

Long-Term Mental Health and Wellbeing Outcomes Associated with Naturalistic Ayahuasca Consumption

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ABSTRACT

The durability of ayahuasca's effects on mental health and the influence of clinical diagnoses on therapeutic response is unclear. Adults with no prior exposure to ayahuasca ($n = 66$) participating in neo-shamanic ayahuasca ceremonies completed questionnaires at baseline, 7 days, and 1, 6, and 12 months. Mixed models were used to characterize temporal trajectories in mental health, alcohol and cannabis use, affect, personality, spirituality, and relationships and examine the longevity of effects in individuals with and without a depressive or anxiety disorder. After multiple comparison correction, ayahuasca use was associated with decreases in depression, anxiety, stress, negative affect, negative emotionality, acceptance of external influence, and self-alienation at all time points. Improvements in mental health, self-efficacy, and spirituality were observed up to 12 months post-ceremony. Individuals with depression and anxiety diagnoses maintained significant symptom reductions, whereas those without a diagnosis experienced short-term benefits. Decreases in alcohol and cannabis use were only observed at month 1. Naturalistic ayahuasca use was associated with persisting improvements in mental health and wellbeing, with the largest magnitude of symptom reduction observed in those diagnosed with a depressive or anxiety disorder. Differing trajectories of change were identified across psychological constructs, suggestive of both enhancement and attenuation of gains over time.

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Introduction

Ayahuasca is a psychedelic plant decoction that has emerged as a promising candidate for the psychiatric treatment of mental health conditions. Ayahuasca contains the psychoactive compound *N,N*-dimethyltryptamine (DMT), and several harmala alkaloids which render DMT orally bioavailable (Werneck et al. 2020). Clinical trials, prospective observational studies, and large cross-sectional surveys of ayahuasca users suggest that ayahuasca use can lead to rapid, robust, and enduring improvements in symptoms of depression and anxiety.

In a double-blind clinical trial, Palhano-Fontes et al. (2019) randomized patients with major depressive disorder (MDD) to ayahuasca or an active placebo with purgative effects. Significant antidepressant response was observed 7 days after dosing, with remission rates of 64% in the ayahuasca group and 27% in the placebo group (Palhano-Fontes et al. 2019). Prospective

observational studies have found reductions in anxiety and depression symptoms out to 6-months in mixed samples, and reductions in depression in patients with MDD out to 12-months after administration, but a separate study did not find therapeutic effects 4–7 years later (Jiménez-Garrido et al. 2020; Ruffell et al. 2021; Santos et al. 2018; van Oorsouw, Toennes, and Ramaekers 2022a).

Cross-sectional research has found only slight, or nil associations between the number of years since ayahuasca was last drunk and better mental health and reduced alcohol/drug/tobacco use, suggesting effects may be highly durable or diminish at a very slow rate over longer time scales (Daldegan-Bueno et al. 2022; Perkins et al. 2021, 2023). Other clinically relevant changes have been observed, including increases in life satisfaction, mindfulness, cognitive flexibility, empathy, and connection to self, others, and nature, and alterations to personality traits, which are consistent with enhanced resiliency

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(Kiraga et al. 2021; Murphy-Beiner and Soar 2020; Ruffell et al. 2023; van Oorsouw, Toennes, and Ramaekers 2022a). Corroborating these relationships, cross-sectional survey studies have found that regular ayahuasca users report better general well-being and cognitive performance, fewer diseases and symptoms of psychopathology, and healthier lifestyles relative to normative samples (Bousso et al. 2012; Kohek et al. 2023; Lawn et al. 2017).

Despite the health benefits reported in these studies, it is unclear how long psychological changes persist over time, whether negative long-term consequences arise after the purported short-term benefits, and whether effects are specific to individuals with clinical diagnoses. We previously published an analysis of data from a prospective observational study which identified increases in relationship satisfaction, nature relatedness, spirituality, authenticity, self-efficacy, and body connection 1 month after a neo-shamanic ayahuasca ceremony in first-time users of ayahuasca (Perkins et al. 2022). In this report, we characterize mental health and psychological outcomes and trajectories in this sample over a 12-month period. We also evaluate whether clinical diagnosis of a depressive or anxiety disorder impacts the longevity of antidepressant or anxiolytic effects, respectively. This study contributes important longitudinal data to better understand the time course of changes in mental health and psychological wellbeing associated with naturalistic ayahuasca use.

