Treating Addiction: Perspectives from EEG and Imaging Studies on Psychedelics

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Abstract

Despite reports of apparent benefits, social and political pressure beginning in the late 1960s effectively banned scientific inquiry into psychedelic substances. Covert examination of psychedelics persisted through the 1990s; the turn of the century and especially the past 10 years, however, has seen a resurgent interest in psychedelic substances (eg, LSD, ayahuasca, psilocybin). This chapter outlines relevant EEG and brain imaging studies evaluating the effects of psychedelics on the brain. This chapter also reviews evidence of the use of psychedelics as adjunct therapy for a number of psychiatric and addictive disorders. In particular, psychedelics appear to have efficacy in treating depression and alcohol-use disorders.

1. INTRODUCTION

Psychedelics have long been used by native cultures in various rituals (Schultes, 1979). In spite of countercultural connotations of the term

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psychedelic—coined by Sir Humphrey Osmond to mean "mind manifesting"—this appellation has been carefully chosen by scientists involved in "psychedelic renaissance" studies (Sessa, 2012). The term may include substances with a number of different pharmacological profiles, including serotonin agonists, glutamatergic *N*-methyl-D-aspartate receptor antagonists, κ-opioid receptor agonists, anticholinergic agents, and cannabinoids (Szabó, Kazai, Frecska, & Brys, 2015). Depending on the drug, dose, setting, and personal predisposition, the altered state of consciousness associated with psychedelics often includes cognitive changes; broad perceptual changes; profound experiential changes in mood, thought, insight, and memory; and mystical and transpersonal experiences including illusions and hallucinations (Nichols, 2004).

Based on their effects, these compounds can be categorized into deliriants, dissociatives, and classic psychedelics. Deliriants, such as plant-derived scopolamine and atropine and synthetic dimenhydrinate and trihexyphenidyl, commonly involve acetylcholine antagonism and tend to induce true hallucinations, delusions, and delirium (eg, stupor, confusion, confabulation). Dissociative hallucinogens, apart from perceptual changes, invoke a sense of detachment or dissociative anesthesia, described as oneirophrenia (dreamlike mind). Mechanisms of action of dissociative hallucinogens include NMDA receptor antagonisms (eg, ketamine and phencyclidine—PCP) and κ-opioid agonism (eg, salvinorin A, the active component of *Salvia divinorum*). Ibogaine is also a NMDA receptor antagonist and considered a dissociative hallucinogen, but its pharmacodynamics are complex and may include serotonin and opioid systems (Popik, Layer, & Skolnick, 1995). This chapter will focus on the properties of classic or serotonergic psychedelics. Methylenedioxymethamphetamine (MDMA, also known as "ecstasy" or "molly") and other phenethylamines with empathogenic properties are sometimes considered psychedelics, since they also act on serotonin receptors but because they also have amphetamine-like characteristics and are rarely hallucinogenic in the classical sense, they will not be included herein.

Based on their chemical profiles, classic psychedelics can be classified into three main categories: tryptamines, such as psilocybin, found in "magic mushrooms," and *N*,*N*-dimethyltryptamine (DMT); phenethylamines, such as mescaline and dl-2,5-dimethoxy-4-methylamphetamine (DOM); and lysergamides, such as lysergic acid diethylamide (LSD), with both

tryptamine and phenethylamine properties, have efficacy primarily as partial agonists at serotonin $5HT_{2A}$ receptors.

Classic psychedelics modulate serotonin ($5HT_{2A}$) receptors, although recent work suggests involvement of sigma-1 receptors (Fontanilla et al., 2009). They include psilocybin, ayahuasca, mescaline, and LSD, which have very low addictive potential (Shmulewitz, Greene, & Hasin, 2015) and increasing evidence suggests that they may be an alternative tool in the treatment of addiction (Bogenschutz, 2013; Bogenschutz et al., 2015; Bogenschutz & Johnson, 2016; Bogenschutz & Pommy, 2012; Dakwar, Levin, Foltin, Nunes, & Hart, 2014; Dyck, 2009; Liester & Prickett, 2012; Mangini, 1998; Ross, 2012; Sewell, Halpern, & Pope, 2006; Vollenweider & Kometer, 2010; Winkelman, 2014).

This chapter has two aims. The first aim is to present the available studies that have used electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) to investigate the human brain under the influence of classic psychedelics. The second aim is to discuss their use as therapeutic options to treat drug addiction.

2. BRAIN RESEARCH STUDIES OF CLASSIC PSYCHEDELICS

Knowledge about plants and substances with psychedelic properties is not new to modern science: mescaline was isolated by Arthur Heffter in the late 19th century, and the effects of LSD were identified by Albert Hofmann in 1943 (Stafford, 1992). Nevertheless, our knowledge about the mechanisms of action of these substances remains superficial, in part due to the research embargo this field has been subjected for many decades, at least since the end of the 1960s, as a result of the "war on drugs" (Oram, 2014; Rowe, 2006).

While scientific studies using psilocybin have been taking place since the end of the 20th century (Carhart-Harris, Bolstridge, et al., 2016; Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris et al., 2011; Gouzoulis-Mayfrank, Schreckenberger, et al., 1999; Gouzoulis-Mayfrank, Thelen, et al., 1999; Kraehenmann et al., 2015; Palhano-Fontes et al., 2015), LSD, the most paradigmatic of all psychedelics, has only recently reentered the scope of modern science (Gasser et al.,

2014). This is also true for the evaluation of psychedelics using modern neuroimaging techniques: in spite of the rapid proliferation of MRI-based psychiatric, pharmacological, and psychological studies, relatively few publications have used MRI to assess the effects of psychedelics on the human brain.

2.1 Ayahuasca

Ayahuasca (the "vine of the spirits" in Quechua) is a psychedelic brew traditionally used by Amerindians that reached Brazilian urban centers around 1930, where it has since been used as a sacrament in syncretic churches such as the Santo Daime, the União do Vegetal (UDV), and Barquinha. More recently, the use of ayahuasca has expanded to the United States and Europe (Labate & Cavnar, 2011). There are numerous recipes that may be used to prepare ayahuasca, although it is most frequently produced by the decoction of the bark of a liana named *Banisteriopsis caapi* (*B. caapi*) with the leaves of a DMT-containing plant, *Psychotria viridis* (Ott, 1994). Indigenous traditions consider the *B. caapi* vine to be the main ingredient of ayahuasca and name the brew after the native species (eg, ayahuasca, natem, yagé, nixi pae). In research studies, it is important to keep in mind the potential diversity of components of ayahuasca (Brierley & Davidson, 2012), since it has come from a number of different plants and cultivars collected at different times.

