Sub-acute and long-term effects of ayahuasca on mental health and well-being in healthy ceremony attendants: A replication study

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ABSTRACT

Background and aims: There is a growing body of evidence suggesting that the psychedelic plant tea, ayahuasca, holds therapeutic potential. Uthaug et al. (2018) demonstrated that a single dose of ayahuasca improved mental health sub-acutely and 4-weeks post-ceremony in healthy participants. The present study aimed to replicate and extend these findings. A first objective was to assess the sub-acute and long-term effects of ayahuasca on mental health and well-being in first-time and experienced users. A second aim was to extend the assessment of altered states of consciousness and how they relate to changes in mental health. **Method:** Ayahuasca ceremony attendants ($N = 73$) were assessed before, the day after, and four weeks following the ceremony. **Results:** We replicated the reduction in self-reported stress 4-weeks post ceremony, but, in contrast, found no reduction in depression. Also, increased satisfaction with life and awareness the day after the ceremony, and its return to baseline 4 weeks later, were replicated. New findings were: reduced ratings of anxiety and somatization, and increased levels of non-judging 4-weeks post-ceremony. We replicated the relation between altered states of consciousness (e.g., experienced ego dissolution during the ceremony) and mental health outcomes sub-acutely. The effects of ayahuasca did not differ between experienced and first-time users. **Conclusion:** Partly in line with previous findings, ayahuasca produces long-term improvements in affect in non-clinical users. Furthermore, sub-acute mental health ratings are related to the intensity of the psychedelic experience. Although findings replicate and highlight the therapeutic potential of ayahuasca, this needs to be confirmed in placebo-controlled studies.

KEYWORDS

Ayahuasca, field study, depression, Anxiety, stress, mindfulness, somatization, ego dissolution

INTRODUCTION

Ayahuasca is a psychotropic plant brew that originates from the Amazon and that has been used for healing purposes by indigenous tribes for thousands of years (Freckska, Bokor, & Winkelman, 2016). In the past decade, ayahuasca has become more attractive in Western countries to people as part of their search for purpose, spiritual development but also healing from (mental) health problems (Winkelman, 2005).

Ayahuasca generally consists of two plants, with the most frequently used combination being the N,N-dimethyltryptamine (DMT) containing Psychotria Viridis, and the

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monoamine oxidase (MAO) inhibitor containing Banisteriopsis Caapi (B-caapi) (Riba et al., 2001). DMT is a short-acting psychedelic tryptamine that is also naturally present in other plants, mammals and human beings (Barker, 2018). The MAO inhibitors enable DMT, which is usually rapidly broken down in the gut, to pass the blood brain barrier and interact with serotonergic (5-HT) receptors in the central nervous system (Cameron & Olson, 2018). Acute effects of ayahuasca include perceptual, cognitive, emotional and affective changes that last between 4 and 6 h after administration (Riba et al., 2001). Although ayahuasca drinkers often report nausea, vomiting or diarrhea, its use is generally safe, non-addictive nor harmful to cognitive or psychological functions (Barbosa et al., 2016; Bouso et al., 2012; Dos Santos, Balthazar, Bouso, & Hallak, 2016; Dos Santos, Osório, Hallak, 2016; Dos Santos et al., 2016; Netzband, Ruffell, Linton, Tsang, & Wolff, 2020).

