International Journal of Mental Health and Addiction
https://doi.org/10.1007/s11469-025-01489-z

ORIGINAL ARTICLE

Patterns of Internalizing Problems, Substance Use and Cognitive Flexibility Before and After Naturalistic Psilocybin Use: A Repeated Measures Latent Profile Analysis

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Accepted: 10 April 2025

Abstract
The classic psychedelic psilocybin is receiving renewed interest in naturalistic and clinical research settings. Despite trends indicating increased rates of use outside of research settings, longitudinal data on the association between psilocybin use, mental health, and other substance use remains limited. A prospective longitudinal online survey study comprising six sequential assessments from adults planning to take psilocybin in naturalistic settings was conducted. A total of 2,850 respondents completed the survey 2 weeks before they planned to use psilocybin, 1,551 completed the 2–4-week follow-up, and 657 completed the 2–3-month follow-up after psilocybin use. A repeated measures latent profile analysis of internalizing problems, substance use, and cognitive flexibility was conducted. The repeated measures latent profile analysis identified a four-profile model as best fitting the data provided across the three measurement periods: "Improved Mental Health with Low Substance Use" (30.25%), "Stable Mental Health with Low Substance Use" (53.12%), "Persistent Mental Health Symptoms with Persistent Substance Use" (8.84%), and "Improved Mental Health with Persistent Substance Use" (7.79%). Sociodemographic and personality characteristics prior to psychedelic use were associated with profile membership, with the profiles also differing significantly on measures of the acute subjective effects of psilocybin. Although psilocybin use was associated with improvements in internalizing problems for the majority of participants, persisting mental health difficulties and substance use problems were also noted. These findings highlight the heterogeneous associations between psilocybin use, mental health, and patterns of other substance use in non-clinical settings.

Keywords Internalizing problems · Latent profile analysis · Longitudinal survey · Psilocybin · Psychedelic · Substance use

The classic psychedelic psilocybin acts as a prodrug of psilocin, which has a variety of effects at 5-HT receptors including being a partial agonist of the 5-HT2A receptor (Dodd et al., 2023). Psilocybin is found in many species of mushrooms and has been synthesized for use in clinical research. When ingested in high doses, psilocybin can

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result in acute alterations in perception, cognition, and affect that have been associated with sustained changes in cognition, creativity, emotional processing, and personality (Aday et al., 2021). Historically, classic psychedelics such as psilocybin have been used in traditional medicinal, ritual, and religious contexts (Celidwen et al., 2022; Schultes, 1969). Over the past two decades, there has been a growing body of clinical research exploring psilocybin's potential effectiveness for treating various health conditions (Madden et al., 2024) including major depressive disorder (Carhart-Harris et al., 2021; Goodwin et al., 2022, 2025; Haikazian et al., 2023; Raison et al., 2023) and cancer-related existential distress or anxiety (Agrawal et al., 2024; Griffiths et al., 2016; Ross et al., 2016). Psilocybin has also been applied in clinical research contexts as a potential novel intervention for substance use disorders (SUDs) including alcohol and tobacco use disorder (Bogenschutz et al., 2015, 2022; Johnson et al., 2014, 2017; Richard & Garcia-Romeu, 2025).

Although commonly regarded a distinct categorical entities as part of the Diagnostic Statistical Manual (DSM-5; American Psychiatric Association, 2013) and International Classification of Diseases (ICD-11; World Health Organization, 2019), psychiatric conditions including mood disorders, anxiety disorders, and SUDs are highly comorbid (Lai et al., 2015; Saha et al., 2021) and have been identified as sharing underlying etiological factors (Caspi et al., 2020; Kotov et al., 2017). When represented within the Hierarchical Taxonomy of Psychopathology (HiTOP), mood and anxiety disorders are identified as lower dimensions of the internalizing spectrum, whereas SUDs are identified as lower dimensions of the disinhibited externalizing spectrum (Cicero et al., 2024). The modeling of these problems is such that although depression and anxiety tend to be more closely related within the internalizing spectra, there remain significant associations across internalizing and externalizing spectra and associated overlaps in symptomatology (Blondino & Prom-Wormley, 2022). One potential underlying transdiagnostic psychological mechanism relevant to the manifestation of both internalizing problems and SUDs is cognitive inflexibility (Lee & Orsillo, 2014; Melugin et al., 2021; Piccoli et al., 2024; Yu et al., 2020). This would be in line with broader findings on psychological resilience whereby the capacity for successful adaption and mental wellbeing is positively associated with cognitive flexibility (Parsons et al., 2016).

There is converging evidence across both animal and human research that psychedelics have the potential to increase cognitive flexibility, a mechanism by which psychedelics are hypothesized to have therapeutic effects alongside their acute subjective effects (Campo et al., 2025; Doss et al., 2021; Romeo et al., 2025; Sayalı & Barrett, 2023; Torrado Pacheco et al., 2023). Given the clinical associations between internalizing problems, substance use problems and cognitive flexibility, in addition to the potential effects on psychedelics on all of these domains of psychological functioning, there is a need to better understand patterns of change across these dimensions of mental health and behavior before and after psychedelic use.

A growing number of studies have explored the effects of classic psychedelic use outside of clinical trials. This research is especially important as rates of psychedelic or hallucinogen use among adults reached historic highs in 2022 and remained at these levels in 2023 (Patrick et al., 2024). This research typically employs observational methodologies (i.e., cross-sectional or retrospective designs) to elucidate the impact of psychedelics on mental health and substance use (Garcia-Romeu et al., 2020; Nayak et al., 2023; Raison et al., 2022; Romeo et al., 2023). Generally, these studies have indicated greater beneficial effects of psychedelics when used in ceremonial, religious, or treatment settings, especially among participants with

intentions to decrease their substance use (Argento et al., 2019; Garcia-Romeu et al., 2019, 2020; Johnson et al., 2017; Lake et al., 2023; Malcolm et al., 2018; Richard & Garcia-Romeu, 2025). Moreover, the acute subjective experiences resulting from the use of psychedelics (e.g., experiences of connectedness, ego dissolution, positive mood, psychological insight; Yaden et al., 2024) have been associated with a more positive psychological and behavioral outcomes in both clinical trials and observational studies (Atiq et al., 2024; Ko et al., 2022; Richard & Garcia-Romeu, 2025). Correspondingly, there is an emerging literature on the potential harms of psilocybin when used in non-clinical contexts, reporting on potential negative outcomes, including the exacerbation of preexisting psychiatric diagnoses (Bremler et al., 2023; Raison et al., 2022).