Compared to other psychedelics, the pharmacology of ayahuasca is particularly complex. DMT is mostly inactive when taken orally due to the presence of monoamine oxidase (MAO) enzymes in the gut. However, *B. caapi* is rich in β-carboline alkaloids (eg, harmine and harmaline), which are reversible MAO inhibitors. The constituents of ayahuasca therefore protect DMT from degradation, allowing its access to the central nervous system (McKenna, 2004). Also, MAO inhibition likely has direct impact on the brain, as these enzymes protect other monoamines, such as serotonin, dopamine, and norepinephrine, from oxidative deamination. Furthermore, β-carbolines may have psychoactive properties independent of MAO inhibition. For example, another component of ayahuasca, tetrahydroharmine (THH), is a serotonin reuptake inhibitor (SSRI). It is still in dispute to what extent harmine, harmaline, and THH have independent psychedelic effects (Naranjo, 1987; Ott, 1994; Shulgin, 1980).

The acute effects of ayahuasca begin approximately 30–40 min after oral intake, and last up to 4 h. Autonomic responses include increases in cardiac and respiratory rates, blood pressure, temperature, and pupil diameter

(Callaway et al., 1996; Riba et al., 2003). Ayahuasca effects also include changes in perception, altered spatiotemporal scaling, enhanced visual imagery (especially with eyes closed), increased introspection, changes in mood, and the memories with high emotional salience (Shanon, 2003).

Results of several research studies using ayahuasca are presented in Table 1. The first EEG study using ayahuasca was conducted in 11 members of the Santo Daime church in a ritual setting. Increased gamma power was observed in left occipital–temporal–parietal electrodes, during the eyes-closed condition. With eyes open, significant increased gamma power was restricted to occipital electrodes (Don et al., 1998). In another EEG study of 12 experienced individuals after three doses, ayahuasca increased power of both alpha and theta bands when compared to baseline. The strongest increase of alpha activity was observed in occipital electrodes; alpha was unchanged in the frontal electrodes and theta power significantly increased in both occipital and frontal areas (Hoffman et al., 2001).

The first set of well-controlled experiments was performed with a low (0.6 mg/kg of DMT) and high (0.85 mg/kg of DMT) dose of encapsulated, freeze-dried ayahuasca administered to 18 volunteers with previous psychedelic experience, in a double-blind crossover, placebo-controlled design. Absolute power decreased in all frequency bands, most prominently in theta; relative power of delta decreased. There was also an increase in beta power. Observed EEG changes began 15–30 min after ayahuasca intake, reached a peak between 45 and 120 min, and thereafter decreased to baseline 4–6 h after administration (Barbanoj et al., 2008; Riba et al., 2004, 2002). The spatial distribution of brain electrical activity was investigated using low-resolution electromagnetic tomography (LORETA) and a high dose (ie, 0.85 mg/kg of DMT) compared to placebo. Statistically significant differences, found at 60 and 90 min after ayahuasca intake, showed decreases in the alpha, delta, theta, and beta bands. Analysis with LORETA indicated that power decreases in delta, alpha, and beta bands occurred in the temporo-parieto-occipital junction, while theta decrease was localized to temporomedial and frontomedial regions (Riba et al., 2004).

To investigate the impact of daytime ayahuasca consumption on sleep, as measured by polysomnography (Barbanoj et al., 2008), freeze-dried ayahuasca (equivalent to 1 mg/kg of DMT), and an active placebo of D-amphetamine (20 mg) were administered to 22 healthy male volunteers in a randomized, double-blind, placebo-controlled, crossover design. Subjects ingested ayahuasca or amphetamine during the day, and sleep was evaluated the following night. In contrast with D-amphetamine, ayahuasca did not

Table 1 EEG and Imaging Studies with Ayahuasca

Method	Subjects	Dose					Design	Start of Acquisition After Dosing	Results	Reference(s)
		Presentation	DMT	HRM	HRL	THH				
EEG	11 Santo Daime members	Liquid Average dose (75 mL)	0.546 mg/mL 41 mg	0.741 mg/mL 55.6 mg	0.061 mg/mL 4.6 mg	0.585 mg/mL 43.9 mg	Religious ritual setting, single dose, no placebo	45–60 min	Increased power in higher frequencies (36–44 Hz) in left occipital–temporal–parietal scalp electrodes with eyes closed. Effect extended to most of the posterior scalp with eyes open. Tendencies toward decrease in power of slow (theta and alpha) waves and increases in beta	Don et al. (1998)
EEG	12 Healthy volunteers	Not quantified					Shamanic setting, acquisition after three doses, no placebo	1–2 h After the third dose (4–6 h after the first one)	Strong increases in alpha and theta mean amplitudes. Beta amplitudes unchanged. Strongest increases of alpha activity in occipital lobes, unchanged in the frontal lobes. Theta amplitudes increased in all parts of the brain, except for the right temporal and posttemporal areas	Hoffman, Hesselink, and Silveira-Barbosa (2001)
Topographic EEG	18 Healthy volunteers	Original liquid Low dose (dried) High dose (dried)	0.53 mg/mL 0.6 mg/kg 0.85 mg/kg	0.90 mg/mL 1.02 mg/kg 1.44 mg/kg	0.06 mg/mL 0.07 mg/kg 0.1 mg/kg	0.72 mg/mL 0.82 mg/kg 1.15 mg/kg	Double-blind crossover design with placebo and two doses (low and high) of freeze-dried ayahuasca	"Regular intervals"	Absolute power decreased in all frequency bands, most prominently in theta. Relative power decreased in delta and theta and increased in alpha and beta (especially faster beta-3 and beta-4). Findings were dose dependent	Riba et al. (2002)
EEG/LORETA								30, 60, 90, 120, 180, 360, and 480 min	Only the high dose was assessed. Differences found at 60 and 90 min of intake. Power density decreased in alpha-2, delta, theta, and beta-1. Power decreases in delta, alpha-2, and beta-1 detected over temporo-parieto-occipital junction. Theta power reductions registered in temporomedial and frontomedial regions	Riba, Anderer, Jane, Saletu, and Barbanoj (2004)
EEG/PSG	22 Male healthy volunteers	Freeze dried	1.0 mg/kg	1.70 mg/kg	0.11 mg/kg	1.36 mg/kg	Double-blind crossover design; administration of ayahuasca, D-amphetamine (20 mg) and placebo	9 h	No deterioration of sleep quality or PSG disruptions of sleep initiation or maintenance with ayahuasca, different from D-amphetamine. Both ayahuasca and D-amphetamine decreased REM, with a trend increase in REM sleep onset latency. While D-amphetamine decreased slow-wave sleep (SWS) power in the first nigh cycle, the opposite happened with ayahuasca	Barbanoj et al. (2008)
Topographic EEG	20 Healthy volunteers	Liquid	0.328 mg/mL 1.39 mg/kg	1.08 mg/mL 4.58 mg/kg	0.18 mg/mL 0.75 mg/kg	1.28 mg/mL 5.43 mg/kg	Open-label, pre-, and postayahuasca comparison	25, 50, 75, 100, and 125 min	First phase (from 50 min, associated with DMT and harmine plasma levels): reduced power in alpha, mostly at the left parieto-occipital cortex. Second phase (between 75 and 125 min,	Schenberg et al. (2015)

