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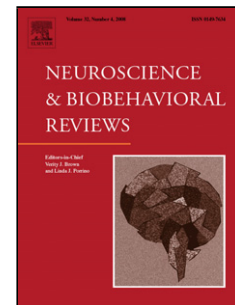


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Serotonergic psychedelics and personality: a systematic review of contemporary research

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Highlights

- Serotonergic psychedelics act as agonists at cortical 5-HT_{2A} receptors
- 5-HT_{2A} receptors are expressed in fronto-temporo-parieto-occipital areas
- Some personality traits seem to be related to 5-HT_{2A} receptor expression
- Acute and long-term use of psychedelics is associated with personality changes
- Personality changes induced by psychedelics may have therapeutic effects

Abstract

Serotonergic psychedelics act as agonists at cortical 5-HT_{2A} receptors and seem to induce personality changes. We conducted a systematic review of studies assessing the effects of these drugs on personality. Papers published from 1985 to 2016 were included from PubMed, LILACS, and SciELO databases. Three hundred and sixty-nine studies were identified, and 18 were included. Specific personality traits, such as Absorption and Self-Transcendence, seem to influence the effects of psychedelics, and psychedelic drug users and nonusers appear to differ in some personality traits. Psychedelics administered in controlled settings may induce personality changes, such as increased Openness and Self-Transcendence. Increases in global brain entropy induced by acute psychedelic administration predicted changes in Openness, and Self-Transcendence was negatively correlated with cortical thinning of the posterior cingulate cortex in long-term religious ayahuasca users. Acute and long-term use of psychedelics is associated with personality changes that appear to be modulated by 5-HT_{2A} receptors. These changes seem to induce therapeutic effects that should be further explored in randomized controlled studies.

Keywords: hallucinogens; psychedelics; personality; serotonin; 5-HT_{2A} receptor.

1. Introduction

Psychedelics are drugs that have always been surrounded by some kind of special mythic attributions related with personal and psychological change (for the better or for the worse, depending from the source of the message). If narcotics like heroin and/or psychostimulants like cocaine are associated with personal degradation, addiction and crime,¹⁻³ psychedelics are conceptualized for some as a potential inductor of madness,⁴ and for others as tools for beneficial personal change.⁵ Several studies performed in the early times of psychedelic

research reported that acute administration of these drugs induced changes on personality measures,⁶⁻⁹ although it was less clear if those changes were maintained on time. For some, the eventual long-term personal changes induced by psychedelics were classically considered as a direct consequence of their dramatic effects on the mind, which induced deep changes in the person world view that could produce long-term changes on personality.^{10,11} In fact, the meme-acting quote from the infamous guru of the 1960's psychedelic era Timothy Leary "Turn on, tune in, drop out" was referring precisely to that eventual potential power of psychedelic drugs to induce personality change, allowing youth to get liberated from the symbolic chains that attached them to a world culture based on materialism and interpersonal possessiveness. At the same time, the potential psychotherapy properties of psychedelic drugs have been classically attributed precisely to that potential for personality change that inside the context of a psychotherapeutic setting could enhance therapeutic outcomes. Psychiatrists that worked with alcoholics, neurotics, terminal patients and other clinical populations attributed the good results of their treatment to the personality changes induced by the psychedelic experiences of their patients in controlled settings.¹²

The discrepancy regarding the eventual changes on personality that could be a consequence of repeated recreational use of psychedelics was also a theme of discussion since the 1960's, when the term *acid heads* was popularized to refer precisely to some kind of special, while not aberrant, kind of personality expressed by a set of magical-mystical beliefs and profound nonaggressive attitudes that some researchers related with an intensive use of high and repeated doses of psychedelics.¹³ Other researchers asserted that such abnormal personality profile was the cause, not the consequence, of the involvement in that intensive and repeated use of psychedelics.¹⁴ These controversies persisted at least until the mid-1990's.¹⁵ **A similar dilemma between the possible consequences of drug exposure and the potential cause of drug use was also present in the debate of other drugs, such as 3,4-**

methylenedioxymethamphetamine (MDMA, “ecstasy”, “molly”): the retrospective nature of most cross-sectional studies does not allow a conclusion of whether the identified deficits (involving psychological/personality, functional and structural findings) were due to the MDMA exposure or predisposed the subjects to the MDMA abuse.¹⁶⁻¹⁸

The fact is that most of the former studies relating psychedelic drug use both in controlled and/or in uncontrolled settings with personality change were done with poor and/or unethical methodologies,¹⁹ and most of the assertions regarding that phenomena usually came from a mixture of prejudices, biased clinical observations, and media articles reflecting the most sensationalist side of psychedelics use. But in recent years, with the renewed interest of researchers in the study of the neurobiological basis of the effects of psychedelic drugs, as well as their psychotherapeutic potential (a new scenario coined by some researchers as ‘Psychedelic Renaissance’,^{20,21} following the expression that firstly appeared in 2010 in the *Playboy* magazine²²), interest has also reemerged regarding the potential effects of these drugs on eventual personality change.²³

The malleability of personality is a classical controversial theme in psychology and psychiatry sciences, where researchers find different kind of evidences depending on their particular theoretical framework used in the design of their respective studies.^{24,25} **For instance, there are several models of personality and personality disorders, and the terms used to characterize personality domains are not always equivalent among models and are in fact in permanent transformation.²⁴⁻²⁶ Furthermore, recent advances in molecular biology and epigenetics suggest that personality could be modulated by gene X environment interactions, where changes in gene expression could be caused by psychological (e.g., distress) or toxicological (e.g., drugs) factors, suggesting that personality is not as stable over time or as predictable as previously thought.²⁵**

One of the scientific expressions of the renewed interest in psychedelic research has focused in studying if these drugs can induce personality changes, thus offering other type of evidences to the debate. Moreover, these new investigations also began to explore the possible mechanisms of action involved in these personality changes, as well as their neural basis and neurochemistry, since it is well known that these compounds act as agonists at cortical serotonergic 5-HT_{2A} receptors expressed in fronto-temporo-parieto-occipital areas.²⁷ In the present work, we performed a systematic review of all of these contemporary clinical trials where personality has been studied related with administration of psychedelics/hallucinogens and/or with long-term use of these compounds. Our results show that these evidences come both from clinical studies where short and long-term personality changes have been studied after the administration of a psychedelic drug, and from studies comparing long-term psychedelic drug users with controls (nonusers).

2. Material and Methods

Data for this systematic review were collected in accordance with the Systematic Reviews and Meta-Analyses guidelines (PRISMA).²⁸

2.1. Search strategy

Electronic search was performed using the PubMed, LILACS, and SciELO databases. The following search terms were used: (psychedelic OR hallucinogen OR mescaline OR psilocybin OR lysergic acid diethylamide OR dimethyltryptamine OR ayahuasca) AND (personality). All studies published in English from 01 January 1985 until 14 December 2016 were included. Additionally, the reference lists of all included studies identified in the database search were manually screened for relevant studies. We restricted the search to 1985 because the mid-1980's was the time when research on personality structure increased dramatically, and thus the personality tests started to be constructed and analyzed using proper factorial methods of analysis,²⁹ so the comparison between different measures

employed in different studies could be made. The review was also restricted exclusively on serotonergic psychedelics/hallucinogens (5-HT_{2A} receptor agonists).

2.2. Selection criteria and study selection

Inclusion criteria were: i) publication in a peer-reviewed journal, ii) observational or interventional study design, iii) investigation of acute and non-acute effects of psychedelics/hallucinogens on personality, and iv) the psychedelic/hallucinogen should be a 5-HT_{2A} receptor agonist. Animal studies, review papers, qualitative studies, books or book chapters, opinion pieces or comments, case reports, letters or editorials, conference abstracts or posters, and published abstracts were excluded. After inspection for duplicates, the titles and abstracts of all records were reviewed. Publications that clearly did not meet inclusion criteria were excluded. The decision for inclusion or exclusion of the remaining publications was made based on the review of the full texts. All studies were screened by two independent reviewers (JCB, RGDS). In case of disagreement, reviewers discussed their reasons for initial inclusion and exclusion, and if consensus was not reached a third reviewer (JECH) was included.

2.3. Recorded variables, data extraction and analysis

Recorded variables included authors, year of publication, study location (country), study design, number of subjects, drug type and dose, personality measure, and main findings (including statistical thresholds).

3. Results

3.1. Study selection

A flow diagram illustrating the different phases of the systematic review is presented in Figure 1.

[insert Figure 1 here]

The search of the literature yielded 369 separate references that were reviewed for abstract screening (first pass). Following the first pass, 14 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports, all 14 citations were included.³⁰⁻⁴³ After handsearching the bibliography of the selected citations, four more references were found.⁴⁴⁻⁴⁷ Thus, 18 citations were included in the systematic review.

