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ORIGINAL INVESTIGATION

Acute effects of ayahuasca on neuropsychological performance: differences in executive function between experienced and occasional users

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Abstract
Background Ayahuasca, a South American psychotropic plant tea containing the psychedelic 5-HT_{2A} receptor agonist *N*,*N*-dimethyltryptamine, has been shown to increase regional cerebral blood flow in prefrontal brain regions after acute administration to humans. Despite interactions at this level, neuropsychological studies have not found cognitive deficits in abstinent long-term users.
Objectives Here, we wished to investigate the effects of acute ayahuasca intake on neuropsychological performance, specifically on working memory and executive function.
Methods Twenty-four ayahuasca users (11 long-term experienced users and 13 occasional users) were assessed in their habitual setting using the Stroop, Sternberg, and Tower of London tasks prior to and following ayahuasca intake.
Results Errors in the Sternberg task increased, whereas reaction times in the Stroop task decreased and accuracy was maintained for the whole sample following ayahuasca intake. Interestingly, results in the Tower of London showed significantly increased execution and resolution times and number of movements for the occasional but not the experienced users. Additionally, a correlation analysis including all subjects showed that impaired performance in the Tower of London was inversely correlated with lifetime ayahuasca use.
Conclusions Acute ayahuasca administration impaired working memory but decreased stimulus–response interference. Interestingly, detrimental effects on higher cognition were only observed in the less experienced group. Rather than leading to increased impairment, greater prior exposure to ayahuasca was associated with reduced incapacitation. Compensatory or

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neuromodulatory effects associated with long-term ayahuasca intake could underlie preserved executive function in experienced users.

Keywords Psychedelics · Ayahuasca · Neuropsychology · Executive functions

Introduction

Drugs inducing transient modified states of consciousness are receiving renewed attention as models of disease and also as potential therapeutic tools (Geyer and Vollenweider 2008; González-Maeso and Sealfon 2009a; Vollenweider and Kometer 2010). Serotonergic psychedelics containing the tryptamine moiety such as psilocybin (4-hydroxy-*N*,*N*-dimethyltryptamine) and *N*,*N*-dimethyltryptamine (DMT) have been shown to act as serotonin (5-HT) 2A/1A/2C receptor agonists, with their behavioral effects most likely related to activation of the 5-HT_{2A} receptor sites (González-Maeso and Sealfon 2009b; Halberstadt et al. 2011; Vollenweider et al. 1998). Because of the profound impact of psychedelics on thought processes, their recently uncovered capacity to stimulate intrinsic activity within the prefrontal cortex and the similarities between the subjective effects they induce and endogenous psychoses (Béïque et al. 2007; Geyer and Vollenweider 2008; Gouzoulis-Mayfrank et al. 1998a; Vollenweider and Kometer 2010; Carhart-Harris et al. 2012a), psychedelics are being proposed as tools to investigate the role of 5-HT_{2A} receptors in higher cognitive function (Gouzoulis-Mayfrank et al. 1998b; Studerus et al. 2011; Vollenweider et al. 2007).

Performance of the most complex aspects of human cognition relies on the adequate functioning of prefrontal and other cortico-subcortical networks involved in cognitive control. Sophisticated neuropsychological skills such as working memory and executive functions, which are responsible for performance monitoring, set-shifting, planning, error detection, and inadequate response inhibition, are subserved by these networks (Miller and Cohen 2001). 5-HT_{2A} receptors are highly expressed in pyramidal cells of the prefrontal cortex (Hannon and Hoyer 2008). Most glutamatergic neurons in layers II-V express 5-HT_{2A} receptors (86–100 %), with a maximum (almost 100 %) in layers III and V (de Almeida and Mengod 2007). Serotonergic modulation of neural activity in the prefrontal cortex (Robbins and Arnsten 2009) is involved in performance monitoring (Jocham and Ullsperger 2009), working memory (Williams et al. 2002), response execution (Passetti et al. 2003), and executive function (Lane et al. 2008), suggesting a potential role for the 5-HT_{2A} receptors in these processes.