									correlated with harmaline and THH levels): increased in slow-gamma power at left centro-parieto-occipital, left frontotemporal, and right frontal cortices, and of fast-gamma at left centro-parieto-occipital, left frontotemporal, right frontal, and right parieto-occipital cortices	
SPECT	15 Healthy male volunteers	Original liquid Freeze dried	0.53 mg/mL 1.0 mg/kg	0.90 mg/mL 1.70 mg/kg	0.06 mg/mL 0.11 mg/kg	0.72 mg/mL 1.36 mg/kg	Double-blind, placebo controlled	100–110 min	Increased blood perfusion observed bilaterally in the anterior insula (more intense in the right hemisphere), and right anterior cingulate/frontomedial cortex increased blood flow in the left amygdala/parahippocampal gyrus	Riba et al. (2006)
SPECT	17 Patients with recurrent depression	Liquid	0.8 mg/mL 1.76 mg/kg	0.21 mg/mL 0.46 mg/kg	Not detected	Not informed	Open-label, single dose, no placebo	8 h	Increases in blood perfusion in the left nucleus accumbens, right insula, and left subgenual area	Sanches et al. (2016)
fMRI/BOLD	9 Healthy members of Santo Daime						Open-label, single dose, no placebo, before/after intake comparisons	40 min	Acquisition made during a mental imagery task with eyes open and closed. Robust increases in the activation of several occipital, temporal, and frontal areas during mental imagery task with eyes closed, but not with eyes open. Potentiated activity of parahippocampal gyrus, right fusiform, and right middle occipital gyrus. Positive modulation of middle and superior frontal gyrus	de Araujo et al. (2012)
fMRI								Resting state	Decreased activity through most parts of the default mode network, including its most consistent hubs: the posterior cingulate cortex (PCC)/precuneus and the medial prefrontal cortex. Functional connectivity within the PCC/precuneus was decreased. No decrease in orthogonality (enhanced connectivity) between the default mode and the task-positive networks	Palhano-Fontes et al. (2015)
sMRI	22 Regular ayahuasca users and 22 controls	Ayahuasca users were members of Santo Daime; average lifetime use: 123 times (range: 50–352)					Case-control study	Does not apply	Differences from controls were found in midline brain structures. With a thinning in the posterior cingulate cortex of ayahuasca users. PCC cortical thickness was inversely correlated with intensity and duration of prior ayahuasca use and with self-transcendence scores	Bouso, Palhano-Fontes, Rodríguez-Fornells, et al. (2015)

Note: *BOLD*, blood-oxygen-level-dependent contrast imaging; *DMT*, *N,N*-dimethyltryptamine; *EEG*, electroencephalography; *fMRI*, functional magnetic resonance imaging; *HRM*, harmine; *HRL*, harmaline; *LORETA*, low-resolution electromagnetic tomography; *PCC*, posterior cingulate cortex; *SPECT*, single-photon emission computed tomography; *sMRI*, structural magnetic resonance imaging; *THH*, tetrahydroharmine.

induce any subjectively perceived deterioration of sleep quality or disruptions of sleep initiation and/or maintenance. Both ayahuasca and D-amphetamine inhibited rapid eye movement (REM) sleep, decreasing its duration in absolute values and as a percentage of total sleep time, and showed a trend to increase REM onset. On the other hand, D-amphetamine decreased slow-wave sleep (SWS) power, while ayahuasca increased SWS power (Barbanoj et al., 2008).

The most recently published EEG study on ayahuasca investigated the relationship between temporal changes in EEG measures with serum concentrations of the main components of ayahuasca. Ayahuasca, donated by UDV, was given *in natura* to 20 individuals with previous experience. There was no blinding or placebo control. A biphasic effect of ayahuasca was found. The first phase showed reduced alpha power, 50 min after ingestion; the second phase was characterized by an increase in slow- and fast-gamma (30–50 and 50–100 Hz, respectively) power 75 and 125 min after ingestion. Alpha power decrease was most evident on the left parieto-occipital cortex. Slow-gamma increases were localized to the left centro-parieto-occipital, left frontotemporal, and right frontal cortices, while the fast-gamma increases were found on the left centro-parieto-occipital, left frontotemporal, right frontal, and right parieto-occipital cortices. These effects were significantly associated with circulating levels of DMT, harmine, harmaline, THH, and some of their metabolites (Schenberg et al., 2015).

A SPECT study using freeze-dried ayahuasca in a placebo-controlled design evaluated healthy male volunteers ($n = 15$) with previous psychedelic experience, scanned 100–110 min after ayahuasca administration. Significantly increased cerebral blood flow (CBF) was observed bilaterally in the anterior insula, asymmetric to the right hemisphere, in the right anterior cingulate cortex (ACC)/frontomedial cortex, and in the left amygdala/parahippocampal gyrus (Riba et al., 2006).

fMRI has also been used to investigate the acute effects of ayahuasca (de Araujo et al., 2012; Palhano-Fontes et al., 2015). fMRI was acquired before and after (40 min) ayahuasca, from nine members of the Santo Daime church, who performed a visual perception and a mental imagery task. This study suggests that ayahuasca selectively increases the activity of the primary and higher visual cortices (BA17, 18, and 19), the parahippocampal gyrus (BA30), and the right fusiform gyrus (BA37). A positive modulation was also found in the frontopolar cortex (BA10) (de Araujo et al., 2012). In another fMRI study, ayahuasca significantly decreased the activity in many regions

of the Default Mode Network (DMN), particularly the posterior cingulate cortex (PCC)/precuneus. Also, decreased functional connectivity between the PCC/precuneus and other regions was observed during the effects of ayahuasca (Palhano-Fontes et al., 2015). The DMN is a set of brain regions with higher activity at rest (eyes-closed) relative to externally oriented tasks and has been associated with a variety of mental states, including mind wandering and rumination (Hamilton, Farmer, Fogelman, & Gotlib, 2015; Tops, Boksem, Quirin, IJzerman, & Koole, 2014).

2.2 Psilocybin

Psilocybin, an indolealkylamine and tryptamine, is the main active ingredient of the group of fungi known as "magic mushrooms." Psilocybin is a prodrug, that is, a substance that is metabolized after administration to become pharmacologically active as psilocin. When given orally, psilocybin is almost entirely transformed into psilocin during first-pass liver metabolism. Intravenous administration requires conversion of psilocybin to psilocin in the kidneys, a process that may be less efficient (Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997; Passie, Seifert, Schneider, & Emrich, 2002). The neuropsychological effects of psilocin appear to be mediated by stimulation of serotonergic receptors, namely, subtypes $5HT_{2A}$, $5HT_{2C}$, and $5HT_{1C}$. Psilocybin is well tolerated and safe for human studies at oral doses of 8–25 mg and intravenous doses of 1–2 mg (Passie et al., 2002; Shulgin, 1980; Tylš, Páleníček, & Horáček, 2014).