The studies included comprised 10 observational studies,^{30-33,34,36,38,39,41,44,46} and eight interventional.^{33,35,37,40,42,43,45,47} Seven of the observational studies assessed the effects of ayahuasca,^{32,33,36,38,39,41,46} one investigated the effects of psilocybin-containing mushrooms,³⁰ one evaluated the effects of LSD in polydrug (cannabis) users,⁴⁴ and one assessed the effects of hallucinogens in general (LSD, mescaline, etc.).³¹ Regarding interventional studies, four assessed the effects of psilocybin,^{33,35,37,47} three investigated the effects of LSD,^{42,43,45} and one assessed the effects of hallucinogens in general (LSD, mescaline, etc.).⁴⁰ The main information of each citation is presented in Table 1.

[insert Table 1 here]

Despite the small number of studies, the small sample sizes in most of them, the observational design of several studies, and the high degree of heterogeneity, most observational studies included a matched control group, and all interventional studies were placebo-controlled. Moreover, despite some inconsistencies, the reported results suggest that acute administration of serotonergic hallucinogens to healthy volunteers in experimental settings is associated with significant increases in Openness. Results also suggest that these effects seem to be persistent, enduring from days to several weeks/months. Furthermore, long-term consumption of hallucinogens in ritual contexts does not seem to be associated with personality disorders.

Instead, the continued ritual use of these compounds is apparently associated with significant differences in personality measures, which in turn seem to be related to antidepressant, anxiolytic, and antiaddictive effects. Nevertheless, given the observational nature of these results, it is not possible to conclude that the observed positive changes were in fact caused by these drugs. These findings will be further discussed in detail below.

3.2. *Drugs*

3.2.1. Psychedelics/hallucinogens in general

An observational study performed in the United States among 309 industrial plant workers (78% males, mean age 25.8 years; final sample $N = 298$) assessed possible correlations of hallucinogenic drug use (cannabis [*marijuana* or *hashish*], LSD, and other psychedelics [e.g., mescaline, tetrahydrocannabinol/THC]), personality, and attitude.³¹ Personality and attitude were assessed with the following instruments: the Eysenck Personality Inventory (EPI, also known as the Eysenck Personality Questionnaire, EPQ), which measures behaviors related to self and others, including the subscales Extroversion, Neuroticism, Psychoticism, and Lie (a validity scale); the Zuckerman Sensation-Seeking Scale (ZSS), which measures stimulation or arousal and includes the subscales Boredom-Susceptibility, Disinhibition, Experience Seeking, Thrill/Adventure Seeking, and General Sensation-Seeking; the Marlowe-Crowne Social Desirability Scale (SDS), measuring social approval-seeking behavior; and the Self-System Perception Questionnaire (SSPQ), which measures how people prefer to behave in a workplace setting and included the subscales Social Alienation, Traditionalism, Equalitarianism, and Hedonism.

Considering only serotonergic hallucinogens (LSD and other psychedelics, although this last group also included THC), 24% of the sample tried LSD and 23% tried other psychedelics. Among current users, 36% of the sample reported less than monthly use for both LSD and other psychedelics, while monthly use was reported by 4% for LSD and 6% for other

psychedelics. The ZSS subscales Experience Seeking, Disinhibition, and Boredom-Susceptibility, as well as the SSPQ subscales Social Alienation and Traditionalism, significantly ($P < 0.001$, uncorrected) predicted one or more drug use scores, but only the ZSS subscales Experience Seeking and Boredom-Susceptibility and the SSPQ subscale Social Alienation significantly contributed to the variance of all drug variables ($P < 0.001$, uncorrected). Disinhibition and Traditionalism were associated with *marijuana* and *hashish* scores, while Traditionalism was also associated with scores for other psychedelics. The authors concluded that hallucinogen use was significantly associated with the need for novel or unconventional experiences and to negative attitudes toward conventionally defined social values.

In an observational study performed in Brazil, Schneider et al.⁴⁰ conducted a cross-sectional web survey to assess possible associations between personality traits and occasional use, abuse, and dependence of alcohol, cannabis, cocaine, benzodiazepines, and hallucinogens (not specified) in adults. The sample consisted of 8,646 participants (24.7% men, mean age 36.3 years; 75.3% women, mean age 34.7 years). Drug use was assessed with the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), and personality was assessed with a Brazilian Portuguese version of the Temperament and Character Inventory - Revised (TCI-R) with 240 items. The ASSIST measures frequency of use (lifetime and last 3 months) and drug-related problems (financial, social, legal, and health issues), and classifies individuals as nonusers, occasional users (tried at least one drug but did not experience any negative outcomes), abusers (past or current users of one or more drugs who may have had negative outcomes related to drug use or frustrated trials to reduce drug use), and dependent individuals (current users who experience drug-related negative outcomes and failed attempts to reduce use). The TCI-R evaluates four dimensions of temperament (harm avoidance, novelty seeking, reward dependence, and persistence) and three dimensions of character (self-

directedness, cooperativeness, and self-transcendence). Regarding use of hallucinogens specifically, compared to people who never used hallucinogens occasional users showed significantly lower scores on harm avoidance and significantly higher scores on self-directedness; abusers showed significantly lower scores on persistence and significantly higher scores on self-transcendence (for all comparisons: $P < 0.05$, corrected). In contrast, novelty seeking was the trait most associated with increased use of alcohol, cannabis, and cocaine. The authors suggested that these results could indicate that while most drug users apparently display higher levels of impulsiveness and extravagance, hallucinogen users are more prone to thoughts and feelings related to spiritual contemplation and realization and to overcome the limits of the individual self.

3.2.2. Ayahuasca

In an observational study performed in Brazil among 15 long-term (≥ 10 years) members of the *União do Vegetal* (UDV) (mean age 35.9 years), Grob et al.³² assessed the personality of these subjects in comparison to 15 matched controls with no prior history of ayahuasca use using the Tridimensional Personality Questionnaire (TPQ), the previous version of the TCI and TCI-R questionnaires, which measures three dimensions of temperament: novelty seeking (subscales/facets exploratory excitability vs. stoic rigidity; impulsiveness vs. reflection; extravagance vs. reserve; and disorderliness vs. regimentation), harm avoidance (subscales/facets anticipatory worry vs. uninhibited optimism; fear of uncertainty vs. confidence; shyness with strangers vs. gregariousness; and fatigability and asthenia vs. vigor), and reward dependence (subscales/facets sentimentality vs. insensitiveness; persistence vs. irresoluteness; attachment vs. detachment; and dependence vs. independence). UDV members scored significantly lower on the novelty seeking scale (summation of all subscales: $P < 0.0054$, uncorrected), including significantly greater stoic rigidity vs. exploratory excitability ($P < 0.049$, uncorrected) and regimentation vs. disorderliness ($P < 0.016$, uncorrected). UDV

members also scored lower on the harm avoidance scale (summation of all subscales: $P < 0.011$, uncorrected), including significantly greater confidence vs. fear of uncertainty ($P < 0.043$, uncorrected). The authors concluded that these results indicated that, compared to the control group, UDV members had reduced impulsivity and shyness, and were more reflective, confident, gregarious and optimistic. This study also reported an absence of current psychiatric diagnosis among the UDV members, as well as no evidence of cognitive deterioration.

In an observational study conducted in Brazil, Bresnick and Levin⁴⁶ assessed personality measures in 21 volunteers (17 men, mean age 44.2 years; seven were previously naïve to ayahuasca use) attending a 10-day ayahuasca seminar. Personality was evaluated with the Tellegen Absorption Scale (TAS) in the first day of the seminar, and participants ingested ayahuasca on the third, fifth, seventh, and ninth day (dose not specified). Participants showed higher TAS scores compared to normative data, and absorption scores were significantly ($P < 0.05$, uncorrected) related to synesthesia during the acute effects of ayahuasca.

In another observational study conducted in Brazil, Barbosa et al.³⁴ assessed personality at baseline and after six months in a sample of 23 subjects (8 men, mean age 37 years) who were previously naïve to ayahuasca use, using a Brazilian Portuguese version (translation and back-translation) of the Temperament and Character Inventory with 125 items (TCI-125). Subjects participated in ayahuasca rituals in *Santo Daime* ($N = 15$) and UDV ($N = 8$) religious institutions, and were further separated in irregular (< 10 uses, $N = 17$) and regular users (> 10 uses, $N = 6$). The TCI-125 measures the same temperament and character dimensions of the TCI-R. Compared to baseline scores, ayahuasca use (total sample) was significantly ($P = 0.028$, uncorrected) associated with lower scores in reward dependence. Subjects who ingested ayahuasca in the UDV context also had significantly lower scores in reward dependence ($P = 0.017$, uncorrected), while subjects in the *Santo Daime* group only had

significantly lower scores in harm avoidance ($P = 0.035$, uncorrected). In the total sample, lower scores on reward dependence were positively correlated with the intensity of ayahuasca use ($P = 0.014$, uncorrected). The lower scores in harm avoidance in the *Santo Daime* group were positively correlated ($P = 0.018$, uncorrected) to significant reductions in minor psychiatric symptoms as measured by the Clinical Interview Schedule – Revised Edition (CIS-R), while in the UDV group lower scores on reward dependence were positively correlated with the intensity of ayahuasca use ($P = 0.029$, uncorrected) and negatively correlated with the length of wash-out period (time passed since last ayahuasca ingestion and the evaluation) ($P = 0.009$, uncorrected). Compared to the UDV group, the *Santo Daime* group scored significantly higher on novelty seeking ($P = 0.025$, uncorrected). Regular users showed significantly ($P = 0.026$, uncorrected) lower scores on reward dependence. Moreover, compared to irregular users, regular users had significantly ($P = 0.005$, uncorrected) higher scores on reward dependence at baseline and also significantly ($P = 0.009$, uncorrected) higher scores on self-directedness at the six-month follow-up. The authors suggested that these results show that ayahuasca use was associated with less dependence of social approval and more confidence, optimism and independence.