Studies in animals have shown that 5-HT_{2A} receptor activation induces excitatory postsynaptic potentials in the frontomedial cortex (Aghajanian and Marek 1997), an effect mediated by glutamate release (Klodzinska et al. 2002). Using electrophysiological recordings of brain slices, Béïque et al. (2007) identified a subpopulation of layer V neurons in the prefrontal cortex that are excited and depolarized following psychedelic drug administration. The authors showed that the 5-HT_{2A} facilitates intrinsic network activity independently from thalamocortical afferents. In line with these data, neuroimaging studies using SPECT and PET have found patterns of frontal hyperactivity in humans after administration of mescaline (Hermle et al. 1992), psilocybin (Gouzoulis-Mayfrank et al. 1999a; Vollenweider et al. 1997), and the DMT-containing preparation ayahuasca, described below (Riba et al. 2006). A recent study using magnetic resonance imaging has corroborated the involvement of the medial prefrontal/anterior cingulate cortex in the effects of psychedelics (Carhart-Harris et al. 2012b). Studies in humans on the acute effects of psychedelics on various cognitive tasks have shown that these compounds can disrupt sustained attention (Hasler et al. 2004; Heekeren et al. 2008; Umbricht et al. 2003), whereas contradictory results have been obtained regarding their capacity to alter spatial working memory (Carter et al. 2005a; Vollenweider et al. 1998; Wittmann et al. 2007).

In a recent investigation, we assessed neuropsychological performance in a large sample of long-term ayahuasca users. This DMT-containing plant decoction is typically obtained by boiling together the stems of the vine *Banisteriopsis caapi* and the leaves of *Psychotria viridis* (Riba 2003). The resulting tea contains β-carboline alkaloids with monoamine oxidase-inhibiting properties that block the metabolic breakdown of the labile DMT and render it orally active. The acute subjective effects of ayahuasca are characterized by changes in the conscious state, which include perceptual modifications in the visual, auditory, and tactile spheres. Visions with eyes closed are frequently accompanied by intense emotions and increased rate of thinking. These effects start after 45–60 min after administration, reaching their maximum intensity between 90–120 min and return to baseline after 4–6 h (Riba et al. 2001; Riba et al. 2003; dos Santos et al. 2011; dos Santos et al. 2012). The overall pattern of effects is in line with that of other serotonergic psychedelics, such as mescaline (Hermle et al. 1992), intravenous DMT (Strassman et al. 1994), and psilocybin (Gouzoulis-Mayfrank et al. 1999b). In the long-term user study, we tested a sample of 127 ritual ayahuasca users who were drug-free following a period of abstinence from the drug and compared it with 115 controls. Interestingly, the long-term users scored better than the controls on the Stroop test, the Wisconsin Card Sorting test, and the Letter–Number Sequencing task of the WAIS-III (Bouso et al. 2012). Thus, despite the fact that the prefrontal cortex is a key region targeted by psychedelics, chronic use of ayahuasca was not associated with specific impairment using these neuropsychological tests.

In the present study, we wished to investigate the acute effects of ayahuasca on neuropsychological performance, specifically on working memory and executive function tasks that are subserved by cognitive control networks. As explained below, we administered a battery of neuropsychological tests before and during the acute effects of ayahuasca. Given the lack of detrimental effects observed in our previous study in abstinent long-term users, we also wished to explore the role of prior experience with ayahuasca in the degree of impairment observed. We postulated that experienced users would be more able to correctly perform the neuropsychological tasks than their less experienced counterparts.

Materials and methods

Participants and study procedure

Twenty-four individuals (12 female) participated in the study. To assess the role of prior ayahuasca use in current neuropsychological performance after acute ayahuasca intake, participants were classified as either experienced or occasional users (see Results section below). Based on the typical pattern of ayahuasca use of twice a month or more practiced by regular ayahuasca users, we defined an occasional user as a person who had taken ayahuasca between 8 and 60 occasions (once every 3 weeks in the past 3 years). Participants exceeding this value were considered experienced users. All participants had abstained from ayahuasca for at least 15 days before the first of two experimental sessions, i.e., the pre-ayahuasca assessment and the subsequent retest 24 h later in the course of an ayahuasca session (post-ayahuasca assessment). Participants were evaluated in the same setting, where they usually took ayahuasca. Urine samples were collected to exclude subjects testing positive for other psychoactive drugs and/or alcohol. Years of education were recorded for each participant as were their scores on verbal and fluid IQ tests. The verbal IQ test used was a Spanish version of the NART (Nelson and O'Connell 1978) known as TAP—"Test de Acentuación de Palabras" (Word Accentuation Test) (del Ser et al. 1997). The fluid IQ test used was a computerized version of the matrix reasoning from the WAIS-III (Wechsler 1997). All participants signed an informed consent prior to participation. The study was approved by the ethics committee at Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

