Degree project

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Psychedelic Oscillations: A Systematic Review of the Electrophysiological Correlates of Classic Psychedelics

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Abstract

Background: Recently there has been a revitalization in research on classic psychedelic substances. This class of drugs has been found to produce intense and profoundly meaningful experiences, and offers a unique opportunity to study the neural correlates of the sense of self. The objective of this research was to systematically review the effects of classic psychedelics on spontaneous brain activity, as measured on three electrophysiological modalities: spectral analysis, signal diversity, and functional connectivity. ***Method:*** We searched Pubmed to identify papers in English, published between January 1990 to May 2021, where electrophysiological methods were used to evaluate the effects of classic psychedelics in healthy individuals during non-task resting states. ***Results:*** Sixteen papers were included. Classic psychedelic substances generally decrease spectral power in most frequency bands, mainly in the alpha range, increase signal diversity, and decrease the flow of information throughout the brain. ***Conclusion:*** Decreases in alpha power, increased signal diversity, and decreases in default mode network activity might be important neural correlates of the psychedelic state. However, inconsistencies in the results and heterogeneity in study design are some of the limitations that have to be considered when interpreting these results.

Keywords: electrophysiological, psychedelic, signal diversity, spectral analysis, functional connectivity

Psychedelic Oscillations: a Systematic Review of the Electrophysiological Correlates of Classic Psychedelics

Classic Psychedelics

The term "psychedelics" commonly refers to a subcategory of hallucinogenic drugs; classic serotonergic psychedelics (Nichols, 2016). These compounds act mainly as agonists (or partial agonists) on the serotonin- (5-hydroxytryptamine [5-HT]) 2A receptors in the brain (Glennon et al., 1983, 1984; Nichols, 2016; Vollenweider et al., 1998). Furthermore, they can be broken into two main structural categories; indoleamines which include structural variations of tryptamine, and phenethylamines, which include structural variations of phenethylamine (Halberstadt, 2015; Johnson et al., 2019). Indoleamines include lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), *N,N*-dipropyltryptamine (DPT), 4-phosphoryloxy-*N,N*-dimethyltryptamine (psilocybin) and its active metabolite 4-hydroxy-*N,N*-dimethyltryptamine (psilocin; Halberstadt, 2015; Nichols, 2012). Phenethylamines include 3,4,5-trimethoxyphenethylamine (Mescaline), 2,5-dimethoxy-4-bromophenethylamine (2C-B), and 2,5-dimethoxy-4-iodophenethylamine (2C-I; Halberstadt, 2015; Nichols, 2012).

Classic psychedelics produce remarkably similar subjective effects, despite them having distinct chemical structures (Hollister & Hartman, 1962; Isbell, 1959; Trulson et al., 1977; Wolbach et al., 1962). Typical effects of classic psychedelics include considerable alterations in cognitive, perceptual, and affective functions as well as sensory changes in vision and audition (Isbell, 1959; Wolbach et al., 1962). Perhaps the most characteristic subjective effect of classic psychedelics is a mystical-type of altered state of consciousness (Griffiths et al., 2006, 2008, 2011). Central aspects of mystical experiences are a deep sense of introspective unity and dissolution of the "self" or "ego" (Barrett & Griffiths, 2018; Griffiths et al., 2006).

Classic psychedelics offer a unique opportunity to study the neural correlates of the sense of self using various neuroimaging techniques (Lebedev et al., 2015). Several recent studies have utilized electroencephalography (EEG) and magnetoencephalography (MEG) in a variety of ways to investigate the effects of classic psychedelics on brain activity (Carhart-Harris et al., 2016; Kometer et al., 2015; Muthukumaraswamy et al., 2013; Pallavicini et al., 2021; Schenberg et al., 2015; Timmermann et al., 2019; Valle et al., 2016).

Spontaneous Brain Activity

Since the first EEG recording in 1924 by Hans Berger, EEG has been extensively used to study brain activity (Buzsáki, 2006; Haas, 2003). In his first paper on EEG, Berger identified the EEG as a continuous curve with continuous oscillations (Berger, 1929). Furthermore, when measuring eyes closed spontaneous brain activity, i.e. when the subject is in a non-task resting state, Berger observed a large-amplitude rhythm which he later termed the alpha rhythm (8 - 12 Hz; Berger, 1929; Buzsáki, 2006; Herrmann et al., 2016).

Forty years after Berger's first publication on EEG, the first paper on MEG, in which the alpha rhythm was also observed, was published (Cohen, 1968). Both EEG and MEG are electrophysiological methods for measuring brain activity, while EEG measures electrical activity (passive currents) through electrodes placed on the scalp, MEG measures magnetic fields generated by electrical activity through ultrasensitive superconducting quantum interference devices (Hämäläinen & Lundqvist, 2019). Furthermore, since EEG measures electrical currents directly on the scalp, it is significantly affected by volume conduction between the electrode and the source. The magnetic fields measured by MEG are not distorted by intervening tissues (Hari & Puce, 2017).

What distinguishes EEG and MEG from other noninvasive neuroscientific methods is their capability of directly measuring neuronal activity with a superior temporal resolution in the millisecond range (Hämäläinen & Lundqvist, 2019; Hari & Puce, 2017). However, since both methods record neuronal signals from the scalp, the spatial resolution is fundamentally limited (Hari & Salmelin, 2012). The neuronal activity measured by EEG and MEG consists mainly of postsynaptic currents generated by groups of cortical pyramidal neurons that are aligned perpendicular to the cortical surface (Hämäläinen & Lundqvist, 2019; Hari & Puce, 2017).

Spontaneous neuronal oscillations, such as the alpha rhythm, reflect fluctuations in the synchronous activity of large neuronal ensembles (Boly et al., 2016; Buzsáki, 2006). The fine temporal resolution of EEG and MEG allows for the decomposition of spontaneous brain activity into its oscillatory frequency components (Hämäläinen & Lundqvist, 2019). Since Berger discovered the alpha frequency band, several frequency bands have been discovered and delineated, delta (0.5 – 4 Hz); theta (4 – 8 Hz); alpha (8 – 12 Hz); beta (12 – 30 Hz); gamma (> 30 Hz), albeit somewhat arbitrarily and not necessarily based on function or mechanism (Buzsáki, 2006; Buzsáki et al., 2013). Further, different researchers might define these frequency bands slightly differently and include various sub-bands, e.g. low-gamma (30 – 50 Hz) and high-gamma (50 – 100 Hz). Despite this, the different frequency bands have traditionally been associated with distinct functions.

Oscillations within the alpha frequency band, the most dominant oscillations in the human brain, have been associated with semantic orientation, i.e. knowledge-based attention of the environment (Klimesch, 2012). Delta activity has been associated with slow-wave sleep, motivation, and attention (Başar et al., 2000; Klimesch, 2012; Knyazev, 2007). Theta activity has been associated with processing new episodic information and emotional arousal (Klimesch, 2012; Knyazev, 2007). Beta activity has been associated with cognitive control of sensorimotor activity (Engel & Fries, 2010; Klimesch, 2012). Gamma activity has been associated with a large variety of perceptual, motor, and cognitive processes (Engel & Fries, 2015; Klimesch, 2012). Furthermore, low-frequency oscillations (e.g., delta, theta, and alpha)

are generally thought to modulate long-range neural communication between distant neural regions (Buzsáki et al., 2013; von Stein & Sarnthein, 2000).

