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Ayahuasca’s Antidepressant Effects Covary with Behavioral Activation as well as Mindfulness

By

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Abstract

Ayahuasca, a plant-based hallucinogen that serves as a spiritual medicine in South America, has improved depression in at least one placebo-controlled clinical trial. Case studies suggest that dramatic behavioral changes often follow the Ayahuasca ceremony, but most explanations of antidepressant effects focus on observed changes in mindfulness. The present study investigated if both mindfulness and behavioral activation might also contribute to these anti-depressant effects. We surveyed individuals (N = 152) about their changes in depressive symptoms, Behavioral Activation, and mindfulness after an Ayahuasca experience. Mindfulness was strongly associated with reduced depression severity ($r = .670$, $p < .001$), while behavioral activation was moderately linked ($r = .474$, $p < .001$). Changes in depressive symptoms (Center for Epidemiological Sciences Depression Short Form [CES-D-10]) covaried with subscales from the Five Facet Mindfulness Questionnaire [FFMQ] and Experiences Questionnaire [EQ], confirming previous findings ($\beta = .57$, [95% CI (- 5.70) - (- 3.25)], $p < .001$). In addition, a modification of the Behavioral Activation for Depression Scale-Short Form [BADS-SF] accounted for significant unique variance in the improvements in depression ($\beta = .16$, [95% CI (-6.32) - (-0.08)], $p < .05$). These results suggest that changes in behavioral activation likely serve as an important mechanism underlying Ayahuasca’s antidepressant effects. Future clinical trials could benefit from tracking behavioral activation. In addition, a concerted focus on increasing valued, positive activities might enhance Ayahuasca’s anti-depressant effects.

Keywords: Ayahuasca; hallucinogens; mindfulness; behavioral activation; depression
Preface

This work includes an expanded and revised version of the author’s previously published material of which she was the lead researcher: Mian, M. N., Altman, B. R., & Earleywine, M. (2019). Ayahuasca’s Antidepressant Effects Covary with Behavioral Activation as Well as Mindfulness. Journal of Psychoactive Drugs, 1-8.

https://doi.org/10.1080/02791072.2019.1674428. The study was part of programmatic line of research consisting of a coherent and appropriately sequenced investigation for purposes of this thesis. Permission has been obtained from the publisher:

Ayahuasca’s Antidepressant Effects Covary with Behavioral Activation as well as Mindfulness

Introduction

In the United States alone, the National Survey on Drug Use and Health estimated 16.2 million adults experienced a major depressive episode in the past year in 2016, and 64% of such individuals experienced severe impairment (Substance Abuse and Mental Health Services Administration, 2017). Individuals diagnosed with Major Depressive Disorder are likely to experience low mood and loss of pleasure in previously enjoyed activities, and can suffer from irregular sleep, fatigue, and poor concentration, among a number of other symptoms as well (APA, 2000). Depression frequently co-occurs with other psychopathological problems, such as anxiety, substance use, and post-traumatic stress disorder.

At present, psychopharmacological interventions remain the most dominant treatment choice among patients, and professionals continue to prescribe antidepressants at an increasingly high rate (Cetin & Acikel, 2009). Depressed individuals encounter significant difficulty complying with treatment in general, and nonadherence rates are particularly high for those treated with medication (DiMatteo, Lepper, & Croghan, 2000; Sansone & Sansone, 2012). Results from meta-analyses have shown that 30-80% of patients stopped taking their antidepressant medication without informing their provider (Bull et al., 2002; Bultman & Svarstad, 2002; Melfi et al., 1998). Conventional antidepressant therapy might cause side effects, be inaccessible, require significant activation time, or induce fears about addiction or poor efficacy (Fortney et al., 2011; Jacob, Ab Rahman, & Ahmad Hassali, 2015; Kennedy, Tuleu, & Mackay, 2008; Zarate et al., 2006). Patients consistently cite side effects as the reason for noncompliance to psychopharmacological treatment, which can impact sleep, sexual drive, energy, weight, and gastrointestinal functioning (Cipriani et al., 2009). One study examining
compliance among two kinds of antidepressants found that more than a quarter of patients dropped from treatment because of side effects, irrespective of medication type (Balsikci et al., 2014). Furthermore, a meta-analysis found that side effects accounted for nearly a third of all instances of noncompliance (Song et al., 1993). Given the negative outcomes associated with traditional antidepressants, a call for a safer and more accessible alternative is warranted.

