Summer 7-26-2018

Neuropsychological effect on long-term Ayahuasca use

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by

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A Thesis Submitted in Fulfillment of the Requirements for the Honors Research Distinction for the

Undergraduate degree, Bachelor of Science, Psychology

in the College of Arts and Sciences

Georgia State University

2018

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Under the Direction of Dr. Jessica Ann Turner, PhD

ABSTRACT

Ayahuasca is a hallucinogenic tea used in religious ritual ceremonies in eastern parts of South America. Ayahuasca is becoming more popular in western countries for therapeutic use for depression, drug addiction, and emotional distress (Domínguez-Clavé et al., 2016). Previous research has explored the effects ayahuasca may have on cognition, neurological functioning, and psychopathology. Although several studies have been done on cognition and psychopathology, few studies have examined the long term use of neurological functioning. This study focused on neuropsychological effects chronic recurrent religious users of Ayahuasca may develop, using an existing data set. This study analyzed the default mode network (DMN) comprised of the posterior cingulate cortex, angular gyrus, and the medial prefrontal cortex. To assess the DMN functional magnetic resonance images (fMRI) scans were collected. This study included 12 Ayahuasca users from the U.S. branch of União do Vegetal (UDV) and 13 non-Ayahuasca-using controls from Albuquerque Protestant and Catholic churches. No differences were found between groups on connectivity in any region of interest nor in relation to mood assessments. However, the right medial prefrontal cortex and the angular gyrus revealed a positive associated with sleepiness. Possible effects can be assessed on default mode network (DMN) connectivity using a larger sample size. These findings display evidence that long term use of Ayahuasca does not have essential lasting neuropsychological effects.

INDEX WORDS: Ayahuasca, default mode network (DMN), angular gyrus, right medial prefrontal cortex, posterior cingulate cortex/gyrus, serotonin, monoamine-oxidase inhibitor

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DEDICATION

I would like to dedicate this project to my wonderful support system. This project would not have been possible without the support of my husband, Larvarus Tucker, my mother Sharon DeVaughn, and my sister Crystal DeVaughn. I want to thank you all for continually encouraging me through this process.

ACKNOWLEDGEMENTS

I want to acknowledge Dr. Jessica Turner, Dr. Mathew Turner, and Dr. Sharee Light for being amazing mentors to me in the duration of this project, and my time in their labs. I send out a special thank you to everyone involved in my undergraduate process, from advisors, teachers, students, and financial staff for helping me complete my degree here at Georgia State University. I also want to acknowledge Jessica Snellings' contributions to this study, as well as those who collected the data, Dr. Michael Bogenshutz the principal investigator, Dr. Barbosa who ran the study, and Jessica Pommy who helped with recruitment.

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Introduction:

From the beginning of civilization, the role of plants has been essential to human consumption in regards to food and medicine. Religious use of psychoactive plants among indigenous people dates back to pre-history. These plants that alter the state of the mind are viewed as sacred, often called “Plants of the Gods” (Schultes, Hofmann & Rätsch, 2001). One specific plant that has been under question for its effects on the mind is ayahuasca.

Most users of ayahuasca are active members of the Brazilian religion União do Vegetal (UDV) and Santo Daime (Halpern, Sherwood, Passie, Blackwell, & Ruttenber, 2008). These religious groups were established in 1930 by a blend of Amazonian Christian Shamans and Afro-Brazilian beliefs (Labate & MacRae, 2016). Santo Daime and UDV members have a presence in 38 countries (Labate & Feeney, 2012). Reportedly in 2012, 16,500 UDV member were established in South and North America and Europe (Barbosa et al., 2016). Santo Daime and UDV established themselves as Christians focused on spiritual growth in morality, positive outlooks, and reincarnation (Barbosa et al., 2016).

Ayahuasca is a hallucinogenic tea comprised of psychoactive plants, which originated in religious ritual ceremonies in eastern parts of South America. Ayahuasca is incorporated into different spiritual services as a part of the many rituals that take place, ayahuasca sessions last for a duration of 4 -12 hours (Barbosa et al., 2016). These ceremonies include the intake of ayahuasca, along with hours of preaching, singing, and dancing (Barbosa et al., 2009). These ceremonies are designed to provide spiritual enlightenment, as well as providing members with structural guidance for their daily lives (Taylor, Stewart, Hopkins, & Ehlers, 1999).

Government History

In the United States, ayahuasca falls under the classification of a schedule I drug according to the Controlled Substance Act of 1970 regulated by the FDA and DEA. However, UDV members argued that banning the use of ayahuasca was a violation of the Religious Freedom Restoration Act of 1993 (RFRA). There was no substantial evidence to show that the use of this formulated tea was a danger to this religious group or others, so the ban was overturned (Gonzales v. O Centro Espírita Beneficente União Do Vegetal, 546 U.S. 418 (2006) n.d.). Although existing data has suggested that ayahuasca use has shown no lethal effects to users, there is limited information on continuous effects on neurological activity and functioning. This case is subject to investigation again if new evidence of harm is found.

Ayahuasca Chemical Mixture

Ayahuasca also known as (Hoasca) is composed by boiling a mixture of the vine (Banisteriopsis caapi), and the leaves referred to as chacruna (Psychotria viridis). The boiling display of Ayahuasca is shown in Figure 1. Banisteriopsis caapi contains β-carboline alkaloids such as harmine, harmaline, and tetrahydroharmine, while psychotria viridis contains N, N-dimethyltryptamine (DMT) (Halberstadt, 2016). N, N-dimethyltryptamine(DMT) is a tryptamine hallucinogen which is thought to act primarily on 5HT2A, 5HT2C, and 5HT1A receptors (Barbosa et al., 2016). DMT and serotonins (5-HT) closely related chemical structure implicates DMTs ability to display similar biological characteristics to serotonin (5-HT). However, DMT in humans is not orally active, monoamine- oxidase neurons degrade DMT before it has a chance to act.