However, many oscillatory frequencies co-occur and the traditional dichotomizing view of the brain's oscillations into different frequency bands has been criticized (Buzsáki, 2006; Buzsáki et al., 2013; Jensen & Mazaheri, 2010; Steriade, 2006). Some researchers suggest a more unified framework accounting for the interplay between neuronal oscillations which is generally hierarchical and universal in nature, e.g., the power of high-frequency oscillations is modulated by the phase of low-frequency ones (Buzsáki et al., 2013; Steriade, 2006).

EEG has been widely used in studies on the effects of various psychoactive drugs, such as cocaine, morphine, barbiturates, and scopolamine (Berger, 1931, 1933; Fink, 1984). While MEG only recently started being used for psychopharmacological research, both EEG and MEG are now able to differentiate a variety of drugs and dosages based on alterations in brain oscillations (Hari & Salmelin, 2012; Kähkönen, 2006; Saletu et al., 2002). Many of the analytical procedures for EEG are also identical for MEG (Schomer & Lopes da Silva, 2017).

Event related potentials (ERPs) in EEG and event related fields (ERFs) in MEG, i.e. the averaged measured brain response to a cognitive, motor, or sensory input, are along with spontaneous brain activity the core topics of electrophysiological research. However, ERPs and ERFs are beyond the scope of this review and deserve a separate paper. Thus, the focus of this review will be on spontaneous brain activity in a non-task resting state.

Spectral Analysis

EEG and MEG signals are very complex and a standard method for analyzing spontaneous brain activity is by spectral analysis (Dressler et al., 2004; Schomer & Lopes da Silva, 2017). Spectral analysis consists of studying the different frequencies that make up the EEG and MEG signal (Schomer & Lopes da Silva, 2017). Typically the fast Fourier transform algorithm is used to calculate what frequencies are present in the signal or the distribution of signal power over frequency as reflected by power spectral density (Dressler et al., 2004; Schomer & Lopes da Silva, 2017). The power spectrum can then be displayed as frequency power over time or plotted on a topographic map (Schomer & Lopes da Silva, 2017). Total power and spectral band power are commonly reported parameters from the power spectrum when studying pharmacological effects on spontaneous brain activity with EEG and MEG (Alonso et al., 2012; Dressler et al., 2004; Fink, 1984; Mucci et al., 2006; Muthukumaraswamy, 2014; Schomer & Lopes da Silva, 2017). Generally, drugs within the same class display similar effects on the power spectrum (for review see Saletu, 1989). For example, neuroleptics (such as chlorprothixene) tend to increase the combined delta/theta power while decreasing alpha and beta power; and benzodiazepines (such as diazepam) typically decrease low alpha activity and increase delta and beta activity (Barbanoj et al., 1994; Saletu, 1989).

Signal Diversity and Entropy

The diversity of brain activity has recently been applied to measure the "level of consciousness", i.e. to distinguish between wakeful rest, sleep, and general anesthesia (Casali et al., 2013; Sarasso et al., 2015; Schartner et al., 2015). Signal diversity in this context reflects the variability of spontaneous brain activity or the number of distinct patterns in the signal (Schartner et al., 2015, 2017). Lempel-Ziv complexity (LZc) and measures of entropy reflect signal diversity and are especially suitable for EEG and MEG data given the high temporal resolution (Casali et al., 2013; Schartner et al., 2015). Based on their research with classic psychedelics, Carhart-Harris et al. (2014) proposed a mechanistic model of states of consciousness, the entropic brain hypothesis (EBH). Entropy here refers to a quantity used to measure the level of uncertainty (or randomness) within a physical system and is thought to correspond to the richness of conscious content (Carhart-Harris et al., 2014; Johnson et al., 2019). Signal diversity measures, such as LZc, are considered to reflect the level of entropy according to the EBH (Carhart-Harris, 2018; Carhart-Harris et al., 2014). Furthermore, the EBH states that "primary states" of consciousness (such as the psychedelic state, dreaming, and early psychosis) are characterized by high entropy whereas "non-primary states" (such as deep sleep, sedation, and anesthesia) are characterized by low entropy (Carhart-Harris et al., 2014). Recently the EBH has been integrated with the "free-energy principle", which is closely related to hierarchical predictive coding, to form a unifying model called Relaxed Beliefs Under Psychedelics (REBUS) and the anarchic brain (Carhart-Harris & Friston, 2019). Briefly, the REBUS/anarchic brain model hypothesizes that increased brain entropy during psychedelics reflects attenuation of top-down predictive processes and simultaneously strengthened bottom-up information flow (Carhart-Harris & Friston, 2019).

Functional Connectivity

The human brain is considered to be organized according to two functional principles, functional segregation and functional integration (Friston, 1994, 2002). Functional segregation refers to the division of distinct cortical and subcortical anatomical brain regions based on function (Friston, 2002). Functional integration refers to the coordination and coupling of specialized areas within and between each other (since no area of the brain performs a cognitive, motor, or sensory process by itself; Eickhoff & Müller, 2015; Friston, 2002). Functional integration can further be divided into functional and effective connectivity (Friston, 1994).

Functional connectivity (FC) refers to statistical dependence or mutual information (patterns of correlation) of neuronal activity in spatially distant brain areas (Friston et al., 1993, 2013). Effective connectivity (EC) refers to the influence of one node over another within a specific neuronal system (Breakspear, 2004; Friston, 1994; Friston et al., 2003). When analyzing functional networks, FC is a much more direct approach that cannot imply causality whereas EC relies on several assumptions of the underlying models and implies causality

(Eickhoff & Müller, 2015; Friston et al., 2013). FC has been measured extensively with EEG and MEG with various techniques such as coherence, power correlations, transfer entropy, and Granger causality (Brookes et al., 2019; Eickhoff & Müller, 2015; Seth et al., 2015). Further, FC can be divided into two categories, directed and undirected FC. Undirected measures, such as correlation and coherence, reflect the "shared information" between variables whereas directed measures, such as Granger causality and transfer entropy, reflect "information flow" between variables (Alonso et al., 2015; Barnett et al., 2020).

The Default Mode Network

When individuals are left undisturbed in a non-task resting state a specific set of brain regions are reliably found to be engaged, the default mode network (DMN; Buckner et al., 2008; Raichle et al., 2001). Beyond freethinking or "mind-wandering", the DMN is also engaged in self-referential processing and self-projection, i.e. shifting the perspective from the present moment to other perspectives (anticipation of the future, remembering the past, and pondering about what other people might think; Buckner & Carroll, 2007; Gusnard et al., 2001; Mason et al., 2007). Furthermore, the DMN has been called the "task-negative network" because it is negatively correlated with external attentional networks, e.g. task-related networks (Buckner et al., 2008; Fox et al., 2005). Primary nodes of the DMN include the medial prefrontal cortex (MPFC), the posterior cingulate cortex, the inferior parietal lobule (IPL), and the parahippocampal cortex (PHC; Buckner et al., 2008; Fox et al., 2005).