Methods

Participants

Ayahuasca naïve participants ($n = 66$) were recruited using convenience sampling from two independent ayahuasca churches in North America from 2019 to 2021. Inclusion criteria for participating in the study were being 18 years of age or older, an English speaker, and having never used ayahuasca in the past. See Perkins et al. (2022) for a detailed description of recruitment and enrollment procedures. The research team was not involved in recruitment, administration of ayahuasca, or conducting the ceremony – all of which were performed by the ayahuasca church sites. All participants provided written informed consent. The study protocol was approved by the University of Melbourne Human Research Ethics Committee (HREC number 1,852,071.1). As

part of the churches' intake processes, independent of this study, all attendees with a confirmed or suspected diagnosis of a psychotic disorder or using a contraindicated medication use (e.g., antipsychotics, antidepressants, etc.) were excluded.

Design and setting

Ayahuasca ceremonies were conducted in a neo-shamanic mestizo-styled setting at both church sites between November 2018 and December 2019. The churches were not organizationally affiliated. At each site, participants attended a 1-day, 2-day, or 3-day ceremony led by a facilitator. For more information on the ceremonial setting, see Perkins et al. (2022).

Measures

Mental health

Participants reported lifetime mental health diagnoses, including depression and anxiety disorders. The DASS-21 (Depression, Anxiety, and Stress Scale) and Positive and Negative Affect Scale (PANAS) were administered at baseline (BL), day 7 (D7), 1 month (1 m), 6 months (6 m), and 12 months (12 m). The DASS-21 is a 21-item survey with subdomain scores for depression, anxiety, and stress (Lovibond and Lovibond 1995). The PANAS is a 10-item survey with subscale scores for positive and negative affects (Watson, Clark, and Tellegen 1988). The Short-Form Health Survey (SF-12) was administered at BL, 1 m, 6 m, and 12 m, and features a mental health and physical health summary score (Ware et al. 2009).

Alcohol and cannabis use

The 8-item World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was used to calculate a total risk score for alcohol and cannabis use at BL, 1 m, 6 m, and 12 m (Humeniuk et al. 2008). Three categorical items were used in the Alcohol Use Disorder Identification Test (AUDIT) that evaluated the 1) frequency of alcohol use, 2) average amount of alcohol consumed on a -drinking day, and 3) frequency of binge-related drinking episodes at BL, 1 m, 6 m, and 12 m (Bradley et al. 1998).

Wellbeing and personality

All wellbeing measures were collected at BL, 1 m, 6 m, and 12 m. The 10-item General Self-efficacy Scale (GSE) total score was used to measure general perceived self-efficacy (Schwarzer and Jerusalem 1995); the 30-item Barratt Impulsivity Scale (BIS-30) total scores was used to measure

impulsivity (Vasconcelos, Malloy-Diniz, and Correa 2012); the 15-item short form Big Five Inventory-2 (BFI-2-XS) was used to measure the personality traits Extraversion, Agreeableness, Conscientiousness, Negative Emotion, and Open-mindedness (Soto and John 2017). Quality of interpersonal relationships was measured using the 7-item Relationship Satisfaction Scale (RS) (Wooden, Freidin, and Watson 2002). Interpersonal and intrapersonal influences were measured using the 12-item Authenticity Scale (AS), which contains the subscales Authentic Living, External Influence, and Self-alienation (Wood et al. 2008). Bodily awareness was measured using the 20-item Scale of Body Connection (SBC), which contains the subscales Body Awareness and Bodily Dissociation (Price et al. 2017). Relationships with nature were measured using the 21-item Nature Relatedness Scale (NR), which contains the subscales Self, Perspective, and Experience (Nisbet, Zelenski, and Murphy 2008). Spirituality was measured using the 6-item Intrinsic Spirituality Scale (ISS) (Hodge 2003). Fruit and vegetable consumption was collected with the question “Approximately how many servings of vegetables/fruit do you eat on a usual day?”. Body Mass Index was calculated using the formula: $\text{weight (kg)} / [\text{height (m)}]^2$.

Statistical analysis

Data were collected and managed using the REDCap data collection tool hosted at the University of Melbourne. All records were imported into R statistical software version 4.1.2 where data analysis was conducted. Linear Mixed Models (LMM) through the lmerTest package were used to test differences between groups and between time points within groups for all instruments unless stated otherwise (Kuznetsova, Brockhoff, and Christensen 2017). In all LMM models, an individual was set as a random effect. Fixed effects included time point and whether an individual had consumed ayahuasca after the initial treatment period. The impact of each predictor was assessed by generating ANOVA results from the LMM with Satterthwaite’s method for estimating degrees of freedom. LMMs were utilized due to being well-suited to handling partially missing data, thus reducing potential bias due to differences between responders and non-responders. To analyze results involving ordinal scales, Cumulative Link Mixed Models (CLMM) were employed, utilizing functionalities from the ordinal and RVAideMemoire packages in R (Christensen 2019). The model implemented used the same fixed and random effects as LMM. Furthermore, odds ratios (ORs) were calculated using the ordinal package (Christensen 2019). Effect sizes