Monoamine-oxidase (MAO) are enzymes in the body that metabolize substances before getting into the bloodstream. The B-carboline alkaloids harmine, harmaline, and

tetrahydroharmine (THH), from the B-Caapi vine are monoamine-oxidase inhibitors (MAOI). These psychoactive alkaloids share similar chemical structures; harmine acts as the main MAO inhibitor because it is more potent than THH, and more abundant than harmaline in ayahuasca (Riba, 2003). Therefore, inhibiting these enzymes allows DMT which would normally not be orally active to move through the bloodstream. Inhibiting monoamine-oxidase also effects the breakdown of other monoamines such as dopamine and norepinephrine. Interestingly, the B-carboline alkaloid THH has been identified as an inhibitor of 5-HT as well, supporting the regulation effects of DMT (Riba, 2003). The chemical structures found in ayahuasca are shown in **Figure 2**.

Figure 1. The boiling mixture of Banisteriopsis caapi vine and Psychotria viridis leaves. Photo supplied by: Jana Klintoukh

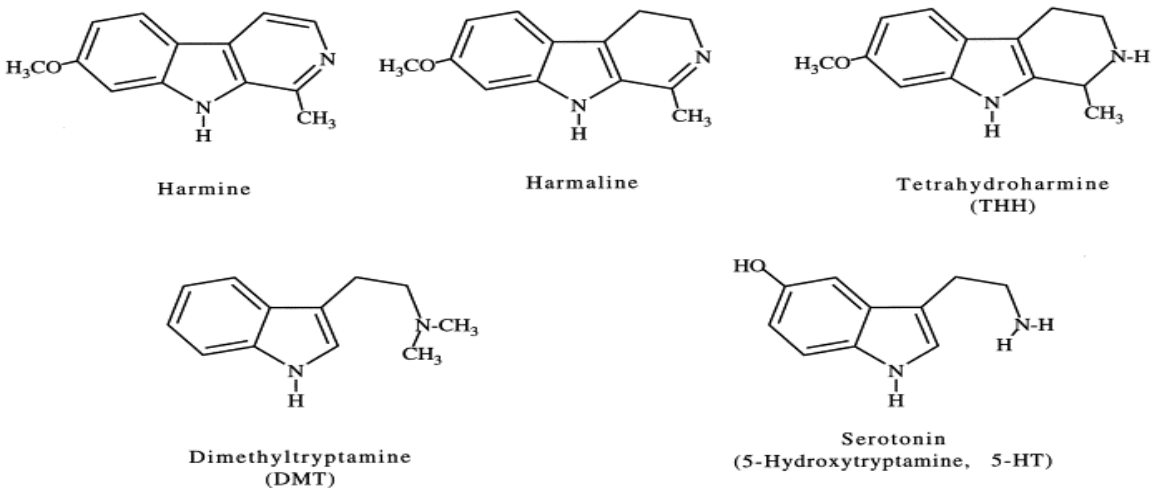

Figure 2. Chemical structures of β-carboline alkaloids found in the Banisteriopsis vine (harmine, harmaline, and tetrahydroharmine), Psychotria viridis leaves (N, N-dimethyltryptamine), and the chemical structure of serotonin.

Nonetheless, DMT in the P. virdis leaves is the main psychoactive ingredient found in the mixture of ayahuasca. DMT also happens to be a common alkaloid found in multiple plants, but was first identified in the roots of the Mimosa tenuiflora tree in 1946 (Domingues-Clave et al., 2016; Ott, 1999). The substance presently referred to as DMT was first identified as nigerine (cited in McKenna and Riba, 2015), and later named DMT in 1955 (Fish et al., 1955). One of the first studies done on DMT by Szara, 1956, found that DMT has the ability to induce visionary effects. As of today, oral intake of ayahuasca has been identified for causing induced visual illusions, change in mood (Domínguez-Clavé et al., 2016), high blood pressure, vomiting, and increase pulse rate (Riba et al., 2001b), all which are characteristics closely related to serotonin effects**.**

Relevance

Although religious groups are still the main consumer of these psychoactive plants, interest for recreational use has grown over the years. In the 21st century ayahuasca is increasing in popularity in western countries for therapeutic use from depression, drug addiction, and

emotional distress (Domínguez-Clavé et al., 2016). Some studies have found that ayahuasca has significant acute antidepressant results, compared to the two-week reported onset of prescribed antidepressants (Osório et al., 2015). According to research, unhappiness is associated with hyper connectivity in the default mode network (Luo, Kong, Qi, You, & Huang, 2016), therefore, if ayahuasca decreases these regions' activity, there is evidence for antidepressant properties. Ayahuasca's effects on addiction has also been a major therapeutic discovery. Liester and Prickett (2012) suggested that ayahuasca's ability to act on different neurotransmitters by directly increasing one and indirectly decreasing another is the key component in addiction treatment. Thus, broader research is needed on the neurological effects long term use of ayahuasca can have.

Region of Interest (ROI)

Scans of the brain during resting state shows the spatially separated brain regions' neuronal activity when the participant is not performing a directed task (Van den Heuvel & Hulshoff Pol, 2010). Regions of the brain are classified as connected if the regions' neuronal time series activity are correlated (Craddock, Tungaraza, Milham, 2015). This study used functional magnetic resonance imaging resting state scans to assess the brain's connectivity during rest in long-term ayahuasca users and controls. The scans can provide insight to possible differences in brain connectivity for participants who have used ayahuasca over a long time period.

Knowing that serotonin is active in multiple areas of the brain, the activation region that ayahuasca influences is most commonly expressed in the paralimbic and frontal brain regions (as cited in dos Santos, Bouso, & Hallak, 2017). As cited in Palhano-Fontes, (2015), studies show that the main effects of ayahuasca deals with introspection (Riba et al., 2001b), self-reflection

(Strassman, Qualls, Uhlenhurth, Kellner, 1994), visual association (Riba et al., 2006), and working memory (Bouso et al., 2013). These finding leads one to hypothesis that the default mode network might be involved.

