The Hierarchy of Psychedelic Effects: Three Systematic Reviews and Meta-Analyses

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Abstract:
Serotonergic psychedelics induce altered states of consciousness and have shown potential in treating a variety of neuropsychiatric disorders, including depression and addiction. Yet their modes of action are currently not fully understood. Here, we provide three systematic reviews and meta-analyses of three hierarchical levels relevant to the effects of psychedelics, i.e., 1) their molecular pharmacology, 2) whole-brain neuroimaging and 3) subjective experience (phenomenology). Our meta-analyses link each of the classic psychedelics (DMT, LSD, and psilocybin) to specific neural fingerprints at each level of this tripartite hierarchy. The results show a highly non-linear relationship between these fingerprints. Overall, the results point to the need for standardising experimental procedures and analysis techniques, as well as for more research on the emergence between different levels of psychedelic effects. Future work could use our tripartite hierarchy framework to investigate the dose-dependent effects of different psychedelics in the same participants.

Keywords:
psychedelics, ayahuasca, LSD, psilocybin, meta-analysis, fMRI, functional connectivity, BOLD activation, pharmacology, receptor affinity, receptor agonism, phenomenology, subjective experience, consciousness

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Section 1. Introduction

Psychedelics have been utilised by early cultures for millennia within diverse sociocultural contexts, as well as spiritual and healing rituals (Garcia & Maia, 2022; Nichols, 2016; Tupper et al., 2015). Western research into psychedelics, having blossomed in the '50s and '60s following the first study of lysergic acid diethylamide (LSD) in 1947 (Stoll, 1947), came to a halt in the late 1960s due to changes in government regulations and the classification of these substances as "drugs of abuse" with "no recognised medical value" (Tupper et al., 2015). Revitalisation of psychedelic research commenced in the 1990s (Hermle et al., 1992; Strassman et al., 1994; Strassman & Qualls, 1994), with three key factors inspiring the current interest: scientific advances, evidence of therapeutic potential, and increased public interest (Aday et al., 2021). Researchers have come to recognise that psychedelics may be effective tools in the treatment of psychiatric disorders such as depression (Muttoni et al., 2019; Nutt et al., 2020) and addiction (Tófoli & de Araujo, 2016).

The effects of psychedelic substances have been examined at several levels. Pharmacological research has measured their interaction with various receptors in the brain (e.g. Glennon et al., 1984; Watts et al., 1995), while other research domains have explored the subjective experience of a psychedelic 'trip'. Neuroimaging research has examined changes in brain activity and functional connectivity under the influence of psychedelics, yet there are still relatively few studies and a plethora of different analysis techniques. Here, we report the findings of a systematic meta-analysis focused on synthesising the evidence from three classic psychedelics: DMT, LSD, and psilocybin. The main aim is to provide an overview and analysis of the literature across three levels of description: (1) phenomenology—to discuss key differences in the states of consciousness induced by these psychedelics; (2) functional neuroimaging—to compare the changes in brain activity, functional connectivity, and entropy that are induced by psychedelics; and (3) pharmacology—to discuss the binding affinities and functional activity of psychedelics with respect to various neural receptors.

Section 1.1. Phenomenology

Psychedelics produce altered states of consciousness (ASCs) that are characterised by ego dissolution, feelings of connectedness, and "mystical" experiences (Griffiths et al., 2018; Yaden et al., 2021). Ego dissolution can be defined as a breakdown or distortion of one's sense of self or ego, and machine learning classifiers trained only on ego dissolution ratings are able to accurately distinguish between psychedelics and other drugs (Lebedev et al., 2015; Nour et al., 2016). The feeling of connectedness after a psychedelic trip has been categorised into three components, including the connection to oneself, others, and the world (Watts et al., 2017). Furthermore, this feeling endures for weeks, if not months, after the trip is over (Carhart-Harris et al., 2017). Finally, mystical experiences on psychedelics can be defined by six components: a sense of unity; transcendence of time and space; positive mood; feeling of awe, reverence and wonder; meaningfulness of insight gained; and ineffability (Maclean et al., 2012; Pahnke, 1969a). Individuals who had taken one of the classic psychedelics were significantly more likely to meet pre-determined criteria for having had a 'complete' mystical experience than people who had other kinds of meaningful experiences (Griffiths et al., 2019).