In an observational study conducted in Brazil, Bouso et al.³⁶ evaluated the personality of long-term (≥ 15 years) members of the Brazilian ayahuasca religions *Santo Daime* and *Barquinha*. Ayahuasca users were assessed in a jungle community ($N = 56$; 29 men, mean age 36 years) and in an urban community ($N = 71$; 33 men, mean age of 37.32 years), and were compared with rural ($N = 56$; 24 men, mean age of 33.71 years) and urban ($N = 59$; 31 men, mean age of 38.15 years) controls, respectively. Moreover, participants were assessed again one year later. Personality was assessed with a Brazilian Portuguese version of the TCI with 240 items measuring the same dimensions of temperament and character of the TCI-R and its subscales or facets (with slight differences compared with the temperament subscales/facets of the

TPQ): harm avoidance (anticipatory worry vs. uninhibited optimism; fear of uncertainty vs. confidence; shyness with strangers vs. gregariousness; fatigability and asthenia vs. vigor), novelty seeking (exploratory excitability vs. stoic rigidity; impulsiveness vs. reflection; extravagance vs. reserve; disorderliness vs. regimentation), reward dependence (sentimentality vs. insensitivity; attachment vs. detachment; dependence vs. independence), and persistence. The TCI-R also assesses three dimensions of character: self-directedness (responsibility vs. blaming; purposefulness vs. lack of goal-direction; resourcefulness; self-acceptance vs. self-striving; congruent second nature), cooperativeness (social acceptance vs. social intolerance; empathy vs. social disinterest; helpfulness vs. unhelpfulness; compassion vs. revengefulness; integrated conscience), and self-transcendence (self-forgetfulness vs. self-conscious experience; transpersonal identification vs. self-isolation; spiritual acceptance vs. rational materialism).

Compared to controls, in the first assessment ayahuasca users showed significantly higher scores on reward dependence ($P = 0.009$, uncorrected) and its subscales attachment ($P = 0.006$, uncorrected) and dependence ($P = 0.002$, uncorrected); self-transcendence ($P < 0.001$, uncorrected) and its subscales self-forgetfulness ($P = 0.035$, uncorrected), transpersonal identification ($P < 0.001$, uncorrected), and spiritual acceptance ($P < 0.001$, uncorrected); and in the cooperativeness subscale helpfulness ($P = 0.006$, uncorrected). Ayahuasca users showed significantly lower scores on harm avoidance ($P < 0.001$, uncorrected) and its subscales anticipatory worry ($P < 0.001$, uncorrected), shyness ($P = 0.003$, uncorrected), and fatigability and asthenia ($P = 0.013$, uncorrected); self-directedness ($P = 0.002$, uncorrected) and its subscales responsibility ($P = 0.004$, uncorrected), purposefulness ($P = 0.042$, uncorrected), resourcefulness ($P = 0.001$, uncorrected), and self-acceptance ($P < 0.001$, uncorrected); in the novelty seeking subscale disorderliness ($P = 0.035$, uncorrected); and in the cooperativeness subscale compassion ($P = 0.026$, uncorrected). Compared with the urban

sample, the jungle sample showed significantly higher scores on the reward dependence subscales attachment ($P = 0.044$, uncorrected) and dependence ($P = 0.042$, uncorrected); on the harm avoidance subscale fatigability and asthenia ($P = 0.042$, uncorrected); and in the self-directedness subscale resourcefulness ($P < 0.05$, uncorrected).

In the second assessment, a year later, most of the results remained stable: compared to controls, ayahuasca users showed significantly higher scores on self-transcendence ($P = 0.008$, uncorrected) and its subscales transpersonal identification ($P = 0.007$, uncorrected) and spiritual acceptance ($P < 0.001$, uncorrected); and on the cooperativeness subscale helpfulness ($P = 0.043$, uncorrected). Ayahuasca users also showed lower scores on harm avoidance ($P = 0.030$, uncorrected) and its subscales anticipatory worry ($P = 0.016$, uncorrected), shyness ($P = 0.027$, uncorrected), and fear of uncertainty ($P = 0.041$, uncorrected), an effect not observed in the first assessment; and self-directedness ($P = 0.001$, uncorrected) and its subscales responsibility ($P < 0.001$, uncorrected) and self-acceptance ($P = 0.001$, uncorrected). This study also reported that, compared to controls, ayahuasca users showed significantly higher scores on scales measuring spiritual orientation, purpose in life, and psychosocial well-being, as well as significantly lower psychopathology. Overall, these results were also stable one year later.

In an observational study performed in Spain, Bouso et al.³⁸ used the revised version of the TCI with 240 items (Temperament and Character Inventory-Revised, TCI-R) to compare the personality of Spanish members of the *Santo Daime* ($N = 22$; men, mean age years) with a matched control group of non-ayahuasca users ($N = 22$; men, mean age years) in the context of a neuroimaging study. *Santo Daime* members had used ayahuasca an average of 123 times (range: 50–352), had been using it for an average of 5.3 years (range: 2–13), and the age of initial use was 35.6 years (range: 5–55). Compared to controls, ayahuasca users showed significantly lower scores on harm avoidance ($P = 0.044$, uncorrected) and its subscale

anticipatory worry ($P = 0.005$, uncorrected), and significantly higher scores on self-transcendence ($P < 0.001$, uncorrected) and its subscales self-forgetfulness ($P < 0.001$, uncorrected), transpersonal identification ($P = 0.001$, uncorrected), and spiritual acceptance ($P < 0.001$). Moreover, scores on self-transcendence ($P = 0.024$, uncorrected) and its subscale transpersonal identification ($P = 0.009$, uncorrected) were negatively correlated with a significant cortical thinning of the posterior cingulate cortex (PCC) observed in the ayahuasca group. Thus, greater scores on the personality measures were associated with increased thinning of the PCC. However, no significant differences were found between the groups regarding psychopathology measures, suggesting that the cortical thickness alterations do not appear to be associated with increased psychopathology.

An observational study performed in the Czech Republic and in Peru evaluated the personality of foreigners that had travelled to South America with the aim of using ayahuasca and had participated in at least one ayahuasca session.³⁹ Personality was assessed with the long (Czech, 140 items) and short (English/Spanish, 56 items each) versions of the Personality Styles and Disorders Inventory (PSSI), which evaluates 14 personality styles (assertive, distrustful, aloof, self-critical, conscientious, intuitive, optimistic, ambitious, critical, loyal, spontaneous, charming, quiet, and helpful). PSSI scores of ayahuasca users were compared to population norms from a German sample. Participants ($N = 77$; 47 men, mean age 36.6 years) were from the Czech Republic ($N = 47$) and from other European countries, South America, the United States and Canada ($N = 30$), and the mean number of ayahuasca sessions was 17.7 (range: 1–130). Two questionnaires were excluded because of incomplete answers, thus reducing the final sample to 75 volunteers. Compared to the population sample, ayahuasca users showed significantly higher scores on the PSSI scales intuitive ($P < 0.001$, uncorrected), optimistic ($P < 0.001$, uncorrected), ambitious ($P < 0.01$, uncorrected), charming ($P < 0.001$, uncorrected), and helpful ($P < 0.01$, uncorrected), and

significantly lower scores on the scales distrustful ($P < 0.05$, uncorrected) and quiet ($P < 0.01$, uncorrected). The effect size (Cohen's d) was intermediate for ambitious (0.67) and large for intuitive (> 15), optimistic (5.04), charming (1.52), and helpful (0.8). The authors suggested that ayahuasca users seem to have an emphatic, pleasant, trustful, and optimistic personality style, also characterized by inhibition of analytic thinking and valorization of intuitive behavior.

In an observational study performed in the United States, Barbosa et al.⁴¹ compared the personality of 30 experienced UDV members (16 men, mean age 42.5 years; mean of 32.5 ceremonies in the last year, mean of 60 months of regular attendance) with 27 matched controls (14 men, mean age 45 years) with no history of ayahuasca use with the Big Five Inventory (BFI), a questionnaire assessing personality with the following scales: extroversion, agreeableness, conscientiousness, neuroticism, and openness. Compared to controls, UDV members scored significantly higher on the agreeableness ($P = 0.028$, uncorrected) and openness ($P = 0.037$, uncorrected) subscales of the BFI. Moreover, compared to controls, UDV members showed better scores on mood and quality of life, and there were no significant differences in cognitive performance.