The DMN is a network that can be identified in resting state scans, and is commonly composed of the posterior cingulate cortex/precuneus, the angular gyrus, and the medial prefrontal cortex. Studies show that the DMN is the most active at rest, and it is the network most associated with mind wandering, memories, imaging the future, and the reflection of one's self (Palhano-Fontes et al., 2015). Specifically, the medial prefrontal cortex (mPFC) is associated with self-reflection, perception, and understanding one's self (Grossmann, 2013). The angular gyrus located in the parietal lobe deals with visual concepts and helps the DMN develop mental scenes and manipulation of conceptual knowledge (Seghier, 2013). Lastly, the posterior cingulate cortex (PCC) in the DMN is associated with planning for the future and life history memories (Leech & Sharp, 2014).

In one study that looked at structural effects of long-term psychedelic drugs, they found ayahuasca users exhibit thinning in the posterior cingulate cortex, which is an important element of the default mode network (Bouso et al., 2015). In addition, according to Palhano-Fontes et al., 2015, ayahuasca use during acute administration exhibited a decrease in the default mode network activity, containing the posterior cingulate cortex/precuneus and the medial prefrontal cortex. These findings are inconsistent with the increased functional connectivity associated in this brain region during rest (Raichle, et al., 2001). The DMN shows decreased functional connectivity when attention is externally directed (Spreng, 2012), however, some internal attention based task such as mediation has been known to deactivate the DMN network as well

(Mrazek et al., 2013). Concluding the assessment of the above findings, in this study we will look at the effects chronic recurrent use of ayahuasca has on the default mode network overtime.

The psychoactive effects of oral Ayahuasca intake findings

After several literature reviews (Palhano- Fontes et al., 2015; Riba et al., 2001b; & dos Santos et al., 2017), there has been no long term psychoactive reactions to direct ayahuasca substances. Some studies have reported lethal effects and/or dramatic psychotic episodes from DMT consumption associated with participants who combined ayahuasca with other psychoactive substances, antipsychotic drugs, and/or with participants who report previous history of psychotic disorders, or predisposed disorders within their family history (Riba et al., 2001b; Domínguez-Clavé et al., 2016; Osório et al., 2015; Palhano- Fontes et al., 2015; & dos Santos et al., 2016).

Predominantly, these findings suggest that ayahuasca use in a controlled environment, taken by healthy individuals, have few lasting psychopathic, cognitive, or personality effects. However, these studies have based their findings off of self-evaluations and assessments. Knowing that ayahuasca does contain psychoactive substances, concern is placed on the long-term neurological effects. This study focused on those long-term neurological effects recurrent religious users of ayahuasca may develop. Part of the data has already been published in Barbosa et al. (2016).

Purpose

Assessments were made to determine differences in connectivity in the default mode network between groups, correlating differences in neurological activity and mood association. We hypothesized that if there is a difference in connectivity between groups in the default mode network, this may relate to differences in neurocognitive functioning and positive affective

outlooks. Ayahuasca has become more popular in North America, and many studies are discovering its antipsychotic effects. A few celebrities have also publically endorsed its effects (Johnson, 2016), which is why sufficient data needs to be done on the outcomes of ingestion. This study will help further the knowledge on whether ayahuasca is neurologically safe for human consumption long term.

Methods:

Sample

This data is part of a larger study reviewed and approved by the Human Subjects Protections Office at the University of New Mexico Health Sciences Center. Exclusions included current use of psychiatric, neurological, or any other psychoactive drug/medication (Barbosa et al., 2016). This study recruited 20 U.S. branch of União do Vegetal (UDV) members, and 16 control subjects from Albuquerque Protestant and Catholic churches who matched in similar religious beliefs and age to UDV members. Both groups were required to be 18 years or older to participate in this study. Of the 20 UDV subjects, 8 are female, and 12 are males; of the control subjects, 6 are female, and 10 are male, see **Table 1**.

The sample consisted of 25 total participants who passed quality assurance measures noted below, 12 ayahuasca users with a mean age of 42 years (SD: 12.2), and 13 matched non-ayahuasca using controls; mean age of 40 years (SD: 13.4). Of the 12 UDV subjects, 6 are female, and 6 are male; of the control subjects, 3 are female, and 10 are male. The minimum age of all participants is 20 years old, maximum age is 60 years old.

Mood assessments

Participants were assessed using a 60-item expanded version of the Positive and Negative Affect Schedule (PANAS), the PANAS-X, 1994. This assessment is used to identify negative

and positive affect. Each participant is given a list consisting of several words and phrases that describe different emotions. Participants are required to scale each word or phrase ranging from 1 to 5, with 1 being not at all and 5 being extremely. Scores are calculated and grouped into general negative affect (fear, sadness, guilt, hostility, shyness, and fatigue) and general positive affect (joviality, self-assurance, attentiveness, serenity, and surprise), and more shown in **Table 2**

Table 1. Demographics and PANAS-X Scores

Demographics & Positive and Negative Mood Scores								
Variables	***Ayahuasca***				***Control***			
	N	*Mean*	*Min*	*Max*	*N*	*Mean*	*Min*	*Max*
Gender								
Women	*8*				*6*			
Men	*12*				*10*			
Age	*20*	*41.6*	*22*	*60*	*16*	*38.9*	*20*	*60*
Years of Usage		*7yrs*	*2yrs*	*16yrs*				
PANAS-X Scores								
General Negative		**10.75*	*10.00*	*13.00*		**15.44*	*10.00*	*26.00*
Fear		**6.60*	*6.00*	*10.00*		**8.69*	*6.00*	*17.00*
Sadness		**5.45*	*5.00*	*9.00*		**8.13*	*5.00*	*17.00*
Guilt		**6.20*	*6.00*	*8.00*		**9.50*	*6.00*	*18.00*
Hostility		**6.15*	*6.00*	*7.00*		**8.19*	*6.00*	*15.00*
Shyness		*4.70*	*4.00*	*8.00*		*5.60*	*4.00*	*9.00*
Fatigue		**9.30*	*4.00*	*16.00*		**8.31*	*4.00*	*15.00*
General Positive		*31.60*	*25.00*	*43.00*		*29.60*	*20.00*	*37.00*
Joviality		*26.40*	*18.00*	*38.00*		*23.38*	*9.00*	*34.00*
Self Assurance		*14.55*	*11.00*	*20.00*		*14.25*	*7.00*	*23.00*
Attentiveness		*13.95*	*9.00*	*18.00*		*12.75*	*10.00*	*16.00*
Serenity		**11.90*	*7.00*	*15.00*		**10.06*	*5.00*	*15.00*
Surprise		*4.75*	*3.00*	*10.00*		*4.25*	*3.00*	*8.00*

*Significant difference between groups; $p < .05$

Table 1. represents the demographic and the mood scores recorded for each group.