Ayahuasca, a psychoactive plant brew, is traditionally consumed as a tea for spiritual and medicinal purposes by native communities in the Amazon Basin (Luna, 2011; Spruce & Wallace, 1908). The beverage is a combination of *Psychotria viridis*, which contains the psychedelic N,N-dimethyltryptamine (DMT), and *Banisteriopsis caapi*, which contains a number of reversible monoamine oxidase inhibitors (MAOi), specifically beta-carbolines alkaloids (Carbonaro et al., 2015; McKenna, Towers, & Abbott, 1984; Riba, 2003). The three most prevalent Beta-carboline alkaloids found in Ayahuasca are harmine, tetrahydroharmine (THH), and harmaline. Ayahuasca use can prompt a range of cognitive and physical sensations, such as visions, feelings of elation, and gastrointestinal distress. These effects typically begin within an hour of ingestion, and can last up to four hours (Riba, 2003).

Ayahuasca use appears to create numerous therapeutic gains, including decreased hopelessness and increased openness and mindfulness, and has potential for the treatment of addiction, post-traumatic stress disorder, and anxiety (de Araújo, 2019; Hamill, Hallak, Dursun, & Baker, 2018; Loizaga-Velder & Pazzi, 2014; Santos, Landeira-Fernandez, Strassman, Motta, & Cruz, 2007; Soler et al., 2018, 2016). Despite the considerable history of ritual Ayahuasca use in the Amazon, reports of abuse of this drug or related problems are rare (Doering-Silveira et al., 2005; Fábregas et al., 2010; Gable, 2007). In fact, Ayahuasca use can reduce use of addictive substances, such as alcohol, as well as substance-use-related problems (Grob et al., 1996). An
Ayahuasca-assisted therapy for addiction among First Nation participants demonstrated reductions in alcohol, tobacco, and cocaine use following the intervention, while another suggested the therapy was important for preventing relapse and mitigating cravings (Loizaga-Velder & Pazzi, 2014; Loizaga-Velder & Verres, 2014; Thomas et al., 2013). Additionally, a global study of over 90,000 participants further revealed reduced alcohol use among Ayahuasca users compared to non-psychedelic users or non-Ayahuasca users (Lawn et al., 2017).

Researchers have also investigated the application of Ayahuasca on anxiety. Preclinical models demonstrated a dose-response curve for harmine, inducing both anxiolytic- and anxiety-like behavior, but investigators have yet to administer Ayahuasca directly in such studies (Hilber & Chapillon, 2005). Another study investigating panic signs, and both trait and state anxiety, administered Ayahuasca or a placebo to experienced Ayahuasca users (Santos et al., 2007). The results showed a marked decrease in panic signs and hopelessness, but not state anxiety. Other research reveals that Ayahuasca users report reductions in anxiety symptoms compared to non-users (Grob et al., 1996).

In addition, Ayahuasca shows potential as a treatment for post-traumatic stress disorder (Nielson & Megler, 2014). Ayahuasca administration activates brain areas focused on emotional functioning and memory, compared to placebo, as well as the HPA-axis, the main stress-response system (dos Santos et al., 2011; Riba et al., 2006). Anecdotal reports describe Ayahuasca ceremonies as a “life-changing” experience, suggesting therapeutic potential for reframing and processing past traumatic experiences, though more empirical work would offer considerable support for efficacy.

Similar to any psychoactive substance, Ayahuasca can prompt adverse reactions upon use. Devotees recommend ceremonial use, under the guidance of an experienced shaman, to
avoid unintended consequences and monitor effects. Commonly, Ayahuasca results in significant gastrointestinal distress; on rare occasions, psychotic symptoms can also occur, but typically return to baseline within a few hours (de Araújo, 2019; de Araújo et al., 2012; Lima, Tófoli, Labate, & Jungaberle, 2011; Palhano-Fontes et al., 2018; Sanches et al., 2016). Subtle increases in respiratory rate, heart rate, and body temperature appear frequently, but also typically diminish shortly after ingestion (Callaway et al., 1999; dos Santos et al., 2011). The typical amount of Ayahuasca administered during ceremonial use (100 mL) appears nonlethal (Pic-Taylor et al., 2015). Examinations of the religious communities who consistently use Ayahuasca seem to suggest that the tea does not incur any psychosocial or physical health problems (Barbosa-Leiker et al., 2016; Barbosa et al., 2018; Grob et al., 1996).

In addition to other therapeutic applications, Ayahuasca has also demonstrated considerable efficacy for depressed individuals. Typically, individuals who consume the brew experience a period of intense introspection and heightened emotional arousal, which in turn prompts new insights into their problems (Riba et al., 2001). Compared to control-matched non-users, long-term, frequent Ayahuasca users have described profound changes in their depressive symptoms, and overall improvement in attitude towards life (Grob et al., 1996; Santos et al., 2007). First time Ayahuasca use also appears to increase both joy and vivacity, and reduce hopelessness (Barbosa, Giglio, & Dalgalarondo, 2005). Single dose administrations of Ayahuasca have produced similar results, with inpatients in one study endorsing up to an 82% reduction in reported depressive scores 24 hours after administration for up to 21 days (Osório et al., 2015). Investigators conducted a follow-up study with SPECT, an imaging procedure examining blood flow among brain regions. Similarly, patients experienced rapid antidepressant effects 40 minutes following administration, which was also maintained for 21 days (Sanches et
al., 2016). While conventional antidepressant medication typically requires several weeks to take effect, Ayahuasca can potentially deliver therapeutic benefits much sooner.