Results of several research studies using psilocybin are presented in Table 2, together with the few mescaline and LSD studies available. A PET study used [^{18}F]-fluorodeoxyglucose (FDG) to assess cerebral metabolic rate of glucose utilization (MRglu) following psilocybin administration (Vollenweider et al., 1997). Ten healthy volunteers were scanned before and 90 min after receiving a single oral dose of psilocybin (15 mg to subjects $\leq$ 50 kg or 20 mg to subject $\geq$ 51 kg body weight). Psilocybin produced a global increase (~25%) of MRglu, most prominent in frontomedial and frontolateral cortices, ACC, and temporomedial cortex. Increased MRglu was also found in the basal ganglia (~19%) and in sensorimotor and occipital cortices (~14%). Significant correlations were found between "psychotic-like symptoms" and increased MRglu in the prefrontal cortex.

EEG/MEG studies with psilocybin have shown decreased parieto-occipital alpha power (Kometer, Schmidt, Jancke, & Vollenweider, 2013).

Table 2 EEG and Imaging Studies with Psilocybin, Mescaline, and LSD

Method	Subjects	Drug	Dosage	Design	Start of Acquisition After Dosing	Effects of Psychedelic Substance	References
SPECT	23 Male healthy volunteers	Mescaline (oral)	500 mg	Open design: 11 in mescaline and 12 in placebo group; ^{99m}Tc-HMPAO-assessed CBF	4½ h	Pattern of hyperfrontality with emphasis on right hemisphere in mescaline group	Hermle et al. (1992)
						Right-hemisphere lateralization only on the anterior cortical regions in mescaline group	Hermle, Gouzoulis-Mayfrank, and Spitzer (1998)
PET/MRglu	10 Healthy volunteers	Psilocybin (oral)	15 mg (subjects $\leq$ 50 kg) or 20 mg ($\geq$51 kg)	Single-blind design (volunteers received one of three drugs); [^{18}F] FDG-assessed MRglu	90 min	Global increase in brain MRglu. Greatest increases in frontomedial, frontolateral, anterior cingulate, and temporomedial cortex. Smaller increases in the basal ganglia and sensorimotor and occipital cortices. Correlation of psychotomimetic symptoms with increases in prefrontal, anterior cingulate, and temporomedial cortices and putamen	Vollenweider et al. (1997)
PET/binding	7 Male healthy volunteers	Psilocybin (oral)	0.25 mg/kg	Randomized single-blind design. Binding of [^{11}C] raclopride to D2 receptors in striatum	Not clear: after 80 min and before 140 min	Decreased [^{11}C] raclopride receptor binding potential bilaterally in caudate and putamen, consistent with an increase in endogenous dopamine. Changes were correlated with depersonalization associated with euphoria	Vollenweider, Vontobel, Hell, and Leenders (1999)
PET/MRglu	8 Healthy volunteers	Psilocybin (oral)	0.2 mg/kg	Double-blind, placebo-controlled design; [^{18}F] FDG-assessed MRglu	110–120 min	Increased MRglu in different right hemispheric frontotemporal cortical regions, predominantly in anterior cingulate. Metabolic rates decreased in the thalamus. Attenuation of cognitive activation-related increases in left frontocortical regions	Gouzoulis-Mayfrank, Schreckenberger, et al. (1999) and Gouzoulis-Mayfrank, Thelen, et al. (1999)
EEG	50 Healthy volunteers	Psilocybin (oral)	0.17 or 0.215 mg/kg	Data from three different studies, all of them with a placebo-controlled fixed-order (placebo then psilocybin) double-blinded design	60 min	Decreased density of neuronal oscillations at 1.5–20 Hz within a neural network composed by the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and parahippocampal regions. Intensity levels of psilocybin-induced spiritual experience and insightfulness correlated with lagged phase synchronization of delta oscillations (1.5–4 Hz) between the retrosplenial cortex, the parahippocampus, and the lateral orbitofrontal area	Kometer, Pokorny, Seifritz, and Volleinweider (2015)

MEG	15 Male healthy volunteers	Psilocybin (IV)	2 mg	Fixed-order (first placebo, then psilocybin) single-blinded design	Immediate	Spontaneous cortical oscillatory reduced by psilocybin in posterior association cortices from 1 to 50 Hz and from 8 to 100 Hz in frontal association cortices. Large decrease in the oscillatory power was observed in regions of the default mode network. No effect on low level visually induced and motor-induced gamma-band oscillations	Muthukumaraswamy et al. (2013)
fMRI/BOLD	10 Healthy volunteers	Psilocybin (IV)	2 mg	Volunteers submitted to drug and placebo separated by about 7 days	7½ min	Data acquisition during 16 s period while subjects imagined reexperiencing positive memories, after being exposed to visual cues for 6 s. Increased activity of visual and other sensory cortices during recollection. Stronger memory vividness and visual imagery. Significant correlation between subjective well-being at follow-up and memory vividness	Carhart-Harris, Leech, Williams, et al. (2012)
fMRI/ASL and BOLD	30 Healthy volunteers	Psilocybin (IV)	2 mg	Task-free placebo-controlled design; 15 volunteers for arterial spin-labeling perfusion and 15 for BOLD fMRI	Immediate	Only decreases in cerebral blood flow and BOLD signal were present. Decreases were more intense in thalamus, ACC, and PCC. Magnitude of decreased activity in ACC/medial prefrontal cortex (mPFC) predicted the intensity of the subjective effects. Connectivity analysis using medial prefrontal seed indicated significant decrease in positive coupling between mPFC and PCC	Carhart-Harris, Erritzoe, et al. (2012)
fMRI/BOLD	15 Healthy volunteers	Psilocybin (IV)	2 mg	Task-free placebo-controlled design	Immediate	Increased connectivity (ie, decreased orthogonality) between DMN and task-positive network. Different from sedation (where DMN–TPN orthogonality is also increased), decrease in thalamocortical functional connectivity was absent	Carhart-Harris et al. (2013)
						Wider repertoire of connectivity	Tagliazucchi, Carhart-Harris, Leech, Nutt, and Chialvo (2014)
						Higher connectivity defined by the appearance of several low stability transient structures and a few persistent structures	Petri et al. (2014)