Pharmacological changes can explain the (sub) acute effects of psychedelic substances like ayahuasca, however long-term changes may be related to psychological insights gained during or after the psychedelic experience (Davis et al., 2021; Yaden & Griffiths, 2020). Ayahuasca, as well as other psychedelic substances such as 5-MeO-DMT and psilocybin, induce experiences beyond the normal states of consciousness, such as ego-dissolution and spiritual or challenging experiences (further referred to as ‘altered states of consciousness’) which have been associated with relief of depression and anxiety symptoms (Dos Santos, Balthazar, et al., 2016; Dos Santos, Balthazar, Bouso, & Hallak, 2016; Frecka et al., 2016; Griffiths et al., 2011; Roseman, Nutt, & Carhart-Harris, 2018; Uthaug et al., 2019). Psychological insights, a more positive life stance, and changed worldview are commonly reported outcomes after ingestion of ayahuasca (Bouso et al., 2012; González et al., 2020; Halpern, Sherwood, Passie, Blackwell, & Ruttenber, 2008). Likewise, Grob et al. (1996) studied UDV members who reported to become more optimistic, confident and reflective after consuming ayahuasca compared to a matched control group that never drank ayahuasca. Moreover, addiction, depression, and anxiety was found to be reduced in ayahuasca drinkers, who also reported improvement in mental and physical health, interpersonal relationships and work (Grob et al., 1996; McKenna et al., 1998). Furthermore, adolescents who regularly consumed ayahuasca reported less signs of anxiety, were more optimistic, self-confident, insistent, and emotionally mature than their peers (Da Silveira et al., 2005). All of these findings reflect both (sub)acute as well as long-term changes on a psychological, social and spiritual level.

Uthaug et al. (2018) are one of the few to investigate persisting ayahuasca effects in a larger sample ($N = 57$) of healthy participants in ayahuasca ceremonies for at least 4 weeks after drinking. They found significant reductions in stress and depression symptoms in participants of ayahuasca retreats that lasted at least 4 weeks, as compared to baseline. They also found short-term increases in mindful observing, awareness, and non-judgment, which is partly in line with findings by Soler et al. (2016), as well as an imaging study

that found that post-acute changes in functional connectivity predicted sustained changes in non-judgment 2 months after the experience (Murphy-Beiner & Soar, 2020). Other studies measured significant anti-depressant and anxiolytic effects 7 days (Palhano-Fontes et al., 2019), up to 21 days (de Lima Osório et al., 2011, 2015; Sanches et al., 2016) after intake of a single dose of ayahuasca within relatively small groups of depressed patients (respectively 29, 6, 17 patients). Recently, Jiménez-Garrido et al. (2020) found reductions in anxiety, depression and substance use disorder in a sample of first time ayahuasca users that met the clinical diagnostic criteria for these disorders before ayahuasca intake that lasted up to 6 months after intake. This suggests that ayahuasca has fast acting antidepressant properties lasting up to three weeks in clinical and up to 6 months in non-clinical participants.

As Roseman et al. (2018) and Uthaug et al. (2018) propose, the therapeutic effect of psychedelics like ayahuasca may depend on the psychedelic experience itself, such as increased sense of unity, insight or ego-dissolution participants experienced under the influence. For example, higher levels of ego dissolution as measured with the Ego Dissolution Inventory (EDI; Nour, Evans, Nutt, & Carhart-Harris, 2016) were negatively related to levels of depression and stress the day after drinking ayahuasca (Uthaug et al., 2018). Similarly, higher levels of oceanic boundlessness and lower levels of anxious ego dissolution predicted a reduction in depression 5 weeks after taking psilocybin in patients with treatment-resistant depression (Roseman et al., 2018). Oceanic boundlessness (OB) refers to a state common to classic mystical experiences including feelings of unity and transcendence of time and space, whereas anxious ego dissolution (AED) refers to negative, aversive and anxious experiences. Both dimensions have been found predictive for long-term positive mental health outcomes (Roseman et al., 2018).

The present study aimed to replicate and extend findings by Uthaug et al. (2018). A first objective was to investigate whether a single dose of ayahuasca could elicit sub-acute (i.e. 24 h-2 days)- and/or long-term (4 weeks post intake) improvements in mental health related measures (i.e., depression, anxiety and stress), mindfulness and satisfaction with life in healthy ayahuasca drinkers in a naturalistic setting. Secondly, we aimed to extend findings on the previously found relationship between levels of ego dissolution (as measured with EDI) experienced during the ceremony and changes in mental health by adding a more exhaustive measure of altered states of consciousness, namely the 5D-ASC (Dittrich, Lamparter, & Maurer, 2010; Studerus, Gamma, & Vollenweider, 2010). Finally, we aimed to explore whether a previous experience with ayahuasca might be of influence on the outcome measures. We predicted that participant’s self-reported mental health, mindfulness and life satisfaction would improve after drinking ayahuasca as compared to baseline. Furthermore, we expected that ayahuasca-induced changes would still be present four weeks after the ceremony as compared to baseline. Finally, we expected that in line with previous findings, positive changes

in the dependent variables would be related to higher subjective ratings of EDI (Uthaug et al., 2018) and OB, and lower ratings of AED (Roseman et al., 2018). Regarding previous ayahuasca experience, we had no specific hypothesis. First-time users might be more anxious and have higher expectations, which may bias subsequent improvements in mental health outcomes. Alternatively, mental health improvements could be larger in naïve users because their experience might be more intense as compared to more experienced users.