The ayahuasca-taking session started at 12:00 noon, and all subjects took a single oral dose of ayahuasca in a glass containing about 100 ml of the tea. Presence of DMT and other typical ayahuasca alkaloids was later confirmed by thin layer chromatography. Two hours after ayahuasca intake, coinciding with the reported time-window of maximum effects (dos Santos et al. 2011; dos Santos et al. 2012; Riba et al. 2002; Riba et al. 2003; Riba et al. 2006), participants were assessed in a separate and quiet room. Computerized tasks were executed on portable computers under the supervision of one of the authors (JR), while another author (JCB) administered the noncomputerized test (see below). Immediately before testing started, participants were asked to rate the intensity of the ayahuasca-induced subjective effects from 0 to 100.

The order of administration of the tests was counterbalanced between participants, and the total time to complete the battery was around 20 min.

Neuropsychological testing

The Sternberg working memory task

A computerized version of this verbal working memory test based on Sternberg (1966) was used. A series of consonants was shown in succession on a computer screen for 1 s. The length of each series varied between three and eight letters across trials. After each series, a fixation cross appeared on the screen for 1 s followed by the target letter. The target letter was shown on the screen until a response was given. Subjects had to indicate whether the target was present or not in the consonant series by pressing a button. The probability of the target letter having been shown in the series was set at 50 %. After each button press, feedback was given as to the correctness and speed of the response. Two initial training trials were presented followed by 42 test trials (14 trials showing series of 3 elements, 14 trials showing series of 5 elements, and 14 trials showing series of 8 elements). Trial type order was randomized. Whenever a subject gave an incorrect answer, an additional trial of the same type was presented, so that the total number of correctly responded trials was the same for all participants (42 trials). Subjects were given feedback after each of the two training trials (their reaction time in milliseconds) and were encouraged to respond in less than 2,000 ms. Reaction time (RT) for correct responses and performance quality (number of errors) was evaluated. Previous research has shown that RT and errors increase the longer the series. Overall task duration was around 10 min. Neuroanatomically, this task recruits the ventrolateral and the dorsolateral prefrontal cortex (D'Esposito et al. 2000). A recent neuroimaging study found activation in the inferior frontal and anterior cingulate regions, among others (Kirschen et al. 2010).

The Stroop color and word test

A modified computerized version of the task (Golden 1978) was used. Color names were written either in the same or a different colored ink to that denoted by the name shown on the computer screen. Participants had to press one of three different color keys: red, green, or blue according to the color of the

ink the word was written in. Each word was shown for 1 s. A total of 120 words were presented: 60 color-name congruent words and 60 color-name incongruent words. Stimuli were presented randomly, and overall task duration was 5 min. The test measures selective attention, cognitive flexibility, conflict monitoring, and resistance to interference. Performance (number of errors) and reaction time measures in compatible and incompatible conditions as well as the difference between them were computed. Neuroanatomically, this task has been associated to activation in the anterior cingulate cortex and the dorsolateral prefrontal cortex (DLPC) (Carter and van Veen 2007; Strauss et al. 2006).

The Tower of London

This task developed by Shallice (1982) measures different components of executive function such as planning, inhibition, impulsivity, and working memory (Strauss et al. 2006). Participants were requested to arrange colored beads in pegs using the least number of movements and the least time possible. Beads can be moved according to certain rules only. To reduce the total duration of the task in the post-ayahuasca assessment, subjects were required to solve only the three most difficult problems (numbers 10, 11 and 13) of the total 13 problems used in the pre-ayahuasca assessment the previous day. Target variables were latency time (i.e., time to the first movement), execution time (i.e., total time needed to solve a given problem), resolution time (i.e., the difference between total time and latency time), number of movements for each problem, and the differential number of movements (i.e., the difference between the number of movements and the stipulated minimum required to solve the problem). Neuroanatomically, the network activated during this task includes the DLPC, the anterior cingulate cortex, and parietal regions (Dockery et al. 2009; Lazaron et al. 2000; Schall et al. 2003). The test took less than 5 min to complete per participant.

Statistical analysis

Mean pre- and post-ayahuasca scores and standard deviations (SD) were calculated from individual scores for each target variable and are reported as summary statistics. Individual data were subjected to a general linear model analysis (GLM) with drug intake (pre vs. post) as a within-subjects factor and group (experienced vs. occasional) and sex (male vs. female) as between-subjects factor. Pairwise comparisons were performed using Student's *t* test (between- or within-subjects as required), and correlations with lifetime ayahuasca use were calculated using Pearson's correlation coefficient. Given the statistically significant difference in age between experienced and occasional users (see below), age was included as a covariate in the analysis. Differences were considered statistically significant for p values lower than 0.05.