The DMN has been mainly studied using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI; Buckner et al., 2008; Fox et al., 2005; Raichle et al., 2001). While electrophysiological research has been conducted to identify frequency domain correlates of the DMN the results have been inconsistent (Jann et al., 2009; Knyazev et al., 2011; Laufs et al., 2003; Mantini et al., 2007; Meltzer et al., 2007; Scheeringa et al., 2008). Alpha oscillations are related to internal mental processing, such as semantic memory retrieval, and have been suggested to reflect top-down inhibitory control (Klimesch, 1999, 2012; Klimesch et al., 2007; von Stein & Sarnthein, 2000). While positively correlated with internal mental processing, alpha oscillations are also negatively correlated with processing of sensory information and attention to the external world (Knyazev et al., 2011). This has led some researchers to consider alpha oscillations as closely related to the self-referential mental processes that are central to the DMN (Carhart-Harris & Friston, 2019; Knyazev et al., 2011).

Deactivation of the DMN is generally considered to be a hallmark consequence of classic psychedelics (Barrett & Griffiths, 2018; Carhart-Harris et al., 2014; Carhart-Harris & Friston, 2019). Several resting-state fMRI studies have found decreased activity in the MPFC and the posterior cingulate cortex, central hubs of the DMN, in subjects under the influence of classic psychedelics (Carhart-Harris et al., 2012, 2016; Palhano-Fontes et al., 2015).

Incidentally, the distribution of 5-HT2A receptors is dense in these areas (Carhart-Harris et al., 2012; Erritzoe et al., 2009).

The decreased activity of the DMN, as a result of classic psychedelics, has also been found to correlate with a decreased sense of self or "ego" and increased intensity of drug effects (Carhart-Harris et al., 2012, 2016). These findings have led to the DMN being considered at the top of top-down processes as part of the REBUS/anarchic brain model (Carhart-Harris & Friston, 2019). The sense of dissolution of the self or ego is commonly reported by subjects undergoing a psychedelic experience and is related to a profound sense of introspective unity, a defining aspect of the mystical experience (Barrett et al., 2020; Barrett & Griffiths, 2018; Griffiths et al., 2006, 2011, 2016; Smigielski et al., 2019; Tagliazucchi et al., 2016).

Aim

The underlying mechanisms by which classic psychedelics produce profound subjective experiences are still largely unknown. While electrophysiological studies focusing on the effects of classic psychedelics on spontaneous brain activity are increasing, no review of these recent findings has, to the best of our knowledge, been conducted. The aim of this paper is thus to systematically review the effects of classic psychedelics on three electrophysiological modalities: spectral analysis, signal diversity, and functional connectivity, and relate these to current theories on the mechanism of action of these drugs, as well as to electrophysiological effects of other drug classes and interventions that share some similarities with classic psychedelics.

Methods

Search Strategy

This systematic review was conducted according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). A literature search was conducted using the electronic database PubMed. The following search string was used to find relevant studies; (Electroencephalography OR Magnetoencephalograph* OR EEG OR MEG OR Brainwave* OR oscillation* OR electrophysiological) AND (Hallucinogen*[MeSH Terms] OR Hallucinogen*[Title/Abstract] OR Psychedelic*[Title/Abstract] OR N,N-Dimethyltryptamine OR 5-methoxy-N,N-dimethyltryptamine OR 5-MeO-DMT OR Psilocybin OR Psilocin OR "Lysergic Acid Diethylamide" OR LSD OR DMT OR Ayahuasca). The search results were scrutinized and selected based on title or abstract.

Inclusion and Exclusion Criteria

Original studies using either EEG, MEG, or both, were included in this review. Furthermore, only studies published between January 1990 and May 2021 were included. The following criteria for population, intervention, control, and outcome (PICO) were used to select studies; Population: only healthy subjects; Intervention: any classic psychedelic;

Control: baseline or placebo; Outcome: spectral analysis, signal diversity, and/or functional connectivity. Animal studies and studies focusing on ERP/ERF (see above) were excluded.

Data Extraction

The following data were extracted from all included studies: Spectral band power changes, results from measures of signal diversity (LZc or coalition entropy), and changes in functional connectivity using various methods (such as phase synchronization, coherence, correlation, or Granger causality).