METHODS

Data in the present observational study were collected at ayahuasca-ceremonies at different locations in the Netherlands ($N = 49$) and Czech Republic ($N = 24$). Either by e-mail or on site, ceremony participants were asked to participate in the study. Participation was voluntary and no incentives were provided. Participants were screened by the facilitators for their physical and mental capability to drink ayahuasca and received preparatory instructions (e.g. to abstain from medication, processed food and alcohol at least 4 days prior to participation). Initially 93 participants consented to the study and started completion of the baseline measure. Twenty participants (14 Dutch, 6 Czech) completed the baseline measure but not the post-and follow-up measures and were therefore not included in further analyses, resulting in a total sample size of 73 participants. This study was approved by the standing Ethical Review Committee. The research team was not involved in the screening, preparation, organization, administration, and supervision of the ayahuasca ceremonies that were visited. Except for using paper/pencil or computer, there were no differences between online or on-site data collection, so the data will be treated identically.

Participants

Seventy-three participants (37 males, 36 females, Mean age 40.54 ($SD = 10.43$)) completed the questionnaires of at least pre-and post-measure. The majority (95%) came from Europe while the rest of the participants were from Asia (2.5%) and North America (2.5%). Their motivation for ayahuasca use included ‘understanding myself’ (34.2%), ‘solving issues’ (30.1%), ‘curiosity’ (4.1%), or a combination of these reasons (8.2%) and ‘other’ (23.4%). Participants’ highest level of education was high school (28%), higher education (25%) or scientific education (47%). None of the participants were currently on any medication that could have affected their ayahuasca intake. In total, 48 participants reported they had no previous experience with ayahuasca (66%) and were classified as first time users. Eleven participants used ayahuasca for the second time (15%) and 14 had used it more often (19%). Forty participants (61.5%) reported having had experience with other entheogenic drugs in the past.

Study procedure

Participants were assessed 3 times: at baseline, between 24 h and 2 days after (hereafter referred to as: sub-acute), and 4 weeks after the ayahuasca ceremony (hereafter referred to as: long-term). After being informed about the study and giving their consent, participants completed a 30-min survey in the week before they took part in an ayahuasca ceremony either online via a Qualtrics Survey link ($n = 11$), or on site ($n = 62$) (baseline measure). The survey was repeated once again the morning after the ceremony ($n = 65$) or if they were unable within 2 days after the ceremony online ($n=8$) (sub-acute measure). The second survey additionally asked about the ayahuasca experience using open-ended questions, including a questionnaire about ego-dissolution and altered states of consciousness. The follow-up ayahuasca assessment at 4 weeks after the ceremony (long-term measure) was administered through an online survey and was identical to the first assessment.

Ceremonial setting

The ayahuasca brew was taken in a non-religious setting, and participants were not affiliated to any ayahuasca religion. All ayahuasca ceremonies were conducted in the evenings, starting between 8 and 10 pm and lasting between 6 and 8 h. The ritual was led by a trained shaman who served two rounds of ayahuasca (approximately 50 ml) to the participants, and performed rituals during the ceremony such as burning herbs and tobacco (mapacho), playing musical instruments (e.g., guitar, flute), and singing healing songs (icaros). In a particular ceremony, between 8 and 12 participants were lying down on mattresses and were provided with a pillow, blanket, bucket, bottle of water and tissue box. Additionally, 2–4 caretakers were present to help participants if needed during the ceremony (e.g., bathroom visit). After the ceremony ended participants were offered fresh fruit or soup. Participation to our study was voluntary and of each ceremony approximately 8–10 ceremony attendants agreed to take part in our study.