Results

Demographics

Demographic data are shown in Table 1. The overall study sample consisted of 24 participants (12 women), with a mean age of 46 years (range 29–62). Experienced users (4 men and 7 women) had taken ayahuasca on an average of 179 occasions, ranging from 70 to 352. Occasional users (8 men and 5 women) had taken ayahuasca on an average of 33 occasions (from 8 to 60). Values differed significantly between groups [$t(22)=4.86$, $p=001$]. The two subgroups did not differ in years of education [$t(22)=-1.12$, $p=0.28$], and all subjects had intelligence scores in the normal range. No differences were found between the two subgroups in performance in the WAIS matrices test $t(22)=-0.34$, $p=0.74$ or in the verbal intelligence (TAP) assessment $t(22)=-0.10$, $p=0.92$. Gender distribution did not differ between groups $\chi^2(1)=1.5$, $p>0.1$. However, age was found to be significantly greater in the occasional users than in the experienced users $t(22)=-3.25$, $p=0.004$. To account for this difference as a possible confound, we used age as a covariate in the statistical analysis of scores on the neuropsychological tests.

Subjective effects and neuropsychological assessment

All participants reported having experienced intense psychotropic effects at the time of the neuropsychological assessment following ayahuasca administration. Scores for subjective effects were statistically different from zero [$t(23)=21.3$, $p<0.001$]. As shown in Table 1, mean intensity of effects was 72 for the experienced users and 77 for the occasional users. Scores were not significantly different between the two subgroups $t(22)=-0.65$, $p=0.52$.

Mean data for the neuropsychological tests and results of the statistical comparison between pre- and post-administration values are shown in Table 2.

The statistical analysis of the data from the Sternberg task by means of the GLM showed a main effect of drug (pre vs. postadministration) for total errors [$F(1,19)=8.75$, $p=0.008$]. More errors occurred under the effects of ayahuasca for the whole sample. No main effects of group (experienced vs. occasional) or sex were observed. However, we found a trend interaction between drug and group [$F(1, 19)=3.87$, $p=0.063$]. To look further at the potential differences between groups, the difference value in total errors (postadministration–preadministration) was calculated and compared between groups by means of an independent-samples *t* test. This test showed a marginally significant

Table 1 Demographic data of participants and scores on the subjective effects assessment. Data expressed as mean (standard deviation) for age, prior ayahuasca intake, years of education, score on the WAIS-III matrices (number of correct responses), and TAP ("Test de Acentuación de Palabras") for each subgroup. The intensity of subjective effects (from 0 to 100) is expressed as mean (standard deviation) for each subgroup. The *p* value column shows the result of the statistical comparison between subgroups

	Study sample		
	Experienced users	Occasional users	*P* value
Sociodemographic variables			
N (men/women)	11 (4/7)	13 (8/5)	NS
Age	40.5 (8.5)	51.0 (7.4)	$p=0.004$
Prior ayahuasca intake	179 (99)	33 (16)	$p=0.001$
Years education	13.0 (2.5)	14.5 (3.6)	NS
WAIS matrices	15.5 (3.8)	16.0 (2.8)	NS
TAP test	24.8 (4.8)	25.0 (3.7)	NS
Subjective effects			
Intensity	72.3 (17.9)	76.9 (17.0)	NS

NS not significant

effect [$t(22)=-2.07$, $p=0.051$], with a larger mean number of total errors in the occasional users than in the experienced ayahuasca users. Given the known effects of age on memory, we tested for any effects of the covariate "age". A trend interaction was observed between drug and age but did not reach statistical significance [$F(1,19)=3.6$, $p=0.073$]. No other main effects or interactions were observed for the other Sternberg variables.

The GLM analysis of data from the Stroop task showed main effects of drug (pre vs. postadministration) for reaction times in the compatible correct [$F(1,19)=4.50$, $p=0.047$] and incompatible correct trials [$F(1,19)=4.90$, $p=0.039$]. Thus, reaction times were shorter under the effects of ayahuasca. The mean number of omitted responses also decreased after ayahuasca administration, but this effect only showed a statistical trend in the analysis [$F(1,19)=3.74$, $p=0.068$]. No differences were found between groups, and no other main effects or interactions were observed for the rest of the Stroop variables. No effects were observed for the covariate "age" in the analysis.