Continued

Table 2 EEG and Imaging Studies with Psilocybin, Mescaline, and LSD—cont'd

Method	Subjects	Drug	Dosage	Design	Start of Acquisition After Dosing	Effects of Psychedelic Substance	References
				Comparison with a similar study using MDMA		Increased between-network RSFC with psilocybin and not MDMA. Decreased RSFC between visual and sensorimotor resting-state networks was also observed	Roseman, Leech, Feilding, Nutt, and Carhart-Harris (2014)
fMRI/BOLD	25 Healthy volunteers	Psilocybin (oral)	0.16 mg/kg	Double-blind crossover design; focus on the amygdala	70–90 min	Lower amygdala reactivity to negative and neutral stimuli. Correlation between psilocybin-induced attenuation of right amygdala reactivity in response to negative stimuli and psilocybin-induced increase in positive mood state	Kraehenmann et al. (2015)
fMRI/ASL and BOLD MEG	20 Healthy volunteers	LSD (IV)	75 μg	Placebo-controlled, within-subjects/ crossover balanced-order design	ASL 100 min BOLD 135 min MEG 225 min	Increased visual cortex CBF, RSFC, and decreased alpha power, correlating with visual hallucinations; decreased DMN integrity, parahippocampus–retrosplenial cortex RSFC, and delta and alpha power (in the PCC), correlating with ego dissolution; decreased DMN activity	Carhart-Harris, Muthukumaraswamy, et al. (2016)

Note: *ASL*, arterial spin labeling; *ACC*, anterior cingulate cortex; *BOLD*, blood-oxygen-level-dependent contrast imaging; *CBF*, cerebral blood flow; *DMN*, default mode network; *EEG*, electroencephalography; *fMRI*, functional magnetic resonance imaging; *FDG*, fluorodesoxiglicose; *MEG*, magnetoencephalography; *MRglu*, glucose metabolic rate; *mPFC*, medial prefrontal cortex; *PET*, positron emission tomography; *PCC*, posterior cingulate cortex; *RSFC*, resting-state functional connectivity; *SPECT*, single-photon emission computed tomography; *TPN*, task-positive network.

Psilocybin decreased power (1.5–20 Hz) was observed within a neural network comprising the anterior and posterior cingulate cortices and the parahippocampal regions. Furthermore, the intensity of the psilocybin-induced spiritual experience correlated with the phase-lagged synchronization of delta oscillations between the retrosplenial cortex, the parahippocampus, and the lateral orbitofrontal area (Kometer et al., 2015). Psilocybin, D-methamphetamine, and 3,4-methylenedioxyethylamphetamine (MDE, an empathogen with properties similar to MDMA) were evaluated in healthy volunteers ($n = 8$) in another double-blind, placebo-controlled ^{18}F FDG PET study. Psilocybin increased MRglu in various frontotemporal cortical regions, predominantly in the ACC, and mostly in the right hemisphere. Psilocybin-induced mental state was compared to acute psychosis, where frontal hyperreactivity is present at rest, but is also associated with a reduced capacity to recruit prefrontal regions upon cognitive demand (Gouzoulis-Mayfrank, Schreckenberger, et al., 1999; Gouzoulis-Mayfrank, Thelen, et al., 1999).

fMRI has also been used to study the acute effects of psilocybin. Ten healthy volunteers recalled positive autobiographical memories during two fMRI sessions under the influence of psilocybin (2 mg, intravenous), or placebo, separated by approximately 7 days. Psilocybin was associated with increased activity in visual cortices. Vividness of the memory and visual imagery was stronger with psilocybin. Furthermore, there was a significant correlation between subjective well-being at follow-up and vividness of the positive memory (Carhart-Harris, Leech, et al., 2012).

In another fMRI study, arterial spin labeling was used to evaluate CBF-related changes after intravenous administration of psilocybin (2 mg) or saline. Decreased activity in ACC/mPFC correlated with the intensity of subjective effects, as measured by a visual analog scale. Moreover, functional connectivity analysis revealed a significant decrease in positive coupling between the mPFC and the PCC (Carhart-Harris et al., 2013). In a follow-up study, different functional connectivity patterns were explored, suggesting that psilocybin increases brain connectivity overall when compared to placebo (Tagliazucchi et al., 2014). The psychedelic state is characterized by higher connectivity, defined by the appearance of several low stability, transient structures and a few persistent ones that were not observed with placebo (Petri et al., 2014). In a reanalysis of the same data, changes in resting-state functional connectivity (RSFC) between different resting-state networks (RSN) were measured. Data following exposure to psilocybin were compared to data following MDMA exposure. Psilocybin, but not MDMA, generally increased between RSFC networks (Roseman et al.,

2014). Decreased RSFC between visual and sensorimotor RSN was also observed. Thus, current evidence suggests that RSFC networks become less differentiated in the psychedelic state (eg, Muthukumaraswamy et al., 2013).

Amygdala reactivity to negative or neutral stimuli was lower following psilocybin than following placebo administration. A correlation was found between psilocybin-induced attenuation of the BOLD response in the right amygdala in response to negative stimuli and a psilocybin-induced increase in positive mood state (Kraehenmann et al., 2015, 2016). Such results indicate a positive effect of psilocybin on emotion processing, which suggests possible therapeutic properties.

2.3 Mescaline

Mescaline, isolated by Arthur Heffter in 1897, is the active component of psychedelic cacti such as peyote (*Lophophora williamsii*) and wachuma (*Echinopsis pachanoi*, also known as San Pedro). Similar to the other classic psychedelics, mescaline is a $5HT_{2A/2C}$ agonist and one of the most selectively serotonergic psychedelic (Ray, 2010). The usual dose of mescaline in humans is between 300 and 500 mg and its effects last for 6–8 h (Halberstadt, 2015; Shulgin, 1980). Twelve healthy, male volunteers, ingesting a dose of 500 mg of mescaline sulfate were compared to 12 age-matched male who were given placebo. After intake (4.5 h), subjects were scanned with ^{99m}Tc-HMPAO SPECT, and showed a pattern of hyperfrontality when compared to placebo (Hermle et al., 1992), which was correlated with psychotomimetic symptomatology (Hermle et al., 1998).

2.4 Lysergic Acid Diethylamide

LSD is psychoactive in very small amounts: effects are noticeable at about 25 μg, with typical doses between ~50 and 150 μg. Effects of LSD can last 8–14 h depending on the dose and tolerance due to repeated ingestion (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008; Shulgin, 1980). As seen in EEG studies of mescaline and psilocybin (eg, Loosemore & Harley, 2010; Monroe, Heath, Mickle, & Llewellyn, 1957), early EEG studies with LSD reported consistent findings including decreased broadband power and increased peak frequencies particularly in the frontal cortex (eg, Fink, 1969; Itil, 1968; Oughourlian, Rougeul, & Verdeaux, 1971). More recently, it was found that LSD has significant effects on the visual system, showing increased visual cortex CBF, decreased visual

cortex alpha power, and a greatly expanded primary visual cortex (V1) functional connectivity profile. Moreover, likewise other psychedelics, LSD decreases the DMN connectivity (Carhart-Harris, Muthukumaraswamy, et al., 2016).