Ayahuasca has promise to provide acute relief for treatment-resistant major depression as well. A double-blind randomized placebo-controlled trial found that depression scores were significantly lower for individuals following a single dose of Ayahuasca up to one week later when compared to those who received the placebo (Cohen’s $d = .98$; Palhano-Fontes et al., 2018). Compared to ketamine, where the largest effect of reduced symptoms was found on the first day of administration but diminished over time, Ayahuasca demonstrated an opposite pattern (Romeo, Choucha, Fossati, & Rotge, 2015). Initial reductions were considerable (Cohen’s $d = .84$) but were largest one week following dosing (Cohen’s $d = 1.49$). Furthermore, a follow-up randomized control trial examined cortisol modulation among Ayahuasca-treated and placebo-treated individuals with treatment resistant depression (Galvão et al., 2018). This work demonstrated that while placebo-treated individuals displayed a blunted awakening salivary cortisol level, Ayahuasca-treated individuals exhibited cortisol levels comparable to healthy controls. While findings on long-term consequences are limited, results from the existing RCTs importantly demonstrate that Ayahuasca does appear to have profound impact on users. Depressed patients who used Ayahuasca five years earlier counted the session among the most important experiences of their life, though specific effects were short-lived (Dos Santos, Sanches, Osório, & Hallak, 2018).

In addition to pharmacological approaches, cognitive and behavioral treatments decrease depression quite reliably (Dobson et al., 2008). While some treatments focus primarily on cognitive change, others target behavioral changes consistent with a client’s positive activities and values (Beck, 2002; Cuijpers, van Straten, & Warmerdam, 2007; Kanter et al., 2010; Lejuez,
Hopko, & Hopko, 2001; López, Sanderman, & Schroevers, 2016). Traditional cognitive models conceptualize depression as a result of negatively skewed thoughts and beliefs, which are further attended to and reinforced through social learning (Beck, Rush, Shaw, & Emery, 1979; Jacobson et al., 1996). Following an initial focus on behavioral activation, cognitive behavioral therapy primarily teaches clients to identify and challenge negative cognitive distortions and disrupt related core beliefs. While this therapy appears effective for depressed individuals, therapeutic gains often appeared early in treatment. To better understand the treatment’s efficacy, components of cognitive behavioral therapy were examined more specifically (Jacobson et al., 1996). Importantly, the overall treatment was no more effective than any of its individual pieces. Furthermore, standalone behavioral activation treatment that focuses on overt behavior change could still change relevant cognitive processes without explicitly targeting them.

This cognitive-behavioral work suggests mechanisms for Ayahuasca’s impact. Previous data indicate that Ayahuasca alters relevant cognitions, including facets of mindfulness (Soler et al., 2018, 2016; Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017). Specifically, work by Soler and colleagues demonstrates Ayahuasca targets inner reactivity and judgmental processes of experiences, as well as increases in decentering (Soler et al., 2016). Follow-up work examined these same facets of mindfulness before and after four sessions of Ayahuasca, compared to a standard mindfulness stress reduction course (Soler et al., 2018). Individuals in the Ayahuasca group reported increased “non-judgmental” acceptance following use, which was comparable to the significant increase also found in the mindfulness condition. In contrast to work targeting mindfulness processes with Ayahuasca use, research on improved behavioral activation has lagged.
The present study aimed to survey individuals on their experiences or expected experiences with Ayahuasca, specifically on changes in mindfulness and behaviors following use. In accordance with the current literature, we hypothesized that changes in mindfulness would predict decreases in depression severity. We also hypothesized that behavioral activation changes from Ayahuasca use would produce a similar effect.

**Methods**

*Participants*

Participants responded online via Facebook (N=152), and volunteered for a single, anonymous survey hosted on SurveyMonkey™. All procedures were in accordance with and approved by the local Institutional Review Board.

*Measures*

Demographics and Ayahuasca Use. Participants provided demographic information, including age, gender, ethnicity, and level of education, as well as lifetime Ayahuasca use: (“Approximately how many times have you used Ayahuasca?”). For all subsequent items, all non-users (N = 11) were asked to report on their expectancies of how Ayahuasca would impact that item.