were measured by using effect size R package and partial eta-squared (η_p^2) with 95% confidence intervals (Ben-Shachar, Lüdtke, and Makowski 2020). Effect sizes are considered small from 0.01 to 0.06, medium from 0.06 to 0.14, and large 0.14 or above (Miles and Shevlin 2001). Multiplicity across measures was controlled for with false discovery rate (FDR) correction using the Benjamini-Hochberg method (Benjamini and Hochberg 1995). FDR correction was performed using the p-values from the main effects of time (the primary effect of interest) for all 42 measures. Post-hoc pairwise comparisons using Holm-Bonferroni’s adjustment were conducted to examine significantly simple effects of time. Those comparisons were performed using R’s emmeans package, and the results are reported with estimated marginal means (EMM), mean difference scores (M_{diff}), and their corresponding standard error (SE) (Lenth and others 2022). P-values less than 0.05 after the FDR correction were considered significant.

Results

Participants

The sample sizes for the linear mixed models for each respective instrument and time point are presented in Supplemental Table S1. The baseline sample size was 66 participants (26 men and 40 women) with a mean age of 37.56 (*SD*: 10.16, range 19–64). Among this sample, the vast majority of participants were US citizens (97%), with relatively high levels of education: almost half (49.9%) reported a bachelor’s degree or above (bachelor’s degree, 30.3%; a masters or other professional degree, 12.1%; doctoral degree, 6.1%). Twenty-four participants reported previously receiving a depressive disorder diagnosis (e.g., major depression) and 15 reported receiving an anxiety disorder diagnosis (e.g., generalized anxiety disorder) (Table S1). During the follow-up period, 27 participants reported additional instances of drinking ayahuasca, and 39 participants did not.

Mental health

Depression, anxiety, and stress

Significant main effects of time were detected on the DASS-21 subscales for Depression ($\eta_p^2 = 0.20$), Anxiety ($\eta_p^2 = 0.16$), and Stress ($\eta_p^2 = 0.33$), all of which survived correction ($p\text{-FDR} < 0.001$). Relative to the baseline, depressive symptoms were reduced across the full sample by 75% at 7d, 59% at 1 m, and 51% at 12 m (Figure 1a, Table S2). Relative to baseline, anxiety, and