Table 2. Positive and Negative Affect Schedule words scale

General Dimension Scales	
Negative Affect (10)	afraid, scared, nervous, jittery, irritable, hostile, guilty, ashamed, upset, distressed
Positive Affect (10)	active, alert, attentive, determined, enthusiastic, excited, inspired, interested, proud, strong
Basic Negative Emotion Scales	
Fear (6)	afraid, scared, frightened, nervous, jittery, shaky
Hostility (6)	angry, hostile, irritable, scornful, disgusted, loathing
Guilt (6)	guilty, ashamed, blameworthy, angry at self, disgusted with self, dissatisfied with self
Sadness (5)	sad, blue, downhearted, alone, lonely
Basic Positive Emotion Scales	
Joviality (8)	happy, joyful, delighted, cheerful, excited, enthusiastic, lively, energetic
Self-Assurance (6)	proud, strong, confident, bold, daring, fearless
Attentiveness (4)	alert, attentive, concentrating, determined
Other Affective States	
Shyness (4)	shy, bashful, sheepish, timid
Fatigue (4)	sleepy, tired, sluggish, drowsy
Serenity (3)	calm, relaxed, at ease
Surprise (3)	amazed, surprised, astonished

Note. The number of terms comprising each scale is shown in parentheses.

Table 2. represents the selective words on the PANAS-X assessment. Table adapted from PANAS-X Manual (Watson and Clark, 1994, Table 2).

Scanning procedure

This study used functional magnetic resonance images (fMRI) of resting state scans using a 3T Siemens TIM Trio scanner at the Mind Research Network (MRN), Albuquerque NM. Ayahuasca users were scanned the day after their usual weekly ritual including the consumption of the brew. A T1-weighted scan, a T2-weighted scan, and two echo-planar BOLD-weighted resting state scans were collected. The resting state EPI protocol included 165 frames at TR = 2s, TE = 40 ms, Flip Angle = 77 deg, with 33 axial slices of 4 mm thickness (with no gap), 64 x 64

in-plane matrix of 3.75 x 3.75 mm voxels, with a standard head coil. During the resting state scans each participant was scanned with their eyes opened while remaining still.

Preprocessing Steps

The Configurable Pipeline for the Analysis of Connectomes (C-PAC), was used to analyze the seed based connectivity in the regions of interest. C-PAC is a configurable, open-source, scriptable, automated processing pipeline for resting state fMRI data (Craddock et al., 2015). The C-PAC processing and analysis pipeline is implemented through a configuration file, which permits the inclusion and exclusion of different steps. These steps included nuisance signal removal and volume censoring (motion scrubbing), spatial and temporal filtering, slice timing correction, and the regression of white matter and CSF signals. A total of eleven participants were excluded from the original sample, nine participants did not receive a scan and one participants was excluded for insufficient data. Using the scanning technique proposed by Smyser et al. (2011) computing DVARS, we were able to remove inadequate scans. One participant who displayed too much head movement during the scan was also excluded. **Figure 3** shows the seed based regions acquired. We used the correlation coefficients from the following pairs as input to the analyses: (posterior cingulate cortex paired with the left angular gyrus; posterior cingulate cortex paired with the right angular gyrus; posterior cingulate cortex paired with the left medial prefrontal cortex; posterior cingulate cortex paired with the right medial prefrontal cortex; left & right angular gyrus paired together; left medial prefrontal cortex paired with the left angular gyrus; and the right medial prefrontal cortex paired with the right angular gyrus).

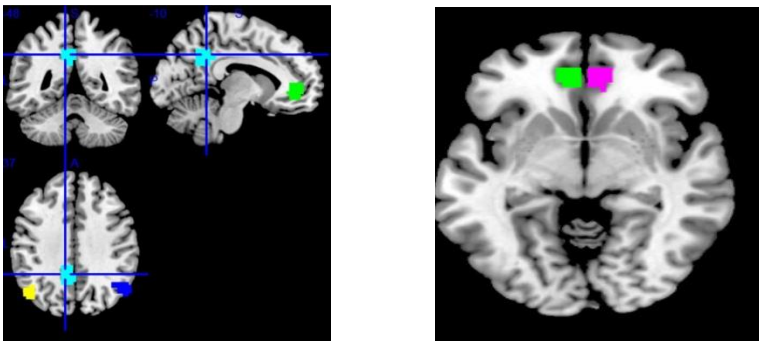

Figure 3. Shows the seed based regions of interest (ROI) assessed in this study. Angular Gyrus (yellow and blue), Posterior Cingulate Gyrus (Light blue), and the Medial prefrontal cortex right and left (green and pink).

Statistical Analyses

Statistical analyses were conducted using SPSS 23 to test differences in connectivity patterns within the default mode network, and affective mood measures between groups. An independent sample t-test was conducted to compare affective mood scores between ayahuasca users and the control group, using a significant threshold of $p < .05$.

Prior to the comparisons between groups on connectivity and moods, we tested the potential nuisance covariate effects from gender, handedness, DVARS, and sleepiness. The age of the participant was also checked to exclude any possible confounding aging effects; previous research suggests nonlinear changes in the DMN connectivity over one's lifespan (Staffaroni et al., 2018 & Sala-Llonch, Bartrés-Faz, & Junqué 2015).