3.2.3. Psilocybin

In an observational study conducted in the United States, Anglin et al.³⁰ compared the personality of 53 college undergraduates users of psilocybin-containing hallucinogenic mushrooms (mostly from the *Psilocybe* genera) (60% men, mean age 19.22 years; 40% women, mean age 18.66 years) with 53 matched controls with no history of mushroom use (60% men, mean age 19.19 years; 40% women, mean age 18.33 years). A variable percentage of mushroom users used other drugs concurrently with mushrooms (alcohol [men: 84.4%; women: 71.4%], *marijuana* [men: 78.1%; women: 38.1%], *hashish* [men: 34.4%; women: 0%], cocaine [men: 28.1%; women: 9.5%], amphetamines [men: 3.1%; women: 9.5%], LSD

[men: 9.4%; women: 0%], tranquilizers and barbiturates [men: 0%; women: 4.8%], and *peyote*/mescaline [men: 3.1%; women: 0%]), and controls reported both no use of illicit drugs and use of other drugs (but not mushroom use). Personality was evaluated with the Zuckerman Sensation-Seeking Scale (ZSS), the Eysenck Personality Questionnaire (EPQ, also known as the Eysenck Personality Inventory, EPI), the Socialization subscale of the California Psychological Inventory (CPI), and the Zenhausern Preference test (PRE). The Socialization subscale of the CPI assesses the acceptance or deviance from cultural norms (asocial vs. social), and the PRE evaluates thinking style (right cerebral dominance-deductive mode of reasoning vs. left cerebral dominance-inductive mode of reasoning). Compared to male nonusers, male users showed significantly higher scores on the Experience Seeking subscale of the ZSS ($P < 0.05$, uncorrected), and significantly lower scores on the Lie subscale of the EPQ and on the Socialization subscale of the CPI (both comparisons: $P < 0.01$, uncorrected). Compared to female nonusers, female users showed significantly higher scores on the General Sensation-Seeking and Disinhibition subscales of the ZSS (both comparisons: $P < 0.05$, uncorrected), and significantly lower scores on the Socialization subscale of the CPI ($P < 0.05$, uncorrected). However, personality traits were not the most important variables predicting mushroom use, which were specially predicted by number of using friends for male users and fathers' *marijuana* use for female users. There was no evidence of increased psychopathology in mushroom users.

In an experimental study conducted in the United States, Griffiths et al.⁴⁷ performed a double-blind, between-group, crossover study that included a 2-month follow-up assessing the effects of a high psilocybin dose (30 mg/70 kg) in 36 hallucinogen-naïve adults (16 men, mean age 46 years) reporting regular participation in religious/spiritual activities. Methylphenidate (40 mg/70 kg) was administered as an active placebo. Volunteers were randomly assigned to participate in two ($N = 30$) or three ($N = 6$) experimental sessions; those participating in two

sessions were randomly assigned to ingest oral psilocybin or methylphenidate on the first session (15 per group), and the other drug on the second session; those participating in three sessions received methylphenidate on the first two sessions and unblinded psilocybin on the third session. Personality was evaluated before and 2 months after each drug session with the Measurement of Actualization Potential (a measure of measure of self-actualization) and the NEO Personality Inventory (NEO PI-R), which has the same subscales of the BFI (extroversion, agreeableness, conscientiousness, neuroticism, and openness). Compared to methylphenidate, both at screening and two months after the experimental session psilocybin administration was not associated with significant effects on personality.

In 2008, Griffiths et al.³³ performed a 14-month follow-up of their original double-blind study from 2006.⁴⁷ Relative to adult norms, at baseline the psilocybin group showed significantly lower scores on the neuroticism subscale of the NEO PI-R, and significantly higher scores on the extroversion, openness, and agreeableness subscales of the NEO PI-R and on the Measure of Actualization Potential. However, no significant changes were observed across the study.

MacLean et al.³⁵ combined the data from two double-blind controlled studies of psilocybin to analyze personality changes using the NEO PI-R.^{47,48} The study from 2011⁴⁸ was not included in the systematic review because personality measures were not included in that report. In that study, participants did not receive only a single high-dose of psilocybin or methylphenidate as the original study from 2006.⁴⁷ Instead, participants received four psilocybin doses (5, 10, 20 and 30 mg/70 kg) across four sessions in ascending or descending order (50% random assignment). Moreover, a fifth session using a placebo was quasi-randomly included in the study. The final analyses by MacLean et al.³⁵ included 52 participants ($N = 35$ in the study from 2006, 14 men, mean age 46 years; $N = 17$ in the study from 2011, 8 men, mean age 46 years). Personality measures were assessed 1–2 months after the high-dose (30 mg/70 kg) psilocybin session and again 16 months later. Moreover, the

authors hypothesized that mystical experiences acutely induced by psilocybin (measured with the States of Consciousness Questionnaire, SOCQ) would lead to increases in the Openness factor of the NEO-PI-R. Therefore, changes in Openness were compared among participants who met ($N = 30$) and who did not meet ($N = 22$) the criteria for having had a “complete mystical experience” (60% increases on all subscales of the SOCQ).

No significant differences in personality were observed between participants of both studies at screening. Compared to baseline, Openness scores increased significantly 1-2 months after drug sessions ($P < 0.023$, uncorrected), and there were no significant changes in Openness scores of the participants who received inactive placebo, methylphenidate, or 5 mg/70 kg psilocybin ($N = 30$). These results suggest that increases in Openness scores were induced by psilocybin administration. Furthermore, changes in Openness scores were positively correlated with scores on the SOCQ, on the Mysticism Scale, and on the Altered States of Consciousness questionnaire (APZ) ($P < 0.05$, uncorrected). However, compared to the other scales, this correlation was mainly driven by score changes in the SOCQ. The group that had a “complete mystical experience” showed significant increases in Openness scores and in the scores of five of its six facets (Fantasy, Aesthetics, Feelings, Ideas and Values, but not Actions) at the 1-2-month follow-up ($P < 0.05$, uncorrected), while the group who did not meet this criterion did not. Although Openness scores in the “complete mystical experience” group did significantly differ at the 1-2-month and at the 16-month follow-ups, scores on the last follow-up were only marginally higher than baseline values ($P = 0.05$, uncorrected), **but the magnitude of this last change was quite large (increase of more than 4 *T*-score points), although the effect size was rather small ($M = +4.2$; $F(1, 29) = 4.17$; $\eta^2 = 0.13$).** Participants who did not meet the criteria for a complete mystical experience had similar scores at baseline and at the 16-month follow-up.

In an experimental study performed in Zurich, Studerus et al.³⁶ investigated the possible predictor variables of the acute response to psilocybin by analyzing the pooled data of 23 placebo-controlled experimental studies conducted between 1992 and 2011 involving 409 psilocybin administrations to 261 healthy volunteers (62% men, mean age 27.8 years; 59% hallucinogen-naïve). Participants received placebo or 1-4 different doses of psilocybin (mean \pm SD: 214 ± 63 mg/kg, range: 115-315 mg/kg) in randomized, double-blind studies ($N = 16$) and in open-label trials ($N = 7$). Twenty-four predictor variables were analyzed (including age, sex, education, personality traits, drug pre-experience, mental state before drug intake, experimental setting, and psilocybin dose) in relation to 15 response variables (APZ scales and subscales). Personality measures were assessed at screening and were evaluated with the TAS and with the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ), which assesses the personality dimensions Impulsive Sensation Seeking (with the facets Impulsivity and Sensation Seeking), Neuroticism-Anxiety, Aggression-Hostility, Activity (with the facets Need for General Activity and Work Activity), and Sociability (with the facets Parties and Friends and Isolation Intolerance). The TAS was applied in four of the 23 studies and was completed by 73 participants, while the ZKPQ was applied in 11 of the 23 studies and was completed by 125 participants. Psilocybin dose had the strongest predictive effect on drug response, as it was significantly associated with all response variables and had the highest effect size in most models analyzed. However, other variables also significantly predicted the effects of psilocybin. For instance, an emotionally excitable and active mental state before drug intake, as well as reduced psychological problems in past weeks, were associated with highly enjoyable, positively valued, and mystical-type experiences, while high emotional excitability, low age, and performing positron emission tomography (PET) experiments were associated with unpleasant or anxious experiences. Regarding personality measures, high TAS (Absorption) scores significantly ($P < 0.05$, uncorrected) predicted pleasant and

mystical-type experiences, whereas high Sociability scores significantly ($P < 0.05$, uncorrected) predicted few mystical-type experiences and increased perceptual alterations.