Table 2 Mean (SD) and results of the general linear model analysis of scores on the neuropsychological tests. *P* values for the main effect of drug (post vs. predrug) and for the interaction between drug and group (experienced vs. occasional users). Reaction times in the Sternberg and Stroop tests are in milliseconds. Times in the Tower of London test are given in seconds

Neuropsychological tests	Experienced users $n=11$		Occasional users $n=13$		Drug	Drug × group
Sternberg	Predrug	Postdrug	Predrug	Postdrug	*P* value	*P* value
Total errors	6.72 (3.9)	7.27 (5.7)	5.92 (3.2)	10.38 (5.2)	0.008	0.063
Errors 3 elements	0.73 (1.0)	0.73 (1.6)	0.31 (0.6)	1.30 (1.3)	>0.1	>0.1
Errors 5 elements	2.00 (1.9)	2.36 (2.3)	2.07 (1.6)	3.30 (2.8)	>0.1	>0.1
Errors 8 elements	4.00 (2.4)	4.18 (3.7)	3.51 (1.8)	5.77 (2.7)	0.078	>0.1
Reaction time 3 elements	737 (176)	842 (325)	817 (137)	986 (387)	>0.1	>0.1
Reaction time 5 elements	829 (185)	860 (289)	968 (149)	1054 (392)	>0.1	>0.1
Reaction time 8 elements	949 (200)	871 (260)	1074 (311)	1106 (322)	>0.1	>0.1
Stroop	Predrug	Postdrug	Predrug	Postdrug	*P* value	*P* value
% Compatible correct	97.1 (2.6)	97.9 (3.3)	94.6 (5.3)	95.3 (4.1)	>0.1	>0.1
% Compatible incorrect	1.06 (1.9)	1.51 (2.9)	1.28 (1.39)	1.67 (2.15)	>0.1	>0.1
% Incompatible correct	94.7 (6.0)	95.3 (5.8)	90.6 (10.8)	93.6 (4.0)	>0.1	>0.1
% Incompatible incorrect	3.64 (4.8)	3.48 (5.2)	5.26 (10.2)	2.05 (2.56)	>0.1	>0.1
% Omitted responses	1.36 (1.4)	0.68 (1.0)	1.28 (1.30)	0.70 (1.01)	0.068	>0.1
RT Compatible correct	634 (101)	585 (85)	672 (72)	654 (84)	0.047	>0.1
RT Incompatible correct	717 (143)	655 (106)	733 (104)	700 (75)	0.039	>0.1
RT Incompatible–compatible	82 (51)	70 (36)	61 (50)	46 (36)	>0.1	>0.1
% Errors Incompatible–compatible	2.58 (3.8)	1.97 (3.3)	3.98 (10.6)	0.38 (3.0)	>0.1	>0.1
Tower of London	Predrug	Postdrug	Predrug	Postdrug	*P* value	*P* value
M. Latency time	2.87 (1.2)	3.43 (1.8)	3.95 (2.2)	5.90 (2.3)	0.065	>0.1
M. Execution time	26.87 (16.4)	24.57 (11.4)	28.57 (10.0)	52.05 (27.6)	>0.1	0.011
M. Resolution time	24.00 (15.8)	21.27 (10.1)	24.61 (9.2)	46.15 (28.4)	>0.1	0.012
M. Number of movements	11.13 (3.4)	10.23 (2.8)	10.38 (2.2)	11.90 (3.5)	>0.1	0.034
M. Differential number of movements	4.80 (3.4)	3.90 (2.9)	4.05 (2.2)	5.56 (3.5)	>0.1	0.034

M.=mean

Data from one subject was lost for the Tower of London. Thus, the GLM was performed for 23 participants. The analysis did not show any main effects of drug (pre vs. postadministration). However, significant interactions between drug and group (experienced vs. occasional) were found for mean execution time [F(1, 19)=8.10, p=0.011], mean resolution time [F(1,19)=7.89, p=0.012], mean number of movements [F(1,19)=5.26, p=0.034], and mean differential number of movements [F(1,19)=5.28, p=0.034]. No other main effects or interactions were observed for the rest of the Tower of London variables, and again no effects were observed for the covariate "age" in the analysis.