Behavioral Activation. Participants also reported post-ceremony behavior change with nine items from the Behavioral Activation for Depression Scale-Short Form [BADS-SF] (“Compared to before ceremony, in the month afterwards...”) (Manos, Kanter, & Luo, 2011). Examples of the items included: “I did things that were enjoyable,” and “I was an active person and accomplished the goals I set out to do.” In an effort to capture behaviors that might prove relevant to Ayahuasca, we asked 19 (11 female) experienced Ayahuasca users to respond to the prompt “How do your activities change in the weeks after you use Ayahuasca?” These responses
informed the generation of four additional items ("I spent more time out in nature;" "I exercised in a healthier way;" "I stopped procrastinating on some tasks;" "I got in touch with people I hadn't talked to in a while.") Responses to these items were included in the total behavioral activation score [BA]. Participants chose from a 5-point Likert scale to indicate behavior change: 1 ("not at all") to 5 ("completely, or a great deal"). Cronbach’s alpha for all behavioral activation items was .865.

Mindfulness. The survey included mindfulness scales that appeared sensitive to Ayahuasca in previous work. Specific subscales of the Five Facet Mindfulness Questionnaire [FFMQ] (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) and the Experiences Questionnaire [EQ] (Fresco et al., 2007) have increased after Ayahuasca use (Soler et al., 2014, 2016). Participants rated changes on a 3-point Likert scale from 1 ("not at all") to 3 ("a great deal") in five items from each of the “observing” and “nonreactivity to inner experience” subscales of the FFMQ following the Ayahuasca ceremony ("Please describe how you thought or felt the month before and the month after the ceremony;" Cronbach’s alpha = .855). Participants similarly rated changes for nine items of the “decentering” subscale of the EQ (Cronbach’s alpha = .906). Cronbach’s alpha for all mindfulness items was .927.

Depression Severity. Participants recalled depression severity a month “before” and a month “after” the ceremony, with endorsement of ten items from the Center for Epidemiological Sciences Depression Short Form [CES-D-10] (Björgvinsson, Kertz, Bigda-Peyton, McCoy, & Aderka, 2013)—a scale with documented convergent and discriminant validity (Van Dam & Earleywine, 2011). Items included, "I felt that everything I did was an effort," and "I felt lonely," among others, and participants responded on 3-point Likert scale from 1 ("not at all") to 3 ("a
great deal”). Cronbach’s alpha for the difference between pre and post-depression severity was .849.

Additional items unrelated to the primary research question of this paper were also included in the survey.

Data Analysis

Descriptive analyses assessed demographics and Ayahuasca use frequencies. Bivariate correlations between mindfulness, behavioral activation, and percent change depression score appear below for illustrative purposes. The sum of the standardized EQ and FFMQ subscales served as a mindfulness score. A linear regression model predicted percent change in depression severity scores from gender, age, mindfulness, Ayahuasca use, and behavioral activation.

Results

Demographics

The largest group of participants in this sample (N = 152) reported falling between the ages of 40-49 (28.3%), followed by 25% who reported an age between 30-39, 17.1% who reported an age of 50-59, 16.4% who reported 21-29, 11.8% who reported 60 or older, and about 1% who reported an age of 18-20 (M = 40-49 years old, 51% Male). The sample was highly educated, with over half reporting completing either a Bachelor’s degree or graduate degree (60.5%). The majority of participants identified as White (86.2%).

Ayahuasca use

Ayahuasca use ranged from 0 to 1100 times in life (M = 40.20, SD = 133.72, skew = 6.10). A BoxCox transformation was applied to reduce positive skew (transformed skew = 0.738; Osborne, 2013). Subsequent analyses included the transformed use variable.

Bivariate Associations
Mindfulness responses ranged from 0 to 54 ($M = 20.6$, $SD = 11.5$, skew = .135), and behavioral activation responses ranged from 24 to 68 ($M = 46.7$, $SD = 9.5$, skew = -.277). Ayahuasca use had a small, positive association with behavioral activation ($r = .162, p < .05$), but did not covary with depression severity. Mindfulness was strongly associated with reduced depression severity ($r = -.670, p < .001$), while behavioral activation was moderately linked ($r = -.472, p < .001$). Additionally, mindfulness had a strong positive correlation with behavioral activation ($r = .510, p < .001$). Full results appear in Table 4. Following the procedure for comparing correlated correlation coefficients by Meng, Rosenthal, and Rubin (1992), we found the association of reduced depression severity with mindfulness to be significantly stronger than the association with behavioral activation ($p < .001$).

Altered Depression scores predicted from Mindfulness and Behavioral Activation

We regressed percent change in depression scores on mindfulness, behavioral activation, Ayahuasca use, age, and gender. The overall model was significant ($F(5, 117) = 20.812, p < .001$), and accounted for 47.1% of the total variance ($R^2 = .471$). Behavioral activation was significant ($\beta = -.16, p < .05$) as was mindfulness ($\beta = -.57, p < .001$), demonstrating that both factors predicted decreases in depression scores, or improvement in depression severity. Further examination of the squared semi-partial correlations indicates that while mindfulness ($sr^2 = -.488$) and behavioral activation ($sr^2 = -.137$) account for unique variance in predicting this reduction, mindfulness does account for considerably more variance. Age and gender were not significant predictors in this model. The full set of analyses appear in Table 4.