A multivariate analysis of covariance (MANOVA) was conducted to test the effect of group membership on connectivity between pairs of ROI's. Specifically, group membership, ayahuasca users and controls, was the independent variable, and pairs of connectivity as the dependent variable. Significance threshold for analysis was placed at $p<.05$.

A multivariate analysis of covariance (MANCOVA) was conducted to test effect of group membership on connectivity between pairs of ROI's or three-way interaction on connectivity between pairs of ROI, while using sleepiness as a covariate. Group membership,

ayahuasca users or controls, was a fixed factor, pairs of connectivity as the dependent variable, and sleepiness as a covariate. Significance threshold for analysis was placed at $p<.05$.

Using a significance threshold of $p< .05$, a bivariate correlation was computed to examine the relationship between affective mood scores and connectivity between pairs of ROI.

A multivariate analysis of variance (MANOVA) was conducted to test effect of group membership on mood. Mood analysis was conducted in an effort to corroborate the differences found from the larger study in Barbosa et al, (2016). Precisely, using group membership, ayahuasca users or controls as the independent variable, and affective mood scores as the dependent variable. Significance threshold for analysis was placed at $p<.05$.

Additional analysis was done using analysis of covariance (ANCOVA) to assess the relationship between sleepiness and the correlation between the right medial prefrontal cortex with the right angular gyrus, using group membership as a factor.

Results:

Psychological assessments:

Participants recorded their feelings towards each affective mood on a scale of 1 to 5, ranged from very slightly/not at all (1), a little (2), moderately (3), quite a bit (4), and extremely (5) (PANAS-X, 1994). Ayahuasca users tend to show higher scores on all positive measures than controls; however, with the exclusion of participants our sample showed no significant differences. After including all excluded participants, serenity showed a significant difference between groups, results of the t-test are shown in **Table 3.** Serenity showed significantly higher scores for ayahuasca users ($M=11.90$, $SD=1.65$) than controls ($M=10.06$, $SD= 2.67$); $t (23.82) =2.41$, $p=.024$.

Table 3: t-Test Results comparing Positive Affective Mood scores

Group	*N*		*M*	*SD*	*T-Value*	*P-Value*
General Positive Affect	Ayahuasca	20.00	31.60	5.45	***T*=** 1.06	***P* <** 0.296
	Controls	16.00	29.63	5.66		
Joviality	Ayahuasca	20.00	26.40	4.81	***T*=** 1.49	***P* <** 0.145
	Controls	16.00	23.38	7.31		
Self-Assurance	Ayahuasca	20.00	14.55	2.91	***T*=** 0.22	***P* <** 0.831
	Controls	16.00	14.25	4.92		
Attentiveness	Ayahuasca	20.00	13.95	2.39	***T*=** 1.48	***P* <** 0.147
	Controls	16.00	12.75	2.44		
Serenity	Ayahuasca	20.00	11.90	1.65	***T*=** 2.41	* ***P* <** 0.024
	Controls	16.00	10.06	2.67		
Surprise	Ayahuasca	20.00	4.75	2.05	***T*=** 0.81	***P* <** 0.423
	Controls	16.00	4.25	1.53		
Note: N: Number of participants, M: Mean, SD: Standard deviation; P-value t-Test results; * p<.05						

Table 3. represents the statistical t-test results comparing the mean scores for ayahuasca users and controls on positive affective mood.

As for the negative outlooks our sample without exclusion and with exclusions both showed significant differences between groups, see **Table 4.** Ayahuasca users tend to show lower negative scores than controls on all factors except for shyness. Specifically, there were significant differences found in the following measures: fear in ayahuasca users (M=6.6, SD=.99) and controls (M=8.69, SD= 2.96) conditions; t(17.72)=-2.7, p=.015, sadness in ayahuasca users (M=5.45, SD=.94) and controls (M=8.13, SD= 3.69) conditions; t(16.58)=-2.83, p=.012, guilt in ayahuasca users (M=6.20, SD=.52) and controls (M=9.50, SD= 4.13) conditions; t(15.39)=-3.18, p=.006, hostility in ayahuasca users (M=6.15, SD=.37) and controls (M=8.19, SD= 2.81) conditions; t(15.40)=-2.88, p=.011, and general negative affective outlooks total in ayahuasca users (M=10.75, SD=.97) and controls (M=15.44, SD= 4.50) conditions; t(16.11)=-4.09, p=.001.

Table 4: t-Test Results comparing Negative Affective Mood scores

Group	*N*		*M*	*SD*	*T-Value*	*P-Value*
General Negative Affect	Ayahuasca	20	10.75	0.97	***T*= -4.09**	***P* < 0.001**
	Controls	16	15.44	4.5		
Fear	Ayahuasca	20	6.6	0.99	***T*= -2.70**	***P* < 0.015**
	Controls	16	8.69	2.96		
Sadness	Ayahuasca	20	5.45	0.94	***T*= -2.83**	***P*< 0.012**
	Controls	16	8.13	3.69		
Guilt	Ayahuasca	20	6.2	0.52	***T*= -3.18**	***P* < 0.006**
	Controls	16	9.5	4.13		
Hostility	Ayahuasca	20	6.15	0.37	***T*= -2.88**	***P* < 0.011**
	Controls	16	8.19	2.81		
Shyness	Ayahuasca	20	4.7	1.26	***T*= -1.63**	***P* < 0.117**
	Controls	15	5.6	1.84		
Fatigue	Ayahuasca	20	9.3	3.63	***T*= -4.09**	***P* > 0.001**
	Controls	16	8.31	3.16		
Note: N: Number of participants, M: Mean, SD: Standard deviation; P-value t-Test results; * p<.05						

Table 4. represents the statistical t-test results comparing the mean scores for ayahuasca users and controls on negative affective mood.