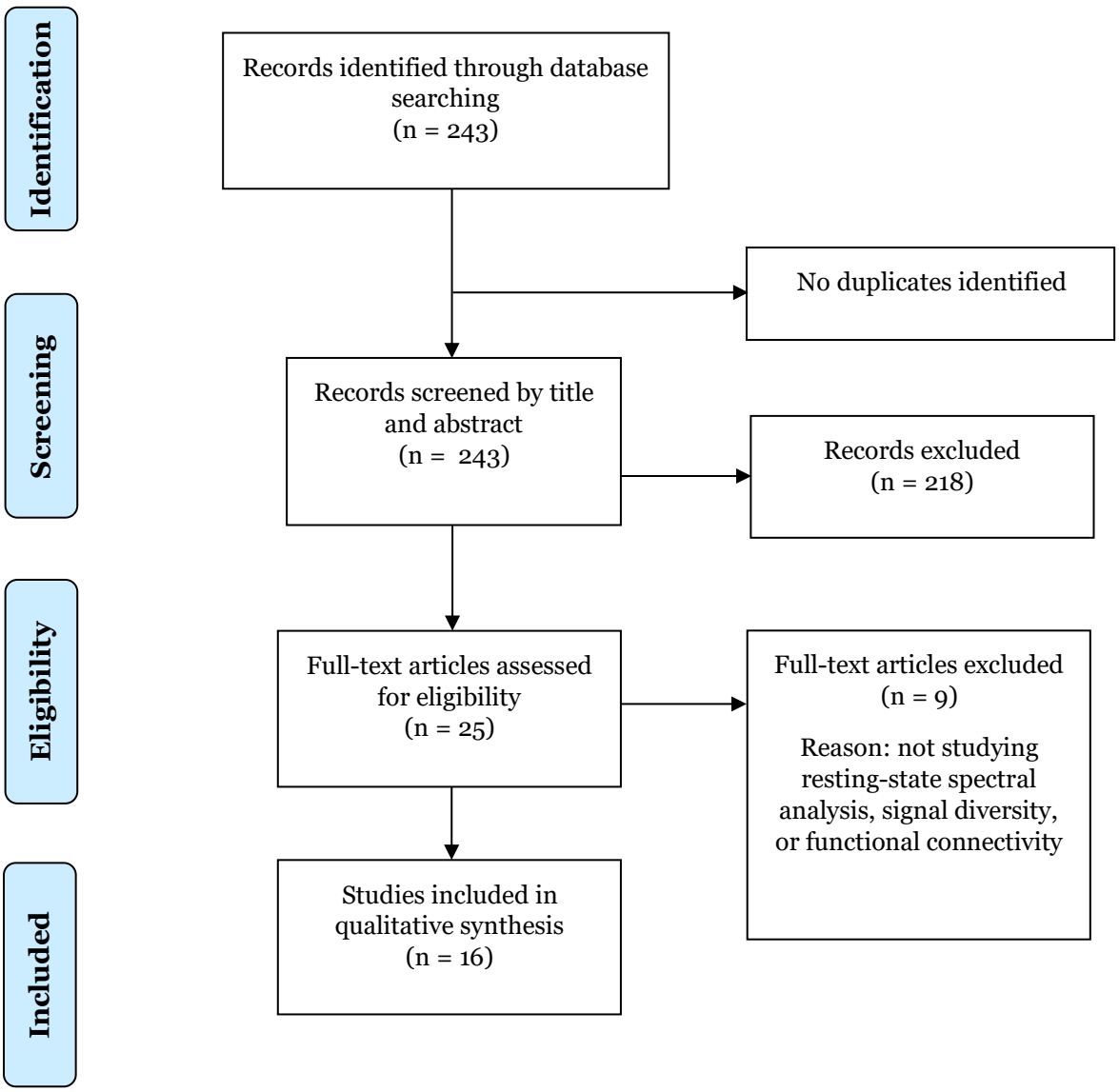
Results

Search Results

The literature search yielded 243 records from PubMed (Figure 1). There were no duplicates and thus 243 records were screened by title or abstract. Of these, 218 records were irrelevant: these studies were preclinical, non-clinical, and other types of studies not focusing on classic psychedelics and thus excluded. Twenty-five full-text articles were further assessed for eligibility, which resulted in the exclusion of nine additional articles, either because they did not focus on the acute effects, or focused on event related effects (ERP or ERF). In all, 16 articles were included in this review. Table 1 summarizes the articles included for analysis.

Figure 1

PRISMA flow chart



Note. The literature search process, illustrated in a PRISMA flow diagram. Adapted from "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement." by Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., 2009, *PLoS Med, 6*(7), p. 3 (doi:10.1371/journal.pmed1000097). CC BY-NC.

Table 1

Summary of studies included

Reference per drug	*N* (included in analysis)	Administration (dose)	Study design	Measure
LSD				
Carhart-Harris et al. (2016)	20 (14)	IV (75 µg)	Single-blind, fixed-order	Power spectral density
Ayahuasca				
Alonso et al. (2015)	10 (10)	PO (0.75 mg DMT/kg BW)	RCT	Transfer entropy, Granger causality
Don et al. (1998)	11 (11)	PO (0.67 mg DMT/kg BW)	Open-label	Power spectral density
Riba et al. (2004)	18 (18)	PO (0.85 mg DMT/kg BW)	RCT	Power spectral density
Riba et al. (2002)	18 (18)	PO (0.6 & 0.85 mg DMT/kg BW)	RCT	Power spectral density
Schenberg et al. (2015)	20 (17)	PO (1.39 mg DMT/kg BW)	Open-label	Power spectral density
Stuckey et al. (2005)	2 (2)	PO (unknown dose)	Open-label	Power spectral density, coherence
Valle et al. (2016)	12 (12)	PO (0.75 mg DMT/kg BW)	RCT	Power spectral density
Psilocybin				
Kometer et al. (2015)	55 (50)	PO (170 & 215 µg/kg BW)	RCT	Power spectral density, phase synchronization
Kometer et al. (2013)	17 (15)	PO (215 µg/kg BW)	RCT	Power spectral density
Muthukumaraswamy et al. (2013)	15 (14)	IV (2 mg)	Single-blind, fixed-order	Power spectral density
DMT				
Pallavicini et al. (2021)	35 (29)	IN (40 mg)	Open-label	Power spectral density, LZc, coherence
Timmermann et al. (2019)	13 (12)	IV (7 – 20 mg)	Single-blind, fixed-order	Power spectral density, LZc
Re-analyses (LSD & psilocybin)				
Barnett et al. (2020)	35 (29)	IV (75 µg LSD & 2 mg psilocybin)	Single-blind, fixed-order	Granger causality, Coherence, Correlation
Pallavicini et al. (2019)	35 (29)	IV (75 µg LSD & 2 mg psilocybin)	Single-blind, fixed-order	Correlation
Schartner et al. (2017)	35 (29)	IV (75 µg LSD & 2 mg psilocybin)	Single-blind, fixed-order	LZc, SCE, ACE

Note. LSD = lysergic acid diethylamide; DMT = *N*,*N*-dimethyltryptamine; IV = Intravenous; PO = Peroral; BW = Body weight; IN = Inhalation; RCT = Randomized double-blind control

trial; LZc = Lempel-Ziv complexity; SCE = Synchrony coalition entropy; ACE = Amplitude coalition entropy.

The Effects of Classic Psychedelics on Spectral Analysis

Twelve of the studies included investigated the effects of classic psychedelics on spectral power. These are summarized in Table 2.

Table 2

Summary of the results on spectral power

Outcome	Drug < control	Drug = control	Drug > control
Delta power	Carhart-Harris et al. (2016); Riba et al. (2004); Riba et al., (2002); Valle et al. (2016); Kometer et al. (2015); Muthukumaraswamy et al. (2013)	Schenberg et al. (2015); Timmermann et al. (2019)	Pallavicini et al. (2021)
Theta power	Carhart-Harris et al. (2016); Riba et al. (2004); Riba et al., (2002); Stuckey et al. (2005); Valle et al. (2016); Kometer et al. (2015); Muthukumaraswamy et al. (2013)	Don et al. (1998); Schenberg et al. (2015); Pallavicini et al. (2021); Timmermann et al. (2019)	
Alpha power	Carhart-Harris et al. (2016); Riba et al. (2004); Riba et al., (2002); Schenberg et al. (2015); Stuckey et al. (2005); Valle et al. (2016); Kometer et al. (2015); Kometer et al. (2013); Muthukumaraswamy et al. (2013); Pallavicini et al. (2021); Timmermann et al. (2019)	Don et al. (1998)	
Beta power	Carhart-Harris et al. (2016); Riba et al. (2004); Riba et al., (2002); Stuckey et al. (2005); Kometer et al. (2015); Muthukumaraswamy et al. (2013); Timmermann et al. (2019)	Don et al. (1998); Valle et al. (2016); Pallavicini et al. (2021)	
Gamma power	Muthukumaraswamy et al. (2013)	Timmermann et al. (2019)	Don et al. (1998); Schenberg et al. (2015); Kometer et al. (2015); Pallavicini et al. (2021)

Note. Less than sign (<) = Significantly decreased; equal to sign (=) = No significant change; greater than sign (>) = Significantly increased.