3.2.4. Lysergic acid diethylamide (LSD)

In an observational study conducted in a drug dependence unit of a hospital in the United Kingdom,⁴⁴ the personality of 29 polydrug users (cannabis, LSD, etc., drug use frequency not specified, neither were gender and age) was assessed using the EPQ. Patients answered the EPQ within 24 hours of their hospital admission. The Neuroticism dimension of the EPQ showed a significant ($P < 0.01$, uncorrected) positive correlation with the frequency of unpleasant LSD experiences (“bad trips”), the occurrence of unpleasant visual hallucinations during the experience, and the recurrence of drug effects after acute effects have subsided (“flashbacks”). Moreover, the Extroversion dimension showed a significant ($P < 0.05$, uncorrected) negative correlation with the frequency of “bad trips”.

In an experimental study conducted in Germany, Lienert and Netter⁴⁵ evaluated the possible associations between personality measures and acute LSD effects (“thinking disturbances”, “affective reactions”, and “blackouts”) in a dataset from 1987 of 65 student volunteers (gender and age not specified) that received a single oral LSD dose ($1 \mu\text{g/kg}$) in an apparently open-label study (with no control group) a week after responding the Maudsley Personality Inventory (MPI; assessing high and low extraversion and neuroticism). Significant ($P < 0.0125$, corrected) personality-related responses to LSD were observed. All three acute effects were reported by 11 of the 16 “hysteries/extraverted neurotics” (high extraversion and neuroticism), while eight of 16 “stable extraverts” (high extraversion and low neuroticism) reported only “affective reactions” (laughter, weeping), six of 11 “dysthymics/introverted neurotics” (low extraversion and high neuroticism) reported only “thinking disturbances”, and seven of 17 “stable introverts” (low extraversion and neuroticism) reported only “blackouts”.

In a single-blind, placebo-controlled, within-subjects study performed in the United Kingdom, Carhart-Harris et al.⁴² administered LSD (75 μ g, intravenously) or placebo in a balanced order to 20 healthy volunteers (16 men, mean age 30.9 years) and assessed acute subjective effects and subacute (two weeks) personality measures (the Revised Life Orientation Test (LOT-R), which measures optimism, and the NEO PI-R). Compared to placebo, LSD administration acutely improved mood and psychosis-like symptoms, and significantly increased Optimism ($P = 0.005$, corrected) and Openness ($P = 0.03$, corrected) scores two weeks after the experimental sessions.

The same volunteers from the study by Carhart-Harris et al.⁴² underwent resting state functional magnetic resonance imaging (fMRI) scans and the results were reported in a subsequent study.⁴³ Volunteers underwent three eyes-closed resting-state fMRI scans (one including music listening), and the possible relationship between modifications in brain dynamics induced by LSD or placebo and the previously observed significant increases in Openness scores two weeks after the drug sessions⁴² was investigated. Relative to placebo, LSD significantly increased brain entropy both globally and specifically in clusters located in the frontoparietal, medial occipital, posterior and dorsal cingulate regions, which included primary and secondary sensory systems and associative networks, and hierarchically higher cognitive brain networks such as the Default Mode Network (DMN). Increases in global brain entropy predicted changes in Openness ($P = 0.035$, uncorrected), and the predictive value of this relationship was enhanced by music-listening ($P = 0.0005$, uncorrected). This relationship was also observed at the network level (both sensory and higher cognitive networks), both independently and mediated by music ($P < 0.05$, uncorrected). Moreover, increases in “ego-dissolution” (visual analogue scale) after music-listening and in brain entropy at the orbitofrontal ($P = 0.048$, uncorrected) and superior frontoparietal ($P = 0.026$, uncorrected) networks significantly predicted increases in Openness scores.

4. Discussion

In the present systematic review, we found several studies that assessed the effects of psychedelics on personality measures, both after acute administration and in long-term regular users compared with controls (nonusers). We restricted our search to studies done with serotonergic hallucinogens from January 1985 to December 2016, since around 1985 the psychometric properties of personality questionnaires began to improve. Furthermore, after that date was the time when researchers started to design personality studies with psychedelics with better methodologies and settings. Our systematic review of the literature showed that the main psychedelic drugs studied were LSD, psilocybin and ayahuasca. Moreover, we found mainly three kinds of studies: 1) observational studies with subjects who have used psychedelics at some time of their lives in recreational settings; 2) observational studies with subjects who use psychedelics, mainly ayahuasca, in a regular basis and for long-time periods in the contexts of religious ceremonies within the framework of the so-called “ayahuasca religions”; and 3) assessments of the mid- and long-term changes in personality measures within the context of clinical trials and in naturalistic settings after the administration of a psychedelic drug. Also, we found a diversity of personality measures employed in the different studies. The NEO-PI-R (NEO Personality Inventory) was the questionnaire most used in the clinical trials, and the TCI (Temperament and Character Inventory) in its different versions was the measure most used in the studies researching long-term ayahuasca religion practitioners, while in the studies with recreational users there were more diversity of measures employed.

Some studies with recreational users explored the possible relation between certain personality traits and the reactions to psychedelic drugs. For instance, Hemsley and Ward⁴⁴ found that neuroticism (assessed with the EPQ) was related to unpleasant LSD experiences and that extroversion (EPQ) was negatively correlated with “bad trips”. These results are in

accordance with clinical studies where psilocybin was administered to healthy volunteers and high scores in neuroticism predicted negative reactions,³⁷ and in some studies that personality trait is an exclusion criterion.⁴⁹ Furthermore, although extraverted subjects seem to enjoy more the psychedelic experience, as well as subjects with high scores in Sociability, in the contexts of clinical trials they do not seem to achieve mystical-type experiences.³⁷

A very interesting finding was the association between recreational psychedelic drug use and Experience Seeking, General Sensation Seeking, and Disinhibition,^{30,32} personality traits that were not found in studies done with ayahuasca religion practitioners.^{32,35,38} Since in both kinds of studies subjects scored lower in “Lie” subscales, these effects do not seem to be related to answers according to social desirability. The explanation may be that recreational psychedelic drug users were generally polydrug users, a type of drug users that seem to score high in Novelty Seeking.⁵⁰ Mabry and Khavari³¹ also found high scores in social Alienation and Traditionalism. Social alienation could be one of the reasons to get involved in polydrug use,⁵¹ but the high scores found in Traditionalism are more difficult to interpret, since it is considered a protective factor for drug abuse.^{52,53} In another study with Brazilian drug users, Schneider et al.⁴⁰ found some differences in personality traits between occasional recreational psychedelic drug users and abusers (the psychedelic drugs were not specified). Although both groups scored high in Self-Transcendence, the occasional users scored lower in Harm Avoidance, while the abusers scored high in Persistence. As we will see later, ayahuasca religious practitioners also scored high in Self-Transcendence, low in Harm Avoidance, and there were no significant differences in Persistence compared with nonusers. Persistence is considered a positive trait in preventing drug abuse,⁵⁴ so this specific result in psychedelic abusers is also difficult to interpret. Since psychedelic drug users do not seem to have increased rates of psychopathology compared with the general population,^{55,56} with some evidence suggesting that they may in fact have better mental health,⁵⁷ the results relating

psychedelic abuse with Traditionalism and Persistence do not necessarily reflect psychological problems, except for the recreational use of a drug.

Two studies assessed the personality traits of people who decided to participate in nonreligious ayahuasca retreats, finding a profile characterized by increased scores on intuitivism, optimistic, ambitious, charming, and helpful.³⁹ The lack of a control group could increase the chances of bias by self-selection, since subjects participating in the study may have a specific personality profile that fits with the stereotype of people who usually attend this kind of ceremonies, a stereotype that may be similar to that used in the 1960's to refer to the *acid heads*.¹³ However, in this new post-modern version, some ayahuasca “advocates” portrait it as an inductor of transpersonal states or “transpersonal circles” that seems to be characterized by a Changed Worldview and New Orientation to Life,⁵⁷ or as a remedy to avert global ecological catastrophe.⁵⁹

The other noncontrolled study showed that ayahuasca retreatment attenders scored higher compared to normative data in the TAS.⁴³ Higher scores in the TAS have been shown to produce pleasant mystical-type experiences in controlled clinical trials using psilocybin,³⁷ so it seems reasonable to speculate that people that score high in that personality trait may be more predisposed to get involved in, and to enjoy, psychedelic experiences. Indeed, a positron emission tomography (PET) study reported that subjects that scored high on Self-Transcendence had lower 5-HT_{1A} receptor levels,⁶⁰ and a genetics study showed that subjects with the T/T genotype of the T102C polymorphism, implying higher 5-HT_{2A} receptor levels, had higher TAS scores.⁶¹ These findings suggest that the personality traits of Absorption and Self-Transcendence (and maybe other traits) may have their neurobiological substrates regulated by cortical 5-HT_{1A/2A} receptors, the main targets of the pharmacological actions of serotonergic psychedelics.²⁷

Furthermore, these results add new evidence to the biological theories of personality by showing that modulation of specific serotonergic receptors (**and maybe other serotonergic modulators such as the serotonin transporter**) expressed in specific brain areas modulate specific personality traits. Agonism at these cortical 5-HT_{2A} receptor by psychedelics is associated with modifications on perceptions, memory, emotion, and self-awareness, and also with anxiolytic, antidepressive, and antiaddictive effects.^{27,62,63} Thus, investigation of the neural basis of personality traits and their possible modulation by psychedelic drugs could result in a better understanding of their therapeutic potentials.