To illustrate the effect size for these mindfulness and behavioral changes from Ayahuasca use on depression severity, a binomial effect size display (BESD) was calculated (Table 4; Rosnow, Rosenthal, & Rubin, 2000). Although critiques of the approach exist, the BESD
provides a rough estimate of how many in a treatment group might respond relative to a no-treatment control (Randolph, 2005). The approach has proven helpful for making effect sizes easier to interpret. Results suggest that Ayahuasca-induced alterations in mindfulness and behavioral activation might prove 5.4 times more likely to improve outcome than no such alterations.

**Discussion**

The present study aimed to corroborate previous work demonstrating that Ayahuasca-induced mindfulness mitigated depression severity and investigate if behavioral activation might also contribute. Both mindfulness and behavioral activation were significant predictors of reduced depression severity, though associations with improvement were significantly larger for mindfulness than for behavioral changes. These findings have a number of important implications. First, this work provides further evidence of Ayahuasca affecting cognitive processes (Domínguez-Clavé et al., 2016; Kuypers et al., 2016; Uthaug et al., 2018). Previous work revealed that Ayahuasca can meaningfully enhance mindfulness, notably in the decentering, acceptance, and non-judgmental facets of mindfulness, with effects comparable to standardized mindfulness training programs (Sampedro et al., 2017; Soler et al., 2018, 2016). Our work found that changes in mindfulness following Ayahuasca did mitigate depressive symptoms. This result is consistent with work that demonstrates targeting cognitive processes can provide therapeutic relief for depressed individuals (DeRubeis et al., 1990; Garratt, Ingram, Rand, & Sawalani, 2007).

Second, the current study broadens the therapeutic scope of Ayahuasca to include behavioral activation. While qualitative work underscored marked changes for individuals who experience an Ayahuasca ceremony, the current study demonstrates that Ayahuasca does
promote increased behavioral activation as part of its perceived impact on depression severity.
These changes in behavior might also underlie Ayahuasca’s impact on other problems. Previous
work demonstrated that Ayahuasca alleviates substance use problems and PTSD symptoms
(Bouso & Riba, 2013; Hamill et al., 2018; Loizaga-Velder & Pazzi, 2014; Palhano-Fontes et al.,
2014). Comparable problems benefit from behavioral activation as well (Jakupcak, Wagner,
Paulson, Varra, & McFall, 2010; Reynolds, MacPherson, Tull, Baruch, & Lejuez, 2011). Future
opportunities to examine the behavioral processes linked to Ayahuasca might shed some light
around its efficacy in these areas. Though our study did not have a control group, we were able
to determine the binomial effect size for Ayahuasca on depression severity improvement (.85 for
depression severity improvement with Ayahuasca). Previous work has demonstrated that
conventional pharmacological and psychotherapy treatment for depression have small to
moderate treatment effect sizes for improving depression symptoms, compared to control groups
(d = .30 and d = .67, respectively; Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010;
Khan & Brown, 2015). Conversion of these effect sizes to binomial effect sizes (binomial e.s. = .57 for pharmacotherapy and .84 for psychotherapy, for the improvement of depression severity
if in treatment) demonstrates that Ayahuasca could improve depression severity at comparable or
even larger magnitudes to conventional treatments, compared to a control group (Rosenthal,
1994). Though this comparison is illustrative and has several caveats, notably differences in
measures of depression severity and methodology, it provides context for therapeutic Ayahuasca
use among current treatment options.

Compared to conventional antidepressants, psychedelics appear to operate in an entirely
different manner. Antidepressant medications, such as SSRI’s, address chemical imbalances in
the brain through restorative mechanisms (Ballesteros, 2018). Such drugs attempt to mitigate and
extinguish depressive symptoms from the individual, often resulting in an overall blunted affect that is less than desirable (Carhart-Harris & Goodwin, 2017). Alternatively, psychedelics, such as Ayahuasca, enhance experiences and connections based on the context they are taken in (Watts et al., 2017). A number of neurobiological studies posit how these processes diverge, though both substances impact the same brain areas relevant to depression (Carhart-Harris & Nutt, 2017; Watts et al., 2017). While both psychedelics and SSRI’s increase neuroplasticity, modulate the DMN, and target relevant neurotransmitters, receptors and pathways related to serotonin, psychedelics work more quickly (Baumeister, Barnes, Giaroli, & Tracy, 2014; Kyzar & Kalueff, 2016; Ly et al., 2018). Furthermore, these structural changes may stem from opposing mechanisms. Carhart-Harris and colleagues proposed a bipartite model to explain how conventional antidepressants, such as SSRI’s, and psychedelics affect the neuroplasticity of the serotonergic system through two distinctive paths (Carhart-Harris & Nutt, 2017; Carhart-Harris & Goodwin, 2017). The model suggests that the serotonin-receptor-mediated pathway, 5-HT1AR, could be activated by inhibited reuptake action by SSRI’s. Another serotonin receptor pathway, 5-HT2AR, could be activated by a psychedelic agonist. These processes could partially explain the improvement of depression symptoms by different pharmacological treatments.