LSD

One study investigating the effects of LSD on spectral power was identified (Carhart-Harris et al., 2016). Carhart-Harris et al. (2016) used a single-blind, within-subjects design with an inert placebo to assess the effects of LSD on spectral power in 20 volunteers using MEG. They found significant reductions in power for the lower frequency bands (< 30 Hz [delta, theta, alpha, and beta]). For these frequency bands, significance was reached for most sensors. Source localization revealed that the power decreases were spatially distributed throughout the brain with significant effects in the posterior cingulate cortex/precuneus. Analysis of the relationship between subjective ratings and power changes revealed that decreased delta and alpha power correlated significantly with an increased sense of "ego dissolution". Further, the study applied not only MEG but also arterial spin labelling and blood oxygen level dependent imaging which allowed for combined analysis of the results from the different modalities. Decreased alpha power in the posterior (occipital lobe) sensors correlated significantly with increased cerebral blood flow in the visual cortex and increases in V1 resting-state functional connectivity (Carhart-Harris et al., 2016).

Ayahuasca

Six studies investigating the effects of ayahuasca on spectral power were identified. All studies used EEG to measure neuronal oscillations. Don et al., (1998) used an open-label naturalistic design with 11 volunteers. They found that ayahuasca produced no significant changes ($p > .10$ for all comparisons) in the lower frequency bands (theta, alpha, and beta) for either eyes closed or eyes open conditions. However, there were slight decreases in theta and alpha power for most electrodes. Significant power increases were found within the gamma range in both the eyes closed and eyes open ayahuasca conditions vs baseline. The significant increases in gamma power during the eyes closed ayahuasca condition vs baseline were found in electrodes placed over the left posterior temporal cortex and left occipital lobe. For the eyes open ayahuasca condition vs baseline, the increases in gamma power were more prominent and more spatially distributed, covering most of the posterior regions (Don et al., 1998).

Riba et al., (2002) used a double-blind, randomized crossover, placebo controlled design with 18 participants. They observed a significant reduction in total power for all frequency bands measured in the ayahuasca condition vs placebo. This effect peaked at 90 min post ayahuasca ingestion and had a wide spatial distribution. Ayahuasca-induced reductions in power were observed for all measured frequency bands (delta – beta). The most prominent reductions in power were observed for the delta, theta, and beta bands.

Additionally, decreases in the alpha band were most prominently observed in left temporal and centro-parieto-occipital electrodes (Riba et al., 2002).

Riba et al., (2004) also used a double-blind, randomized crossover, placebo controlled design with 18 participants. They applied low-resolution electromagnetic tomography (LORETA) to assess the effects of ayahuasca on regional power in the brain compared to placebo. They observed that ayahuasca decreased power in the delta, theta, alpha, and beta bands, with the most prominent decrease in the alpha band. This effect was primarily localized to posterior areas; predominantly in parietal (angular gyrus, supramarginal gyrus, precuneus), occipital (superior and middle occipital gyrus), temporal (superior and middle temporal gyri and fusiform gyrus), and limbic (cingulate and parahippocampal gyrus) regions. Further, ayahuasca induced significant power decreases in the delta band that were mainly observed at left occipital-temporal regions. Ayahuasca-induced decreases in theta power also displayed a trend towards significance in the medial frontal cortex (Riba et al., 2004).

Stuckey et al. (2005) used an open-label naturalistic design with two volunteers. They found that ayahuasca induced global power reductions for the theta, alpha, and beta frequency bands compared to an eyes closed baseline condition. Decreases in the alpha band were most strongly observed over the occipital lobe (Stuckey et al., 2005).

Schenberg et al., (2015) used an open-label design with 20 participants. They found that ayahuasca significantly reduced power in the alpha band. This effect was localized to a cluster of electrodes at left parieto-occipital regions. Further, ayahuasca significantly increased power in the gamma band for three clusters at the right frontal, left fronto-temporal, and left centro-parieto-occipital electrodes. No significant power changes were found for the delta and theta bands. Further, significant increases in beta power were found at fronto-temporal regions but this effect disappeared after post-hoc analysis (Schenberg et al., 2015).

Valle et al. (2016) used a double-blind, randomized, balanced, crossover, placebo controlled design with 12 participants. They applied standardized LORETA (sLORETA) to estimate the effects of ayahuasca on regional power in the brain. They found that ayahuasca significantly decreased power in the delta, theta, and alpha frequency bands compared to placebo. No effect was seen on the beta band. sLORETA revealed that ayahuasca induced the largest decreases in the alpha band localized mainly to occipital, parietal, and temporal regions. The strongest decrease in alpha power was localized to the visual cortex. Significant decreases in theta power were mainly found in lateral and medial frontal regions, while significant decreases in delta power were mainly localized to temporal regions. The authors also investigated the interaction between ayahuasca and ketanserin, a 5HT2A receptor antagonist. A pretreatment of ketanserin before ayahuasca administration abolished the

decreases in alpha power induced by ayahuasca. The effects of ketanserin were consistent with lower ratings of the subjective effects induced by ayahuasca. Further, decreases in alpha power under ayahuasca correlated negatively with subjective ratings of the intensity of visual effects, and reductions in delta and theta power correlated negatively with subjective ratings of "contact with external reality" (Valle et al., 2016).

Two additional studies, which were not found during the initial literature search, were identified in one of the studies reviewed (Schenberg et al., 2015). These studies investigated the effects of ayahuasca on spectral power (dos Santos et al., 2011, 2012). Both studies adopted a double-blind, placebo-controlled, randomized crossover design and measured only relative power in the beta band. These studies reported that ayahuasca increased relative power in the beta band (dos Santos et al., 2011, 2012).

Psilocybin

Three studies investigating the effects of psilocybin on spectral power were identified (see Table 1). Kometer et al., (2013) applied a double-blind, placebo controlled, within-subject, randomized design and used EEG to assess the effects of psilocybin on spectral power in 17 participants. Further, they only investigated power changes in the alpha band. They found that psilocybin significantly decreased alpha power in parieto-occipital regions. This reduction in alpha power disappeared when participants were pretreated with ketanserin (Kometer et al., 2013).

Muthukumaraswamy et al. (2013) applied a single-blind, within-subjects design with an inert placebo and used MEG to assess the effects of psilocybin on spectral power in 15 volunteers. They found that psilocybin decreased power on a broad frequency range mostly localized to association cortices, including the posterior cingulate cortex, precuneus, anterior cingulate gyri, superior and middle frontal gyri, and supramarginal and precentral gyri. Psilocybin-induced power reductions were especially pronounced for the posterior cingulate cortex, a central hub of the DMN. Significant power reductions were observed for all frequencies < 50 Hz (delta, theta, alpha, beta, and low gamma) in posterior areas. Significant power reductions ranging from alpha to high gamma were also found in bilateral prefrontal cortices. Further, psilocybin-induced decreases in alpha power in the posterior cingulate cortex correlated significantly with a sense of dissolution of the "self" or "ego" and with experiencing "supernatural" qualities (Muthukumaraswamy et al., 2013).