2.5 Summary of Current Brain Research in Psychedelics

Despite gaps in our current knowledge, occasional contradictory reports, and problems inherent to pharmacological research studies (eg, differentiating a brain response due to the direct action of the pharmaceutical agent from a "psychological" effect; consistency/standardization of substance preparation, dosing, administration, etc.; unique pharmacodynamics properties of each psychedelic compound), there are some consistent findings in the current psychedelic literature (please refer to Figs. 1 and 2). For example, EEG studies suggest that psychedelics induce a broad power reduction, most prominent in alpha and theta bands and increased peak frequency, especially for alpha (Dafters, Duffy, O'Donnell, & Bouquet, 1999; Hughes, 1996). SPECT/PET studies suggest that psychedelics increase CBF in key regions involved in emotional processing, such as the ACC and insula. A common finding in neuroimaging studies (eg, fMRI) is reduced activity in key hubs of the DMN, particularly of the PCC/precuneus (Carhart-Harris et al., 2013; Palhano-Fontes et al., 2015).

Another persistent finding is that psychedelics have pronounced effects on the visual system (Carhart-Harris, Muthukumaraswamy, et al., 2016; de Araujo et al., 2012). This area of investigation now requires a more refined description of the effects of psychedelics on the visual system since literature does not clearly differentiate true hallucinations, visual illusions, pseudohallucinations, or visual imagery facilitation. The valence of images and their integration with memories and affective states may be important in considering the therapeutic value of psychedelics.

3. PSYCHEDELICS AS THERAPEUTIC TOOLS

Psychedelics (eg, LSD, mescaline, psilocybin, DMT) were extensively explored as therapeutic tools before they became classified as illicit substances. Indeed, a rich literature focusing on the therapeutic potential of psychedelics, including treatment of depression, neurosis, obsessive–compulsive disorder, and addiction flourished in the 1950–1960s. The feeling of subjective wellness after the use of psychedelics, referred to as

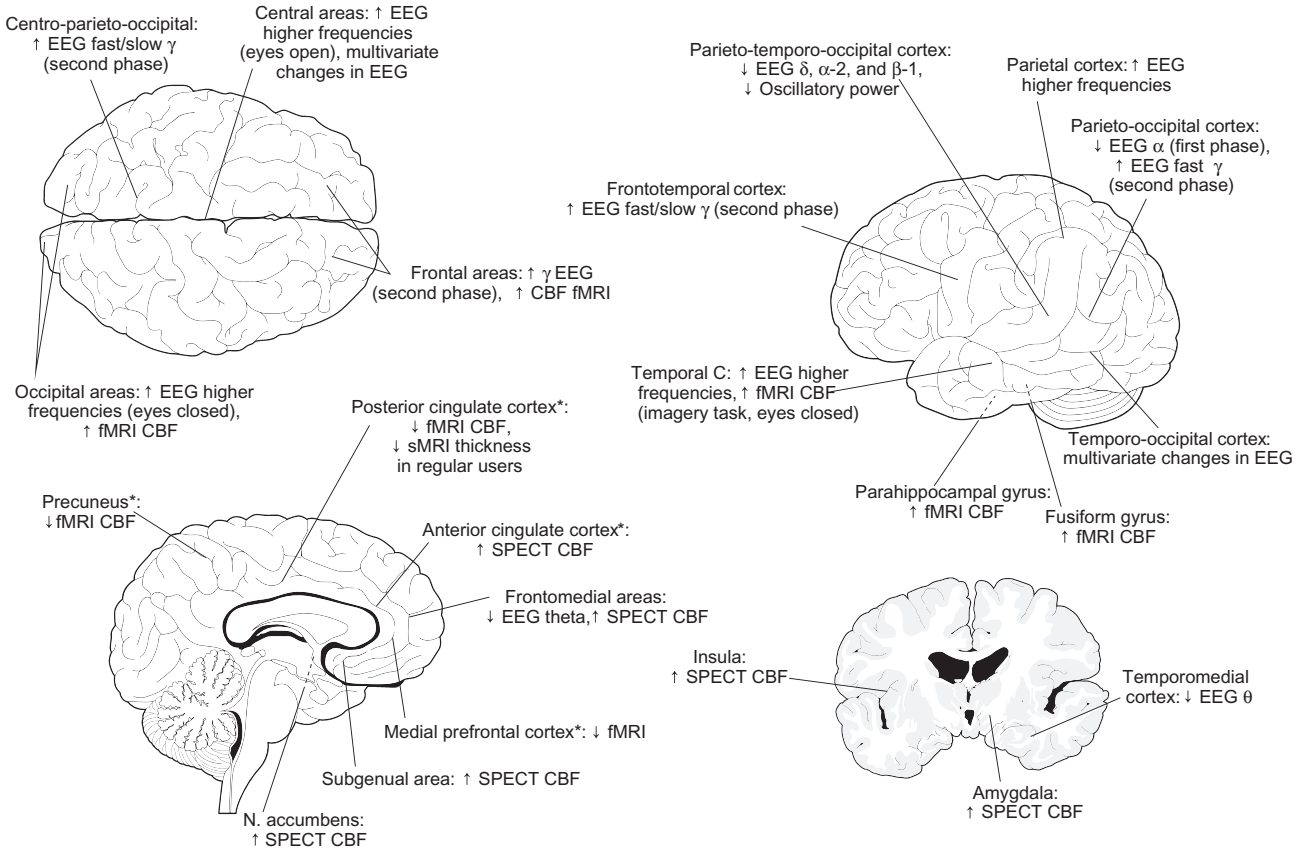

Fig. 1 Summary of results of EEG and imaging studies with ayahuasca: localized effects in the central nervous system. Default mode networks hubs are marked with an asterisk (*). *Note*: *CBF*, cerebral blood flow; *EEG*, electroencephalography; *fMRI*, functional magnetic resonance imaging; *MR*, metabolic rate; *MEG*, magnetoencephalography; *PET*, positron emission tomography; *psilo*, psilocybin; *PO*, per os; *IV*, intravenous; *RSFC*, resting-state functional connectivity.

