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Classical hallucinogens and neuroimaging: A systematic review of human studies
Hallucinogens and neuroimaging

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ABSTRACT

Serotonergic hallucinogens produce alterations of perceptions, mood, and cognition, and have anxiolytic, antidepressant, and antiaddictive properties. These drugs act as agonists of frontocortical 5-HT_{2A} receptors, but the neural basis of their effects are not well understood. Thus, we conducted a systematic review of neuroimaging studies analyzing the effects of serotonergic hallucinogens in man. Studies published in the PubMed, Lilacs, and SciELO databases until 12 April 2016 were included using the following keywords: "ayahuasca", "DMT", "psilocybin", "LSD", "mescaline" crossed one by one with the terms "mri", "fmri", "pet", "spect", "imaging" and "neuroimaging". Of 279 studies identified, 25 were included. Acute effects included excitation of frontolateral/frontomedial cortex, medial temporal lobe, and occipital cortex, and inhibition of the default mode network. Long-term use was associated with thinning of the posterior cingulate cortex, thickening of the anterior cingulate cortex, and decreased neocortical 5-HT_{2A} receptor binding. Despite the high methodological heterogeneity and the small sample sizes, the results suggest that hallucinogens increase introspection and positive mood by modulating brain activity in the fronto-temporo-parieto-occipital cortex.

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1. Introduction

Serotonergic hallucinogens have been used from time immemorial in different human cultures all over the world for ritual and therapeutic purposes and to produce modifications in perceptions, mood, and cognition (Grispoon and Bakalar, 1981; Schultes and Hofmann, 1992; Ott, 2004). The semisynthetic ergoline lysergic acid diethylamide [LSD], the phenethylamine mescaline, present in the peyote cactus [*Lophophora williamsii*], and the tryptamines psilocybin, found in several species of *Psilocybe* mushrooms and related species, and dimethyltryptamine [DMT], present in the Amazonian beverage ayahuasca, are among the main serotonergic hallucinogens used worldwide for recreational, ritual, and therapeutic purposes (Schultes and Hofmann, 1992; Ott, 2004; Guzmán, 2008; Labate et al., 2009; Labate and Jungaberle, 2011; Labate and Cavnar, 2014; Hintzen and Passie, 2010; McKenna and Riba, 2015). However, use of serotonergic hallucinogens is incidental and transient for most consumers, and with the exception of Latin America, where prevalence of LSD use increased from 0.2% in 2009 to 0.95% in 2012, several surveys suggest strong declines in LSD use: from 1996 to 2013, prevalence declined from 4.5 to 0.4% in England and Wales, and from 8.8 to 2.2% in the United States (UNODC, 2014).

Moreover, hallucinogens are less harmful than most licit and illicit drugs (Nutt et al., 2010; van Amsterdam et al., 2011; Morgan et al., 2013; van Amsterdam et al., 2013, 2015), and recent observational (Krebs and Johansen, 2013, 2015; Hendricks et al., 2014, 2015; Johansen and Krebs, 2015), experimental (Studerus et al., 2011; dos Santos et al., 2016a, 2016b; Nunes et al., 2016), and clinical (Moreno et al., 2006; Grob et al., 2011; Gasser et al., 2014; Johnson et al., 2014; Bogenschutz et al., 2015; Osório et al., 2015; dos Santos et al., 2016a, 2016b; Nunes et al., 2016) studies suggest that these compounds are not only reasonably safe when administered in controlled settings, but appear to have antidepressive, anxiolytic, and antiaddictive effects, especially in treatment-resistant patients.

Activation of frontocortical glutamate receptors secondary to serotonin 5-HT_{2A} receptor-mediated glutamate release seems to be the main mechanism of action of serotonergic hallucinogens, although they are also agonists of 5-$HT_{1A/2C}$ receptors, which appear to have a less prominent role in their pharmacology (Vollenweider et al., 1998; Moreno et al., 2011; Kometer et al., 2012, 2013; Hanks and González-Maeso, 2013; Tylš et al., 2014; Carbonaro et al., 2015; Halberstadt, 2015; Domínguez-Clavé et al., 2016; Nichols, 2016; Valle et al., 2016). However, the neural basis of the effects of these drugs on perceptions, emotions, and cognition are still poorly understood.

Since the early 1990′s, neuroimaging studies have been trying to elucidate the effects of serotonergic hallucinogens on the human brain. However, to the best of our knowledge, there is no systematic review on this topic. Thus, considering the recent interest in the possible therapeutic utility of these drugs, we conducted a systematic review of human studies applying neuroimaging techniques to analyze the effects of serotonergic hallucinogens. We chose a systematic rather than a meta-analysis review for several reasons, such as: i) the effect sizes were not always available and could limit our analysis to a small subset of studies; ii) the types of drugs used varies widely in the studies, preventing accurate comparison; iii) there is a wide difference in the secondary variables throughout studies (i.e. gender, dosages of the compounds, method of assessments, medication, co-morbidities); iv) very few imaging studies are available for some hallucinogenic drugs, hampering quantitative analyses; v) meta-analysis has intrinsic limitations in estimating negative findings that do not get published [the "file drawer" problem]. Therefore, a meta-analytic approach is still not appropriate for a review of this broad scope of neuroimaging techniques, which covers more than one specific hallucinogenic drug.

2. Methods

Data for this systematic review was collected in accordance with the Systematic Reviews and Meta-Analyses guidelines [PRISMA] (Moher et al., 2009).

2.1. Search strategy

Electronic search was performed using the PubMed, Lilacs, and SciELO databases. The following search terms were used: (ayahuasca OR DMT OR psilocybin OR LSD OR mescaline) AND (mri OR fmri OR pet OR spect OR imaging OR neuroimaging). All studies published until 12 April 2016 were included, without any language restriction. Additionally, the reference lists of all included studies identified in the database search were manually screened for relevant studies.

2.2. Selection criteria and study selection

Inclusion criteria were: i) original publication in a peer-reviewed journal, ii) observational or interventional study design, iii) application of structural, functional or neurochemical neuroimaging techniques, iv) investigation of acute and non-acute effects of hallucinogens on the human brain. Animal studies, review papers, qualitative studies, opinion pieces or comments, letters or editorials, conference abstracts or posters, books or book chapters, case reports, 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 publications was made on the basis of a review of the full texts. The whole process was conducted by two reviewers independently. In case of disagreement, reviewers discussed their reasons for initial inclusion and exclusion. If consensus was not reached, a third reviewer was included.

2.3. Recorded variables, data extraction and analysis

Recorded variables included authors, year of publication, study location [country], study design [experimental, observational, clinical], number of subjects, drug type and dose [mescaline, DMT, psilocybin, LSD or ayahuasca; dosage in mg or episodes], imaging method [PET, SPECT, MRI or fMRI], regions analyzed, statistical thresholds, and main findings.

3. Results

3.1. Identified studies

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

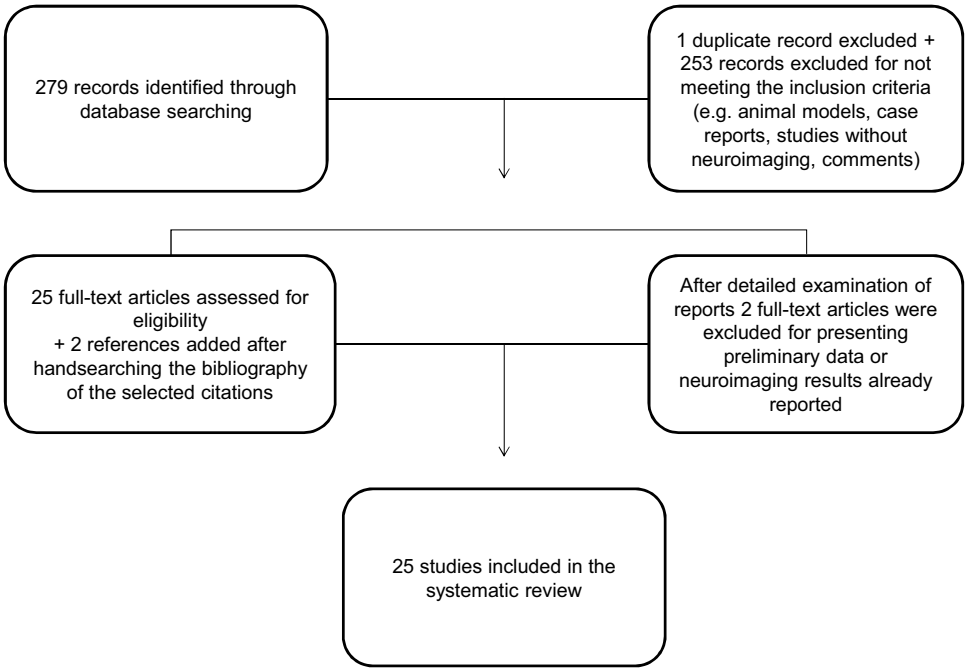

Fig. 1. Flow diagram illustrating the different phases of the systematic review.