Kometer et al. (2015) applied a double-blind, placebo controlled design and used EEG to assess the effects of psilocybin on spectral power in 55 volunteers. They used exact LORETA (eLORETA) to compute source localization. Both eyes closed and eyes open conditions were assessed for psilocybin and placebo. They found significant power reductions for all frequency bands < 20 Hz (delta, theta, alpha, and low-beta) during the eyes closed psilocybin condition, and for all frequency bands < 30 Hz (delta, theta, alpha, and beta)

during the eyes open condition. Further, power reductions in the theta and alpha bands were more spatially distributed than other frequency bands. Significant power increases in the high-gamma band were observed in the eyes closed condition in the left retrosplenial cortex, with a trend towards significance in the eyes open condition. However, no significant effects were found for the low-gamma band (Kometer et al., 2015).

DMT

Two studies were identified assessing the effects of DMT alone (in contrast to ayahuasca) on spectral power using EEG. Timmermann et al. (2019) assessed the effects of DMT in 13 volunteers using a single-blind, fixed-order design with an inert placebo. They found that DMT significantly decreased total power in the alpha and beta frequency bands compared to placebo. However, power reductions were most pronounced in the alpha band and were observed on all channels. Further, the decreases in alpha and beta total power were consistent after decomposing the EEG spectra into its oscillatory and fractal (1/f) components, while significant reductions in power were observed across all frequency bands < 30 Hz (delta, theta, alpha, and beta) for the fractal component. DMT induced no significant effects on total power in the delta, theta, or low-gamma bands. The averaged minute-by-minute data revealed a stable decrease in power for alpha activity throughout 5 minutes post injection of DMT compared to baseline. The power decreases in beta activity were also relatively stable when looking at total power and the fractal component. Further, a transient decrease in power for the delta and theta bands was also observed at 1 minute post DMT injection but these changes normalized at 2-3 minutes post injection, at the time of peak subjective intensity. The changes in total alpha power correlated negatively with subjective ratings of intensity for all recorded channels under DMT. This relationship was similar for total beta power. Looking at oscillatory power, both delta and theta power displayed significant positive correlations with subjective intensity (Timmermann et al., 2019).

Pallavicini et al. (2021) assessed the effects of DMT in an open-label, naturalistic design with 35 participants. They measured spectral power in three conditions, eyes open, eyes closed, and DMT (eyes closed). They found that DMT induced significant decreases in alpha power compared to the eyes closed condition. Further, DMT significantly increased power in the delta and gamma bands. While DMT decreased power in the theta and beta bands, these changes were not significant, and there were no significant differences between the DMT and the eyes open condition. Only two significant correlations were found between subjective ratings and changes in spectral power. Decreases in beta power correlated positively with the “cognition” component of the Near-Death Experience scale (NDE) and with the “anxiety” component of the 5-Dimensional Altered States of Consciousness (5D-ASC) rating scale. Increased gamma power correlated positively with several items assessing

mystical qualities (such as unity, transcendence of time and space, etc.) from the 5D-ASC, NDE, and the 30-item Mystical Experience Questionnaire (Pallavicini et al., 2021).

The Effects of Classic Psychedelics on Signal Diversity

Three studies were identified that assessed the effects of classic psychedelics on signal diversity. One study assessed the effects of both LSD and psilocybin on signal diversity, and two studies assessed the effects of DMT on signal diversity. These are summarized in Table 3.

Table 3

Summary of the results on signal diversity

Outcome	Drug < control	Drug = control	Drug > control
LZc			Schartner et al. (2017); Pallavicini et al. (2021); Timmermann et al. (2019)
SCE		Schartner et al. (2017)	
ACE			Schartner et al. (2017)

Note. Less than sign (<) = Significantly decreased; equal to sign (=) = No significant change; greater than sign (>) = Significantly increased; LZc = Lempel-Ziv complexity; SCE = Synchrony Coalition Entropy; ACE = Amplitude Coalition Entropy.

LSD and Psilocybin

Schartner et al. (2017) re-analyzed MEG data from two previous studies mentioned above, Carhart-Harris et al. (2016) and Muthukumaraswamy et al. (2013), using LSD and psilocybin, respectively. To assess signal diversity Schartner et al. (2017) applied several signal diversity measures, including LZc, single-channel LZc (LZcs), synchrony coalition entropy (SCE), and amplitude coalition entropy (ACE). Since LZc captures both the temporal as well as the spatial (across channels) aspect of signal diversity, the researchers also applied LZcs which only measures temporal signal diversity. SCE measures entropy over time and is based on synchronous channels. ACE also measures entropy over time but is based on the level of activation of channels. They found increased signal diversity for all measures (except for the normalized SCE) in the drug condition compared to placebo. The most consistent increase in signal diversity for psilocybin and LSD compared to placebo was found for LZc and the normalized LZcs. The increase in normalized LZcs was mainly localized to pariteo-occipital regions for both psilocybin and LSD. These regions were also where most of the decrease in alpha power was found. None of the diversity measures reached significance for the psilocybin vs placebo condition despite most participants having higher values. All LZc measures, as well as the ACE, were significant for the LSD vs placebo condition. Further, a significant decrease was observed for the normalized SCE in the LSD vs placebo condition

despite increased signal diversity in all other measures. Only the normalized LZcs showed a substantial correlation ($r > 0.5$) with questionnaire scores assessing drug effects. For the psilocybin vs placebo condition, increased normalized LZcs correlated substantially with an increased sense of spatial distortion, dissolution of the self or ego, and with the total questionnaire scores. For the LSD vs placebo condition, increased normalized LZcs correlated substantially with overall subjective intensity of drug effect (Schartner et al., 2017).

DMT

Timmermann et al. (2019) investigated the effects of DMT on signal diversity by measuring LZc. They found that DMT significantly increased LZc compared to placebo. This increase was also seen for the normalized LZc. The increase in LZc was consistent throughout the post-injection period and the normalized LZc increased from peak subjective intensity onwards. Further, a significant positive correlation was found between LZc under DMT and subjective intensity in posterior and central channels. This relationship remained only in posterior channels after normalization (controlling for changes in spectral power; Timmermann et al., 2019).

Pallavicini et al. (2021) also investigated the effects of DMT on signal diversity by measuring LZc. They measured LZc in three conditions, eyes open, eyes closed, and DMT (eyes closed). They found that DMT significantly increased LZc for all channels compared to the eyes closed baseline condition. The strength and distribution of these changes were comparable with the difference between both baseline conditions (eyes closed vs eyes open conditions). Further, they did not find any significant correlations between changes in LZc and subjective ratings (Pallavicini et al., 2021).

The Effects of Classic Psychedelics on Functional Connectivity

Six studies assessing the effects of classic psychedelics on functional connectivity (FC) were identified. These are summarized in Table 4.

Table 4

Summary of the results on functional connectivity

Reference	Changes in functional connectivity
LSD and Psilocybin	
Barnett et al. (2020)[a]	Decreased broadband information flow widely distributed across the cortex. Increased undirected functional connectivity (correlation and coherence) in the gamma frequency band.
Pallavicini et al. (2019)[b]	Decreased broadband undirected functional connectivity (correlation).
Ayahuasca	
Alonso et al. (2015)	Decreased top-down information flow from anterior to posterior regions. Increased bottom-up information flow from posterior to anterior regions.
Stuckey et al. (2005)	Increased global coherence in the gamma frequency band.
Psilocybin	
Kometer et al. (2015)	Increased undirected functional connectivity (lagged phase synchronization) in the delta frequency band between the retrosplenial cortex, the parahippocampus, and the lateral orbitofrontal cortex.
DMT	
Pallavicini et al. (2021)	Decreased coherence in the alpha frequency band. Increased coherence in the gamma frequency band.