However, perhaps the strongest predictor of therapeutic outcomes from psychedelic research is so-called 'emotional breakthrough' experiences, as assessed by the emotional breakthrough inventory or EBI (Roseman et al., 2019). After some studies found that ratings of psychological insight correlate with the therapeutic effects of psychedelics on depression (Roseman, Nutt, et al., 2018) and alcohol use disorder (Garcia-Romeu et al., 2019), two research groups have independently developed a psychological insight

questionnaire/scale to probe into the specific insights that psychedelic trips tend to occasion, such as awareness of previously repressed emotions (Davis et al., 2021; Peill et al., 2022).

These experiential themes – insight, mystical experiences, and ego dissolution – are all captured by the Altered States of Consciousness (ASC) scale. Stemming from Dittrich's Abnormal Mental States questionnaire (Dittrich, 1998), the 5D-ASC measures altered states of consciousness along five different dimensions: oceanic boundlessness (e.g. a sense of interconnectedness), anxious ego dissolution, visionary restructuralisation (e.g. visual hallucinations), auditory alterations, and reduction of vigilance. Subsequent factor analyses led to the extraction of 11 lower-order dimensions from the 5D-ASC, resulting in the development of the 11D-ASC: experience of unity, spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, elementary imagery, complex imagery, audio-visual synesthesia, and changed meaning of percepts (Studerus et al., 2010). Because the ASC is the most common subjective questionnaire in the literature on the neuroimaging of psychedelics, we performed a meta-analysis on both the 5D- and 11D-ASC scores of DMT, LSD, and psilocybin.

However, the ASC is just one of many scales for rating the subjective effects of psychedelics. The multiplicity of scales makes it difficult to comprehensively evaluate the literature on the phenomenology of psychedelics. To date, only two studies have used a single set of scales to compare the subjective effects of LSD and psilocybin in the same group of participants (Holze et al., 2022; Ley et al., 2023). More recent research has attempted to draw direct comparisons by qualitatively examining larger datasets, such as the Erowid corpus of trip reports (Ballentine et al., 2022; Coyle et al., 2012; Qiu & Minda, 2021; Sanz et al., 2018; Zamberlan et al., 2018). The key findings from these comparative studies are discussed in *Section S3*.

Section 1.2. Neuroimaging

After a long pause in psychedelic research on humans, the pioneering positron emission tomography (PET) scans by Vollenweider and Gouzoulis-Mayfrank in the late 1990s ushered in a new era of research on the human brain under psychedelics (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997, 1999). Forty to fifty years after the initial spate of electroencephalography (EEG) studies on psychedelics (see Tagliazucchi (2020) for a review), several studies used electroencephalography (EEG) to measure human brain activity under psychedelics, especially ayahuasca (Hoffmann, 2001; Riba, Anderer, et al., 2002; Riba et al., 2004; Riba, Rodríguez-Fornells, et al., 2002; Stuckey et al., 2005) and psilocybin (Umbricht et al., 2002, 2003).

However, many of these studies were predicated on the notion that psychedelics are principally useful as a model for psychosis and schizophrenia. For instance, Vollenweider et al. (1997) considered the feeling of ego dissolution on psychedelics to be a model of psychosis. However, the last decade has seen a huge rise in more explorative, data-driven or hypothesis-free neuroimaging studies on psychedelics, as well as studies on their therapeutic benefits for clinical populations, e.g. patients with depression. The first functional neuroimaging study of psychedelics, published in 2012 (Carhart-Harris, Erritzoe, et al., 2012), was an exploratory analysis of psilocybin-induced changes in cerebral blood flow and BOLD activity in healthy human participants. Since then, dozens of fMRI studies have been performed on human participants under the influence of ayahausca, LSD, psilocybin and DMT, including several studies on depressed patients (Carhart-Harris et al., 2017; Daws et al., 2022; Doss et al., 2021; Mertens et al., 2020; Roseman et al., 2018; Wall et al., 2022). Additionally, in the last decade, two studies collected primary magnetoencephalography (MEG) data on healthy human participants who had been administered LSD and psilocybin (Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013).