To date, there are few large-scale prospective longitudinal studies that comprehensively assess a range of mental health constructs and their potential fluctuations in the weeks before and after psychedelic use. In one study that recruited individuals planning to use a psychedelic ($n = 302$ at baseline), reductions in depressive symptoms were identified from baseline to 4 weeks ($n = 109$) post-psychedelic experience (Nygart et al., 2022). In a smaller observational study of first-time ayahuasca users ($n = 40$), over 80% of participants meeting diagnostic criteria for a psychiatric disorder showed clinical improvements that persisted for six months (Jiménez-Garrido et al., 2020). However, not only positive effects have been noted after psychedelic use. In a case analysis, Bremler and colleagues (2023) interviewed 15 people who reported long-term negative psychological responses to psychedelics. Results from these qualitative interviews pointed to how prior psychological vulnerabilities and unpleasant acute experiences (e.g., challenging experiences including fear, grief, isolation, and physical distress) can be associated with a worsening of mood and anxiety after psychedelic use.

More recently, Nayak and colleagues (2023) reported findings from a prospective longitudinal survey including measures from 2 weeks before to 2 to 3 months after psilocybin use. In this study, general trends in the results were presented with the overall sample indicating persistent reductions in anxiety, depression and alcohol use, and improvements in cognitive flexibility (Nayak et al., 2023). Although the general findings presented as part of this study were indicative of potential lasting improvement in mental health symptoms following psilocybin use, analyses did not investigate potential differential patterns of responding between participants. This is an increasingly important consideration as previous clinical trial data have noted differential patterns of individual response to psilocybin with regard to changes in depression, anxiety, and substance use (Bogenschutz et al., 2022; Goodwin et al., 2022, 2025; Gukasyan et al., 2022; Johnson et al., 2017; Ross et al., 2016). This includes patterns of significant and maintained psychological improvement, experiences of symptom recurrence despite initial benefit, and even experiences of non-response to treatment (e.g., Goodwin et al., 2025; Gukasyan et al., 2022).

Given the identified gaps in the literature, the present study aims to provide a person-centered analysis via latent profile analysis (Howard & Hoffman, 2018) of patterns of internalizing problems (i.e., depression and anxiety), substance use problems, and cognitive flexibility before and after the naturalistic use of psilocybin. Given the presence of differing profiles of change in these characteristics, the present study also aims to identify whether there are differences between profiles based on sociodemographic characteristics, personality traits, and psilocybin experience-related characteristics including mindset prior to psilocybin use, settings of use, and acute subjective effects.

Materials and Methods

Participants and Procedures

This study was approved by an Institutional Review Board at the Johns Hopkins University School of Medicine and was carried out in accordance with the Declaration of Helsinki. A prospective, longitudinal online survey study enrolled English-speaking adults (≥ 18 years old) planning to take psilocybin outside a clinical research setting. The study was comprised of six sequential web-based surveys, administered through the Qualtrics XM secure online platform. Recruitment advertisements were shared online through social media and via word of mouth. Initial study information was provided with a clear statement indicating that the aim of the research study was to collect data from individuals who have already formulated the intent to take psilocybin, and not to advocate or promote the use of psilocybin. Responses for this longitudinal online survey study were collected from July 2020 to July 2022.

A total of 8006 participants completed the initial survey where they provided informed consent for participation and sociodemographic information (Time 1 [T1]). Participants provided their email address in order to receive the subsequent surveys and reminders via an automated system. Following this initial online survey, participants completed five additional surveys timed relative to their planned psilocybin experience: 2 weeks before (Time 2 [T2], $n = 2{,}850$), 1 day before (Time 3 [T3], $n = 1{,}802$), 1–3 days after (Time 4 [T4], $n = 1{,}551$), 2–4 weeks after (Time 5 [T5], $n = 1{,}182$), and 2–3 months after (Time 6 [T6], $n = 657$). As fraudulent responses are an important consideration when conducting online research (Shaw et al., 2025), a number of protections were in place to deter these types of responses including the study design (i.e., longitudinal study with six survey periods including hidden participant IDs with subsequent survey links being unique to the ID and sent to a valid email address), compensation structure (i.e., $50.00 USD compensation awarded via specific sponsor company coupon codes and awarded in a prorated manner at T4 and T6), IP address tracking, and the Qualtrics XM "Prevent Ballot Box Stuffing" measure. During data cleaning procedures, responses with duplicate email addresses were removed ($n = 278$ at T1, $n = 45$ at T2, $n = 7$ at T3, $n = 5$ at T4, $n = 3$ at T5, $n = 7$ at T6). Additionally, prior to analysis, data cleaning procedures were implemented to remove responses with patterns of inconsistent responding and responses with unreliable data with regard to self-reported psilocybin grams (g) ingested (i.e., < 0.1 g or > 15 g, $n = 33$).

Measures

Sociodemographic Data (T1) and Personality Characteristics (T2)

Sociodemographic characteristics including age, gender, race/ethnicity, level of education, and marital status were collected as part of the initial survey. The 44-item Big Five Inventory (BFI; John et al., 1991) was utilized to measure personality characteristics 2 weeks before the planned psilocybin experience. Responses for each item on the BFI range from 1 ("Strongly disagree") to 5 ("Strongly agree"). Average scores within each of the five personality subscales are measured, with higher scores indicating a stronger expression of that trait, with research identifying that trait neuroticism is negatively related to psychological resilience or successful adaptation and all other traits being positively associated with

resilience (Oshio et al., 2018). Cronbach alpha (α) for each subscale were in the acceptable to good range (extraversion, $\alpha = 0.86$; agreeableness, $\alpha = 0.75$; neuroticism, $\alpha = 0.87$; conscientiousness, $\alpha = 0.81$; openness to experience, $\alpha = 0.74$).

Internalizing Problems (T2, T5, and T6)

To measure internalizing problems, two scales measuring depression and anxiety, respectively, were utilized. A modified 20-item Beck's Depression Inventory II (BDI-II; Beck, 1996), excluding an item on suicidality (due to inability to respond to imminent risk) was used to measure depressive symptoms. This scale was scored 0 to 60 with higher scores indicating greater severity of depression. The BDI-II indicated excellent reliability ($\alpha = 0.93$ at T2, T5, and T6). The 10-item trait anxiety subscale of the Short State Trait Anxiety Inventory (S-STAI; Spielberger et al., 1970) was used to measure general anxiety. This scale was scored 10 to 40, with higher scores indicating greater severity of anxiety. The S-STAI indicated excellent reliability ($\alpha = 0.90$ at T2, T5, and T6).

