the effect size of each of the groups, whereas the significance star annotations represents the statistical significance of this effect size derived from running an ANOVA on the linear regression model. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

things (effect size 0.18SD, $F_{(1,37,379)} = 5.63$, $p = 0.02$), irritability (effect size 0.3SD, $F_{(1,37,379)} = 16.07$, $p < 0.001$), and overall mood problems (effect size 0.15SD, $F_{(1,37,360)} = 3.99$, $p = 0.049$).

Neither psychedelics and cannabis or MDMA and cannabis users displayed significant effect size differences relative to users of cannabis only in any domains of pandemic-specific resilience.

4. Discussion

Our results illustrate that recreational drug use during the March 2020–June2021 period can be framed by 10 distinct clusters defined in a data-driven way on the basis of the combinations of drugs participants reported using (Figure 1). These distinct clusters indicate preferences for certain substances over others (eg primarily cannabis or primarily cocaine users), or a preference for an associated pattern of use (eg psychedelics and cannabis, cocaine and cannabis, MDMA and cannabis, extreme polydrug use). Most importantly, they are characterised by different levels of mood and resilience profiles during the COVID-19 pandemic.

Perhaps most strikingly, all but one drug cluster had consistently negative associations with mood, the exception being the MDMA plus cannabis cluster, where we observed positive associations with mood. Conversely, while we expected to see those who chose to use psychedelics as having better mood and higher resilience than users of other drugs or participants who never used drugs, this was not the case. In fact, we observed, contrary to our hypothesis, that those who used psychedelics indicated higher levels of anxiety, worrying about different things, irritability, apathy, depression and overall mood problems relative to individuals who never used drugs. We also found that while they reported a more relaxed lifestyle as a result of the pandemic, they disagreed that the pandemic effects could be associated with an improvement in the environment and spent less time with loved ones. Considering almost all psychedelics users in our sample were polydrug users, especially in association with cannabis, we carried out the same analysis but this time calculating effect size differences relative to the cannabis only cluster. This produced similar results; specifically, relative to those who only used cannabis, those who used psychedelics plus cannabis reported higher levels of anxiety, worrying about different things, irritability and overall mood problems; though depression levels were not significantly different.

Our findings concerning the naturalistic use of psychedelics diverge from the anticipated outcomes, but in doing so help contextualize the optimistic landscape painted by prior investigations. Prior to the COVID-19 pandemic the overwhelming majority of studies found a positive association between naturalistic psychedelics use and dimensions of mental wellbeing. For example, in a prospective naturalistic study of depressed participants, reductions in depressive symptoms were observed for up to a month after using a psychedelic (43). A cohort of Indigenous people in Canada and the United States reported the incidence of fewer depressive symptoms, anxiety and stress within a month after taking a psychedelic relative to a previous baseline (44). Subjective improvements in depression and anxiety were also reported to be associated with the naturalistic use of mescaline (26). This effect has been observed to increase as a function of higher psychedelics exposure, up to a ceiling (45). Ceremonial use of psychedelics such as ayahuasca has also been linked to improvements in depression lasting for up to 6 months (46). Interestingly, significant reductions in anxiety and depression were also identified in ayahuasca-naive participants who underwent such a ceremony (29). Using psilocybin truffles in supportive group settings has been linked to a reduction in anxiety (47, 48). Those who microdosed psilocybin also report short to medium term improvements in mood and mental health (49). It is worth noting that all of these investigations have demonstrated enhancements in various dimensions of mental wellbeing relative to participants' own baseline, that is, in a within-subjects experimental design, instead of comparing those who used psychedelics versus those who used other drugs, or never used drugs in their lifetime. While prior findings offer valuable insights into the potential of psychedelics to ameliorate low mood following experiences in naturalistic settings, it remains unclear whether the magnitude of these improvements was substantial enough to match (or go beyond) the mood levels of non-drug users or users of other drugs, thus potentially resulting in psychedelics users as having better mood than other subsets of the population.

Findings concerning naturalistic psychedelics use during COVID-19 pandemic offer a more particular basis for drawing direct comparisons with our results. A few studies did attempt to explore the relationship between use of psychedelics and mental health outcomes during the COVID-19 pandemic and reported that people did indeed use psychedelics with the intention of better coping with pandemic stresses (50, 51) and that lifetime use of psychedelics was associated with better mental health indicators (52). Psychedelics have even been proposed for the purpose of treating mental health conditions due to or aggravated by COVID-19 viral infection (53). (50) indicated two thirds of their sample claimed that pandemic use of psychedelics helped them deal with the global situation better. (51) reported those who used psychedelics (and also MDMA) used problem-focused coping strategies in response to the global crisis more often than non-users and (54) (on a different cross-sectional analysis of data from the same study as (51)) reported that users of psychedelics, especially regular ones, reported less psychological distress than non-users. However, a survey carried out in the United States of America (USA) found an association between psychedelics use, namely between past use of psilocybin mushrooms, and worse mood self-assessment scores at the time of assessment (55). Our findings agree with those of Matzopoulos et al. (55), who employed similar mood self-assessment scales as ours to survey the USA general population, but differ to those of (53) who used different mental wellbeing assessments and carried out the survey mainly in Spain and Brazil through snowball sampling on social media.

The obvious question prompted by our results is - why is it that we are not seeing, in the light of the positive effects demonstrated by clinical studies on psychedelics as well as naturalistic surveys, a positive association between naturalistic psychedelics use and mental health during times of crisis? Some of the earliest theories aimed at explaining the variability in the effects of psychedelics have converged around the concept of set and setting (56), and their potential for acting as non-specific context amplifiers (57). *Set and setting* refer to the mindset and intention of the individual experiencing the psychedelic, and the characteristics of the environment where the experience is taking place, respectively, (58, 59). In modern clinical studies, for example, in order to ensure an optimal "set," careful attention is given to provide participants with psychological support before, during and after the experience, and to ensure an optimal "setting" the same attention is paid to the environment in which the psychedelic intervention takes place (60). Given the importance that this notion of *set and setting* is given in the clinical environment, it is potentially unsurprising that the benefits seen there are not transferred to the naturalistic setting where these variables may not be controlled optimally. Not only was the context of the experiences captured in our study not explicitly therapeutic, but it was also heavily marked by a global mental health crisis as well as significant disruptions in the immediate environment of individuals as a result of the COVID-19

pandemic. As demonstrated by our findings, lifestyle disruptions were common in the majority of drug use clusters, as was spending less time with loved ones, and in certain instances an increase in conflict at home. These factors undoubtedly had imminent effects on the *set and setting* of psychedelic experiences during that period, and it is reasonable to infer that the disruptive context would have likely contributed to the associations we observe between use of psychedelics and mood self-assessment scores.

Another major difference between the present study and the previous literature is the socio-cultural context in which the psychedelics have been taken. Different countries will have different cultural acceptance, cultural significance and general stigma around psychedelic drug use to that of the UK. Adding to this, local regulation due to the pandemic may have produced differences in access to drugs. Since context can influence psychedelic experiences in a naturalistic setting (61), it cannot be ruled out that these factors contributed to the outcomes we report. More specifically, it is not excluded that psychedelics use in the UK (where strict lockdown and infection control guidelines were employed) during the COVID-19 pandemic could have led to the amplification of general distress, which would have in turn influenced the outcome of psychedelic experiences. It is worth noting, in support of this perspective, that our findings align with those emerging from the USA during a similar timeframe (54), but not to findings from Spain or Brazil (53). While political climate, healthcare access and infection control guidelines differed in these countries and undoubtedly affected their population in differential ways, the specific socio-cultural nuances related to the use of psychedelics also need to be considered. Neither the USA or the UK have a recent history of general cultural acceptance of psychedelics use, nor were these substances legal for recreational use at the time of assessment. Given the above, there is a question as to what extent our findings generalize outside the borders of the UK or the USA.

Despite the issues with naturalistic psychedelic drug use studies with regards to uncontrolled set and setting, the majority of these studies (both the within-subjects design pre-pandemic studies as well as the cross-sectional study of (53) carried out during the pandemic) still report a positive association with mental wellbeing. Another key difference between our study and most of the other studies mentioned above that could explain the reported outcomes is the nature of participant recruitment methodology. With few exceptions, the above mentioned studies advertised psychedelics-related research in psychedelic-profiled social media groups. Members of these groups who respond to such advertisements may not be representative of those groups or of the people who use drugs more generally. Recruitment bias has been previously called out to be a confound in surveys specifically recruiting psychedelics users, since openly advertising such studies opens the door for self-selecting participants who, on the basis of enthusiasm, positive experiences, and/or desire to contribute to research to advance a global societal movement, might not yield objective datasets and consequently allow scientists to draw the right conclusions (62–65). In particular, biases in sampling related to positive past experiences, but also as pertains to a prospective study-related expectation that there may be a mental health benefit associated with psychedelic use, could confound the results.

There are other reasons why we might observe different outcomes. None of the past studies looking at naturalistic use of psychedelics used a data-driven approach to cluster the use of psychedelics with the use of other drugs alongside to expose effects of common drug interactions. Additionally, none directly compared the data of psychedelics users from clusters derived in this way with data from users of other drugs who do not use psychedelics. Notwithstanding the debate on what constitutes a psychedelic to begin with (66), in past studies classical and non-classical psychedelics were often assessed concomitantly under the umbrella term of 'psychedelics', regardless of the use of other drugs. This is an important consideration as drugs with different pharmacology and subjective effects could produce varying outcomes. Our own data, for example, reveals that within the cluster of individuals who primarily used psychedelics and cannabis during the pandemic a small proportion have also used MDMA. (53) also included MDMA users as part of their 'psychedelics users' group in a cross-sectional analysis of users vs. non users of psychedelics. Notably though, MDMA users were more prevalent in their sample compared to ours. The implications of this observation are significant, particularly considering that our results demonstrate a contrasting association between the use of primarily MDMA and cannabis (in the absence of psychedelics) and dimensions of mental wellbeing. Specifically, individuals within this cluster exhibited better mood relative to those who never used drugs in their lifetime at the time of assessment, drawing further attention to the question pertaining to whether the proportion of MDMA experiences captured within the 'psychedelics' label is what could be driving the differential outcomes.

Our analysis focuses on modeling the choices of drugs used specifically during the pandemic timeframe, rather than the frequency or underlying motivations for these choices. It is not excluded that using psychedelics in conjunction with other substances (e.g., as was evident in our sample that the majority of those who chose to use psychedelics were polydrug users and also chose to use cannabis, whereas a minority used other substances too) during a global mental health crisis cancels out therapeutic effects that could potentially be derived from naturalistic experiences with psychedelics. The effects on mental wellbeing would be contingent on prior experiences, the frequency of use of each individual substance, on their dosage, whether they were consumed together or separately and under which circumstances (as discussed above). Within our data-driven clusters, we anticipate capturing a diverse range of such patterns. For instance, some individuals may use cannabis daily while only occasionally using psychedelics, whereas others may frequently engage in microdosing psychedelics while rarely using cannabis. These patterns might have been in place prior to the pandemic or adopted because of it. Furthermore, the dosage of these substances is expected to have varied among the individuals surveyed, in turn leading to varying acute and long-term effects mediated by different degrees neurobiological changes and the resulting intensity of those experiences. Additionally, it is reasonable to assume that the individuals we surveyed would have used psychedelics or cannabis for a variety of reasons not limited to self-medication, recreationally, as a social catalyst, or for spiritual purposes. These motivations would have differentially influenced their mood post-experience. Moreover, whether therapeutic effects even exist subsequent to naturalistic use, they might be short lived [maximum documented has been 6 months post experience by Ruffell et al. (46)] and our participants might have had their experiences months apart from answering our survey, and/or modulated by subsequent use of other substances (or even prescription medications) not limited to the ones captured in our assessment.

A core difficulty in interpreting our findings is to do with potential causal links between psychedelics use, mood self-assessment and resilience metrics in the general population. Contextual variability affecting the outcome of drug-induced experiences aside, it might also be that people with poor mental health to begin with take psychedelics, and therefore their perceived improvements in mood might be visible only in a within-subjects study design rather than something comparable across large segments of non-drug using population. It has been previously documented that people with poor mental health indeed engage in drug use to self-medicate (67), and it is possible that individuals experiencing low mood during the pandemic turned to psychedelics for this reason. Drawing upon prior research findings, psychedelics could have indeed contributed to improvements in the mood of our participants, suggesting that our results could be driven by baseline differences in mood that preceded the experiences rather than a lack of benefits derived from psychedelics use. However, this observation raises the possibility that the improvements in mood resulting from psychedelic experiences in naturalistic settings may not reach a level that equals or surpasses the mood levels of individuals with no history of drug use. This could be the case particularly during times of global crisis but also beyond. On the other hand, it is also plausible that our results are influenced by fundamental differences in dimensions other than mood between individuals who choose to use psychedelics and those who use other drugs or have no history of drug use, which were not captured in our assessment –genetics, brain and body health status, co-morbidities and psychological history to name a few. To add to the complexity, there might be differences between people who chose to use psychedelics during the pandemic versus people who chose to use psychedelics before the pandemic, or those who will choose to use psychedelics after the pandemic. These underlying differences could potentially contribute to baseline variations in mental health levels that persist regardless of any potential positive effects on mood resulting from psychedelic experiences in naturalistic settings. It is also possible that a combination of these factors – limited magnitude of psychedelic effects on mood as well as fundamental differences between user groups – might be at play in determining cross-sectional differences. Importantly, the severity of the pandemic impact highlights that it is crucial to consider these factors when evaluating survey data on psychedelic use collected as the world recovers from disruption.

Our results reflecting a positive association between MDMA/ecstasy and cannabis use are interesting and surprising, though we would like to exert caution interpreting them and their generalisability to the wider spectrum of MDMA users. The within group variation was high and the sample size of this cluster low ($N = 90$) relative to the other clusters, consistent with previous work reporting a decrease in typical 'party' drugs such as MDMA/ecstasy during the COVID-19 pandemic (68), thus the effects we report reflect a bias toward more extreme values in this particular case. Additionally, as this is a self-report sample we cannot exclude that some mood self-assessments might be inaccurate either due to dishonesty or as a function of personal awareness, and in lower samples this raises higher levels of skepticism in interpretation. However, if these results were to be replicated in a larger sample, a possible interpretation would be that since acute MDMA effects are associated with feelings of bonding, love and social connection (69), MDMA-catalyzed social interactions during the pandemic could have acted as a protective mechanism on the mood of users, relative to those who did not have these experiences.

Our study has a number of strengths which confers us the ability to draw the present inferences with confidence. First and foremost, we present one of the few studies assessing effects of naturalistic use of psychedelics, MDMA and other drugs in the absence of recruitment bias toward social media groups discussing psychedelics, since the questions which participants were asked were not advertised either at the time of recruitment or prior to the follow-ups, and our study was never advertised on social media channels pertaining to drug use/related activities. What's more, in our analysis we employ a diverse population inclusive of a very large control population who has never used drugs but has answered the same questions during the same timeframe. We also acknowledge that drug use behavior is dynamic, and that psychedelics are most often not used in isolation, with cannabis specifically being the substance of choice that participants might use during the same period of time, thus making it generally difficult to disentangle specific drug effects when these are being used naturalistically.

There are also certain limitations our work possesses, in part owed to the main reason our study is unique - that the study design was not drug-use specific. Recreational drug use is a prevalent lifestyle decision that covers choices of both licit and illicit drugs. In our study we only model choices of recreational drugs that are illicit in the UK, and control for the frequency of otherwise licit drugs alcohol and tobacco in the multivariate analysis. This distinction in our analysis is not to imply that licit drugs are less harmful than illicit drugs. While characterization of harm based on this dichotomy is beyond the scope of this manuscript, we note the extensive evidence to suggest that alcohol and tobacco use is at least as harmful as is the use of the other recreational drugs analysed in this study (70–77). Furthermore, due to a variety of reasons not limited to stigma, it is difficult to recruit drug users from the general population, since this category of individuals, particularly if they have a high level of polydrug use, are less likely to engage with traditional survey methods (78). Therefore, we might have undersampled the population with problematic use (as reflected by the extreme poly-drug users cluster having the lowest number ($N = 35$) of respondents). With regards to polydrug use, at the point when the present data were collected we have not collected extensive details about participants (who declared having used a drug at least once) drug use history prior to the COVID-19 pandemic, thus diminishing our ability to draw inferences about an accumulation of experiences throughout their lifetime potentially influencing mood and/or resilience during the pandemic timeframe. We expect that within our data-driven clusters people would have had different frequencies of specific drug use prior as well as during the pandemic. However, we have not collected extensive details about participants drug use frequencies during the pandemic timeframe itself, and are therefore not able to assess the relationship between frequency of use and effects on mental wellbeing in the present study. These dimensions of mental wellbeing, too, were studied independent of clinical diagnoses of either psychiatric or neurological disorders, and given the large dataset it is not excluded that some participants might have had clinical levels of anxiety, depression, post-traumatic stress disorder or even diagnosed substance use problems. Other factors such as living conditions, quality of interpersonal relationships, and

various ramifications within the umbrella term of 'social misery' have not been addressed in the present analysis, and it is not excluded that there would potentially be significant differences in these aspects between the different drug use clusters, with effects on mood and resilience. Lastly, we highlight that our sample, although large, is >90% represented by members of the British population, and therefore it is possible that associations between naturalistic use of psychedelics (as well as other recreational drugs) might look different for individuals residing in other parts of the world.

The effects of naturalistic use of recreational drugs on mood, and mental wellbeing more generally, warrant further attention and research since these substances are growing increasingly more popular and available beyond clinical setups. In particular, we advise for other studies to try to replicate our findings in existent/future large datasets that also collected data on naturalistic drug use. Concerning our results on MDMA and cannabis use, this is particularly important, since unintended "hype" might arise as a result of the noted positive associations, which if it results in increased naturalistic use to self-medicate for mood disturbances is of concern due to potential toxicity of prolonged MDMA exposure (79). Concerning our results related to psychedelics use, the effect of different contexts and more granular investigations of how particular set and setting features influence the quality of the experience and its long term outcomes might prove useful in advancing our understanding of psychedelics effects in naturalistic settings and inform the development of harm reduction guidelines. We note special attention might be given to cultural contexts, as perceptions of psychedelics are tied to ethnographic backgrounds (80). Amongst key survey/experimental design approaches we highlight the importance of selecting participants as agnostically as possible in relation to the study outcome, *and where possible not disclosing the study hypothesis*. Aiming to recruit control-participants and even users of other drugs, too, and test them on objective mental health metrics alongside psychedelics users would also strengthen and contextualize conclusions. Perhaps even more importantly, collecting non-psychedelic drug use history, lifestyle and personality data in such studies and then adequately accounting for these variables at the analysis stage might yield more holistic insights as to what exactly psychedelics modulate and in relation to/independent of what other factors. The underlying effects on brain chemistry and activity where drug interactions of potent pharmacological agents are used in conjunction with one another is also something that might be worth exploring in association with behavioural metrics. Specifically, attention ought to be given to the intersection of different patterns of using distinct drugs in parallel, both licit and illicit.

4.1. Conclusion

In the present study we found a positive association of MDMA and cannabis use, but did not find a positive association of psychedelics and cannabis use with better mood and resilience during the COVID-19 pandemic in users relative to those who only used cannabis during the same timeframe or never used drugs in their lifetime. Mapping out with precision how sociodemographic and lifestyle factors (inclusive of socio-cultural context, use of alcohol or tobacco, being a single drug or polydrug user, history of drug use, personality type, compulsivity) or drug experience factors (set and setting during the acute experience, dosage, interaction between drugs used at the same time/subsequently) are driving the associations observed between data-driven clusters of drug use choices and mood is challenging due to the complex interplay among all of these variables. While we find positive associations with mood in the MDMA and cannabis use cluster, we indicate these results must be replicated before stronger conclusions can be drawn. In the case of psychedelics, it is reasonable to infer based on past studies that in appropriate conditions (set and setting, clear intention, appropriate dose) psychedelics taken in naturalistic settings could potentially lead to improved mood and wellbeing in specific individuals. However, contrary to our initial hypothesis, our analysis provided evidence that individuals who used psychedelics during a global crisis did not exhibit better mood and resilience compared to those who used other drugs or did not use drugs in their lifetime. We posit that psychedelics effects and associations with mood and resilience in naturalistic settings are variable rather than unequivocally positive, and future research should aim to map out with greater precision what factors predict outcomes at either end of the positive–negative spectrum, and how these outcomes inform cross-sectional differences between users and non-users.

Data availability statement

Data presented are part of a longitudinal study that is still ongoing, and can only be shared via institutional agreements in compliance with local GDPR guidelines. Data sharing inquiries should be directed to Prof. Adam Hampshire: a.hampshire@imperial.ac.uk

Ethics statement

This study was run in accordance with the Helsinki Declaration of 1975, as revised in 2008. All procedures were approved by the Imperial College Research Ethics Committee (17IC4009). All participants provided informed consent prior to completing the survey.

Author contributions

MB, WT, and AH: conceptualisation. MB and AH: methodology. MB: investigation, visualization, and writing—original draft. AH: supervision. WT, PH, and AH: software. MB, WT, PH, and AH: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AH is owner and director of Future Cognition LTD and H2 Cognitive Designs LTD, which support online studies and develop custom cognitive assessment software respectively. PH is co-owner and director of H2 Cognitive Designs LTD and reports personal fees from H2 Cognitive Designs LTD outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1184681/full#supplementary-material

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Imprinting: expanding the extra-pharmacological model of psychedelic drug action to incorporate delayed influences of sets and settings

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Background: Psychedelic drug experiences are shaped by current-moment contextual factors, commonly categorized as internal (set) and external (setting). Potential influences of past environments, however, have received little attention.

Aims: To investigate how previous environmental stimuli shaped the experiences of patients receiving ketamine for treatment-resistant depression (TRD), and develop the concept of "imprinting" to account for such time-lagged effects across diverse hallucinogenic drugs.

Methods: Recordings of treatment sessions and phenomenological interviews from 26 participants of a clinical trial investigating serial intravenous ketamine infusions for TRD, conducted from January 2021 to August 2022, were retrospectively reviewed. A broad literature search was undertaken to identify potentially underrecognized examples of imprinting with both serotonergic and atypical psychedelics, as well as analogous cognitive processes and neural mechanisms.

Results: In naturalistic single-subject experiments of a 28-year-old female and a 34-year-old male, subjective ketamine experiences were significantly altered by varying exposures to particular forms of digital media in the days preceding treatments. Higher levels of media exposure reduced the mystical/emotional qualities of subsequent psychedelic ketamine experiences, overpowering standard intention-setting practices and altering therapeutic outcomes. Qualitative data from 24 additional patients yielded eight further spontaneous reports of past environmental exposures manifesting as visual hallucinations during ketamine experiences. We identified similar examples of imprinting with diverse psychoactive drugs in past publications, including in the first-ever report of ketamine in human subjects, as well as analogous processes known to underly dreaming.

Conclusions/interpretation: Past environmental exposures can significantly influence the phenomenology and therapeutic outcomes of psychedelic experiences, yet are underrecognized and understudied. To facilitate future research, we propose expanding the contextual model of psychedelic drug actions to incorporate imprinting, a novel concept that may aid clinicians, patients, and researchers to better understand psychedelic drug effects.

Clinical trial registration: ClinicalTrials.gov, identifier NCT04701866.

KEYWORDS

psychedelics, ketamine, set and setting, hallucinations, imprinting, extra-pharmacological model, dreaming, preparation

Introduction

Psychedelic-assisted psychotherapies are currently generating tremendous scientific, corporate, and public interest, prompting many to refer to an ongoing "second wave" of psychedelic research. Recent reviews have identified promising evidence for psychedelic therapies in depression and other psychiatric disorders (Chi and Gold, 2020; Rosenblat et al., 2022), and more than 100 psychedelic clinical trials have been registered on clinicaltrials.gov since 2007—the majority in the past six years (Kurtz et al., 2021).

Given this level of interest, understanding the effects of psychedelic drugs is of critical scientific and clinical importance. While psychedelic-induced alterations of consciousness are well known to be influenced by current-moment environments, the potential influences of *past* environments have received very little attention.

Much like serotonergic psychedelics, the N-methyl-D-aspartate (NMDA) antagonist ketamine has been shown to produce rapid and potent antidepressant effects at subanesthetic doses (McIntyre et al., 2021). Public and private ketamine services have arisen around the world and the s-enantiomer of ketamine, esketamine, has been approved as a novel treatment for Treatment-Resistant Depression (TRD) in the United-States, Canada, and Europe (Walsh et al., 2022). Although the altered states of consciousness that ketamine induce are typically referred to as "dissociative" (Schartner et al., 2017; McIntyre et al., 2021), their phenomenology and neural basis overlap significantly with serotonergic psychedelics (Studerus et al., 2010).

Similar to the serotonergic psychedelics, ketamine has been employed as an adjunct to psychotherapy in psychedelic models of care since the 1970s (Kolp et al., 2014; Greenway et al., 2020). Though psychedelic approaches to ketamine are far from universal, some recent evidence suggests that ketamine's psychiatric benefits are at least partially mediated by its capacity to facilitate mystical-type experiences, similar to those induced by serotonergic psychedelics (Dakwar et al., 2018; Dore et al., 2019; Garel et al., 2022).

Irrespective of the substance, a key aspect of the psychedelic-assisted psychotherapy approach since at least the 1960s is the concept of "set and setting" (Leary et al., 1963). This guiding axiom describes how psychedelic experiences are shaped by current-moment "mindsets" (expectations, intentions, and personality traits) and "settings" (physical, social, and cultural environments) (Carhart-Harris et al., 2018). Optimizing sets and settings is thus a key aim of the preparation and treatment phases of psychedelic therapy, due to posited therapeutic impacts (Pahnke et al., 1970; Johnson et al., 2008). Indeed, given that psychedelic drugs have been described as "amplifiers" of contextual influences, one may expect even greater benefits with patient-tailored approaches to psychedelic therapies versus conventional psychiatric treatments (Swift et al., 2018).

How set and setting might be optimized is largely an open question and current practices vary greatly (Hartogsohn, 2017). Leading psychedelic protocols recommend that preparation include psychoeducation about drug effects, efforts to enhance therapeutic alliances, and the establishment of behavioral, psychological, and/or spiritual therapeutic intentions (Johnson et al., 2008; Watts and Luoma, 2020). Additional practices can be found in the first wave of psychedelic research; for instance, Timothy Leary (who coined the term set and setting) recommended meditation, introspection, and self-examination (Leary et al., 2007; Horowitz et al., 2018). Further distinct preparatory activities can be found in traditional psychedelic practices, including fasting, dream incubation, and sexual abstinence (Winkelman, 2021). However, in spite of decades and even centuries of accumulating knowledge, there have been few modern experimental examinations of set and setting and there is little consensus regarding best practices (Griffiths et al., 2018; Golden et al., 2022).

One reason for this lack of consensus is that psychedelic drug effects—and, by extension, the effects of preparatory practices—are heavily influenced by the sociocultural contexts in which they are embedded (Lifshitz et al., 2018). Researchers and clinicians seeking to understand and optimize psychedelic drug effects must therefore grapple with the complex interactions between a given individual and their society at large.

In Western societies, there have been major sociocultural shifts since psychedelic therapy practices were largely developed in the mid-20th century—especially regarding the quantities and patterns of media exposure. This includes much more time now being spent on personal electronic devices and less on print media or outdoors (Twenge et al., 2019), and the appearance of relatively new digital-behavioral phenomena such as "binge-watching" and "doomscrolling" (Starosta and Izydorczyk, 2020; Sharma et al., 2022).

