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Review article

Psychedelic resting-state neuroimaging: A review and perspective on balancing replication and novel analyses

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A B S T R A C T

Clinical research into serotonergic psychedelics is expanding rapidly, showing promising efficacy across myriad disorders. Resting-state functional magnetic resonance imaging (rs-fMRI) is a commonly used strategy to identify psychedelic-induced changes in neural pathways in clinical and healthy populations. Here we, a large group of psychedelic imaging researchers, review the 42 research articles published to date, based on the 17 unique studies evaluating psychedelic effects on rs-fMRI, focusing on methodological variation. Prominently, we observe that nearly all studies vary in data processing and analysis methodology, two datasets are the foundation of over half of the published literature, and there is lexical ambiguity in common outcome metric terminology. We offer guidelines for future studies that encourage coherence in the field. Psychedelic rs-fMRI will benefit from the development of novel methods that expand our understanding of the brain mechanisms mediating its intriguing effects; yet, this field is at a crossroads where we must also consider the critical importance of consistency and replicability to effectively converge on stable representations of the neural effects of psychedelics.

Abbreviations: 5-HT, 5-Hydroxytryptamine; BOLD, Blood-Oxygen-Level-Dependent; DMN, Default Mode Network; DMT, N,N-Dimethyltryptamine; ECN, Executive Control Network; EPI, Echo-planar Imaging; fMRI, Functional Magnetic Resonance Imaging; ICA, Independent Component Analysis; IV, Intravenous; LSD, Lysergic Acid Diethylamide; REBUS, Relaxed Beliefs Under Psychedelics; ROI, Region of Interest.

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LSD
Ayahausca

1. Introduction

Serotonergic psychedelics (historically referred to as "hallucinogens" or "psychotomimetics" and hereafter referred to as "psychedelics") have re-emerged in research since the early 2000s. This class of drugs includes, e.g., psilocybin (prodrug to psilocin, the psychoactive component in "magic mushrooms"), lysergic acid diethylamide (LSD), ayahuasca, which contains the psychedelic component *N*,*N*-dimethyltryptamine (DMT) and monoamine oxidase inhibitors that enable the oral bioavailability of DMT (Carbonaro and Gatch, 2016) and mescaline (3,4,5-trimethoxyphenethylamine).

Small clinical trials over the past 15 years with psilocybin and ayahuasca provide intriguing preliminary evidence for efficacy in treating major depressive disorder (including otherwise treatment-resistant individuals) (Carhart-Harris et al., 2021, 2018; Davis et al., 2020; de Osório et al., 2015; Palhano-Fontes et al., 2019), obsessive compulsive disorder (Moreno et al., 2006), smoking addiction (Johnson et al., 2017), alcohol abuse (Bogenschutz et al., 2015), demoralisation (Anderson et al., 2020), and depressive and anxiety symptoms associated with diagnosis of life-threatening diseases (Gasser et al., 2015, 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Remarkably, there is also preliminary clinical evidence that psychedelics can produce lasting positive psychological effects in healthy individuals (Barrett et al., 2020a; Griffiths et al., 2011; Kettner et al., 2021; MacLean and Griffiths, 2013; Madsen et al., 2020; Schmid and Liechti, 2018; Stenbæk et al., 2020; Uthaug et al., 2019, 2018).

1.1. Pharmacology of psychedelics

At doses that produce clear psychoactive effects, psychedelics bind various receptor targets, including alpha-adrenergic receptors and most serotonin receptors, while some also bind other monoamine, trace amine and sigma receptors (Nichols, 2016). However, the psychedelic effects of these drugs in humans appear to be driven primarily by agonist effects at the serotonin 2A (5-HT2A) receptor. Pre-treatment with the non-selective 5-HT2A receptor antagonist ketanserin has been shown consistently to abolish the psychoactive effects of serotonergic psychedelics (Kometer et al., 2012; Madsen et al., 2019; Preller et al., 2019, 2017; Vollenweider et al., 1998). The effect of psychedelic binding to non-5-HT2A receptors on the acute and persistent effects remains un-investigated in clinical trials, with the exception of small studies investigating a potentially inhibitory role of 5-HT1A (Pokorny et al., 2016; Strassman, 1995).

The psychoactive effects of typical doses of orally ingested psychedelics last approximately 1–6 h for ayahuasca (Riba et al., 2001); 4–6 h for psilocybin (Madsen et al., 2019), and 8–12 h for LSD (Holze et al., 2021), each aligning with plasma concentrations. These time-courses are substantially condensed when administered intravenously (IV), with the exception of IV LSD, which can last up to 10 h (Carhart-Harris et al., 2016a; Passie et al., 2008). Subjectively, psychedelic experiences are characterised by profound alterations in affect (Roseman et al., 2019), perceptual alterations and atypical synaesthesia (Preller and Vollenweider, 2018; Terhune et al., 2016), and mystical-like experiences (Barrett et al., 2015).

1.2. Functional neuroimaging of psychedelics

These potent, acute and persistent effects have motivated research into how psychedelics affect features of brain activity and connectivity, both as a means of understanding atypical states of consciousness as well as the pathological conditions that psychedelics show early promise in treating. These studies have provided novel and exciting new insights into brain mechanisms which may underlie the acute psychoactive experience, therapeutic outcomes, and possibly the lasting effects on personality.

Resting-state functional magnetic resonance imaging (fMRI) is a common strategy for estimating brain function and connectivity while a participant is lying still in the scanner and not engaged in a specific task (sometimes referred to as "task-free fMRI"). Although participants consciously and subconsciously engage in cognitive processes during these scan periods, perhaps more so under the influence of psychedelics, we consider "resting-state" here to represent fMRI acquisitions in the absence of an explicit task or external stimulus intentionally presented by the researcher. A primary analysis endpoint in resting-state fMRI is the correlation or covariance in BOLD signal between pairs or sets of brain regions, commonly referred to as "functional connectivity" (Biswal et al., 1997; Lee et al., 2013). The richness of the resting-state fMRI data structure (i.e., three spatial dimensions and time) is exemplified by the explosion of research and collaborations focused on acquiring and aggregating data as well as developing novel analytical and computational methods for decomposing and quantifying metrics from resting-state fMRI data (Atasoy et al., 2016; Bullmore and Sporns, 2009; Calhoun et al., 2001; Cole, 2010; Deco et al., 2011).