Alcohol and Drug Use (T2, T5, and T6)

Alcohol and drug use behaviors were assessed 2 weeks before the psilocybin experience, 2–4 weeks after, and 2–3 months after. The Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) and Drug Use Disorders Identification Test (DUDIT; Berman et al., 2003) were utilized as measures of alcohol and drug consumption and related problems, respectively, at T2 and T6. The AUDIT is a 10-item scale, with higher scores indicating greater alcohol consumption and use problems (de Meneses-Gaya et al., 2009). The AUDIT indicated good reliability ($\alpha = 0.84$ at T2; $\alpha = 0.82$ at T5 and T6). The DUDIT is an 11-item scale, with higher scores indicating more frequent drug consumption and severe drug use problems (Hildebrand, 2015). The DUDIT indicated acceptable to good reliability ($\alpha = 0.83$ at T2; $\alpha = 0.81$ at T5; and $\alpha = 0.77$ at T6). Both the AUDIT and DUDIT include specific questions to assess frequency of substance consumption (i.e., AUDIT-C [sum of the first 3 items] and DUDIT-C [sum of the first 4 items]) including frequency of alcohol or drug use, number of alcohol or drug uses per typical day using, and the frequency of heavy alcohol or drug use episodes. The additional item on the DUDIT-C is related to the frequency of concurrent polysubstance use. Additionally, binary (yes or no) data on regular (at least weekly) substance use was collected 2 weeks before the psilocybin experience.

Cognitive Flexibility (T2, T5, T6)

The 12-item Cognitive Flexibility Scale (CFS; Martin et al., 1995) was utilized to assess one's self-reported ability to think and behave adaptively. The CFS is scored from 12 to 72 with higher scores indicating greater cognitive flexibility with average normative scores being around 55. The CFS indicated good reliability ($\alpha = 0.81$ at T2; $\alpha = 0.83$ at T5; and $\alpha = 0.82$ at T6).

Psilocybin Use Characteristics (T2, T4, T5) and Psychological Surrender (T3)

Participants were asked how many times they had previously taken psilocybin prior to study participation (T2). On the day before their planned psilocybin session (T3),

participants completed the 12-item State of Surrender (SoS) scale (Sease et al., 2024). This measure assesses a person's willingness to relinquish control, trust, and accept an experience and experience surrender as transformative or spiritual. Each item has a response on a 5-point Likert scale ranging from 1 ("Strongly disagree") to 5 ("Strongly agree"), with higher total average scores indicating a greater capacity to surrender and accept changes in acute subjective experiences. The SoS indicated good reliability ($\alpha = 0.86$). One to 3 days after the dosing session (T4), participants were asked to report the dosage (in grams) of psilocybin-containing mushrooms ingested with images provided for reference. Moreover, participants were asked about contextual characteristics of the setting when they ingested psilocybin, including who they were with (e.g., alone, with a sober friend, with friends also consuming) and where they spent the majority of their time (e.g., home or private residence, party, concert or festival, outdoors in nature, religious or spiritual setting). Finally, participants were asked and how many additional times they had used psilocybin following their planned psilocybin experience 2–4 weeks after their psilocybin experience (T5).

Acute Subjective Effects of Psilocybin (T4)

To measure the acute subjective effects of psilocybin, the Mystical Experiences Questionnaire (MEQ; Barrett et al., 2015), Challenging Experiences Questionnaire (CEQ; Barrett et al., 2016), and Awe Experience Scale (AWE-S; Yaden et al., 2019) were completed 1–3 days after the psilocybin experience (T4). The MEQ (30 items) and CEQ (26 items) inquire about the entirety of the psilocybin experience and the degree to which certain sensations, feelings, and thoughts were experienced on a 6-point Likert scale ranging from 0 ("None at all") to 5 ("Extreme"). The MEQ has four subscales including experiences of oneness, positive mood, transcendence of time and space and ineffability (i.e., incapable of being described in words). The MEQ indicated excellent reliability ($\alpha = 0.98$). The CEQ has seven subscales covering experiences including grief, fear, physical distress, insanity, isolation, paranoia and death. The CEQ indicated excellent reliability ($\alpha = 0.93$). The AWE-S has six subscales measuring the cognitive and emotional states associated with awe on a 5-point Likert scale ranging from 1 ("Strongly disagree") to 5 ("Strongly agree") including time alteration, vastness, connectedness, self-diminishment, physical sensations and need for accommodation. The AWE-S indicated excellent reliability ($\alpha = 0.95$). For all three scales, the response scores across all subscales are reported as a total average score, with higher scores indicating a greater degree of mystical, challenging or awe experiences, respectively.

Data Analysis

Data analysis was performed using M*plus* Editor version 8.10 (Muthén & Muthén, 2023) and IBM SPSS version 29. A repeated measures latent profile analysis (RMLPA) was conducted using a stepwise mixture modeling technique with the maximum likelihood robust (MLR) estimation method in order to produce robust standard errors in managing data that are non-normally distributed. The following continuous indicators measured at T2, T5, and T6, were entered into the RMLPA: (1) BDI-II total sum score, (2) S-STAI trait anxiety total sum score, (3) CFS total sum score, (4) AUDIT total sum score, and (5) DUDIT total sum score, for a total of 15 indicators across the three measurement periods. Missing data on the included indicators were assumed to be missing at random and were handled using M*plus*' full information likelihood estimation procedure. Maximum likelihood

solution identification was confirmed using 1000 initial stage random starts and 250 final stage optimizations. Beginning with a parsimonious one-class model, a series of models with an increasing number of profiles was fit to identify the model that provided the best fit to the data. The ideal number of profiles was identified through a combination of indices including (1) information-theoretic methods including the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample-Size Adjusted Bayesian Information Criterion (SSABIC), with lower values indicating superior model fit; (2) likelihood ratio statistical tests including the adjusted Lo-Mendell-Rubin likelihood ratio (aLMR) test, Vuong-Lo-Mendell-Rubin (VLMR) test, and bootstrap likelihood ratio test (BLRT), providing *p*-values assessing whether adding a class provides a statistically significant improvement to the model; and (3) entropy-based criterion values, with values closer to 1.0 indicating better classification of individual cases into profiles (optimal values > 0.80). Class separation based on clinical utility and external validation via outcomes of interest was also considered (Nylund-Gibson & Choi, 2018; Sinha et al., 2021; Weller et al., 2020).

Second, IBM SPSS version 29 was used to calculate descriptive statistics and to investigate potential differences between profiles utilizing univariate parametric tests (i.e., one-way analysis of variance [ANOVA] or Chi-square tests) based on the types of variables included (i.e., categorical or continuous variables). Differences between profiles were investigated based on participant characteristics before psilocybin use (i.e., T1 demographic characteristics, T2 personality characteristics, T2 substance use behaviors, T3 psychological surrender [SoS]) and the acute subjective effect of psilocybin (i.e., T4 mystical experience [MEQ], T4 challenging experience [CEQ], and T4 awe experience [AWE-S]). Categorical variables with multiple responses (i.e., setting [who] and setting [where]) were dummy coded to convert categorical variables into dichotomous variables for analysis. For these between-profile comparisons, a Bonferroni adjusted alpha value of 0.002 was applied (0.05/26).