The search of the literature yielded 279 references, but since one citation appeared in two databases it was considered only once, thus yielding 278 separate references. All these citations were reviewed for title and abstract screening [first pass]. Following the first pass, 25 potentially relevant references were identified. The remaining citations did not meet the inclusion criteria [e.g. animal models, case reports, studies without neuroimaging, comments] and were thus excluded. Full-text reports of the 25 selected citations were obtained for more detailed evaluation [second pass]. Following detailed examination of the reports, two citations (Oepen et al., 1989; Hermle et al., 1998) were excluded because they presented preliminary data (Oepen et al., 1989) or neuroimaging results already reported (Hermle et al., 1998), so only the original report was included (Hermle et al., 1992). Two other citations were found after hand search of the bibliography of the selected reports (Erritzoe et al., 2011; Roseman et al., 2014). Thus, 25 citations were included in the systematic review.

Studies were classified according to drug [ayahuasca, DMT, mescaline, LSD or psilocybin] and neuroimaging technique [PET, SPECT, MRI or fMRI]. The studies included comprised one study with mescaline [using SPECT: Hermle et al., 1998], two studies with DMT [both using fMRI: Daumann et al., 2008, 2010], 12 studies with psilocybin [three studies using PET: Vollenweider et al., 1997, 1999; Gouzoulis-Mayfrank et al., 1999; and nine using fMRI: Carhart-Harris et al., 2012a,b, 2013; Petri et al., 2014; Roseman et al., 2014; Tagliazucchi et al., 2014; Kraehenmann et al., 2015a, 2015b; Lebedev et al., 2015], four studies with LSD [all using fMRI: Carhart-Harris et al., 2016; Kaelen et al., 2016; Speth et al., 2016; Tagliazucchi et al., 2016], five studies with ayahuasca [two studies using SPECT: Riba et al., 2006; Sanches et al., 2016; two using fMRI: de Araujo et al., 2012; Palhano-Fontes et al., 2015; and one using MRI: Bouso et al., 2015], and one study of polydrug use [using PET: Erritzoe et al., 2011]. A summary of the main findings of each study included in the systematic review is described in Table 1.

Most included citations [23/25] were studies of acute drug administration [open-label, single- or double-blind placebo-controlled studies], and only two used a retrospective, observational design (Erritzoe et al., 2011; Bouso et al., 2015). Most acute studies used a within-subjects, placebo-controlled, cross-over design with no control groups, with one exception (Hermle et al., 1992), while both observational studies included a control group. Despite the small number of studies, the small sample sizes [7–22 volunteers], and the high degree of heterogeneity among studies, the reported results consistently show that serotonergic hallucinogens [i.e., mescaline, DMT, psilocybin, LSD, ayahuasca] modulate neural networks implicated in visual information [occipital cortex] and cognitive functions and emotional processing [frontolateral/frontomedial cortex, medial temporal lobe, and amygdala]. These findings will be further discussed in detail below.

3.2. Drugs

3.2.1. Mescaline

In an open-label study in Germany, 11 male healthy volunteers [mean age 35.5] ingested 0.5 mg mescaline and performed a face/nonface decision task with known right hemisphere affinity, and neurometabolic effects were analyzed using technetium-99m-labed[^{99m}Tc]-HMPAO [hexamethyl propylene amine oxime] SPECT (Hermle et al., 1992). The study included a control group matched for age and gender. At the peak of drug effects [240–270 min], statistically significant [$P < 0.05$] increases in regional cerebral blood flow [rCBF] in frontal cortical regions [especially of the right hemisphere] were observed, which were correlated with the intensity of mescaline's subjective effects, while posterior cortical regions showed decreased activity. No statistical significant effects were observed in subcortical [limbic] areas, and no significant differences were observed in the performance of the face test.

3.2.2. Dimethyltryptamine [DMT]

In Germany, Daumann et al. (2008) investigated the neural correlates underlying orienting of attention in 14 healthy volunteers [eight men; mean age 32.1 years] in a randomized, double-blind, cross-over, placebo-controlled, event-related blood oxygenation level-dependent [BOLD] fMRI study with DMT and *S*-ketamine. Subjects were scanned during a covert orienting of attention task with nonpredictive peripheral cues, which assesses deficits of inhibition of return [IOR]. The two dose regimens were: [1] DMT: bolus

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

References	Study characteristics, sample	Drug	Neuroimaging technique	Main findings
Acute neuroimaging studies				
Hermle et al., 1992	Germany, open-label, control group matched for age and gender 11 male healthy volunteers (mean age 35.5 years)	Mescaline 0.5 mg, oral	^{99m}Tc-HMPAO SPECT + face/nonface decision task	Statistically significant ($P < 0.05$) increases in CBF in frontal cortical regions, especially of the right hemisphere, which were correlated with the intensity of subjective effects
Vollenweider et al., 1997	Switzerland, open-label, no control group 10 healthy volunteers (8 men; mean age 33.3 years)	Psilocybin 15–20 mg, oral	^{18}F-FDG PET	Psilocybin induced a significant ($P < 0.01$, uncorrected) global increase in CMRglu, especially in the frontomedial and frontolateral cortex, AC, and temporomedial cortex, and CMRglu increases in the PFC, AC, temporomedial cortex, and putamen were positively correlated with psilocybin's dose and subjective effects
Vollenweider et al., 1999	Switzerland, randomized, single-blind, placebo-controlled, cross-over 7 male healthy volunteers (mean age 27 years)	Psilocybin 0.25 mg/kg, oral	[^{11}C]raclopride PET	Psilocybin significantly ($P < 0.05$, uncorrected) decreased [^{11}C]raclopride BP bilaterally in the striatum, and decreased [^{11}C]raclopride BP in the ventral striatum was correlated with increased depersonalization
Gouzoulis-Mayfrank et al., 1999	Germany, pseudo-randomized, double-blind, placebo-controlled, cross-over 32 healthy volunteers (21 men; mean age 34.2 years); $n = 8$ per group	Psilocybin, MDE[1], METH[1] Psilocybin: 2 mg/kg, oral	^{18}F-FDG PET	Psilocybin significantly ($P < 0.05$, uncorrected) increased rMRGlu in the right AC and in the right frontal operculum, and decreased rMRGlu in the right thalamus and in the left precentral region; psilocybin-induced increases in rMRGlu in the right AC correlated positively with stereotyped thoughts and negatively with anxiety, and rMRGlu increases in the right frontal operculum were associated with low general activation; reduced rMRGlu in the left thalamus was associated with general psychopathology, tension, anxiety, depressive feelings, and less stereotyped thoughts
Riba et al., 2006	Spain, randomized, double-blind, placebo-controlled, cross-over 15 healthy male volunteers (mean age 28 years)	Oral dose of encapsulated freeze-dried ayahuasca 1 mg DMT/kg	^{99m}Tc-ECD SPECT	Ayahuasca induced significant ($P < 0.002$, uncorrected) bilateral activation of the anterior insula/inferior frontal gyrus and activation of the AC/medial frontal gyrus of the right hemisphere and of the amygdala/parahippocampal gyrus in the left hemisphere
Daumann et al., 2008	Germany, randomized, double-blind, placebo-controlled, cross-over 14 healthy volunteers (8 men; mean age 32.1 years)	DMT + *S*-ketamine[1] DMT: bolus of 0.15 mg/kg over 5 min followed by a break of 1 min and a continuous infusion with 0.01 up to 0.01875 mg/kg*min over 20 min	BOLD fMRI + IR task	DMT significantly slowed down reaction times and blunted IOR, but failed to induce significant IOR-associated brain activation effects ($P < 0.05$, corrected)
Daumann et al., 2010	Same sample of Daumann et al., 2008	Same DMT dose of Daumann et al., 2008	BOLD fMRI + target-detection task	DMT significantly reduced BOLD response in extrastriate regions during visual alerting, and in temporal regions during auditory alerting ($P < 0.001$, uncorrected)
Carhart-Harris et al., 2012a	United Kingdom, single-blind, within-subjects, counterbalanced-order, placebo-controlled 15 healthy volunteers (ASL fMRI: 10 men; mean age 34.1 years; BOLD fMRI: 13 men; mean age 32 years)	Psilocybin 2 mg (i.v.) manually infused over 60 s, beginning 6 min after the start of each scan	ASL fMRI + BOLD fMRI + RSFC	Psilocybin significantly ($P < 0.05$, corrected) decreased CBF in bilateral thalamus, putamen, hypothalamus, PCC, retrosplenial cortex, precuneus, bilateral angular gyrus, supramarginal gyrus, rostral and dorsal ACC, paracingulate gyrus, mPFC, frontoinsular cortex, lateral orbitofrontal cortex, frontal operculum, precentral gyrus, superior, middle and inferior frontal gyrus, and visual areas; CBF decreases correlated positively with the intensity of the subjective effects of psilocybin, and a significant decrease in the positive coupling between the mPFC and the PCC was observed
Carhart-Harris et al., 2012b	10 healthy volunteers from the sample of Carhart-Harris et al., 2012a	Same psilocybin dose of Carhart-Harris et al., 2012a	BOLD fMRI + personal memory cues task	Psilocybin induced significant ($P < 0.001$, corrected) memory-related activations in the amygdala, hippocampus, putamen, Nac, mid-cingulate cortex, pre-sensorimotor area, precuneus, SCC, temporal pole, mPFC and frontal pole, and visual and other sensory cortical areas; psilocybin induced significant ($P < 0.05$) increases in ratings of memory vividness and visual imagery, and a significant positive correlation was observed between vividness and subjective wellbeing in a two-week follow-up