[a] Barnett et al. (2020) investigated both LSD and psilocybin. [b] Pallavicini et al. (2019) investigated both LSD and psilocybin.

LSD and psilocybin

Two studies assessing the effects of both LSD and psilocybin on functional connectivity were identified. However, these studies use the same data but applied different methods and thus produced different results (Barnett et al., 2020; Pallavicini et al., 2019). Like Schartner et al. (2017), Barnett et al. (2020) re-analyzed MEG data from the same two studies mentioned previously, Carhart-Harris et al. (2016) and Muthukumaraswamy et al. (2013). Barnett et al. (2020) applied both undirected and directed measures of functional connectivity. The authors measured correlation and Granger causality for FC in the time domain as well as coherence and Granger causality for FC in the time domain decomposed by frequency. They found significant reductions in FC measured by Granger causality (directed) for both psilocybin and LSD vs placebo. This effect was mainly observed between parietal and other regions for psilocybin while it had a wide spatial distribution for LSD. Significant changes in FC measured by correlation (undirected) were only found for LSD compared to placebo. This effect was observed as an increase mainly between occipital and cingulate

regions among the regions of interest (ROI) measured. When decomposing the time domain results by frequency, the strongest increase in coherence (undirected) was found in the gamma band for LSD compared to placebo. There was a trend towards a slight increase in gamma coherence for psilocybin vs placebo, but little to no effect on coherence on the other frequency bands. Broadband (alpha – gamma) decreases in Granger causality were most pronounced for LSD but were also observed for psilocybin vs placebo (Barnett et al., 2020).

Like Schartner et al. (2017) and Barnett et al. (2020), Pallavicini et al. (2019) re-analyzed MEG data from the same two studies mentioned previously. Both Pallavicini et al. (2019) and Barnett et al. (2020) measure undirected FC; Pallavicini et al. (2019) measure correlation while Barnett et al. (2020) measure both correlation and coherence. However, their methodology differs greatly and the results might not be directly comparable. Pallavicini et al. (2019) found that LSD significantly decreased FC for all frequency bands compared to placebo. The most widespread decrease was observed in the beta band, followed by the theta. Psilocybin on the other hand only produced slight decreases in FC with sparse significant changes in the low and high beta bands (Pallavicini et al., 2019).

Ayahuasca

Two studies assessing the effects of ayahuasca on functional connectivity were identified. Stuckey et al. (2005) assessed the effects of ayahuasca on FC by measuring global coherence. They found that ayahuasca increased global coherence mainly in the gamma range compared to eyes closed baseline (Stuckey et al., 2005).

Alonso et al. (2015) measured directed FC using transfer entropy (TE) in a double-blind, randomized, crossover, placebo controlled design with ten participants. They found that ayahuasca induced significant increases in TE at 2 hours post ingestion compared to placebo. This increase in TE was preceded and followed by significant decreases in TE at 1.5 and 2.5 hours post ingestion. Most of the increases in TE at 2 hours originated from posterior regions which then mainly influenced signals at more frontal regions, i.e. increased information flow from posterior to anterior regions. The significant decreases in TE at 1.5 and 2.5 hours were observed as reduced information flow from anterior to posterior regions. This pattern of increases in TE from posterior-to-anterior regions and decreases in TE from anterior-to-posterior regions was found at all measured time points from 45 min post ingestion and onwards. Further, changes in TE correlated with subjective ratings of the drug experience. The highest values for each measure were found between 1.5 and 2.5 hours post ingestion. Only decreases in TE correlated significantly with intensity of subjective effects (Alonso et al., 2015).

Psilocybin

One study investigating the effects of psilocybin alone on functional connectivity was identified. Kometer et al. (2015) applied eLORETA, as mentioned previously, to compute

lagged phase-synchronization which measures FC via the dynamic coordination of oscillations between different brain regions. They found that the interhemispheric lagged phase synchronization of delta oscillations increased slightly in the eyes open psilocybin condition vs placebo. Significance was reached between right Brodmann area (BA) 7 and left BA 39. There was a trend towards a significant increase in lagged phase synchronization of delta oscillations for the eyes closed psilocybin condition vs placebo. Worth noting, increased lagged phase synchronization within a network involving the lateral orbitofrontal area, the parahippocampus, and the retrosplenial cortex significantly correlated positively with intensity of spiritual experience and insightfulness during the eyes closed psilocybin condition (Kometer et al., 2015).

DMT

One study investigating the effects of DMT alone on FC was identified (Pallavicini et al., 2021). Pallavicini et al. (2021) measured FC with coherence (global synchrony) and metastability (the fluctuation or variance of coherence). DMT decreased both coherence and metastability in the alpha band and increased these measures in the gamma band compared with baseline (Pallavicini et al., 2021).

Discussion

The aim of this paper was to systematically review the effects of classic psychedelics on three electrophysiological modalities: spectral analysis, signal diversity, and functional connectivity. In this section, the results will be summarized and discussed followed by limitations, ethics, and a conclusion.

Spectral Analysis

While there are some discrepancies between the reviewed studies, classic psychedelics seem to robustly and consistently decrease spectral power in most frequency bands, particularly in the alpha band. Notably, reductions in alpha power were observed in the posterior cingulate cortex, a central hub of the DMN (Carhart-Harris et al., 2016; Kometer et al., 2015; Muthukumaraswamy et al., 2013; Riba et al., 2004). This is consistent with several fMRI studies that have found classic psychedelics to decrease DMN activity (Carhart-Harris et al., 2012, 2016; Palhano-Fontes et al., 2015). Correlations between alpha power decreases in the posterior cingulate cortex and subjective ratings of ego dissolution have been observed for both LSD and psilocybin (Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013). Further, meditation and psychedelic experiences may share some phenomenology as the aim of several meditation practices is to explicitly dissolve the sense of self or ego (Millière et al., 2018). However, an increase in alpha activity is considered a signature of meditation while the opposite is true for classic psychedelics (Lomas et al., 2015). Ketamine, an N-methyl-D-aspartate receptor (NMDA) antagonist, has also been shown to decrease alpha power,

suggesting that it reflects a more general process not unique to classic psychedelics (Muthukumaraswamy et al., 2015; Pallavicini et al., 2019; Vlisides et al., 2018).