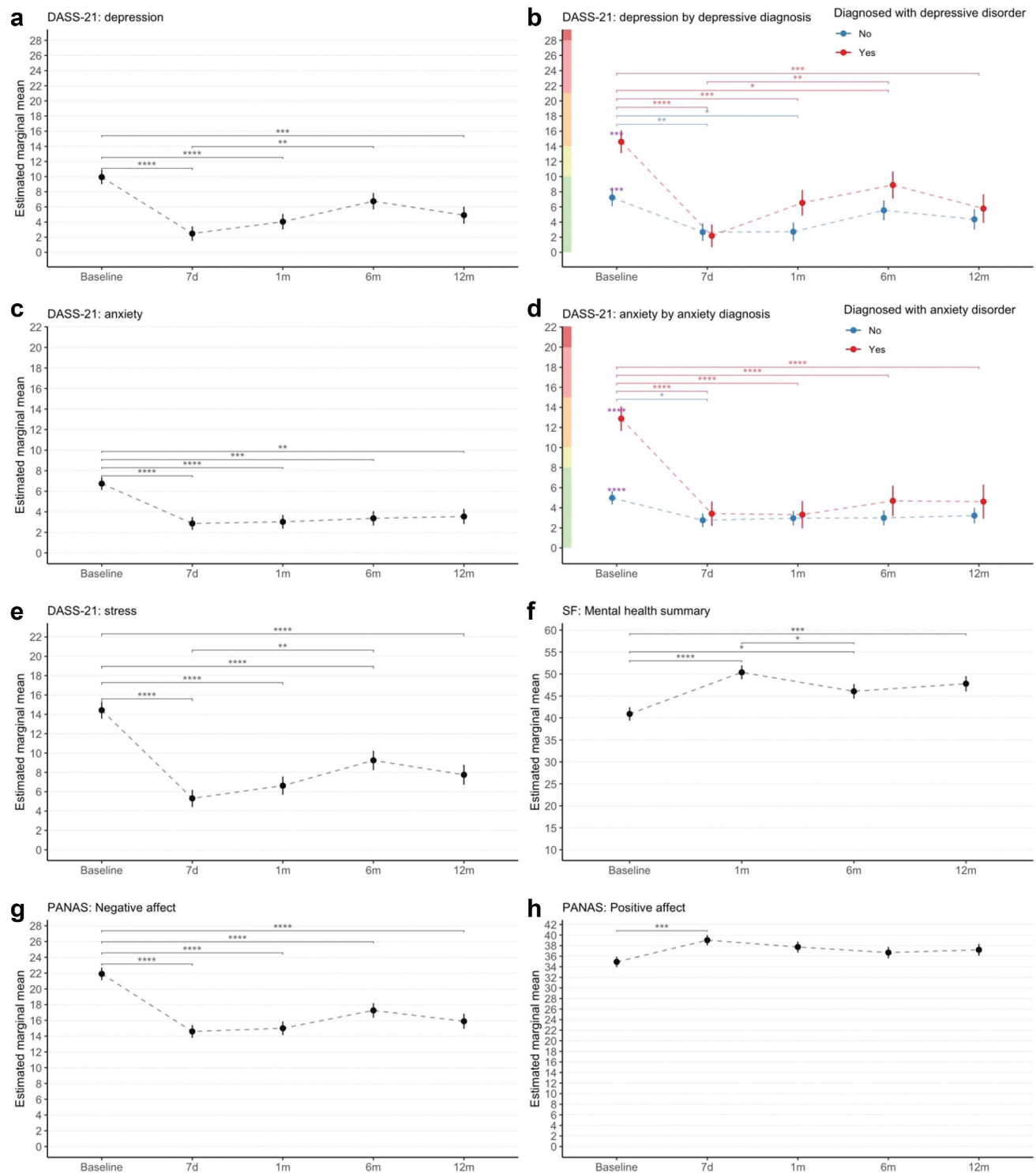


Figure 1. DASS-21 scores for (a) depression, (b) depression by depressive diagnosis, (c) anxiety, (d) anxiety by anxiety diagnosis (e) stress. SF-12 score for (f) mental health summary. PANAS scores for (g) negative affect and (h) positive affect. Scores were measured at baseline, 7 days (7d), 1 month (1m), 6 months (6m) and 12 months (12m) post-ayahuasca ceremony, except for (f), where 7d was not collected. Estimated marginal means (EMM) with standard errors (SE) are shown with asterisks representing statistical significance levels of $*p < .05$, $**p < .01$, $***p < .001$, and $****p < .0001$. Colors on the Y-axis of (b) and (d) correspond to the severity of either depression or anxiety, with normal (green), mild (yellow), moderate (orange), severe (light red) and extremely severe (dark red). Purple asterisks show differences between groups.

stress symptoms were reduced across the full sample by 57% and 63% at 7d, 55% and 54% at 1 m, 50% and 36% at 6 m, and 47% and 46% at 12 m, respectively (Figure 1(c,e) Table S2). Symptoms of depression and stress were statistically higher at 6 m compared to 7d, suggesting a temporary attenuation of therapeutic gains (Figure 1(a,e), Table S2).

When the categorical variable for the lifetime history of a depressive disorder was included in the model for the DASS-21 depression subscale, a main effect of diagnosis was detected ($\eta_p^2 = 0.07$). When the categorical variable for the lifetime history of an anxiety disorder was included in the model for the DASS-21 anxiety subscale, a main effect of diagnosis was detected ($\eta_p^2 = 0.08$). In these two models, the main effects of time were retained for depression ($\eta_p^2 = 0.24$) and anxiety ($\eta_p^2 = 0.25$). At baseline, those with clinical diagnoses exhibited statistically greater values than those without diagnoses on the DASS-21 depression and anxiety subscales, suggesting that the diagnostic cutoff segregated those with lower and higher baseline symptomatology. In those with a diagnosis of depression or anxiety, reductions in depressive or anxiety symptoms were evident at all follow-up time points relative to baseline, with the 12 m follow-up point showing a 60% and 64% reduction in depression and anxiety, respectively (Figure 1(b,d), Table S2). Notably, individuals with either depression or anxiety diagnosis showed significant improvement, with symptoms improving from a moderate to a normal range. They maintained reductions within a normal range throughout the follow-up period, closely approximating the symptom levels of the group without the diagnosis.

Negative and positive affect

Significant main effects of time were detected on the PANAS subscales Negative Affect ($\eta_p^2 = 0.27$) and Positive Affect ($\eta_p^2 = 0.09$; Table S2), which survived correction (p -FDR < 0.01). Relative to baseline, Negative Affect was significantly diminished by 33% at 7d, 32% at 1 m, 21% at 6 m, and 27% at 12 m compared to baseline (Figure 1g). Relative to baseline, Positive Affect was only statistically higher at 7d (Figure 1h, Table S2).