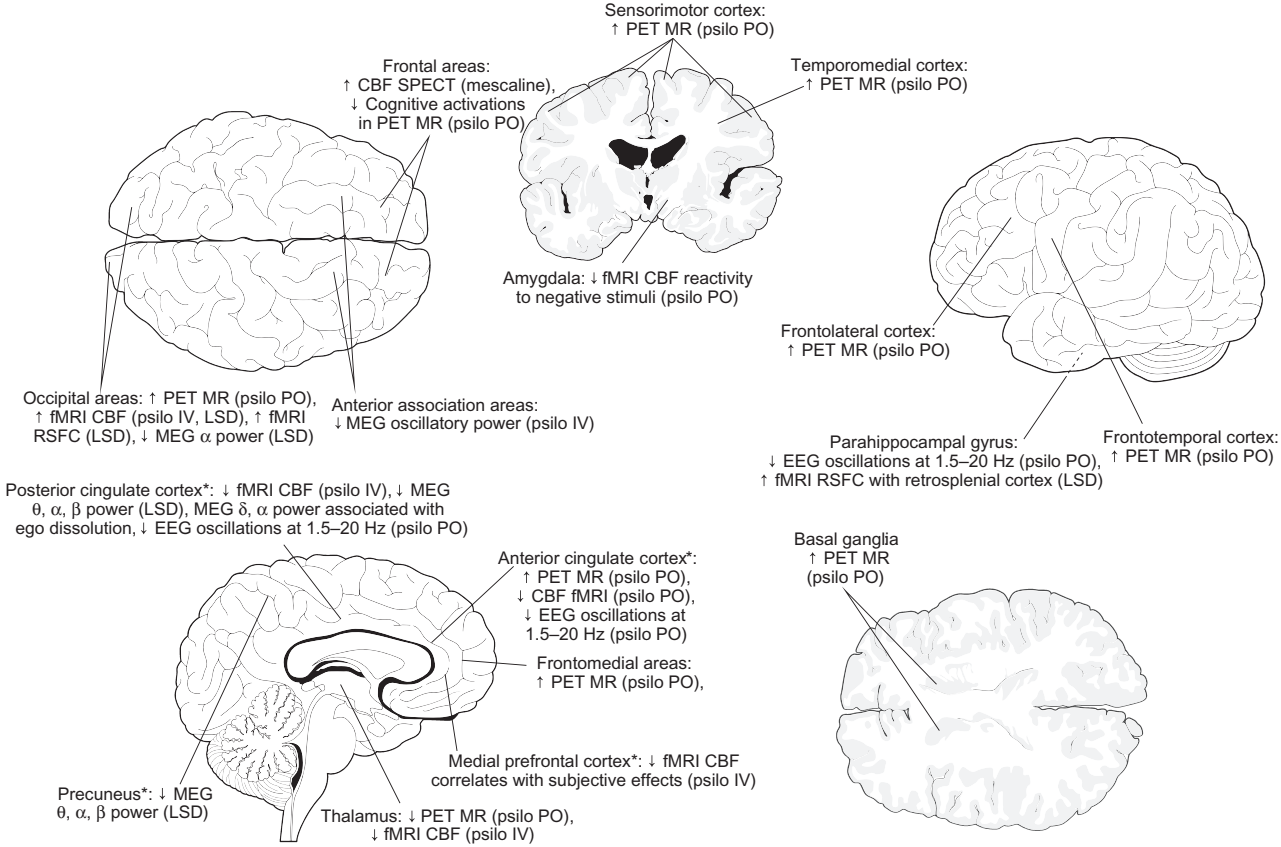

Fig. 2 Summary of results of EEG and imaging studies with psilocybin, mescaline, and LSD: localized effects in the central nervous system. Default mode networks hubs are marked with an asterisk (*). *Note*: *CBF*, cerebral blood flow; *EEG*, electroencephalography; *fMRI*, functional magnetic resonance imaging; *sMRI*, structural magnetic resonance imaging.

an "afterglow" (Majić, Schmidt, & Gallinat, 2015), has been reported in the literature since the 1960s (eg, Pahnke, 1969). In contrast to most antidepressants, psychedelics promote a positive mood almost immediately (Carhart-Harris, Bolstridge, et al., 2016; Osório et al., 2015; Sanches et al., 2016).

Early evaluation of psychedelics as chemical models of psychosis (ie, psychotomimetics or substances that induce states that mimic psychosis) suggested that at least some psychotic symptoms are induced by endogenous activations of $5HT_{2A}$ pathways, as observed using LSD in drug-discriminant animal studies. Such findings led to development of risperidone, an antipsychotic that in addition to blocking dopamine receptors, inhibits $5HT_{2A}$ receptors (Colpaert, 2003). Modern studies continue to use psychedelics as a source of insight into psychosis in general and schizophrenia in particular (Halberstadt & Geyer, 2013).

Treatment of both depression and addiction with psychedelics has shown promise. A growing literature indicates that psychedelics have antidepressant effects. Ayahuasca (Osório et al., 2015; Sanches et al., 2016) and psilocybin (Carhart-Harris, Bolstridge, et al., 2016) in open-label studies show potential antidepressant effects. As part of an ongoing investigation on the potential of ayahuasca to treat depressive states (Osório et al., 2015), a SPECT study was performed in 17 patients with recurrent depression 8 h after intake (Sanches et al., 2016). Ayahuasca, donated by Santo Daime, was administered *in natura* using an open-label design, and depression severity was assessed using the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery–Åsberg Depression Rating Scale (MADRS). A significant decrease in ratings of depression was reported on both scales at 80 min after intake, a finding that persisted for 21 days. SPECT, performed 8 h after ayahuasca intake, showed significant CBF increases in the left nucleus accumbens, right insula, and left subgenual area. Similarly, two oral doses (10 and 25 mg) of psilocybin were given to 12 patients with moderate-to-severe treatment-resistant depression. Outcomes were measured with the quick inventory of depressive symptoms. Compared to baseline, depression symptoms were significantly reduced after 1 week and effects were sustained after 3 months after high-dose treatment (Carhart-Harris, Bolstridge, et al., 2016).

Based on results of early studies using LSD and other psychedelics, the scientific studies of ayahuasca in humans (Doering-Silveira et al., 2005; Fábregas et al., 2010; Grob et al., 1996), and anthropological and qualitative accounts from the ritual and religious use of psychedelics (Labate, Dos Santos, Anderson, Mercante, & Barbosa, 2014; Loizaga-Velder & Verres, 2014;

Mercante, 2013), a number of scientists began to explore the use of psychedelics for the treatment of drug-related disorders (eg, Bogenschutz & Johnson, 2016; Bogenschutz & Pommy, 2012; Brierley & Davidson, 2012; Dos Santos, Osório, Crippa, & Hallak, 2016; Frecska, Bokor, & Winkelman, 2016; Halpern, 1996, 2007; Liester & Prickett, 2012; Nunes et al., 2016; Ross, 2012; Winkelman, 2014). Indeed, a contemporary meta-analytic examination of early LSD studies found evidence for a beneficial effect of LSD on alcohol-use disorders (Krebs & Johansen, 2012). Results from modern observational and clinical trials are currently in a preliminary phase. Taken together, though, they are promising and seem to suggest a therapeutic effect of psychedelics on some psychiatric disease states.