After checking for nuisance covariate effects of gender, handedness, head movement (DVARS), and age, results revealed that there were no significant effects of these measures on connectivity or mood. However, a positive Pearson correlation was found between sleepiness and the connectivity pair, the right medial prefrontal cortex and the right angular gyrus; **Figure 4** shows this result.

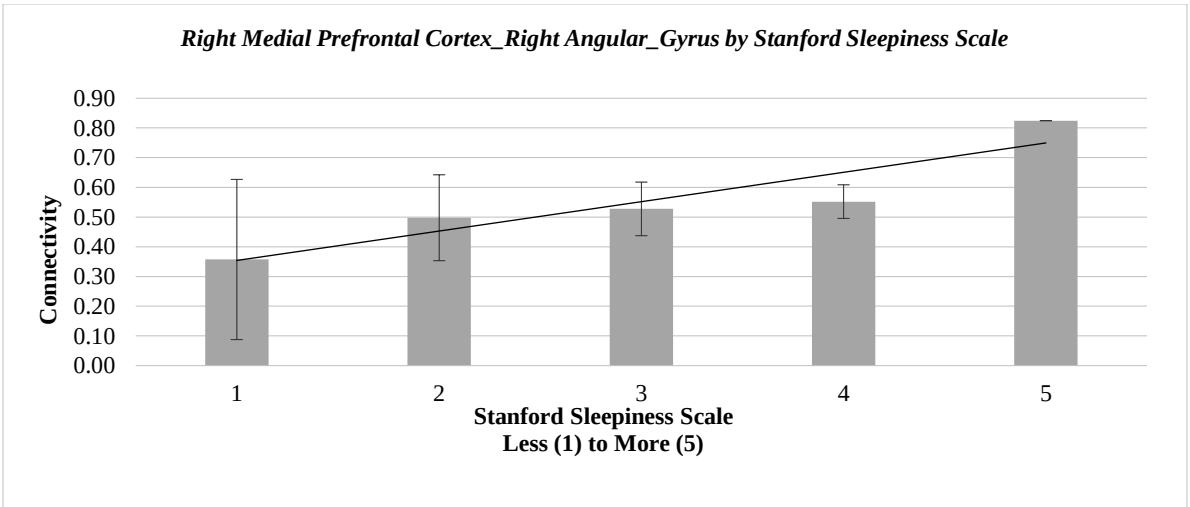

Figure 4 shows a positive relationship between Sleepiness on the Right Medial Prefrontal Cortex and the Right Angular Gyrus pair of connectivity, r = 0.429, n = 25, p = 0.032.

Results of the MANOVA examining group effects on connectivity are shown in **Figure 5**. The MANOVA revealed that there was no significant effect of group membership on any of the pairs of connectivity.

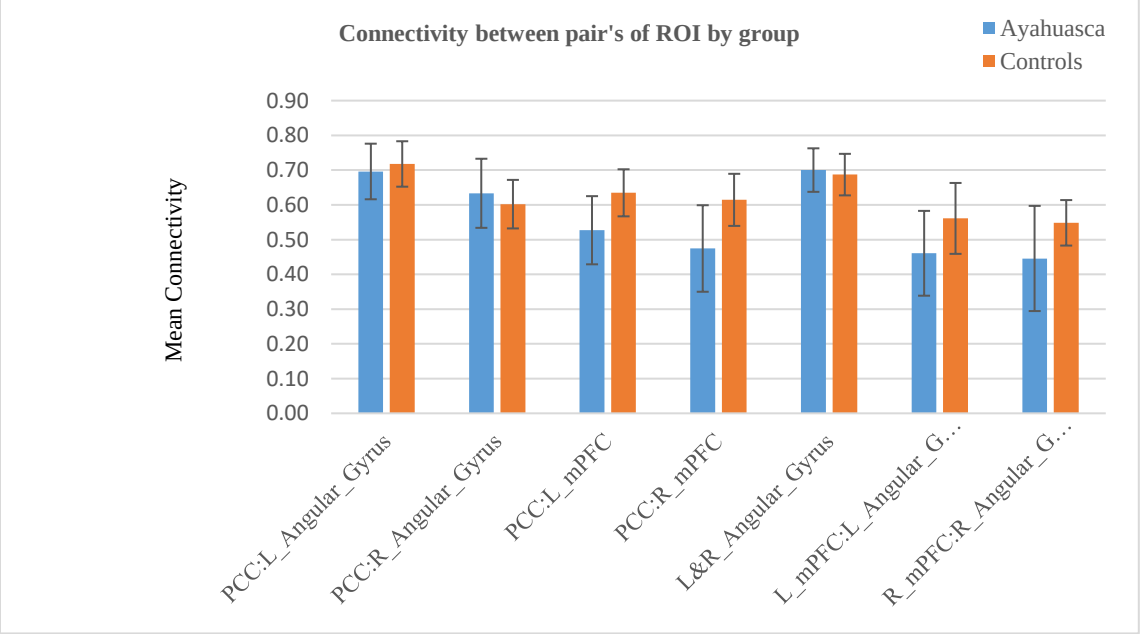

Figure 5. represents means of connectivity pairs between groups, significant threshold p <.05.

For the purpose of completeness, all MANOVA values of connectivity pairs showing no effects of group differences presented **in Figure 5** above, are shown in **Table 5** below**.**

Table 5: MANOVA statistical results of connectivity pairs from **Figure 5**.

Posterior Cingulate Cortex_ Left Angular Gyrus	F (1, 21) =.21 p< .65
Posterior Cingulate Cortex_Right Angular Gyrus	F (1, 21) =.24 p< .63
Posterior Cingulate Cortex_Left Medial Prefrontal Cortex	F (1, 21) =2.94 p< .10
Posterior Cingulate Cortex_Right Medial Prefrontal Cortex	F (1, 21) =3.51 p< .08
Left & Right Angular Gyrus	F (1, 21) =.07 p< .80
Left Medial Prefrontal Cortex_Left Angular Gyrus	F (1, 21) =1.36 p< .26
Right Medial Prefrontal Cortex_ Right Angular_Gyrus	F (1, 21) =1.43 p< .25

Table 5: represents the MANOVA statistical output for each connectivity pair from **Figure 5**. No significant differences are present.