Media exposures are known to influence conscious and unconscious minds in both immediate and delayed ways. For example, video game and television content frequently appear in mind wandering, daydreaming episodes, and dreams (Stickgold et al., 2001; Nielsen and Stenstrom, 2005; Gackenbach et al., 2011). Although dreams have long served as analogies to psychedelic experiences (Hartogsohn, 2016; Kraehenmann, 2017; Greenway et al., 2020), no studies to our knowledge have investigated whether digital media, or indeed other forms of environmental stimuli, may similarly influence later psychedelic drug experiences.

This article provides preliminary evidence from several independent lines of inquiry to argue that environmental exposures—especially digital media—can exert significant influences on subsequent psychedelic experiences, days or more later. Based on our recent clinical results from patients receiving ketamine in a psychedelic model, prior phenomenological reports of a variety of serotonergic and atypical psychedelic experiences, and research on cognitive processes underlying dreaming, we propose expanding the current model of psychedelic "set and setting" to account for such delayed influences with the concept of imprinting. We provide a theoretical framework for imprinting and discuss scientific and clinical implications.

Materials and methods

We present qualitative and quantitative data from 26 patients who received a series of intravenous ketamine-assisted psychotherapy treatments over four weeks for TRD in the context of a clinical trial investigating the effects of music (ClinicalTrials.gov: NCT04701866). This randomized controlled trial was conducted from January 2021 to August 2022 at two McGill University hospitals in Montreal, Quebec, Canada. All ketamine infusions (0.5 mg/kg bodyweight, infused over 40 minutes) were administered with key aspects of psychedelic therapy, including preparative psychotherapy, treatment sessions that included psychological support and eyeshades, and follow-up integration therapy sessions (Johnson et al., 2008).

The study involved the structured collection of qualitative data for 26 of 32 enrolled patients, including audio recordings of ketamine treatment sessions and semi-structured phenomenological interviews conducted two weeks following the treatment course. A variety of validated scales were administered following each treatment to characterize patient experiences in this trial, including the Mystical Experience Questionnaire (MEQ) (Barrett et al., 2015), the results of which are reported for the two single-subject series. Manuscripts reporting the full trial results are currently under preparation.

We focus on two single-subject cases that involved varying quantities of exposure to specific forms of media, in addition to further examples of imprinting identified by reviewing the transcripts of treatment sessions and interviews of the 24 additional patients for whom qualitative data was collected. All patients consented to participate in this trial, approved by the research ethics boards at the Douglas Mental Health University Institute (#IUSMD-20-28) and the Jewish General Hospital (#MEO-14-2022-2854), and both single-subject participants gave additional written consent for their results to be detailed in this article. In addition to the eight-week follow-up of the clinical trial, these two patients were briefly interviewed by phone 8–12 months after the trial to discuss the long-term consequences of their experiences described below.

In the aim of identifying past unrecognized examples of imprinting, we searched the PubMed, Embase, and APA PsycInfo databases for studies published in English or French prior to October 1st, 2022 using the following query: (Psychedelic$ or Psilocybin or Lysergic acid diethylamide or LSD or Ibogaine or Mescalin$ or Dimethyltryptamine or Salvia or 3,4-Methylenedioxymethamphetamine or MDMA or Ketamine) and (Phenomen* or Hallucinat* or image$ or scene$) and (Screen$ or Television$ or Picture$ or Film$ or Movie$ or Cartoon$ or Disney or priming). Abstracts of the 2084 retrieved articles were screened by at least two authors and relevant article were retrieved. Additional articles were identified by iteratively reviewing references and conducting related web searches. A consensus amongst all authors was reached for all presented potential examples of imprinting.

Results

Patient 1— "hijacking"

A 28-year-old female, diagnosed with TRD following 14 years of unsuccessful pharmacotherapy and psychotherapy, initially received two ketamine infusions over one week while hospitalized for depression and suicidal ideation. She was also known for generalized anxiety disorder, type one diabetes mellitus, and a chronic neuromuscular condition, and no lifetime history of self-harm or suicide attempts During this hospitalization, the patient had nearly no access to electronic devices, including in the weeks prior to her first ketamine infusion.

The patient responded robustly to these first two ketamine treatments and described them as having many typical features of psychedelic therapy: feelings of connection, introspection, emotional processing, and mysticism. They resulted in rapid and significant improvements in depressive symptoms and suicidality, and the patient was discharged after six weeks in hospital with the plan for further infusions if necessary.

Six months later, as an outpatient enrolled in the aforementioned clinical trial, she received a course of six ketamine infusions over four weeks with the same team, a nearly identical treatment protocol, and a similar treatment setting. Despite reporting a similar *degree* of psychedelic effects, her first outpatient ketamine treatment was described as having remarkably different phenomenology. Namely, the patient reported that involuntary visual hallucinations of Disney iconography "hijacked" her experience, greatly diminishing its mystical and emotional qualities.

As demonstrated in the following verbatim quotes from the session's recordings, the discrepancies between this treatment and the two that she received while hospitalized were a source of significant disappointment and frustration for the patient:

> Patient 1: "*And then I just saw Disney stuff. I don't want to! I didn't want to!*"

> Therapist: *"This is your mind, you can't really control it."*
> Patient 1: *"It hijacked it! And it's my fault for always scrolling through the 'pins'. . . I'm just annoyed that I felt like I had the Band-Aid on. It felt like I almost ended up going to important things and then Disney frickin' covered it up."*

As evidenced by this excerpt, the patient readily drew a link between this treatment's visual images of Disney characters and her previously undisclosed habit of trading commemorative Disney pins on a social media forum. She described spending approximately six hours per day on this digital activity since many years, with the notable exception of her month-long hospitalization when she received her first two ketamine infusions. Of note, she also described various Disney-themed physical objects in her home environment though precise details are not available.

Given her disappointment with this experience and its lack of emotional or mystical content, a collaborative decision was made that she would reduce her consumption of online Disney content in preparation for the subsequent ketamine treatments without any change to her physical environment. She reported thereafter reducing her daily online exposure to Disney content to approximately zero. Except for her next treatment (less than two days later), the phenomenology of her subsequent experiences over the following weeks shifted significantly, coming to resemble her initial two ketamine infusions in terms of visual phenomena and emotional/mystical content. As **Figure 1** demonstrates, she reported significant increases in MEQ scores including two "complete" mystical experiences (> 60% of max score on all subscales) (Barrett et al., 2015) during these treatments—and no Disney imagery.

In her qualitative interview two weeks after the series of psychedelic ketamine treatments, the patient described an important insight resulting from the manipulation of her media habits:

> "*Well, before the ketamine, I was shopping for Disney pins, like, a lot of the day, and then I felt like the first treatment was ruined because I just saw Disney and stuff, and now I'm aware when I'm doing that to numb myself, basically, and to cope, but I'm not going to lie, I'm doing it right now. But at least when I'm doing it, I know.*"

As described, the patient reported resuming her daily habit of Disney pin trading after her final ketamine treatment, albeit at a markedly reduced quantity of about one hour per day. When contacted one year following the ketamine treatments, the patient reported that this significant behavioural change persisted. Although the overall benefits of ketamine against her anxiety, depression, and suicidality were modest and short-lived, her insight regarding the effects of digital media on her mind was described as profound and lasting.

Patient 2— "a pixelated consciousness"

A 34-year old man with TRD, in addition to morbid obesity and obstructive sleep apnea, received a series of six ketamine infusions over four weeks as an outpatient after 18 years of poor responses to numerous medications and psychotherapies. On evaluation, he described spending nearly all his waking hours outside of work playing various video games, regularly up to 16 h per day.

This patient's first three ketamine experiences were characterized by vivid visual hallucinations described as "videogame-like" in both content and form. I.e., he reported that most of his time during the infusion was spent reliving recent game experiences and he described "pixelated" complex hallucinations that strongly resembled the aesthetic of video games like Minecraft, which he had played frequently in the days preceding the treatment sessions. He summed up his experiences as evidence that he had "a pixelated consciousness".

Unlike the first patient, this patient was not immediately distressed by these experiences. He instead described them as "fun"—much like his experience of the videogames themselves, which he recognized as their likely source. However, like the first patient, he spontaneously drew links between these experiences and negative aspects of his lifestyle, stating: ". . .all I do is distract myself, play, and try to have fun." He did not attribute significant meaning to these three ketamine experiences, and his MEQ scores were low throughout.

Like the first patient, this second patient and his therapists decided to experiment with reducing his video game playing to check if the subsequent ketamine experiences might become more personally meaningful and/or mystical-like, and ultimately more beneficial. He thus reduced his consumption by roughly half, for the four days prior to his fourth treatment. The result was a more emotionally intense ketamine experience that featured some video game imagery, but also marked feelings of grief related to past relationships. I.e., the patient reported vividly re-experiencing a series of events that led to the end of a friendship, which evoked strong feelings of shame and regret. The MEQ score remained low.

Despite this fourth treatment being more psychologically challenging, the patient was encouraged by its greater degree of meaningful autobiographical content and agreed to further reduce his video game exposure in preparation for the two remaining ketamine experiences. Thus, for the first time in roughly 20 years, he entirely stopped playing videos for multiple days, instead spending time with family and friends. Subsequently, his fifth and sixth ketamine experiences differed dramatically from the prior infusions, being characterized by intense visual hallucinations that reflected prominent themes of nature and his relationships which were no longer reported to be videogame-like or pixelated in form. His MEQ scores for these treatments roughly doubled.

On follow-up, eight months later, the patient reported significant levels of video game playing but also active engagement in weekly psychodynamic psychotherapy (that had been initiated alongside the ketamine treatments), persistent reductions in symptoms of depression and anxiety, and an increased "interest in [his] subconscious mind".

Additional spontaneous patient reports of imprinting

In addition to these cases, which were exceptional in terms of relatively extreme quantities of media exposure, a review of

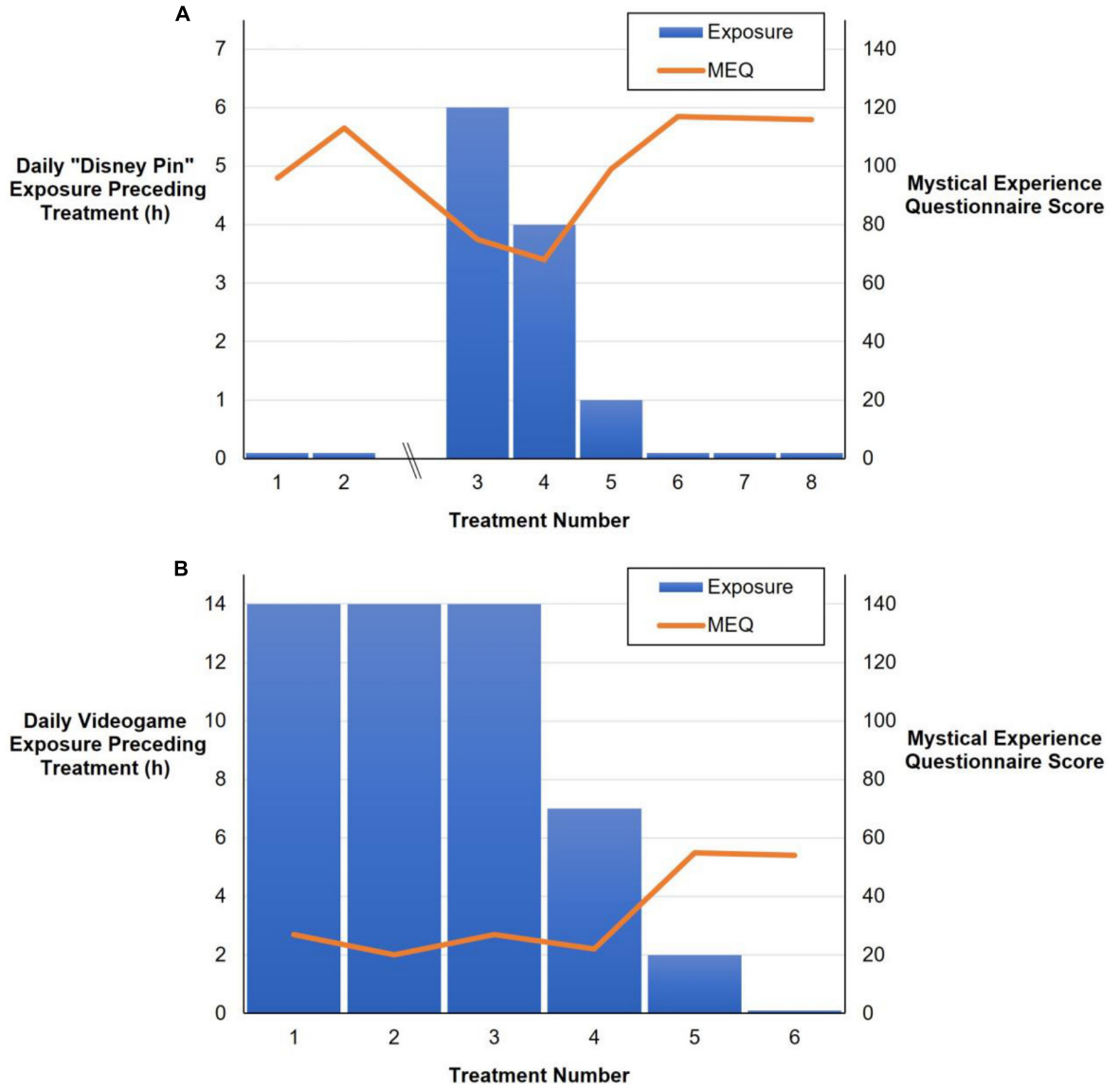

FIGURE 1
Daily hours of particular media exposure (blue bars) in the days preceding ketamine treatments and Mystical Experience Questionnaire (MEQ) total scores (orange line) for patient 1 **(A)** and patient 2 **(B)**.

transcripts from 24 patients receiving the same ketamine treatment protocol yielded further examples of imprinting from eight other patients. These ten patients with unipolar or bipolar TRD ranged in ages from 27 to 63 and were characterized by substantial psychiatric comorbidity and chronicity. Their sociodemographic and baseline characteristics are provided in **Supplementary Table 1** of the **Supplementary material**.

The supporting patient quotes are summarized in **Table 1** with more detailed transcripts provided in **Supplementary Table 2**. All instances were defined by spontaneous descriptions of (mostly visual) hallucinations during ketamine experiences which vividly reflected environmental exposures of the preceding days. The majority of these exposures were digital in nature, with the exception of three examples of imprinting from recent real-life environments: a museum visit, time in nature, and a visit to a city.

Discussion

Imprinting and the extra-pharmacological model

The extra-pharmacological model of psychedelics posits that drug effects are strongly influenced by the immediate environment, i.e., set and setting (Carhart-Harris and Nutt, 2017; Lifshitz et al., 2018). In this article, we present recent evidence from two single-subject case series and eight additional patients suggesting that environmental exposures can also exert pronounced delayed effects on drug phenomenology.

Both single-subject series above were notable for the quantity of daily exposure to particular forms of digital media, as well as their impact on ketamine phenomenology and therapeutic effects. The

TABLE 1 Examples of imprinting from the excerpts of eight different patients describing their ketamine treatment experiences.

Recent exposure	Supporting quote
Video	*"I was on the outside. I was looking down; I could see the set from the top. And they were shooting scenes of Handmaid's tale. . . It's a TV show that I'm watching right now."*
Video	*"It was really beautiful, but there was one strange thing. I kept seeing faces from that show my sister loves. . . She always makes me watch it."*
Video	*"I did see myself as a fish. . . Yesterday I watched 'Luca', which is a sea monster movie"*
Video	*"I just felt like I was in a pod in space and I was thinking "Oh, it's like that movie. . . that I just watched."*
Video	*"It was a moving performance. I love dance and I always watch ballet videos on my cell phone. It was like being in a show."*
Countryside	*"Well, in my head I saw the country environment again, the fields. . . I also hear the sounds of little birds, the same then when I was lying in my bed in my trailer yesterday."*
City	*"We were in colors, shapes, much more urban. . . That's because we talked a lot about urbanism in the car on the way there, too."*
Museum	*"I was definitely in the museum, again, but.in the paintings. . . I was in the art."*

first case resembled an n-of-1 trial of A-B-A design (Lillie et al., 2011)—a pragmatic research design that has been recommended for studying psychedelic drug effects (Carhart-Harris et al., 2022)—where both exposure to Disney social media content and its subsequent manifestations in psychedelic experiences were absent, then present, then again absent across eight ketamine sessions over six months.

In the second single-subject series, video game-playing was gradually decreased over several weeks rather than abruptly stopped, with the results suggesting a potential "dose-response relationship". I.e., a reduction in exposure to video games by approximately 50% reduced their impact on visual hallucination content and form, and several days of abstention produced two experiences free of videogame imagery with significantly increased MEQ scores. The findings of these two single-subject series led to the review of other patient transcripts and the identification of additional examples of imprinting where both the quantities of identified environmental exposures and their manifestations were more subtle.

Based on these results, we propose expanding the current extra-pharmacological model of psychedelic drug effects to account for delayed environmental influences with the novel concept of imprinting (**Figure 2**). We define imprinting as a phenomenon whereby environmental exposures prior to psychedelic sessions involuntarily and spontaneously manifest in the content and/or form of the perceptual changes of the experiences. All of the above examples of imprinting were only, or primarily, visual hallucinations, which could be described with a variety of existing terms including closed-eyes visuals, complex hallucinations, or pseudo-hallucinations (given that they were not confused with reality) (Blom, 2010). In the following section, we compare imprinting to related but distinct processes.

Distinctions between imprinting and prior concepts

The concept of imprinting has analogies to other previously described phenomena such as priming and suggestion, which have been used in hypnosis and previous psychedelic therapies (Levine and Ludwig, 1966; Oakley and Halligan, 2013). Hypnotic suggestions are defined as declarations made to induce, or made during, hypnotic states that prescribe changes in behavior, cognition or perceptual experience that do not require volitional engagement of the participant to occur (Oakley and Halligan, 2013). Suggestion is an important comparator to imprinting given that it also occurs without voluntary engagement and because increased suggestibility has been demonstrated both in hypnotic states and during the acute effects of a wide variety of psychoactive drugs, including the serotonergic psychedelic LSD, cannabis, nitrous oxide, and ketamine (at least in some individuals) (Kelly et al., 1978; Whalley and Brooks, 2009; Carhart-Harris et al., 2015; Patterson et al., 2018). Indeed, hypnosis and suggestion have been explicitly utilized to shape psychedelic experiences to increase therapeutic benefits in an approach known as "hypnodelic therapy", first described in the first wave of psychedelic research (Levine and Ludwig, 1966).

A major difference between imprinting versus priming or suggestion is that, in the case of our examples, the stimuli were encountered naturalistically and were not intended nor expected to be imprinted by patient or therapists. Expectancy, therefore, plays a less important role in imprinting relative to hypnotic suggestion. We also emphasize that imprinting takes place well before the experience of an altered state consciousness (drug- or hypnosis-induced). I.e., in contrast to hypnotic suggestion that generally results from immediate-environment *external* stimuli (Oakley and Halligan, 2013), imprinting is the product of past stimuli having been *internalized*—or imprinted, in other words.

Another concept from the psychedelic literature that resembles imprinting is that of "eidetic images", or "eidetic memory images": images "seen" with eyes closed during psychedelic experiences that are distinguished by their vividness and even photo- or film-like qualities (Masters and Houston, 2000). These terms are not commonly used at present but were discussed at length in the landmark 1966 text, *The Varieties of the Psychedelic Experience*, which defined them as images of persons, animals, architecture, and landscapes "previously recorded by the brain or, in some cases, possibly a part of the phylogenetic (or "Racial") inheritance" (Masters and Houston, 2000). We distinguish eidetic images from imprinting in that the former are often fantastical amalgamations of multiple memories which are understood to be abstract and symbolic in nature (Masters and Houston, 2000), rather than straightforward manifestations of identifiable environmental exposures in psychedelic hallucination form or content.

The closest concept to imprinting, to our knowledge, is the uncommon pathological condition known as palinopsia, which refers to the persistence or recurrence of visual images after the stimulus has been removed and has two distinct subtypes

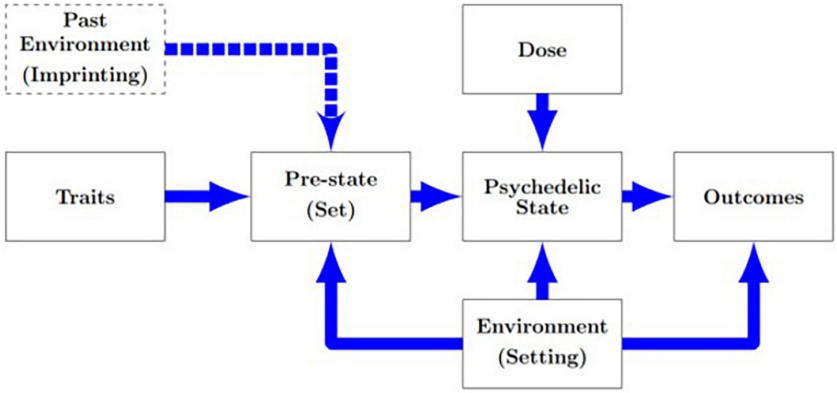

FIGURE 2
Proposed modification of the extra-pharmacological model of psychedelic drug actions (Carhart-Harris and Nutt, 2017) to incorporate imprinting effects. I.e., that in addition to current-moment environments, past sensorial exposures exert time-lagged influences on (mind)sets and psychedelic drug experiences.

(Gersztenkorn and Lee, 2015). Illusory palinopsia refers to indistinct images occurring in the same location of the visual field as an external stimulus, influenced by ambient light and motion, similar to physiological afterimages. Hallucinatory palinopsia refers to previously observed visual images or short scenes being visually hallucinated with remarkable fidelity and clarity for seconds, minutes, hours, or even days.

Although palinopsia overlaps significantly with imprinting and there are possible neural commonalities, there are also important differences. For one, hallucinatory palinopsia has never been associated with psychedelic drugs, and illusory palinopsia has only been considered in the context of post-acute psychedelic effects like hallucinogen persisting perception disorder (Gersztenkorn and Lee, 2015; Schimansky et al., 2022). Rather, palinopsia most commonly arises from posterior cortical lesions, seizures, and other central nervous system pathologies. Secondly, we define imprinting as a *process* and hypothesize that the underlying factors are identifiable and measurable, as discussed below. In contrast, palinopsia is a *symptom*, and the factors influencing the content of hallucinatory palinopsia are not known. Thirdly, and crucially, we provide examples of imprinting that go beyond re-experiencing certain images or scenes as they were previously encountered, but instead include the apparent generation of novel content whose *form* resembles previous environmental exposures. For instance, our second patient described a series of visual hallucinations characterized by unfamiliar content but a familiar "pixelated" form that strongly resembled a particular videogame's aesthetic.

For these reasons, we believe that imprinting is a phenomenon distinct from suggestive priming, eidetic images, and palinopsia. Rather, as discussed below, we propose that dreaming as the most analogous process.

Unimportant or underrecognized? Further evidence for imprinting with ketamine

Despite decades to centuries of research on psychedelic drug phenomenology, this report is, to our knowledge, the first explicit description of imprinting effects. This raises the question: is this effect unimportant, or has it been underrecognized? One argument in support of the latter is that our psychedelic-ketamine protocol has unique aspects that facilitated the recognition of imprinting effects.

Most psychedelic ketamine or serotonergic-psychedelic protocols in the clinical literature involve only one or two dosing sessions (Griffiths et al., 2018; Watts and Luoma, 2020; Carhart-Harris et al., 2021). In contrast, our protocol employed at least six ketamine treatments administered over at least four weeks, yielding roughly the same amount of time in an altered state of consciousness as two doses of psilocybin, but more spread out in time. While briefer but more frequent treatments may have disadvantages—for instance, requiring more patient visits—this treatment rhythm permitted the manipulation of media exposure, and the relatively long active treatment length aided both patients and clinicians in observing links between recent environmental exposures and a later treatment's phenomenology. Indeed, single-subject experiments may be particularly promising approaches for the study of contextual factors in psychedelic therapy for much the same reasons (Lillie et al., 2011; Carhart-Harris et al., 2022).

Once aware of imprinting effects, we were able to retrospectively identify numerous examples in the phenomenological reports of our patients as well as unrecognized examples in the broader literature. To take one striking example, the first-ever report on the effects of ketamine in human subjects, published in 1965, described patient experiences that are consistent with imprinting:

> *"At times some of the subjects had vivid dreamlike experiences or frank hallucinations. Some of these involved the recall of television programs or motion pictures seen a few days before. . . Some of these phenomena were so real that the subjects could not be certain that they had not actually occurred."* (Domino et al., 1965)

Further, therapeutic guidance for ketamine-assisted psychotherapy implicitly suggests that at least some therapists have developed an awareness of imprinting and its therapeutic

importance. In a 2014 publication, one of the pioneers of this approach, Eli Kolp, "advise[d] de-stressing the mind by limiting screen time beyond that which is required for each individual participant's employment" (no more than two hours per day) in order to increase the likelihood of "transcendental experiences." (Kolp et al., 2014). Although not directly stated as such, this advice is consistent with minimizing imprinting by digital media in order to promote more meaningful ketamine experiences, in perfect alignment with our two single-subject studies.

Is imprinting unique to ketamine?

Evidence of imprinting can also be found in the psychedelic literature beyond ketamine. One of the first modern psychedelic phenomenological studies, exploring the experiences of 15 volunteers receiving psilocybin, identified nine broad categories of experiences (Turton et al., 2015). One of these categories, "Effect of Memories", was defined as "recent memories influencing the contents of their experience, similar to the influence of recent thoughts and experiences on dream content." For example, one participant reported: "I've just been on holiday in Tunisia. . . [I] kept seeing Tunisian-Moroccan imagery in my mind." Three of 15 volunteers reported such effects which, despite being labeled as memories, may well be better conceptualized as imprinting. I.e., the example of Tunisian-Moroccan imagery was not described as remembering or reliving, but rather the spontaneous appearance of related visual hallucinations.

Another potential example of imprinting can be found in one of the definitive texts on the phenomenology of ayahuasca (Shanon, 2003, p. 96), a serotonergic psychedelic brew. Based on the authors' extensive experience, this work proposes five "styles" of ayahuasca experiences of which the first is reminiscent of our first single-subject's experience of Disney imagery:

> *"Even without being asked about the style of the Ayahuasca visualizations, informants mentioned that what they saw resembled cartoons and animated movies similar to those encountered in pop art. Quite a few indicated that the visions reminded them of Disney-like designs."*

In addition to these ayahuasca visions, similar descriptions of Disney iconography have been reported with LSD and other classical psychedelics (Masters and Houston, 2000). These accounts could simply reflect Disney being used as a shared cultural reference point or, conversely, that psychedelic drug experiences were shaped by past Disney imagery exposure as was the case for our first patient above.

Another suggestive example of imprinting comes from a phenomenological study of users of ibogaine, a hallucinogenic substance that has also received attention for therapeutic applications (Heink et al., 2017). Forty-six percent of 27 participants undergoing facilitated ibogaine treatment ceremonies reported prominent visual hallucinations of "television screens" during their experiences. Although the details of these hallucinations of screens were not reported, this phenomenology contrasts significantly with ethnographic reports of ibogaine ceremonies in Africa's Bwiti communities, which are generally notable for movement within landscapes and interrogatory verbal exchanges with ancestors and archetypal beings (Fernandez, 2020). We propose that this discrepancy may well reflect imprinting of television screen exposure in the survey responders, a population consisting almost entirely (96%) of people who identified as White/Caucasian/European (Heink et al., 2017).

Outside of the academic literature, other probable examples of imprinting effects can be found in online accounts of drug experiences. For instance, although 3,4-Methylenedioxymethamphetamine (MDMA) is not typically associated with prominent visual hallucinations, one online "phenomenological inventory" described a variety of the author's closed-eye visuals (Ball, 2018). Several such descriptions are strongly suggestive of imprinting effects, including a vivid film-like hallucination of John F. Kennedy's assassination and a hallucination of a hand changing the "visual scene" by "swiping left", an experience the author describes as ". . .clearly related to using a touch-screen mobile device".