Since 1996, several studies compared regular religious ayahuasca users with matched nonusers in several neuropsychological, neuroimaging, and psychological measures, including personality.⁶⁴ One study was performed with Brazilian urban members of the UDV,³² other study compared Brazilian rural members with urban members belonging to the *Santo Daime* and *Barquinha* religions,³⁶ another study was done with Spanish urban members,³⁸ and the last study was performed with North American urban members of the UDV.⁴¹ The first three studies employed different versions of the Cloninger's model of personality:⁶⁵ the Tridimensional Personality Questionnaire (TPQ), the Temperament and Character Inventory (TCI), and its revised form (TCI-R), respectively.

Regarding temperament variables, all three studies found lower scores in Harm Avoidance compared to controls. Only Grob et al.³² found lower scores in Novelty Seeking, while the other studies did not find differences in that variable. Bouso et al.³⁶ found higher scores in Reward Dependence only in the rural sample, while no differences were found in that variable in the other studies and samples. The authors suggested that the difference in Reward Dependence between rural and urban samples could be related to the life in the jungle, where people may need to establish closer ties between the members of the community to survive in a hostile environment. There was also a high consistence across studies in character variables.

The TPQ does not measure character variables, so only the studies by Bouso and collaborators can be directly compared.^{36,38} There were no differences between ayahuasca users and nonusers in Persistence and Cooperation, and all samples scored higher than controls in Self-Transcendence. An interesting finding was that the two Brazilian samples (rural and urban) scored lower in Self-Directedness than controls,³⁶ while there were no differences in the Spanish sample.³⁸ The Brazilian samples were matched in religiosity,³⁶ so the higher scores in Self-Transcendence may be a direct effect of the ritual use of ayahuasca, and these results were replicated one year later. The authors suggested that the lower scores in Self-Directedness in the Brazilian samples could probably reflect cultural differences: maybe the Brazilian ayahuasca users drive their lives based on their religious doctrine more intensively than the Spanish sample. Another explanation may be that the Brazilian sample studied by Bouso et al.³⁶ had a much larger history of ayahuasca use and ceremony attendances than the Spanish sample.³⁸ However, in the Spanish sample, cortical thinning of the PCC was inversely correlated with the intensity and duration of prior use of ayahuasca and with scores on Self-Transcendence. These differences with Brazilian samples in those character traits could also be related to genetic differences related to personality traits, such as **polymorphisms and expression of cortical 5-HT_{1A/2A} receptors⁶¹ and the 5-HT transporter,⁶⁶** or to differences in the organization of the studied communities, in the level of engagement with the doctrine rules, or just to other strange biological or cultural variables not controlled in the study.

One additional study done with urban religious ayahuasca users in the US found differences compared with nonusers in the traits of Agreeableness and Openness of the Big Five Questionnaire, results that are in accordance with those found in other studies that used different personality questionnaires.⁴¹

Although the results found by Bouso et al.³⁶ were replicated one year later, it is not possible to attribute causality to ayahuasca intake in the differences observed between ayahuasca users and nonusers. In that sense, Barbosa et al.³⁴ did a six-month follow-up study of naïve ayahuasca users after they started to participate in religious ayahuasca ceremonies, finding that participation in ayahuasca ceremonies was associated with changes in the traits of Harm Avoidance, Reward Dependence, Novelty Seeking, and Self-Transcendence of the TCI. Thus, maybe the differences found in some personality traits between ritual ayahuasca users and nonusers could be a consequence of participating in ayahuasca ceremonies and continuous stimulation of cortical 5-HT_{1A/2A} receptors.

The last series of evidences relating personality changes after the use of a psychedelic drug came from one open-label study performed with LSD in Germany,⁴⁵ and from a series of placebo-controlled clinical trials performed with psilocybin^{33,35,47} and LSD.^{42,43} The study by Griffiths et al. from 2008³³ was a 14-month follow-up of the original study from 2006,⁴⁷ where no changes in personality were found using the NEO PI-R questionnaire. In a subsequent analysis of the data combining results from two double-blind-controlled studies involving administration of 30 mg/70 kg psilocybin (oral), MacLean et al.³⁵ found significant increases in Openness scores 1-2 months after drug sessions compared to baseline that correlated with scores on the States of Consciousness Questionnaire (SOCQ). **Moreover, although Openness scores at the 16-month follow-up were only marginally higher than baseline values, the magnitude of this change increased more than 4 T-score points from screening to follow-up, a quite large change (although the effect size was rather small).**

Regarding the studies with LSD, Lienert and Netter⁴⁵ found different responses to the drug depending on the type of personality measured with the Maudsley Personality Inventory (MPI), but no data were reported regarding eventual mid- or long-term changes. In a placebo-controlled clinical trial that assessed personality changes using the NEO PI-R after the

administration of LSD, significant increases in Optimism and Openness were found two weeks after the experimental session.⁴² Moreover, increases in global brain entropy induced by LSD predicted changes in Openness, suggesting that this personality trait could be regulated by cortical 5-HT_{1A/2A} receptors.⁴³

Since there are no consistent long-term changes in personality after the controlled administration of psilocybin, these series of evidences of changes in some personality traits after the controlled administration of a psychedelic drug seems to be weak, so replication of these results is necessary before stating that the controlled administration of a psychedelic drug can induce permanent changes on personality traits. Also, the objectives of the studies done with psilocybin and LSD were quite different: while the psilocybin studies were designed to induce mystical experiences, the study with LSD was more focused in studying basic neuropsychological processes.

New studies designed specifically to study eventual personality changes, as the studies developed by Griffiths' group, are warranted to obtain stronger evidences of personality changes induced by the administration of a psychedelic drug. Moreover, neuroimaging studies using different techniques should be further developed to investigate the possible biological and neural substrates of personality traits and to study possible ways to modulate them in beneficial and therapeutic ways. **Future studies should also investigate the possible impact of other biological factors on personality, such as gender, age of exposure to psychedelics (i.e., potential different reactions between teenagers and adults), and the participation of other neurotransmission systems (e.g., dopamine and glutamate).**

It is important to contextualize the findings of the present review with the broader discussion regarding if and to what extent personality traits may be changed as a result of specific life events or therapeutic interventions.^{67,68} Prior generations of researchers argued that personality traits typically are stable or change slowly and gradually over

many years. However, research from the last decades showed that personality traits can and do change more quickly (few weeks or months) than commonly thought (many years).^{67,68} For instance, observational studies suggest that love- and work-related life events (e.g., first romantic relationship, marriage, parenthood, transition from school to college, promotions, unemployment, and retirement) can lead to changes in personality traits over the years,⁶⁷ and experimental studies show that therapeutic interventions (pharmaco- and psychotherapies) can also lead to changes, but in a shorter period of time (few weeks to months) and with prolonged effects (years).⁶⁸

Some of the results discussed in the present review suggest that acute administration of single (or few) doses of serotonergic psychedelics associated (or not) with psychotherapies can lead to fast (few weeks to months) and enduring (several weeks or months) changes in personality. Thus, further research is needed to assess if administration of psychedelics can indeed induce fast and enduring therapeutic changes in personality. The specific compound, dosage, and form of intervention (ritual or clinical) are important topics for future studies.

Finally, the data reviewed should be interpreted with caution not only because most studies have small sample sizes and show great heterogeneity among them, but because the different measures of personality not always are measuring the same personality traits and also have different psychometric reliability, which is critical for interpreting the broad array of findings reviewed.

We found that classical (oldest) studies studying the relationships between personality traits and psychedelic use used mainly the EPQ (also known as EPI), whose validity was fairly well established, its construct validity and test-retest reliability are high, and all the scales (with the exception of boredom susceptibility) have shown internal consistency and test-retest reliability.³⁰

The studies comparing personality traits between psychedelic users and nonusers used mainly the TCI (in its different versions and in different cultures –Brazil, Spain, and US) and the BFI (US). The BFI is another classical instrument to assess personality, with versions in several languages and used in several settings and populations.⁶⁹ The internal consistency reliability estimates for the BFI scales are Extraversion (.86), Agreeableness (.79), Conscientiousness (.82), Neuroticism (.87), and Openness to Experience (.83).²⁹ Regarding the TCI, the Brazilian Portuguese version both of the TCI and of the TCI-R have been validated and there is evidence of very good internal consistency reliability, as denoted by Cronbach's alpha values > 0.80 for all scales.^{30,70} For the Spanish version of the TCI-R, the reliability of the dimensions is also high with values of 0.77 to 0.87.⁷¹

The clinical trials studying the eventual personality changes induced by a psychedelic experience used mainly the NEO PI-R, one of the most standard measures within personality psychology. Meta-analytic reliability estimates (α) for the NEO-PI-R scales are Extraversion (.86), Agreeableness (.86), Conscientiousness (.91), Neuroticism (.90), and Openness to Experience (.85).⁷² However, although the psychometric properties and the factor solutions of both the NEO PI-R and the TCI-R are consistent across studies and cultures, confirmatory factor analyses (CFA) offers unsatisfactory goodness-of-fit and it is necessary to increase the complexity of the models towards a complete structure to obtain a satisfactory adjustment to data.⁷³

Other personality tests used in some of the reviewed studies are the ZSS and the TAS. The reliability coefficients for the ZSS range between 0.72 and 0.83, indices that have been shown to be stable across cultures.^{74,75} A recent cross-validation study of the TAS found that its subscales have acceptable internal consistency and construct reliability (≥ 0.70), and excellent fit indices.⁷⁶

Therefore, considering the good psychometric properties of most personality measures used in the reviewed studies, the data presented in them seem to reflect correctly what they are supposed to measure.