The MANCOVA results revealed there were no significant effects on connectivity within the ROI's or three-way interaction between connectivity within the ROI's, and membership group while using head movement as a covariate. However, as expected there was a significant effect of sleepiness, shown in **Table 6**.

Table 6. MANCOVA results of covariates on connectivity

Covariates				
Source		df	F	Sig.
Sleepiness	Posterior Cingulate Cortex_ Left Angular Gyrus	1	0.08	0.77
	Posterior Cingulate Cortex_Right Angular Gyrus	1	0.39	0.54
	Posterior Cingulate Cortex_Left Medial Prefrontal Cortex	1	0.12	0.73
	Posterior Cingulate Cortex_Right Medial Prefrontal Cortex	1	1.33	0.26
	Left & Right Angular Gyrus	1	0.40	0.53
	Left Medial Prefrontal Cortex_Left Angular Gyrus	1	0.55	0.47
	Right Medial Prefrontal Cortex_ Right Angular_Gyrus	1	4.96	***** 0.04
Mean_head movement (DVARS)	Posterior Cingulate Cortex_ Left Angular Gyrus	1	1.26	0.27
	Posterior Cingulate Cortex_Right Angular Gyrus	1	1.84	0.19
	Posterior Cingulate Cortex_Left Medial Prefrontal Cortex	1	0.22	0.64
	Posterior Cingulate Cortex_Right Medial Prefrontal Cortex	1	0.00	0.97
	Left & Right Angular Gyrus	1	1.77	0.20
	Left Medial Prefrontal Cortex_Left Angular Gyrus	1	0.25	0.63
	Right Medial Prefrontal Cortex_ Right Angular_Gyrus	1	2.00	0.17
Note: df: degrees of freedom over 22; F: MANCOVA results; * p< .05				

Table 6: represents the MANOVA results on each connectivity pair in association with sleepiness and head movement (DVARS).

There was a significant positive relationship between sleepiness and connectivity between the right medial prefrontal cortex and the right angular gyrus. Ayahuasca users tend to show greater increases on connectivity in this pair of ROI than controls; results are shown in **Figure 6.**

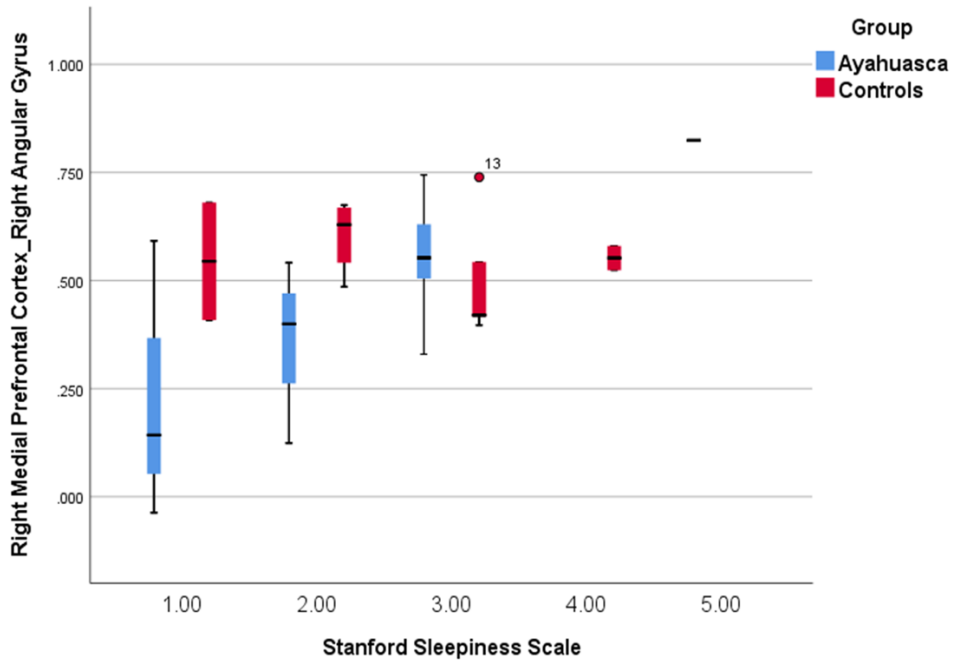

Figure 6. ANOVA test between subjects show a main effect of sleepiness on the right medial prefrontal cortex (p = .037).

Discussion

We hypothesized that there would be significant differences found between ayahuasca users and the controls, based on previous studies (Bouso et al., 2015 & Palhano-Fontes et al., 2015). Specifically, we expected to see a decrease in connectivity in the default mode network for long-term ayahuasca users. According to the results found in this study, there were no significant differences on connectivity between any pair of regions based on gender, age, and head movement. Compellingly, despite our subjects being continual users of ayahuasca for several years, there were also no significant results found between groups on connectivity in any pair of regions. These findings are inconsistent with Palhano-Fontes et al., 2015 results stating a decrease on connectivity in the DMN during acute administration of ayahuasca in consistent monthly users for at least 5 years. However, unlike our present study, Palhano-Fontes et al., 2015 did not use a control group to compare connectivity results.

Several ROI's in this study exhibited the possibility of significant findings with an increased sample size, shown in **Table 7.** In order to asses the possible type II error in this study, the mean scores of ayahuasca and controls for each connectivity pair and the standard deviations were calculated using power analysis (Brant, n.d.; Rosner, 2011). The sample sizes needed are predicted based on using the desired power of 0.80, or an 80% chance of seeing a significant effect. The measure with the largest effect size was the connectivity between the posterior cingulate cortex and the right medial prefrontal cortex, having twice our current sample would produce significant effects, if the estimates in the current study are reliable. This is in contrast to the connectivity between the posterior cingulate cortex and the left angular gyrus, for example, which would need over 1300 participants to possibly see a significant difference.