Results

Descriptive Statistics

An overview of the total sample sociodemographic, personality, and substance use characteristics at baseline and 2 weeks before the psychedelic experience is included in Table 1. Overall, participants were predominantly White (81.4%), male (54%), with an average age of 39.77 years (SD = 13.07). Most participants had completed a bachelor's degree or advanced graduate degree (58.5%), with a high percentage being either married or in a committed relationship (57.7%). At baseline, the most commonly reported weekly substance use behaviors were cannabis (53.4%), alcohol (36.7%), and tobacco (22.7%) use. The average lifetime psilocybin use for the sample was an average of 17.11 prior psilocybin uses (SD = 21.81).

Repeated Measures Latent Profile Analysis

Model fit indices from the RMLPA models are presented in Table 2, with the four-profile model providing the optimal fit for the data based on a combination model fit indices, noted improvements in fit indices based on the likelihood ratio tests, and an entropy value remaining above 0.80. No significant improvement in model fit was noted from the

Table 1 Sociodemographic characteristics, personality, and substance use 2 weeks before the psilocybin experience

	Total sample ($n = 2850$)	Profile 1 ($n = 862$)	Profile 2 ($n = 1514$)	Profile 3 ($n = 252$)	Profile 4 ($n = 222$)	p-value
Age [*M*, *SD*]	39.77 (13.07)	38.44 (12.45)	41.22 (13.85)	37.89 (11.49)	37.16 (10.24)	< .001
Gender						< .001
Female	1244 (43.6%)	395 (45.8%)	622 (41.1%)	143 (56.7%)	84 (37.8%)	
Male	1540 (54.0%)	436 (50.6%)	874 (57.7%)	95 (37.7%)	135 (60.8%)	
Transgender or other	66 (2.3%)	31 (3.6%)	18 (1.2%)	14 (5.6%)	3 (1.4%)	
Race						.24
Caucasian/White	2321 (81.4%)	691 (80.2%)	1231 (81.3%)	201 (79.8%)	198 (89.2%)	
African American/Black	45 (1.6%)	12 (1.4%)	25 (1.7%)	7 (2.8%)	1 (0.5%)	
Native American, Hawaiian	33 (1.2%)	11 (1.2%)	15 (1.0%)	4 (1.6%)	3 (1.4%)	
Mixed Race	217 (7.6%)	65 (7.5%)	118 (7.8%)	23 (9.1%)	11 (5.0%)	
Asian	97 (3.4%)	34 (3.9%)	48 (3.2%)	9 (3.6%)	6 (2.7%)	
Other/prefer not to say	137 (4.8%)	49 (5.7%)	76 (5.1%)	8 (3.2%)	3 (1.4%)	
Ethnicity						.32
Hispanic or Latino (Yes)	303 (10.6%)	89 (10.3%)	171 (11.5%)	27 (10.7%)	16 (7.2%)	
Education						< .001
No high school diploma	38 (1.3%)	10 (1.2%)	17 (1.1%)	8 (3.2%)	3 (1.4%)	
High school diploma	202 (7.1%)	65 (7.5%)	99 (6.5%)	22 (8.7%)	16 (7.2%)	
Some college credit	548 (19.2%)	215 (24.9%)	246 (16.2%)	53 (21.0%)	34 (15.3%)	
Trade, tech., vocational	206 (7.2%)	49 (5.7%)	118 (7.8%)	19 (7.5%)	20 (9.0%)	
Associate's degree	188 (6.6%)	51 (5.9%)	90 (5.9%)	25 (9.9%)	22 (9.9%)	
Bachelor's degree	901 (31.6%)	268 (31.1%)	487 (32.2%)	71 (28.2%)	75 (33.8%)	
Master's degree	539 (18.9%)	158 (18.3%)	295 (19.5%)	45 (17.9%)	41 (18.5%)	
Advanced or doctoral degree	228 (8.0%)	46 (5.3%)	162 (10.7%)	9 (3.6%)	11 (5.0%)	
Marital status						.10
Single	848 (29.8%)	284 (32.9%)	406 (26.8%)	90 (35.7%)	68 (30.6%)	
In a committed relationship	677 (23.8%)	191 (22.2%)	365 (24.1%)	58 (23.0%)	63 (28.4%)	

Table 1 (continued)

	Total sample ($n=2850$)	Profile 1 ($n=862$)	Profile 2 ($n=1514$)	Profile 3 ($n=252$)	Profile 4 ($n=222$)	p-value
Married	965 (33.9%)	285 (33.1%)	541 (35.7%)	71 (28.2%)	68 (30.6%)	
Separated	74 (2.6%)	17 (2.0%)	44 (2.9%)	8 (3.2%)	5 (2.3%)	
Divorced	251 (8.8%)	75 (8.7%)	137 (9.0%)	22 (8.7%)	17 (7.7%)	
Widowed	35 (1.2%)	10 (1.2%)	21 (1.4%)	3 (1.2%)	1 (0.5%)	
Personality (BFI) [*M*, *SD*]						
Extraversion	3.19 (0.86)	2.95 (0.81)	3.44 (0.79)	2.61 (0.82)	3.08 (0.89)	<.001
Agreeableness	3.85 (0.60)	3.71 (0.58)	4.02 (0.55)	3.48 (0.66)	3.08 (0.89)	<.001
Conscientiousness	3.52 (0.70)	3.32 (0.66)	3.76 (0.63)	3.04 (0.74)	3.26 (0.63)	<.001
Neuroticism	2.98 (0.89)	3.43 (0.67)	2.50 (0.72)	4.09 (0.56)	3.24 (0.78)	<.001
Openness to experience	4.09 (0.54)	4.03 (0.52)	4.19 (0.50)	3.84 (0.67)	3.99 (0.55)	<.001
Substance use behaviors						
Weekly alcohol use (Yes)	1047 (36.7%)	244 (28.4%)	563 (37.2%)	63 (25.0%)	177 (79.7%)	<.001
Weekly tobacco (Yes)	648 (22.7%)	225 (26.1%)	281 (18.6%)	62 (24.6%)	80 (36.0%)	<.001
Weekly cannabis (Yes)	1522 (53.4%)	495 (57.4%)	752 (49.7%)	147 (58.3%)	128 (57.7%)	<.001
Weekly benzodiazepine use (Yes)	90 (3.2%)	25 (2.9%)	27 (1.8%)	24 (9.5%)	14 (6.3%)	<.001
Weekly opioid use (Yes)	29 (1.0%)	10 (1.2%)	11 (0.7%)	5 (2.0%)	3 (1.4%)	.26
Weekly cocaine use (Yes)	10 (0.4%)	3 (0.3%)	3 (0.2%)	1 (0.4%)	3 (1.4%)	.06
Weekly stimulant use (Yes)	123 (4.3%)	33 (3.8%)	56 (3.7%)	18 (7.1%)	16 (7.2%)	.01
Lifetime psilocybin use [*M*, *SD*]	17.11 (21.81)	14.96 (19.37)	18.25 (22.74)	14.43 (21.50)	19.81 (23.38)	<.001

P-values reflect the values for a one-way ANOVA for continuous dependent variables, and chi-square tests for categorical dependent variables. *BFI* Big Five Inventory