Table 1 (*Continued*)

References	Study characteristics, sample	Drug	Neuroimaging technique	Main findings
de Araujo et al., 2012	Brazil, open-label, no placebo or control group 10 healthy frequent ayahuasca users (5 men; mean age 29 years)	Oral dose of liquid ayahuasca 1.76 mg DMT/kg	BOLD fMRI + imagery task	During an imagery task, ayahuasca induced significant ($P < 0.05$, corrected) activation in the primary visual area comparable to the activation levels of a natural image with the eyes open, and ayahuasca also induced activation of the cuneus and lingual gyrus and parahippocampal, retrosplenial, and frontopolar cortices; ayahuasca administration also reversed fronto-occipital connectivity
Carhart-Harris et al., 2013	Same sample of Carhart-Harris et al., 2012a	Same psilocybin dose of Carhart-Harris et al., 2012a	BOLD fMRI + RSFC	Psilocybin significantly ($P < 0.001$, corrected) increased DMN-TPN FC
Petri et al., 2014	Same sample of Carhart-Harris et al., 2012a	Same psilocybin dose of Carhart-Harris et al., 2012a	BOLD fMRI + RSFC	Psilocybin reduced the stability of the brain's functional patterns by creating several transient connectivity structures of low stability and short average cycle persistence ($P < 10^{-35}$), and also some longer-lived and persistent cycles ($P < 10^{-30}$), which suggests an increased integration between cortical regions
Roseman et al., 2014	Same sample of Carhart-Harris et al., 2012a	Same psilocybin dose of Carhart-Harris et al., 2012a +MDMA[1]	BOLD fMRI + RSFC	Psilocybin induced significant ($P < 0.05$, corrected) changes in between-network RSFC, generally in the direction of increased coupling between RSNs, with an additional decrease in coupling between visual and sensorimotor networks
Tagliazucchi et al., 2014	Same sample of Carhart-Harris et al., 2012a	Same psilocybin dose of Carhart-Harris et al., 2012a	BOLD fMRI + RSFC	Psilocybin induced significant ($P < 0.05$, corrected) increases on BOLD signal variance and total spectral power in the ACC and bilateral hippocampi, and decreases in LFP and FSE in the DMN, executive control, and dorsal attention networks, and increases in ACC/hippocampi entropy
Kraehenmann et al., 2015a	Switzerland, double-blind, randomized, placebo-controlled, cross-over 25 healthy volunteers (16 men; mean age 24.2 years)	Psilocybin 0.16 mg/kg, oral	BOLD fMRI + emotional picture discrimination task	Psilocybin significantly attenuated right amygdala activation to both negative ($P = 0.001$, corrected) and neutral ($P < 0.001$, corrected) pictures, and this effect was significantly correlated with increases in positive mood
Kraehenmann et al., 2015b	Same sample of Kraehenmann et al., 2015a	Same psilocybin dose of Kraehenmann et al., 2015a	BOLD fMRI + emotional picture discrimination task	Psilocybin significantly ($P = 0.01$, corrected) decreased the threat-induced modulation of top-down connectivity from the amygdala to primary visual cortex
Lebedev et al., 2015	Same sample of Carhart-Harris et al., 2012a	Same psilocybin dose of Carhart-Harris et al., 2012a	BOLD fMRI + RSFC	Under psilocybin, a negative correlation was observed between "ego-dissolution" and decreased diversity of aPHC connections, and lower connection diversity of left dlPFC/superior parietal regions at baseline predicted "ego-dissolution", which was associated with decreased salience network integrity and reduced interhemispheric communication ($P < 0.05$, corrected)
Palhano-Fontes et al., 2015	Same sample of de Araujo et al., 2012	Same ayahuasca dose of de Araujo et al., 2012	BOLD fMRI + verbal fluency task + RSFC	Ayahuasca significantly ($P < 0.05$, uncorrected) decreased activation of key hubs of the DMN (PCC/precuneus, mPFC) and decreased functional connectivity within the PCC/precuneus
Sanches et al., 2016	Brazil, open-label, no placebo or control group 17 volunteers with MDD (3 men; mean age 42.71 years)	Oral dose of liquid ayahuasca 1.76 mg DMT/kg	^{99m}Tc-ECD SPECT	Ayahuasca significantly ($P < 0.01$, corrected) increased blood perfusion in the left Nac, right insula, and lSGA, and induced significant ($P < 0.05$) reductions in depressive and anxiety scores between baseline and 1, 7 and 21 days after drug intake
Speth et al., 2016	United Kingdom, single-blind, within-subjects, counterbalanced-order, placebo-controlled 20 healthy volunteers (16 men; mean age 30.9 years)	LSD 75 μg (i.v.) manually infused over 60 s, beginning 6 min after the start of each scan	BOLD fMRI + RSFC	LSD significantly ($P = 0.017$, uncorrected) increased the number of words in the reports and induced fewer mental spaces for the past ($P = 0.022$, uncorrected)

Table 1 (*Continued*)

References	Study characteristics, sample	Drug	Neuroimaging technique	Main findings
Carhart-Harris et al., 2016	Same sample of Speth et al., 2016	Same LSD dose of Speth et al., 2016	ASL fMRI + BOLD fMRI + RSFC + MEG	LSD significantly ($P < 0.05$, corrected) increased CBF in the visual cortex and RSFC in primary visual cortex-cortical/subcortical regions, parahippocampal region-dmPFC/right dlPFC, and vmPFC-bilateral caudate/inferior frontal gyrus; decreased RSFC was observed in parahippocampal region-retrosplenial cortex/PCC, vmPFC-PCC, and in RSNs including the DMN, while increased RSFC occurred in OPN/right FPN networks; LSD also significantly ($P < 0.05$, corrected) decreased oscillatory power in lower-frequency bands (1–30 Hz) throughout the brain
Kaelen et al., 2016	12 healthy volunteers from the sample of sample of Speth et al., 2016	Same LSD dose of Speth et al., 2016	BOLD fMRI + music/imagery task + RSFC	The interaction between LSD and music was associated with significant ($P < 0.05$, corrected) increases in RSFC between the parahippocampal cortex and the primary visual cortex, left anterior insula, and left inferior frontal cortex, and also with increased parahippocampal cortex to visual cortex information flow, which correlated positively with ratings of complex visual imagery
Tagliazucchi et al., 2016	15 healthy volunteers from the sample of sample of Speth et al., 2016	Same LSD dose of Speth et al., 2016	BOLD fMRI + RSFC	LSD significantly ($P < 0.05$, corrected) increased global RSFC in the thalamus and frontoparietal and inferior temporal cortices, and also increased communication between association and sensory cortices; cortical areas with increased functional connectivity overlapped with 5-HT_{2A} receptor densities, and increased RSFC in the bilateral temporo-parietal junction/insular cortex correlated with "ego dissolution"; and a reanalysis of the psilocybin/fMRI data from Tagliazucchi et al. (2014) showed increased global RSFC in the same cortical regions modulated by LSD
Long-term neuroimaging studies				
Erritzoe et al., 2011	Denmark, observational, retrospective, inclusion of a control group 24 polydrug users (MDMA, hallucinogens, other drugs; 21 men; mean age 24.6 years) compared to 21 nonusing controls (17 men; mean age 24 years)	Serotonergic hallucinogens used included psilocybin (19/24), LSD (18/24), DMT (11/24), mescaline (4/24), and ayahuasca (3/24), but also other drugs	[^{18}F]altanserin and [^{11}C]DASB PET	Hallucinogen users had normal cerebral SERT binding, but slightly lower ($P = 0.03$, corrected) neocortical 5-HT_{2A} receptor binding than controls
Bouso et al., 2015	Spain, observational, retrospective, inclusion of a control group 22 long-term STD members (six men, mean age 40.9 years) compared with 22 controls matched for age, gender, years of education, and verbal and fluid IQ with no prior history of ayahuasca use (six men; mean age 41.5 years)	Time of regular ayahuasca use: average 5.3 years, range 2–13	Structural MRI + CT	Regular ayahuasca use was associated with significant ($P < 0.02$, uncorrected) cortical thinning in mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, PCC and superior occipital gyrus, while increased thickening was observed in precentral gyrus and ACC; no evidence of increased psychopathology was observed, and inverse correlations were observed between cortical thickness changes in the posterior cingulate cortex and age of onset and intensity of prior ayahuasca use, and "self-transcendence"