Given the differences found between groups in the Tower of London, a correlational analysis was conducted between variables in this test (the difference between post and preadministration values) and lifetime ayahuasca use. The number of lifetime ayahuasca sessions for each participant was transformed to the natural logarithm to correct for the skewed nature of their distribution. The log-transformed values showed statistically significant negative correlations with the difference values (postdrug–predrug) for mean execution time (r=−0.607, p=0.002), mean resolution time (r=−0.588, p=003), mean number of movements (r=−0.482, p=0.020), and mean differential number of movements (r=−482, p=0.020). The corresponding scatter plots are shown in Fig. 1.

To rule out any confounds associated with age, partial correlations were calculated controlling for this variable. Effects were maintained in all four instances: mean execution time (r=−0.618, p=0.002), mean resolution time (r=−0.606, p=003), mean number of movements (r=−0.565, p=0.006), and mean differential number of movements (r=−0.566, p=0.006).

Control experiment

A control experiment was conducted to assess the influence of practice in the performance of the administered tasks. The same three tests used in the main study were administered twice with a 2 h interval to a sample of 10 drug-naive individuals (7 women) with a mean (SD) age of 40.1(9.4)years, 12.3(2.5)years of education, a 15.7 (3.1) score on the WAIS matrices, and 25.1 (3.8) on the TAP test. No statistical differences were found between the control group and the two main study samples for any of the demographic variables assessed, except age, which was significantly lower than that of the occasional user group [t(21)=3.1, p=0.005].

Mean data for the neuropsychological tests and results of the statistical comparison (Student's t-test) between pre- and post-administration values for the control sample are shown in Table 3.

No statistically significant differences were observed between the first and the second assessment for any of the variables of the Sternberg or Tower of London tasks. In the Stroop test, difference in errors (incompatible–compatible conditions) showed a trend increase at retest.

Thus, no evidence was found of learning effects improving performance at retest in the absence of drug administration.

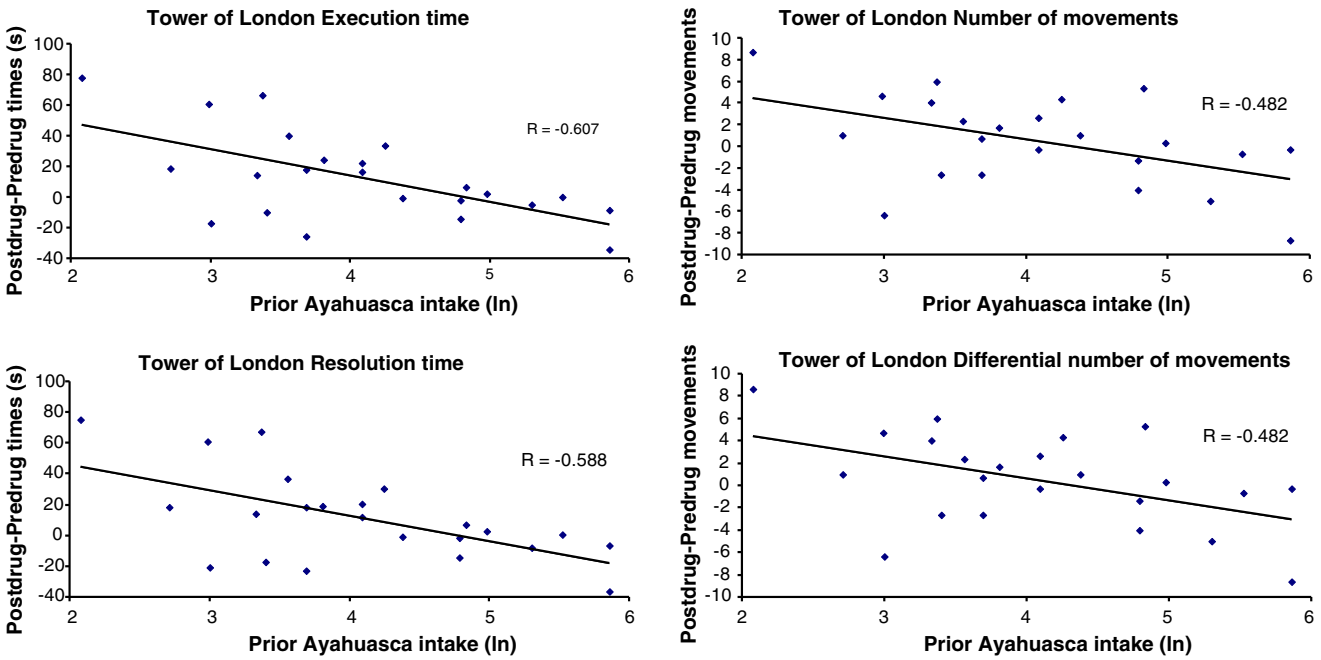

Fig. 1 Scatter plots showing the negative linear relationship found between lifetime ayahuasca use and performance in the Tower of London. The natural logarithm (*ln*) of lifetime ayahuasca use was used in the correlation. n=23 participants