5. Conclusions

In this systematic review, we have found three types of evidences: 1) some specific personality traits may influence the effects of the psychedelic experience; 2) there are evident differences in some personality traits between psychedelic users and nonusers, independently if that use is recreational or religious; and 3) psychedelics administered in controlled settings may induce some permanent changes in personality. At the same time, there are a series of limitations for each of those evidences: 1) there is a lack of well controlled studies researching the responses of different people with different personality profiles to the psychedelic experience; 2) there is a need of prospective studies to better understand the causal relations that may help to explain the personality differences between users and nonusers; and, 3) the evidences of permanent personality changes after a controlled psychedelic experience are still weak and further studies are warranted before having a more definitive answer to this interesting topic.

Based on the reviewed data, it seems plausible to suggest that the transitory effects of psychedelics could be related to functional synaptic changes induced by these drugs on 5-HT receptors, while the long-term and persistent effects could be related to psychological changes or changes in gene expression.

Regarding the implications of the research between psychedelic use and personality, there are at least two: 1) this type of research may offer new evidences to the classic discussion on whether personality is or isn't a constant and stable psychological trait; and 2) how personality measures can be used as outcome variables in psychotherapy or, on the other side, how to consider them as process variables that could help to improve psychotherapeutic

treatments. In this sense, to keep implementing personality measures in psychedelic research is a very promising field in psychology and in psychopathological and psychotherapeutic research and practices.

Conflicts of Interest: JCB is the Scientific Director of ICEERS. ICEERS is a non-profit organization that promotes the scientific research of plant hallucinogens such as ayahuasca and ibogaine. RGS is a member of the ICEERS Advisory Board. The authors have no conflict of interests to disclose. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

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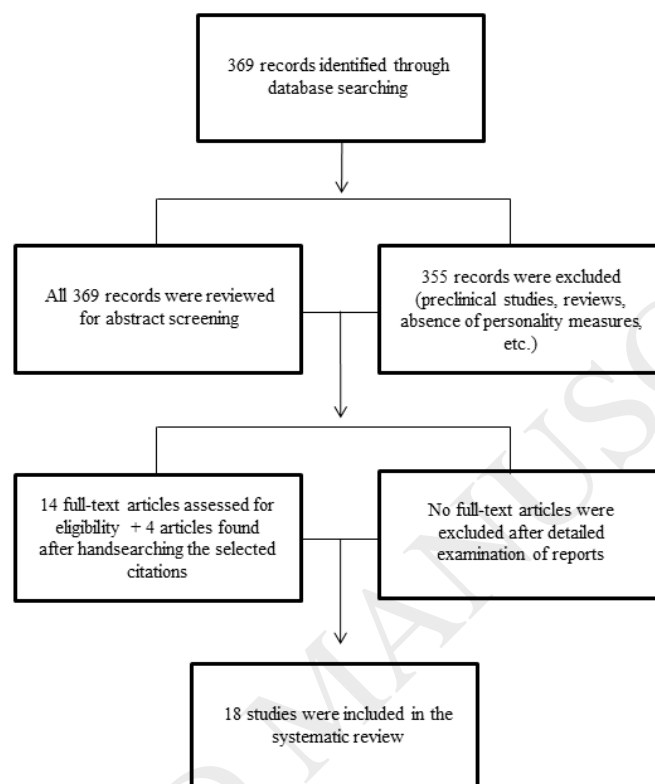
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Figures

Figure 1. Flow diagram illustrating the different phases of the systematic review



Tables

Table 1. Main findings of the studies included in the systematic review

References	Study characteristics, sample	Drug, dose	Personality measure	Main findings
Hemsley and Ward, 1985	United Kingdom, observational, no control group 29 polydrug users (gender and age not specified)	Polydrug use (cannabis, LSD; drug type or frequency not specified)	EPQ ¹	Significant ($P<0.01$, uncorrected) positive correlation between EPQ1 and frequency of unpleasant LSD experiences (“bad trips”), occurrence of unpleasant visual hallucinations during the experience, and recurrence of drug effects after acute effects have subsided (“flashbacks”); and significant ($P<0.05$, uncorrected) negative correlation between EPQ2 and frequency of “bad trips”
Anglin et al., 1986	United States, observational, inclusion of a control group 53 mushrooms users (60% mem, mean age 19.22 years; 40% women, mean age 18.66 years) compared to 53 matched controls with no prior history of mushroom use (60% mem, mean age 19.19 years; 40% women, mean age 18.33 years)	Psilocybin (mushrooms, oral) Dose/frequency of use not specified	EPQ ¹ , ZSS, CPI-S, PRE	Compared to male nonusers, male users showed significantly higher scores on ZSS1 and significantly lower scores on EPQ3 and CPI-S. Compared to female nonusers, female users showed significantly higher scores on ZSS2 and ZSS3 and significantly lower scores on CPI-S ($P<0.05$, uncorrected)
Mabry and Khavari, 1986	United States, observational, no control group 309 volunteers (78% males, mean age 25.8 years; final sample $N = 298$)	Cannabis/THC (smoked), LSD (oral), mescaline (oral) Less than monthly use for LSD and other psychedelics: 36%; monthly use: 4% for LSD and 6% for other psychedelics	EPI ¹ , ZSS, SDS, SSPQ	Significant associations between hallucinogen use and ZSS1, ZSS2, ZSS4, SSPQ1 and SSPQ2 ($P<0.05$, uncorrected)
Grob et al., 1996	Brazil, observational, inclusion of a control group 15 long-term UDV members compared with 15 matched controls with no prior history of ayahuasca use (15 men; mean age 35.9 years)	Ayahuasca (oral) ≥10 years of ritual use	TPQ	UDV group: lower scores on NS (NS1, NS2, NS total) and HA (HA1, HA total score) ($P<0.05$, uncorrected)

Lienert and Netter, 1996	Germany, experimental (analysis of a dataset from 1987 from an apparently open-label study with no control group) 65 students (gender and age not specified)	LSD (oral) 1 µg/kg	MPI	Significant ($P<0.0125$, corrected) personality-related responses to LSD were observed: “thinking disturbances”, “affective reactions”, and “blackouts” were all reported by 11 of the 16 “hysteries/extraverted neurotics” (high extraversion and neuroticism), while eight of 16 “stable extraverts” (high extraversion and low neuroticism) reported only “affective reactions” (laughter, weeping), six of 11 “dysthymics/introverted neurotics” (low extraversion and high neuroticism) reported only “thinking disturbances”, and seven of 17 “stable introverts” (low extraversion and neuroticism) reported only “blackouts”
Bresnick and Levin, 2006	Brazil, observational, no control group 21 volunteers (17 men, mean age 44.2 years)	Ayahuasca (oral) Four sessions (dose not specified)	TAS	Participants showed higher TAS scores compared to normative data, and TAS scores were significantly ($P<0.05$, uncorrected) related to synesthesia during the acute effects of ayahuasca
Griffiths et al., 2006	United States, experimental (double-blind, between-group, crossover, placebo-controlled study, 2-month follow-up) 36 hallucinogen-naïve adults (16 men, mean age 46 years)	Psilocybin (oral) Single dose, 30 mg/70 kg Active placebo: methylphenidate (40 mg/70 kg)	NEO PI-R	NSR
Griffiths et al., 2008	United States, experimental (14-month follow-up of the study by Griffiths et al., 2006)	Psilocybin (same doses of the study by Griffiths et al., 2006)	NEO PI-R, MAP	NSR
Barbosa et al., 2009	Brazil, observational, no control group, inclusion of follow-up 23 volunteers participating in STD ($N=15$) and UDV ($N=8$) rituals for the first time, with a 6-month follow-up (8 men; mean age 37 years)	Ayahuasca (oral) 17 irregular users (<10 uses), 6 regular users (>10 uses)	TCI-125	<i>STD group</i> : lower scores on HA (positively correlated to significant reductions in minor psychiatric symptoms (CIS-R)) <i>UDV group</i> : lower scores on RD (positively correlated with intensity