Resting-state fMRI is a particularly appealing framework for evaluating psychedelic effects on the brain because it is acquired in the absence of explicit task instructions. Participants who have received psychoactive doses of psychedelic drugs often undergo intense, personally meaningful experiences that are largely introspective and itinerant (Griffiths et al., 2006), which can be disrupted and inhibited by excessive external task or cognitive attention demands. Thus, resting-state fMRI provides a framework for relatively passively observing brain function during psychedelic sessions wherein participants can "go with" the experience as in a more naturalistic setting. Thus, it is of no surprise that the field of psychedelic functional brain imaging that has emerged over the past 10 years has largely applied resting-state fMRI. Nevertheless, it is worth noting that the first psychedelic functional imaging studies examined glucose metabolism (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997) and blood flow (Hermle et al., 1992; Riba et al., 2006), and more recent studies have examined task-related effects during (Barrett et al., 2018; Carhart-Harris et al., 2012a; Daumann et al., 2010; Kraehenmann et al., 2015; Mueller et al., 2017; Preller et al., 2016, 2017; Schmidt et al., 2018; Spitzer et al., 2001) or after (Barrett et al., 2020a) the psychedelic session. We see potential in the use of task-based fMRI to investigate specific hypotheses, but due to the inherent variability in collection and analysis, we limit our review to task-free imaging. PET, and potentially fMRI, can provide measures of target occupancy, manipulation of known pathologies, and prognostic/diagnostic biomarkers that could help to shape both supporting psychotherapy and drug development (Carmichael et al., 2018).

In 2012, Carhart-Harris and colleagues published the first study investigating psychedelic effects on resting-state functional connectivity (Carhart-Harris et al., 2012b). To date, 42 studies have been published investigating both the acute or persistent effects of psychedelics on resting-state fMRI measures. The current paper aims to review this literature, focusing on their core methodological decisions with the aim of providing a comprehensive overview and facilitate suggestions to the future steps of this promising research field. We acknowledge that heterogeneity in neuroscience is not unique to the field of psychedelic research but believe that by characterising methodological variation, we stand a greater chance of producing replicable and clinically relevant results.

2. Methods

We attempted to evaluate the methodologies of all published original research papers describing resting-state functional connectivity either during or following the administration of a classical serotonergic psychedelic. A search on PubMed for ("mescaline" or "psilocybin" or "dimethyltryptamine" or "lysergic acid diethylamide" or "ayahuasca") and fMRI yielded 81 results. Removing those that did not refer to serotonergic psychedelics yielded 73 results. Removing reviews, non-English studies, non-MRI, population studies, and preclinical studies yielded 54 results. Removing analyses that did not include resting-state fMRI resulted in a total of 37 publications: (Atasoy et al., 2017; Barrett, 2020a, 2020b; Bershad et al., 2020; Burt et al., 2021; Carhart-Harris et al., 2012b, 2016b; Carhart-Harris et al., 2013, 2017; Daws et al., 2022; Deco et al., 2018; Girn et al., 2022; Jobst et al., 2021; Kaelen et al., 2016; Kringelbach et al., 2020; Lebedev et al., 2015, 2016; Lord et al., 2019; Luppi et al., 2021; Madsen et al., 2021; Mason et al., 2020; McCulloch et al., 2021; Müller et al., 2017, 2018; Palhano-Fontes et al., 2015; Pasquini et al., 2020; Preller et al., 2018a, 2019, 2020; Roseman et al., 2016; Sampedro et al., 2017; Smigielski et al., 2019; Speth et al., 2016; Tagliazucchi et al., 2014, 2016; Varley et al., 2020; Viol et al., 2017). Four additional papers did not appear in our search but were identified as relevant and added (Carhart-Harris et al., 2014; Mason et al., 2021; Petri et al., 2014; Roseman et al., 2014). Finally, one additional relevant paper is currently in review and is available on preprint servers (Singleton et al., 2021). Only papers made available before the 12th of July 2021 were included. See Fig. 1 for an overview of search methodology.

3. Findings

3.1. Data collection

Seventeen unique datasets investigating resting-state fMRI have been collected from participants given psychedelics; data from these studies have been published in 42 empirical research journal articles (See Fig. 2 for an overview). These datasets range in size from 9 to 24 participants, with some datasets excluded from analyses due to image quality (e.g., excessive motion); evidence suggests that larger samples sizes are required to detect stable effects in functional neuroimaging (Marek et al., 2020). Administration of psychedelic drugs in a clinical setting demands extensive resources especially in combination with neuroimaging. This may be why, despite significant interest in the field, only 299 sessions have been collected so far. However, the effects of psychedelics appear potent and thus replicable changes may be detectable with smaller samples sizes. Ten datasets administered psilocybin, four LSD and three ayahuasca. Eight datasets administered a fixed dose, whereas nine dosed by bodyweight, although the importance of this distinction is debated (Garcia-Romeu et al., 2021; Madsen and Knudsen, 2021). Dosing strategies are relatively homogenous across datasets; one dataset investigated so-called "microdoses" (13 μg of LSD), whereas 16 examined doses expected to produce substantial subjective effects; Two studies administered the drug IV, whereas 15 administered the drug orally. Two datasets were collected in cohorts of individuals with major depressive disorder whereas 15 were in healthy volunteers, of which two were experienced meditators. Notably, a pair of studies used the same analysis framework on two separate datasets, one with psilocybin and one with LSD and one combined psilocybin data from two datasets. Three datasets evaluated between-subject effects, whereas 14 evaluated within-subject effects, of which six utilised a placebo-controlled crossover design. As psychedelics have been shown to have lasting effects, it is particularly important that crossover designs looking to investigate effects of psychedelics take into account the potential persistent effects of the first treatment in the crossover when evaluating data, or pursue between-subject designs. Additionally, as placebo and expectancy effects are a particularly large confounding factor in measurements of the acute and lasting effects of psychedelics (Muthukumaraswamy et al., 2021), substantial effort should be made to control for this in subsequent study designs.

Seven datasets have investigated the persistent effects of psychedelics on brain function. Four datasets investigated the effects 24–48 h after administration, one dataset investigated effects three weeks after the second of two doses, two datasets investigated effects one-week after, one of which also investigated changes one-month after and the other, three-months after drug administration. Ten datasets imaged subjects who were under the influence of the drug at the time of scanning. Of the studies investigating persistent effects, five used psilocybin and two used ayahuasca. Of the studies investigating acute effects, only three studies investigate how plasma drug levels correlate with connectivity changes. This offers a more direct measure of the effect of drug than, for example, administered dose, on neural activity at minimal cost (Madsen and Knudsen, 2021). Thus, we recommend future research to draw regular blood samples during the psychedelic sessions where feasible. Similarly, we urge researchers to consider the subjective experience of participants and attempt to establish the relation between measures of the acute experience and the measured neuroimaging metric.