In the seminal Project Hoasca, 15 male members of the UDV and 15 matched controls were given standardized questionnaires. Though the data were retrospective and the sample was small, the religious use of ayahuasca seemed to present a strong and positive impact in the lives of UDV members (Grob et al., 1996). UDV membership was also associated with reduced drug abuse in teenagers (Doering-Silveira et al., 2005). A survey of almost 1700 UDV members suggested lower rates of addiction relative to the general population (Barbosa, Tófoli, Bogenschutz, & Winkelman, 2014). Similarly, members of Santo Daime relative to the general population appear to have fewer psychiatric diagnoses of drug abuse (Fábregas et al., 2010). Therefore, although more studies are clearly necessary, current data seem to suggest that psychedelics have antiaddictive properties.

Additional studies have shown reduced addict-like behaviors in addicted patients who participated in an ayahuasca workshop with South American shamans (Thomas, Lucas, Capler, Tupper, & Martin, 2013). A study with mice demonstrated that ayahuasca inhibits the development of an animal model of alcohol dependence (Oliveira-Lima et al., 2015). Open-label study with psilocybin presented encouraging results for both alcohol and tobacco cessation: significant decreases in drinking behaviors were observed (Bogenschutz et al., 2015), and 80% of participating subjects achieved tobacco abstinence at 6-month follow-up (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014).

4. POTENTIAL MECHANISMS OF PSYCHEDELIC TREATMENT EFFICACY

Functional activity of the DMN appears to be disrupted in a number of mental disorders, including addiction (Carhart-Harris & Nutt, 2013;

Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011; Ma et al., 2011, 2015; Müller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2015; Weiland, Sabbineni, Calhoun, Welsh, & Hutchison, 2015; Wetherill et al., 2015). These disruptions are complex and still not clearly elucidated, and it is too soon to suggest that the potential therapeutic role of psychedelics may come from their effect on the DMN. Such a mechanism would also seem contradictory based on findings that with the exception of alcohol, most addictive substances show reduced DMN connectivity and most psychedelics have also been shown to acutely reduce DMN connectivity.

In subjects with alcohol-use disorders relative to controls, DMN regions appear to be hyperconnected (Zhu, Cortes, Mathur, Tomasi, & Momenan, 2015; Zhu, Dutta, et al., 2015). Increased functional connectivity correlated with scores on an alcohol dependence scale. Alcohol-dependent subjects compared to controls also showed decreased functional connectivity of the precuneus after alcohol administration (Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2016). Considering such findings, alcoholism seems to be the most promising candidate for DMN studies investigating psychedelics for the treatment of addiction.

Another use of psychedelics in treatment is to increase interoception and self-awareness (DeWitt, Ketcherside, McQueeny, Dunlop, & Filbey, 2015), which may help in both psychiatric and addictive states. Mindfulness, likewise psychedelics, decreases activity of the DMN (Doll, Holzel, Boucard, Wohlschlager, & Sorg, 2015; King et al., 2016). Evaluation of the interaction between mindfulness techniques and psychedelic states may provide insights into better quality of life (Mackenzie, 2014; Soler et al., 2016).

Indirect activity of psychedelics on brain dopamine systems may be relevant to substance-use disorders (eg, Everitt, 2014; Kalivas, Volkow, & Seamans, 2005; Moeller, London, & Northoff, 2016; Volkow, Fowler, & Wang, 2003; Zou et al., 2015). For example, harmine and psilocin can increase dopamine in the ventral striatum/nucleus accumbens via $5HT_{2A/2C}$ receptor stimulation (Brierley & Davidson, 2013). LSD, psilocybin, and DMT may also effect dopamine transmission, though not necessarily in the nucleus accumbens. Imaging studies do not generally note a remarkable effect of psychedelics on the mesolimbic dopaminergic reward system. By contrast, a number of brain regions with an emerging role in the initiation or maintenance of addiction (eg, amygdala, hippocampus, insula, and medial prefrontal cortex) are directly influenced by psychedelics.

From a molecular perspective, available evidence suggests that psychedelics increase the expression of brain-derived neurotrophic factor

(BDNF) (Vollenweider & Kometer, 2010). BDNF increases are associated with the mitigation of symptoms of anxiety and depression: the increase in BDNF associated with use of antidepressants (eg, SSRI) coincides with the beginning of their therapeutic efficacy, typically 2 weeks after initiation (Bjorkholm & Monteggia, 2016). A more rapid effect of psychedelics may be associated with BDNF increases primarily in cortical pyramidal cells of layer V via a mechanism involving stimulation of $5HT_{2A}$ receptors (Vollenweider & Kometer, 2010).

Ayahuasca may additionally increase BDNF via at least one of the β-carbolines, namely, harmine, as demonstrated in animals. Indeed, β-carbolines may have independent antidepressant and anxiolytic properties possibly associated with direct stimulation of serotonin receptors or by MAO inhibition (Dos Santos et al., 2016). Similarly, THH can act as an SSRI and increase serotonin levels. Such hypotheses, however, fail to explain the apparently immediate antidepressant properties of ayahuasca.

DMT, in the few isolated studies in humans, seems to have antianxiety effects (Dos Santos et al., 2016). This is likely due to stimulation of serotonin $5HT_{2A}$ receptors. However, DMT is also a natural ligand for the sigma-1, intracellular chaperone receptor. Although the molecular roles of sigma-1 receptors remain to be explored, DMT has been identified as one of its natural and endogenous ligands (Fontanilla et al., 2009). Indeed, it has been hypothesized that dysfunction of sigma-1 receptors is associated with depression, anxiety, and substance-use-related disorders. A number of antidepressants have been shown to bind to sigma-1 receptors, and conversely, ligands of sigma-1 receptors have antidepressant effects in animal models of depression (Hayashi, Tsai, Mori, Fujimoto, & Su, 2011).

5. CLOSING REMARKS

There are many aspects of psychedelic consumption that may be beneficial beyond what may be adequately quantified in a laboratory setting (Garcia-Romeu, Griffiths, & Johnson, 2014; Griffiths, Richards, Johnson, McCann, & Jesse, 2008; MacLean, Johnson, & Griffiths, 2011). For example, traditional users of psychedelic plants often note the presence of a guiding instance, as well as visions that can be therapeutic as "didactic scenes" are common during ayahuasca use (eg, Shanon, 2003). Finally, psychedelic users often report spiritual experiences (eg, Barrett, Johnson, & Griffiths, 2015) and the ritual and religious use of peyote or ayahuasca is legal in many countries. Such considerations are not outside the scope of our

modern attempts to treat addiction since after all, Alcoholics Anonymous, still one of the mainstays of treatment of alcoholism, includes a spiritual dimension. The goal then is not to deny, but to understand the spiritual/mystical components of psychedelics and provide research to assist therapists and other health professionals to exploit such properties of psychedelics to help those seeking relief from psychiatric symptoms or addiction. This is an open path for exploration with modern EEG and imaging techniques.

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