General mental and physical health

A significant main effect of time was detected on the SF-12 Mental Health Component Score (MCS) ($\eta_p^2 = 0.21$), but not Physical Health Component Score ($p = .37$). MCS survived correction (p -FDR < 0.001). Relative to

baseline, significant improvements in mental health were found at 1 m, 6 m, and 12 m. Additionally, mental health showed a significant drop in scores from 1 m to 6 m but remained significantly higher than baseline at 6 m (Figure 1f, Table S3).

Alcohol and cannabis use

Significant main effects of time were detected on the ASSIST alcohol risk ($\eta_p^2 = 0.16$) and cannabis risk scores ($\eta_p^2 = 0.20$), which survived correction (p -FDR < 0.01). Relative to baseline, reductions in alcohol and cannabis total risk scores were detected at 1 m, but not subsequent time points ($p > .38$) (Figure 2(a,b), Table S3). An effect of time was found on the AUDIT for frequency of alcohol consumption (p -FDR < 0.01), which was significantly reduced at 1 m and 6 m, but not at 12 m ($p > .05$) (Table S3). An effect of time was also detected on the AUDIT for average alcohol beverages but is not interpreted since there were no significant changes between specific time points ($p > .29$) and it did not survive correction (p -FDR = 0.08). No effect of time was observed on the AUDIT for frequency of binge drinking episodes.

Wellbeing

Personality

Main effects of time were identified for the BFI personality traits Agreeableness ($\eta_p^2 = 0.06$), Negative Emotionality ($\eta_p^2 = 0.17$), and Open-Mindedness ($\eta_p^2 = 0.06$). Negative Emotionality survived correction (p -FDR < 0.001), but Agreeableness (p -FDR = 0.066) and Open-Mindedness (p -FDR = 0.073) did not. Relative to baseline, trait Agreeableness was significantly higher at 12 m; trait Negative Emotionality was significantly lower at 1 m, 6 m, and 12 m; and Open-mindedness was significantly higher at 1 m (Figures 2(c-g), Table S3).

Generalized self-efficacy

A main effect of time was detected on the GSES ($\eta_p^2 = 0.12$) that survived correction (p -FDR < 0.01). Relative to baseline, significant increases in self-efficacy were found at 1 m and 12 m, but not 6 m (Figure 2k, Table S3).

Impulsivity

No significant main effects of time were found on the BIS Total Score ($p = .13$) or the BIS subscales Cognitive Impulsivity and Behavioral Impulsivity ($p > .05$).

Relationship satisfaction

Main effects of time were detected for relationship satisfaction with: friends ($\eta_p^2 = 0.08$) and partner's