Table 3 Descriptive statistics (mean (SD)) and results of the test–retest statistical analysis of scores for the control group. Reaction times in the Sternberg and Stroop tests are in milliseconds. Times in the Tower of London test are given in seconds n=10

Neuropsychological tests	First assessment	Second assessment	Second vs. first *T* value	Second vs. first *P* value
Sternberg				
Total errors	7.20 (4.9)	7.50 (4.1)	−0.17	>0.1
Errors 3 elements	1.10 (1.4)	1.00 (1.1)	0.32	>0.1
Errors 5 elements	3.00 (2.1)	2.40 (2.0)	0.65	>0.1
Errors 8 elements	3.10 (2.8)	4.10 (2.1)	−0.90	>0.1
Reaction time 3 elements	760 (147)	814 (296)	−0.59	>0.1
Reaction time 5 elements	941 (245)	921 (300)	0.17	>0.1
Reaction time 8 elements	966 (236)	941 (282)	0.37	>0.1
Stroop	First assessment	Second assessment	*T* value	*P* value
% Compatible correct	91.0 (6.9)	90.0 (7.2)	0.33	>0.1
% Compatible incorrect	3.50 (3.8)	3.50 (3.1)	0.001	>0.1
% Incompatible correct	85.83 (10.5)	82.70 (9.6)	0.67	>0.1
% Incompatible incorrect	6.0 (5.7)	9.17 (5.6)	−1.46	>0.1
% Omitted responses	2.92 (3.9)	3.17 (4.6)	−0.12	>0.1
RT Compatible correct	638 (123)	607 (130)	0.71	>0.1
RT Incompatible correct	694 (140)	699 (190)	−0.97	>0.1
RT Incompatible–compatible	54 (39)	92 (90)	−1.46	>0.1
% Errors incompatible–compatible	2.50 (3.1)	5.7 (5.2)	−2.01	0.076
Tower of London	First assessment	Second assessment	*T* value	*P* value
M. Latency time	6.93 (2.8)	6.57 (3.7)	0.26	>0.1
M. Execution time	38.00 (16.2)	30.2 (6.7)	1.31	>0.1
M. Resolution time	31.06 (17.0)	23.7 (5.7)	1.20	>0.1
M. Number of movements	10.63 (3.1)	10.23 (1.6)	0.33	>0.1
M. Differential number of movements	4.30 (3.1)	3.90 (1.6)	0.33	>0.1

M.=mean

Discussion

In the present study, we found that acute ayahuasca intake led to a disruption of verbal working memory (Sternberg task), with a trend towards higher impairment in the occasional users, whereas stimulus–response interference was decreased. Speed in the Stroop task was increased, and importantly, subjects did not respond more impulsively and inaccurately. Mean values of incorrectly answered incompatible stimuli were lower after ayahuasca in both participant groups and the percentage of omitted responses showed a statistical trend to decrease. Higher cognition, as measured by the Tower of London, was selectively affected in the occasional ayahuasca users but not in the experienced subgroup.

Prior research on the cognitive effects of psychedelics has found disruptions of spatial working memory after psilocybin in some studies (Vollenweider et al. 1998; Wittmann et al. 2007) but not in others (Carter et al. 2005a). Psilocybin (Umbricht et al. 2003) and DMT (Heekeren et al. 2008) consistently impaired performance in sustained attention (Hasler et al. 2004), visual–spatial attention (Carter et al. 2005a; Gouzoulis-Mayfrank et al. 2002), and alertness (Daumann et al. 2010). Psychedelic tryptamines are known to disrupt processes such as binocular rivalry (Carter et al. 2005b; Carter et al. 2007; Frecska et al. 2004), global motion perception (Carter et al. 2004), time perception and temporal control (Wittmann et al. 2007), time interval reproduction (Wackermann et al. 2008), model object completion (Kometer et al. 2011), and inhibition of return (Daumann et al. 2008; Gouzoulis-Mayfrank, et al. 2006). However, not all studies show detrimental effects. Whereas the mismatch negativity was found to be blunted after DMT (Heekeren et al. 2008), it was not after psilocybin (Umbricht et al. 2003). Also, indirect semantic priming was increased after psilocybin (Spitzer et al. 1996).