AC: anterior cingulate; ACC: anterior cingulate cortex; aPHC: anterior parahippocampal region; ASL: arterial spin labeling; BOLD: blood oxygenation level-dependent; BP: receptor binding potential; CBF: cerebral blood flow; CMRglu: cerebral metabolic rate of glucose; CT: cortical thickness; DASB: 3-amino-4-[2-[(di(methyl)amino)methyl] phenyl] sulfanylbenzonitritile; DMN: default-mode-network; dlPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; FC: functional connectivity; fMRI: functional magnetic resonance imaging; FPN: Frontoparietal Network; FSE: frequency scaling exponent; IQ: intelligence quotient; i.v.: intravenous; IR: inhibition of return; lPFC: lateral prefrontal cortex LFP: low frequency power; lSGA: left subgenual area; METH: *d*-methamphetamine; MDD: Major Depressive Disorder; MDE: 3,4-methylenedioxyethylamphetamine; MEG: magnetoencephalography; mPFC: medial prefrontal cortex; MRI: magnetic resonance imaging; Nac: nucleus accumbens; OPN: Occipital Pole Network; PET: positron emission tomography; PCC: posterior cingulate cortex; PFC: prefrontal cortex; rMRGlu: metabolic rate of glucose; ROIs: regions of interest; RSFC: resting-state functional connectivity; RSNs: resting-state networks; SCC: subgenual cingulate cortex; SERT: serotonin transporter; SPECT: single-photon emission computed tomography; STD: Santo Daime; TPN: task-positive network; vmPFC: ventromedial prefrontal cortex; ^{18}F FDG: ^{18}F-fluorodeoxyglucose; ^{99m}Tc-ECD: technetium-99m-labeled ethyl cysteinate dimer; ^{99m}Tc-HMPAO: technetium-99m-labeled hexamethyl propylene amine oxime. [1]See text for details on other drugs not included in the systematic review.

injection of 0.15 mg/kg over 5 min followed by a break of 1 min and a continuous infusion with 0.01 up to 0.01875 mg/kg*min over 20 min; [2] *S*-ketamine: bolus injection of 0.1 mg/kg followed by a break of 1 min and a continuous infusion with 0.0066 up to 0.015625 mg/kg*min over 20 min. Compared with placebo, DMT [but not *S*-ketamine] significantly slowed down reaction times and blunted IOR [$P < 0.05$, corrected]. Relative to placebo, *S*-ketamine increased activation in the IOR condition in the right superior frontal gyrus, left superior temporal gyrus, and right midfrontal frontal gyrus. The contrast between placebo and DMT failed to show any significant IOR-associated BOLD differences at the chosen threshold.

In the same group of volunteers and using the same doses of *S*-ketamine and DMT, Daumann et al. (2010) performed a randomized, double-blind, cross-over, placebo-controlled, BOLD fMRI study analyzing the neural correlates of the mental states induced by both drugs during a target-detection task measuring the pharmacological modulation of visual and auditory alertness. Compared with placebo, administration of DMT was associated with significant [$P < 0.001$, uncorrected] reduced BOLD activity in extrastriate regions during visual alerting and in temporal regions during auditory alerting, with visual effects being more pronounced. *S*-ketamine administration was associated with increased cortical activation in the left insula and precentral gyrus during the auditory modality.

3.2.3. Psilocybin

In an open-label study in Switzerland, Vollenweider et al. (1997) administered psilocybin [15–20 mg] to 10 healthy [eight men; mean age 33.3 years] volunteers and assessed cerebral metabolic rate of glucose [CMRglu] with PET and ^{18}F-fluorodeoxyglucose [^{18}F-FDG]. Psilocybin was administered 90 min after ^{18}F FDG injection. Psilocybin administration was associated with a significant [$P < 0.01$, uncorrected] global increase in CMRglu, with significant increases especially in the frontomedial and frontolateral cortex, anterior cingulate, and temporomedial cortex, but also in the basal ganglia and in the sensorimotor and occipital cortex. CMRglu increases in the prefrontal cortex, anterior cingulate, temporomedial cortex, and putamen were positively correlated with psilocybin's dose and subjective effects.

In a randomized, single-blind, cross-over, placebo-controlled study, the same Swiss group used PET to analyze the effects of psilocybin [0.25 mg/kg, oral] on the binding of [^{11}C]raclopride to D2-dopamine receptors in the striatum of seven healthy male volunteers [age: 27 ± 2.3 years] (Vollenweider et al., 1999). Psilocybin was administered 80 min before [^{11}C]raclopride injection. Compared with placebo, psilocybin significantly [$P < 0.05$, uncorrected] decreased [^{11}C]raclopride receptor binding potential (BP) bilaterally in the striatum, suggesting an increased D2-dopamine receptor occupancy by endogenous dopamine. Moreover, decreased [^{11}C]raclopride BP in the ventral striatum was correlated with increased in depersonalization.

In Germany, Gouzoulis-Mayfrank et al. (1999) performed a pseudo-randomized, double-blind, cross-over, placebo-controlled, ^{18}F FDG PET study involving a prefrontal activation task [a word association task compared with a word repetition task] and the oral administration of psilocybin [2 mg/kg], 3,4-methylenedioxyethylamphetamine [MDE, 2 mg/kg] and *d*-methamphetamine [0.2–0.4 mg/kg] [32 healthy volunteers: 21 men; mean age 34.2 years; each group: $n = 8$]. Compared with placebo, psilocybin significantly [$P < 0.05$, uncorrected] increased the absolute metabolic rate of glucose [rMRGlu] in the right anterior cingulate and in the right frontal operculum, and decreased rMRGlu in the right thalamus and in the left precentral region. MDE reduced rMRGlu in the left precentral and in the right superior prefrontal region, in the composite bilateral frontal neocortex, and in the entire neocortex, and increased rMRGlu in the cerebellum [bilaterally] and in the right putamen. Bilateral rMRGlu increases in the cerebellum were also observed with *d*-methamphetamine, which also induced rMRGlu decreases in the composite bilateral entire neocortex region. Psilocybin-induced increases in rMRGlu in the right anterior cingulate correlated positively with stereotyped thoughts and negatively with anxiety, and rMRGlu increases in the right frontal operculum were associated with low general activation. Reduced rMRGlu in the left thalamus was associated with general psychopathology, tension, anxiety, depressive feelings, and less stereotyped thoughts. MDE-induced rMRGlu reductions in the composite bilateral frontal region and increases in the right anterior cingulate were associated with cognitive disturbances, while *d*-methamphetamine-induced reductions in rMRGlu in the posterior cortical regions were associated with a state of general activation and increased drive. MDE- and *d*-methamphetamine-induced rMRGlu cerebellar increases and reduced cortical rMRGlu were associated with anxiety, negative feelings, cognitive dysfunction, and general psychopathological signs.

In a single-blind, within-subjects, counterbalanced-order, placebo-controlled study performed in the United Kingdom, Carhart-Harris et al. (2012a) investigated the effects of intravenously [i.v.] administered psilocybin [2 mg] using arterial spin labeling [ASL] perfusion fMRI and task-free BOLD fMRI to map rCBF and changes in venous oxygenation in 15 healthy volunteers [ASL fMRI: 10 men; mean age 34.1 years; BOLD fMRI: 13 men; mean age 32 years]. Psilocybin was infused manually over 60 s, beginning 6 min after the start of each 18 min functional scan. In the ASL perfusion fMRI study, psilocybin induced significant [$P < 0.05$, corrected] rCBF decreases in bilateral thalamus, putamen, hypothalamus, posterior cingulate cortex, retrosplenial cortex, precuneus, bilateral angular gyrus, supramarginal gyrus, rostral and dorsal anterior cingulate cortex, paracingulate gyrus, medial prefrontal cortex, frontoinsular cortex, lateral orbitofrontal cortex, frontal operculum, precentral gyrus, and superior, middle and inferior frontal gyrus, when compared with placebo, and the magnitude of rCBF decreases correlated positively with the intensity of the subjective effects induced by psilocybin. The task-free BOLD fMRI study showed significant [$P < 0.05$, corrected] decreases in similar regions, including the medial prefrontal cortex, ventral posterior cingulate cortex, putamen, and subthalamic nuclei, but also signal decreases in higher order visual areas. Functional connectivity analysis using a ventromedial prefrontal seed showed that psilocybin administration induced a significant decrease in the positive coupling between the medial prefrontal cortex and the posterior cingulate cortex.