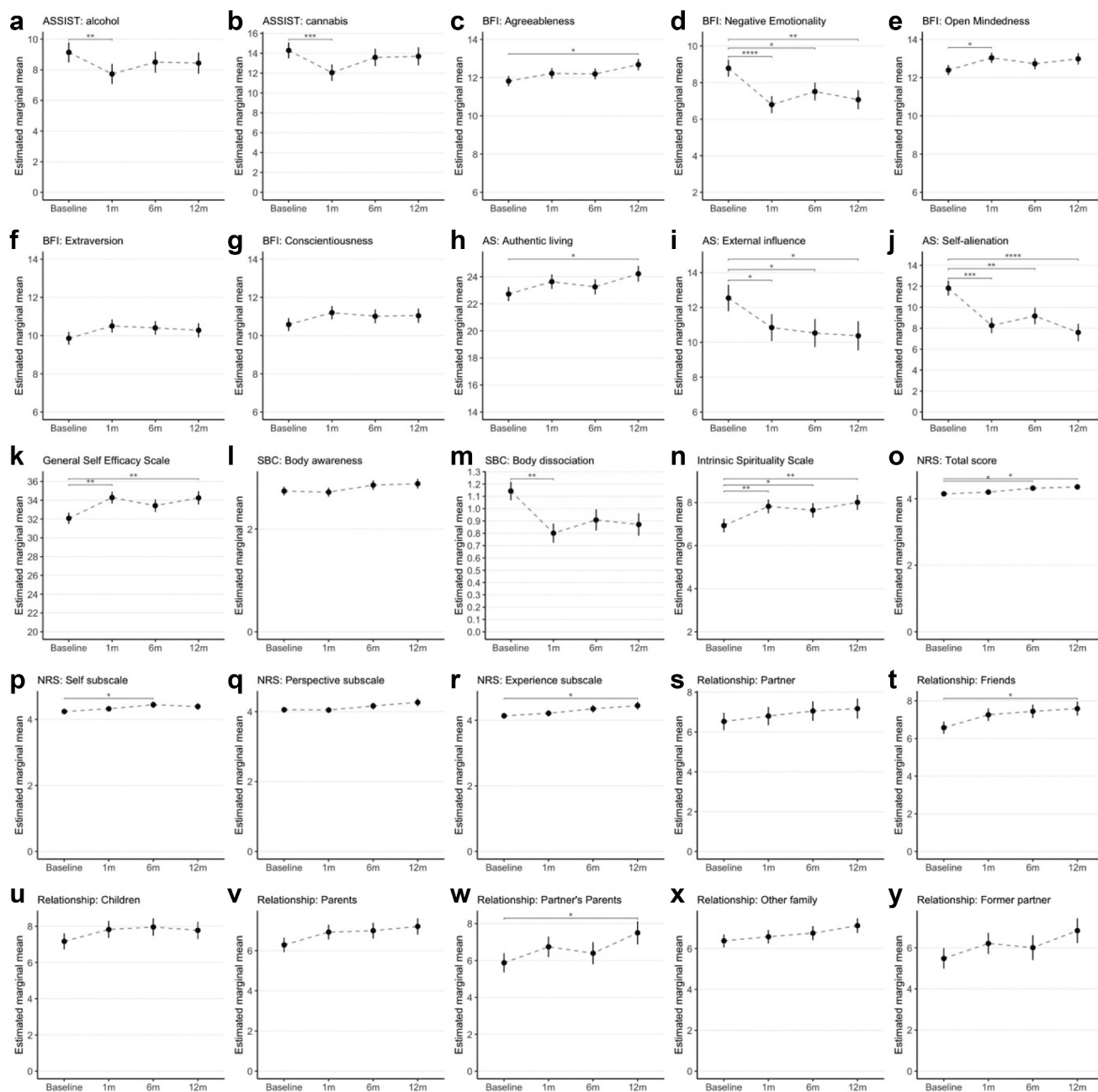


Figure 2. ASSIST for (a) Alcohol and (b) Cannabis; BFI for (c) Agreeableness, (d) Negative Emotionality, (e) Open-mindedness, (f) Extraversion, and (g) Conscientiousness; as for (h) Authentic Living, (i) External Influence, and (j) Self-alienation; (k) GSES total; SBC for (l) Body Awareness and (m) Body Dissociation; (n) Intrinsic Spirituality Scale total; NRS for (o) Total, (p) Self subscale, (q) Perspective subscale, and (r) Experience subscale; Relationship Satisfaction for (s) Partner, (t) Friends, (v) Parents, (w) Partner's Parents, (x) Other Family, and (y) Former Partner. Scores were measured at baseline (BL), and 1 month (1m), 6 months (6m) and 12 months (12m) post-ceremony. BFI = Big Five Inventory; as = Authenticity Scale; GSES = General Self-efficacy Scale; SBC = Scale of Body Connection; NRS = Nature Relatedness Scale. Estimated marginal means (EMM) with standard errors (SE) are shown with asterisks representing statistical significance levels of * $p < .05$, ** $p < .01$, *** $p < .001$, and **** $p < .0001$.

parents ($\eta_p^2 = 0.14$). Relationship satisfaction with friends survived correction (p-FDR = 0.042), but satisfaction with partner's parents did not (p-FDR = 0.066). Relative to baseline, improvements in relationship satisfaction with friends and partner's parents were found at 12 m (Figure 2(s-y), Table S3).

Authenticity

Main effects of time were identified on the AS subscales Authentic Living ($\eta_p^2 = 0.06$), External Influence ($\eta_p^2 = 0.09$), and Self-alienation ($\eta_p^2 = 0.17$). External Influence and Self-Alienation survived correction (p-FDR = 0.01 and p-FDR < 0.001, respectively), but Authentic Living

did not ($p\text{-FDR} = 0.063$). Relative to baseline, Authentic Living was increased at 12 m; External Influence was reduced at 1 m, 6 m, and 12 m; and Self-alienation was reduced at 1 m, 6 m, and 12 m, showing a 50% reduction at 12 m (Figure 2(h-j); Table S3).

Body connection

A significant main effect of time was identified on the SBC subscale Body Dissociation ($\eta_p^2 = 0.10$), but not Body Awareness ($p = .06$) (Figure 2(l-m)). Body Dissociation survived correction ($p\text{-FDR} = 0.011$). Relative to baseline, Body Dissociation was statistically lower at 1 m (Table S3).