Four studies reported that classic psychedelics increased power in the gamma band (Don et al., 1998; Kometer et al., 2015; Pallavicini et al., 2021; Schenberg et al., 2015). These results should be interpreted with caution since they might be confounded by muscle artifacts (see Limitations). However, they are interesting as some researchers suggest that increased gamma power might be the underlying mechanism of mystical experiences (Pallavicini et al., 2021). Interestingly, ketamine has also been reported to induce mystical-type experiences and has been shown to increase gamma power (Muthukumaraswamy et al., 2015; Rothberg et al., 2020). In addition, increased gamma power has been found in long-term meditation practitioners during various types of meditation (Braboszcz et al., 2017; Lutz et al., 2004). This might, perhaps in contrast to the findings above, explain the similar phenomenology between psychedelic-induced mystical experiences and aspects of the meditative state (Millière et al., 2018). However, other studies have not observed increased gamma power under classic psychedelics (Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013; Timmermann et al., 2019).

Signal Diversity

Classic psychedelics seem to reliably increase signal diversity in the brain. While there are some discrepancies in significance almost all results point towards increased signal diversity during the psychedelic state. Ketamine and specific types of meditation have also recently been observed to increase signal diversity (Schartner et al., 2017; Vivot et al., 2020). This suggests that increased signal diversity might not be unique to the psychedelic state or mystical experiences, but rather be related to the subjective intensity of such experiences, as observed by Timmermann et al. (2019), or to the richness of conscious content as stated by the REBUS/anarchic brain model (Carhart-Harris & Friston, 2019). However, Pallavicini et al. (2021) found no correlation between increased signal diversity and subjective ratings of the psychedelic state. Further, the use of signal diversity as a reliable measure of the level of consciousness is still preliminary and more studies are needed to establish this.

Functional Connectivity

Both Barnett et al. (2020) and Alonso et al. (2015) observed decreased flow of information. Barnett et al. (2020) reported a broadband and widely distributed decrease in information flow, while Alonso et al. (2015) observed that ayahuasca decreased top-down information flow while increasing bottom-up information flow. Stuckey et al. (2005) and Pallavicini et al. (2021) observed that ayahuasca and DMT respectively increased gamma coherence. Additionally, Barnett et al. (2020) reported that LSD increased gamma coherence. Interestingly, patients with schizophrenia have also been found to have increased gamma connectivity, and different meditation practices and have been found to increase gamma

connectivity (Andreou et al., 2015; Vivot et al., 2020). This might further explain the similar phenomenology between the meditative and the psychedelic state, as well as why classic psychedelics previously have been classified as psychotomimetics (psychosis mimicking; Millière et al., 2018; Nichols, 2016).

While both Barnett et al. (2020) and Kometer et al. (2015) found increased undirected functional connectivity, Pallavicini et al. (2019) found the opposite despite analyzing the same data as Barnett et al. (2020). The results reported by Pallavicini et al. (2019) are partially consistent with the results reported by Pallavicini et al. (2021) which observed decreased coherence in the alpha band. The network in which Kometer et al. (2015) observed increased phase synchrony of delta oscillations overlap with the DMN. This is consistent with previously mentioned findings that classic psychedelics decrease activity in the DMN. However, modulation of the DMN is not unique to classic psychedelics, as selective serotonin reuptake inhibitors (McCabe et al., 2011; van de Ven et al., 2013), ketamine (Scheidegger et al., 2012), and 3,4-methylenedioxymethamphetamine (MDMA; Müller et al., 2021) have also been reported to reduce FC in the DMN.

REBUS/Anarchic Brain

The results from several studies in this review are part of the empirical foundation of the REBUS/anarchic brain model (Alonso et al., 2015; Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013; Schartner et al., 2017). Beyond these studies, however, the results are generally consistent with the REBUS/anarchic brain model. The model hypothesizes that classic psychedelics attenuate top-down processing and beliefs, while increasing bottom-up processing (Carhart-Harris & Friston, 2019). The decrease in alpha power that classic psychedelics induce is compelling when considering the association between alpha activity and top-down processes, such as semantic orientation and self-referential processing (Carhart-Harris & Friston, 2019; Klimesch, 2012; Knyazev, 2007). Increased signal diversity is also consistent with the REBUS/anarchic brain model when considering it as corresponding to the richness of conscious content (Carhart-Harris & Friston, 2019). While the studies measuring FC report discrepancies in the results, a decrease in information flow is consistent with the REBUS/anarchic brain model. However, the evidence from correlations between increased signal diversity and subjective effects is inconsistent and weak, and it is not clear whether the model can account for increased gamma coherence, increased gamma power, or increased undirected FC.

Limitations

There are several limitations with the present paper. In discordance with PRISMA guidelines, only one author screened titles and abstracts and extracted outcome data from the included articles. Further, only one database (PubMed) was searched, and only papers published in English were included. To the best of our knowledge, no other possibly relevant

papers in other languages have however been published. The heterogeneity in study design, e.g., RCT vs open-label naturalistic, is a considerable limitation when comparing outcomes of studies with classic psychedelic substances. Since the environment and mental state of the participants ("set and setting") are central aspects of the psychedelic experience, it is plausible that differences in study design might cause divergent results. Further, finding a suitable placebo is notoriously difficult for clinical studies with classic psychedelics. Since the effects are so pronounced, the blinding is usually broken as soon as the subject starts to feel the effects of the drug (Schenberg et al., 2015). Different methods of data analysis might also yield different results as in the obvious case with Pallavicini et al. (2019) and Barnett et al. (2020). Further, results reporting increases in gamma power should be interpreted with caution as these might be confounded by fine muscle artifacts (Muthukumaraswamy, 2013).

Another limitation is differences in times of measurements between studies. Often the data only represents a glimpse of the experience since different classic psychedelic compounds produce experiences of varying lengths. LSD for example usually produces 8-12h long experiences while DMT produces experiences seldom longer than 15 min (Barnett et al., 2020; Pallavicini et al., 2021). Divergence in the results might also stem from differences in the route of administration of the drug. For example, both Pallavicini et al. (2021) and Timmermann et al. (2019) investigated the effects of DMT, inhaled and intravenously, respectively, but differed slightly in their results. Further, inconsistencies in results from studies with ayahuasca might stem from differences between batches and origin. This is plausible since ayahuasca does not only contain DMT but also additional psychoactive beta-carbolines (such as harmine, harmol, and harmaline). The concentration of these substances might vary between different batches and origins.

Ethics

The increased interest in classic psychedelic substances is not only limited to the scientific community but recreational use has also increased considerably during the past two decades (Johnson et al., 2019). Thus, evidence-based and harm-reducing education and policy are important for broader aspects of society to be able to handle the increased use of these substances appropriately.

Conclusion

This review has demonstrated that classic psychedelic substances alter neurophysiological activity in several ways. While there are inconsistencies in the results to take into consideration, there are some general patterns in the electrophysiological research on classic psychedelics. These substances generally decrease spectral power in most frequency bands, mainly in the alpha range, increase signal diversity, and decrease the flow of information (directed FC) throughout the brain. Correlations between subjective experiences and neurophysiological activity are somewhat inconclusive. However, it is

tempting to consider decreases in alpha power, increased signal diversity, and decreases in DMN activity to be central neural correlates of the psychedelic state, as formulated by the REBUS/anarchic brain model. While these results are promising, more evidence is needed to establish these findings as solid. Nonetheless, classic psychedelic substances offer a unique opportunity to study the neural correlates of the sense of self.

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