Dreaming as a mechanistic model for imprinting

Dreams have long served as analogies to serotonergic psychedelic and ketamine experiences (e.g., "ketamine dreams") due to both phenomenological and neural overlap (Hartogsohn, 2017; Kraehenmann, 2017). Indeed, one of the first names proposed for serotonergic psychedelics was "oneirogens"—drugs that produce dreams—a label that has also been proposed for a variety of other psychedelic drugs (Goutarel et al., 1993; Greenway et al., 2020). Perhaps unsurprisingly then, analogous processes to imprinting can be found in the study of dreaming.

A wide body of literature supports the popular notion that dream content often reflects recent environmental exposures, via a process known as dream incorporation. Children's nightmares for example, shifted from "bogeyman" content in the 1920s to film characters in the 90s, with video game imagery arising in the early 2000s (Schredl et al., 2008). Dream incorporation has been divided into two types: "day residue", a term coined by Freud in 1898 referring to memories from the previous day appearing in dreams (Strachey and Freud, 2010), and the "dream-lag effect", whereby dream content is influenced by stimuli from days or even years before (Nielsen and Powell, 1992; Stenstrom et al., 2012).

The day residue effect has been robustly documented in observational and experimental studies of both night-time dreams and hypnagogic hallucinations (Nielsen, 2017). One notable study even provided evidence that this effect does not require conscious memory formation: exposure to the video game Tetris led to frequent reports of Tetris-like shapes in the hypnagogic visuals of temporal lobe amnesiacs lacking conscious memories of the intervention, much like healthy controls (Stickgold et al., 2000).

In addition to such direct effects, exposure to specific forms of media can also exert more subtle and time-lagged influences (Solomonova et al., 2015). In one study, exposure to a virtual reality flying-based game not only resulted in dreams of that game's content over the next week, but also increased the frequency of a broader variety of flying dreams (Picard-Deland et al., 2020). Indeed, beyond dream *content*, the *form* of dreams can be markedly

TABLE 2 Hypothesized factors influencing the strength and nature of imprinting effects for a given stimulus.

Factor	Relationship to increased imprinting
Distance in time	More recent stimulus
Duration/ Repetition	Greater duration and repetition of stimulus
Homogeneity	Greater homogeneity of stimulus
Form/Intensity	More information-rich and immersive stimuli, particularly audiovisual electronic media
Emotional arousal/Valence	Greater arousal associated with stimulus

influenced by even distant media exposure—e.g., true greyscale dreams occur almost exclusively in people with significant and early histories of black-and-white media exposure (Murzyn, 2008).

Day residue typically consists of memory elements of banal but potentially sensorily salient experiences, typically rated by dreamers themselves as personally unimportant (Vallat et al., 2017). On the other hand, the dream-lag effect more often incorporates personally relevant details of lived experiences (van Rijn et al., 2015). In hypnagogic experiences, for example, references to films have manifested due to both day residues and remote memories, dating back days or even weeks (Stenstrom et al., 2012).

In other words, the content, themes, and aesthetic qualities of dreams are known to be shaped by recent and distant environmental stimuli in a variety of ways, and similar processes may be observed in the various examples of imprinting provided above. For instance, video game exposure leading to "pixelated" forms of visual hallucinations in the second single-subject patient resembles the way that past exposure to black and white media can result in grayscale dreams. Similarly, repeated and early exposure to Disney iconography may partially explain why serotonergic psychedelic experiences are commonly Disney-like (Masters and Houston, 2000; Shanon, 2003), regardless of recent exposure.

Factors influencing imprinting

Based on the scientific literature of dream incorporation, and memory formation more broadly, we provide preliminary hypotheses regarding the factors that may influence the intensity and frequency of imprinting following a particular exposure (**Table 2**).

As is the case for dream incorporation, memory, and priming effects of perceptual stimuli on subsequent stimuli, we hypothesize that imprinting effects are most likely to result from recent and prolonged exposure to a homogenous stimulus (Lavoie and O'Connor, 2013; Solomonova et al., 2015; Pearson, 2019). This is evident in both single-subject series above, where significant imprinting resulted from 6 to 18 h of daily exposure to one particular form of media, and then faded within days of that exposure being reduced or removed.

Moreover, the form/intensity of a given exposure likely influences imprinting; indeed, nearly all our examples involved visual phenomena attributed to forms of electronic media exposures. This agrees with evidence from dreaming that a stimulus's information density and immersiveness influence its impact. For example, an experimental study found that high-fidelity video goggles with surround-sound headphones exerted greater influences on subsequent dream content than the same content delivered by lower quality, less immersive equipment (Gackenbach et al., 2011). Similarly, in the psychedelic literature, one whole-brain magnetoencephalography study found that video exposure may be uniquely powerful at "driving" neurodynamics, relative to music or the absence of external audiovisual stimuli, as reflected in brain entropy changes (Mediano et al., 2020).

An alternative possibility is that our examples of imprinting from digital media were also particularly salient—and thus particularly likely to be reported and recognized—because the imprinted content clashed with expectations for the ketamine experiences. E.g., images of Disney cartoons were interpreted as "hijacking" the experience for our first single-subject series given her expectations for mystical-type experiences.

Finally, experiences associated with greater emotional arousal and non-neutral valence are more likely to lead to dream incorporation (de Koninck and Koulack, 1975), as well as memory formation (Lavoie and O'Connor, 2013). This finding is likely equally applicable to imprinting; most of our examples involved stimuli that evoked positive emotions. On the other hand, this apparent relationship may simply reflect the fact that pleasurable media are more likely to be consumed in greater quantities.

Imprinting, predictive processing, and the anarchic brain

The phenomenon of imprinting is harmonious with—and provides some support for—the leading neural model of psychedelic drug actions: the relaxed beliefs under psychedelics (REBUS) model (Carhart-Harris and Friston, 2019). REBUS postulates that psychedelic drugs weaken the hierarchical control of high-level processes over neural information transmission. Constraints on lower-level neural systems are thus decreased, yielding an increase in bottom-up signaling, potentially due to disruption of the brain's default mode network (DMN).

Within the REBUS framework, imprinting may be understood as the process by which recent and prolonged (low-level) environmental exposures produce overweighted intermediate-level perceptual priors (i.e., imprints). Under the effects of psychedelics, these imprints shape the drug-increased sensory prediction errors resulting from reduced higher-level constraints, and thereby acutely manifest in conscious awareness.

To take the example of the second patient described above, near-constant exposure to pixelated videogame imagery may have temporarily created a strong attractor for the brain to interpret visual stimuli in pixelated patterns. Under the effects of ketamine, this previously inappreciable overweighted prior (imprint) of pixelation now vividly manifests as visual Minecraft-like hallucinations. Over the subsequent weeks, with reduced videogame exposure, the "pixelated prior" gradually fades in intensity, resulting in weaker effects on prediction errors and ketamine phenomenology. This fading allows for other intermediate-level priors (like past emotional experiences) to more strongly shape the perceptual prediction errors during the ketamine experience—leading to, in this case, more meaningful

and mystical experiences. Such mechanisms could be investigated by neuroimaging experiments designed, for instance, to quantify the effects of previous environmental exposures on brain entropy (Mediano et al., 2020) or on resting-state functional connectivity (McCulloch et al., 2022).

Nearly all of our identified examples of imprinting are visual, which is congruent with the DMN being particularly involved in contextualizing visual processing (Huang and Sereno, 2013). Further, the fact that imprinted content arises from prior environmental exposures adds support to the REBUS model's emphasis on psychedelic drug actions on intermediate and high neural levels, rather than lower levels such as those involved with current-moment visual perception.

Clinical and scientific implications

We have provided preliminary examples across a variety of hallucinogenic drugs where the imprinting of various environmental exposures influenced later drug experiences in a delayed manner, including two examples with notable therapeutic consequences. In these single-subject series, reducing digital media exposures in preparation for subsequent ketamine treatments led to experiences that were more autobiographical and more mystical-like, and experienced as more beneficial—in agreement with research suggesting greater benefits with mystical or "emotional breakthrough" psychedelic experiences (Johnson et al., 2008; Dakwar et al., 2018; Griffiths et al., 2018). Accordingly, we believe that the concept of imprinting has utility for psychedelic-assisted therapy, particularly in terms of optimizing preparatory practices.

Despite a general consensus regarding some goals of preparation—to increase the likelihood of safe and beneficial psychedelic experiences (Johnson et al., 2008; Watts and Luoma, 2020)—actual practices vary greatly. Our results suggest that, when establishing therapeutic intentions prior to a psychedelic experience, it is vital to consider how behavioural patterns may support or interfere with those intentions. Excessive consumption of digital entertainment may be imprinted such that psychedelic experiences are more reflective of one's media habits than one's lived experiences or relationships, regardless of underlying intentions.

Our results provide some support for the benefits of preparatory practices like meditation and introspection that have been recommended by experts for decades (Leary et al., 1963; Kolp et al., 2014). In addition to direct benefits, engaging in these activities may lead to reduced time spent on countertherapeutic activities like excessive digital media consumption. As an illustration, in the only modern psychedelic study to experimentally manipulate preparatory practices to our knowledge, 50 healthy participants were randomized to receive either standard or high levels of spiritual support to facilitate the development of spiritual practices like meditation during a psilocybin treatment protocol (Griffiths et al., 2018). The group receiving additional support engaged in greater amounts of meditation practice, and reported psilocybin experiences that were somewhat more mystical and emotional (as evidenced by significantly greater rates of crying during the treatment session).

This study's findings may not only reflect that the high-support group dedicated *more* time to spiritual practices, but also that they likely spent *less* time on digital media. Indeed, in our two single-subject series, psychedelic experiences with greater emotional and mystical content resulted from simply less time spent on digital media without any reported increase in time spent on spiritual practices. To evaluate this possibility, future studies should examine how various psychedelic therapy preparation practices influence the ways in which subjects spend their time prior to psychedelic experiences, including both increases in recommended activities as well as corresponding decreases in others.

Additionally, the concept of imprinting offers a useful lens for both therapists and patients to make sense of the phenomenology of drug experiences. A given visual hallucination may be understood as an abstract representation of the unconscious mind or as evidence of associated personal significance, as prevailing wisdom suggests (Masters and Houston, 2000; Kometer and Vollenweider, 2016). Alternatively, it may also be understood to have resulted from imprinting of a particular environmental exposure, owing more to the quantity and nature of that exposure than its intrinsic meaning.

These various contributors to psychedelic drug phenomenology are, of course, not distinct, but are rather intwined within an individual's life experiences and sociocultural contexts (Lifshitz et al., 2018). Recent and childhood exposures to religious symbols and rituals, for example, may contribute to spiritual visions during subsequent psychedelic experiences through a complex interplay of unconscious symbolism, personal meaning, and imprinting. Such imprinting effects may be most likely to be enduring when they occur during one's formative years, as the example of childhood black-and-white media shaping the aesthetic of dreams decades later would suggest (Murzyn, 2008).

Although interpreting psychedelic experiences through the lens of imprinting may lack in romanticism, it may also lead to important insights and or behavioural changes as our first case suggests. Indeed, this case provides very preliminary evidence that psychedelic-assisted psychotherapies may eventually find novel indications as treatments of internet gaming disorder and related conditions by making the psychological consequences of excessive media habits readily apparent.

Finally, we suggest that imprinting effects may not be limited to external stimuli but may also extend to internal stimuli like memories and imagination. In terms of brain activity, visual imagery produced by imagination can be seen as analogous to a weak form of visual perception: both involve similar patterns of neural activation in similar areas of the brain including the visual cortex, both can undergo associative learning, both can prime the subsequent interpretation of stimuli, and so on (Pearson, 2019). It is thus possible that imagining or remembering a certain image or scene may have similar, if somewhat weaker, imprinting effects relative to visually observing that image.

This may help explain why psychedelic therapists frequently report that the most important content for a particular patient tends to emerge spontaneously during psychedelic experiences (Johnson et al., 2008; Kolp et al., 2014; Mithoefer, 2017). For instance, patients with post-traumatic stress disorder or significant distress related to terminal illnesses will, almost by definition, spend significant quantities of time imagining or reliving distressing images related to these conditions. This internal exposure may

serve to imprint the distressing content on the mind, such that it readily manifests during psychedelic experiences, much like repeatedly watching a related video might.

Limitations

In this preliminary report, multiple limitations warrant consideration. This data presented were not initially collected with the intent of studying the concept of imprinting, which instead arose from our observations of patient experiences and clinical outcomes. On the upside, this means that the patterns of phenomenology we observed are unlikely to have occurred solely due to unintentionally suggestive interactions. However, the small sample size, the absence of controlled environmental exposures, and the lack of systematic or prospective information to corroborate and quantify patient reports of media habits, such as daily diaries, are all important limitations. Additionally, the imprinting outcomes were not pre-registered, and the single-subject-series were not true n-of-1 trials in that they were not designed before the intervention began (Lillie et al., 2011), but rather undertaken during naturistic collaboration between patients and clinicians. Finally, although we have identified probable examples of imprinting with multiple psychedelic drugs in diverse contexts, we are unable to determine the prevalence and magnitude of these effects or the influence of dosing contexts, such as the presence or absence of eyeshades.

Conclusion

In this article, we have presented preliminary empirical and theoretical evidence suggesting that environmental stimuli can exert delayed and often underrecognized influences on psychedelic drug phenomenology. These effects may be subtle, or of sufficient intensity as to alter the potential benefits of the experiences (e.g., by "hijacking" them), thereby warranting consideration and study.

We introduce the concept of imprinting to account for these delayed effects and provide evidence that they may arise with a wide variety of hallucination-inducing drugs. Based on analogous cognitive processes, including from the science of dream phenomenology, we propose several probable factors that may underlie such imprinting effects from a given exposure. Future research is needed to confirm these factors, to determine whether internal stimuli (e.g., imagined images) have similar effects, and to more broadly assess the neural mechanisms, prevalence, intensity, and clinical impacts of imprinting across various psychoactive drugs.

These results have potential consequences for research and clinical practice. We suggest that future psychedelic studies examining set and setting should not focus only on immediate treatment environments. Rather, potential influences of recent and past environmental exposures require investigation and consideration, especially in populations where there may be excessive use of digital media. Further phenomenological studies are also needed to better understand, for instance, whether the common references to Disney during psychedelic experiences reflect imprinted visual exposures, or rather shared cultural references (Masters and Houston, 2000; Shanon, 2003).

For clinicians, we recommend routine consideration of how a patient's behavioural habits may support or undermine their hopes and desires for psychedelic experiences. Excessive media exposure, as with our cases, can exert countertherapeutic imprinting effects that may well overpower intentions for personally-significant or mystical-like psychedelic experiences. Activities like meditation or introspection may therefore not only yield direct psychospiritual benefits, as experts have long recommended, but also indirect benefits via reduced countertherapeutic imprinting. On the other hand, as digital tools increasingly find roles in psychedelic-assisted psychotherapies, immersive technologies like virtual reality may well be used to shape subsequent psychedelic experiences by imprinting desired themes or images on participants' minds in the hours-days leading up to their drug sessions.

Lastly, we suggest that it is insufficient for patients and therapists to consider only the symbolic or personal associations of particular hallucinations, nor only immediate environmental influences. Rather, in line with our proposed revision of the extra-pharmacological model (**Figure 2**) and as our cases demonstrate, one of the many lessons that may be learned from psychedelic experiences is how the human mind can be shaped by its environment. In essence, that what you put into your mind, you may well get out.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The study was reviewed and approved by Douglas Mental Health University Institute and the Jewish General Hospital research ethics boards. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NG and KG: concept and design, drafting of the manuscript. KG, SR-D, and JT: administrative, technical, or material support. KG: supervision. All authors: acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Trait mindfulness and personality characteristics in a microdosing ADHD sample: a naturalistic prospective survey study

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Background: Microdosing (MD), repeatedly taking psychedelics in small, non-hallucinogenic amounts, has been practiced by individuals to relieve attention deficit hyperactivity disorder (ADHD) symptoms. Generally, adults diagnosed with ADHD have lower levels of mindfulness and differ in personality structure from non-ADHD adults. How MD affects mindfulness and personality in adults with ADHD remains unexplored.

Aim: This study aimed to investigate the effects of 4 weeks of MD on mindfulness and personality traits in adults diagnosed with ADHD and those experiencing severe ADHD symptoms. It was expected that mindfulness and the personality traits conscientiousness, extraversion, agreeableness, and openness would increase and neuroticism would decrease after 4 weeks of MD compared to baseline. It was explored if using conventional ADHD medication alongside MD and/or having comorbidities influenced MD-induced effects.

Methods: An online prospective naturalistic design was used to measure participants before MD initiation and 2 and 4 weeks later. Validated self-report measures were used assessing mindfulness (15-item Five Facet Mindfulness Questionnaire) and personality traits (10-item version of the Big Five Inventory) at three time points.

Results: The sample included $n = 233$, $n = 66$, and $n = 44$ participants at the three time points, respectively. Trait mindfulness, specifically description and non-judging of inner experience, was increased, and neuroticism was decreased after 4 weeks of MD compared to baseline. The remaining personality traits remained unchanged. Using conventional medication and/or having comorbid diagnoses did not change the MD-induced effects on mindfulness and personality traits after 4 weeks.

Conclusion: MD induced changes in otherwise stable traits. Future placebo-controlled studies are warranted to confirm whether these changes occur in a controlled setting.

KEYWORDS

ADHD, microdosing, psychedelics, mindfulness, personality

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders worldwide; with a prevalence rate of 2.5% in adults (1–3). ADHD is characterized by symptoms of inattention, hyperactivity, and/or impulsivity, with diverse combinations of symptoms possible. Survey research has shown that some adults diagnosed with ADHD report using low, sub-hallucinogenic doses of psychedelic substances repeatedly, referred to as microdosing (MD), to self-treat their symptoms and as such to improve daily life functioning (4–7). Next to ADHD symptoms, which is mainly the focus of intervention studies, it has also been shown that this population has a different personality and trait mindfulness profile than the neurotypical population. Previous research has established a strong link between certain personality traits and mindfulness (8–10) and it has been suggested that MD could potentially alter personality traits and mindfulness in healthy and general population samples [e.g., (6, 11–13)]. It is not yet clear whether MD affects these stable traits in adults with ADHD.

Trait mindfulness can be described as the inherent general tendency to be mindful in daily life, to be able to allocate and maintain attentional resources to the present experience (e.g., being able to pay attention to the sensation of water when taking a shower), and to be non-judgmental and non-reactive toward arising thoughts (e.g., being able to notice distressing thoughts without reacting to them) (14, 15). Mindfulness can broadly be divided into two dimensions: self-regulation of attention and acceptance (16). First, self-regulation of attention is characterized by attending, observing, and becoming aware of one's thoughts, feelings, and sensations without getting caught in ruminative thought streams. Mindfulness facets that belong to this domain include observation, description, and acting with awareness (14). Second, the acceptance domain involves taking an open, and accepting stance toward one's observed experience, thereby inhibiting emotional impulsive responses to whatever is observed. Mindfulness facets that belong to this domain include non-judging of inner experience and non-reactivity to inner experience (14). Generally, individuals diagnosed with ADHD scored on average lower on trait mindfulness compared to individuals without an ADHD diagnosis (17). Interestingly, enhanced levels of mindfulness have been reported after MD (6) and mindfulness scores were higher in current and former microdosers compared to MD-naïve controls (11). Though one prospective (survey) study investigating adults (excluding individuals with mood, anxiety, substance use, psychotic or dissociative disorders) did not find a change in mindfulness scores after MD (13), and another prospective study investigating a general population sample could not attribute changes to MD solely (18). However, the effects of MD on mindfulness in individuals diagnosed with ADHD, or individuals experiencing severe ADHD symptoms, have not been investigated yet.

Mindfulness was strongly and positively related to conscientiousness (i.e., being well-organized, responsible, and efficient) and negatively related to neuroticism (i.e., negative affectivity and emotionally unstable) (8–10). While the relationships between mindfulness and conscientiousness and neuroticism have been a consistent finding, the relationships between mindfulness and the other personality traits agreeableness (i.e., compromising with, and trusting others), extraversion (i.e., positive emotionality and socially engaged), and openness (i.e., curious and willing to explore new experiences) (19) were overall positive, yet less strong (8, 9). Individuals diagnosed with ADHD score generally lower on conscientiousness and higher on neuroticism compared to controls (20–24). Though the associations between ADHD and extraversion and agreeableness are less strong, both traits tend to be lower in ADHD (20, 21, 23–26). Openness is generally unrelated to ADHD (20, 23, 24). Interestingly, openmindesness (i.e., openness) was higher and negative emotionality (i.e., neuroticism) was lower in current and former microdosers compared to MD-naïve controls (27). Also, a qualitative interview study reported that participants experienced increases in openness and extraversion following MD, although no explicit mention of other personality traits was made (28). Prospective MD studies have also reported alterations in personality traits after MD. Namely, conscientiousness was increased in healthy adults after MD (29), but other studies did not find this effect in a general population sample (12) and a general sample without individuals diagnosed with a mood, anxiety, substance use, psychotic or dissociative disorder (13). Agreeableness was increased after MD in a general population sample (12), though other studies investigating healthy individuals did not find this effect (13, 29). Neuroticism decreased after MD in healthy adults (29) and a general population sample (12), but was increased in a sample consisting of adults without mood, anxiety, substance use, and psychotic or dissociative disorders (13). If and in which direction personality traits are altered by MD in individuals diagnosed with ADHD and/or experiencing severe ADHD symptoms remains unexplored.

Therefore, the current study aimed to investigate mindfulness and personality traits in individuals diagnosed with ADHD and/or experiencing severe ADHD symptoms before and after self-initiated MD. First, it was expected that trait mindfulness would increase after MD compared to baseline. No hypotheses were formulated regarding the effect of MD on the different mindfulness facets, because of a lack of research investigating this. Second, based on previous studies, conscientiousness, agreeableness, extraversion, and openness were expected to increase after MD. Previous results of MD effects on neuroticism were somewhat conflicting. However, given that neuroticism is generally higher in ADHD and survey studies reporting potential therapeutic effects of MD in ADHD, we expected neuroticism to decrease in the current study. Lastly, it was investigated if using conventional medication alongside MD or having comorbidities alongside ADHD would influence the change in mindfulness and personality traits induced by MD.

2. Materials and methods

2.1. Study design and participants

The current study was part of a larger study (7), which used a prospective naturalistic design. The current study set out to assess trait mindfulness and personality traits in an ADHD sample at baseline, before MD initiation, and at 2 and 4 weeks later. Adults diagnosed with ADHD and adults without an ADHD diagnosis who experienced ADHD symptoms to the extent that these interfered with daily life were invited to participate in the study. ADHD symptom severity was determined at baseline using the Conners' Adult ADHD Rating Scale (CAARS-S:SV) (30). Those without an ADHD diagnosis, who had T-scores lower than 65 on all CAARS-S:SV subscales were excluded

from all analyses, as T-scores of 65 and above are indicative of clinically elevated symptoms (see section 2.3.4.). Lastly, all participants had the intention to start MD with psychedelics on their initiative to relieve these symptoms and provided informed consent prior to starting the study.

2.2. Study procedure

Participants were recruited through an online advertisement that was placed on a website providing information about MD with psychedelics.[1] Interested individuals could click the link below the advertisement and were subsequently provided with information regarding the study rationale, procedure, and contact details of the researchers to ask questions about the study. The information included the request to sign up for the study between 1 and 3 days before MD initiation to receive the surveys at the correct moments. After providing informed consent, participants were redirected to the baseline measure. When finishing the baseline survey, participants were enrolled in an emailing system, sending links to the following surveys exactly 2 and 4 weeks after completing the baseline survey. All three surveys took between 15 and 20 min to complete. Furthermore, through daily short surveys, participants were asked if they had taken a microdose that day and if yes, what substance and dose they took. These daily surveys were sent the day after completing the baseline survey until the 4-week time point. Data collection started in November 2020 and ended in July 2021. The Ethics Review Committee of Psychology and Neuroscience at Maastricht University approved the study (reference number: ERCPN-215_05_11_2019_A1).

2.3. Measures

2.3.1. Demographic information and history of substance use

Demographic information, such as biological sex, gender, age, continent of residence, educational level, and daily occupation, was collected at baseline. Additionally, information about participants' previous experience with psychedelics (i.e., ayahuasca, DMT, 5-MeO-DMT, LSD, novel lysergamides (e.g., 1P-LSD, ALD-52), psilocybin, Salvia divinorum, ibogaine, and mescaline) in both full and microdoses was collected at baseline.

2.3.2. Experience with mindfulness/meditation

At baseline, participants were asked if they had any experience in the practice of meditation/mindfulness. If this question was answered with 'yes', it was asked what meditation/mindfulness tools were used, where they could choose multiple answers from the following options: 'I followed an online course', 'I use(d) a mobile application', 'I watch(ed) Youtube videos', 'I follow(ed) sessions at a retreat', or the option to provide an answer through free text entry. Subsequently, it was asked when the last time was that the participant practiced meditation/mindfulness (i.e., 'more than one year ago'; 'less than one year ago, more than one month ago'; 'less than one month ago, more than one week ago'; or 'within the past seven days'). A variable 'recent mindfulness' was created to group individuals based on the recentness of their mindfulness practice (0 = no experience with meditation/mindfulness or practiced it more than 7 days ago; 1 = practiced meditation/mindfulness within the past 7 days), to differentiate respondents who recently practiced meditation/mindfulness from respondents who did not.

2.3.3. Psychiatric and physical diagnoses

Participants were asked if they had been diagnosed by a medical doctor or a therapist with a psychiatric, neurological, or physical disorder, and if so, what these diagnoses were. Pre-set answer options included 'ADHD', 'depression', 'anxiety disorder', 'substance use disorder', 'dyslexia', 'autism/Asperger syndrome', 'obsessive-compulsive disorder', 'bipolar disorder, chronic pain', 'cluster headaches', 'epilepsy', 'migraines', 'post-traumatic stress disorder (PTSD)', 'schizophrenia', 'I do not want to mention', or the option to provide another answer in a textbox. A variable 'comorbidity' was constructed differentiating participants with at least one comorbid diagnosis alongside ADHD from participants without comorbid diagnoses alongside ADHD or without an ADHD diagnosis (0 = only ADHD or no ADHD; 1 = ADHD and at least one other diagnosis).

Respondents who indicated having an ADHD diagnosis were asked at what age they received the diagnosis and if they were currently using prescribed ADHD medication, stopped using it, or never used it. If they indicated to be using prescribed medication, it was asked what type of medication this was (i.e., 'Adderall (amphetamine)', 'Concerta (methylphenidate)', 'Dexedrine (amphetamine)', 'Focalin (dexmethylphenidate)', 'Ritalin (methylphenidate)', 'Strattera (atomoxetine hydrochloride)', 'I do not want to mention', or a free text entry). In the case prescribed ADHD medication was discontinued in the past, it was asked what the reasons were for this: 'it did not relieve my symptoms', 'because of psychological side effects', 'because of physical side effects', 'I do not want to mention', or the option to provide another reason through free text entry. A variable 'medication use' was constructed differentiating participants using conventional medication alongside MD during the study from participants without conventional medication, who were only MD during the study (0 = only MD; 1 = MD and using conventional ADHD medication).