Table 7: Represents the estimated Cohen's d and needed sample sizes

Connectivity Regions	**Estimated Cohen's d**	**Sample Size needed**
Posterior Cingulate Cortex_Right Medial Prefrontal Cortex	*d=.74*	29 participants each group
Posterior Cingulate Cortex_Left Medial Prefrontal Cortex	*d=.67*	36 participants each group
Left Medial Prefrontal Cortex_ Left Angular Gyrus	*d=.50*	63 participants each group
Right Medial Prefrontal Cortex_ Right Angular Gyrus	*d=.55*	63 participants each group
Posterior Cingulate Cortex_Right Angular Gyrus	*d= -.20*	393 participants each group
Posterior Cingulate Cortex_Left Angular Gyrus	*d=.15*	664 participants each group
Left and Right Angular Gyrus	*d= -.09*	1900 participants each

Table 7 represents the estimated Cohen's d and needed sample sizes for significant findings from our current data, from the connectivity of each pair of regions to show a group effect.

Connectivity involving the posterior cingulate and the right and left medial prefrontal cortex, the anterior and posterior regions of the default mode network, tend to show the largest effects in connectivity, specifically showing hypo connectivity in ayahuasca users in these regions (see figure 3). Possibilities could support the found effects that acute ayahuasca administration has on visual hallucinations, self reflection, and imagery (Riba et al., 2001b), all effects most commonly associated with the posterior cingulate cortex and the medial prefrontal cortex (Raichle et al., 2001).

Even though differences have been found in acute administration (Palhano-Fontes et al., 2015), structurally (Bouso et al.., 2015), and potentially long term based on this study, these differences have been suggested to enhance cognitive abilities and not impair them (Bouso et al., 2012). However, caution should be placed on ayahuasca use, as previous studies have stated, it can be potentially dangerous when mixed with other SSRI's (Callaway & Grob, 1998; dos Santos, 2013; Halpern et al., 2008). Too much serotonin can induce serotonin syndrome, which symptoms include confusion, tremors, loss of consciousness, and possibly death (Callaway et al., 1998). Ayahuasca has also been found to induce psychotic states during acute administration, but might possibly have long lasting effects for participants who are susceptible to psychotic imbalances in their system. (dos Santos, 2013). These type of risk should be considered when using ayahuasca.

Interestingly, all subjects showed an increase in connectivity in the right medial prefrontal cortex associated with sleepiness; however, ayahuasca users showed greater increases. There have been studies with similar findings with ours, stating that the DMN increases during rest (Buckner, Andrews-Hanna, & Schacter, 2008), which is associated with mind wandering, and discontinuity of the mind, which correlates with sleepiness (Stoffers et al., 2015). Ayahuasca

users may show greater increases, due to the fact that they were up for most of the previous night for their ritual. Previous studies have reported sleep disturbances being common the night following administration (Barbanoj et al., 2008).

Moreover, in efforts to corroborate Barbosa et al, (2015), ayahuasca users did demonstrate higher scores on negative mood assessments, such as fear, sadness, guilt, hostility, and fatigue. These findings are consistent with multiple previous studies concluding enhanced spirituality and positive outlooks on life (Busto et al., 2012, 2015; & Barbosa et al., 2015). These findings are also consistent with previous studies reporting a decrease in depression (Osório et al., 2015), and anxiety (dos Santos et al., 2016); which are states positively correlated with negative moods.

Parallel with those findings, no significant differences were found on the PANAS-X scores regarding any of the positive affective outlooks. The collective beliefs of the UDV religion is possibly the predominate factor into why we do not see a difference between groups in positive measures. These findings differ from that of Barbosa et al, (2015) who reported ayahuasca users having significantly higher scores than controls on positive assessments; however, our study used only a subset of that data, and our results do show ayahuasca users generally scored higher on these measures, though it was not significant. Another factor in the inconsistent findings is possibly due to the different types of assessments reported. Specifically, Barbosa et al, (2015) used the Big Five assessment which generalizes overall personality traits such as agreeableness and openness, where as this study choose to use a mood assessment, the PANAS-X, which for example scales the participant's current mood such as, alert and happy.

Furthermore, our results do not show any significant difference in ROI's connectivity associated with mood. These results are inconsistent to previous studies, finding that increases in

DMN functional connectivity is related to reduced levels of happiness (Luo et al., 2016). Knowing that assessment on functional connectivity (Luo et al., 2016) and the findings of decreases in the DMN connectivity during acute administration of Ayahuasca (Palhano-Fontes et al., 2015), one would expect to see a significant relationship of connectivity on mood in this study.

Limitations:

In addition, there are two limitations to report in this study. One limitation is our small sample size due to multiple exclusions; our sample size consisted of 12 ayahuasca users and 13 religious belief matched controls. Further research should look into obtaining at least 30 to 60 participants in each group when assessing connectivity. Moreover, this study is also vulnerable to selection bias, in regards to positive and negative mood assessments. Reported weekly church attendance is centered around spiritual and religious enlightenment (Schultes, Hofmann & Rätsch, 2001), which involves one's since of hope, joy, and assurance in life. Future studies might look at comparing religious users to those who do not attend church regularly.

Conclusion

In conclusion, our results indicated that there are no significant differences on connectivity in the default mode network between long term ayahuasca users and controls. However, consideration should be placed on the possible significant hypo connectivity effects in ayahuasca users, if the sample sizes were increased. In this study the decrease in negative outlooks could possibly correlate with connectivity decreasing in the DMN in larger studies. Specifically, the areas that have the potential to show these significant differences deal with the posterior and anterior parts of the brain, areas that are most commonly known to deal with introspection and problem solving (cited in Palhano-Fontes et al., 2015). Based on this study and

comparisons of others, ayahuasca use shows evidence of positively regulated moods by decreasing activity in the posterior and anterior default mode networks. These results can be further examined to assess the effects of long term use of ayahuasca.

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