3.1.1. Publication distribution

Eleven datasets have yielded one publication each, three have yielded two publications each, one has yielded three, and two studies have yielded eleven and thirteen publications each, respectively, with two publications drawing data from both of these datasets (Fig. 2). Put another way, 52% (22 of 42 studies) of the published literature of psychedelic effects on resting-state fMRI is derived from two original data sets. Also, noteworthy, these studies are the only two studies using IV administration and participants in both studies were exclusively individuals with previous experience with psychedelics. This extensive reanalysis of data demonstrates an admirable initiative on the part of this group to share their data. It also highlights a clear opportunity in the field to attempt to independently replicate the findings from these papers, optimally utilising several datasets simultaneously. This is especially relevant here considering that drug administration (IV versus peroral) methodologically distinguishes these datasets. As such, we encourage other groups in this space to make their data and analysis scripts available to encourage collaboration. Additionally, we urge groups acquiring new data to attempt to replicate previously published methodologies especially if data is of similar content. In order to reduce inertial friction in this process, groups are encouraged to publish their analysis methodologies and scripts on public repositories for verification and replication. Useful resources for data and methodology sharing include GitHub and OpenNeuro and we recommend any neuroimaging data is formatted according to BIDS (Gorgolewski et al., 2016).

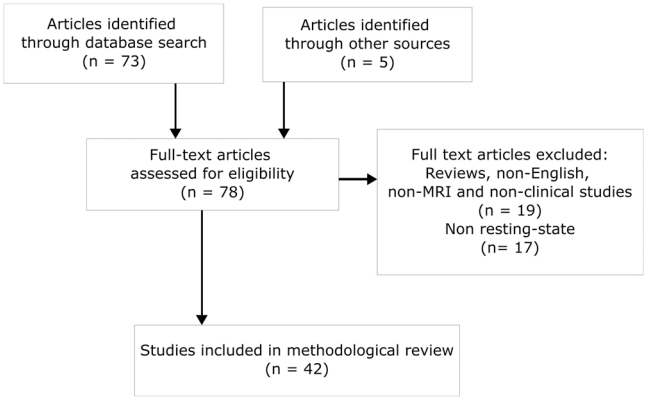

Fig. 1. PRISMA diagram. PRISMA flow diagram detailing procurement of papers included in this review.

First Publication	Drug	Dose & Administration	Participants	Timepoints	Scan Duration	Eyes	Design	Total Publications
Carhart-Harris 2012	Psilocybin	2 mg Intravenous	15 Healthy	Single acute	12	Closed	Within	10
Carhart-Harris 2017	Psilocybin	10 mg then 25mg Oral	15 TRD	+24h	8	Closed	Within	2
Smigielski 2019	Psilocybin	22 mg/70kg Oral	20 Meditators	+48h	7	Closed	Between	1
Barrett 2020a	Psilocybin	25 mg/70kg Oral	12 Healthy	+1wk & 1mnth	8	Open	Within	1
Barrett 2020b	Psilocybin	10 mg/70kg Oral	15 Meditators	Single Acute	6	Closed	Within	1
Preller 2020	Psilocybin	14 mg/70kg Oral	23 Healthy	Three acute	10	Closed	Within (XOVR)	1
Mason 2020	Psilocybin	0.17 mg/kg Oral	22 Healthy	Single Acute	6	Open	Between	2
Madsen 2021	Psilocybin	0.2-0.3 mg/kg Oral	15 Healthy	Four acute	10	Closed	Within	1
McCulloch 2021	Psilocybin	0.2-0.3 mg/kg Oral	10 Healthy	+1wk & 3mnth	10	Closed	Within	1
Daws 2022	Psilocybin	25 mg then 25 mg Oral	21 MDD	+3wk	10	Closed	Within (XOVR)	1
Palhano-Fontes 2015	Ayahuasca	1.76 mg/kg DMT + MAOI Oral	9 Healthy	Single acute	4.25	Closed	Within	2
Sampedro 2017	Ayahuasca	45 ± 9 mg DMT + MAOI Oral	16 Healthy	+24h	7	Closed	Within	1
Pasquini 2020	Ayahuasca	0.36 mg/kg DMT + MAOI Oral	22 Healthy	+24h	7	Unspecified	Between	1
Carhart-Harris 2016	LSD	75 µg Intravenous	20 Healthy	Three acute	7.2	Closed	Within (XOVR)	14
Muller 2017	LSD	100 µg Oral	20 Healthy	Single acute	9	Closed	Within (XOVR)	2
Preller 2018	LSD	100 µg Oral	24 Healthy	Two acute	10	Closed	Within (XOVR)	3
Bershad 2019	LSD	13 µg Oral	20 Healthy	Single acute	6	Unspecified	Within (XOVR)	1

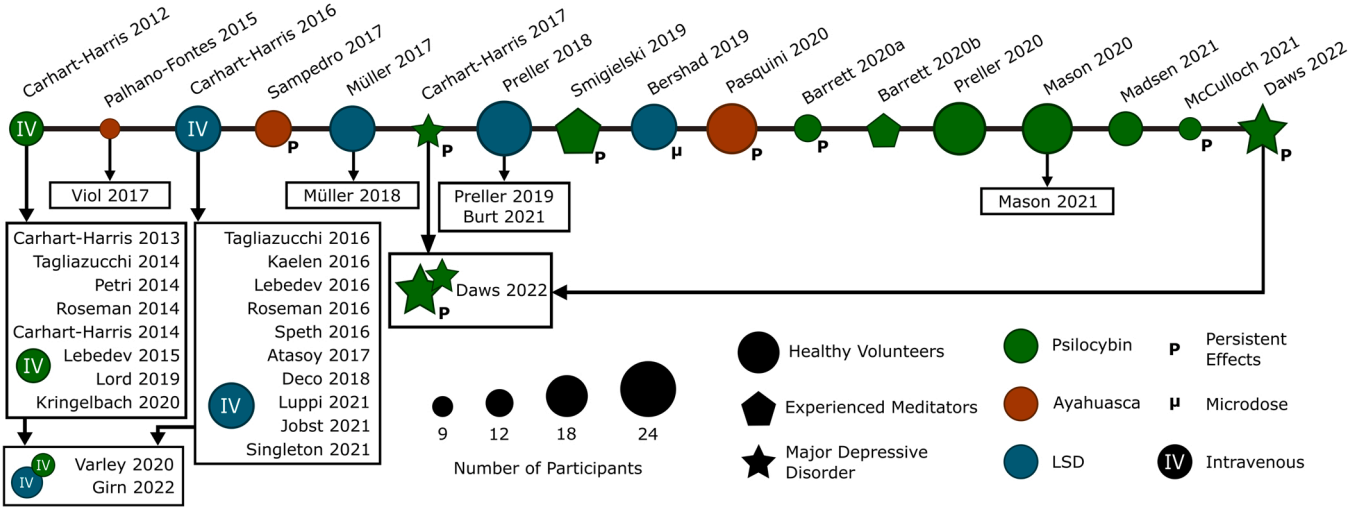

Fig. 2. Psychedelic resting-state datasets and publication timeline. Table (upper portion) displaying in chronological order by drug, the 17 datasets investigating psychedelic effects on resting-state functional connectivity. Timeline (lower portion) presents chronological order of publication. Arrows point to boxes containing lists of publications published secondarily to initial publication of a respective dataset. See figure for symbol legend. XOVR: crossover study design, DMT: N,N-Dimethyltryptamine, MAOI: Monoamine Oxidase Inhibitor, MDD: Major Depressive Disorder, TR: Treatment Resistant, LSD: Lysergic Acid Diethylamide.