2.3.4. ADHD symptoms

The self-report, short screening version of the Conners' Adult ADHD Rating Scale (CAARS-S:SV) (30) was used to assess ADHD symptoms at baseline. This 30-item questionnaire assesses the core ADHD symptoms (i.e., inattention and hyperactivity/impulsivity) as well as related problem areas like problems with self-concept. Participants indicated to what extent the items described them on a four-point Likert scale from 0 (not at all, never) to 4 (very much, very frequently). Nine items belong to the *inattention* subscale, capturing problems experienced with attention and containing items such as 'I lose things necessary for tasks or activities (e.g., to-do lists, pencils, books, or tools)'. Nine items belong to the *hyperactivity/impulsivity* subscale, capturing symptoms related to both hyperactivity and impulsivity and containing items such as 'I have trouble waiting in line or taking turns with others'. The remaining 12 items belong to the *ADHD index*, capturing features of ADHD that are not included in the DSM diagnostic criteria, such as 'sometimes my attention narrows so

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much that I am oblivious to everything else; other times it's so broad that everything distracts me'. A *DSM-IV ADHD total symptom* score can be calculated by summing the scores of the inattention and hyperactivity/impulsivity subscales. The CAARS-S:SV has good internal consistency and inter-rater reliability (31), high criterion validity and moderate concurrent validity (32).

T-scores were calculated for each subscale using the scores of the standardization sample provided in the technical manual consisting of non-clinical adults in the same age range and of the same sex. Subscale T-scores equal or above 65 indicate clinically elevated symptoms according to the technical manual (30). Therefore, participants without an ADHD diagnosis who had T-scores below 65 on all CAARS-S:SV subscales were excluded from all analyses. Although the CAARS-S:SV was included in the surveys at all three time points, only the baseline scores were used in the current study. For details about the ADHD symptom scores at all time points, see Haijen and colleagues (7).

2.3.5. Trait mindfulness

To assess trait mindfulness, the 15-item Five Facet Mindfulness Questionnaire (FFMQ-15) was used (33). The FFMQ-15 consists of five subscales, with every three items capturing one aspect of mindfulness. The first subscale *observation* refers to attending to or noticing internal and external experiences and contains items such as 'when I take a shower or a bath, I stay alert to the sensations of water on my body'. *Description* assesses the ability to put one's experiences into words and contains items such as 'I'm good at finding words to describe my feelings'. *Acting with awareness* captures the ability to attend to the present moment activity, without behaving automatically and while the attention is focused elsewhere. This subscale contains three reverse-phrased items such as 'I do not pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted'. *Non-judging of inner experience* describes accepting and not evaluating emotions and thoughts as good or bad and contains three reverse-phrased items such as 'I believe some of my thoughts are abnormal or bad and I should not think that way'. *Non-reactivity to inner experiences* involves detachment of emotions and thoughts allowing them to come and go without being carried away by them and contains items such as 'when I have distressing thoughts or images, I "step back" and am aware of the thought or image without getting taken over by it' (34). Items were rated on a five-point Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true). Subscale scores range from 3 to 15 and can be summed to achieve a total score ranging from 15 to 75. Reverse-phrased items were recoded. High scores on each mindfulness facet reflect a higher level of mindfulness. The FFMQ-15 showed adequate internal consistency and did not differ from the long form of the FFMQ in terms of convergent validity (34).

2.3.6. Personality

To assess personality traits, the 10-item version of the Big Five Inventory (BFI; (35)) was included. This short questionnaire contains two items, of which one is reverse-phrased, describing each of the five Big Five personality traits. Example items include for *extraversion* 'I see myself as someone who is outgoing, sociable', for *agreeableness* 'I see myself as someone who is generally trusting', for *conscientiousness* 'I see myself as someone who does a thorough job', for *neuroticism* 'I see myself as someone who gets nervous easily', and for *openness* 'I see myself as someone who has an active imagination'. Items are rated on a five-point Likert scale ranging from 1 (disagree strongly) to 5 (agree strongly). Reverse-phrased items were recoded. The scores of the two items belonging to one subscale were summed and divided by two to achieve an average subscale score ranging from 1 to 5. The BFI-10 has shown to be an adequate assessment of personality, with good validity and reliability metrics (35).

2.3.7. MD substance and dose

Through short daily surveys starting from the day after the baseline survey until the 4-week time point, participants were asked each day if they had taken a microdose that day (yes/no), if yes, what substance (LSD, novel lysergamides (e.g., 1P-LSD), psilocybin/psilocin (magic mushrooms/truffles), mescaline (e.g., san pedro), or free text) and dose they took (free text).

2.4. Statistical analyses

All data were entered into the statistical program IBM SPSS Statistics version 26. Descriptive statistics were used to describe the demographic variables, information regarding psychiatric and physical diagnoses, previous experience with psychedelics, experience with meditation/mindfulness, and drug types and doses that were used for MD during the study. Linear mixed model (LMM) analysis was used to assess changes in personality traits and mindfulness after 2 and 4 weeks of MD compared to baseline. All LMMs contained the within-subject factor time [three levels: baseline (0 W), 2- (2 W), and 4-week (4 W) time point]. The binary factors, medication use and comorbidity were included as covariates in all LMMs. The fixed part of the models consisted of time, medication use, and comorbidity, and the interaction terms Time x Medication use and Time x Comorbidity.

To test whether MD increased mindfulness, the total score of the FFMQ-15 and the subscale scores (i.e., observation, description, acting with awareness, non-judging of inner experience, and non-reactivity to inner experiences) were included as dependent variables into separate LMMs. To control for a potential effect of recent experience with mindfulness and/or meditation, the LMMs were run again with the addition of the variable recent mindfulness as a covariate, by including recent mindfulness and the interaction between time and recent mindfulness as additional fixed factors in the LMMs.

To test whether MD affected personality traits, the subscale scores of the BFI-10 (i.e., conscientiousness, neuroticism, extraversion, agreeableness, and openness) were included as dependent variables in separate LMMs.

To find the best-fitting covariance structure for each LMM, Akaike's information criterion (AIC) was used. Restricted maximum-likelihood (REML) estimation was used to estimate missing data. In case of significant main effects, pairwise comparisons between time points were conducted and corrected for multiple comparisons using Bonferroni correction. A significance level of 0.05 was used. Effect sizes were described by partial eta squared (η_p^2) values, where 0.01, 0.09, and 0.25 were considered small, medium, and large, respectively (36). Effect sizes were calculated using an online effect size calculator.[2]

2 www.effect-size-calculator.herokuapp.com

TABLE 1 Previous experience with psychedelic substances in full/regular psychedelic doses and low/micro doses of the whole sample (n = 233).

	Full or MD	Full dose experience	Microdose experience
n (%)	191 (82.0%)	178 (76.4%)	101 (43.3%)
Psilocybin/psilocin (e.g., magic mushrooms, truffles)	165 (70.8%)	152 (65.2%)	77 (33.0%)
LSD	111 (47.6%)	102 (43.8%)	43 (18.5%)
Ayahuasca	40 (17.2%)	38 (16.3%)	4 (1.7%)
DMT	38 (16.3%)	37 (15.9%)	5 (2.1%)
Salvia divinorum	24 (10.3%)	24 (10.3%)	1 (0.4%)
Novel lysergamides (e.g., 1P-LSD, ALD-52)	18 (7.7%)	16 (6.9%)	10 (4.3%)
Mescaline	14 (6.0%)	13 (5.6%)	3 (1.3%)
5-MeO-DMT	8 (3.4%)	7 (3.0%)	1 (0.4%)
Ibogaine	2 (0.9%)	2 (0.9%)	1 (0.4%)

TABLE 2 Substances and doses used during the study.

	Frequency (% of 117)	Mean dose (SD)
Psilocybin-containing mushrooms, truffles[1]	91 (77.8)	722 mg (485.5)
Novel lysergamides (e.g., 1P-LSD, ALD-52)	14 (12.0)	17.5 µg (31.1)
LSD	11 (9.5)	12 µg (6.4)
Ayahuasca	1 (0.9)	–

[1]No further data was collected on whether psilocybin-containing mushrooms/truffles were dried or fresh.

3. Results

3.1. Demographic information and history of substance use

In total, 247 participants completed the baseline survey. Fast responses (i.e., below 50% of the median response time) were visually checked for inconsistencies in responding, leading to the exclusion of two respondents. Furthermore, 12 respondents who did not have an ADHD diagnosis had T-scores lower than 65 on all CAARS-S:SV subscales at baseline and were therefore excluded from all analyses. Sample sizes included in the analyses were 233, 66, and 44 at the three time points, respectively. Half of the sample at baseline consisted of female participants (n = 117; 50.2%), over 80 percent resided in Europe (n = 193; 82.8%), and most participants completed a tertiary level of education (n = 170; 73%). The most common daily occupations included computer/office work (n = 57; 24.5%), studying (n = 43; 18.5%), and working with people (n = 39; 16.7%). The majority of the sample at baseline had used a psychedelic substance at least once before (n = 191; 82%), see Table 1 for previously used psychedelic substances in both full and low doses at baseline. For demographic information at the 2- and 4-week time points, see Haijen and colleagues (7).

3.2. Psychiatric and physical diagnoses

The majority of the sample at baseline had a current diagnosis of a psychiatric, neurological, or physical disorder (n = 166; 71.2%). ADHD was the most common diagnosis (n = 159; 68.2%), followed by depression (n = 44; 18.9%), anxiety disorder (n = 39; 16.7%), and PTSD (n = 17; 7.3%). Of the respondents diagnosed with ADHD (n = 159), had 86 individuals at least one comorbid diagnosis (54.1%). Depression (n = 42; 48.8%), anxiety disorder (n = 36; 41.9%), PTSD (n = 16; 18.6%), and dyslexia (n = 12; 14%) were the most reported comorbid diagnoses alongside ADHD. Of the respondents without an ADHD diagnosis, seven (9.5%) reported having a current diagnosis of a psychiatric, neurological, and/or physical disorder other than ADHD. Almost half of the participants who were diagnosed with ADHD, received this diagnosis when they were aged between 20 and 29 years old (n = 71; 44.7%), almost one quarter were between 30 and 39 years old (n = 38; 23.9%), 15 percent were between 10 and 19 years old (n = 24; 15.1%), and 10 percent were older than 40 when receiving the ADHD diagnosis (n = 17; 10.1%). Almost 14 percent of those diagnosed with ADHD never used any prescribed ADHD medication (n = 22; 13.8%) and one-third were using prescribed ADHD medication during the study (n = 53; 33.3%), with amphetamines (n = 27; 50.1%) and methylphenidate (n = 21; 39.6%) being the most common types of medication. The majority of ADHD-diagnosed individuals had tried prescribed ADHD medication in the past but stopped using it prior to baseline (n = 84; 52.8%). The most often reported reasons for discontinuing the prescribed ADHD medication were: because of physical side effects (n = 53; 63.1%), because of psychological side effects (n = 51; 32.1%), and because it did not relieve the symptoms (n = 17; 10.7%).

3.3. Experience with mindfulness/meditation

Over 80% (n = 194, 83.3%) of the sample indicated having experience with the practice of meditation/mindfulness. Of these, most respondents indicated to have used a mobile application for meditation/mindfulness purposes (n = 97; 50%), followed by watching Youtube videos (n = 84; 43.3%), following sessions at a retreat (n = 69; 35.6%), and/or following online courses (n = 51; 26.3%). Of those with meditation/mindfulness experience, the majority practised meditation/mindfulness for the last time within the past 7 days (n = 108; 55.7%), 30 respondents between 1 and 4 weeks ago (15.5%), 34 respondents more than 1 month ago (17.5%) and the remaining 22 respondents practised meditation/mindfulness more than 1 year ago for the last time (11.3%).

3.4. MD substance and dose

See Table 2 for the substances and average doses used during the study by the respondents who reported information through daily reports (n = 117; 50.2%). Two participants switched from using LSD or a novel lysergamide (e.g., 1P-LSD, ALD-52) to psilocybin-containing mushrooms/truffles, and one participant switched from psilocybin-containing mushrooms/truffles to LSD during the study.

3.5. Trait mindfulness

3.5.1. FFMQ-15 total score

Compound symmetry was used as a covariance structure for this LMM. A main effect of time was found on the total score of the

FFMQ-15 [$F_{(2,\ 120.9)} = 19.29$, $p < 0.001$, $\eta_p^2 = 0.24$]. Pairwise comparisons showed that total mindfulness scores were higher at both 2 W (Δ2W–0 W = 3.62, $p < 0.001$) and 4 W (Δ4W–0 W = 5.97, $p < 0.001$) compared to baseline. Scores were also higher at 4 W compared to 2 W (Δ4W–2 W = 2.35, $p = 0.043$) (see Figure 1A). Further, a significant interaction between time and medication use was found [$F_{(2,\ 120.8)} = 3.77$, $p = 0.026$, $\eta_p^2 = 0.06$]. The estimates of fixed effects showed that scores were lower at 2 W in respondents using conventional ADHD medication compared to respondents who did not use conventional medication ($\beta = -5.16$, $p = 0.009$). The difference in scores was not significant at baseline ($\beta = -0.25$, $p = 0.847$) or 4 W ($\beta = -1.41$, $p = 0.544$). No interaction between comorbidity and time was found [$F_{(2,\ 121.3)} = 0.35$, $p = 0.704$, $\eta_p^2 = 0.01$].

When including the variable recent mindfulness in the model, the effect of time [$F_{(2,\ 120.9)} = 11.18$, $p < 0.001$, $\eta_p^2 = 0.16$], including the pairwise comparisons, and the interaction between time and medication use [$F_{(2,\ 121.2)} = 3.30$, $p = 0.040$, $\eta_p^2 = 0.05$] remained significant. There was no interaction between time and recent mindfulness [$F_{(2,\ 121.1)} = 0.18$, $p = 0.833$, $\eta_p^2 = 0.00$].

3.5.2. Observation

Compound symmetry was used as the covariance structure for this model. The LMM showed an effect of time on the FFMQ-15 observation scores [$F_{(2,\ 119.1)} = 3.10$, $p = 0.049$, $\eta_p^2 = 0.05$]. Pairwise comparisons showed that scores were higher at 4 W compared to baseline (Δ4W–0 W = 0.75, $p = 0.008$). Scores did not differ between 2 W and baseline (Δ2W–0 W = 0.40, $p = 0.158$) and 2 W and 4 W (Δ4W–2 W = 0.35, $p = 0.545$). Furthermore, no interaction effect between time and medication use [$F_{(2,\ 119.5)} = 1.80$, $p = 0.170$, $\eta_p^2 = 0.03$] or time and comorbidity [$F_{(2,\ 119.8)} = 0.01$, $p = 0.989$, $\eta_p^2 = 0.00$] was found.

When including the variable recent mindfulness in the model, the effect of time was no longer significant [$F_{(2,\ 117.1)} = 0.33$, $p = 0.718$, $\eta_p^2 = 0.00$; see Figure 1B]. No interaction between time and recent mindfulness was found [$F_{(2,\ 117.2)} = 1.96$, $p = 0.146$, $\eta_p^2 = 0.02$].

3.5.3. Description

The First-order autoregressive (AR1) covariance structure was the best fit for this model. A main effect of time was found on the

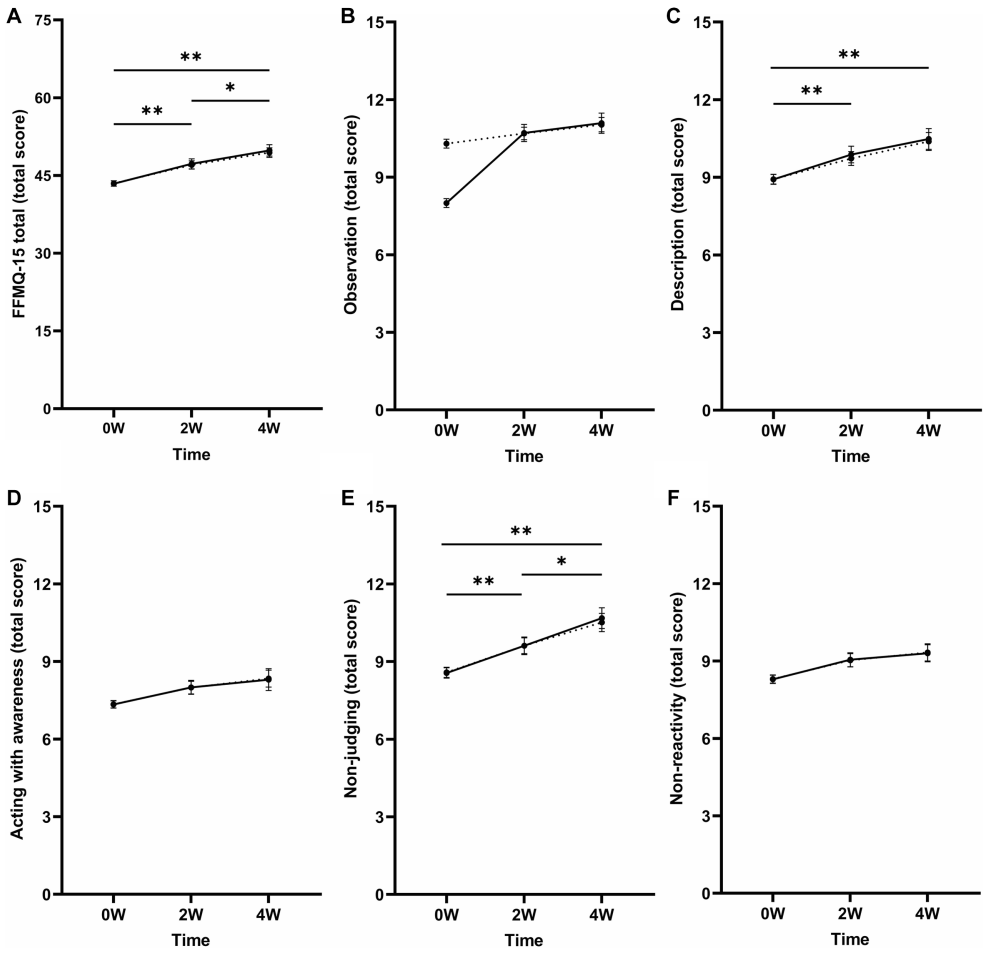

FIGURE 1
Mean total scores of the FFMQ-15 **(A)** total and the separate subscales **(B)** observation, **(C)** description, **(D)** acting with awareness, **(E)** non-judging of inner experiences, **(F)** and non-reactivity of inner experiences at baseline (0 W) and 2 (2 W) and 4 weeks (4 W) after MD. Corrected means (dotted line) are presented alongside the raw means (solid line) to aid the interpretation of the change in FFMQ-15 scores after including the covariates in the model (i.e., medication use, comorbidity, and recent mindfulness). The dotted and solid lines overlap when the means did not change after including the covariates. Mean differences that remained significant after including the recent mindfulness variable and after correction for multiple testing are indicated with asterisks (*). Error bars represent mean ± SEM. *$p < 0.05$; **$p < 0.001$.

FFMQ-15 scores [$F_{(2,\ 117.1)} = 7.75$, $p < 0.001$, $\eta_p^2 = 0.12$; see Figure 1C]. Pairwise comparisons revealed that scores were higher at 2 W (Δ2W–0 W = 0.81, $p = 0.002$) and 4 W (Δ4W–0 W = 1.42, $p < 0.001$) compared to baseline. The scores did not differ between the 2 W and 4 W (Δ4W–2 W = 0.61, $p = 0.121$). No interaction between time and medication use [$F_{(2,\ 119.4)} = 1.86$, $p = 0.161$, $\eta_p^2 = 0.03$] or time and comorbidity [$F_{(2,\ 119.6)} = 0.69$, $p = 0.505$, $\eta_p^2 = 0.00$] was found.

When including the variable recent mindfulness in the model, the effect of time remained significant [$F_{(2,\ 117.1)} = 6.87$, $p = 0.002$, $\eta_p^2 = 0.11$] and the results of the pairwise comparisons remained unchanged. Additionally, no interaction effect between time and recent mindfulness was found [$F_{(2,\ 117.2)} = 2.32$, $p = 0.103$, $\eta_p^2 = 0.02$].

3.5.4. Acting with awareness

An unstructured covariance structure was used for this model. A main effect of time was found on the FFMQ-15 acting with awareness scores [$F_{(2,\ 51.3)} = 4.70$, $p = 0.013$, $\eta_p^2 = 0.16$]. Pairwise comparisons showed that scores were higher at both 2 W (Δ2W–0 W = 0.64, $p = 0.029$) and 4 W (Δ4W–0 W = 1.01, $p = 0.005$) compared to baseline. Scores did not differ between 2 W and 4 W (Δ4W–2 W = 0.37, $p = 0.490$). Furthermore, the interaction effects between time and medication use [$F_{(2,\ 51.7)} = 1.09$, $p = 0.343$, $\eta_p^2 = 0.04$] and time and comorbidity [$F_{(2,\ 51.4)} = 0.23$, $p = 0.792$, $\eta_p^2 = 0.01$] were not significant.

When including the variable recent mindfulness in the model, the time effect was no longer significant [$F_{(2,\ 50.7)} = 2.88$, $p = 0.066$, $\eta_p^2 = 0.10$; see Figure 1D]. Further, the interaction effect between time and recent mindfulness was not significant [$F_{(2,\ 50.3)} = 0.49$, $p = 0.616$, $\eta_p^2 = 0.10$].

3.5.5. Non-judging of inner experience

Compound symmetry was used as a covariance structure. A main effect of time was found on the FFMQ-15 non-judging of inner experience scores [$F_{(2,\ 115.3)} = 13.40$, $p < 0.001$, $\eta_p^2 = 0.19$; see Figure 1E]. Pairwise comparisons showed that scores were higher at 2 W (Δ2W–0 W = 1.04, $p < 0.001$) and 4 W (Δ4W–0 W = 1.94, $p < 0.001$) compared to baseline. Scores were also higher at 4 W compared to 2 W (Δ4W–2 W = 0.90, $p = 0.036$). Further, a significant interaction between time and medication use was found [$F_{(2,\ 115.9)} = 4.82$, $p = 0.010$, $\eta_p^2 = 0.08$]. Estimates of fixed effects showed that non-judging of inner experience scores were lower at 2 W ($\beta = -2.32$, $p = 0.002$), not at baseline ($\beta = -0.23$, $p = 0.643$) or 4 W ($\beta = -0.90$, $p = 0.306$) for respondents using conventional medication alongside MD compared to respondents not using conventional medication. No interaction between time and comorbidity was found [$F_{(2,\ 116.4)} = 0.79$, $p = 0.456$, $\eta_p^2 = 0.01$].

When including the variable recent mindfulness in the model, the main effect of time [$F_{(2,\ 115.0)} = 8.46$, $p < 0.001$, $\eta_p^2 = 0.13$], including the pairwise comparisons, and the interaction between time and medication use [$F_{(2,\ 115.2)} = 4.55$, $p = 0.013$, $\eta_p^2 = 0.07$] remained significant. Additionally, no interaction effect between time and recent mindfulness was found [$F_{(2,\ 115.2)} = 0.00$, $p = 0.999$, $\eta_p^2 = 0.00$].

3.5.6. Non-reactivity to inner experience

First-order autoregressive (AR1) was used as a covariance structure for this LMM. A main effect of time was found on the FFMQ-15 non-reactivity to inner experience scores [$F_{(2,\ 131.0)} = 5.24$, $p = 0.006$, $\eta_p^2 = 0.07$]. Pairwise comparisons showed higher scores at both 2 W (Δ2W–0 W = 0.73, $p = 0.011$) and 4 W (Δ4W–0 W = 1.05, $p = 0.007$) compared to baseline. Scores did not differ between 2 W and 4 W (Δ4W–2 W = 0.32, $p = 0.960$). No interaction between time and medication use [$F_{(2,\ 132.6)} = 1.86$, $p = 0.159$, $\eta_p^2 = 0.03$] or time and comorbidity [$F_{(2,\ 133.4)} = 0.06$, $p = 0.945$, $\eta_p^2 = 0.00$] was found.

After including the recent mindfulness variable in the model, the main effect of time was no longer significant [$F_{(2,\ 132.0)} = 2.43$, $p = 0.092$, $\eta_p^2 = 0.04$; see Figure 1F]. No interaction between time and recent mindfulness was found [$F_{(2,\ 132.2)} = 0.22$, $p = 0.806$, $\eta_p^2 = 0.00$].

3.6. Personality traits

3.6.1. Conscientiousness

A First-order autoregressive (AR1) covariance structure was used for this model. A main effect of time on BFI-10 conscientiousness scores was found [$F_{(2,\ 136.3)} = 3.77$, $p = 0.025$, $\eta_p^2 = 0.05$]. Bonferroni-corrected pairwise comparisons showed that scores were higher at 4 W compared to baseline (Δ4W–0 W = 0.40, $p = 0.002$). Scores did not differ between baseline and 2 W (Δ2W–0 W = 0.16, $p = 0.159$) or between 2 W and 4 W (Δ4W–2 W = 0.24, $p = 0.060$; see Figure 2A). No interactions between time and medication use [$F_{(2,\ 137.9)} = 0.69$, $p = 0.502$, $\eta_p^2 = 0.01$] and time and comorbidity [$F_{(2,\ 138.3)} = 0.10$, $p = 0.909$, $\eta_p^2 = 0.00$] were found. After correcting for multiple testing, the effect found on conscientiousness scores was no longer significant.

3.6.2. Neuroticism

An Ante-Dependence: First-Order covariance structure was the best fit for the model. A significant effect of time on BFI-10 neuroticism scores was found [$F_{(2,\ 60.8)} = 7.19$, $p = 0.002$, $\eta_p^2 = 0.19$]. Scores were lower at 4 W compared to baseline (Δ4W–0 W = −0.60, $p < 0.001$) and 2 W (Δ4W–2 W = −0.34, $p = 0.014$; see Figure 2B). Scores were not significantly lower at 2 W compared to baseline (Δ2W–0 W = −0.26, $p = 0.056$). No interactions between time and medication use [$F_{(2,\ 60.2)} = 1.08$, $p = 0.350$, $\eta_p^2 = 0.034$] and time and comorbidity [$F_{(2,\ 60.4)} = 0.23$, $p = 0.796$, $\eta_p^2 = 0.01$] were found. The variable comorbidity did have a main effect on the neuroticism scores [$F_{(1,\ 103.6)} = 6.65$, $p = 0.011$, $\eta_p^2 = 0.06$], showing higher neuroticism scores for respondents with comorbid diagnoses alongside the ADHD diagnosis compared to respondents without comorbidities alongside ADHD at baseline ($\beta = 0.38$, $p = 0.007$) and 2 W ($\beta = 0.51$, $p = 0.048$), but not at 4 W ($\beta = 0.58$, $p = 0.064$).

3.6.3. Extraversion

A compound symmetry covariance structure was the best fit for this model. A main effect of time was found on the BFI-10 extraversion scores [$F_{(2,\ 123.8)} = 3.58$, $p = 0.031$, $\eta_p^2 = 0.06$]. Corrected pairwise comparisons showed that scores were higher at 2 W compared to baseline (Δ2W–0 W = 0.24, $p = 0.039$) (see Figure 2C). Scores did not differ between baseline and 4 W (Δ4W–0 W = 0.20, $p = 0.249$), or between 2 W and 4 W (Δ4W–2 W = −0.04, $p > 0.999$). No interaction between time and medication use [$F_{(2,\ 124.6)} = 1.55$, $p = 0.217$, $\eta_p^2 = 0.02$] or time and comorbidity [$F_{(2,\ 125.0)} = 0.43$, $p = 0.652$, $\eta_p^2 = 0.01$] was found. Comorbidity had an overall effect on extraversion scores [$F_{(1,\ 316.8)} = 8.49$, $p = 0.004$, $\eta_p^2 = 0.03$]. Respondents with at least one comorbid diagnosis alongside ADHD had lower scores at baseline ($\beta = -0.48$, $p = 0.001$) and 4 W ($\beta = -0.62$, $p = 0.019$), but not at 2 W ($\beta = -0.38$, $p = 0.103$). After correcting for multiple testing, the effect found on extraversion was no longer significant.