Presently, the underlying mechanisms of change related to Ayahuasca remain unclear, though Ayahuasca effects contribute to a number of important processes relevant to depression. While depressed individuals demonstrate increased REM sleep, and lowered REM latency, Ayahuasca has decreased REM sleep, and increased latency to REMS (Barbanoj et al., 2008; Minkel, Krystal, & Benca, 2017; Palhano-Fontes et al., 2015; Sheline et al., 2009). In addition, depressed individuals reportedly have increased activity and increased cortical thickness in key regions of the default mode network (DMN), which include brain regions associated with
contemplation, reflection, and imagination. Ayahuasca blunts DMN responses and covaries with cortical thinning in DMN brain areas, potentially targeting cognitive processes associated with depression, such as rumination (Bouso et al., 2015; Carhart-Harris et al., 2012; dos Santos, Osório, Crippa, & Hallak, 2016).

Ayahuasca induces profound mystical experiences through vivid auditory and visual hallucinations, and activated brain areas associated with the primary visual cortex (Draulio B de Araújo et al., 2012). This result implicates perception, memory, and sensory processes, which are notably blunted in depressed individuals (Frecska, Bokor, & Winkelman, 2016; Sternberg & Jarvik, 1976). Psychopharmacological studies further demonstrate that N, N-DMT, one of the major psychoactive components of Ayahuasca, serves as a sigma-1 receptor agonist (Cai, Huang, & Hao, 2015; Carbonaro & Gatch, 2016). Such agonists can reduce depression-like behavior in behavioral models. Ayahuasca is no exception; not only are results comparable, but in some cases, Ayahuasca has produced more effective results than conventional antidepressant drugs. (Cameron, Benson, Dunlap, & Olson, 2018; da Silva et al., 2018; Fortunato et al., 2010). In clinical studies, both intramuscular and inhalation delivery of DMT induced a more relaxed and positive mood among participants (Gillin, Kaplan, Stillman, & Wyatt, 1976; Riba, 2003; Riba, Mcilhenny, Bouso, & Barker, 2015; Strassman, Qualls, Uhlenhuth, & Kellner, 1994). Beta carboline alkaloids, the other major psychoactive component of Ayahuasca, serve as reversible MAOi’s and potentially play a significant role in its antidepressant effects. The beta carbolines modulate serotonin, dopamine, and norepinephrine, neurotransmitters believed to contribute to depression. The alkaloids serve both as antagonists for NMDA receptors and as selective serotonin reuptake inhibitors, both of which are pharmacological targets for antidepressants (Buckholtz & Boggan, 1977; Araújo, 2019). Finally, as previously stated, Ayahuasca use
modulates cortisol and other hormones among depressed individuals, suggesting some association with the endocrinological system (Frecska et al., 2016; Galvão et al., 2018; Szabo & Frecska, 2016). With continued research, Ayahuasca can prove to be a beneficial and potentially more efficacious alternative to traditional antidepressants.