The dataset first presented in Carhart-Harris et al., 2016b contains three 7.2 min, eyes-closed resting-state acquisitions between 70 and 130 mins after the IV administration of 75 µg of LSD. During the second acquisition, music was played. As noted earlier, this dataset has been reported on in a total of thirteen studies (Table 1). Of these, seven analysed only the non-music sessions, three separately considered all three sessions (Deco and colleagues primarily analysed the music scans only), two studies report all three scans combined, one analysed the pre-music scan only and one contrasted the music and non-music scans. Although music appears to play a powerful role in shaping psychedelic experiences, thus warranting exploration, acquisitions during music listening must be clearly demarcated and distinguished from resting-state. Where used, it is crucial that the specifics of a music paradigm are described clearly and playlists made publicly available.

Table 1
Analysis of Resting-State Scans Including Music. A breakdown of how data first presented in Carhart-Harris et al. (2016b) has been evaluated in subsequent studies. The dataset contain three resting-state scans, one before, one during and one after listening to music.

Both non-music scans	All three scans separately	All three scans combined	First scan only	Music > no music contrast
Roseman et al. (2016)	Lebedev et al. (2016)	Lebedev et al. (2016)	Tagliazucchi et al. (2016)	Kaelen et al. (2016)
Speth et al. (2016)	Atasoy et al. (2017)			
Varley et al. (2020)	Deco et al. (2018)			
Luppi et al. (2021)	Jobst et al. (2021)			
Girn et al., 2022				
Singleton et al. (2021)				
Carhart-Harris et al., 2016b				

3.1.2. Eyes-open vs eyes-closed

Across the seventeen unique datasets, resting-state scan duration ranged between 6 and 12 min per scan session. Four studies performed multiple resting-state scans during the psychedelic sessions. Resting-state data can be collected while the participant has eyes closed, open without fixation or open and fixated on an object in the visual field (e.g., crosshair, "+" on a screen); each of these strategies produce different connectivity estimates (Agcaoglu et al., 2019). Across most psychedelic studies, participants were instructed to close their eyes during the resting-state session. In two datasets this is not specified and in two, participants were instructed to keep eyes open during the resting-state sessions, which in one case were between emotional recognition tasks (Barrett et al., 2020a) (see Fig. 2). Psychedelics produce potent open-eye visual alterations that may be uncomfortable for participants within an MRI scanner, and most of the data collected so far has opted for

eyes-closed imaging. Recent work has shown that opening the eyes during a psychedelic experience can induce changes in brain dynamics, while subjective ratings related to the experience appear maximised with eyes closed (Mediano et al., 2020). Thus, unless explicitly examining effects associated with eyes open/eyes closed, we suggest that researchers request that their participants close their eyes during resting-state scans. Scans can be performed towards the beginning of scan sessions to avoid issues with participants falling asleep. To the extent feasible, it may also be informative to ask the participant about their state of wakefulness and what they thought about during the scan session (Diaz et al., 2013; Gonzalez-Castillo et al., 2021).

3.1.3. Analyses

3.1.3.1. Seed, network and ROI-based analyses. The 42 published studies differ substantially in how the BOLD data are analysed; Fig. 3 summarises the categories of applied analysis methods.

Most studies perform static functional connectivity analyses, investigating the average correlation of the BOLD signal between regions across whole scans. The a priori regions selected for functional connectivity analyses can be small seeds, large-scale networks or predefined regions-of-interest (ROIs).

Of the 42 articles, 13 applied a "seed-based connectivity" analysis wherein the time series from a pre-defined region (or regions) is