Relationship with nature

Significant main effects of time were detected on the NRS subscales Self ($\eta_p^2 = 0.08$) and Experience ($\eta_p^2 = 0.11$) but not Perspective ($p = .09$; Figure 2(p-r)). Experience survived correction ($p\text{-FDR} = 0.032$), but Self did not ($p\text{-FDR} = 0.074$). Relative to baseline, Self was increased at 6 m and Experience was increased at 12 m (Table S3).

Spirituality

Significant main effects of time were detected on the ISS ($\eta_p^2 = 0.12$), which survived correction ($p\text{-FDR} = 0.003$). Relative to baseline, spirituality was significantly increased at 1 m, 6 m, and 12 m (Figure 2n, Table S3).

Lifestyle

No significant main effects of time were found on BMI ($p = .14$) or vegetable ($p = .07$) or fruit ($p = .32$) consumption (Table S3).

Effects of further ayahuasca use

Significant differences between those reporting/not reporting further ayahuasca consumption were identified in the models for negative emotionality ($\eta_p^2 = 0.09$), relationship satisfaction, with an intimate partner [$\eta_p^2 = 0.13$] and parents [$\eta_p^2 = 0.10$] and fruit ($\eta_p^2 = 0.09$) and vegetable consumption ($\eta_p^2 = 0.24$). However, the only significant difference from baseline was in those with no further ayahuasca consumption, who reported greater relationship satisfaction with parents at 12 m. Only between-group differences were observed for vegetable consumption and relationship satisfaction. Those who consumed more ayahuasca reported higher vegetable intake at all time points, including baseline, and reported higher parental relationship satisfaction at baseline and the 1-month follow-up ($p < .05$).

Effect sizes

Large effect sizes were observed for depression, anxiety, stress (DASS), and overall mental health (SF12-MCS). Of the well-being measures, constructs encompassing negative mood demonstrated large effect sizes, including subscales for negative affect (PANAS), negative emotionality trait (BFI), body dissociation (SBC), and self-alienation (AS). Additionally, large effect sizes were observed for alcohol and cannabis risk scores (ASSIST), self-efficacy (GSES), and relationships with partner's parents (RS). Medium effect sizes were observed for other measures of well-being, including positive affect (PANAS), agreeableness and openness (BFI), authentic living and external influence (AS), nature relatedness (NRS), spirituality, and relationships with friends (RS).

Discussion

Despite growing observational evidence for the therapeutic potential of naturalistic ayahuasca consumption, the breadth and durability of improvements remain unclear. This study identified large improvements in mental health and wellbeing that were sustained over a 12-month follow-up period in ayahuasca naive participants. Particularly novel to this study, we found that reductions in depression and anxiety associated with ayahuasca consumption were maintained longer in individuals with a lifetime diagnosis of a depressive or anxiety disorder relative to those without. Ayahuasca use was also associated with a short-term enhancement of positive affect and a sustained reduction in negative affect.

Trajectories of change across the psychological measures were varied, with some effects diminishing, some growing, and others remaining stable over the 1-year follow-up period. For example, Body Dissociation was only significantly altered from baseline at 1 month, while Nature Relatedness and Relationship Satisfaction were only significantly different from baseline at later assessments. Significant changes in Negative Emotionality, External Influence, Self-alienation, and Spirituality were maintained across the entire follow-up duration, raising the possibility that these are stable (trait) changes. The effect sizes for most of these well-being measures were moderate in magnitude, and generally not as robust as the large effect sizes observed on the mental health measures.

Our findings contribute to the literature suggesting that structured use of ayahuasca may have therapeutic effects on psychopathology. Clinical and naturalistic studies have reported antidepressant and anxiolytic effects in healthy and psychiatric samples, ranging

from 7 days to 6 months after consumption (Jiménez-Garrido et al. 2020; Palhano-Fontes et al. 2019; Ruffell et al. 2021). One small study identified reductions in depression symptoms up to 12 months in clinically depressed patients (van Oorsouw, Toennes, and Ramaekers 2022b). Another study at the Takiwasi Ayahuasca Center in Peru reported significant reductions in depression, anxiety, and alcohol use at 12 months (Rush et al. 2023) but was confounded by the multifactorial treatment program and long length of treatment (27.9 weeks). Cross-sectional research supports a negative relationship between the frequency of ayahuasca consumption and the level of alcohol and drug use, but longitudinal studies are scant (Perkins et al. 2023). Although decreases in alcohol and cannabis use were detected 1 month after the ceremony, none of the subsequent time points were significant from baseline. Participants exhibited low-risk alcohol use and moderate-risk cannabis use at baseline, which may have presented floor effects. Combined with the small sample size, the analysis may be underpowered but the effect sizes hint toward large effects.