We chose to perform a meta-analysis exclusively on the fMRI data and not on any of the other modalities used to measure brain activity. There were too few primary PET (4), SPECT (4), or MEG (2) datasets to merit a meta-analysis; by comparison, 30 fMRI studies have collected original data. While there are many more primary EEG datasets (25) from the post-1960s era (and even more from the 1950s-1960s era) than PET, SPECT, or MEG, most of the EEG studies do not spatially localise the brain activity recorded at EEG electrodes. In order to tease apart the differences in the spatial distribution of brain activity under the various psychedelics, we need high spatial specificity in the data. However, without the raw data, which may be difficult to access when some of the studies are nearly 20 years old, we cannot source-localise the EEG activity ourselves. On the other hand, the published fMRI data on psychedelics reports the specific coordinates corresponding to regions of the brain that become more or less active under psychedelics. In general, EEG has higher temporal resolution than fMRI (Haufe et al., 2018), so a future meta-analysis that focuses on the temporal, rather than spatial, characteristics of brain activity on psychedelics could consider the EEG rather than fMRI data.

The fMRI studies assess three different metrics of brain activity: BOLD activation, connectivity, and entropy. Studies on BOLD activation analyse changes in the trajectory of BOLD time series with a rapidly-acting psychedelic, e.g. intravenously-administered psilocybin. Connectivity studies can examine undirected, instantaneous correlations between different regions (a type of functional connectivity) or model the experimental factors that modulate directed connections between regions, using dynamic causal modeling (a tool for measuring effective connectivity). The entropy of spontaneous brain activity is best assessed with MEG and EEG, but efforts to compute entropy on the spontaneous BOLD signal, as well as the entropy rate (Lempel-Ziv complexity) and indices of criticality, have also been attempted (see *Section S1.2* for a full list of citations).

While studies on BOLD activation and functional connectivity are common for most subject areas within cognitive neuroscience, entropy is a rather unique feature of the psychedelic neuroimaging literature. The studies on entropy were motivated by Robin Carhart-Harris' influential *Entropic Brain Hypothesis* (EBH) (Carhart-Harris et al., 2014; Carhart-Harris, 2018), which states that psychedelics alter consciousness by elevating the entropy of spontaneous brain activity across time. While entropy is typically associated with the amount of disorder in a system, it is more accurate to think of entropy as a measure of informational variability or unpredictability. In statistical mechanics, the entropy of a system of particles is proportional to the number of possible microscopic states, i.e. states of each particle, that are consistent with the macroscopic state of the system. (A box in which all the particles are clustered together in one corner is less entropic than a box in which the particles are scattered.) Similarly, according to EBH, the brain would be more entropic if, for instance, individual regions were to exhibit a greater number of possible connectivity motifs. Tagliazucchi et al. (2014) found that psychedelics raise entropy in this manner, and since then, ten other fMRI studies and several MEG and EEG studies have all shown that entropy increases during psychedelic use (Alonso et al., 2015; Atasoy et al., 2017; Lebedev et al., 2015, 2016; Lord et al., 2019; Luppi et al., 2023; Mediano et al., 2020; Pallavicini et al., 2021; Schartner et al. 2017; Singleton et al., 2022; Timmermann et al., 2019, 2023; Varley et al., 2020; Viol et al., 2017, 2019).

While there have been prior qualitative reviews of the fMRI literature on psychedelics (e.g. McCulloch, Knudsen, et al. (2022)), there has not yet been an exhaustive, quantitative meta-analysis of the research. Castelhano et al. (2021) used the GingerALE software to compute common clusters of BOLD activation across studies, but they neglected many studies in their meta-analysis (n = 16 compared to n = 58 for us).

Our meta-analysis is the first to not only include all the fMRI studies on psychedelics to date, but also quantitatively synthesise phenomenological and pharmacological data on psychedelics.

For the neuroimaging data, we performed a quantitative meta-analysis of the BOLD activation and the pairwise functional connectivity data using GingerALE and a novel algorithm developed in-house, respectively. Due to their heterogeneity, we also provide a qualitative discussion of studies on entropy.

Section 1.3. Pharmacology

Chemically, psychedelics fall into three categories: tryptamines (e.g. DMT, psilocybin, ayahuasca), ergolines (e.g. LSD), and phenethylamines (e.g. mescaline, 2C-B) (Nichols, 2018). The molecular structure of tryptamine psychedelics strongly resembles that of serotonin; in fact, serotonin is itself a tryptamine, as both are synthesised from the same amino acid, tryptophan (Brandt et al., 2004). Ergolines are rigid and more complex analogues of tryptamines (Nichols, 2004), whereas the chemical backbone of phenethylamines is not the same as that of tryptamines; it is instead constituted from the amino acid phenylalanine (Fantegrossi et al., 2008).