				<p>of ayahuasca use, and negatively correlated with length of wash-out period)</p> <p><i>Total sample:</i> lower scores on RD (positively correlated with intensity of ayahuasca use)</p> <p><i>STD vs. UDV:</i> higher NS (STD)</p> <p><i>Regular users:</i> lower scores on RD</p> <p><i>Regular vs. irregular users:</i> higher scores on RD (baseline) and SD (6 months) (regular users) ($P<0.05$, uncorrected)</p>
MacLean et al., 2011	<p>United States, experimental</p> <p>Combined data from two double-blind, placebo-controlled studies (1-2- and 16-month follow-ups)</p> <p>52 hallucinogen-naïve adults (22 men, mean age 46 years)</p>	<p>Psilocybin (oral)</p> <p>30 mg/70 kg</p>	NEO PI-R	<p>Compared to baseline, Openness scores increased significantly 1-2 months after drug sessions ($P<0.023$, uncorrected), and there were no significant changes in the scores of the participants who received inactive placebo, methylphenidate, or 5 mg/70 kg psilocybin; changes in Openness scores were positively correlated with scores on the SOCQ ($P<0.05$, uncorrected); participants who had a “complete mystical experience” showed significant increases in Openness scores and in the scores of five of its six facets (Fantasy, Aesthetics, Feelings, Ideas and Values) at the 1-2-month follow-up ($P<0.05$, uncorrected), but scores at the 16-month follow-up were only marginally higher than baseline values ($P=0.05$, uncorrected)</p>
Bouso et al., 2012	<p>Brazil, observational, inclusion of a control group and follow-up</p> <p>Jungle- ($N=56$) and urban-based ($N=71$) long-term STD/BRQ members compared with rural ($N=56$) and urban ($N=59$) matched controls with no prior history of</p>	<p>Ayahuasca (oral)</p> <p>≥ 15 years of ritual use</p>	TCI	<p><i>First assessment:</i> ayahuasca users showed higher scores on RD (RD1, RD2), ST (ST1, ST2, ST3), and C1; and lower scores in HA (HA2, HA3, HA4), NS2,</p>

	ayahuasca use, with a 1-year follow-up (jungle users: 29 men, mean age 36 years; jungle controls: 24 men, mean age of 33.71 years; urban users: 33 men, mean age of 37.32 years; urban controls: 31 men, mean age of 38.15 years)			C2, and SD (SD1, SD2, SD3, SD4) <i>Jungle vs. urban samples:</i> higher scores on RD1, RD2, HA4, SD3 (jungle sample) <i>Follow-up:</i> ayahuasca users showed higher scores on ST (ST2, ST3) and C1, and lower scores in HA (HA1, HA2, HA3) and SD (SD1, SD4) ($P<0.05$, uncorrected)
Studerus et al., 2012	Zurich, experimental Pooled data of 23 placebo-controlled studies 261 volunteers (62% men, mean age 27.8 years)	Psilocybin (oral) 409 psilocybin administrations Mean \pm SD: 214 \pm 63 mg/kg, range: 115-315 mg/kg	ZKPQ, TAS	High TAS scores significantly predicted pleasant and mystical-type experiences, whereas high Sociability scores significantly predicted few mystical-type experiences and increased perceptual alterations ($P<0.05$, uncorrected).
Bouso et al., 2015	Spain, observational, inclusion of a control group 22 long-term STD members (six men, mean age 40.9 years) compared with 22 matched controls with no prior history of ayahuasca use (six men; mean age 41.5 years)	Ayahuasca (oral) 5.3 years (mean) of ritual use	TCI-R	Ayahuasca users showed lower scores on HA (HA2) and higher scores in ST (ST1, ST2, ST3); scores on ST and ST2 were negatively correlated with significant cortical thinning of the PCC ($P<0.05$, uncorrected)
Kavenská and Simonová, 2015	Czech Republic/Peru, observational, no control group (population values from a German sample) 77 volunteers (47 men, mean age 36.6 years; final sample $N = 75$)	Ayahuasca (oral) 17.7 sessions (mean)	PSSI	Ayahuasca users showed significantly higher scores on the scales intuitive, optimistic, ambitious, charming, and helpful, and significantly lower scores on the scales and quiet ($P<0.05$, uncorrected)
Schneider et al., 2015	Brazil, observational, no control group (web survey) 8.646 volunteers (24.7% men, mean age 36.3 years; 75.3% women, mean age 34.7 years)	Hallucinogens (not specified) No use, occasional use, abuse, dependence	TCI-R	Occasional users showed significantly lower scores on HA and significantly higher scores on SD, and abusers showed significantly lower scores on P and significantly higher scores on ST ($P<0.05$, corrected)

Barbosa et al., 2016	United States, observational, inclusion of a control group 30 long-term UDV members (16 men, mean age 42.5 years) compared with 27 matched controls with no prior history of ayahuasca use (14 men; mean age 45 years)	Ayahuasca (oral) 32.5 ceremonies (mean) in the last year; 60 months (mean) of regular attendance	BFI	UDV members scored significantly higher on agreeableness and openness ($P<0.05$, uncorrected)
Carhart-Harris et al., 2016	United Kingdom, experimental (single-blind, within-subjects, placebo-controlled study, 2-week follow-up) 20 volunteers (16 men, mean age 30.9 years)	LSD (i.v.) 75 μ g	NEO PI-R, LOT-R	Compared to placebo, LSD significantly increased Optimism ($P=0.005$, corrected) and Openness ($P=0.03$, corrected) two weeks after the experimental sessions
Lebedev et al., 2016	United Kingdom, experimental (same design/participants of the study by Carhart-Harris et al., 2016)	LSD (same dose of the study by Carhart-Harris et al., 2016)	NEO PI-R	Relative to placebo, LSD significantly increased brain entropy in sensory systems, associative networks, and hierarchically higher cognitive brain networks such as the DMN; increases in global brain entropy predicted changes in Openness ($P=0.035$, uncorrected), and the predictive value of this relationship was enhanced by music-listening ($P=0.0005$, uncorrected); this relationship was also observed at the network level (both sensory and higher cognitive networks), both independently and mediated by music ($P<0.05$, uncorrected); increases in “ego-dissolution” after music-listening and in brain entropy at the orbitofrontal ($P=0.048$, uncorrected) and superior frontoparietal ($P=0.026$, uncorrected) networks significantly predicted increases in Openness scores

BFI: Big Five Inventory; BRQ: *Barquinha*; C: Cooperativeness (C1-Helpfulness vs. Unhelpfulness; C2-Compassion vs. Revengefulness); CIS-R: Clinical Interview Schedule – Revised Edition; CPI-S: California Psychological Inventory-Socialization subscale; DMN: Default Mode Network; EPQ/EQI: Eysenck Personality Questionnaire/Inventory (EPQ1-Neuroticism; EPQ2-Extroversion; EPQ3-Lie); HA: Harm Avoidance (HA1-Fear of Uncertainty vs. Confidence; HA2-Anticipatory Worry vs. Uninhibited Optimism; HA3-Shyness with Strangers vs. Gregariousness; HA4-Fatigability and Asthenia vs. Vigor); i.v.: intravenously; KSP: Karolinska Scales of Personality; LOT-R: Revised Life Orientation Test; LSD: lysergic acid diethylamide; MAP: Measurement of Actualization Potential; MPI: Maudsley Personality Inventory; NEO PI-R: NEO Personality Inventory; NS: Novelty Seeking (NS1-Exploratory Excitability vs. Stoic Rigidity; NS2-Disorderliness vs. Regimentation); NSR: nonsignificant results; PCC: posterior cingulate cortex; PRE: Zenhausem Preference test; PSSI: Personality Styles and Disorders Inventory; RD: Reward Dependence (RD1-Attachment vs. Detachment; RD2-Dependence vs. Independence); SD: Self-directedness (SD1-Responsibility vs. Blaming; SD2-Purposefulness vs. Lack of Goal-Direction; SD3-Resourcefulness; SD4-Self-Acceptance vs. Self-Striving); SDS: Marlowe-Crowne Social Desirability Scale; SOCQ: States of Consciousness Questionnaire; SSPQ: Self-System Perception Questionnaire (SSPQ1-Social Alienation; SSPQ2-Traditionalism); ST: Self-Transcendence (ST1-Self-Forgetfulness vs. Self-Conscious Experience; ST2-Transpersonal Identification vs. Self-Isolation; ST3-Spiritual Acceptance vs. Rational Materialism); STD: *Santo Daime*; TAS: Tellegen Absorption Scale; TCI: Temperament and Character Inventory; TCI-R: Temperament and Character Inventory-Revised; TCI-125: Temperament and Character Inventory – 125 items; THC: tetrahydrocannabinol; TPQ: Tridimensional Personality Questionnaire; UDV: *União do Vegetal*; ZKPQ: Zuckerman-Kuhlman Personality Questionnaire; ZSS: Zuckerman Sensation-Seeking Scale (ZSS1-Experience Seeking; ZSS2-General Sensation-Seeking; ZSS3-Disinhibition; ZSS4-Boredom-Susceptibility).

¹Same instrument.