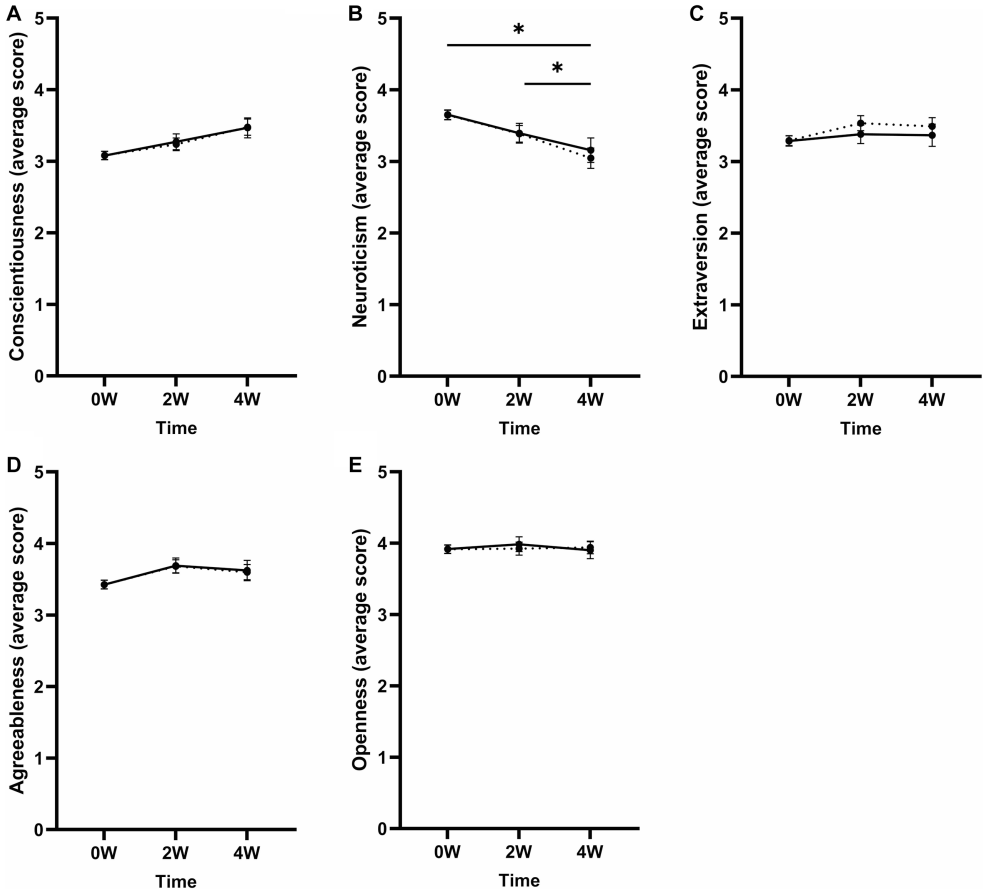

FIGURE 2
Mean scores of the BFI-10 subscales **(A)** conscientiousness, **(B)** neuroticism, **(C)** extraversion, **(D)** agreeableness, and **(E)** openness to experience at baseline (0 W), 2 (2 W), and 4 weeks (4 W) after MD. Corrected means (dotted line) are presented alongside the raw means (solid line) to aid the interpretation of the change in BFI-10 scores after including the covariates in the model (i.e., medication use and comorbidity). The dotted and solid lines overlap when the means did not change after including the covariates. Error bars represent mean ± SEM. Effects that remained significant after correction for multiple testing are indicated by an asterisk (*). *$p < 0.05$; **$p < 0.001$.

3.6.4. Agreeableness

Compound symmetry was chosen as the covariance structure for this LMM. No effect of time was found on BFI-10 agreeableness scores [$F_{(2,\ 129.5)} = 2.05$, $p = 0.133$, $\eta_p^2 = 0.03$; see Figure 2D]. Further, no interaction between time and medication use [$F_{(2,\ 130.3)} = 2.16$, $p = 0.120$, $\eta_p^2 = 0.03$] or time and comorbidity was found [$F_{(2,\ 130.8)} = 0.28$, $p = 0.755$, $\eta_p^2 = 0.00$].

3.6.5. Openness

An unstructured covariance matrix was the best fit for this model. The time effect on BFI-10 openness scores was not significant [$F_{(2,\ 51.4)} = 0.42$, $p = 0.662$, $\eta_p^2 = 0.02$; see Figure 2E]. No interaction between time and medication use [$F_{(2,\ 51.8)} = 0.27$, $p = 0.766$, $\eta_p^2 = 0.01$] or time and comorbidity [$F_{(2,\ 51.7)} = 1.07$, $p = 0.350$, $\eta_p^2 = 0.04$] was found.

4. Discussion

The current study aimed to investigate the effects of MD on mindfulness and personality traits in individuals diagnosed with ADHD and individuals without an ADHD diagnosis, who experienced severe ADHD complaints. In line with the expectations, mindfulness was increased after 2 weeks of MD compared to baseline and was further increased 2 weeks later. All facets of mindfulness (i.e., observation, description, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience) were increased 4 weeks after MD compared to baseline. However, when taking recent mindfulness into account, only description and non-judging of inner experience remained significantly increased at both 2 and 4 weeks. Furthermore, the personality trait neuroticism was decreased after 4 weeks of MD compared to baseline. Extraversion and conscientiousness were increased after 2 and 4 weeks of MD compared to baseline, respectively, but these effects did not survive correction for multiple testing. The remaining personality traits agreeableness and openness remained unchanged after MD initiation. Using conventional medication alongside MD or having comorbid diagnoses next to the ADHD diagnosis did not influence the change in any of the mindfulness or personality traits after 4 weeks of MD compared to baseline.

At baseline, the current sample showed on average a lower total mindfulness score as well as lower scores for each mindfulness facet compared to the mean scores of general population samples (37, 38). This lower score was expected, based on the population, if it were not that the majority of the current sample did have

previous experience in meditation and/or mindfulness within 7 days prior to completing the baseline measure. After 4 weeks of MD, the current sample reported total and subscale mindfulness scores that were similar to the mean scores of general population samples, except for the acting with awareness subscale (37, 38). The finding that mindfulness was enhanced in MD individuals is in line with previous studies reporting this association (6, 11), but in contrast to one previous prospective MD study that did not find any changes in mindfulness after 6 weeks of MD (13). Polito and Stevenson (13) used the Mindful Attention Awareness Scale (MAAS) to assess mindfulness making a one-on-one comparison not possible. The discrepancy between the findings by Polito and Stevenson (13) and the current study could potentially be explained by different sample characteristics as they excluded individuals with certain mental disorders, such as mood and anxiety disorders. It may be that MD effects are more pronounced in clinical populations as there is more room to detect changes. However, it might be concluded that the MD-induced changes in mindfulness are most pronounced for non-judging of inner experience and description as these were the only two subscales that still showed MD-induced changes when controlling for recent mindfulness/meditation experience.

At baseline, the personality traits conscientiousness and extraversion were on average lower compared to the mean BFI-10 scores of general population samples (39, 40). In contrast, neuroticism, agreeableness, and openness were at baseline on average higher compared to the mean BFI-10 scores of general population samples (39, 40). The reported baseline conscientiousness, extraversion and neuroticism scores were in line with previously reported associations between ADHD and personality traits (20, 21, 25). In contrast, agreeableness and openness were relatively high in the current sample at baseline while previous studies reported a negative or no relationship between ADHD symptoms and agreeableness and openness, respectively (20, 23, 24, 26). After 4 weeks of MD, conscientiousness and extraversion scores were on average higher than the mean scores of the general population sample reported by Rettenberger and colleagues (39) but remained below the mean scores reported by Blüml amd colleagues (40). Although neuroticism significantly decreased within the current sample after 4 weeks of MD, scores remained on average higher than the mean scores reported by general population samples (39, 40). The decrease in neuroticism reported here is consistent with two previous prospective MD studies (12, 29). In contrast, Polito and Stevenson (13) found an increase in neuroticism after MD. However, as was discussed by Dressler and colleagues (29), the increase in neuroticism might be seen in individuals who have little to no experience with MD or psychedelics in general. The majority of the current sample (80%) had previous experiences with psychedelics and were perhaps well-prepared regarding what to expect, preventing an increase in neuroticism. Based on previous studies, it was expected that the current sample would increase on the remaining four personality traits after MD. However, the increase in conscientiousness seen after 4 weeks and the increase in extraversion seen after 2 weeks of MD in the current study did not survive correction for multiple testing and additionally, the effect sizes were small. Agreeableness and openness to experience did not change at all after MD compared to baseline in the current study, contrasting results from earlier MD studies (12, 28). The lack of findings here might be because of a ceiling effect since the current sample scored already high on these personality traits at baseline.

A limitation of the current study design was the lack of experimental control. Uncertain and perhaps inaccurate reports of the doses and substances used limited the possibility to make inferences about what exactly participants had taken and whether differences in substance and/or dose could have led to different effects on mindfulness and/or personality traits in adults experiencing ADHD symptoms. On the other hand, a strength of the employed design was the ecological validity as it captured MD-induced changes that occur in individuals who are MD on their own initiative, a practice we know is prevalent in current Western societies. Additionally, a strength of the current design compared to retrospective and cross-sectional designs was the use of multiple time points, enabling a comparison of mindfulness and personality after MD initiation to the participant's baseline traits. Thereby, it allows making causal inferences with less uncertainty compared to retrospective and cross-sectional studies. In contrast, a disadvantage of including multiple time points was the large drop-out rate, which could lead to biased results, since participants who perhaps did not have a pleasant MD experience stopped prematurely, potentially creating a more "positive" picture of the effect of MD in ADHD than is truly the case. Related to this, the large drop-out led to a relatively small sample size at the 4-week time point ($n = 44$). The finding that the changes in the mindfulness facets observation, acting with awareness, and non-reactivity to inner experience were no longer significant after including an additional, third, covariate could also be a consequence of a reduction in power or overfitting of the model as in general, more observations per predictor lead to more reliable estimates (41).

Future research should investigate whether the MD-induced effects on mindfulness and neuroticism are long-lasting by including follow-up measurements after several months post-MD. Furthermore, the effects of MD on adult ADHD should be tested in a controlled setting, to ensure drug and dose uniformity, including a (placebo) control group. However, it is important to consider that lab-based measures generally have low ecological validity, and it is therefore also a pressing need to start developing measures that are ecologically valid and sensitive to the effects induced by low doses of psychedelics. Additionally, it would be of interest to compare the effects of MD on mindfulness to a non-pharmacological mindfulness intervention as well as the combination of MD with a mindfulness intervention in adults experiencing ADHD symptoms, to test whether effects induced by MD are comparable to a mindfulness intervention, or whether the combination of both elicits synergistic effects. Lastly, given the previously mixed findings regarding the effects of MD on the personality trait neuroticism, it would be of interest to test whether an increase in neuroticism induced by MD is related to the lack of previous experience with psychedelics. If that is the case, this is an important consideration for future clinical applications and emphasizes the importance of preparation prior to treatment with MD for ADHD, but also other patient populations that might benefit from MD.

To conclude, the current study found positive changes in mindfulness, specifically the mindfulness facets description and non-judging of inner experience, and in the personality trait neuroticism after 4 weeks of MD compared to baseline in adults with an ADHD diagnosis or severe ADHD symptoms. These positive changes might be reflective of the therapeutic properties of MD in this

patient population. Future (placebo) controlled studies are warranted to confirm these findings.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The Ethics Review Committee of Psychology and Neuroscience at Maastricht University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KK and EH designed the study. EH collected and analyzed the data under supervision of KK and PH. EH wrote the first version of the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

KK is a principal investigator on research projects, not including the current study, that are sponsored by Mind Medicine (MindMed) Inc., a company that is developing psychedelic medicines, and she is a paid member of the scientific advisory board of Clerkenwell Health.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ayahuasca-induced personal death experiences: prevalence, characteristics, and impact on attitudes toward death, life, and the environment

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Introduction: Despite an emerging understanding regarding the pivotal mechanistic role of subjective experiences that unfold during acute psychedelic states, very little has been done in the direction of better characterizing such experiences and determining their long-term impact. The present paper utilizes two cross-sectional studies for spotlighting – for the first time in the literature – the characteristics and outcomes of self-reported past experiences related to one's subjective sense of death during ayahuasca ceremonies, termed here Ayahuasca-induced Personal Death (APD) experiences.

Methods: Study 1 (n =54) reports the prevalence, demographics, intensity, and impact of APDs on attitudes toward death, explores whether APDs are related with psychopathology, and reveals their impact on environmental concerns. Study 2 is a larger study (n =306) aiming at generalizing the basic study 1 results regarding APD experience, and in addition, examining whether APDs is associated with self-reported coping strategies and values in life.

Results: Our results indicate that APDs occur to more than half of those participating in ayahuasca ceremonies, typically manifest as strong and transformative experiences, and are associated with an increased sense of transcending death (study 1), as well as the certainty in the continuation of consciousness after death (study 2). No associations were found between having undergone APD experiences and participants' demographics, personality type, and psychopathology. However, APDs were associated with increased self-reported environmental concern (study 1). These experiences also impact life in profound ways. APDs were found to be associated with increases in one's self-reported ability to cope with distress-causing life problems and the sense of fulfillment in life (study 2).

Discussion: The study's findings highlight the prevalence, safety and potency of death experiences that occur during ayahuasca ceremonies, marking them as possible mechanisms for psychedelics' long-term salutatory effects in non-clinical populations. Thus, the present results join other efforts of tracking and characterizing the profound subjective experiences that occur during acute psychedelic states.

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KEYWORDS

ayahuasca, psychedelics, death, self, environmental concern, coping, life fulfillment

1 Introduction

Psychedelic substances such as psilocybin, lysergic acid diethylamide (LSD), and ayahuasca (a potent Amazonian brew containing N,N-Dimethyltryptamine and Harmala alkaloids) have gained considerable popular and scientific attention in recent years (1). Their potential use as adjuncts for treating various mental health conditions has been recognized (2), with institutions such as the U.S. Food and Drug Administration (FDA), even granting them breakthrough therapy designations (3). Research on psychedelics has also centered around the profound experiences they induce, rendering them uniquely situated from advancing research on the phenomenology and neurophysiology of consciousness and the self (4). Common acute experiential effects of psychedelics include intense visual and auditory hallucinations, alterations in perception, changes in mood and thought processes, a shift in the sense of self, as well as a profound feeling of being transported to an alternative reality or dimension (5–7). Some of these experiences are so deeply profound and personally significant that they have been referred to using words such as 'mystical' (8) or 'spiritual' (9). Among these factors, the phenomenon of 'ego dissolution', marked by a profound sense of unity and the dissolution of boundaries between the self and the external world, has garnered significant attention (10).

The effects of these profound experiences outlast the acute state (11). The prevailing view among researchers is that such experiences are the primary drivers of psychedelics' long-term effects [(12); but see (13, 14)]. This perspective is supported by a growing body of research, which has revealed a robust correlation between the quality of subjective experiences during psychedelic use and the enduring changes observed in human beliefs, emotions, and behavior over the long term (11). Multiple subjective effects, including but not limited to mystical-type experiences, ego dissolution, feelings of connectedness, psychological flexibility and emotional breakthroughs, have been found to be associated with the enduring changes observed over the long term (11, 15). For example, research has shown that the mystical-type acute experience which is characterized by a sense of transcendence and unity, along with ineffable and noetic qualities (16) is linked to increased long-term interpersonal closeness, a heightened sense of life meaning and purpose, shifts in coping strategies (17), increased belief in the transcendence of death (17–20), enhanced connection with nature (21), as well as a decrease in symptoms of depression and addiction behavior (22, 23). Such findings highlight the potential of psychedelic-induced experiences in bringing about profound changes in the individual's relationship with the extended world on social, environmental, and spiritual levels – thus enhancing one's sense of meaning in life and changing his relationship with it.

Another intriguing but underexplored profound experience that may arise during acute psychedelic states is the experience of 'personal death'. In Ayahuasca-induced Personal Death (APD) experiences, an individual may feel an overwhelmingly authentic and convincing sensation of acutely dying or being dead, to the extent that it becomes indistinguishable from the 'actual' experience of dying or death (24, 25). APDs may be accompanied by anxiety and confusion (26) or/and with the experience of rebirth, salvation, mystical experience and the feeling of knowing what happens after death (25, 27). Reports of this phenomenon are well-documented in the psychedelics literature (5, 24–33), and it is widely believed that such experiences significantly impact users by allowing a deep realization of the human vulnerability and impermanence, potentially leading to radical personal transformations (24–26, 29). These transformations, as described by Grof and Halifax (24), frequently involve a profound realignment of core values. As a result, aspirations for worldly success, competitive drive, and the relentless pursuit of status, power, fame, prestige, and possessions often lose their allure. Simultaneously, these experiences often serve as gateways to the exploration of spiritual and religious dimensions, providing individuals with profound insights into the significance of the spiritual realm and its relevance within the broader context of existence.

While death experiences are not unique to any particular psychedelic substance, cultural, phenomenological, and pharmacological perspectives suggest they have a special affinity with ayahuasca. Culturally, the link between ayahuasca and the theme of death is present already in its original indigenous Amazonian context (25, 34), where the word ayahuasca means in Quechua *the dead-liana* (35) or *the vine of death* (36). Phenomenologically, some of the groundbreaking work regarding the phenomenology of ayahuasca was conducted by Benny Shannon based on a corpus of some 2,500 ayahuasca experiences descriptions summarized in the book "The Antipodes of the Mind" (25). Shannon recognizes the importance of APDs as some of the most potent and transformative experiences related to the brew and describes death-related experiences as some of the most prevalent cross-cultural subjective themes associated with the brew. Pharmacologically, the ayahuasca brew and its compounds, and in particular the N,N-Dimethyltryptamine (DMT), are related to experiences associated with the feeling of dying such as Near Death Experiences (NDEs) in terms of their phenomenology (7, 32, 37) and long term outcomes (25, 32, 38–40). Ayahuasca users, compared to other psychedelic users, report higher scores on questionnaires adapted from the NDE literature (32). The similarity between DMT/ayahuasca experiences and NDEs has even led to a popular theory that endogenous DMT is released during the dying process (31), a theory which has been met with skepticism by other researchers (41). For a recent review of the endogenous role of DMT in mammals see (42). However, it is important to note that other psychoactive drugs have also been proposed to elicit experiences that resemble NDEs (43, 44).

In sum, given the transformational and therapeutic efficacy of profound psychedelic acute experiences, and the cultural, phenomenological, and pharmacological affinity of ayahuasca to personal death experiences, investigating the APD phenomenon is timely. Thus, the primary objective of the current paper is to empirically explore, for the first time in the literature, the prevalence, characteristics, and long-term outcomes of APDs. It consists of two cross-sectional studies. Study 1 is a preliminary study of veteran ayahuasca users ($n = 54$) aiming at measuring the lifetime prevalence

and characteristics of past APDs, as well as their association with death-related beliefs, attitudes, and connection with the extended world on social and environmental levels. Study 2 is a larger and more representative internet-based study ($n = 306$) aiming at generalizing Study 1's findings regarding the prevalence and characteristics of APDs, and in addition, exploring the long-term associations of lifetime APDs with life engagement on the levels of both life values, as well as the ability to cope with difficult life situations. It is important to clarify that while both studies shared items allowing the basic characterization of APDs, their overall aims varied as each was part of a larger project associated with the neurophenomenology of death processing (Study 1) and public health (Study 2) in ayahuasca users in Israel. The study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies (45).

2 Study 1

Study 1 was designed as an initial, proof-of-concept exploration of the APD experience. It is part of a larger project studying death processing in ayahuasca veterans using phenomenology, neural and behavioral tasks, and self-report measures. Here, our aim was to provide the literature's first characterization of lifetime APD experiences in terms of prevalence and intensity. As the prevalence of APDs is unknown, to increase the chances of detection we recruited participants who had significant experience with ayahuasca. To be able to link our results specifically to ayahuasca, only participants who considered ayahuasca as their main psychedelic were recruited. We also aimed at examine the effects of having undergone such experiences on attitudes toward death (46), and anxiety of death (47). We examined whether having such experiences was associated with psychopathology, and whether it could be predicted by certain personality traits – previously linked with other phenomenological aspects of the psychedelic experience (48) and NDE (49). Finally, we examined whether such past '*in vivo* experiences of dying' (50) would soften one's self-focus thus extending cognitive resources and emotional concern toward beyond-personal facets of life, including the social world (other people) and the natural world (environmental concern). The former was assessed using a well-established self-other bias perceptual task (51), and the latter via the gold standard in measuring environmental attitudes (52).

Based on the anecdotal evidence linking ayahuasca to the theme of death, we hypothesized that APD experiences (our independent variable) would regularly occur among veteran ayahuasca users, but could not make more precise hypotheses regarding actual rates due to the lack of previous structured inquiry. We also hypothesized that APD experiences would be retrospectively reported as being typically powerful and impactful and would be associated with stronger perceptions of having transcended death and reduced death anxiety (dependent variables). As psychedelic usage is closely linked with non-materialistic ontological beliefs (53), we did not expect categorization (continuation vs. annihilation) differences related to APD experiences due to a ceiling effect. We did, however, explore whether the degree of certainty in these views (as a dependent variable) were linked with past APDs. Possible associations between lifetime APD experiences and various exploratory control variables such as demographic factors, personality types, and psychopathology measures (depression, anxiety, and depersonalization) were examined. Finally, we hypothesized APD experiences to be associated with an increase in beyond-personal cognitive processing and concern (dependent variables), expressed as a reduction in the degree of behavioral bias toward 'self' (increased accuracy and reduced response times, see measures below) in comparison to 'other', as well as increased self-reported concern toward the environment. Importantly, to distinguish APD-specific effects from the ego dissolution literature, we also administered the Ego Dissolution Inventory (EDI) (54) as a dependent measure controlling of mystical experiences in general.

2.1 Materials and methods

2.1.1 Participants

Fifty-four experienced ayahuasca users were recruited via social media and personal connections. Inclusion criteria were: multiple ayahuasca usage (>8 times), consideration of ayahuasca as their main psychedelic substance-of-use (their "medicine" of choice using the participants' jargon), and no use of ayahuasca or other psychedelics in 28 days preceding the assessment, willingness to sign the informed consent, no current use of psychoactive medications (antidepressants, mood stabilizers, anxiolytics, and antipsychotics), no current use of drugs of abuse (cocaine), and less than twice a month of cannabis intake, no neurological or active psychiatric illnesses (e.g., epilepsy, depression), and no loss of a first degree relative (spouse, parent, child, or sibling) within the last 12 months. As the study was part of a larger neurophenomenological project, inclusion criteria included also Magnetoencephalography-compatibility factors including no history of head injury with loss of consciousness, not pregnant or lactating, and no claustrophobia or metal implants. Considerations relating to the larger project, neuroscientific ones in particular, also determined the study's sample size. The study was approved by the Institutional Review Board of the Education Faculty, the University of Haifa, Israel. Together with other parts of the study not detailed here, participants spent around 4 h at home and in the lab completing the tasks and were compensated for their time by a sum of 100 Euros.

2.1.2 Measures

2.1.2.1 Demographics, personality, and ayahuasca use habits

Demographic items included age, gender, marital status, income, and education.

Personality was assessed using the Big Five Inventory [BFI, (55)], a commonly used personality assessment instrument that measures the five major personality traits, including openness, conscientiousness, extraversion, agreeableness, and neuroticism. The inventory consists of 44 items rated on a 5-point Likert scale (ranging from 1 – strongly disagree to 5 – strongly agree). Scores for each trait are calculated by averaging scores for the relevant items, with higher scores indicating higher levels of the trait. We used a well-established Hebrew version of the BFI (56). The resulting Cronbach's alpha coefficients for BFI sub-scales extraversion, agreeableness, conscientiousness, neuroticism, and openness were 0.71, 0.71, 0.55, 0.83, 0.72, respectively.

Ayahuasca use habits included items on lifetime use, age of first ayahuasca consumption, time (in months) since last ayahuasca intake

and since strongest ayahuasca experience. We also collected data regarding the lifetime usage of other psychedelics (Psilocybin, LSD, Mescaline).

2.1.2.2 APD experiences: lifetime prevalence and characteristics

APD experiences were probed using 4 questions asking participants whether they (1) had personal death experiences during ayahuasca ceremonies (yes/no). If yes, participants were further asked (2) how many times they had such experiences (3-level ordinal scale of 1–5, 6–10, more than 10 times), (3) how intense these experiences were (Visual Analog Scale (VAS) ranging from 1 to 100, with 1 indicating "not intense at all" and 100 indicating "the most intense possible"), and (4) whether these experiences changed their attitudes toward death (1–4 point scale ranging from "no change" to "changed extremely). The term "intensity" was used as in prior research in the field (54, 57), with the goal of assessing the overall intensity of these experiences (which can differ across various senses, affectivity, valence, and spiritual tone).

2.1.2.3 Ego dissolution

Ego dissolution was measured by the Ego Dissolution Inventory (EDI) (54). EDI is a 16-item self-report measure that assesses past ego dissolution experiences. Each item in the inventory is rated using a visual analog scale format (0–100, with incremental units of one) with zero defined as "No, not more than usually" and 100 defined as "Yes, entirely or completely. As in the original article, we used 2 EDI scales evaluating the strength of the: (1) "most intense" Ego Dissolution experience (EDI-S); (2) a "typical" Ego Dissolution experience (EDI-T). Total ego dissolution score was calculated by averaging the scores for all items, with higher scores indicating a greater level of ego dissolution. The EDI was translated as described in Section 2.1.3. The resulting Cronbach's alpha was 0.93, matching the one reported in the original EDI English study (54).

2.1.2.4 Death anxiety, beliefs, and attitudes

Death anxiety was gauged via the Death Anxiety Scale [DAS, (47)]. The DAS is the most widely-used and validated tool applied in both clinical and research settings for assessing death anxiety levels and its impact on individuals' functioning. We employed the Likert scale version (58, 59) which consists of 15 items rated as a 1–5 Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The total score is calculated by averaging the scores for all items, with higher scores indicating a greater level of death anxiety. The DAS was translated as described in section 2.1.3. The resulting Cronbach's alpha coefficient was 0.78, in the range of other studies using the translations of the scale to other languages (58).

Ontological Afterlife Beliefs (ALB) were probed via an in-house two-part self-report question indexing dis/belief in the continuation of soul/consciousness after death, as well as degree of certainty in the belief. Participants chose which of the following statements better suited their beliefs: "when the heart and brain stop working the soul/consciousness terminally ends" or "The soul/consciousness continues on after death." Then, the participants rated their level of certainty in their answers using a VAS ranging from 0–100. A rating of 1 indicated "I do not know" while a rating of 100 indicated "I'm totally sure."

Death transcendence attitudes were probed via the Death Transcendence Scale (DTS, Vandecreek, 1999). The DTS is a validated scale that measures death transcendence-attitudes and adaptations to the finitude of life and the sense of continuity after death. It includes 26 questions and five factors/subscales (mysticism, religion, nature, creativity, and biosocial). Importantly, the latter three subcategories are agnostic regarding the continuation of soul/consciousness as measured by the ALB scale. Recent research has shown increases in DTS scores following psychedelic Interventions (17–20). Each item is rated on a 5-point Likert scale (ranging from 1 – strongly disagree to 5 – strongly agree). The total score is calculated by summing the scores for all items, with higher scores indicating higher levels of death transcendence. The DTS was translated as described in section 2.1.3. The resulting Cronbach's alpha coefficient was 0.69, in tide with the original published English version (Cronbach's alpha = 0.74) (46).

2.1.2.5 Psychopathology measures

Depression was measured via the Beck Depression Inventory [BDI, (60)]. The BDI is a validated tool commonly used in both clinical and research settings to assess the severity of depression and monitor changes in depressive symptoms over time. The measure consists of 21 items, with each item rated on a 0 to 3 scale, with higher scores indicating greater levels of depression (ranging from 0–63). Here we used a validated BDI Hebrew version (61). The resulting Cronbach's alpha coefficient was 0.69, somewhat lower than described in literature (0.86) (62), but still within the range of reliability.