Table 2 Model fit information for the repeated measures latent profile analysis

No. of profiles	AIC	BIC	SSA-BIC	Entropy	VLMR	aLMR *p*-value	BLRT *p*-value
1	145,109.60	145,288.25	145,192.93	-	-	-	-
2	140,834.55	141,108.48	140,962.32	0.829	0.00	0.00	0.00
3	138,868.30	139,237.52	139,040.52	0.869	0.00	0.00	0.00
4	**137,628.72**	**138,093.22**	**137,845.39**	**0.821**	**0.04**	**0.04**	**0.00**
5	136,708.92	137,268.69	136,970.02	0.839	0.05	0.05	0.00
6	135,898.68	136,553.74	136,204.23	0.832	0.71	0.71	0.00

AIC Akaike information criteria, *aLMR* adjusted Lo–Mendell–Rubin likelihood ratio test, *BIC* Bayesian information criteria, *BLRT* bootstrap likelihood ratio test, *SSA-BIC* Sample size adjusted Bayesian information criteria, *VLMR* Vuong-Lo-Mendell-Rubin test. Bold values present the values for the best fitting model

4-profile to the 5-profile model. Moreover, the number of participants within each profile (see Table 3) remained above the 5% threshold for sample size across all of the indices included within the RMLPA at T2, T5, and T6. In the four-profile model, the average latent profile probabilities for the most likely profile were 0.91, 0.86, 0.91, and 0.91, respectively, indicating a high degree of classification accuracy.

Four-Profile Model of Mental Health and Substance Use Before and After Psilocybin Use

The best fitting model to the data, namely, the four-profile model of mental health and substance use across the three time-points (T2, T5, and T6) is depicted in Fig. 1. Parameter estimates respective to each profile are included in Table 4.

The first profile labelled "Improved Mental Health with Low Substance Use" (IMLS), accounted for 30.25% of the sample. The IMLS profile represents individuals with moderate depression and anxiety at T2 that experienced marked improvements in internalizing problems and a slight increase in cognitive flexibility following psilocybin use. Regarding substance use, the IMLS profile had among the lowest rates of substance use in the sample with the exception of cannabis use at T2. A significant proportion of the IMLS profile scores on the AUDIT and DUDIT were driven by alcohol (AUDIT-C: $M = 2.96$ [$SD = 1.71$]

Table 3 Percentage of the sample within each profile based on the different model solutions

Percentage of profile (%)						
Profiles	1	2	3	4	5	6
1	2850 (100%)					
2	2099 (73.65%)	751 (26.35%)				
3	1966 (68.98%)	294 (10.32%)	590 (20.70%)			
4	**862 (30.25%)**	**1514 (53.12%)**	**252 (8.84%)**	**222 (7.78%)**		
5	208 (7.30%)	1502 (52.70%)	771 (27.05%)	179 (6.28%)	190 (6.67%)	
6	379 (13.30%)	1293 (45.37%)	722 (25.33%)	211 (7.40%)	120 (4.21%)	125 (4.39%)

Bold values present the values for the best fitting model

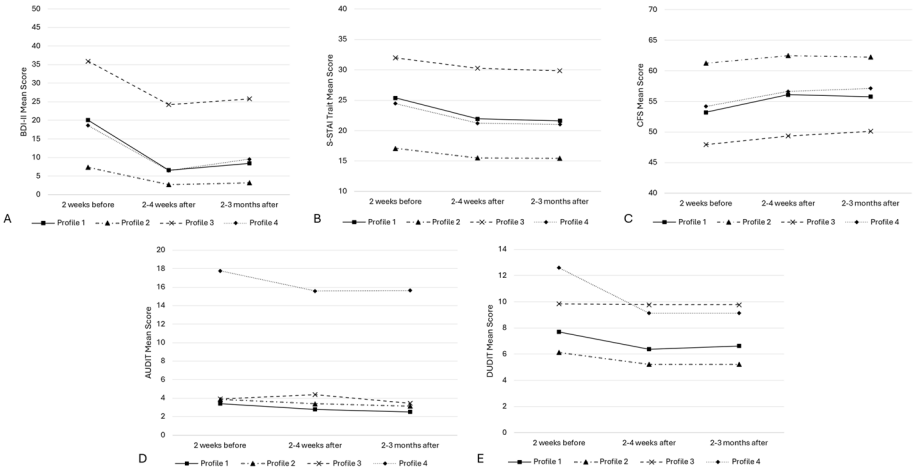

Fig. 1 Mean scores across the five indicators for each of the four profiles across the three measurement periods. *Note.* **A** Mean scores by profile for depressive symptoms based on the BDI-II. **B** Mean scores by profile for trait anxiety based on the S-STAIT. **C** Mean scores by profile for cognitive flexibility based on the CFS. **D** Mean scores by profile for alcohol consumption and problems based on the AUDIT. **E** Mean scores by profile for drug consumption and problems based on the DUDIT

Table 4 Parameter estimates of mental health and substance use across time based on four-profile model

	Profile 1	Profile 2	Profile 3	Profile 4
Profile prevalence *n* (%)	862 (30.25%)	1514 (53.12%)	252 (8.84%)	222 (7.79%)
BDI-II depression[a]	19.53 (0.99)	7.60 (0.31)	35.25 (1.36)	18.47 (1.63)
BDI-II depression[b]	6.47 (0.61)	2.71 (0.16)	24.12 (2.27)	6.44 (1.22)
BDI-II depression[c]	8.31 (1.05)	3.15 (0.21)	25.66 (2.29)	9.38 (2.74)
S-STAI trait anxiety[a]	25.19 (0.48)	17.16 (0.30)	31.70 (0.48)	24.41 (0.76)
S-STAI trait anxiety[b]	21.86 (0.52)	15.50 (0.27)	30.23 (0.63)	21.03 (0.92)
S-STAI trait anxiety[c]	21.54 (0.66)	15.46 (0.26)	29.82 (0.87)	20.78 (1.28)
CFS cognitive flexibility[a]	53.67 (0.51)	61.20 (0.32)	48.38 (0.65)	54.30 (0.95)
CFS cognitive flexibility[b]	56.31 (0.63)	62.48 (0.31)	49.45 (0.82)	56.78 (0.84)
CFS cognitive flexibility[c]	55.96 (0.74)	62.25 (0.34)	50.11 (1.28)	57.28 (1.08)
AUDIT alcohol use/problems[a]	3.44 (0.23)	3.83 (0.18)	3.88 (0.44)	17.52 (1.47)
AUDIT alcohol use/problems[b]	2.79 (0.26)	3.36 (0.22)	4.40 (0.71)	15.43 (1.55)
AUDIT alcohol use/problems[c]	2.54 (0.32)	3.11 (0.24)	3.44 (0.85)	15.49 (1.82)
DUDIT drug use/problems[a]	7.70 (0.42)	6.07 (0.18)	9.87 (0.89)	12.39 (0.75)
DUDIT drug use/problems[b]	6.38 (0.51)	5.19 (0.25)	9.77 (1.15)	8.89 (1.16)
DUDIT drug use/problems[c]	6.56 (0.66)	4.52 (0.24)	7.82 (1.10)	8.90 (1.09)