Following this initial study, several re-**analyses** of the fMRI data from the original sample were published (Carhart-Harris et al., 2012b, 2013; Petri et al., 2014; Roseman et al., 2014,2014; Lebedev et al., 2015). Carhart-Harris et al. (2012b) re-analyzed the fMRI data from 10 participants from the original study regarding facilitation of access to personal memories and emotions using **BOLD** fMRI and a paradigm involving personal memory cues where volunteers viewed each cue for 6 s and then closed their eyes for 16 s and imagined re-experiencing the event. Both placebo and psilocybin induced significant [$P < 0.001$, corrected] memory-related activations in the amygdala, hippocampus, putamen, nucleus accumbens, mid-cingulate cortex, pre-sensorimotor area and precuneus in the early phase [first 8 s], and in the amygdala, subgenual cingulate cortex, pre-sensorimotor area, temporal pole, medial prefrontal cortex and frontal pole in the late phase [last 8 s], where visual and other sensory cortical activations were observed only with psilocybin. Moreover, compared with placebo, psilocybin induced significant [$P < 0.05$] increases in ratings of memory vividness and visual imagery, and a significant positive correlation was observed between vividness and subjective wellbeing in a two-week follow-up.

In another re-analysis of the BOLD fMRI data from the sample of Carhart-Harris et al. (2012a), the effects of psilocybin on resting-state network and thalamocortical functional connectivity were assessed (Carhart-Harris et al., 2013). Compared with placebo, psilocybin significantly [$P < 0.001$, corrected] increased functional connectivity between the default-mode-network [DMN] and the salience network, right frontoparietal network, and auditory network, suggesting a decreased orthogonality between the DMN and a generic task-positive network [TPN]. No significant effects were observed on thalamocortical functional connectivity.

Another re-analysis study assessed resting-state functional connectivity and showed that, compared with placebo, psilocybin reduced the stability of the brain's functional patterns by creating several transient connectivity structures of low stability and short average cycle persistence [$P < 10^{-35}$], and also some topologically long-range and persistent cycles [$P < 10^{-30}$], suggesting an increased integration between cortical regions and a less constrained and more intercommunicative mode of brain function (Petri et al., 2014). These results are in line with another BOLD fMRI resting-state functional connectivity study of the same sample, in which the variability of BOLD signal variance and total spectral power was significantly [$P < 0.05$, corrected] increased following psilocybin administration in the anterior cingulate cortex and bilateral hippocampi, when compared with placebo (Tagliazucchi et al., 2014). Moreover, significant [$P < 0.05$, corrected] diffuse and widespread decreases in low frequency power [0.01–0.1 Hz] and frequency scaling exponent [indicative of a less correlated signal] were observed in frontal and parietal regions corresponding to higher-level association regions such as the DMN, executive control, and dorsal attention networks. Finally, analysis of the entropy of the dynamical functional connectivity states in the network comprised by the anterior cingulate cortex and the bilateral hippocampi showed an entropy increase following psilocybin administration, indicating a wider repertoire of connectivity states post-psilocybin (Tagliazucchi et al., 2014).

Roseman et al. (2014), again using the original fMRI data from the sample of Carhart-Harris et al. (2012a), measured changes in resting-state functional connectivity induced by psilocybin and 3,4-methylenedioxymethamphetanine [MDMA; 100 mg, oral; $n = 13$] using a standard template of different independent components analysis (ICA)-derived resting-state networks [RSNs]. Compared with placebo, psilocybin induced significant [$P < 0.05$, corrected] increases in coupling in the following RSNs: Visual–Medial Network/left Frontoparietal Network, Visual–Medial Network/Dorsal Attention Network 1, Visual–Medial Network/right Frontoparietal Network, Visual–Medial Network/Dorsal Attention Network 2, Visual–Medial Network/Cerebellar Network, Visual–Lateral Network/DMN, Visual–Lateral Network/left Frontoparietal Network, Visual–Lateral Network/right Frontoparietal Network, Visual–Lateral Network/Dorsal Attention Network 2, Visual–Occipital pole Network/Dorsal Attention Network 2, Auditory Network/DMN, Auditory Network/Executive Control Network, Auditory Network/left Frontoparietal Network, Auditory Network/right Frontoparietal Network, Auditory Network/Dorsal Attention Network 2, Sensorimotor Network/Executive Control Network, Sensorimotor Network/left Frontoparietal Network, Sensorimotor Network/right Frontoparietal Network, Sensorimotor Network/Dorsal Attention Network 2, DMN/left Frontoparietal Network, DMN/Dorsal Attention Network 1, DMN2 [an anterior DMN/Executive Control Network hybrid]/Executive Control Network, DMN2/left Frontoparietal Network, DMN2/Dorsal Attention Network 1, DMN2/Dorsal Attention Network 2, Executive Control Network/left Frontoparietal Network, Executive Control Network/right Frontoparietal Network, left Frontoparietal Network/Dorsal Attention Network 1, right Frontoparietal Network/Dorsal Attention Network 1, and Dorsal Attention Network 1/Dorsal Attention Network 2. Psilocybin also induced significant decreases in coupling in the following RSNs: Sensorimotor Network/Visual–Medial Network, Sensorimotor Network/Visual–Lateral Network, and Sensorimotor Network/Visual–Occipital pole Network. Compared with placebo, MDMA only induced significant increases in coupling between the DMN2/Executive Control Network. Since MDMA had less marked effects on between-network resting-state functional connectivity and less intense subjective effects than those induced by psilocybin, these results suggest that psilocybin has more profound effects on global brain function.

In a double-blind, randomized, cross-over, placebo-controlled study performed in Switzerland, Kraehenmann et al. (2015a) administered oral psilocybin [0.16 mg/kg] to 25 healthy volunteers [16 men; mean age 24.2 years] and analyzed amygdala reactivity to negative stimuli using BOLD fMRI and an emotional picture discrimination task. In the whole-brain voxel-wise fMRI data analysis, psilocybin, compared with placebo, significantly attenuated right amygdala activation to both negative [$P = 0.001$, corrected] and neutral [$P < 0.001$, corrected] pictures, and also significantly [$P < 0.05$, corrected] attenuated activation in bilateral occipital gyri, lingual gyrus, fusiform gyrus, and temporal gyri in response to both negative and neutral pictures. In the ROI-based analysis, psilocybin, compared with placebo, significantly attenuated right amygdala activation to both negative [$P < 0.001$, corrected] **and** neutral [$P < 0.001$, corrected] pictures, and also significantly reduced [$P < 0.05$] activation of

the left amygdala to negative but not neutral pictures. Moreover, psilocybin-induced attenuation of amygdala BOLD signal was significantly correlated with increases in positive mood.

Kraehenmann et al. [2015b] performed a re-analysis of the BOLD fMRI data from the same sample of Kraehenmann et al. (2015a) to investigate the modulatory effects of psilocybin on visual–limbic–prefrontal network connectivity during threat processing in an emotional picture discrimination task. Compared with placebo, psilocybin significantly [$P = 0.01$, corrected] decreased the threat-induced modulation of top-down connectivity from the amygdala to primary visual cortex.

In a recent re-analysis of the fMRI data from the sample of Carhart-Harris et al. (2012a), Lebedev et al. (2015) employed functional connectivity analysis to evaluate the neural correlates of psilocybin-induced "ego-dissolution". In contrast to placebo, under psilocybin a negative correlation was observed between "ego-dissolution" intensity and decreased diversity of the anterior parahippocampal connections, suggesting reduced functional connectivity between the medial temporal lobe and high-level cortical regions. Moreover, baseline lower connection diversity of executive network nodes such as left dorsolateral prefrontal and superior parietal regions predicted "ego-dissolution", which was associated with decreased integrity or "disintegration" of the salience network and with reduced interhemispheric communication [$P < 0.05$, corrected].

3.2.4. *Lysergic acid diethylamide (LSD)*

In a single-blind, within-subjects, counterbalanced-order, placebo-controlled study performed in the United Kingdom, Speth et al. (2016) investigated the effects of LSD [75 μg. i.v.] on mental time travel during spontaneous mentation using BOLD fMRI in 20 healthy volunteers [16 men; mean age 30.9 years; only 19 volunteers were included in the final analysis since one male was excluded due to an absent report from the LSD condition]. Six independent, blind judges analyzed mentation reports shortly after the scans [2.5 h after LSD administration] to assess references to mental spaces for the past, present and future. Compared with placebo, LSD significantly [$P = 0.017$, uncorrected] increased the number of words in the reports and induced fewer mental spaces for the past

[$P = 0.022$, uncorrected], suggesting that LSD induces a mental state more focused in the present and therefore less unhappy, since ruminative thinking has been associated with low mood. No differences were observed regarding present or future mental spaces, and no significant correlations were reported. However, a correlation between greater decreases in DMN resting-state functional connectivity [DMN "disintegration"] under LSD and fewer mental spaces for the past almost reached statistical significance [$P = 0.054$, uncorrected].