The present findings show mixed effects of acute ayahuasca on neuropsychological performance. Whereas the Stroop task showed improvements, effects on the Sternberg and on the Tower of London were detrimental, although only for the less experienced users. These results raise the possibility that experienced users may have developed mechanisms to compensate for the acute impairing effects of ayahuasca on

executive function. This possibility is supported by the negative correlations found between performance in the Tower of London and lifetime ayahuasca use. Rather than increasing with previous exposure to ayahuasca, the detrimental effects of acute ayahuasca on this task were decreased. Paradoxical results have been reported for other psychoactive drugs, such as tetrahydrocannabinol (THC). Several studies have found only subtle impairments in complex cognitive performance when THC was administered to experienced marihuana users. However, these experienced subjects showed alterations in neurophysiological measures when compared to infrequent users (Hart et al. 2001; Hart et al. 2010). Daumann et al. (2008) postulated the implementation of compensatory mechanisms as an explanatory mechanism of maintained cognitive performance in inhibition of return, episodic memory, working memory, and verbal fluency after ketamine. It is worth noting that in most studies reporting acute drug-induced impairment, participants had little prior experience with the administered drug.

The observed resistance to impairment or compensatory effect could be due to various mechanisms, both psychological and neurobiological. It cannot be ruled out that tolerance to acute drug effects or mere familiarity with the modified state of awareness induced by ayahuasca could account for the observed results. However, we believe that the tolerance account is unlikely, considering that the intensity of subjective effects was not significantly different between participant subgroups. Familiarity could have played a role in the differential impairment, with experienced users becoming less distracted by the acute effects of ayahuasca while performing the neuropsychological tasks. Nevertheless, we were careful not to recruit drug naive individuals for the study. The occasional users were also familiar with the effects of ayahuasca, having consumed it on average on 33 occasions. On the other hand, recent neuroimaging studies comparing chronic cannabis users with controls show the capacity of long-term psychotropic drug use to induce compensatory functional mechanisms. Cannabis users have been found to exhibit greater prefrontal activations when conducting attention (Abdullaev et al. 2010) and inhibition tasks (Tapert et al. 2007); and greater functional connectivity between frontal and occipitoparietal brain regions in an interference task (Harding et al. 2012). Analogous functional mechanisms could potentially be responsible for compensation in long-term psychedelic drug users.

An alternative explanation is that chronic ayahuasca intake could lead to neural changes that might help to cope with novel tasks and settings facilitating learning. Hallucinogens stimulate c-fos expression in the medial prefrontal and anterior cingulate cortices (Frankel and Cunningham 2002; Gresch et al. 2002) and dramatically increase the expression of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex (Gewirtz et al. 2002; Vaidya et al. 1997). In turn, BDNF influences synaptic efficacy and neural plasticity (Bramham and Messaoudi 2005; Soulé et al. 2006). As the Tower of London is the test with potentially larger task-related learning effects (especially considering that the same items were repeated), faster learning effects could underlie the beneficial effect observed in the experienced users, indicating better cognitive flexibility or adaptability to new task-settings or problems.

We should acknowledge several limitations of the present study. The investigation was not conducted in a laboratory but under field conditions. Furthermore, the order in which participants were tested was not balanced, and they all did the tests in the drug-free condition first. This could potentially have led to learning effects. However, this is unlikely for the Sternberg and Stroop tasks, where the stimuli are randomly presented each time the test is run. Performance in the Tower of London is more susceptible to training effects, but this was probably minimized by our using only three of the most difficult problems. Results should thus be considered preliminary. In any case, even if learning effects were present, these did not prevent us from detecting detrimental effects in working memory and a selective impairing effect in the Tower of London. It is also worth noting that the control experiment we conducted a posteriori did not show any significant learning effects from the first to the second of two consecutive assessments.

To conclude, acute administration of the psychedelic DMT-containing beverage ayahuasca led to mixed effects on neuropsychological performance, negatively affecting working memory but not stimulus–response interference. Detrimental effects on higher cognition, as measured by the Tower of London, were observed in the occasional users but not in the experienced users. Negative correlations between performance in this task and lifetime ayahuasca use do not support a priori an association between chronic use and impaired cognitive abilities. This raises the question of whether direct drug-induced neuromodulatory effects or compensatory mechanisms are present in this population. Future investigations should ideally implement neuroimaging techniques to assess brain function during the execution of cognitive tasks in long-term ayahuasca users.

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