Data reported as estimates (S.E.). *AUDIT* Alcohol Use Disorders Identification Test, *BDI-II* Beck's Depression Inventory II, *CFS* Cognitive Flexibility Scale, *DUDIT* Drug Use Disorders Identification Test, *S-STAI* Short State Trait Anxiety Inventory

[a]2 weeks before psilocybin

[b]2–4 weeks after psilocybin

[c]2–3 months after psilocybin

at T2; $M = 2.82$ [$SD = 1.51$] at T5; $M = 2.61$ [$SD = 1.60$] at T6) and other drug (DUDIT-C: $M = 5.84$ [$SD = 3.02$] at T2; $M = 5.42$ [$SD = 2.76$] at T5; $M = 5.65$ [$SD = 2.90$] at T6) consumption.

The second profile labelled "Stable Mental Health with Low Substance Use" (SMLS), accounted for 53.12% of the sample. The SMLS profile represents individuals with low depression and anxiety and high cognitive flexibility at T2. Despite low scores prior to psilocybin use, minor improvements in internalizing problems were reported. Similar to the IMLS profile, the SMLS profile had among the lowest rates of substance use in the sample at T2, including the lowest frequency of weekly cannabis use. The frequency of weekly alcohol use for the IMLS profile was consistent with the average for the overall sample. A significant proportion of the SMLS profile scores on the AUDIT and DUDIT were driven by alcohol (AUDIT-C: $M = 3.39$ [$SD = 1.94$] at T2; $M = 3.07$ [$SD = 1.74$] at T5; $M = 2.98$ [$SD = 1.72$] at T6) and other drug (DUDIT-C: $M = 5.35$ [$SD = 2.79$] at T2; $M = 4.90$ [$SD = 2.57$] at T5; $M = 4.70$ [$SD = 2.42$] at T6) consumption. Both alcohol and drug use decreased slightly following psilocybin use with DUDIT scores being the lowest across all profiles.

The third profile labelled "Persistent Mental Health Symptoms with Persistent Substance Use" (PMPS), accounted for 8.84% of the sample. The PMPS profile represents individuals with severe internalizing problems, including severe depression, high anxiety, and low cognitive flexibility at T2. Although some improvement in internalizing problems was reported following psilocybin use, depression, and anxiety symptom scores remained elevated in the moderate range. The PMPS profile reported low rates of weekly alcohol and tobacco use, although there was a markedly greater prevalence of weekly benzodiazepine use. Although the PMPS profile scores on the AUDIT and DUDIT were also due to elevated alcohol (AUDIT-C: $M = 3.04$ [$SD = 1.96$] at T2; $M = 2.81$ [$SD = 1.87$] at T5; $M = 2.61$ [$SD = 1.99$] at T6) and other drug (DUDIT-C: $M = 6.95$ [$SD = 3.51$] at T2; $M = 6.23$ [$SD = 3.40$] at T5; $M = 5.53$ [$SD = 2.94$] at T6) consumption, their overall scores on the DUDIT were indicative of consistent problematic patterns of problematic drug use before and after psilocybin use.

The fourth profile labelled "Improved Mental Health with Persistent Substance Use" (IMPS), accounted for 7.79% of the sample. The IMPS profile is similar to the IMLS profile as it represents individuals with moderate depression and anxiety at T2 that experienced marked improvements in internalizing problems and a slight increase in cognitive flexibility following psilocybin use. The IMPS profile is differentiated from the IMLS profile as it had the highest rates of substance use in the sample, including the highest frequency of weekly alcohol and tobacco use. The IMPS profile endorsed the greatest rates of alcohol consumption across all timepoints (AUDIT-C: $M = 7.12$ [$SD = 3.34$] at T2; $M = 6.56$ [$SD = 2.21$] at T5; $M = 6.15$ [$SD = 2.25$] at T6) and total AUDIT scores remained highly elevated despite some reduction following psilocybin use. General patterns of drug consumption were similar to the PMPS profile (DUDIT-C: $M = 6.82$ [$SD = 3.33$] at T2; $M = 5.65$ [$SD = 3.00$] at T5; $M = 5.71$ [$SD = 3.03$] at T6) although total DUDIT scores were indicative of a more marked reduction of drug-related problems following psilocybin use albeit remaining in the problematic range.

Differences Between the Latent Profiles

Comparing the four profiles based on sociodemographic characteristics, Profile 2 (SMLS) was significantly older than the other three profiles ($p < 0.001$) and had a significantly

greater degree of educational attainment compared to Profile 3 (PMPS) ($p < 0.001$). Profile 3 (PMPS) had the greatest proportion of participants identifying as female compared to all other profiles ($p < 0.001$), whereas Profile 4 (IMPS) had the greatest proportion of participants identifying as male ($p < 0.001$). With regard to personality, Profile 2 (SMLS) had the most adaptive personality structure (i.e., a capacity to respond flexibly and effectively to different life situations, cope with stress, and maintain healthy relationships), based on having higher scores in trait extraversion, agreeableness, consciousness, and openness to experience, while having the lowest scores in trait neuroticism ($p < 0.001$). On the other hand, Profile 3 (PMPS) had the most maladaptive profile with elevated scores on trait neuroticism and low scores on the remaining four traits ($p < .001$) with the exception that no differences were present between Profile 3 (PMPS) and 4 (IMPS) for trait conscientiousness ($p = 0.002$) and openness ($p = 0.009$). Lastly, differences indicated that Profile 1 (IMLS) reported fewer lifetime psilocybin experiences compared to Profile 2 (SMLS) ($p = 0.001$), while the difference between the other profiles were not statistically significant.