Despite their chemical differences, both tryptamines and phenethylamines – indeed, all classic psychedelics – activate serotonin receptors. Phenethylamines are very selective for the serotonin-2 (5-HT_2) receptor subtype, including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}, whereas tryptamines exhibit a more "promiscuous" binding profile, as they also have affinity for the 5-HT_1 receptor subtype (Araújo et al., 2015). In spite of the broad range of serotonin receptors that psychedelics, especially tryptamines, bind to, their interaction with the 5-HT_{2A} receptor is their primary mechanism of action (González-Maeso et al., 2007; López-Giménez & González-Maeso, 2018). Multiple studies have demonstrated that blocking the 5-HT_{2A} receptor with antagonists such as ketanserin eliminates their subjective effects (Preller et al., 2017; Quednow et al., 2012; Vollenweider et al., 1998). 5-HT_{2A} is expressed postsynaptically in the apical dendrites of layer V pyramidal neurons (Aleksandrova & Phillips, 2021; Hamada et al., 1998; Jakab & Goldman-Rakic, 1998), which are the primary excitatory neurons in mammalian cortex (Spruston, 2008). Binding to 5-HT_{2A} amplifies the firing rate of pyramidal neurons (Puig et al., 2003) and upregulates the release of glutamate by increasing the amplitude and frequency of excitatory postsynaptic potentials (Aghajanian & Marek, 1997, 1999). 5-HT_{2A} expression is profuse in human cortex, with one study finding highest expression in the posterior cingulate cortex and V1 (Beliveau et al., 2017). In both humans and monkeys, 86-100% of glutamatergic cells in layers II-V of cortex express mRNA encoding 5-HT_{2A} receptors (de Almeida & Mengod, 2007). 5-HT_{2A} has also been identified in many subcortical regions (Nichols, 2016), though human PET imaging implies lower expression than in the cortex (Beliveau et al., 2017).

Although the consciousness-altering effects of psychedelics do primarily arise from their action at the 5-HT_{2A} receptor, we stress that different psychedelics display different binding profiles. For instance, unlike DMT and psilocybin, LSD has moderate affinity for dopamine receptors (de Vos et al., 2021). Differences in binding affinities could partially account for the distinctive phenomenology of each psychedelic.

However, binding affinity paints an incomplete picture of the pharmacology of psychedelics. Another key aspect is their functional activity at receptors. Serotonin and dopamine receptors are G protein-coupled receptors (GPCRs) (Gurevich et al., 2016; Shah et al., 2020), which perform essential roles in neurophysiological processes like smell, taste, light perception, and more (de Oliveira et al., 2019). GPCRs regulate these processes through G protein signaling pathways, which are initiated when agonists bind to GPCRs and activate G proteins (Tuteja, 2009). Different families of G proteins interact with different types

of secondary messengers like calcium, adenylyl cyclase, and others; thus, certain families are selective for particular signaling pathways (Giulietti et al., 2014). Intriguingly, GPCRs can exhibit multiple conformations, each of which couples to a different G protein subtype (Bosier & Hermans, 2007). Furthermore, certain agonists may uniquely activate particular conformations, thereby predisposing neurons towards specific signaling pathways; this "agonist-trafficking" model has been proposed as an explanation for why some 5-HT_{2A} agonists elicit hallucinations, whereas others, such as lisuride or ergotamine, do not (Gonzalez-Maeso & Sealfon, 2009). Additionally, in a phenomenon known as "biased agonism," some agonists may cause conformational changes that lead to the recruitment of the protein β-arrestin, which initiates signaling pathways that are independent of G proteins (Rajagopal et al., 2010).

Functional GPCR assays have been used to measure the effect of psychedelics on G protein signaling and β-arrestin recruitment upon their binding to serotonin receptors. We performed a quantitative meta-analysis of the affinity of DMT, LSD, and psilocin for four serotonin and two dopamine receptors in both humans and rats. Additionally, we conducted a quantitative meta-analysis of their activity at these receptors, as determined by the functional GPCR assays.