Changes across wellbeing measures were in a direction associated with adaptive functioning and improved mental health. For instance, links have been established between mental health and lower Neuroticism and greater Agreeableness (Strickhouser and Zell 2017); wellbeing and Nature Relatedness (Grabowska-Chenczke, Wajchman-Świtalska, and Woźniak 2022); life satisfaction and Interpersonal Relationships (Froh et al. 2007); and lower prevalence of mental illness and Self-efficacy (Andersson et al. 2014). Similarly, the Authenticity Scale subscales correlate strongly with mental health challenges, with External Influence and Self-alienation being positively correlated, and Authentic Living being negatively correlated (Grijak 2017). Thus, the observed decreases in Negative Emotionality, External Influence, and Self-Alienation, and contemporaneous increases in Relationship Satisfaction, Nature Relatedness, and Self-efficacy might reflect a pattern of improved adaptive functioning and mental health. For example, reduced self-alienation and greater relationship satisfaction may support meaningful social connections that foster resiliency toward changing environmental, social, and economic conditions. Further, reduced external influence and greater self-efficacy and connection to nature may improve one's ability to handle stress, recover from adversity, and maintain overall mental health.

Multiple studies have reported alterations in personality structure after naturalistic ayahuasca use characterized by increases in Agreeableness, Open-mindedness,

Conscientiousness, and Extraversion, and decreases in Neuroticism (analogous to Negative Emotionality) (Kiraga et al. 2021; Netzband et al. 2020; Perkins et al. 2022; Weiss et al. 2021). Our findings are partially consistent with these reports, although we did not observe significant changes in Conscientiousness or Extraversion, and increases in Open-mindedness and Agreeableness did not survive correction. Here, we found that personality traits undergo dynamic shifts across time, with numerical increases in Open-mindedness only at the 1 month assessment, increases in Agreeableness only at the 12 month assessment, and significant decreases in Negative Emotionality across the entire follow-up duration. Personality traits qualitatively displayed distinct linear, quadratic, and cubic relationships with time (see Figure 2).

Ayahuasca has also been associated with changes in other psychological constructs and health-related behaviors. Studies point toward enhanced spirituality, nature relatedness, self-efficacy, body connection, and interpersonal relationships (Bathje et al. 2021; Harris and Gurel 2012; Kaasik and Kreegipuu 2020; Perkins; Ruffell et al. 2023, 2024), and positive lifestyle and health-related behaviors, including diet (Perkins et al. 2023). The present study extends this work by demonstrating persistent increases in self-efficacy, nature relatedness, and relationship satisfaction with friends that lasted up to 12 months. Nonsignificant changes in body awareness and impulsiveness suggest some constructs may not be affected by ayahuasca treatment. Further, the absence of changes in some health-related behaviors (i.e., body mass index, vegetable and fruit consumption, and physical activity) is in contrast to several cross-sectional studies (Kohek et al. 2023; Perkins et al. 2023).

Limitations

This study has notable limitations. First, a comparison group was not utilized, and therefore, the potential influence of demand characteristics and elapsed time on treatment effectiveness cannot be ruled out. Non-pharmacological factors (e.g., ceremony, community, etc.), likely contribute to the effects observed in this study (Perkins et al. 2021; Uthaug et al. 2021). Selection and attrition biases are inherent to research and restrict the generalizability of results. Partially mitigating this concern, 81.8% and 63.6% of the original sample were retained for primary mental health measures at months 1 and 12, respectively. Further, linear mixed models were fitted for missing outcome data and have been shown to provide correct inferences (Schafer and Graham 2002). Another limitation is the use of self-

report measures and the lack of expectancy data and the total frequency of ayahuasca use, which preclude conclusive evidence. However, broad coverage and converging results across mental health measures support the validity of these findings.

Future research

Randomized clinical trials using objective measures are needed to elucidate psychological mediators and moderators of therapeutic action, and to disentangle the temporal dynamics and causal mechanisms of ayahuasca-induced trait changes.

Conclusion

This study identified long-term improvements in mental health and wellbeing outcomes following naturalistic ayahuasca consumption among first-time users with relatively poor mental health at baseline.

Acknowledgments

We thank the facilitators and participants of this study for their time and effort in taking part in the research.

Disclosure statement

DP, JS and AH hold equity in a commercial entity, Psycae Therapeutics, which is undertaking research with psychedelic compounds and DP and JS are co-CEOs of the same organisation. MPB serves on the Advisory Board of Ajna Labs LLC, Journey Colab, and Bright Minds Biosciences, Inc. MPB is named as inventor on patent applications relating to the use of psilocybin for alcohol use disorder but has waived all rights and has no prospect of financial benefit.

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Data availability statement

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

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