Beyond psychopharmacological mechanisms, context is singularly important for understanding the effects of psychedelics. By contrast, antidepressants will largely take effect regardless of how or where they are taken (Eisner, 1997). Ayahuasca is notable for inducing a profoundly mystical experience, and like other psychedelics, can reveal and further augment thoughts and feelings to an extraordinary extent (Hartogsohn, 2018). These effects are further altered by the set and setting in which they are taken. The traditional administration of Ayahuasca provides a unique psychotherapeutic opportunity. The ceremony not only provides guidance in the form of a shaman, but participants are likely to seek out the ritual with specific intentions (Metzner, 1998). Informing participants about the behavioral and cognitive mechanisms related to Ayahuasca could potentially amplify therapeutic gain. By deliberately accounting for set and setting, inducing a particular kind of therapeutic outcome is likely possible (Eisner, 1997; Haijen et al., 2018; Hartogsohn, 2016). Previous work has demonstrated that psychedelics promote meaningfulness, connectedness, and empathy, all of which would be generally favorable; with purposeful enhancement, such feelings could even reach clinical significance (Carhart-Harris, Erritzoe, Haijen, Kaelen, & Watts, 2018; Griffiths et al., 2018; Hartogsohn, 2018; Watts et al., 2017). We also know that the quality of psychedelic experience plays a significant role in the longevity and salience of such effects (Maclean, Johnson, & Griffiths, 2011). Moreover, establishing intentions and a positive context for psychedelic use improved the chances of having a positive experience overall (Haijen et al., 2018).
Why target specific psychedelic effects? With the use of a psychedelic, several important features emerge, including feelings of unity, transcendence, elation, reverence, insight, and indescribable joy (Ballesteros, 2018). For depressed individuals, significant and lasting enhancement of any one of these experiences would improve their quality of life. Furthermore, though this area of research is still emerging, such interventions are possible. For severely depressed individuals, combined pharmacotherapy and psychotherapy is far more effective compared to either treatment alone (Thase, 2011). A combination of Ayahuasca and psychotherapy might demonstrate a similar effect, particularly if the psychotherapy elicited behavioral and mindfulness change. While research on therapeutic mechanisms is still limited, Ayahuasca does promote empowerment and hope, factors that are significantly tied to improved outcomes in psychotherapy (Feldman, Adams, Taylor, Schroeder, & Snyder, 2005; Gilman, Schumm, & Chard, 2012; Thomas et al., 2013). First time Ayahuasca users also describe increased energy and assertiveness following their initial ceremony (Barbosa et al., 2005). These acute effects could potentially activate long term change, though more work is needed to examine this idea fully. But the current data reveal that a parsimonious explanation for Ayahuasca-induced improvement is behavioral activation. These results also suggest that booster sessions that highlight changes in mindfulness and behavioral activation could enhance treatment outcome and help maintain gains, even without additional ceremonies or additional doses of Ayahuasca.

Psychedelic-assisted psychotherapy involves using therapy to provide psychoeducation (preparatory sessions), provide support during use (medication sessions), and process experiences around the administration of psychedelic substances (integration session; Nielsen, 2010). Notably, the psychedelic therapy is used to induce life-altering experiences, and promote
growth and insights in clients (Ballesteros, 2018; Majić, Schmidt, & Gallinat, 2015). Currently, psilocybin is a common choice for such interventions. Depressed patients in one study reported increase connectedness and more acceptance with psilocybin-assisted therapy, and found that these experiences markedly contrasted with conventional depression treatments (Watts et al., 2017). Another study found that two therapy-assisted sessions of psilocybin were well-tolerated, and that depression severity was significantly reduced even through follow-up (effect size = 2.3 following treatment, 1.5 at 3 months, 1.4 at 6 months). Depressed individuals who report having a high-quality psychedelic experience are also more likely to report the therapeutic gains from psilocybin (Roseman, Nutt, & Carhart-Harris, 2018). Psilocybin-assisted therapy successfully improved both symptoms and pessimism in depressed patients, and maintained more realistic perceptions in follow-up as well (Lyons & Carhart-Harris, 2018). Though not explicitly a therapy-assisted procedure, participants administered either a low dose or high-dose of psilocybin alongside support from spiritual guides who facilitated conversations around the experiences and exercises in meditation. Participants treated with the high dose reported more connectedness, meaningfulness, and forgiveness both after treatment and six months following treatment, compared to the low dose group (Griffiths et al., 2018)

Ayahuasca-assisted therapy demonstrates early success for addiction, but has yet to target depression (Loizaga-Velder & Pazzi, 2014; Thomas et al., 2013). Previous work with Ayahuasca, coupled with the set and setting manipulations that enhanced the effects of other psychedelics, does suggest potential success for Ayahuasca-assisted treatment of depression (Ballesteros, 2018; Eisner, 1997). In fact, given the essentiality of context for psychedelic use and the traditional ceremony in which Ayahuasca is used, future clinical research must consider both the preparatory and processing stages of use to understand therapeutic opportunities
Client-centered techniques, such as motivational interviewing, elicit and promote change, and find success especially among ambivalent or resistant individuals (Miller & Rollnick, 2012). Combinations of motivational interviewing with other kinds of interventions improves treatment outcomes and adherence to treatment, and strengthens therapeutic alliance (Driessen & Hollon, 2011; Miller, Cano, & Wurm, 2013). Similar benefit might be possible by using motivational interviewing techniques prior to Ayahuasca use and could also elicit clear intentions for use.

The current study does have important limitations. We were not able to administer Ayahuasca directly. We asked participants to provide reports retrospectively, but future work should examine alterations in mindfulness and behavior following the ceremony. Similar to our study, much of the current literature on Ayahuasca is largely cross-sectional; longitudinal designs would provide important information about the long-term efficacy of change induced by Ayahuasca. On average, our sample used Ayahuasca on multiple occasions, which also suggests that repeated dosing might be a crucial feature of meaningful behavioral change. The second limitation relates to the generalizability of our sample. The majority of our participants were older, highly educated, and White. While this sample is a departure from work examining traditional populations of Ayahuasca users in South America, Ayahuasca use among diverse populations requires markedly more attention.