In the same sample of volunteers and using the same dose of LSD, Carhart-Harris et al. (2016) assessed the effects of this compound using resting-state ASL, BOLD fMRI, and magnetoencephalography [MEG]. Compared with placebo, LSD significantly [$P < 0.05$, corrected] increased cerebral blood flow in the visual cortex, and a positive correlation between the magnitude of these increases and subjective ratings of complex imagery was observed. LSD significantly [$P < 0.05$, corrected] increased resting-state functional connectivity between the primary visual cortex and several cortical [e.g., anterior cingulate cortex, insula, frontal pole, precuneus] and subcortical [e.g., striatum, thalamus, putamen] brain regions; parahippocampal region and dorsomedial prefrontal cortex/right dorsolateral prefrontal cortex; and ventromedial prefrontal cortex and bilateral caudate/inferior frontal gyrus. A significant correlation was observed between increased functional connectivity in the primary visual cortex and subjective ratings of simple hallucinations and elementary and complex imagery.

However, decreased functional connectivity was observed between the parahippocampal region and the retrosplenial cortex/posterior cingulate cortex and between the ventromedial prefrontal cortex and the posterior cingulate cortex. Decreased functional connectivity in the parahippocampal region was significantly correlated with subjective ratings of "ego-dissolution" and "altered meaning". LSD also significantly decreased DMN functional connectivity [DMN "disintegration"], which was correlated with subjective ratings of "ego-dissolution". Decreased functional connectivity was also observed in resting-state networks [Lateral Visual Network/Parietal Cortex Network, Lateral Visual Network/Dorsal Attention Network, Occipital Pole Network/Posterior Opercular Network, Auditory Network/Parietal Cortex Network, Auditory Network/right Frontoparietal Network, DMN–salience network, Parietal Cortex Network/Posterior Opercular Network, Posterior Opercular Network/right Frontoparietal Network], with increased functional connectivity occurring only in the Occipital Pole Network/right Frontoparietal Network.

LSD also significantly [$P < 0.05$, corrected] decreased oscillatory power in lower-frequency bands [1–30 Hz] throughout the brain, including the posterior cingulate cortex/precuneus and other high-level cortical regions, and significant relationships were observed between "ego-dissolution" and decreased delta/alpha power; simple hallucinations and decreased alpha power; cerebral blood flow increases in the visual cortex and decreases in alpha power in the occipital cortex; and increases in functional connectivity in the primary visual cortex and decreased alpha power in posterior areas. Moreover, decreased functional connectivity in the above mentioned pairs of resting-state networks correlated with reductions in delta/beta oscillatory power.

Tagliazucchi et al. (2016) investigated the effects of LSD on global and local changes in resting-state functional connectivity using the BOLD fMRI data from a subset of 15 volunteers from the sample of Speth et al. (2016). Compared with placebo, LSD significantly [$P < 0.05$, corrected] increased global functional connectivity in the thalamus and in high-level association cortices such as the frontoparietal and inferior temporal cortices, and also increased communication between association and sensory cortices. Cortical areas with increased functional connectivity significantly overlapped with 5-HT_{2A} receptor densities, and increases in functional connectivity in the bilateral temporo-parietal junction and insular cortex were positively correlated with subjective ratings of "ego dissolution". Moreover, the authors performed a reanalysis of the fMRI data from Tagliazucchi et al. (2014) and observed significant [$P < 0.05$, corrected] increases in global connectivity in high-level association cortices after psilocybin administration.

Using the BOLD fMRI data from a subset of 12 volunteers from the sample of Speth et al. (2016), Kaelen et al. (2016) investigated parahippocampal cortex functional connectivity and its possible interaction with LSD and music during an eyes-closed mental imagery task. Compared with placebo, LSD significantly [$P < 0.05$, corrected] increased personal memory recollection and simple and complex hallucinations. The interaction between LSD and music was associated with significant [$P < 0.05$, corrected] increases in functional connectivity between the parahippocampal cortex and the primary visual cortex, left anterior insula, and left inferior frontal cortex. The interaction between LSD and music was also associated with increased parahippocampal cortex to visual cortex information flow [effective connectivity], which correlated positively with ratings of complex visual imagery.

3.2.5. Ayahuasca

In a randomized, double-blind, cross-over, placebo-controlled study performed in Spain, Riba et al. (2006) assessed the acute effects of a single oral dose of encapsulated freeze-dried ayahuasca [1.0 mg DMT/kg] in 15 healthy male volunteers [mean age 28 years] using ^{99m}Tc-ECD [ethyl cysteinate dimer] SPECT. Compared with placebo, ayahuasca induced significant [$P < 0.002$, uncorrected] bilateral activation of the anterior insula/inferior frontal gyrus, with greater intensity in the right hemisphere, and of the frontomedial wall of the right hemisphere, especially in the anterior cingulate/medial frontal gyrus. A smaller cluster was found in the ventral anterior cingulate/subcallosal gyrus, and in the left hemisphere, ayahuasca activated the amygdala/parahippocampal gyrus. No significant decreases of blood perfusion were observed.

In an open-label study in Brazil, de Araujo et al. (2012) investigated the neural basis of the visual imagery produced by ayahuasca after administering this substance [2.2 mL/kg, 0.8 mg DMT/mL, oral) to nine healthy frequent ayahuasca users [5 men; mean age 29 years] in a BOLD fMRI study using an imagery task. Ayahuasca significantly [$P < 0.05$, corrected] increased activation in the precuneus, cuneus, lingual, fusiform, middle occipital, parahippocampal, posterior cingulate, superior temporal, superior middle, and inferior frontal gyri. After ayahuasca administration, the activation of the primary visual area during the imagery task was comparable in magnitude to the activation levels of a natural image with the eyes open, and was correlated with perceptual changes. Moreover, ayahuasca reversed fronto-occipital functional connectivity, increasing the capacity of the primary visual cortex to lead other cortical areas during imagery.

In a subsequent study by the same tem using data from the same sample, Palhano-Fontes et al. (2015) used BOLD fMRI to assess the effects of ayahuasca on DMN activity during a verbal fluency task and to investigate functional connectivity using resting-state fMRI. During the task, ayahuasca significantly [$P < 0.05$, uncorrected] decreased activation of key hubs of the DMN, including the posterior cingulate cortex/precuneus and the medial prefrontal cortex. Moreover, ayahuasca decreased functional connectivity within the posterior cingulate cortex/precuneus.

In an open-label clinical trial in Brazil using ^{99m}Tc-ECD SPECT, administration of a single 2.2 mL/kg oral ayahuasca dose [0.8 mg DMT/mL] to 17 volunteers [3 men; mean age 42.71 years] with Major Depressive Disorder was associated with significant [$P < 0.01$, corrected] increases in blood perfusion in the left nucleus accumbens, right insula, and left subgenual area (Sanches et al., 2016). Moreover, ayahuasca induced significant [$P < 0.05$] reductions in

depressive and anxiety scores between baseline and 1, 7 and 21 days after drug intake.

3.2.6. Polydrug use

In an observational, retrospective study in Denmark, Erritzoe et al. (2011) analyzed the effects of MDMA and hallucinogen use on cerebral serotonin transporter [SERT] and 5-HT_{2A} receptor binding in a group of 24 users of MDMA and/or hallucinogenic drugs [21 men; mean age 24.6 years] compared with 21 nonusing controls [17 men; mean age 24 years; except for <15 episodes of cannabis use] using both [^{11}C]–labeled 3-amino-4-[2-[(di(methyl)amino)methyl] phenyl] sulfanylbenzonitritile [DASB] and [^{18}F]–labeled altanserin PET. Scans were performed after 11–14 days of drug abstinence. Users were subdivided into hallucinogen- [$n = 10$] and MDMA-preferring users [$n = 14$]. Mean [SD] lifetime uses of hallucinogenic drugs in the group of hallucinogen users was 106.7 ± 84.2, compared with 23.1 ± 24.6 in the MDMA group [$P = 0.004$]. Mean [SD] lifetime MDMA tablets used in the MDMA group was 1296 ± 1801, compared with 60 ± 114 in the hallucinogen group [$P < 0.001$]. Serotonergic hallucinogens used by the participants included, among others, psilocybin [19/24], LSD [18/24], DMT [11/24], mescaline [4/24], and ayahuasca [3/24]. However, non-serotonergic hallucinogens such as *Salvia divinorum* were also used, and users have also been exposed to cannabis, amphetamines, cocaine, gamma-hydroxybutyrate [GHB], and ketamine.