Anxiety was measured with the State–Trait Anxiety Inventory-Trait measure [STAI, (63)]. The STAI is a widely used and validated tool for assessing general anxiety level over time in both clinical and research settings. It consists of 20 self-report items, each rated as a 1–4 Likert scale, with higher scores indicating higher levels of anxiety. Scores are summed to obtain a total score (ranging from 20–80). We used a Hebrew version of the STAI questionnaire (64). The resulting Cronbach's alpha coefficient was 0.91, well within the range of the original published scale (63).

Depersonalization was measured via the Cambridge Depersonalization Scale [CDS, (65)]. The CDS includes 29 self-report items rated on two Likert scales for frequency (1–4, ranging from never to all the time) and duration (0–10, ranging from a few seconds to more than a week) of experience. The total score on the CDS is calculated by summing the scores for all items in their respective subscales for frequency and duration, each of which yields a separate score. Higher scores on either subscale indicate greater degrees of depersonalization. The CDC was translated as described in Section 2.1.3. The resulting Cronbach's alpha coefficient was 0.87, somewhat lower than reported in other translations of this scale but still highly reliable (66).

2.1.2.6 Beyond-personal (others/nature) processing

Relation to nature was gauged via the New Ecological Paradigm Scale Revised [NEP-R, (67)] a self-report scale measuring environmental concern. The scale consists of 15 items rated on a 5-point Likert scale (ranging from 1 – strongly disagree to 5 – strongly agree). Total score is calculated by averaging the scores for all items, with higher scores indicating stronger pro-environmental attitudes. The NEP-R was translated as described in Section 2.1.3. The resulting Cronbach's alpha was 0.78 in line with the original English version (Cronbach's alpha = 0.81) (68).

Relation to others was assessed via the Self Prioritization Task [SPT, (51)]. The SPT task measures self-prioritization, which refers to

the degree to which individuals exhibit an implicit behavioral bias toward the "self" as opposed to the "other." Participants are trained in learning associations between geometric shapes (a triangle, a square, and a circle) and words 'self', best 'friend, and an unfamiliar 'stranger'. For example, they may be told "imagine your good friend is the circle, you are the triangle, and a stranger is the square." Numerous studies (69) reliably show that when shapes are adapted to the "self" label, as opposed to being matched to the "familiar" or "stranger" labels, participants exhibit greater accuracy and faster response times, termed self-prioritization effects.

2.1.3 Procedure

Questionnaires were completed online via a web link to an anonymous survey using the Qualtrics survey tool (Qualtrics, Provo, UT) between the 10.2021–06.2022. Questionnaires for which validated Hebrew translations were not found were translated in Hebrew using a back-translation process (70) for ensuring accurate and culturally appropriate meaning for Hebrew speakers. The process entailed one translator translating each questionnaire from English to Hebrew, and then another independent translator translating them back from Hebrew to English. A third independent translator, who was also a professional translator and editor, then evaluated the translations to identify and correct any discrepancies or errors.

The SPT behavioral task was administered at the Electromagnetic Brain Imaging Unit at Bar-Ilan University, Israel. The SPT task was presented using E-prime 3.0 on a 15.6-inch HD (1,366 × 768) screen on a Dell Vostro Laptop. The SPT task materials and procedure followed published guidelines (51), with the exception of being shortened to 240 trials administered in 4 60-trial rounds (compared to the original format of 3 rounds of 120 trials each). This was done following an in-lab pilot experiment which demonstrated no significant improvements in performance (reaction time and accuracy) beyond 240 trials.

After reading the task instructions on the computer screen and matching each shape to a label (counter-balanced across participants), the participants were given a short training session of twelve trials which were supervised by the experimenter to ensure participant task comprehension. Each trial started with a fixation cross appearing for 500 ms, after which a shape (triangle, circle, or square) and a word label (self, friend, stranger) were displayed for 100 ms above and below the cross, respectively. Immediately after that, a blank frame was presented for 1,300 ms in which time participants were required to judge whether the shape-label pair matched or not, by pressing one of the two response buttons as quickly and accurately as possible. Feedback (correct or incorrect) was immediately presented on the screen for 500 ms. At the end of each block, a frame was displayed informing the participants of their overall accuracy in the block. Responses longer than 1,300 ms were classified as misses and responses faster than 200 milliseconds were excluded from the analysis. Task outcomes were the participants' d-prime (d') accuracy scores and response times (RTs) of correct categorizations. Higher d' and shorter RT scores indicate stronger self prioritization effects.

2.1.4 Statistical analyses

Data analysis was conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and jamovi software (version 2.3.1, The jamovi project). The internal consistency of the self-report scales was assessed using Cronbach's alpha coefficient (71). Between-group (those who experienced or had not experienced APDs, named yAPD and nAPD, respectively) comparisons were performed using two-tailed independent *t*-tests for parametric data, Mann–Whitney *U* tests for non-parametric data, and chi-square tests for categorical data. Pearson's (r) or Spearman's (ρ) correlation coefficients were used (depending on ordinal/continuous nature of the data and its distribution) for exploring relations between APD features and other measures, as well as controlling for the more general mystical experience of ego dissolution. Normality was assessed via the Shapiro–Wilk test, and a significance level of less than 0.05 was used to determine departures from normality. The SPT task was assessed via mixed Anovas (for the d' and RT dependent variables separately), with *identity* (self/friend/stranger) as a within-subject factor and *group* (yAPD/nAPD) as a between-subject factor, and *post hoc* analyses were conducted using *t*-tests. Effect size measures were calculated using Cohen's d (d) and Eta squared (η2) for parametric data, and rank biserial correlation (r_p) for non-parametric data. Significance values equal to or smaller than 0.05 were considered statistically significant.

2.2 Results

2.2.1 Participants characteristics

Table 1 provides a summary of the study sample's characteristics, including demographic variables, ayahuasca use parameters, personality traits, and psychopathology measures. The table also demonstrates a comparison between the yAPD and nAPD groups across these variables. The results show no statistically significant differences between the two groups in terms of ayahuasca use parameters, personality traits, and psychopathology measures. Supplementary Table S1 displays participants' lifetime use of psychedelics (ayahuasca, LSD, Psilocybin, Mescaline) and includes a comparison between the groups in relation to lifetime use of other psychedelic. Results reveal a significantly higher use of ayahuasca compared to other psychedelics, with no significant differences between yAPD and nAPD groups for other psychedelics usge. Briefly, on average, our study participants have used ayahuasca (mean = 69.4 ± 98.7) 6.4 times more than psilocybin (mean = 10.7 ± 15.4, $U = 1{,}378$, $p < 0.01$, $r_p = 1$), 5.7 times more than Mescaline (mean = 12 ± 14.9, $U = 351$, $p < 0.01$, $r_p = 1$) and 7.07 times more than LSD (mean = 9.9 ± 16.6, $U = 976$, $p < 0.01$, $r_p = 1$).

2.2.2 APD experiences prevalence and characteristics

Of the 54 ayahuasca users, 36 participants (66.7%) reported having experienced APDs while 18 participants reported not having experienced APDs (Figure 1A). Within the yAPD group, 17 participants (47.2%) reported experiencing it 1–5 times, 17 participants (47.2%) reported experiencing it 6–10 times, and 2 participants (5.6%) reported experiencing it more than 10 times (Figure 1B). In terms of the perceived intensity of the APD exeriences, the mean subjective intensity of APD experiences was 93.6 (SD = 10), and the median was 100, with only 2 participants reporting APD intensity below 80 (Figure 1C). In terms of subsequent change in attitude toward death, 28 participants (77.8%) reported an extreme change, 6 participants (16.7%) reported a moderate change, only one participant (2.8%) reported a minimal change, and another participant (2.8%) reported no change (Figure 1D).

TABLE 1 Summary of Study 1's sample characteristics.

Variable	yAPD $n = 36$ (66.6%)		nAPD $n = 18$ (33.3%)	Total $n = 54$	Statistics (all n.s.)
Demographics					
Age		38.1 ± 7.5	39.4 ± 10.4	38.5 ± 8.6	$U = 331$
Gender	Male	25 (69.4%)	10 (55.5%)	35 (64.8%)	$X^2 = 1.02$
	Female	11 (30.5%)	8 (44.4%)	19 (35.2%)	
Education	High School or equivalent	9 (25%)	1 (5.5%)	10 (18.5%)	$X^2 = 3.75$
	College Diploma or certification studies	22 (61%)	12 (66.6%)	34 (63%)	
	Master's Degree and above	5 (13%)	5 (27.7%)	10 (18.5%)	
Family status	Unmarried	18 (50%)	7 (38.8%)	25 (46.3%)	$X^2 = 6.25$
	Married	12 (33%)	7 (38.8%)	19 (35.2%)	
	Divorced	6 (16.6%)	4 (22.2%)	10 (18.5%)	
Income	Below average	8 (22.2%)	4 (22.2%)	12 (22.2%)	$X^2 = 1.10$
	Average	14 (38.8%)	9 (50%)	23 (42.3%)	
	Above average	14 (38.8%)	5 (27.7%)	19 (35.1%)	
Ayahuasca parameters	Lifetime use (number of times ayahuasca was taken)	69.4 ± 98.7	29.5 ± 13.7	55.8 ± 82.1	$U = 255$
	Age of first ayahuasca	30.4 ± 6.7	34.2 ± 10.5	31.7 ± 8.2	$T = 107$
	Last use (month)	6.7 ± 6.8	4.3 ± 5.2	8.2 ± 5.2	$U = 252$
	Most intense (month)	38.2 ± 41	24.9 ± 18.6	33.8 ± 35.5	$U = 254$
Psychopathology					
Depression (BDI)		5 ± 4.15	4.11 ± 4.17	4.7 ± 4.1	$U = 279$
Depersonalization (CDS)	Duration	45 ± 14.10	45.6 ± 12.04	45.2 ± 13.3	$U = 566$
	Frequency	46.1 ± 8.8	38.4 ± 9	45.6 ± 8.4	$T = 150$
Trait anxiety (STAI)		35.9 ± 8.6	38.4 ± 9	36.7 ± 8.7	$U = 270$
Personality (BFI)	Extraversion	3.4 ± 0.4	3.3 ± 0.6	3.44 ± 0.53	$T = 0.741$
	Neuroticism	2.42 ± 0.6	2.55 ± 0.6	2.44 ± 0.64	$T = -0.668$
	Agreeableness	3.93 ± 0.4	3.94 ± 0.3	3.94 ± 0.43	$T = -0.146$
	Conscientiousness	3.56 ± 0.4	3.50 ± 0.3	3.54 ± 0.40	$T = 0.524$
	Openness	4.12 ± 0.4	3.92 ± 0.5	4.04 ± 0.45	$T = 1.53$

The table summarizes the characteristics (means, SD and the statistics) of the study sample, including demographic variables, ayahuasca use parameters, personality traits, psychopathology, as a function of APD (yAPD group) or not (nAPD group). APD, Ayahuasca-Induced personal death; CDS, Cambridge personality scale; BDI, Beck Depression Inventory; BFI, Big Five Inventory; STAI, State–Trait Anxiety Inventory. Statistics: T, T-tests; U, Mann–Whitney tests; X^2, chi-square tests. No significant between-group differences were found.

2.2.3 Death related anxiety, beliefs, and attitudes

In distinction to our hypothesis, no differences in death-related anxiety (DAS scores) were found between the yAPD (mean = 2.67 ± 2.67) and nAPD (mean = 2.67 ± 2.53) groups ($t(52) = -0.01$, n.s.). Regarding ontological afterlife beliefs, nearly all the participants (94.4%) endorsed a belief in the continuation of the soul/consciousness after death, with a high degree of certainty (mean = 86.6% ± 19, median = 90). Both measures did not differ between the groups. Regarding death-related attitudes, the findings demonstrated (Figure 2A) a significantly stronger endorsement (higher DTS scores) of death transcendence views [$t(52) = 2.62$, $p = 0.01$, $d = 0.75$] for the yAPD group (mean = 83.3 ± 6.2) relative to the nAPD (mean = 78.6 ± 6.2) group. In addition, within the yAPD group, the perceived impact of APD experiences on attitudes related to death strongly predicted the DTS scores ($\rho = 0.575$ $p < 0.001$). Finally, our analysis revealed also a significant correlation between the DTS score and the EDI-S scale ($\rho = 0.410$, $p < 0.01$) but not the EDI-T scale ($\rho = 0.225$, $p < 0.102$), thus suggesting our results may not be APD-specific.

2.2.4 Beyond-personal (others/nature) processing

The results regarding the effect of APDs on beyond personal factors were mixed, indicating significantly higher [$t(52) = 2.268$, $p = 0.02$, $d = 0.655$] environmental concern (higher NEP-R scores) for the yAPD group (mean = 3.73 ± 0.46) relative to the nAPD group (mean = 3.43 ± 0.45) (Figure 2B), thus confirming our hypothesis regarding the link between APDs and environmental attitudes. Importantly, these results were specific to APD experiences. Both typical and strongest measures of ego dissolution did not predict environmental concern (EDI-S $\rho = 0.218$, p = n.s; EDI-T $\rho = 0.087$, p = n.s).

10.3389/fpsyt.2023.1287961

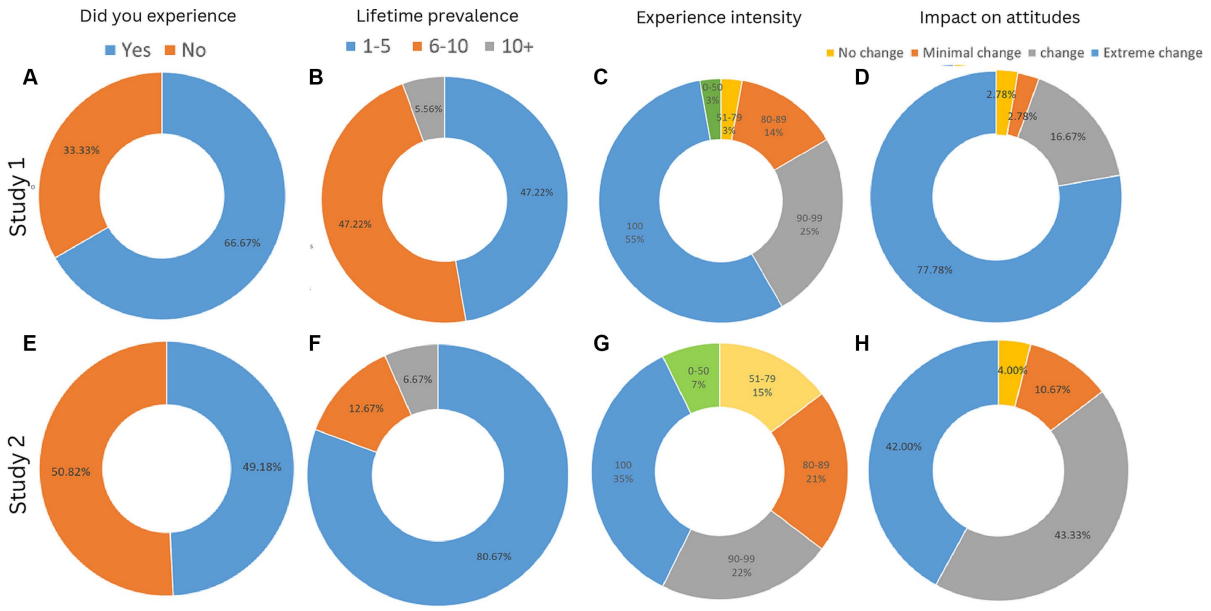

FIGURE 1
Prevalence and characteristics of APD experiences across Studies 1 and 2: Top row **(A–D)** displays results from Study 1 ($n = 54$), and bottom row **(E–H)** from Study 2 ($n = 306$). The overall occurrence (yes/no) of APD experiences are displayed in **(A,E)**. For those who had experienced APDs ($n = 36$ in Study 1, and $n = 155$ in Study 2), **(B,F)** displays their lifetime frequency rates, **(C,G)** displays their perceived intensity, and **(D,H)** their perceived impact on attitudes related to death.

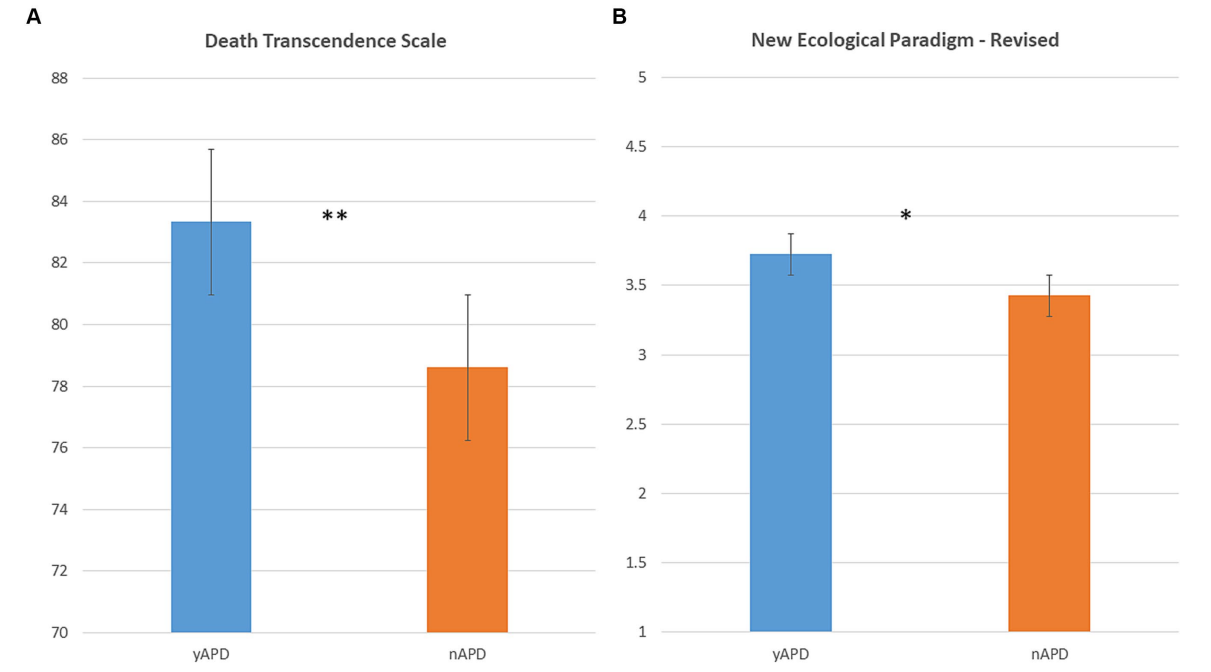

FIGURE 2
Death transcendence attitudes and environmental concern as a function of experiencing APDs. Bar plots comparing the distribution of **(A)** DTS scores (y-axis), and **(B)** NEP-R scores (y-axis), as a function of the yAPD group (in blue) and nAPD group (in orange). Error bars represent the standard error of the mean. DTS, Death Transcendence Scale, NEP-R, New Environmental Paradigm Revised. Statistics: p-values ≤ 0.01 are denoted by **, and p-values ≤ 0.05 are denoted by *.

However, no significant differences were found for beyond personal social processing (d' and RT in the SPT task). The SPT analysis included data from 51 participants (2 did not do the task, and one participant's data was missing). A repeated-measures 2×3 ANOVA with *group* (yAPD/nAPD) and *identity* (self/friend/stranger) as within-participant factors was conducted for d' and RT dependent

variables. The results revealed highly significant main effects of *identity* for both accuracy [$F(2,98) = 10.92$, $p < 0.001$, $\eta^2 = 0.05$] and RTs [$F(2,98) = 28.31$, $p < 0.001$, $\eta^2 = 0.145$], with posthoc tests replicating the task's self-prioritization effect. Participants displayed significantly higher d' scores and faster RTs when responding to self-related stimuli compared to friend-related stimuli (d', $p < 0.001$; RT, $p = 0.006$), compared to stranger-related stimuli (d', $p < 0.001$; RT, $p < 0.001$). Contrary to our hypothesis, the *group* x *identity* interaction was not significant for both d' [$F(2,98) = 0.142$, $p = 0.886$] and RT [$F(2,98) = 0.536$, $p = 0.587$], suggesting that self-prioritization was not affected by having experienced APDs.

3 Study 2

Study 2 had two aims. The first is generalize Study 1's results regarding the prevalence and characteristics of lifetime APD experiences, while addressing its potential selection bias due to its small and unique sample of veteran ayahuasca users with extensive experience with the brew. Thus a larger, more representative internet-based sample of ayahuasca users with any degree of experience were recruited. The second aim was extending Study 1's results by exploring the association between APD's and life engagement. Study 2 aimed at exploring the association between having experienced APDs (independent variable) on the manner in which one engaged with life. Specifically, we focused on assessing the participants' self-reported ability to cope with distressing situations, as well as their values in life (dependent variables). We hypothesized that similar to findings from NDE studies (38, 39, 72–75), APDs would be associated with an enhanced ability to cope with distressing life situations and increased life values and meaning.

3.1 Methods

3.1.1 Participants

Participants were recruited as part of a larger study assessing the public health of ayahuasca users in Israel. 306 ayahuasca users were recruited via ayahuasca contact groups and psychedelic social media groups in Israel. Sample size determination was licensed by the medium to large between-subjects effect sizes reported in Study 1 (*d*s of 0.65 and 0.75 for the DTS and NEPR scales, respectively), as well as the discovered 2 to 1 ratio of participants who had not-experienced vs. experienced APDs. Thus, conservatively assuming a medium effect size of $d = 0.5$, and a 2 to 1 APD experience ratio, our sample size is sufficient for determining group differences ($n = 236$ allows power = 0.95 at $\alpha = 0.05$ for $d = 0.5$, and a 2/1 allocation ratio). Inclusion criteria were: age > 18, at least six months since initial ayahuasca intake, be able to fluently read and understand Hebrew, and provided informed consent. The study protocol was approved by the Institutional Review Board of the Faculty of Education, University of Haifa, Israel. All participants provided written informed consent to participate in the study and did not receive financial compensation.

3.1.2 Procedure

Data were collected via the Qualtrics online survey tool (Qualtrics, Provo, UT) using a web link to an anonymous survey between the 12.2022–02.2023. The back-translation procedure (70) was used for translating questionnaires not available in Hebrew. Participants dedicated around 30 min to complete an online questionnaire including demographics, ayahuasca consumption patterns, information on APD experiences (as in Study 1), and a comprehensive public health survey (to be reported elsewhere). In addition, each participant completed two questionnaires indexing coping style with distress and values in life [see (76, 77)].

3.1.3 Measures

3.1.3.1 Demographics and ayahuasca usage habits

Demographic information included age, gender, marital status, income, education, and lifetime psychedelics use (Psilocybin, LSD, mescaline).

Ayahuasca use habits included lifetime consumption amount, age of first ayahuasca intake consumption, time since last ayahuasca experience, and ayahuasca consumption settings.

3.1.3.2 APD lifetime prevalence, characteristics, and ontological beliefs

APD experiences were probed using the same four questions as in Study 1, described previously.

Ontological afterlife beliefs were gauged using the ALB measure described previously.

3.1.3.3 Life engagement and coping

Coping strategies were assessed using the Hebrew version, shortened (78) Coping Strategies Scale (79). The shortened COPE is a 30-item tool designed to evaluate two categories of coping strategies: problem-focused coping (COPE-p) and emotion-focused coping (COPE-e). Problem-focused coping strategies involve taking actions to manage or solve the distress causing problems (i.e., gathering information, making a plan, or seeking advice from others). Emotional-focused coping strategies involve managing the emotional distress caused by a stressful situation (i.e., seeking emotional support, distracting oneself from the stressor, or engaging in activities that help regulate emotions). Participants were asked to indicate how often they use each coping strategy when faced with a stressful situation, with items rated on a 4-point Likert scale, ranging from 0 (not at all) to 3 (very much). Higher scores indicate a greater use of the respective coping strategy. The resulting Cronbach's alpha coefficient was 0.72 for COPE-p and 0.61 for COPE-e, close to the coefficient values published in the original COPE article (COPE-$p = 0.76$ and COPE-e = 0.64) (78).

Values in life were assessed via the Engaged Living Scale [ELS, (80)]. The ELS is a self-report scale measuring personal values and more specifically "engaged living," as understood in the Acceptance and Commitment Therapy (ACT) model. The scale is composed of two subscales: valued living (ELS-v) and life fulfillment (ELSl-f). The ELS-v consists of 10 items assessing an individual's ability to recognize and comprehend their values, as well as their capacity to engage in actions that are consistent with these values. The ELS-f includes 6 items that evaluate a person's sense of fulfillment in life as a result of recognizing and living in accordance with their values. ELS items are rated on a 5-point Likert scale, ranging from 1 (completely disagree) to 5 (completely agree), with higher scores indicating greater levels of engaged living. The ELS was translated as described in section 2.1.3. The resulting Cronbach's alpha coefficients were 0.89 for ELS-l and

0.86 for ELS-v, in line the coefficients reported in the original article (ELS-l and ELS-v = 0.86) (80).

3.1.4 Statistical analyses

Data analysis was conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and jamovi software (version 2.3.1, The jamovi project). Internal consistency of the self-report questionnaires was assessed using Cronbach's alpha coefficient (71). Between-group comparisons (yAPD and nAPD participants) were performed using two-tailed independent-samples *t*-tests for parametric data, Mann–Whitney *U* tests for non-parametric data, and chi-square tests for categorical data. Effect sizes were calculated to provide additional information about the magnitude of the differences found. Cohen's d (d) was used for parametric data and rank biserial correlation (r_p) was used for non-parametric data. Pearson's (r) or Spearman's (ρ) correlation coefficients were used (depending on ordinal/continuous the nature of the data and whether it was normally distributed) to assess relations between the APD features and other hypothesized measures, as well as to rule out the effects of other ayahuasca parameters. Normality was assessed via the Shapiro–Wilk test, and a significance level of less than 0.05 was used to determine departures from normality. Significance values equal to or smaller than 0.05 were considered statistically significant.

3.2 Results

3.2.1 Participants characteristics

Table 2 provides a summary of the study sample's characteristics, including demographic variables and ayahuasca use parameters. The table also demonstrates a comparison between the yAPD and nAPD groups across these variables. One participant was excluded due to unreliable results (participant answered '1' for all questions). In line with the results of Study 1, no significant group differences were observed in demographics. However, in contrast to Study 1, our findings revealed significant differences between the groups in terms of lifetime ayahuasca use, last ayahuasca intake, and age of first use with the brew. yAPD participants had been in more ayahuasca ceremonies, their last ayahuasca intake was more recent, and they had consumed ayahuasca for the first time earlier than the nAPD group. There was a slight difference between the yAPD and nAPD groups in usage parameters of other psychedelic substances (LSD and Mescaline, see Supplementary Table S2). However, we ensured via correlation analyses tests that these were not associated with the dependent variables. It is important to highlight that the participants in Study 2 were considerably less experienced users compared to those in Study 1. In Study 2, approximately 50% of the sample reported using ayahuasca between 1 and 10 times. On the other hand, in Study 1, the average intake was 69.4 and only one subject reported having consumed ayahuasca fewer than 10 times.

3.2.2 APDs lifetime prevalence, intensity, and impact

Of the 305 ayahuasca users surveyed, 150 (49.2%) reported having experienced past APDs (Figure 1E). The large majority of the ayahuasca users (121 participants or 80.7%) experienced it between one and five times, whereas 19 participants or 12.7% experienced it between six and ten times, and only ten participants or 6.7% experienced it more than ten times (Figure 1F). The participants reported that the perceived intensity of the APD experiences was strong with a mean of 85.01 (SD = 20.3) and a median of 91 (Figure 1G). The APD was also perceived as impactful and changed their attitudes toward death. 63 participants (42%) reported an extreme change in their attitudes toward death, 65 participants (43.3%) reported a moderate change, 16 participants (10.6%) reported minimal change, and six participants (4%) reported no change in their attitudes toward death (Figure 1H). It should be noted that, in comparison to Study 1, the prevalence of APD was smaller and their intensity were less pronounced and impactful. These differences are likely attributable to the distinct sample characteristics of Study 1, where participants were more experienced with ayahuasca. However, we can not rule out that Study 1's veteran sample may differ in other characteristics and psychological traits.