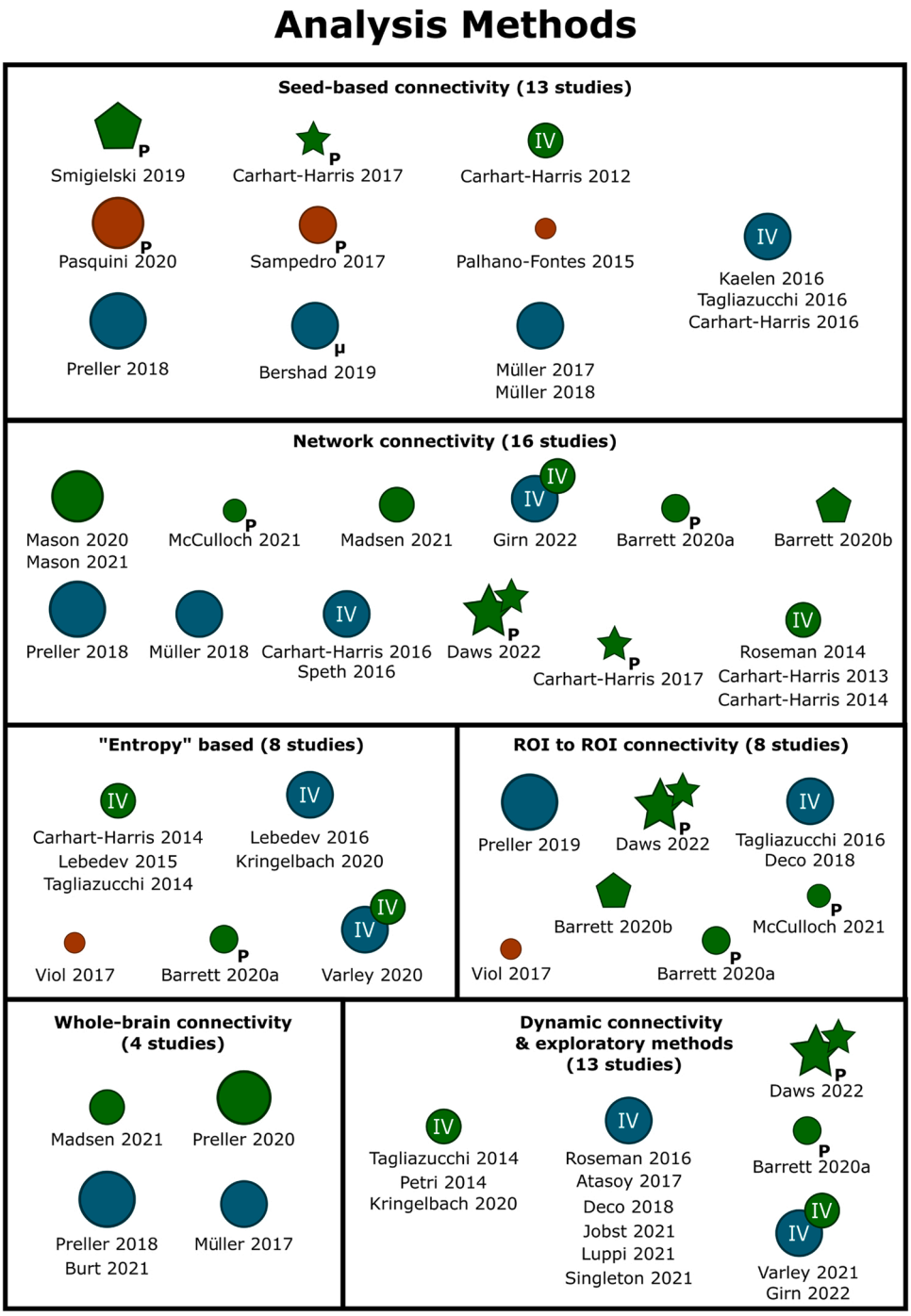

Fig. 3. Analysis Methods. Figure showing the different analysis methods used and which data sets have been analysed in each case. Shapes represent data sets as described in Fig. 2.

correlated against the time series from all voxels in the brain. Of the 13 seed-based studies, 11 used small localised seeds only, one used both small and network seeds and one used network seeds only (see Fig. 4 for an overview). The most commonly selected seeds were the thalamus and prefrontal cortex, each analysed in five articles, then the posterior cingulate cortex (PCC) analysed in four separate articles. The anterior cingulate cortex (ACC) and parahippocampal gyri were analysed in three studies each whereas the amygdala and bilateral angular gyri were studied in two separate studies each. The exact definitions of those seeds vary considerably between these studies according to predefined spatial parcellations as described in Supplementary Figure 1. The intraparietal sulcus, frontal eye field, middle temporal visual area, "Visual area 1″, precuneus, a frontal mask, and several network-based seeds have each only been analysed in one study each and thus would benefit particularly from replication.

Sixteen articles employed a network-based connectivity approach (see Fig. 5 for an overview). Six of these derive networks from an independent component analysis of their own data, while ten use predefined atlases. Nine studies investigated within- and between-network connectivity for all networks. One study each investigated the between-network connectivity of the DMN with all other networks (Carhart-Harris et al., 2013), within-network DMN connectivity (Speth et al., 2016), connectivity of their networks with bilateral claustrum ROI seeds (Barrett et al., 2020b), gradient-based connectivity mapping (Girn et al., 2022), network recruitment and integration (Daws et al., 2022), the entropy of within-network connectivity (Carhart-Harris et al., 2014) and one study investigated the global connectivity of all networks defined (Preller et al., 2018). Notably, no network-based analyses have been performed on an ayahuasca dataset, though Pasquini (2020) utilised network seeds in their seed-based analysis. Two studies use the Van Essen 2013 network definitions; participants from the first study were healthy volunteers given IV LSD and scanned during drug effects and in the other study, patients with treatment resistant depression were given two doses of oral psilocybin and scanned the day after the second dose. Two studies, both involving moderate doses of oral psilocybin, use the Raichle (2011) network definitions but one study investigated acute effects and the other persistent effects. Additionally, two papers utilise the same ICA procedure to identify networks and estimate connectivity, but one study investigates LSD and the other, psilocybin. With the exception of these, no two network-based analyses share methodologies and network definitions. Various studies reporting similar effects with different atlases e.g., a replicated effect on a network connectivity metric, are encouraging. Although it is difficult to advocate for a specific atlas or region set, we encourage future studies that use a novel atlas or region set to consider also evaluating effects with one previously described, where relevant. This has been done to a limited degree, to date, which hinders the ability to align these findings.

Eight studies investigate ROI to ROI connectivity. Two studies report full connectivity matrixes between all ROIs defined by their 268 and 401 region atlases (Barrett et al., 2020a; Tagliazucchi et al., 2016). Three studies estimate brain modularity (Sporns and Betzel, 2016) and related parameters (Daws et al., 2022; Tagliazucchi et al., 2016; Viol et al., 2017). Two studies estimate persistent changes in edge strength using a thresholding technique, one of which replicates the other using the same predefined atlas and method (Barrett et al., 2020a; McCulloch et al., 2021). One study calculates "grand-average static functional connectivity" which reflects the ROI-to-ROI connectivity of each ROI within their 90 ROI atlas using this to build a multimodal whole brain model (Deco et al., 2018). One study examined directed functional connectivity between four a priori selected ROIs using dynamic causal modelling (Preller et al., 2019). One study computes pairwise correlations between bilateral claustral ROIs and all ROIs defined by their 264 ROI atlas (Barrett et al., 2020b).

Five studies investigate whole brain connectivity. Five studies calculate the average connectivity of every brain voxel or every grey-matter voxel to every other brain/grey-matter voxel to give a "Global Brain Connectivity" score and one also calculates the connectivity of each voxel to its neighbouring voxels across the whole brain (Madsen et al., 2021).

3.1.4. Explanatory psychedelic models

An area of psychedelic neuroscience that has seen repeated analysis is the general testing of system-based models of psychedelic effects on perception. Two of the most prominent and tested models are the entropic brain hypothesis, i.e., psychedelics diminish the hierarchical structure across canonical resting-state networks (Carhart-Harris and Friston, 2019) and the thalamic gating theory based on information flow from the thalamus to cortical regions (Vollenweider and Geyer, 2001). There are also additional theories that have begun to be investigated such as the claustro-cortical model, which postulates that claustral 5-HT_{2A} receptor activation leads to the disruption of network states produced by psychedelics (Crick and Koch, 2005; Doss et al., 2021). Despite methodological differences, studies aligned with such hypotheses in mind contribute to the greater understanding of brain-wide theories of psychedelic action. These explanatory models allow researchers to define analyses a priori increasing scientific validity and increasing homogeneity of analyses. There is an opportunity for such theories to be reconciled using novel data, especially if researchers consider contrasting such theories within single studies. This is demonstrated by the relatively consistent effects of psychedelics on decreases in within-network-connectivity and increases in between-network-connectivity, including but not limited to the DMN, despite variation in network-connectivity quantification. Additionally, there is early convergent evidence supporting the association between alterations in thalamic connectivity and acute psychedelic effects (Avram et al., 2021).