Compared to nonusers, hallucinogen users had normal cerebral SERT binding, while MDMA users had significant [$P \leq 0.001$, corrected] reductions in SERT binding compared with hallucinogen users and controls in the pallidostriatum [19% reduction], amygdala [32% reduction], and neocortex [56% reduction: 40% in the orbitofrontal cortex, 53% in the medial inferior frontal cortex, 61% in the superior frontal cortex, 48% in the superior temporal cortex, 51% in the medial inferior temporal cortex, 66% in the sensory motor cortex, 47% in the parietal cortex, and 73% in the occipital cortex]. When both group of users were analyzed separately, no significant differences in global neocortical 5-HT_{2A} receptor binding were found between users and nonusers, but when analyzed together, users had slightly lower [$P = 0.03$, corrected] neocortical 5-HT_{2A} receptor binding than controls, with regional decreases of 9% in the neocortex [13% in the orbitofrontal cortex, 10% in the medial inferior frontal cortex, 7% in the superior frontal cortex, 11% in the superior temporal cortex, 13% in the medial inferior temporal cortex, 7% in the sensory motor cortex, 8% in the parietal cortex, and 4% in the occipital cortex]. However, when two controls with very high 5-HT_{2A} receptor binding values were excluded from the sample, the difference between users and nonusers was no longer statistically significant.

In an observational, retrospective study performed in Spain, Bouso et al. (2015) used structural MRI to investigate cortical thickness in 22 Spanish members of the *Santo Daime* [six men; mean age 40.9 years; time of regular ayahuasca use: average 5.3 years, range 2–13] and 22 controls [six men; mean age 41.5 years] matched for age, gender, years of education, and verbal and fluid intelligence quotient [IQ]. Regular ayahuasca use was significantly [$P < 0.002$, uncorrected] associated with cortical thinning in mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, posterior cingulate cortex and superior occipital gyrus, while increased thickening was observed in the precentral gyrus and anterior cingulate cortex. However, no evidence of increased psychopathology was observed in the ayahuasca group, suggesting that the observed alterations in cortical thickness do not seem be associated with psychiatric symptoms. Moreover, inverse correlations were observed between cortical thickness changes in the posterior cingulate cortex and age of onset and intensity of prior ayahuasca use, and "self-transcendence", a personality trait related to religiousness and spirituality.

4. Discussion

We have conducted a systematic review to examine the acute and long-term effects of serotonergic hallucinogens in humans using neuroimaging methods. Neurochemical imaging studies [PET and SPECT] involving acute oral administration of mescaline, psilocybin, and ayahuasca suggest that these drugs induce excitatory effects in frontolateral/frontomedial cortex, medial temporal lobe, **and amygdala –** regions involved in self-awareness, cognitive functioning, memory and emotion processing. These results were consistent across studies. Furthermore, these studies were performed in separated laboratories and used different drugs and neuroimaging technics. Studies using fMRI and involving acute oral [ayahuasca] or intravenous [DMT, psilocybin, LSD] administration of serotonergic hallucinogens showed less consistent results. Most resting-state fMRI studies showed significant *reductions* in brain activation in the same regions where neurochemical imaging studies showed increased activation, as well as in other regions such as the thalamus, hypothalamus, retrosplenial cortex, precuneus, and visual areas (Daumann et al., 2010; Carhart-Harris et al., 2012a; Palhano-Fontes et al., 2015).

According to Carhart-Harris et al. (2012a), the inconsistence between PET/SPECT and fMRI results could be related to the timescales considered in the different techniques. Thus, the radiotracers used to measure blood perfusion/glucose metabolism have long half-lives [e.g., the radiotracer ^{18}F FDG, used to measure glucose metabolism, has a half-life of 110 min], using much greater timescales than fMRI measures. Therefore, phasic or short-term effects of psilocybin could show some compensating/rebound effect that is detected by PET or SPECT (Carhart-Harris et al., 2012a).

However, nonsignificant (Daumann et al., 2008; Speth et al., 2016), mixed (Tagliazucchi et al., 2014), and opposite (Carhart-Harris et al., 2016) results were also reported in fMRI studies. Moreover, an active-task fMRI study reported significant increases in memory-related activations in the amygdala, hippocampus, putamen, nucleus accumbens, mid-cingulate cortex, pre-sensorimotor area, precuneus, subgenual cingulate cortex, temporal pole, medial prefrontal cortex, frontal pole, and visual and other sensory cortical areas after intravenous psilocybin (Carhart-Harris et al., 2012b), and another fMRI study using an imagery task showed that oral ayahuasca induced a significant activation in the primary visual area comparable to the activation levels of a natural image with the eyes open, and ayahuasca also activated the cuneus and lingual gyrus and parahippocampal, retrosplenial, and frontopolar cortices (de Araujo et al., 2012). Also, an fMRI study reported that oral psilocybin significantly attenuated right amygdala activation to both negative and neutral pictures and that this effect was significantly correlated with increases in positive mood (Kraehenmann et al., 2015a).

Interpretation of functional connectivity results is even more difficult. Functional connectivity alterations in key hubs of the DMN were observed in several studies (Carhart-Harris et al., 2012a, 2013, 2016; Tagliazucchi et al., 2014, 2016; Lebedev et al., 2015; Palhano-Fontes et al., 2015; Kaelen et al., 2016), which partially corroborates the neuroanatomical substrates where PET/SPECT studies found alterations in blood perfusion/glucose metabolism. Moreover, functional connectivity studies reported increased coupling between cortical networks, suggesting an increased integration between cortical regions (de Araujo et al., 2012; Petri et al., 2014; Roseman et al., 2014; Carhart-Harris et al., 2016; Kaelen et al., 2016; Tagliazucchi et al., 2016). Furthermore, psilocybin decreased the threat-induced modulation of top-down connectivity from the

amygdala to primary visual cortex (Kraehenmann et al., 2015b), and the interaction between music and LSD increased parahippocampal cortex/visual cortex functional connectivity and parahippocampal cortex to visual cortex information flow (Kaelen et al., 2016).

Regarding structural MRI studies, one study with regular ayahuasca users reported significant cortical thinning in mesotemporal and inferior frontal gyri, precuneus, superior frontal gyrus, posterior cingulate cortex and superior occipital gyrus; and increased thickening in precentral gyrus and anterior cingulate cortex (Bouso et al., 2015). Importantly, there was no evidence of increased psychopathology in the ayahuasca group, suggesting that the structural alterations were not associated with psychopathologies. Moreover, inverse correlations were found between changes in cortical thickness in the posterior cingulate cortex and age of onset of ayahuasca use, intensity of prior ayahuasca use, and "self-transcendence"/spirituality.

Another structural MRI study investigated SERT and 5-HT_{2A} receptor binding in polydrug, hallucinogen-preferring users and found no effects regarding SERT values and a slight reduction on 5-HT_{2A} receptor densities (Erritzoe et al., 2011). However, significant effects on 5-HT_{2A} receptor densities were observed only when both group of MDMA/hallucinogens users were analyzed together, suggesting that part of this effect might be more related to MDMA than to serotonergic hallucinogens (Mueller et al., 2016). Moreover, regional decreases in neocortical 5-HT_{2A} receptor binding were of only 9% in the neocortex, and when two controls with very high 5-HT_{2A} receptor binding values were excluded from the sample the difference between groups was no longer significant.

The reviewed human data is corroborated by several preclinical studies showing that administration of serotonergic hallucinogens induce genetic, neurochemical, and behavioral alterations in/associated with brain regions such as the medial prefrontal cortex, anterior cingulate cortex, amygdala, and hippocampus [see for review Hanks and González-Maeso, 2013; Nichols, 2016]. A recent study in rats reported that acute ayahuasca administration was associated with decreased concentrations of glycine and γ-aminobutyric acid [GABA] in the amygdala, increased GABA levels in the hippocampus, and an increased utilization rate of noradrenaline, dopamine, and serotonin in the amygdala (de Castro-Neto et al., 2013). In another recent study, prolonged [30 days] ayahuasca administration to rats interfered with emotional memory, a process involving the hippocampus and the amygdala (Favaro et al., 2015), and Pic-Taylor et al. (2015) administered ayahuasca to rats to investigate patterns of neuronal activation using *c-fos* marked neurons and found higher neuronal activation in the dorsal raphe nuclei, amygdaloid nucleus, and hippocampal formation after ayahuasca administration. A recent study showed that acute administration of psilocin [the active metabolite of psilocybin] significantly increased MRI signal in the rat hypothalamus, olfactory regions, amygdala, and other limbic regions, and also increased cerebral blood flow in the somatosensory cortex after sensorial stimuli. However, MRI signal decreases were observed in the cingulate, motor, and somatosensory cortices [among other regions], and the amplitude of neuronal responses [local field potentials] to sensory stimuli in the somatosensory cortex was also decreased, suggesting an altered relationship between evoked neuronal and haemodynamic response magnitudes (Spain et al., 2015).