Measures

Several alterations were made to the original test battery administered by Uthaug et al. (2018). We added a measure to assess symptoms of anxiety, depression and somatization (Brief Symptom Inventory 18; BSI-18) and as an addition to the previously used EDI we included the 5D-ASC to make further assessments of the experience of altered states of consciousness (ASC). To keep the test battery brief, we decided to exclude the time-consuming measure of cognitive thinking style (or convergent and divergent creativity, as measured with the Picture Concept Test) and used a shortened version of the Five Facets Mindfulness Questionnaire 15 (FFMQ-15).

In sum, the resulting test battery now included six questionnaires. (Mental) health was measured using the Depression, Anxiety, and Stress Scale-21 (DASS-21; Henry & Crawford, 2005) and the BSI-18 (Derogatis, 2001).

Mindfulness and satisfaction with life were assessed using the FFMQ-15 (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) and the Satisfaction with Life Scale (SWLS; Diener, Emmons, Larsen, & Griffin, 1985). Finally, altered states of consciousness was assessed using the EDI (Nour et al., 2016) and the 5D-ASC (Dittrich et al., 2010; Studerus et al., 2010). Based on previous findings (Roseman et al., 2018; Uthaug et al., 2019) we focused on 5D-ASC dimensions Oceanic Boundlessness (OB) and Anxious Ego Dissolution (AED), which might serve as interesting predictors of mental health outcomes. For detailed test descriptions, see supplementary materials.

Statistical analyses

Data was analyzed with the Statistical Package for the Social Sciences (SPSS version 25).

The original study included mostly European and Latin American participants, in which between group differences were more likely to be found than in the current study with two European samples. In the present study, no significant differences were found between the two (European) samples in any of the (baseline) or follow-up measures, or in the mixed model analyses (Country or Session x Country) when country was included as a factor (all F 's < 1.71, all P 's > 0.05). Therefore, country will not be included as a separate factor and the sample will be described as a whole.

Linear mixed model analyses included Session (3 levels: baseline, sub-acute and 4 weeks follow-up) as within subject factor, Experience (2 levels: experienced vs first-time users) as a between group factor, and the Session x Experience interaction. The covariance structure for the repeated measures was chosen according to best fit and could vary across outcome variables (compound symmetry heterogeneous (CSH) first lag autoregressive (AR1) structures). Significant main effects of Session were followed by pairwise comparisons between baseline and follow-up sessions with Bonferroni adjustments for multiple comparisons. Pearson's correlations were carried out to investigate how the level of ego dissolution (EDI) during the ayahuasca ceremony were related to the dependent measures at the 2 follow-up sessions. Using independent samples t -test, first-time and experienced users' levels of Altered States of Consciousness (5D-ASC) and Ego Dissolution (EDI) were compared.

RESULTS

In total, 73 participants completed the baseline measure, of which 71 completed the post-measure and 39 participants completed the 4-weeks follow-up. Forty-eight participants were new to drinking ayahuasca (66%). Of the twenty-five experienced users, 11 (44%) drank 2 times before, 14 (56%) drank 3 times or more.

Fifty-eight percent of participants who dropped out were first time users. There were no differences between participants who dropped out and those who did not in any of the

baseline- or post-ceremony mental health ratings, or psychedelic experiences measures.

Mental health

The reported mixed model analyses below include Session (baseline, sub-acute and long-term), Experience (yes, no), and the Session x Experience interactions, of which Session and interaction effects were of primary interest.

DASS-21. For depression ratings revealed no Session x Experience interaction, or effects of Session (all F 's < 2.07, P 's > 0.135) was found. For ratings of anxiety, a main effect was found for Session ($F_{2, 90.09} = 7.66$; $P = 0.001$). Anxiety ratings increased slightly but not significantly one day after drinking ayahuasca and decreased significantly 4-weeks post-ceremony both as compared to baseline ($t(93.65) = 3.13$, $P = 0.007$, $d_z = 0.38$) and the day after drinking ayahuasca ($t(56.79) = 3.49$, $P = 0.003$, $d_z = 0.44$). No interaction between Session and Experience was found for self-reported anxiety ($F < 1.0$, $P > 0.50$). For stress, a significant Session effect ($F_{2, 62.68} = 4.35$; $P = 0.017$) was found. Participant stress levels reduced significantly between baseline and the 4 week follow-up session ($t(58.55) = 2.95$, $P = 0.014$, $d_z = 0.38$). No Session x Experience interaction ($F < 1.21$, $P = 0.303$) existed. See Fig. 1.