The burgeoning interest in characterising brain mechanisms underlying psychedelic effects has facilitated the application of novel neurocomputational models to these unique datasets. Ten studies focus on examples of these neurocomputational frameworks, including: dynamic causal modelling (Preller et al., 2019), temporal variability (Tagliazucchi et al., 2014), homological scaffolds (Petri et al., 2014), gradient-based connectivity (Girn et al., 2022), retinotopic coordination (Roseman et al., 2016), whole-brain functional connectivity dynamics (Deco et al., 2018; Kringelbach et al., 2020), connectome-harmonic decomposition (Atasoy et al., 2017; Luppi et al., 2021), and leading eigenvector dynamic analysis (Lord et al., 2019). It is a benefit to the field of psychedelic imaging and functional brain imaging analysis as a whole to apply these models. It is also noteworthy that all but one of these studies are derived from the two aforementioned IV datasets. With recently published studies derived from novel psychedelic datasets, the field is well-positioned to apply these models and attempt to replicate findings across datasets.

3.1.5. Brain entropy

Entropy is a measure earlier applied in thermodynamics and information theory that refers to the amount of information required to describe a system. It is related to its level of randomness, unpredictability, or disorder. Entropy measures subsumed under "entropy" as an umbrella construct have been applied to psychedelic neuroscience data - in part due to the "entropic brain hypothesis" and "RElaxed Beliefs Under Psychedelics" theory (REBUS). These theories hypothesise that the altered state of consciousness evoked by psychedelics stem from a parallel enriching effect on the dynamics of spontaneous population-level neuronal activity, which can be observed empirically by measuring the entropy of neuroimaging signals (Carhart-Harris, 2018; Carhart-Harris et al., 2014; Carhart-Harris and Friston, 2019). Whereas eight studies have investigated psychedelic effects on brain entropy based on BOLD time series, they calculate entropy targeting different aspects of brain activity. The various approaches to calculate brain entropy can be roughly divided in three groups: (i) those that calculate the entropy of aspects of functional connectivity, (ii) those that calculate

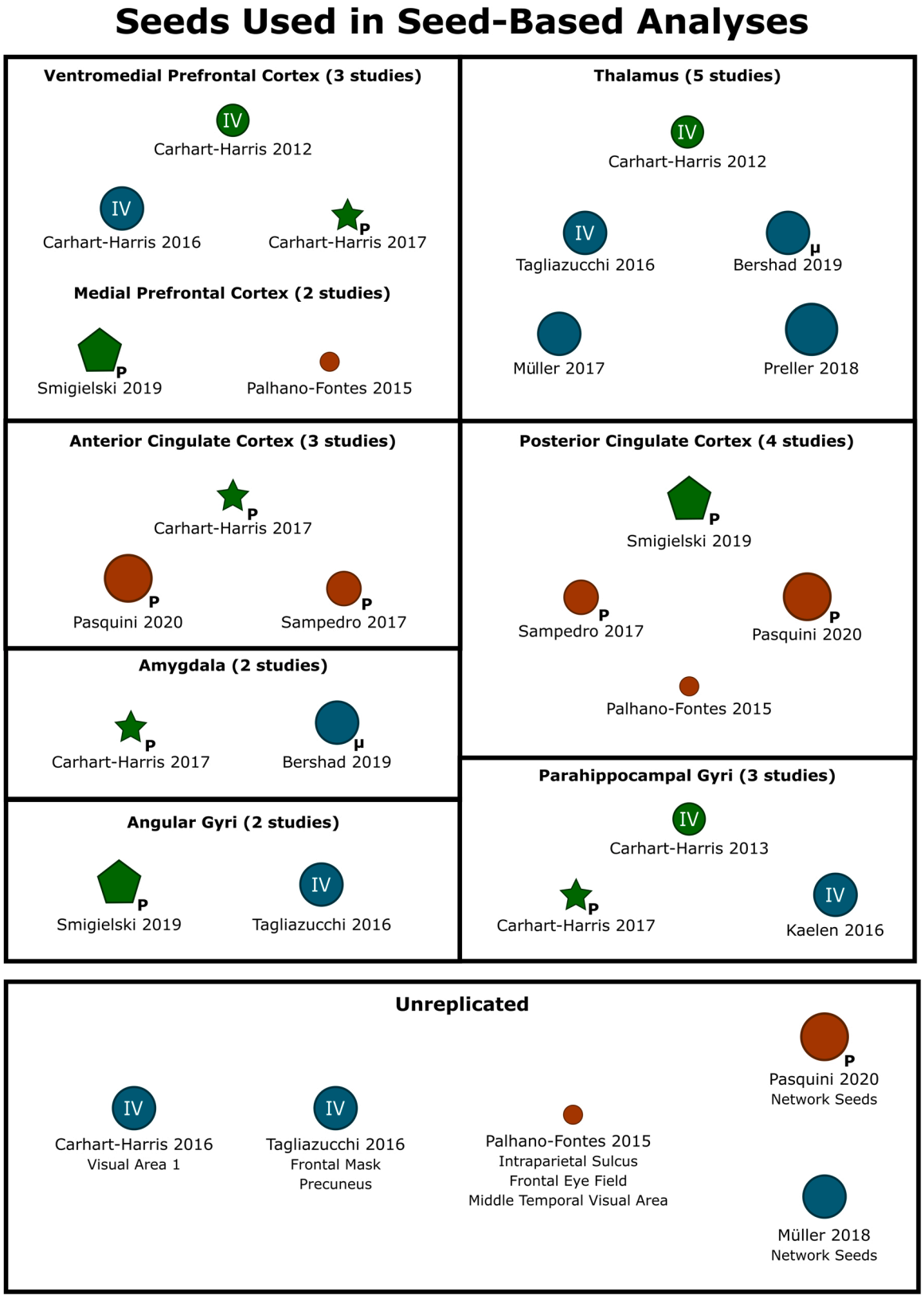

Fig. 4. Seeds Used in Seed-Based Analyses. Figure showing the predefined seeds used in seed-based connectivity analyses. Seeds that have been investigated in only one study are described in the bottom section. This figure represents a more detailed view of the top-most sextant of Fig. 3. Symbols represent datasets as described in Fig. 2.