The results by Spain et al. (2015) are corroborated by a recent study in humans showing that psilocybin induced significant increases on BOLD signal variance and total spectral power in the anterior cingulate cortex and bilateral hippocampi, while significant decreases were observed in local field potentials in the DMN, executive control, and dorsal attention networks (Tagliazucchi et al., 2014). Their study by Spain et al. (2015) could help to explain, at least in part, the discrepancy between PET/SPECT findings of increased blood perfusion/glucose metabolism and fMRI results showing decreased cerebral blood flow. Moreover, neurophysiological studies in humans using electroencephalography [EEG] and MEG consistently show that serotonergic hallucinogens decrease the power of lower frequency oscillations [theta/alpha frequency range, <20 Hz], especially alpha oscillations [8–12 Hz], in key regions of the DMN such as the anterior/posterior cingulate cortices and the parahippocampal region, which induces an excitatory effect (Riba et al., 2002, 2004; Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2013, 2016; Kometer et al., 2015; Valle et al., 2016).

Although the neural effects of serotonergic hallucinogens may involve serotonergic [e.g., 5-$HT_{1A/2A/2C}$ receptors] and non-serotonergic [e.g., dopaminergic and sigma receptors] neurotransmission, the agonist effect of these drugs on deep-layer pyramidal neurons rich in 5-HT_{2A} receptors seem to be the main mechanism of action of these compounds (Vollenweider et al., 1998; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Kometer et al., 2012, 2013; Hanks and González-Maeso, 2013; Baumeister et al., 2014; Tylš et al., 2014; Halberstadt, 2015; Nichols, 2016; Valle et al., 2016; Tagliazucchi et al., 2016). Agonism at these receptors expressed in frontal and medial cortical areas produce altered synchronization of cortical activity (Riba et al., 2002, 2004; Muthukumaraswamy et al., 2013; Petri et al., 2014; Kometer et al., 2015; McKenna and Riba, 2015; Domínguez-Clavé et al., 2016; Valle et al., 2016; Tagliazucchi et al., 2016), "disintegration" of network connectivity (Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2014, 2016; Lebedev et al., 2015; Tagliazucchi et al., 2016), increased excitability of multimodal association hubs (Riba et al., 2004, 2006; Carhart-Harris et al., 2014; Kometer et al., 2015; McKenna and Riba, 2015; Domínguez-Clavé et al., 2016; Tagliazucchi et al., 2016), and altered information flow (Carhart-Harris et al., 2014; Alonso et al., 2015; McKenna and Riba, 2015; Domínguez-Clavé et al., 2016; Kaelen et al., 2016). These effects create a state of "expanded awareness", "ego-dissolution", and "unconstrained cognition" (Carhart-Harris et al., 2012a,b, 2014, 2013; Muthukumaraswamy et al., 2013; Petri et al., 2014; Tagliazucchi et al., 2014, 2016; Gallimore, 2015; McKenna and Riba, 2015; Lebedev et al., 2015; Domínguez-Clavé et al., 2016).

Agonism at frontocortical 5-HT_{2A} receptors also modulates glutamatergic neurotransmission and may increase the expression of neurotrophic factors such as brain-derived neurotrophic factor [BDNF] and glial cell line-derived neurotrophic factor [GDNF], thus enhancing neuroplasticity and neurogenesis by increasing the size of dendritic spines on cortical neurons (González-Maeso et al., 2008; Vollenweider and Kometer, 2010; Moreno et al., 2011, 2013; Hanks and González-Maeso, 2013; Baumeister et al., 2014; Carbonaro et al., 2015; Halberstadt, 2015; Nichols, 2016).

Interestingly, these effects seem to be the neural basis involved in the therapeutic potentials of these compounds. Preclinical and human research suggest that ayahuasca, psilocybin, and LSD have antidepressive, anxiolytic, and antiaddictive properties (dos Santos et al., 2016a, 2016b; Nunes et al., 2016). Indeed, acute administration of DMT (Gillin, 1976; Strassman et al., 1994; Riba et al., 2015), psilocybin (Griffiths et al., 2006, 2008, 2011; Studerus et al., 2011; Kometer et al., 2012; Kraehenmann et al., 2015a), LSD (Schmid et al., 2015), and ayahuasca (Osório et al., 2015; Sanches et al., 2016) is associated with increases in positive mood. Furthermore, the studies reviewed show that serotonergic hallucinogens decrease DMN activity, which is increased during rumination, an important depressive symptom. Together with decreases in amygdala activity (Kraehenmann et al., 2015a, 2015b), reduced DMN activity may be another possible mechanism involved in the antidepressive and anxiolytic effects of these drugs. Moreover, observational studies also suggest that psilocybin, LSD, and ayahuasca may have therapeutic potentials (Krebs and Johansen, 2013; Hendricks et al., 2014,

2015; Johansen and Krebs, 2015; dos Santos et al., 2016a, 2016b; Nunes et al., 2016).

Psychological mechanisms also play a role in the therapeutic properties of these drugs, and appear to be related to neuroimaging findings. For instance, in the retrospective MRI study of long-term ayahuasca users, the ayahuasca group not only scored higher than controls in "self-transcendence", but scores were negatively correlated with cortical thickness in the posterior cingulate cortex (Bouso et al., 2015). "Self-transcendence" is a character dimension related to religiousness and spirituality, and the beneficial effects of serotonergic hallucinogens appear to be related to their ability to elicit religious/mystical experiences (Kurland et al., 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Grof, 2001; Griffiths et al., 2006, 2008, 2011; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; MacLean et al., 2011; Krebs and Johansen, 2012; Baumeister et al., 2014; Kometer et al., 2015; Majić et al., 2015). Indeed, psilocybin induced religious-like experiences in healthy volunteers, with sustained improvements in attitudes, mood, and personality (Griffiths et al., 2006, 2008, 2011; MacLean et al., 2011), and psilocybin-occasioned mystical experience, together with the overall intensity of the experience, were correlated with improvements in tobacco (Garcia-Romeu et al., 2014; Johnson et al., 2014) and alcohol (Bogenschutz et al., 2015) dependence. Moreover, the religious-like effects of LSD were associated with sustained improvements in patients with anxiety associated with life-threatening diseases (Gasser et al., 2014, 2015). Interestingly, decreased DMN activity and decreased DMN-TPN inverse coupling were observed not only after administration of serotonergic hallucinogens, but also in meditation (Carhart-Harris et al., 2012a,b, 2014; de Araujo et al., 2012).

Taken together, the neuroimaging data reviewed suggests that serotonergic hallucinogens produce their effects by modulating brain areas associated with perception and emotion processing, executive functions, and other complex cognitive functions. Specifically, these group of compounds may induce acute increases in blood perfusion/glucose metabolism in prefrontal and limbic areas involved in the regulation of mood, interoception, cognition, and consciousness; decreases in reactivity of brain structures related to anxiety/fear processing such as the amygdala; and reduced brain activity in key regions of the DMN, involved in mind-wandering and self-awareness. Somehow, the altered state of consciousness produced by serotonergic hallucinogens appears to create a disruption of repetitive, rigid, and pathological patterns of negative thoughts **and emotions**, commonly observed in anxiety and mood disorders and in drug dependence, and this effect may be therapeutically relevant. Finally, long-term use of these drugs was also associated with cortical thickness alterations in important areas of the DMN, such as the posterior and anterior cingulate cortices.

A main limitation of the present systematic review is the inclusion of studies with small sample sizes, high degree of heterogeneity, and without placebo or control groups. Other important limitations include the variety of doses of the same compound used in different studies and the difficulty in accurately measuring drug dose/composition in retrospective studies.

However, despite these important limitations, the reviewed results suggest that the neural basis of the effects of serotonergic hallucinogens involve an agonist action of these drugs on 5-HT_{2A} receptors expressed in deep-layer pyramidal neurons in the fronto-parieto-occipito-temporal cortex, involved in perception, memory, and emotion processing, cognitive functions, regulation of neurotrophic factors, and consciousness. Moreover, although the mechanisms of action responsible for the effects produced by serotonergic hallucinogens are not completely understood, the available evidence suggest that these drugs may not only improve our understanding of the neurobiology of psychiatric disorders, consciousness, and other complex topics, but may also have therapeutic uses in treatment-resistant patients with anxiety and mood disorders or drug dependence. Further development of neuroimaging techniques, better sample and drug delivery standardizations and the integration of data across neuroimaging modalities may extend progress in this important field.

Conflicts of interest and source of funding

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