BSI-18. As BSI-18 was not part of the original study we are replicating, alpha was set at 0.01. For ratings of depression and anxiety no significant Session or Session x Experience effects was found (F 's < 2.36, P 's > 0.077). For somatization ratings, a significant Session effect emerged ($F_{2, 117.43} = 7.61$; $P < 0.001$). Follow-up comparisons showed a slight but insignificant increase in somatization sub-acute ($P = 0.047$), but a significant decrease from sub-acute to the 4 week follow-up ($t(122.55) = 3.58$, $P = 0.002$, $d_z = 0.54$). No Session x Experience interaction was found [$F < 1.0$, $P = 0.903$]. See Fig. 2.

SWLS

Mixed model analyses revealed a significant Session effect for self-reported satisfaction with life ($F_{2, 53.18} = 21.04$; $P < 0.001$). Satisfaction with life significantly increased the day after the ayahuasca ceremony ($t(69.59) = -4.77$, $P < 0.001$, $d_z = -0.58$), and returned to baseline level 4 weeks later. There was no Experience x Session interaction. See Fig. 2.

FFMQ-15

For mindful *awareness*, a main effect of Session was found ($F_{2, 52.17} = 4.31$; $P = 0.018$). Self-reported mindful awareness increased from baseline to the day after the ceremony ($t(65.69) = -2.90$, $P = 0.017$, $d_z = -0.35$). In addition, the significant Session effect for mindful *non-judging* ($F_{2, 49.36} = 4.38$; $P = 0.018$) showed an increase at the 4-week follow-up measure as compared to baseline ($t(36.58) = -2.73$, $P = 0.028$, $d_z = -0.41$) and the day after the ceremony ($t(38.85) = -2.73$, $P = 0.025$, $d_z = -0.42$) levels. No main or

Fig. 1. Mean (SE) subjective ratings of DASS stress, depression and anxiety as a function of time after ayahuasca. * $P < 0.05$, ** $P < 0.01$: significant difference between baseline/1-day and the 4-week follow-up

interaction effects were found for mindful *observing*, *describing*, or *non-reacting*. See Fig. 2.

The psychedelic experience: experienced vs first-time users

EDI: Overall, Mean (SD) ego dissolution rating was 52.66 (25.72). Overall, total EDI ratings varied between 0 (no dissolution) and 100 (maximal dissolution). Both on the day following and at the 4-week follow-up, no significant correlations between EDI scores and any of the outcome measures were found. There were no differences in EDI scores between experienced ($M = 52.69$, $SD = 28.13$) and first-time ($M = 52.64$, $SD = 24.73$) users ($t(66) = -0.008$, $P = 0.994$).

ASC: Mean ratings on 5D-ASC dimensions overall varied between 26.84 and 51.76, with mean scores on OB and AED being 51.76 ($SD = 24.41$) and 26.84 ($SD = 20.19$), respectively. For 5D-ASC subscales means varied between 24.57 and 57.78, indicating that all participants experienced moderate levels of altered states of consciousness. First-time users did not differ from experienced users on any of the subscales (all t 's < 1.94 , P 's > 0.057). See Fig. 3.

As expected, a significant positive correlation was found between OB and EDI ($r = 0.602$, $P < 0.001$), and between OB and the positive subscales of 5D-ASC such as feelings of Unity, Bliss, Spirituality and insight (all r 's between 0.447 and 0.566, P 's < 0.001). Anxious Ego Dissolution (AED) did not correlate with EDI but did with Disembodiment, Impaired Control and Anxiety (r 's between 0.475 and 0.927, P 's < 0.001).