Section 2. Results

We present the results of our meta-analysis of the phenomenology, neuroimaging, and pharmacology of three classical psychedelics: DMT, LSD, and psilocybin. For the phenomenology research, we performed quantitative meta-analyses of the 5D-ASC and 11D-ASC data on DMT, LSD, and psilocybin, and we also qualitatively reviewed studies that compared the phenomenology of these three drugs, together with ayahuasca. The functional neuroimaging studies consisted of datasets that measured three different metrics of brain activity: BOLD activation, connectivity, and entropy. We executed a quantitative meta-analysis of the BOLD activity and FC of DMT and ayahuasca, LSD, and psilocybin through the GingerALE method and a technique that computed the alignment between functionally connected regions and the Yeo networks, respectively. Due to the heterogeneity of methods for defining and measuring entropy, we qualitatively reviewed the studies on entropy. Finally, for the pharmacology research, we conducted quantitative meta-analyses on the affinity and functional activity of DMT, LSD, and psilocin at six serotonin and dopamine receptors. At each level, we measured the alignment between the corresponding results and the Yeo networks, which facilitated comparisons between the phenomenology, neuroimaging, and pharmacology of each psychedelic.

Section 2.1. Phenomenology

For the ASC meta-analysis, our literature search identified n = 47 studies that met the inclusion criteria, including 5 studies on DMT (5D-ASC: n = 3; 11D-ASC: n = 3), 16 studies on LSD (5D-ASC: n = 10; 11D-ASC: n = 14), and 26 studies on psilocybin (5D-ASC: n = 13; 11D-ASC: n = 17). The eleven dimensions of the 11D-ASC are subscales of three dimensions in the 5D-ASC: oceanic boundlessness (OB), anxious ego dissolution (AED), and visionary restructuralisation (VR). Nevertheless, the 11D-ASC questionnaire contains fewer items than the 5D-ASC questionnaire, so 5D-ASC data cannot be directly compared to 11D-ASC data. Hence, we ran separate meta-analyses for the 5D-ASC and 11D-ASC data. In order to account for the measurement of multiple subjective dimensions, sometimes with more than one dose or drug, in

individual studies, we created multilevel random-effects models to perform the meta-analyses (Assink & Wibbelink, 2016; Harrer et al., 2021).

Pooled 5D-ASC scores for DMT, LSD, and psilocybin are shown in **Figure 1** (numerical data are given in **Table S1**). 5D-ASC scores were significantly greater for LSD than psilocybin in the VR (p = 0.0126) dimension, which measures the quality and intensity of visual hallucinations. This was the only significant difference that we found between any two drugs, for any of the dimensions. The fact that we did not detect any significant differences between DMT and the other drugs, despite its unique phenomenology, may be attributed to the small number of 5D-ASC studies (n = 3) on DMT.

Within-drug differences between the five subjective dimensions were quite similar. For all three of the psychedelics, VR ranked highest, followed by either OB or "reduction of vigilance" (RV), then AED, and finally "auditory alterations" (AA). A clear separation can be seen between two groups of subjective categories: (1) OB, VR, RV, and (2) AA and AED. VR scores were significantly higher than AED scores for all three drugs. RV scores were relatively higher for psilocybin than for LSD and DMT; compared to OB, RV scored lower for DMT and much lower for LSD, but intriguingly, RV scored slightly higher than OB for psilocybin.

The results of the 11D-ASC meta-analysis were similar to those of the 5D-ASC meta-analysis (**Figure S3**; **Table S2**). Note that we could not include DMT in the 11D-ASC meta-analysis because two of the three studies on DMT did not report standard errors, which are necessary for pooling the subjective data. LSD was associated with significantly higher scores than psilocybin in the "impaired control and cognition" and "complex imagery" dimensions. In agreement with the 5D-ASC meta-analysis, three of the VR subscales of the 11D-ASC – complex imagery, elementary imagery, and audio-visual synaesthesia – ranked significantly higher for LSD than all of the AED subscales – disembodiment, impaired control and cognition, and anxiety. However, for LSD, those VR subscales received significantly higher scores than all of the OB subscales as well, which was not an effect that we observed in the 5D-ASC analysis. Comparisons within the same subscale were generally insignificant for LSD, though "changed meaning of percepts" scored significantly lower than all other VR susbscales. On the other hand, psilocybin exhibited a much "flatter" rank-ordering; that is, fewer pairs of dimensions were significantly different from each other. While scores always increased with dose for LSD, they did not for psilocybin, unlike in the 5D analysis; "changed meaning of percepts", "audio-visual synaesthesia", and "insightfulness" peaked for medium (0.2-0.29 mg/kg) doses of psilocybin, and ratings of anxiety were smaller for medium than for low (0.1-0.19 mg/kg) and high doses (>0.3 mg/kg) of psilocybin.