Between-profile comparisons in psilocybin session-related characteristics are presented in Table 5. The day before the psilocybin session (T3), Profile 2 (SMLS) had the highest average levels of psychological surrender based on the SoS compared to all other profiles ($p < 0.001$). As for the acute subjective experiences reported 1–3 days after psilocybin (T4), Profile 3 (PMPS) had the lowest total scores for mystical experience based on the MEQ ($p < 0.001$) and lowest total scores for awe experience based on the AWE-S ($p < 0.001$)

Table 5 Psilocybin dosing-related characteristics and between-profile comparisons

	Total sample	Profile 1	Profile 2	Profile 3	Profile 4	*p*-value
SoS[a]	2.98 (0.45)	2.87 (0.43)	3.09 (0.44)	2.75 (0.45)	2.85 (0.44)	< .001
Dosage[b]	6.13 (5.28)	6.21 (5.23)	6.10 (5.30)	6.16 (5.33)	6.05 (5.25)	.92
MEQ[b]	2.51 (1.24)	2.49 (1.22)	2.63 (1.23)	1.92 (1.32)	2.46 (1.19)	< .001
CEQ[b]	0.72 (0.69)	0.84 (0.72)	0.61 (0.63)	0.94 (0.85)	0.79 (0.69)	< .001
AWE-S[b]	3.59 (1.06)	3.64 (1.05)	3.62 (1.03)	3.18 (1.19)	3.62 (1.05)	< .001
Setting[b] (who) *n* (%)						.08
Alone	661 (42.9%)	207 (44.9%)	342 (41.5%)	57 (44.2%)	55 (43.7%)	
Sober friend	255 (16.5%)	84 (18.2%)	120 (14.5%)	32 (24.8%)	19 (15.1%)	
Friends also consuming	399 (25.9%)	106 (23.0%)	232 (28.1%)	26 (20.2%)	35 (27.8%)	
Other	226 (14.7%)	64 (13.9%)	131 (15.9%)	14 (10.8%)	17 (13.4%)	
Setting[b] (where) *n* (%)						.27
Home/private residence	1072 (69.6%)	331 (71.8%)	551 (66.8%)	103 (79.8%)	87 (69.0%)	
Party	11 (0.7%)	2 (0.4%)	6 (0.7%)	1 (0.8%)	2 (1.6%)	
Concert or festival	18 (1.2%)	2 (0.4%)	13 (1.6%)	1 (0.8%)	2 (1.6%)	
Outdoors in nature	244 (15.8%)	69 (15.0%)	142 (17.2%)	12 (9.3%)	21 (16.7%)	
Religious/spiritual setting	39 (2.5%)	12 (2.6%)	24 (2.9%)	1 (0.8%)	2 (1.6%)	
Other	157 (10.2%)	45 (9.8%)	89 (10.8%)	11 (8.5%)	12 (9.5%)	

AWE-S Awe Experience Scale, *CEQ* Challenging Experiences Questionnaire, *MEQ* Mystical Experience Questionnaire, *SoS* State of Surrender Scale

[a] 1 day before psilocybin

[b] 1–3 days after psilocybin

compared to all other profiles. Regarding challenging experiences, Profile 2 (SMLS) had lower CEQ scores compared to Profile 1 (IMLS) and Profile 3 (PMPS) ($p < 0.001$). No other significant differences were noted across the profiles for these measures. No significant differences between profiles were observed for setting characteristics including who they were with and where the psilocybin session took place. Finally, no differences between the profiles were noted in the total number of additional times they reported taking psilocybin in the 2 to 4 weeks following their psilocybin session ($M = 2.57$, $SD = 2.79$, $p = 0.11$).

Discussion

The present study identified four profiles representing differing baseline levels and degrees of change in internalizing problems, substance use problems, and cognitive flexibility before (T2) and after (T5 and T6) naturalistic psilocybin use. A majority of the sample (~53%) was captured in the SMLS profile experiencing low levels of internalizing problems and substance use across all study periods. The next largest profile (~30%) was the IMLS profile, indicating sustained improvements in depression, anxiety, and cognitive flexibility while substance use remained relatively low across all study periods. The two remaining profiles, PMPS (~9%) and IMPS (~8%) reported persistent substance use problems following psilocybin use, with the prior having greater drug-related problems and the latter greater alcohol and drug-related problems.

A noteworthy difference between the profiles as it relates to baseline sociodemographic and personality characteristics is that the PMPS profile included individuals who were on average younger, female, had the lowest overall educational attainment, and had the most maladaptive personality profile demonstrated by elevated levels of trait neuroticism and low scores on trait extraversion, agreeableness, conscientiousness, and openness to experience when compared to the SMLS and IMLS profiles. Moreover, the PMPS profile indicated the greatest prevalence of weekly benzodiazepine use, which is consistent with data indicative of greater benzodiazepine misuse in younger adults, women, and those with greater psychiatric vulnerabilities including anxiety and depression (Votaw et al., 2020).

Although the PMPS profile did indicate improvement in depressive symptoms following psilocybin use, levels of depression remained in the moderate range, while anxiety symptoms and cognitive flexibility were not indicative of improvement. Within this profile, continued problems with drug use, predominantly cannabis, alcohol, and benzodiazepine use, may reflect a propensity for self-medication, or maladaptive coping with internalizing symptomatology (Robinson et al., 2011; Turner et al., 2018). It is possible that within this profile, psilocybin use had a similar aim (i.e., self-medication). Lastly, it is important to note that the PMPS profile had the lowest total scores for mystical experience and awe, the lowest level of psychological surrender prior to psilocybin use compared to the SMLS profile, and higher challenging experience compared to SMLS profile. These data may point to the psychological characteristics of the PMPS profile and how elevated internalizing symptomatology, low cognitive flexibility, and low willingness to relinquish control prior to a psychedelic experience may be associated with greater acute challenging experiences and a more limited degree of psychological improvement following psilocybin use in non-clinical settings. Although this profile did not appear to experience an exacerbation of preexisting internalizing symptoms in the months following psilocybin use (Bremler et al.,

2023), caution appears to be warranted for this subgroup who had a greater degree of psychological vulnerability prior to naturalistic psilocybin use.

Regarding the IMPS profile, although similar to the IMLS profile with regard to baseline and overall changes in depression, anxiety, and cognitive flexibility, the IMPS profile was comprised of individuals with high rates of alcohol and drug consumption and alcohol and drug-related problems across all study periods. Although drug use decreased to the level of the PMPS profile at T5 and T6, alcohol use problems remained high throughout. At baseline, the IMPS profile had the highest proportion of individuals reporting weekly alcohol use (~80%), with tobacco and cannabis use also being elevated. Data from the IMPS profile suggests that although psilocybin use is associated with improvements in internalizing problems in the months following use in naturalistic settings, problems related to alcohol and drug use can remain largely unchanged. Consequently, for those within the IMLS profile that did improve to a similar degree with regards to depression, anxiety, and cognitive flexibility, no change in their pattern of relatively low alcohol and drug use changed across time. It is possible that vulnerability to SUDs as part of IMPS profile be associated with the overall younger age of the profile in addition to the greater proportion on males (Volkow & Blanco, 2023). For the IMPS profile, it does not appear as though psilocybin was associated with clinically significant improvements in substance use problems and underlines the importance of person-centered analyses that can reveal variations within samples that may otherwise indicate a general improvement in substance use (Nayak et al., 2023).

Lastly, approximately half of the sample was captured by the SMLS profile. This psychologically stable profile was older, had the most adaptive personality profile as evidenced by low levels of trait neuroticism and high levels of trait extraversion, agreeableness, conscientiousness, and openness to experience, and had the greatest number of prior psilocybin experiences next to the IMPS profile. Although minor improvements were noted for depressive symptoms, trait anxiety remained low and cognitive flexibility remained high.