Relationship between the psychedelic experience and mental health changes

In replicating Uthaug et al. (2018) we computed Pearson correlations between the level of Ego Dissolution (EDI) and the mental health variables (DASS-21, BSI-18), Mindfulness (FFMQ-15) and Satisfaction with Life post-ceremony and after 4 weeks. EDI ratings negatively correlated with post-ceremony BSI depression rating ($r = -0.274$, $P = 0.029$, see Fig. 4). In contrast to Uthaug et al. (2018), none of the other correlation reached significance at either sub-acute or long-term.

Sub-acute, a significant negative correlation was found between OB and BSI depression ($r = -0.330$, $P = 0.008$) and a significant positive correlation between AED and DASS anxiety ($r = 0.466$, $P < 0.001$), BSI anxiety ($r = 0.398$, $P = 0.001$), and BSI somatization ($r = 0.392$, $P = 0.002$). After 4 weeks none of the correlations survived Bonferroni correction. These findings suggest that higher levels of OB were related to lower sub-acute depression levels, and higher levels of AED resulted in higher sub-acute levels of anxiety and somatization. See Fig. 4.

Sub-acute and long-term scores on satisfaction with life did not correlate with EDI, OB or AED.

DISCUSSION

The primary aim of the present study was to replicate earlier findings (Uthaug et al., 2018) on the sub-acute and long-term effects of ayahuasca ingested in a naturalistic setting on self-reported measures of mental health, satisfaction with life, and mindfulness. Additional objectives were to investigate if specific alterations in consciousness were related to these effects, and whether using ayahuasca for the first time affected mental outcome measures and the psychedelic experience. Seventy-three attendants of ayahuasca ceremonies in The Netherlands and The Czech Republic participated in the pre- and post-measure of which 39 also completed the online 4-week follow-up questionnaires.

Findings can be summarized as follows (see Table 1): First of all, in contrast to the study we are replicating, self-

Fig. 2. Mean (SE) subjective ratings of BSI-18 somatization, Satisfaction with Life (SWL), and FFMQ scales: Awareness, and Non-Judging. * $P < 0.05$, ** $P < 0.01$: significant difference between baseline and 1-day follow-up (somatization, satisfaction with life and awareness) and between baseline/1-day and 4-week follow-up (somatization, non-judging)

Fig. 3. Mean ratings of the experience of altered states of consciousness as assessed with 5D-ASC (from 0 to 100%) dimensions (top) and subscales (bottom) for first-time ($n = 48$) and experienced users ($n = 25$)

reported depression levels (DASS-21) did not decrease either post-ceremony or at the 4-week follow-up, but anxiety levels (DASS-21) significantly dropped 4 weeks post-ceremony. In

line with Uthaug et al. (2018), ayahuasca reduced long-term stress levels (DASS-21). Second, on BSI-18, a measure that was not included by Uthaug et al. (2018), we found a decrease in somatic complaints 4-weeks post ceremony. Third, in accordance with Uthaug et al. (2018), satisfaction with life and mindful awareness increased on the day after the ceremony but returned to baseline at the 4-week follow-up. In contrast to the study we are replicating, mindful non-judging did not increase immediately after the ceremony, but did after 4-weeks. Fourth, and partly in line with earlier findings, improvements in depression ratings (BSI-18, not DASS-21) was related to higher reports of experienced ego dissolution (EDI). In contrast to Uthaug et al. (2018), this was not the case for stress ratings. Finally, higher levels of Oceanic Boundlessness (OB) were related to lower post-ceremony depression ratings (BSI-18), whereas higher levels of Anxious Ego Dissolution (AED) were related to higher levels of post-ceremony anxiety and somatization reports (DASS-21 and BSI-18).

Interestingly, in the present study a single ayahuasca dose reduced subjective reports of anxiety and stress levels 4-weeks post-ceremony. This decrement in anxiety is in line with the previously reported anxiolytic effect of ayahuasca (e.g., Bouso et al., 2012; Da Silveira et al., 2005; de Lima Osório et al., 2015). However, in the present study, neither anxiety nor depression reports decreased directly after the ceremony, offering no evidence for any sub-acute pharmacological changes. The correlations between ASC scales and self-reported symptoms on our outcome measures showed that Anxious Ego Dissolution (AED) correlated positively with post-ceremony reports of anxiety and somatization. AED refers to aversive aspects of the psychedelic experience such as loss of control and anxiety. Stronger AED experiences may have contributed to higher post-ceremony reports of somatization such as chest pains or difficulty breathing as a consequence of the anxiety response, of which have been

Fig. 4. Post-ceremony correlations between levels of Ego Dissolution (EDI), Oceanic Boundlessness (OB), and Anxious Ego Dissolution (AED) and ratings of depression, anxiety and somatization

Table 1. Displays significant main findings from original study (Uthaug et al., 2018) and present study.