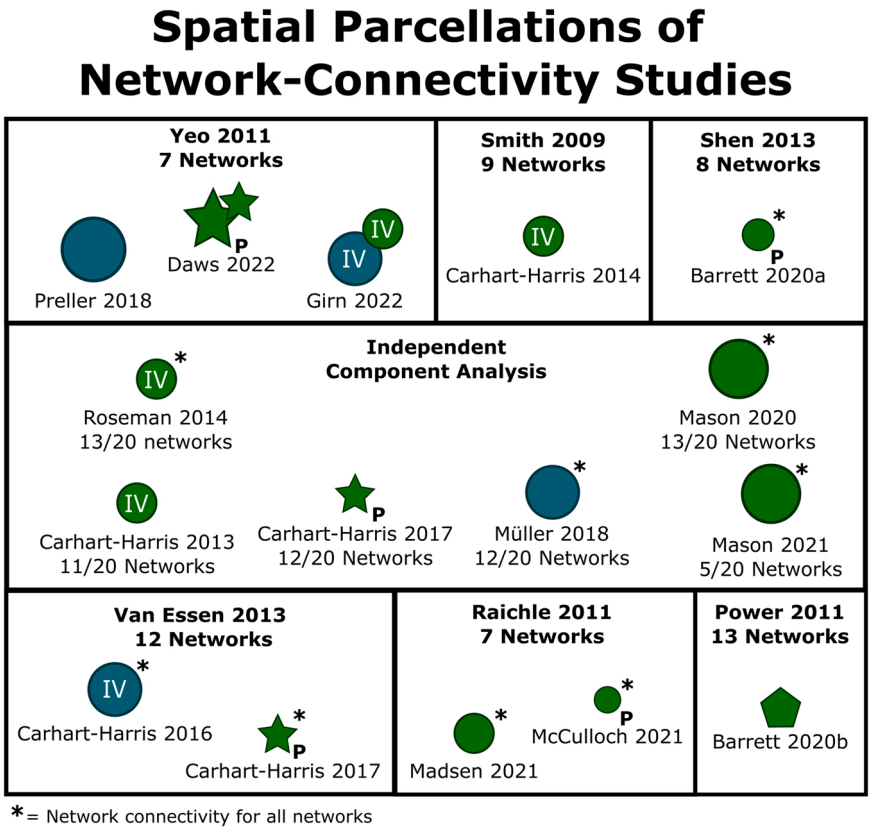

Fig. 5. Spatial Parcellations of Network-Connectivity Studies. Figure describing the network definitions of the analyses that investigated within and between network connectivity. This figure represents a more detailed representation of second section from Fig. 3.

entropy of the dynamics of BOLD signals, and (iii) those that calculate the entropy of dynamical aspects of functional connectivity.

The first group has three papers: Carhart-Harris et al. (2014) investigate the Shannon entropy of intra-network synchrony and connectivity between a specific set of ROIs from the limbic/paralimbic system, Lebedev (2015) calculates the Shannon entropy of the distribution of functional connectivity links between individual ROIs and 5 ROI groups identified via community detection on placebo data. Viol (2017) calculates the Shannon entropy of the overall distribution of the number of significant functional connections per ROI.

The second group has two papers: Lebedev et al. (2016) calculates the multi-scale sample entropy (a measure of predictability) of voxel-wise BOLD signals, parcellated into 17 networks. Varley et al. (2020) calculates the Lempel-Ziv complexity (an estimate of Shannon's entropy rate) of the BOLD signal per ROI.

The third group has three papers: Tagliazucchi et al. (2014) calculates the Shannon entropy of binarized dynamic functional connectivity patterns observed between four ROIs. Barrett et al. (2020a) approximates differential entropy of the distribution of values of dynamical functional connectivity between each pair of ROIs. Kringelbach (2020) calculates the Shannon's entropy rate of the transitions between brain connectivity states.

These results are often reported as "brain entropy," but the categories correspond to entirely different metrics: ones that estimate the "width" of a histogram (e.g., Shannon entropy) and ones that estimate unpredictability (e.g., entropy rate, Lempel-Ziv complexity, and sample entropy). It is notable that, despite the range of methodologies, the findings within each of these categories point towards the same effect, i.e., an increase of the respective entropy estimate under psychedelics. However, it is not straightforward to compare these results because of the different methodologies. To foster the maturation of the field and clarify the comparability of the findings, we suggest those investigating entropic measures of psychedelics make clear what signal is to be assessed (e.g., BOLD activity, functional connectivity, etc.) and what type of entropy is to be quantified. As the term "brain entropy" can mean substantially different things, it will only improve the field if future studies are clearer about their use of this term and its correspondence with preceding studies.

3.1.6. Spatial parcellation

For any seed-, network-, or ROI-based analysis the exact 3D description of the location and boundaries of that area must be rationalised. Many studies opt to use atlases generated from large repositories of independent anatomical or functional imaging data, while others opt to parcellate data based on an independent component analysis (ICA) of the data itself. Precise and consistent parcellations are important for replicable results, as a named ROI (e.g., the prefrontal cortex) from one study may not be at the same co-ordinates as the same named region in another study. Similarly, a network description from a given atlas may vary in number and selection of nodes, as well as the position of those nodes.

Of those studies that parcellated their data using atlases, 28 studies used atlases derived from functional data, 18 used atlases derived from anatomical data and two used atlases that took into account both structural and functional data. Certain studies performed several analyses using different parcellations. Nine studies defined the parcellations of their signals using an ICA of their own BOLD timeseries. Up to 20 components were defined, resulting in subsequently disregarded noise-components. Non-noise components were typically labelled by comparison with known atlases. One study divided the brain into trans- and uni-modal cortices based on gradient-based connectivity mapping. See Supplementary Figure 1 for details.

Of studies that used predefined atlases, six used the Harvard-Oxford Probabilistic anatomical atlas (Desikan et al., 2006) to divide their data.

Four studies used the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Six studies used the Yeo 2011 atlas (Yeo et al., 2011), yet four used the 7 network parcellation and two studies used the 17 network parcellation. Two studies used a network defined from an ICA of a large sample of scans from the human connectome project (Van Essen et al., 2013), two studies used the Shen268 region atlas (Shen et al., 2013) and two studies used the Raichle, 2011 atlas (Raichle, 2011). All other studies either used co-ordinates determined from their own previous research or atlases that were not used by any of the other studies covered in this review.

The fifteen studies investigating the effects of psychedelics on network connectivity use seven different atlases of networks or ICA. These atlases vary in number of networks described (range = 7–13) as well as labels and descriptions of the voxels that constitute each network. For example, networks described by Smith et al. (2009) include an ECN, a DMN, and a DMN2 (a hybrid of anterior DMN and ECN), whereas Yeo's 7 network atlas (2011) has only one DMN and no ECN. In such cases where networks are significantly disparate in their definitions, resting-state network findings become practically incommensurable. As mentioned earlier, this can be helped by future studies evaluating network effects defined by a novel atlas considering whether findings are convergent with similar atlases previously applied.