3.2.3 Ontological afterlife beliefs

The ALB results indicated a clear bias toward literal immortality, as 92.5% of the participants endorsed the view that the soul/consciousness continued on after death. Participants were also very certain about their views (mean = 84.1 ± 23, median = 90). These results align with those of the sample in Study 1. In terms of group differences, there was no significant difference in ALB categorization between the yAPD and nAPD groups [X^2 (1, N = 305) = 0.001, n.s.]. However, ALB certainty was higher (U = 9,472, $p < 0.001$, $r_p = 0.185$) in the yAPD group (mean = 87.8 ± 19.8) than nAPD group (mean = 80.5 ± 25.4).

3.2.4 Life engagement and coping

In terms of coping strategies, results were mixed. As predicted, yAPD participants demonstrated significantly higher scores (U = 8,823, $p < 0.01$, $r_p = 0.24$) on the problem-focused coping strategies with higher COPE-p scores (mean = 2.22 ± 0.31) compared to the nAPD group (mean = 2.07 ± 0.36) (Figure 3A). However, there was no significant group differences [$t(303) = 1.08$, $p = 0.277$, n.s.] in terms of emotional-focused coping strategies (COPE-e scores). Importantly, to ensure that these group differences could not be accounted for by sample differences in lifetime use rates, age of initial intake, and last intake, we ran correlation analyses between the COPE subscales and these variables. The results indicated no significant correlation (all ps > 0.1) between coping strategies and lifetime ayahuasca use (COPE-p, $\rho = -0.02$, n.s.; COPE-e, $\rho = 0.0006$, n.s.), initial intake age (COPE-p $r = -0.005$, n.s.; COPE-e $r = -0.01$, n.s.), and last intake (COPE-p $\rho = -0.06$, n.s.; COPE-e $\rho = -0.004$, n.s.). These findings align with previous results of some of the current authors, where no associations were found between the frequency of ayahuasca use and coping measures (76).

In terms of engaged living, results were mixed as well. As shown in Figure 3B, the yAPD group felt more fulfillment in life with significantly higher scores (U = 10,125, $p = 0.05$, $r_p = 0.12$) on the ELS-f subscale (mean = 3.9 ± 0.70) compared to the nAPD (mean = 3.7 ± 0.68). However, there were no significant differences (U = 10,417, $p = 0.116$, n.s.) observed between the groups in terms of life values (ELS-v scores). An additional correlation analysis within the yAPD group showed that the degree to which death-related attitudes were impacted by APD experiences predicted ELS scores (ELS-v, $\rho = 0.365$, $p < 0.001$; ELS-f, $\rho = 0.231$, $p = 0.004$), thus providing evidence that degree of engaged living was impacted by

TABLE 2 Summary of the Study 2's sample characteristics.

Variable		yAPD $n = 150$ (49.2%)	nAPD $n = 155$ (51.8%)	Total $n = 305$	Statistics
Demographics					
Age		41.4 ± 8.41	43.9 ± 11.4	43 ± 10.3	$U = 10{,}494$, n.s.
Gender	Male	69 (46%)	74 (47.7%)	143 (46.9%)	X^2=0.433, n.s.
	Female	80 (53.3%)	79 (50.9%)	159 (52.1%)	
	Other[a]	1 (0.6%)	2 (1.2%)	3 (0.9%)	
Education	Primary school or less[b]		1 (0.6%)	1 (0.3%)	X^2=11.7, n.s.
	High School or equivalent	69 (46%)	62 (40%)	131 (42.9%)	
	B.A	40 (26.6%)	51 (32.9%)	91 (29.8%)	
	Master's Degree and above	39 (26%)	39 (25.1%)	78 (25.5%)	
Family status	Single	45 (30%)	36 (23.2%)	171 (56%)	X^2=23.4, n.s.
	Married	81 (54%)	90 (58%)	40 (13.1%)	
	Divorced	16 (10.6%)	24 (15.4%)	81 (26.5%)	
	Other	8 (5.3%)	5 (3.2%)	13 (0. 4%)	
Income	Below average	54 (36%)	56 (36.1%)	110 (36%)	X^2=34.2, n.s.
	Average	37 (24.6%)	32 (20.6%)	69 (22.6%)	
	Above average	50 (33.3%)	57 (36.7%)	107 (35%)	
Ayahuasca parameters					
Setting	Local/neo-shamanic	55 (36.6%)	50 (32.2%)	105 (34.4%)	X^2=4.29, n.s.
	Religious, indigenous, or other	95 (63.3%)	105 (67.7)	200 (65.6%)	
Lifetime intake	1–10	56 (37.3%)	94 (60.6%)	150 (49.2%)	**$U = 8{,}539$, $p < 0.01$**
	11–20	22 (14.6%)	22 (14.1%)	44 (14.4%)	
	21–50	29 (19.3%)	16 (10.3%)	44 (14.4%)	
	51–100	20 (13.3%)	13 (8.3%)	33 (10.8%)	
	100+	23 (15.3%)	11 (7%)	34 (11.1%)	
Last intake	Last month or less	48 (23%)	20 (12.9%)	68 (22.3%)	**$U = 9{,}280$, $p < 0.01$**
	Past 1–3 months	25 (16.6%)	34 (21.9%)	59 (19.3%)	
	Past 3–6 months	21 (14%)	23 (14.8)	44 (14.4%)	
	Past 6 months to 1 year	18 (12%)	27 (17.4%)	45 (14.8%)	
	Past 1 year to 3 years	21 (26%)	27 (17.4%)	48 (15.7%)	
	More than 3 years ago	17 (11.3%)	14 (0.9%)	41 (13.5%)	
Age of first intake		33.8 ± 8.7	37.1 ± 11	35.5 ± 10	**$U = 9{,}530$, $p < 0.05$**

The table presents data on demographic characteristics and ayahuasca use parameters for both the yAPD and nAPD groups. Bold markings indicate statistically significant findings. [a]Only male and female participants were compared, as other gender identities were not included in the statistical analysis due to insufficient sample sizes for meaningful comparison. Likewise, [b]The category "Primary school or less" was not included in the statistical analysis. *Percentages reported do not always add up to 100% as some participants did not answer certain questions.

APD experiences. Again we controlled for group differences related to ayahuasca use parameters. No significant correlations ($ps > 0.1$) were found between the ELS subcales and lifetime ayahuasca intake (ELS-v: $\rho = 0.08$, n.s.; ELS-f: $\rho = 0.01$, n.s.), and only marginally significant correlations emerged between the ELS subscales and the age of initial ayahuasca intake (ELS-v: $r = 0.10$, $p = 0.07$; ELS-f: $r = 0.13$, $p = 0.05$). These results partially corroborate previous findings (76), which demonstrated a significant relationship between ELS-v (but not ELS-f) and lifetime ayahuasca use. A significant correlation was found between ELS-v and the last ayahuasca intake intake (ELS-v: $\rho = -0.114$, $p = 0.04$). Furthermore, marginally significant correlations emerged between ELS-f and last ayahuasca intake ($\rho = -0.11$, $p = 0.052$).

4 Discussion

The present study aimed at spotlighting, for the first time in the literature, death experiences occurring during ayahuasca ceremonies. In two independent studies, we examined their prevalence rates, experiential characteristics, and associations with death perceptions. Additionally, we examined the link between lifetime APDs and how

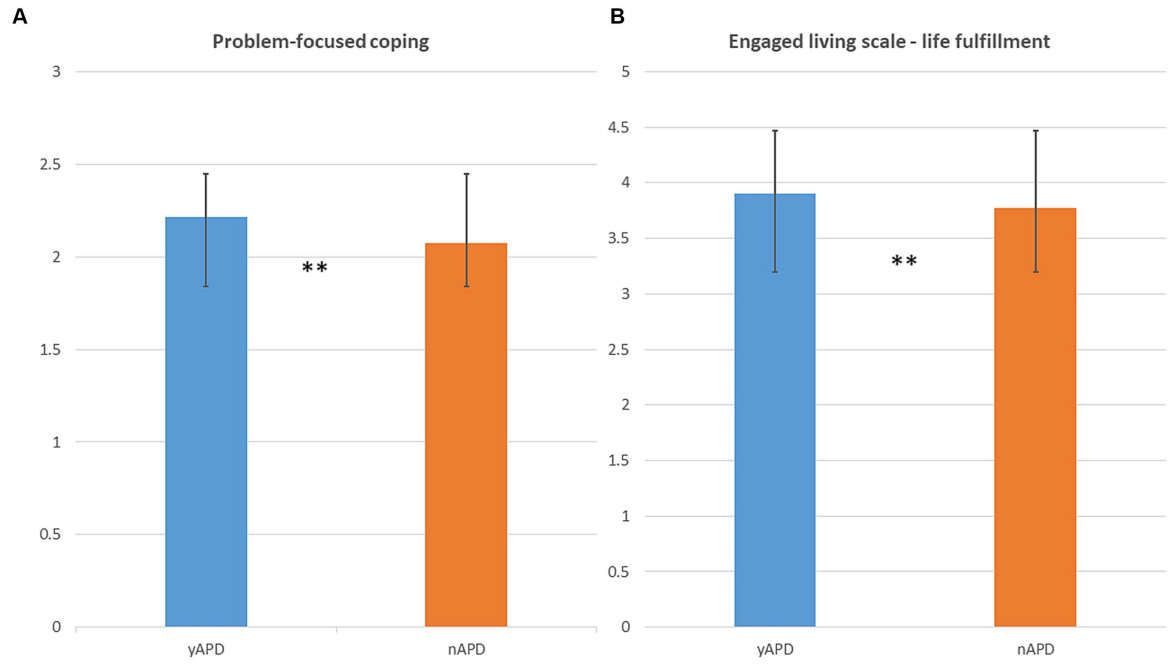

FIGURE 3
Life engagement and coping strategies as a function of APD. Bar plots comparing the distribution of **(A)** COPE-p scores (*y*-axis), and **(B)** ELS-f scores (*y*-axis), as a function of the yAPD group (in blue) and nAPD group (in orange). Error bars represent the standard error of the mean. COPE-p, Problem-focused coping; ELS-f, Engaged Living Scale-life fulfillment. Statistics: *p*-values ≤ 0.01 are denoted by **, and *p*-values ≤ 0.05 are denoted by *.

the extended world was approached (Study 1), as well as on life values and coping strategies (Study 2).

Our findings indicate that APDs are a common experience among those participating in ayahuasca ceremonies, being reported by at least half of the participants. Having such experiences was not related to gender, age, education, personality, or ontological belief. However, while prevalent, these experiences were not very frequent with participants mostly experiencing them no more than 5 times over their lifetime, and very rarely more than 10 times. As expected, these experiences are perceived as powerful and impacted people's attitudes toward death. In both studies, most participants rated APD experiences at the maximum intensity afforded by the scale, and most participants reported APDs to have significantly changed their attitudes toward death. These reports were further validated by other measures showing that lifetime APDs predicted having a stronger sense of having transcended death (in Study 1), and more certainty in the continuation of the soul/consciousness after death (in Study 2). However, in contrast to our expectations APDs did not influence death anxiety levels, and neither were they predictive of psychopathology including depression, anxiety, and depersonalization. In fact, as expected, participants who experienced APDs displayed better problem-solving life coping skills and perceived life as more fulfilling (Study 2). Finally, while APD experiences were not associated with less bias toward the self, in contrast to our expectations, they were associated with increased pro-environmental perceptions as expected (Study 1). Thus, these results establish APDs as frequent, profound, and transformative experiences which have the potency to impact the perception of – or relation to – life, death, and the environment. Important to note, there were differences between Study 1 and Study 2 concerning lifetime experience of APD, intensity, and impact—all of which are lower in Study 2. These variations can be attributed to the distinct sample characteristics of Study 1, where participants were more experienced and considered ayahuasca as their primary psychedelic medicine. Therefore, we postulate that the more one uses ayahuasca, the more possible a strong and transformative APD will be.

4.1 APDs and the perception of death

A structured phenomenological study of the APD experience is still lacking, however, certain anecdotal features gathered from the literature point at an extremely powerful and convincing experience. Participants describe such experiences as consisting of authentic and convincing feelings of dying or being dead, with them often losing the awareness of being in a psychedelic session and undergoing a symbolic experience (24, 25). Other experiential features which may accompany APDs include disembodiment aspects such as seeing oneself from above, the experience of rebirth, salvation, mystical experience, anxiety, confusion and the feeling of knowing what happens after death, while maintaining some self-awareness (25–27).

While APDs do not involve a real situation in which the experiencer is close to actual death, it is experienced that way, and there is evidence that there are similarities between ayahuasca and DMT and NDEs in terms of the phenomenology (5, 7, 31, 32). Similar to NDEs, the experiential realization that consciousness and awareness persist despite the sense of physical bodily death, the encountering mystical beings and other NDE elements may reinforce the belief that consciousness can exist independently of a living body, and even after death (81, 82). Hence, this realization may strengthen the conviction in the existence of an afterlife and may foster a deeper sense of

transcendence in relation to death – in line with the results of the present study. Prior studies show a positive correlation between afterlife beliefs and psychological well-being (83–85), suggesting that these beliefs can liberate individuals from fundamental fears, avoidance patterns, and the continual need for self-worth validation (86–88). However, the impact of afterlife beliefs conduct depends on specific sets of beliefs (85, 89), and therefore, further studies are necessary for examining the specific manifestation of afterlife beliefs in ayahuasca users and their alteration following APD experiences.

While no links were found between APDs and psychopathology, and on the other hand, positive effects in terms of life coping and fulfillment were found, it is premature to classify APDs as inherently positive phenomena. Again drawing parallels from the body of literature concerning NDEs [(90), but see (91)] as well as anecdotal evidence related to psychedelics (92), reports indicate that a certain percentage of individuals undergoing profound experiences develop post-traumatic stress disorder symptomatology, alongside elevated levels of depression and anxiety. Several factors contribute to this outcome, including the possibility that some individuals fail to comprehend or contextualize the essence of these experiences within their existing worldviews. Consequently, they might experience a sense of losing touch with reality, accompanied by apprehension about sharing their experiences with friends and family members.

Previous studies have found analogous results with other psychedelics such as LSD and Psilocybin. Clinical trials involving the administration of these psychedelics have demonstrated an increase in DTS scores subsequent to the experiences, and these increases have been found to correlate with the intensity of acute mystical-type subjective effects (17–20). As our results also indicated a strong correlation between death transcendence and (strongest but not typical) ego-dissolution experiences, it may be the case that attitudes toward death are impacted more generally by strong mystical experiences and are not APD-specific. In addition, contrary to our predictions, death anxiety levels did not differ between those who experienced APDs or not, and were also not correlated with ego-dissolution. Thus, it is possible that there is a floor effect where a few experiences are sufficient for lessening death anxiety. This aligns with studies that illustrate a reduction in death anxiety following the use of psychedelics (32, 93). An alternative explanation is that some of the APD experiences may have been difficult and challenging. Thus, participants may have associated these experiences with their perceptions of actual death, thereby increasing their anxiety. Future studies should thus also probe the valence of the APD experiences and not just their intensity.

Overall, our results, together with the reviewed literature, highlight the transformative nature of psychedelic experiences and their impact on individuals' perspectives toward death. They contribute to the growing literature emphasizing the critical long-term impact of psychedelic-induced mystical experiences, and call for more research aiming at a more fine-grained understanding of their experiential features.

4.2 APDs predict environmental concern

We hypothesized that APD experiences would induce a more selfless mode of psychological functioning as a result of experiencing the self as more flexible (94), thus opening the self to the extended world. Our hypothesis was only partially confirmed. We did not find evidence for reduced self vs. other bias, however, we did find that having experienced APDs predicted higher scores on pro-environmental values and concern. Crucially, ego-dissolution was not predictive of environmental concern, suggesting that among veteran ayahuasca users, APDs are specifically associated with environmental values. The connection between psychedelics and increases in pro-environmental measures such as nature relatedness (21, 95–97), pro-environmental behaviors (98), connection to nature (99), and objective knowledge about climate change (97) has been emerging in the literature. However, the underlying mechanisms remain inadequately explored. To the best of our knowledge, the only studies to date that examine the mechanisms regarding psychedelic-induced increases in pro-environmental attitudes are Lyons & Carhart-Harris (96) and Kettner et al. (21). The latter internet-based prospective study also reported a correlation between heightened nature relatedness and both ego-dissolution as well as the perceived influence of natural surroundings during acute psychedelic states.

One explanation as to why APDs are efficacious in altering environmental attitudes may lie in their efficacy to transform a general conceptual representation of death to a personally-relevant and embodied one. APDs are deeply profound experiences where people have a visceral sense of themselves dying or dead. Such experiences may thus have the potency to break through habitual death denial mechanisms. A recent study (100), adopting a predictive-processing framework, showed that the brain denied death by implementing a powerful and change-resistant top-down prediction that 'death is related to others', but not to oneself, thus shielding the self from existential threat. However, the potency and almost 'real' nature of APD experiences may be sufficient to penetrate this defensive shield and allow the brain to associate *death* with *self,* thus making the prospect of one's death more realistic and personally-relevant. This change in encoding might also transform the abstract existential threat of environmental collapse to a personally-relevant visceral threat which must be addressed. In support, recent theoretical papers have linked death defenses and impeding climate action and sustainability (101–103). While this theory requires further validation through longitudinal studies, it provides initial evidence linking APDs to environmental action and concern through the forging of a more realistic, personal and embodied perception of death.

4.3 APDs are associated with improved life coping and fulfillment

Several studies provided evidence of enhanced coping abilities among psychedelic users (17, 77, 104, 105), and the modulatory role of 5-HT1A and 5-HT2A receptors in shaping coping styles has been suggested (106). However, the particular experiential aspects that serve as mechanisms of change have received minimal investigation. Here we showed that APD experiences were associated with how stressful situations were coped with. The yAPD group demonstrated higher problem-focused coping scores, compared to the nAPD group, albeit emotion-focused coping did not differ between the two groups. These results are aligned with a previous study demonstrating that hallucinogen usage led to increased problem-focused, but not emotional coping engagement when dealing with the challenges posed

by COVID-19 (77). Generally, problem-focused coping involves taking practical steps toward actively addressing the source of stress or problem, while emotion-focused coping focuses on managing and regulating emotions in response to stress without directly addressing the stressor itself (107). While the effectiveness of emotion-focused coping can be influenced by the specific form of strategy employed and various factors and variables, the prevailing consensus in the stress and coping literature is that emotion-focused coping processes are generally maladaptive (107). Problem-focused coping, on the other hand, is generally considered to be an adaptive and constructive approach. Therefore, we can conclude that APDs are associated with enhanced adaptive coping abilities.

Regarding life values, in line with the suggestion that psychedelic-induced personal death experiences lead to transformative changes in life's values and sense of fulfillment (24), our findings show that the yAPD group reported a significant increase in their sense of life fulfillment, as a result of recognizing and living in accordance with their personal values. These results are likely not resulting from mere ayahuasca intake but rather from the APD experience, as our current findings did not find a correlation between lifetime ayahuasca intake frequency and life values. In support, a recent study (108), utilizing the same measure reported here, also found no difference in life values between controls and ayahuasca users, and no correlation between life values and lifetime ayahuasca intake frequency (but see (76), who did). Thus, it may be the case that the profound changes in life values attributed to ayahuasca (25) may be mediated by APDs. These results complement previous existentially-oriented studies describing increased sense of purpose (109), life meaning (104), and changes in personal values (110) to be associated with psychedelics use. From an existential perspective, the perceived confrontation with mortality acts as a catalyst prompting individuals to reassess their priorities, beliefs, and values, as previously suggested (111). This process of re-evaluation has the potential to facilitate a deeper understanding and fulfillment of personal purpose and ignite a renewed drive and coping abilities to pursue meaningful goals (111).

4.4 Study limitations

The current study has several limitations. Firstly, it relies primarily on self-reported measures, which have their inherent limitations. Secondly, the study's cross-sectional design does not allow the attribution of causality to any of the reported results. Thirdly, the trait measures employed assess only attitudes rather than 'real-life' measures of lifestyle and behavior changes. Thus, future studies should employ longitudinal designs and employ also measures of lifestyle and behavioral measures. Ideally, to establish causal effects of APDs while controlling for potential confounds, it would be valuable to conduct interventional clinical studies involving a controlled administration of ayahuasca, meticulously documenting dosage and documenting the occurrence of APDs during the acute state.

Study 1 is also limited by its small sample size and risk for selection bias given its unique sample of veteran ayahuasca users with extensive experience with the brew and ceremonial settings. This limitation was partially addressed by Study 2 which surveyed many more participants, and also did not exclude participants with little experience. Thus Study 2 can be considered as representative of ayahuasca users in Israel. Nevertheless, it is important for future studies to examine APDs in other countries, as well as address other ayahuasca intake settings (e.g., non-ceremonial context). Such an approach would yield a more comprehensive comparison and a deeper exploration of the distinct effects associated with ayahuasca itself, as well as the control of extrapharmacological factors (i.e., set and setting) (112, 113) specifically related to ayahuasca ceremonial use. As previously proposed, extrapharmacological factors may play a significant role in shaping subjective effects of ayahuasca (114) potentially impacting the nature of APDs and their long-term outcomes.

An additional limitation regards the translation of the scales from their original language into Hebrew, with some of the translated tools not undergoing a formal validation process and cultural adaptation. While the practice of reverse translation, as utilized in our study and others, is widely accepted in the literature and cross-cultural research, a formal validation process is recommended.

Finally, we acknowledge a lack of precise definition and rich phenomenological description of the APD experience. As this phenomenon is a profound mystical experience, which may encompass diverse aspects and types of encounters, APDs would benefit from an empirical phenomenological investigation. We anticipate that our forthcoming comprehensive phenomenological study will tease apart personal death experiences from ego dissolution and mystical-type experiences more generally. Future studies might also benefit from incorporating NDE scales, such as the Near-Death Experience Scale (115). This will allow directly examining similarities and differences between APDs and NDEs. This is important as an alternative perspective on our findings could be that some of our observed effects might be linked to mystical experiences in general, which are likewise connected to shifts in perceptions of death (17–20) and highly related to ayahuasca compared to other psychedelics (32). Importantly, this limitation is not relevant in the context of environmental concern, where we showed that ego dissolution did not predict environmental concern.

Despite these limitations, we are confident that the present study makes a significant and innovative contribution to our understanding of APDs and their impact on life, death and the environment. It offers an important addition to the existing literature on psychedelic-induced subjective effects, spotlighting APDs for the very first time. We hope that this study will spark further interest in these profound experiences and further our understanding of the potential they hold for personal and societal transformation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Education Faculty, the University of Haifa, Israel. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JD: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. JB: Resources and Methodology of study 2, Writing – review & editing. MK: Resources and Methodology of study 2, Writing – review & editing. GO: Resources and Methodology of study 2, Writing – review & editing. NT: Investigation of study 2. TA: Investigation of study 2. YD-Z: Conceptualization, Methodology, Formal analysis, Supervision, Funding acquisition, Writing – original draft. AB-O: Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1287961/full#supplementary-material

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Study protocol for "Psilocybin in patients with fibromyalgia: brain biomarkers of action"

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Background: Chronic pain is a leading cause of disability worldwide. Fibromyalgia is a particularly debilitating form of widespread chronic pain. Fibromyalgia remains poorly understood, and treatment options are limited or moderately effective at best. Here, we present a protocol for a mechanistic study investigating the effects of psychedelic-assisted-therapy in a fibromyalgia population. The principal focus of this trial is the central mechanism(s) of psilocybin-therapy i.e., in the brain and on associated mental schemata, primarily captured by electroencephalography (EEG) recordings of the acute psychedelic state, plus pre and post Magnetic Resonance Imaging (MRI).

Methods: Twenty participants with fibromyalgia will complete 8 study visits over 8 weeks. This will include two dosing sessions where participants will receive psilocybin at least once, with doses varying up to 25mg. Our primary outcomes are 1) Lempel-Ziv complexity (LZc) recorded acutely using EEG, and the 2) the (Brief Experiential Avoidance Questionnaire (BEAQ) measured at baseline and primary endpoint. Secondary outcomes will aim to capture broad aspects of the pain experience and related features through neuroimaging, self-report measures, behavioural paradigms, and qualitative interviews. Pain Symptomatology will be measured using the Brief Pain Inventory Interference Subscale (BPI-IS), physical and mental health-related function will be measured using the 36-Item Short Form Health Survey (SF-36). Further neurobiological investigations will include functional MRI (fMRI) and diffusion tensor imaging (changes from baseline to primary endpoint), and acute changes in pre- vs post-acute spontaneous brain activity – plus event-related potential functional plasticity markers, captured via EEG.

Discussion: The results of this study will provide valuable insight into the brain mechanisms involved in the action of psilocybin-therapy for fibromyalgia with potential implications for the therapeutic action of psychedelic-therapy more broadly. It will also deliver essential data to inform the design of a potential subsequent RCT.

KEYWORDS

psilocybin, psychedelic therapy, chronic pain, fibromyalgia, EEG

Introduction

Chronic pain is a leading cause of disability worldwide (1, 2). Fibromyalgia (FM) is a particularly debilitating form of chronic generalized pain (3–5) with reported prevalence rates varying from between 0.4 and 8% (6–10) FM is characterised by widespread pain, fatigue, sleep difficulties and cognitive disturbance including memory and ability to concentrate e.g., brain fog (5). Frequently reported concomitant symptoms are irritable bowel syndrome (IBS), headache, and temporomandibular disorder (6, 11). Compared with other types of chronic pain, people with FM exhibit disproportionately high rates of psychological comorbidity (3, 9) with 60-80% also experiencing comorbid depression and/or anxiety (12–14). Additionally, FM populations present markedly high rates of lifetime (15), and particularly childhood trauma (16, 17). Women are significantly more likely to be affected than men (8, 11, 18).

The aetiology and pathology of FM remain poorly understood (19), although current hypotheses centre around combined immunological (20), psychological (21), stress (21) and trauma-related (22, 23) mechanisms. Certain physiological changes are regularly observed in FM populations, including a hyperexcitable central nervous system via high levels of glutamate, as well as additional dysregulated monoamine neurotransmitter expression, particularly of serotonin and dopamine (23). Still, this limited understanding has resulted in relatively few effective treatment options. First line medical intervention aims to address these molecular changes and commonly includes off-label anti-depressants [e.g., Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)], anticonvulsants (e.g., gabapentin, pregabalin), and opioids (e.g., tramadol) (23, 24), while non-pharmacological options involve physiotherapy, pain-management programmes, and cognitive behavioural therapies (24). While these treatment options have shown results in other specific conditions, their efficacy in FM populations is thought to be moderate at best (25–28). Importantly, even if patients report a decrease in pain, their comorbid mental health symptoms are often left insufficiently addressed (25). Neglecting this essential aspect of the chronic pain experience is especially problematic due to the known bi-directional relationship between pain perception and mental health (2, 29, 30). FM is a highly disabling and growing problem worldwide. The lack of adequate treatment is especially problematic for chronic conditions such as FM where quality of life is severely impacted, thus, novel, and integrative treatment options are urgently needed.

The past decade has witnessed a "renaissance" in clinical psychedelic research. Classic psychedelic drugs include LSD (lysergic acid diethylamide), psilocybin (the active compound in "magic mushrooms"), and DMT (dimethyltryptamine, the active compound in the *ayahuasca*). A growing body of data suggests the safety (31) and efficacy of psychedelics in clinical populations including depression (32–34), addiction (35, 36), obsessive compulsive disorder (37), and end-of-life distress (38–41), as well as in healthy populations (42, 43).