* replicated, ** partially replicated

Ayahuasca effect on:	Uthaug et al. (2018)	Present study
DASS depression	Sub-acute and long-term reduction	No effect
DASS anxiety	No effect	Long-term reduction
DASS stress	Sub-acute and long-term reduction	Long-term reduction **
Satisfaction with life	Sub-acute increase	Sub-acute increase *
FFMQ observing	Sub-acute increase	No effect
FFMQ awareness	Sub-acute increase	Sub-acute increase *
FFMQ describing	No effect	No effect *
FFMQ non-judging	Sub-acute increase	Long-term increase
FFMQ non-reacting	No effect	No effect *
EDI ego dissolution	Negative correlation with DASS depression and DASS stress	Negative correlation with BSI depression **
Experience with ayahuasca	No effect	No effect *

found to predict long-term response (Roseman et al., 2018). Interestingly, a recent study by Mason et al. (2020) demonstrated that under psilocybin, higher levels of glutamate were found in the medial prefrontal cortex (mPFC), which positively correlated with ratings of AED. It has been hypothesized that glutamate increases in the mPFC after psychedelics are due to 5HT_{2A} receptor agonism, a

mechanism also of ayahuasca. Thus it could be of interest for future studies to assess whether ayahuasca induces similar changes in local glutamate concentrations, and whether these correlate with AED and subsequently predict long-term outcomes. Additionally, it should be assessed whether other potential moderators (such as trait anxiety) contribute as well. In any case, it seems that the presence of AED may

have contributed to the lack of sub-acute improvements in mental health, and increased anxiety and distress related somatization symptoms instead.

After 4 weeks, anxiety and somatic complaints dropped significantly and were no longer related to the intensity of the psychedelic experience. Perhaps, integration of the overall psychedelic experience may explain the reductions in self-reported anxiety and stress at the 4-week follow-up. This explanation fits with reported changes in mindfulness related capacities. Four weeks after the ceremony, participants rated themselves to be less judgmental of their thoughts. This is in line with findings reported in earlier studies (Murphy-Beiner & Soar, 2020; Sampedro et al., 2017; Soler et al., 2016, 2018) in which ayahuasca enhanced decentering and acceptance.

We cannot readily explain why the previously found reduction in depression did not materialize in the present study. In both studies, baseline scores were rather low leaving little room for improvement. In line with Uthaug et al., the present study did find a negative correlational pattern between self-reported depression and ego dissolution (EDI). Oceanic Boundlessness ratings (OB), also negatively correlated with post-ceremony depression ratings. EDI and OB measure a similar construct, and were highly correlated with one another. They both refer to dissolving of the self in a positive way. Finding a negative relation between these experiences and self-reported depression in both studies suggests that the ayahuasca experience itself may contribute to acute improvements in mental health. Mason et al. (2020) suggested that acute reductions in hippocampal glutamate may play an important role in the experience of positive ego dissolution, via inducing a temporary loss of access to semantic autobiographical information, resulting in a subsequent breakdown of one's personal identity. Although the present findings offer only indirect self-report evidence for the negative relation between ego dissolution and depression reports immediately post-ceremony, future studies may want to explore this relation more directly. Whether ayahuasca actually improves symptoms of depression should be more thoroughly investigated in clinical patients with established levels of depressive symptoms and in placebo controlled trials (see Palhano-Fontes et al., 2019).