Data on the MEQ and AWE-S did not indicate significant group differences between the SMLS, IMLS, and IMPS profiles. Previous clinical trial research has indicated that mystical experiences under psychedelics and improvements in cognitive flexibility are correlated with positive therapeutic outcomes including improvements in mood and decreases in substance use (Atiq et al., 2024; Bogenschutz et al., 2015; Campo et al., 2025; Doss et al., 2021; Ko et al., 2022; Romeo et al., 2025). Interestingly, the IMLS and IMPS profiles experienced a similar degree of improvement in depression and anxiety over time with slight corresponding increases in cognitive flexibility. Given that the SMLS profile had low levels of depression and anxiety and high levels of cognitive flexibility at baseline, it is reasonable that noted improvements would be of lesser clinical significance. These findings, although preliminary, may be indicative of the underlying neurophysiological and cognitive effects of psychedelics. Specifically, high doses of psychedelics are hypothesized to result in improvements in mood (via modulations in affect) and cognitive control (via modulations in cognitive flexibility) following the acute subjective effects (Sayalı & Barrett, 2023). These hypothesized changes in mood and cognition may be relevant to the concurrent changes in depressive symptoms and cognitive flexibility noted across these profiles.

As for the minimal effects with regard to improvements in alcohol or other drug use, the results from the present study suggest that perhaps it is not the effect of mystical experience per se that results in substance use-related behavioral change, but perhaps a combination of mystical experience with other person-centered or treatment-related factors. Additional research is necessary to investigate these factors and how they relate to changes in substance use following psychedelic use. One potential pathway to investigate

is the domain of intentions as it relates to the desire to stop or reduce substance use, in addition to the settings where psilocybin is taken. Although no significant differences in setting were identified in the present study, there were a low number of participants reporting using psychedelics in treatment or religious/spiritual settings. Future research should investigate whether intentions to better understand (i.e., contemplation) versus intentions to enact change (i.e., preparation and action) in substance use prior to a psychedelic session may be relevant constructs to consider (as elucidated within the transtheoretical stages of change; DiClemente et al., 2004; Prochaska & Velicer, 1997).

As for setting characteristics, prior empirical findings have identified that the use of psychedelics in spiritual or religious settings is more frequently associated with sustained decreases in SUDs as these contexts can provide a container for psychological and/or spiritual growth (Richard & Garcia-Romeu, 2025). Moreover, it is also possible that settings influence what an individual focuses on during the psychedelic experience (e.g., internally versus externally directed experience) which may be associated differing degrees of benefit when it comes to behavioral outcomes (Golden et al., 2022; Kishon et al., 2024; Roseman et al., 2024).

Limitations

The findings of this study should be interpreted in light of several limitations. First, this longitudinal survey study did not include a comparison group of individuals that did not consume psilocybin over the course of the study period. As such, it is not possible to establish the specific effects of psilocybin use on the measured mental health and substance use behaviors. Second, two of the profiles were limited in sample size which limits the generalizability of the conclusions derived from the data. Third, response bias due to convenience sampling and participant self-selection may skew results towards the perspective of those with more positive perceptions of psychedelics. Fourth, response attrition over the course of the study raises issues of bias and generalizability. Fifth, all surveys utilized self-report questionnaire data which are prone to recall, response, and social-desirability bias. Moreover, self-report questionnaires have been associated with an underestimation of substance use (Johnson, 2014; Steinhoff et al., 2023) limiting our ability reliably measure alcohol and drug consumption patterns over the study period. Future studies are encouraged to utilize a combination of more sensitive self-report measures (Santos et al., 2020) and biological testing (e.g., hair samples) in order to more reliably establish prevalence rates and potential changes in substance use. Lastly, the sample was disproportionally White (81.4%) and well-educated (58.5% report at least a bachelor's degree). These factors limit the generalizability of these findings across ethnicity and socioeconomic status, which is an ongoing issue in psychedelic research (Hughes & Garcia-Romeu, 2024; Michaels et al., 2018). Future research should build on the present findings and would benefit from recruiting more diverse and larger representative samples of individuals with substance use problems.

Conclusion

In conclusion, this study identified four distinct profiles based on internalizing problems, substance use problems, and cognitive flexibility measured before and after naturalistic psilocybin use. While a majority of the sample as represented by the SMLS and IMLS profiles demonstrated psychological stability or sustained improvements in depression, anxiety, and cognitive flexibility, the PMPS and IMPS profiles exhibited persistent substance use

problems, with the PMPS profile showing greater psychological vulnerability and lower psychological benefits from psilocybin. These findings highlight the importance of individual differences in psychedelic experiences and outcomes, particularly in relation to baseline personality, mental health, and substance use patterns. The study suggests that while naturalistic psilocybin use is associated with psychological well-being in certain individuals, the general effects of psilocybin on broader substance use remains indeterminate. Moreover, results from this study may be indicative of the importance of sufficient preparation and the clarification of intentions (McAlpine et al., 2024) prior to psilocybin use to increase the potential benefits, alongside the role of integration (Bathje et al., 2022) following the experience to limit the possibility of long-term adverse effects. Future research should explore the role of intention, setting, and treatment-related factors in psychedelic-induced behavioral changes, emphasizing the need for diverse and larger samples to enhance generalizability and clinical application.

Acknowledgements The authors would like to thank study participants, Alex Edwards for her work on Qualtrics, David Champion for his work on the study design, Trey J. Brasher and Del R. P. Jolly for their contributions to participant recruitment, as well as support staff at Unlimited Sciences and the Johns Hopkins University School of Medicine.

Author Contribution JR made substantial contributions to the conceptualization, formal analysis, and interpretation of the data and the drafting of the manuscript. JS made substantial contributions to the formal analysis, interpretation of the data, and drafting of the manuscript. SN, NS, ML, and HJ made substantial contributions to the design of the study, interpretation of the data, and the drafting of the manuscript. AG-R made substantial contributions to the conception and design of the study, the interpretation of the data, and the drafting of the manuscript. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

Funding Funding for this research was provided by the Unlimited Sciences. The Center for Psychedelic and Consciousness Research was funded by philanthropic support from the Steven and Alexandra Cohen Foundation, Tim Ferriss, Matt Mullenweg, Blake Mycoskie, and Craig Nerenberg. Jérémie Richard is a recipient of the Banting Postdoctoral Fellowship awarded by the Canadian Institutes of Health Research (CIHR).

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest AGR is a paid scientific advisor to Innerwell and Otsuka Pharmaceutical Development & Commercialization Inc. AGR has received research funding from MicroDoz Therapy Inc., Mydecine Innovations Group Inc., Unlimited Sciences, the Council on Spiritual Practices, the Heffter Research Institute, and the NIH. 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.

Ethics Approval This study was approved by an Institutional Review Board at the Johns Hopkins University School of Medicine and was carried out in accordance with the Declaration of Helsinki.

Informed Consent Informed consent was obtained from all participants included in the study.

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