Classic psychedelics act primarily through agonism of excitatory serotonin 2A receptors, though 5-HT 1A, 1C, and 2C receptors agonism is also observed, as well as indirect dopaminergic action (31). Activation of serotonin 2A receptors appears to dysregulate population-level spontaneous neural oscillations (44–46) which may subsequently account for increases in markers of anatomical neuroplasticity (47–51). Increased plasticity via serotonin 2A agonist psychedelics may increase an individual's sensitivity to extra pharmacological contextual factors known to guide therapeutic outcomes via psychotherapy (52).

In a therapeutic context, as seen in psychedelic-assisted therapy (PAT), it is theorised that psychedelics could open a window of plasticity that might facilitate the reappraisal of deeply entrenched, maladaptive thought patterns towards therapeutically useful outcomes (52–54). Such increases in psychological flexibility make FM is a particularly attractive target for investigation due to its hallmark psychological rigidity (55) and significant cross-over with depression which is potentially positively impacted by PAT (32, 33). Antidepressant action may also be supported by the abovementioned modulation of monoamine neurotransmitters (31).

While psychedelics have not yet been investigated in a FM context, historical studies suggest potential action in chronic pain conditions including cancer pain (56–60) and phantom limb pain (61–63). Interest has recently re-emerged, with modern work suggesting psychedelics' anti-inflammatory action (63–65) and potential efficacy in treating headache disorders (66–68), phantom limb pain (69), and acute pain (70). Indeed, proposed, and ongoing studies investigating the effects of classic psychedelics in phantom limb pain (71), lower back pain (72), and fibromyalgia (73) are likely to advance our understanding in this area.

Patient and public involvement

A growing body of 'grey' literature of case reports and/or protocols pertaining to psychedelic-use has emerged online on forums such as Reddit, Bluelight, and Erowid. A significant portion of these relates to self-medication for chronic pain (74). Specific, crowd-sourced protocols have emerged as a result; organisations such as Clusterbusters boast over 10,000 members who follow published guidance for psychedelic self-medication for cluster headaches (75). Such anecdotal reports may inspire hypotheses for researchers designing research studies and clinical trials. Indeed, Schindler et al. formally investigated the viability of psychedelics on cluster headaches following the Clusterbusters protocol (68). Accordingly, we sought to learn from the lived experience of people who have self-medicated with classical psychedelics for chronic pain to aid in the design of the present study (see Methods section).

Overview/aims

This paper presents the protocol for a mechanistic study investigating the effects of PAT in a fibromyalgia population. The principal focus of this trial is the central mechanism(s) of psilocybin i.e., in the brain and on associated mental schemata, primarily captured by electroencephalography (EEG) recordings of the acute psychedelic state. Secondary outcomes will aim to capture broad

aspects of the pain experience and related features through Magnetic Resonance Imaging (MRI), self-report measures, behavioural paradigms, and qualitative interviews. This study aims to serve as a preliminary investigation into potential mechanisms of psilocybin in this study population. By publishing our protocol before commencing data collection, we aim to contribute towards a scientific culture of openness and rigor.

Methods and analysis

Here we describe a single arm, fixed sequence, single-blind, within-subjects study. Our primary outcomes investigate psychological flexibility through potential neurophysiological markers (specifically Lempel-Ziv complexity (LZc) recorded acutely using EEG, and the (Brief Experiential Avoidance Questionnaire (BEAQ) measured at baseline and primary endpoint). Secondary outcomes will provide a context to complement these mechanistic EEG data. Pain symptomatology will be measured using the Brief Pain Inventory Interference Subscale (BPI-IS) and broader aspects of health, including physical and mental health functioning will be measured using the 36-Item Short Form Health Survey (SF-36). We will additionally collect self-reported data on the strength of personally held negative beliefs in line with the relaxed beliefs under psychedelics model (55).

Further neurophysiological investigations will include functional magnetic resonance imaging (fMRI and DTI) (changes from baseline to primary endpoint), and EEG (changes from baseline to in putative resting state and ERP plasticity markers. We believe that a breakthrough on the brain mechanisms involved in therapeutically relevant change process catalysed by psilocybin, will have broad and important scientific and clinical implications.

Patient and public involvement (PPI) was used throughout the process of trial preparation and contributed to protocol development. PPI is an emerging research method across mental health and within psychedelic research (76, 77). The method aims to produce research "with" rather than "for" people with lived experience. Such co-created research fosters empowerment and trust in research produces relevant and transparent outputs (78).

PPI informed our therapeutic protocols, inspired further research questions, and resulted in the development of novel measures investigating the somatic elements of the psychedelic experience [see Bornemann et al. (79)]. Further, our panel of patient contributors has provided input to, and approved all patient facing documents.

Recruitment

We will recruit up to twenty participants with fibromyalgia as defined by the American Rheumatological Society 2016 diagnostic criteria (80). Study completion is set as completion of the final study visit (primary endpoint). Full entry criteria are outlined in Table 1.

Recruitment will take place via flyers, word-of-mouth, and from a pool of self-referrals submitted via a secure centralised e-mail address using a standardised referral form. Participant information sheets will be openly accessible on our study website (81). Primary care providers will be contacted to confirm eligibility.

TABLE 1 Key In-/Exclusion criteria.

Inclusion criteria
Fibromyalgia Syndrome as diagnosed by an appropriate medical professional using the American College of Rheumatology diagnostic criteria, lasting for more than 3 months.
Over 18 years of age
UK resident registered with a primary care medical practice
Sufficiently competent in English with capacity to provide written informed consent
Agreement for research team to contact primary and/or secondary care team over the course of the study
No psychedelic use in the past 6 months
Exclusion criteria
Current or previously diagnosed psychotic disorder, bipolar disorder, or mania
Immediate family member with a diagnosed psychotic disorder
History of serious suicide attempts
Currently using medication which could interact with psilocybin including anti-psychotics, mood stabilizers & serotonergic antidepressants including SSRIs, SNRIs, and TCAs.*
Actively enrolled on pain management programme over course of study or awaiting further investigations for pain
On waiting list for interventional treatment for pain (e.g. surgery or targeted injections) Medical contraindications e.g., epilepsy, migraine, focal scalp sensitivity
MRI contraindications (e.g. metal implants)
Blood or needle phobia
People who are pregnant, planning to get pregnant, or currently breastfeeding
Unable to engage with physical demands of dosing session (i.e. attend centre and remain in research facility for an extended period of time)
Unable to access virtual meetings/phone for remote follow-ups
Limited life expectancy (<18 months)
Patients consuming more than 35 units of alcohol per week

*Antipsychotic medications and mood stabilisers may attenuate the effects of psilocybin. In this population, people may be using these medications as adjunctive treatments for coexisting depression, anxiety, and also for sleep. Antipsychotic medications are contraindicated and thus those on antipsychotic medication (e.g., olanzapine) will not be eligible to take part in this study. The same is true for mood stabilizing mediations and many antidepressant medications with serotonergic action, including SSRIs, SNRIs, and TCAs. Therefore, we will not be recruiting patients currently prescribed any antidepressant medication, with the exception of Bupropion, which is not serotonergically active.

Study visits

Participants will attend eight study visits (screening, two preparation sessions, two dosing sessions, and three follow-up sessions) over the eight-week study period (see Figure 1). Participants will attend two dosing sessions and receive psilocybin at least once (up to 25mg). Dosing sessions are separated by four weeks. Long-term follow-ups will be collected for six-months post

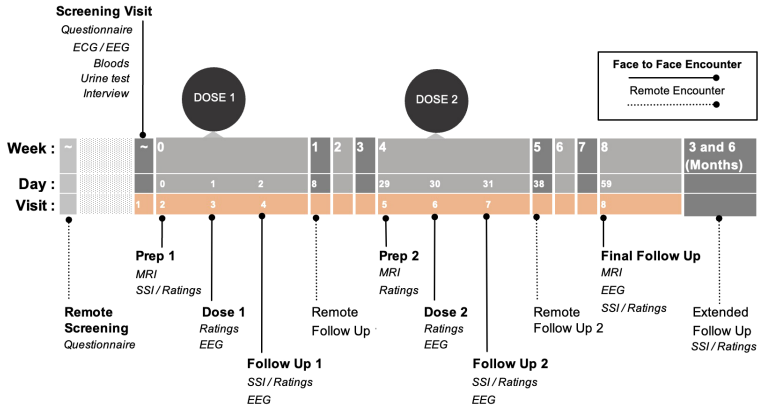

FIGURE 1
Study timeline: Pink background represents the active study period. Dotted lines represent remote encounters. Please note: this dosing figure is intentionally left blinded. Researchers interested in the specific dosing protocol are welcome to contact the communicating authors for additional information. ECG: Electrocardiogram; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; SSI: Semi-structured Interview.

study completion, with two remote in-depth check-ins at three and six months. Researchers interested in the specific dosing protocol are welcome to contact the communicating authors for additional information.

Screening and consent

Eligible self-referrals will be invited to a remote screening call where informed consent to begin the screening interviews will be collected. Remote screening calls serve to provide information to participation and determine initial eligibility.

If the participant passes initial eligibility at the remote screening, they are invited to a screening visit. Following a thorough explanation of the study and screening process, patients will have the opportunity to ask questions before providing full written informed consent to participate in the study. They will then have a physical exam, psychiatric assessment including MINI, electrocardiogram (ECG), urine samples and blood sample for routine blood testing. Baseline EEG resting state measures will be collected. This will also serve as an EEG tolerability test.

Information regarding the screening/enrolment process including retention and demographics will be published upon study completion.

Psychedelic assisted therapy

This study investigates the effects of PAT. While no single unifying PAT protocol exists, common principles are followed across research and will be employed here. Study visits will take place in a comfortable, low-lit environment (82). As comfort allows, patients will be in semi-reclined positions throughout. Music is known to powerfully affect PAT (83); as such, playlists were carefully co-created with music therapists.

As is standard across psychedelic studies, the therapeutic approach is largely self-directed (84) and is informed by humanistic approaches (85). Of particular interest in this context is Acceptance and Commitment Therapy (ACT), a widely used modality in pain-management (28, 86, 87), and an approach increasingly explored for PAT protocols (88–90). We have integrated various aspects of established pain management practices to accommodate the complex needs of our population. Two "guides" will support each participant for the duration of the trial. Guides will prepare the patient for the experience in remote and in-person preparation sessions. Session objectives will be standardised and include areas such as psychoeducation, trust building, and intention setting. The therapeutic manual for this study will be published once data collection is complete. Patients will also have an MRI scan at each preparation visit with visits lasting approximately 4 hours.

Dosing days will occur the day after preparation sessions. Patients will spend ~8 hours at the research facility, with the drug effect lasting for approximately 4-6 hours. Patients will be wearing eye masks and headphones, as comfort allows. EEGs will be recorded before, and during the acute drug state. An on-site medic will ensure participant safety throughout the day and will approve patients before their discharge at the end of the day. Local participants have the option of spending the night at home if accompanied by a trusted person; all participants may stay at provided on-site accommodation.

Integration days will occur the morning after the dosing day. Participants will meet with their guides to discuss their experience and complete EEG recordings. The visit lasts ~4 hours. Guides will check in with participants at remote follow-ups 1 week later as well. The final follow-up will run as the other integration sessions but will also include one final MRI. Patient-reported outcome measures will be collected remotely after each study visit, as well as remotely after primary study endpoint.

Safety, monitoring, and reporting procedures

Participant safety was, and will continue to be, the guiding principle for all study related decisions. Participants will always be chaperoned when under the care of the study team, including

medical supervision on dosing days where discharge may only occur once the doctor on site has deemed it safe for the participant to leave. Patient wellbeing will additionally be assessed the next morning, and the following week.

Participant mood and pain scores will be monitored continually from enrolment to the end of the 6-month follow up period. Automatic alerts will immediately alert the study team of any reports of thoughts of self-harm or suicide. These will be escalated to therapy and medical teams and followed up with as appropriate. All adverse events will be reported.

Outcome measures

We will collect neurophysiological, self-reported, qualitative, and behavioural data. Please see Tables 2–4 for a summary of all outcome measures. Please refer to Table 5 for a breakdown of primary and secondary outcomes.

Mechanistic neurophysiology measures

The present study is conceived as an early-phase mechanistic study, intended to investigate the central action of psychedelics in a population of people living with fibromyalgia. EEG will be recorded at 6 visits: screening, Dose 1, Integration 1, Dose 2, Integration 2, and Final Follow Up (see Table 3).

The primary outcome measure is Lempel-Ziv Complexity (LZc) of the resting state EEG signal during dosing days as detailed above. LZc is a compressibility algorithm used to measure signal diversity and has been previously investigated in psychedelic contexts (91–93). Here we hypothesise an increase in LZc under psilocybin.

In addition to resting state, participants will complete the visual Long-Term Potentiation (vLTP) (94) and roving Mismatch Negativity (rMMN) (95, 96) tasks at integrations to investigate the post-acute neuroplasticity and predictive coding. We also hypothesise reduced alpha power under psilocybin.

We will complement these measures with structural and functional MRI data. We will collect MRI data at 3 timepoints: Prep 1, Prep 2, and Final Follow Up (see Table 3). We will investigate changes in resting-state activity and connectivity, as well as structural changes including diffusion imaging. We hypothesise decreases in brain network modularity after PAT and decreases in diffusivity in prefrontal to subcortical region white-matter tracts, indexed by the diffusion imaging.

Patient reported outcome measures

While the primary interest of the study is in the neural mechanisms involved in psychedelic-mediated action in a fibromyalgia population, we will also collect efficacy measures at every timepoint of the study. Patient-reported outcome measures (PROMs) will be collected in-person and remotely (via video calls and the online survey platform "Alchemer"). All baseline measurements will be taken at Prep 1, except for Symptom Severity Score and the Widespread Pain Index which will be collected at the Screening Visit. Baseline EEG and MRI will be collected at screening and Prep 1 visits, respectively. All primary endpoint measurements (including EEG and MRI) will be collected at final follow up (8 weeks after prep 1). Please see Tables 2, 3 for a full list of PROMs.

PROMs are grouped as "Core Pain Outcomes," "Wellbeing/Mental Health Outcomes," or "Acute mediators" (see table). We will also be collecting "Patient Impression Measures" to assess the effects of expectancy and blinding efficacy. We will assess the therapeutic relationship using the STAR outcome measure, filled in by both patients and their guides. We hypothesise improvements in Core Pain Outcomes and Wellbeing/Mental Health Outcomes.

Behavioural and physiological

We will collect 2 other types of behavioural data investigating interoception and physiology (see Table 4). Changes in interoceptive accuracy will be measured using the Heartrate Discrimination Task (HRD) (97) at Integrations 1 and 2.

Physiological data including heart rate variability (HRV), actigraphy, and sleep staging will be collected using a wearable device throughout the study.

Qualitative

Qualitative data will be collected in the form of semi-structured interviews at Prep 1, Integrations 1 and 2, Final Follow Up, and the 6-month Remote follow up (see Table 4). The aims of these interviews are to assess how they lived experience of fibromyalgia change after psychedelic-assisted therapy, as well as its potential therapeutic mechanisms. Patient reports often capture subtle yet powerful changes in personal narratives before and after psychedelic therapy that quantitative data are not able to record.

Analysis strategy

Our two primary, mechanistic hypotheses relate to EEG and MRI:

H1 (EEG): We hypothesise an increase in signal complexity (LZc) at peak drug effects under psilocybin.
H2 (fMRI): we hypothesise a decrease in brain network modularity after PAT.

Secondary outcomes include:

Reduced alpha power under psilocybin.
A relationship between acute increases in LZc and post-PAT changes in psychological flexibility, measured by the BEAQ.
Changes in mass univariate functional connectivity after PAT.
Changes in PFC-tract diffusivity after PAT.
Changes in EEG ERP related markers of functional plasticity after PAT.
Changes in pain symptomatology after PAT, measured by the BPI-IS.

All secondary outcomes will be exploratory (see Table 5). Sub-acute EEG analyses will follow previously outlined protocols (91–93). With an assumption of high co-linearity between core

TABLE 2 Summary of patient-reported predictor, patient impression, and good clinical practice measures.

Measure	Screen	Remote Baseline	Prep 1	Dosing Day 1		Integration 1	Prep 2	Dosing Day 2		Integration 2	Final Follow Up	Extended Remote Follow Ups		
				Pre-Dose	Post-Dose			Pre-Dose	Post-Dose			Monthly	3 Month	6 Month
Week	~	-1	1	1		1	4	4		4	8	~		
Day	~	-7	0	1		2	29	30		31	59	~		
Visit	1	~	2	3		4	5	6		7	8	~		
Baseline Static														
Demographics	x													
PainDETECT Phenotyping	x													
Predictors														
The Modified Tellegen Absorption Scale (MODTAS)		x												
The Short Suggestibility Scale (SSS)		x												
Stanford Expectations of Treatment Scale (SETS)		x												
Psychedelic Predictor Scale			x					x						
Patient Impression Measures														
Patient Global Impression Of Change Score (PGIC)										x	x			x
Perceived Treatment Questionnaire						x				x	x			
Scale to Assess Therapeutic Relationship (STAR) (Patient Version)			x				x							
Good Clinical Practice Measures (Guides only)														
Scale to Assess Therapeutic Relationship (STAR) (Clinician Version)			x		x	x	x		x	x	x			
Adverse Events & Serious Adverse Events Record			x		x	x	x		x	x	x	x	x	x

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TABLE 3 Summary of patient-reported sub-acute and acute change measures.

Measure	Screen	Remote Baseline	Prep 1	Dosing Day 1		Integration 1	Prep 2	Dosing Day 2		Integration 2	Final Follow Up	Extended Remote Follow Ups		
				Pre-Dose	Post-Dose			Pre-Dose	Post-Dose			Monthly	3 Month	6 Month
Week	~	-1	1	1		1	4	4		4	8	~		
Day	~	-7	0	1		2	29	30		31	59	~		
Visit	1	~	2	3		4	5	6		7	8	~		
Sub-Acute Change Measures														
Brief Pain Inventory Short Form	x	x	x	x		x	x			x	x	x	x	x
Single Item Sleep Score			x	x		x	x	x		x	x			
9-Item Patient Health Questionnaire (PHQ-9)		x									x	x	x	x
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)		x									x	x	x	x
7-Item Generalised Anxiety Disorder Questionnaire (GAD-7)		x									x	x	x	x
Brief Experiential Avoidance Questionnaire (BEAQ)		x									x	x	x	x
Snaith-Hamilton Pleasure Scale (SHAPS)		x				x				x	x			
Chronic Pain Self-Efficacy Scale (CPSS)		x									x			x
Watts Connectedness Scale (WCS)		x									x			
Function of Self-Criticizing/Attacking Scale (FSCS)		x									x			
The Self Experiences Questionnaire (SEQ)		x									x			
8-item Committed Action Questionnaire (CAQ-8)		x									x			x
8-item Chronic Pain Acceptance Questionnaire (CPAQ-8)		x									x			x
Fibromyalgia Impact Questionnaire (FIQ)		x									x			x
Multidimensional Assessment of Interoceptive Awareness (MAIA)		x									x			x
Pain Catastrophizing Scale (PCS)		x				x				x	x			x

(Continued)

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TABLE 3 Continued

Measure	Screen	Remote Baseline	Prep 1	Dosing Day 1		Integration 1	Prep 2	Dosing Day 2		Integration 2	Final Follow Up	Extended Remote Follow Ups		
Experiences in Close Relationships Questionnaire (ECR-M16)		x									x			
Psychological Inflexibility in Pain Scale (PIPS)		x									x			x
Cognitive Fusion Questionnaire (CFQ)		x									x			x
Metaphysical Beliefs Scale (Self-Constructed)		x									x			x
Somatic Processing Questionnaire (Self-Constructed)						x				x				
The Centrality of Events Scale (Short Version)						x				x	x			x
Multifaceted Psychological Integration Assessment (M-PIA)						x				x	x	x		x
Dosing Day Change Measures														
The Emotional Breakthrough Inventory (EBI)					x				x					
Setting Questionnaire (SQ, self-constructed)					x				x					
11 Dimension Altered States of Consciousness Scale (11D ASC)					x				x					
The Challenging Experience Questionnaire (CEQ)					x				x					
The Imperial Overview Item					x				x					
Geneva emotional music scales (GEMS)					x				x					
Awe Experiences Scale					x				x					
Psychological Insight Questionnaire					x				x					
States of Mindfulness Scale (SMS) Body Sub-Scale					x				x					
Relaxed and Embodied Beliefs Questionnaire (Self Constructed)			x		x				x		x			
Embodiment Items (Self-Constructed)					x				x		x			x
Expectation item (self-constructed)		x		x				x						

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TABLE 4 Summary of all other data types.

Measure	Screen	Prep 1	Dosing Day 1			Integration 1	Prep 2	Dosing Day 2			Integration 2	Final Follow Up	Remote Extended Follow Up
			Pre-Dose	+90 mins	+150 mins			Pre-Dose	+90 mins	+150 mins			6 Months
Week	~	1		1		1	4		4		4	8	~
Day	~	0		1		2	29		30		31	59	~
Visit	1	2		3		4	5		6		7	8	~
EEG													
Tolerability Test	x												
Resting State Eyes Closed	x		x	x	x	x		x	x	x	x	x	
Resting State Eyes Open	x		x	x	x	x		x	x	x	x	x	
rMMN						x					x		
vLTP						x					x		
Heart Rate Discrimination Task						x					x		
MRI													
Structural		x					x					x	
Functional		x					x					x	
Behavioural													
Oura Ring (Ongoing)	x	x	x	x	x	x	x	x	x	x	x	x	
Heart Rate Discrimination Task						x					x		
Qualitative													
Unstructured Interview	x												
Semi-structured interview		x				x					x	x	x

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outcomes we would explore data reduction approaches (e.g., factor or principal component analyses or canonical correlation analysis) to investigate key contrasts. Two tailed tests will be performed if findings are not aligned with prior hypotheses. Due to prior hypotheses (above) on directionality, one tailed t-tests will be appropriate to perform for H1 & H2. Multiple comparisons corrections and Bayesian analyses will be performed where deemed appropriate. Please see Table 5 for timepoints for each analysis.

IMP management

A Schedule 1 licence for possession and storage of psilocybin has been obtained from the UK Home Office. Psilocybin supplied by Usona Insitute. Manufacture and encapsulation will be performed by Lonza Pharma and Biotech. Good Manufacturing Practise (GMP) will be maintained at all stages of manufacture. The IMP will be stored in a secure safe at Imperial College London, Hammersmith Campus.

TABLE 5 Summary of timepoints for analysis.

PsiloPain Outcome Measures	
Measure	Timepoints for Analysis
Primary Outcome Measures	
Neurophysiology	
Lempel-Ziv complexity (LZc) (EEG)	DD1 vs DD2
Modularity (MRI)	Prep 1 vs Prep 2 vs FFU
Secondary Outcomes	
Neurophysiology	
Plasticity via vLTP paradigm (EEG)	FU1 vs FU2
Predictive Processing via rMMN (EEG)	FU1 vs FU2
Alpha power (EEG)	DD1 vs DD2
DTI (MRI)	Prep 1 vs Prep 2 vs FFU
Physiology	
Heart rate Variability (Oura)	4 weeks Post-Dose 1 vs 4 weeks Post-Dose 2
Sleep Quality (Oura)	4 weeks Post-Dose 1 vs 4 weeks Post-Dose 2
Interoception (Heartrate Discrimination Task)	FU1 vs FU2
Primary Patient Reported Outcome Measures	
Brief Experiential Avoidance Questionnaire (BEAQ)	Baseline to primary endpoint
Secondary Patient Reported Outcome Measures	
Core Pain Outcomes	FU1 vs FU2
Acute Mediators	DD1 vs DD2
Wellbeing/Mental Health Outcomes	FU1 vs FU2
Qualitative	
Interviews	Prep 1 vs FFU

Data management

Data will be managed as per the Imperial College Data Management Standard Operating Procedures and a study-specific data management plan. All data collection and management softwares have been meet GDPR standards and have been approved by Imperial College London.

Dissemination

The results of this study will be published in academic journals and presented in both the academic and public domain, including at scientific conferences and in the media in public engagement forums. Patient confidentiality will be maintained in all the above. All publications and presentations relating to the study will be overseen by the P.I and C.I. Authorship of parallel studies initiated outside of the Study Co-ordination Team will be according to the individuals involved in the project but must acknowledge the contribution of the Study Coordination Team.

Ethics and trial registration

This study has received a favourable opinion from the London Central Research Ethics Committee and is sponsored by Imperial College London's Research Governance and Integrity Team. All participants will provide their written informed consent to be screened and, if relevant, participate in this study. The Medicines and Healthcare products Regulatory Agency (MHRA) has confirmed its status as a non-clinical trial and waived the need for MHRA approval. The study has been reviewed and approved by the Health Research Authority (HRA). The study protocol has undergone external peer review and was co-developed with patient advisors. All staff have undergone Good Clinical Practice (GCP) training. The study has been adopted by the National Institute of Health Research (NIHR) Clinical Research Network (CRN) and has been registered on clinicaltrials.gov (NCT05548075). All study sessions will take place at the NIHR-funded Imperial College Research Facility (ICRF) and Imperial Clinical Imaging Facility (CIF).

Conclusion

By publishing the study protocol, we aim to improve methodological transparency, rigour, and accountability and subsequently contribute towards more impactful outcomes. We also aim to highlight the importance of patient involvement in protocol design in generating relevant and equitable research. This study will investigate effect of psilocybin on the neural mechanisms in a fibromyalgia population. The results will provide the first EEG recordings of the acute psychedelic state in a clinical population. Further, they may inform the viability of psilocybin as a potential treatment option and help shape subsequent clinical trials.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

RCH: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing, Funding acquisition. JC: Conceptualization, Methodology, Project administration. Investigation, Writing – review & editing. JB: Conceptualization, Methodology, Project administration, Investigation, Writing – original draft, Writing – review & editing. DJN: Conceptualization, Supervision, Project administration, Writing – review & editing. KA: Conceptualization, Project administration, Investigation, Writing – review & editing. DE: Project administration, Investigation, Writing – review & editing. KG: Investigation, Writing – review & editing. LM: Investigation, Writing – review & editing. TB: Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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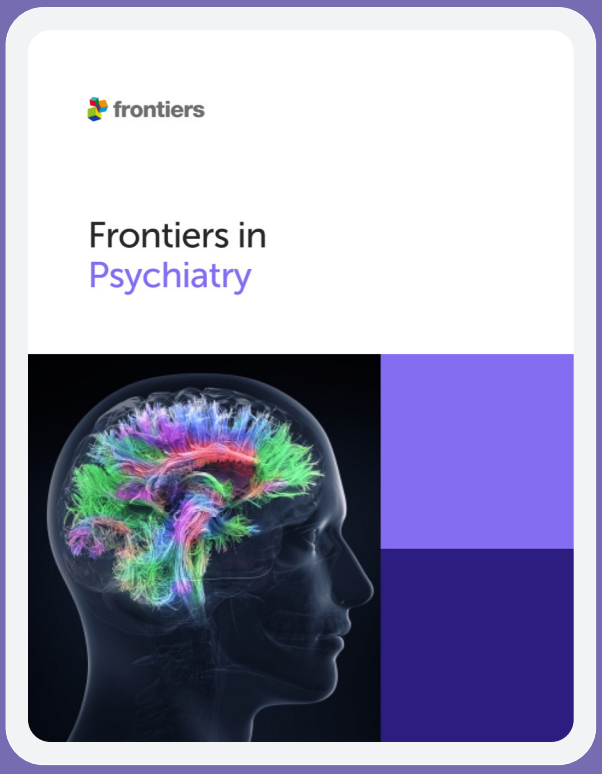

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