We also performed meta-regressions to determine whether there were any methodological covariates that influenced the pooled 5D-ASC scores, but we did not find any significant confounders. Finally, we conducted sensitivity analyses by comparing the pooled 5D-ASC and 11D-ASC scores to studies that directly compared different psychedelics. Two studies administered both LSD and psilocybin to the same group of participants. Holze et al. (2022) gave a low (15 mg) and a high (30 mg) dose of psilocybin, as well as a medium (100 μg) and a high (200 μg) dose of LSD, and then compared both 5D- and 11D-ASC scores. In line with our results, they found that the high and medium dose of LSD were associated with larger mean 5D-ASC (11D-ASC) scores than the high and low dose of psilocybin, respectively, in all five (most of the eleven) dimensions. In the 5D-ASC case, the only differences that reached significance between LSD and psilocybin, when matched by dose, were in the OB and VR scales. In the 11D-ASC case, "complex imagery" and "audio-visual synaesthesia" scores were significantly different between LSD and psilocybin. In our meta-analysis, LSD and psilocybin were significant different in VR but not OB ratings, and in "complex imagery" but not "audio-

visual synaesthesia" ratings. Ley et al. (2023) compared the subjective effects of medium doses of LSD (100 μg) and psilocybin (20 mg), as well as two doses of mescaline, and their findings exhibited similar patterns to those of Holze et al. (2022). Therefore, the results of our meta-analysis are only somewhat supported by studies that conducted comparisons between psychedelics.

In order to directly compare the phenomenology of psychedelics to their neuroimaging and pharmacological profiles (*Section 2.2* and *Section 2.3*), we sought to determine the "phenomenology profiles" of DMT, LSD, and psilocybin based on the extent to which the Yeo networks encode the phenomenology of each psychedelic. We obtained the neural correlates of the subjective effects by conducting a literature search of studies that measured correlations between ASC ratings and fMRI activity. We determined the Yeo network that contained each brain region that exhibited a significant correlation, and then we averaged across the correlations associated with each Yeo network, resulting in the mean correlation between each Yeo network and each ASC scale. The phenomenology profiles were defined by a weighted combination of the mean correlations for each ASC scale, in which the weights were the pooled ASC ratings of each psychedelic for the corresponding scale.

Because there were few significant differences in the pooled ASC scores, the phenomenology profiles of the psychedelics look very similar (**Figure 2**). However, these profiles may not reflect the true neural correlates of the subjective effects of psychedelics. Many studies performed correlations between ASC ratings and brain regions that were active only in specific tasks, and the tasks varied strongly between tasks. Therefore, there is little consistency between the methods of these studies, and activity in certain Yeo networks may have correlated more with the ASC ratings if the studies had happened to choose different tasks. The ventral attention network (VAN) appears to be more strongly associated with the subjective effects than any of the other Yeo networks, but this result is likely a mere artifact of one study's decision to correlate the ASC ratings with a seed in the VAN. There need to be more studies that link fMRI activity to ASC ratings before we can estimate the phenomenology profiles with confidence.

Finally, we also aimed to relate the phenomenology of different psychedelics by qualitatively synthesising the findings of papers that directly compared the subjective experiences of DMT/ayahuasca, LSD, and psilocybin. *Section S3* contains a comprehensive summary of their major aims, analysis approaches and findings, with a specific focus on comparisons and contrasts drawn across the different psychedelics.

Section 2.2. Neuroimaging

As stated above, the fMRI studies on psychedelics measure three different characteristics of brain activity: BOLD activation, functional connectivity, and entropy. We used the GingerALE method to determine common clusters of BOLD activation across studies, quantified aggregate changes in FC between the Yeo networks under psychedelics, and conducted a qualitative review of the research on entropy. Note that we included studies on both ayahuasca and DMT in our neuroimaging meta-analyses.