3.1.7. Data pre-processing

A core methodological aspect of all resting-state fMRI, including psychedelic resting-state fMRI, is image pre-processing. Among the most relevant, and controversial, pre-processing steps is correction for motion-induced, physiological (e.g., respiratory, pulse, etc.), and other noise sources and signal confounds, the correction of which also has a considerable impact (Khalili-Mahani et al., 2013). These noise sources are exacerbated under the influence of psychedelics, which can increase head motion during scanning and have been shown to alter blood pressure, respiration and heart rate (Griffiths et al., 2011; Holze et al., 2021; Olbrich et al., 2021). Denoising procedures such as global signal regression, have been shown to substantively alter psychedelic effects on resting-state measures (Preller et al., 2020, 2018). Despite the development of many denoising tools and strategies (e.g., RETROICOR, aCompCor, AROMA, FIX+ICA, fMRIPrep, multi-echo EPI, 24 motion regressors), the field of resting-state fMRI has not reached a consensus on best practices. With that in mind, we do not see a way to recommend a specific strategy, but instead recommend the acquisition of empirical physiological data where possible and to clearly describe denoising procedures. Where relevant, consider attempting to reproduce previously described denoising procedures when replicating results or evaluating similar outcome measures.

4. Discussion

4.1. Future directions

The burgeoning field of psychedelic resting-state fMRI has many unexplored frontiers. For example, the persistent effects on mood and personality in both healthy and patient population groups is arguably the most remarkable property of psychedelic drugs. More data on the persistent effects of psychedelics on neural function could provide a mechanistic understanding of the remarkable therapeutic effects of psychedelics as well as highlighting potential risks. As the number of participants in clinical trials using psychedelics expands, we urge researchers utilising RSFC to consider evaluating persistent changes where possible, in clinical and non-clinical populations.

Resting-state neuroimaging may also assist in the development and testing of the effect of psychological variables surrounding psychedelic administration, i.e., different psychedelic assisted psychotherapy approaches. Future work may emphasise the effect of these on brain function and connectivity. Although the purpose of this paper is to promote coherence in the field, we naturally acknowledge that study-specific designs are key to testing specific hypotheses. We nonetheless urge researchers to align methodology where possible while optimising individualised study designs.

Thus far, five of the six studies investigating thalamus seed-based connectivity have been performed using LSD (the sixth used psilocybin), whereas brain regions involved in the DMN hypothesis have been tested with psilocybin, ayahuasca and LSD, and in a range of participant populations. Similarly, no studies have investigated the persistent effects of LSD and no acute neuroimaging has been performed in patients. By testing hypotheses with a range of different drugs with similar effects we can increase confidence in certain measures of brain function as being key to psychedelic effects.

At the time of writing, the only neuroimaging studies investigating 5-HT2A receptor agonists have been performed on serotonergic psychedelics LSD, psilocybin and ayahuasca, which are not selective for the 5-HT2A receptor (Halberstadt and Geyer, 2011). However, there are in excess of 200 relatively untested psychedelic drugs that are likely 5-HT2A receptor agonists, as well as targeting other receptors, and provide candidates for investigation as therapeutic agents, such as 2C-B (Trial identifier: NL 8813), 4-OH-DiPT and 5-MeO-DMT (NCT04640831, NCT04698603) (Nichols et al., 2015; Richards, 1975; Shulgin and Shulgin, 1997, 1991; Uthaug et al., 2019). By considering the balance between novel analysis and replication, the field will be better situated to evaluate distinct effects between psychedelic substances which will also inform the role of non-5-HT2A receptor binding on subjective and persistent effects.

One potential move towards standardisation within the psychedelic neuroimaging space could be to create a collaborative consortium of MRI sequences including, among other things, resting-state acquisitions that could be utilised across labs à la the Human Connectome Project (Van Essen et al., 2013). Collection of large, more homogenous data sets may also allow for the utilisation of tools such as pharmacogenomics (Whirl-Carrillo et al., 2012) and pharmacoepigenomics (Peedicayil, 2019) to investigate the underlying causes of biological variability in response to psychedelics drugs, beyond pharmacokinetics.

Based on the above, and in order to maximise homogeneity in methodology, we recommend the following principles to be taken into account for future resting-state psychedelic neuroimaging studies, including in clinical studies:

Design and neuroimaging:

1. To facilitate comparisons within and between studies, plasma drug levels should preferably be monitored when imaging is acquired shortly after drug administration.
2. Data collected while participants are exposed to passive stimuli such as music should be clearly described and distinguished from "resting-state".
3. Resting-state scans should be acquired while participants are instructed to close their eyes and let their mind wander freely; if possible, quantify participant mental state during the scan sessions, e.g., wakefulness, anxiety or tiredness.

Data processing and analysis:

1. Encourage replication with independent data; when replicating seed-, network-, or ROI-based findings, attempt to use the same parcellation from earlier studies.
2. When evaluating novel models, where possible and within reason, examine the convergence between novel outcomes from new methods with previously reported findings from related methods or data.
3. Data analysis strategies should be guided by existing and novel explanatory models of psychedelic action and attempt to validate or refute these models.

4. "Brain entropy" measures should be more clearly defined and the rationale for the particular measure evaluated should be clearly articulated.
5. Secondary and additional analyses of original datasets must be clearly indicated and an attempt should be made, where possible and within reason, to compare the findings of new methods with previously reported findings from the same data.
6. To the extent possible, make data and analysis scripts available, e.g., via online repositories such as GitHub and OpenNeuro.

4.2. Conclusions

The psychedelic resting-state literature is burgeoning with novel datasets and analyses that we anticipate will reveal novel and exciting insights into how these compounds affect brain function. Although an irrefutable component of research is for novel studies to cast new and invigorating perspectives on a field, we believe it is also timely for the psychedelic functional brain imaging community to recognise the critical importance of attempting to replicate findings and clarify methods to more effectively leverage early observations, interrogate theories and hypotheses across datasets and meaningfully grow this exciting and emerging field of research. Here we have highlighted the methodological heterogeneity within the psychedelic resting state neuroimaging literature, which is not unusual of a nascent research field. Acknowledging this heterogeneity and working towards identifying best practices is essential so that the field can mature and resolve robust and reproducible features that limit risk of challenges in replication (Ioannidis, 2005; Tackett et al., 2019). Psychedelic neuroscience is expanding rapidly, and it is our hope that this review will serve as a basis for discussions that will facilitate robust and clinically applicable advances.

Declarations of interest

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Data Availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104689.

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