Nevertheless, the current patterns of findings suggest that the intensity of the psychedelic experience may be related to ayahuasca's therapeutic potential and warrants further investigation (see also Griffiths, Richards, McCann, & Jesse, 2006; Roseman et al., 2018). It is logical to put forward that when participants have an anxious experience, it may take more time to integrate, resulting in lower short-term improvements. Some example responses given by users immediately post-ceremony were: *"I felt confused and disappointed"*, *"things are not clear to me yet"*, *"I learned that I need to work on myself and that was confronting"*, *"I should think more outside the box"*. On the other hand, high scores on ego dissolution and oceanic boundlessness (e.g., insight, spiritual meaning and feeling part of something bigger) as being part of a positive experience could aid integration and explain the found long-term reductions in reports of anxiety,

stress and somatization. Several studies have shown the importance of 'surrendering' (Russ, Carhart-Harris, Maruyama, & Elliott, 2019), 'positive mind set' (Haijen et al., 2018), and 'benefit enhancing strategies such as intention and meditation' (Lancelotta & Davis, 2020) to be predictive of a mystical type experience, and reduce the likelihood of having a challenging experience under psychedelic use. In their ACE (Accept, Connect, Embody) model, Watts and Luoma (2020) also stress the significance of preparation in psychedelic-assisted psychotherapy to help people approach the psychedelic experience with as little resistance as possible. Related to this, Pontual, Tófoli, Collares, Ramakers, and Corradi-Webster (2021) have developed a questionnaire to investigate how setting affects the ayahuasca experience and may shed more light on what aspects of the setting can help people to be more comfortable and have a more intense mystical experience (e.g., sense of safety and leadership). Future studies may want to include measures of motivation/expectations or a broader inventory of set characteristics to get a better idea of how expectations may affect the experience (see also Barbosa et al., 2016; Olson et al., 2020).

There are some limitations to the current study. First of all, the loss of statistical power caused by the drop-out of almost half of the sample may have affected the probability of detecting long-term changes which is also reflected in the small to medium effect sizes. Therefore, our interpretations regarding long-term findings, should be treated with caution. Neither did we include a control group. Ideally future studies should include a control condition, also to control for potential bias of expectation, and to be better able to isolate the pharmacological effect of the substance. Uthaug et al. (2021) have demonstrated that expectancies may contribute to the reported mental health improvements in naturalistic studies. In their study, almost 30 percent of the placebo participants believed they drank ayahuasca. Both the ayahuasca ($N = 14$) and placebo group ($N = 16$) showed post-ceremony reductions in depression, anxiety and stress. In that study, all participants were experienced ayahuasca drinkers. Although in the present study the majority was new to drinking ayahuasca, placebo effect should be considered as an explanation for the found long-term reductions in stress and anxiety. A final limitation is that the ayahuasca brew ingested by participants in the present study was not chemically analyzed. We know from previous studies that there is a great variation in compounds between different ayahuasca brews ingested in naturalistic settings such as ceremonial retreats (Uthaug et al., 2018) or religious gatherings (Kaasik, Souza, Zandonadi, Tófoli, & Susulini, 2020). Lacking chemical analysis in the present study makes it difficult to interpret whether differences between the current study and the one we are replicating are related to chemical differences between the ayahuasca brews in the two studies.

To sum up, in line with previous findings (e.g., Bouso et al., 2012; Jeminez-Garrido et al., 2020; Uthaug et al., 2018) the present study suggests that a single dose of ayahuasca can relieve anxiety and stress symptoms in non-pathological

participants lasting at least 4 weeks. Furthermore, reported somatic complaints reduced and some mindfulness related capacities improved. The intensity of the psychedelic experience seems to be correlated to these improvements subacutely. These findings on reductions in anxiety and stress reports support earlier claims about the therapeutic potential of ayahuasca. Clinical studies have shown that patients suffering from depression benefitted from a single ayahuasca dose up to 21-days post-intake (de Lima Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016). Together with findings in non-clinical samples (as in Uthaug et al., 2018) the presently found reductions in self-reported stress, anxiety, and somatic complaints, support the beneficial effect of ayahuasca on mental health, either as treatment for mental health problems or as a preventive measure for anxiety and stress related disorders, and illustrate the importance of creating a (mind)set and setting in which the most optimal psychedelic experience can be elicited.

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SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at <https://doi.org/10.1556/2054.2021.00174>.

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