Despite these limitations, we demonstrated that the anti-depressant qualities of Ayahuasca might be a function of both changes in both mindfulness and behavior. Our work broadens the therapeutic potential of Ayahuasca and suggests potential mechanisms for its impact on depression and other problems. In addition, these results suggest straightforward ways to enhance Ayahuasca’s impact and duration. Given the need for a rapid intervention that could
have a lasting impact, a randomized clinical trial that takes these new results into account seems warranted. Enhancing readiness to change these cognitive and behavioral components prior to administration of Ayahuasca and tracking the potential mechanisms repeatedly could prove useful. Such approaches could amplify the magnitude of the improvement, enhance its duration, and reveal more about the role of these changes in maintaining gains. The established efficacy of both cognitive therapy and behavioral activation also suggests that brief Ayahuasca treatments could generalize to a broad range of disorders. The potential impact of this approach is hard to estimate but could prove very large.
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Table 1: Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
<td>51</td>
</tr>
<tr>
<td>Female</td>
<td>72</td>
<td>47.7</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>131</td>
<td>86.2</td>
</tr>
<tr>
<td>African American</td>
<td>11</td>
<td>7.2</td>
</tr>
<tr>
<td>Latino</td>
<td>8</td>
<td>5.3</td>
</tr>
<tr>
<td>American Indian</td>
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<td>.7</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1</td>
<td>.7</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some high school</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Finished high school/GED</td>
<td>16</td>
<td>10.5</td>
</tr>
<tr>
<td>Some college</td>
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<td>19.1</td>
</tr>
<tr>
<td>Associates degree</td>
<td>10</td>
<td>6.6</td>
</tr>
<tr>
<td>Bachelors degree</td>
<td>45</td>
<td>29.6</td>
</tr>
<tr>
<td>Advanced degree</td>
<td>47</td>
<td>30.9</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-20</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>21-29</td>
<td>25</td>
<td>16.4</td>
</tr>
<tr>
<td>30-39</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>40-49</td>
<td>43</td>
<td>28.3</td>
</tr>
<tr>
<td>50-59</td>
<td>26</td>
<td>17.1</td>
</tr>
<tr>
<td>60 and older</td>
<td>18</td>
<td>11.8</td>
</tr>
<tr>
<td>Mean SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayahuasca Use Lifetime</td>
<td>40.2</td>
<td>133.7</td>
</tr>
</tbody>
</table>
Table 2. Bivariate associations between mindfulness, behavioral activation, frequency of Ayahuasca use and percent change in depression scores

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Mindfulness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Behavioral Activation</td>
<td>.510**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) % Change in Depression</td>
<td>-.670**</td>
<td>-.472**</td>
<td></td>
</tr>
<tr>
<td>(4) Ayahuasca use</td>
<td>.017</td>
<td>.162*</td>
<td>.023</td>
</tr>
</tbody>
</table>

Note: *p < .01, **p < .001
Table 3. Predicting percent change in depression scores from mindfulness, behavioral activation, Ayahuasca use, age, and gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SEB</th>
<th>T</th>
<th>β [95% CI]</th>
<th>Squared Semi-Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mindfulness</td>
<td>-4.47</td>
<td>0.62</td>
<td>-7.26</td>
<td>-0.57 [(-5.70)(-3.25)]**</td>
<td>-0.488</td>
</tr>
<tr>
<td>Behavioral Activation</td>
<td>-3.20</td>
<td>1.58</td>
<td>-2.03</td>
<td>-0.16 [(-6.32)(-0.08)]*</td>
<td>-0.137</td>
</tr>
<tr>
<td>Ayahuasca use</td>
<td>0.236</td>
<td>1.40</td>
<td>0.17</td>
<td>0.12 [(-2.53)(-3.00)]</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.38</td>
<td>1.03</td>
<td>1.34</td>
<td>0.09 [(-0.66)(3.42)]</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>1.17</td>
<td>2.72</td>
<td>0.43</td>
<td>-0.30 [(-4.21)(6.55)]</td>
<td></td>
</tr>
</tbody>
</table>

Note: *p < .05, **p < .001
Table 4. Binomial effect size display of $r = .690$ in improved depression severity

<table>
<thead>
<tr>
<th></th>
<th>Improved depression severity</th>
<th>No improved depression severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aya Use</td>
<td>0.85</td>
<td>0.15</td>
</tr>
<tr>
<td>Aya Non-Use</td>
<td>0.15</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Figure 1. Scatterplots for associations between mindfulness, behavioral activation [BA], frequency of Ayahuasca use [Aya use], and percent change in depression scores [CESD]
Ayahuasca's Antidepressant Effects Covary with Behavioral Activation as Well as Mindfulness

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