Section 2.2.1. BOLD activation

We identified $n = 17$ studies on BOLD activation that fit our inclusion criteria. The method that we used, GingerALE, takes in a list of the coordinates of peak BOLD activity across all studies and computes clusters of voxels with statistically significant activation likelihood estimate (ALE) values, which correspond to the relative frequency with which that voxel is activated in the literature. Three of the studies did not report the

coordinates of peak BOLD activity, so we qualitatively review them in *Section S5*. We performed a GingerALE meta-analysis on the remaining $n = 14$ studies, as well as a separate GingerALE meta-analysis on the LSD dataset ($n = 7$) and on the psilocybin dataset ($n = 4$). There was not enough data to separately analyse the ayahuasca/DMT BOLD activation dataset, which only consisted of three studies, including one that did not report any significant results.

We found a significant cluster of activation for each of the three datasets (**Figure 3**). The meta-analysis of the LSD dataset produced a bi-hemispheric cluster in the frontal lobe, with local maxima or "peaks" of ALE scores in the left and right medial frontal gyrus and the left superior frontal gyrus (**Table S3**; **Figure 3a**). The cluster also spanned the right anterior cingulate cortex. However, the meta-analysis of the psilocybin dataset yielded a completely different set of neural correlates spanning the occipital lobe (one peak in the left fusiform gyrus and one in the right lingual gyrus) and the cerebellum (one in the anterior region and one in the posterior region) (**Table S4**; **Figure 3b**). Similarly, the meta-analysis of the entire dataset revealed a single cluster of BOLD activations in the right occipital lobe (four peaks in the middle occipital gyrus; two in the cuneus; and one in the inferior occipital gyrus), the anterior cerebellum, and the parahippocampal gyrus (**Table S5; Figure 3c**).

Figure 4 shows the result of performing network analysis on the GingerALE results, in which we computed the alignment between the Yeo networks and the spatial maps of significant ALE clusters for each of the three datasets. Consistent with the GingerALE results described above, we found very different profiles of BOLD activation for LSD and psilocybin. Psilocybin altered BOLD activation almost entirely in the visual network. On the other hand, LSD changed BOLD activation primarily in the DMN and to a lesser extent in the frontoparietal network (FPN), and not at all in the cerebellum. The pattern of networks affected by psilocybin strongly resembled that of the entire dataset, whose ALE clusters also overlapped primarily with the visual network. This suggests that the BOLD peaks in the psilocybin dataset are the principal contributors to the ALE clusters for the entire dataset. The GingerALE analysis confirms that the majority of the foci that contribute to these clusters are from three studies in the psilocybin dataset (Barrett, Doss, et al., 2020; Duerler et al., 2021; Kraehenmann, Schmidt, et al., 2015). The remainder are from DMT (Daumann et al., 2010) and ayahuasca (de Araujo et al., 2011) studies, and none are from studies on LSD.

However, these results are likely confounded by the tasks that happened to be used in the literature. Three of the four studies on psilocybin displayed visual stimuli to participants, so the clusters of activation in the visual cortex reflect coincidental commonalities in experimental procedures more than they reveal the genuine neural correlates of psilocybin.

Section 2.2.2. Functional connectivity

We identified $n = 34$ studies on connectivity under psychedelics. It is difficult to perform a meta-analysis on the FC literature since the studies tended not to use the same parcellation for defining regions of interest (ROIs); therefore, they did not measure connectivity between the same set of regions. Hence, to conduct a meta-analysis, we had to first impose the same parcellation on the published data. We selected the Yeo networks because they are coarse-grained; there are only seven for the entire cortex (Yeo et al., 2011).

Our meta-analysis method determines the pair of Yeo networks that contains each pair of functionally connected ROIs in the literature and then increments the aggregate FC between those Yeo networks. This method is capable of synthesising studies on pairwise FC, such as seed-to-seed, seed-to-voxel, and within- and between-network FC analyses using independent components analysis (ICA) (see **Table S7** for a

description of the inputs). The algorithm cannot accommodate data derived from global, structural metrics of connectivity such as global brain connectivity (GBC) or graph-theoretic modularity. Additionally, the algorithm does not capture any information about the direction of connectivity between regions; therefore, we did not incorporate studies of effective connectivity or directed FC. (However, the vast majority of FC studies measure undirected FC.)

Furthermore, a considerable bias arises from the fact that many FC studies are secondary analyses of the same primary dataset. For instance, the primary FC data from Carhart-Harris et al. (2016) was re-analysed at least seven times with different methods in subsequent studies. To mitigate bias, we only inputted the most informative analysis of each unique dataset into the meta-analysis algorithm, such that each dataset was only represented once in the meta-analysis. Our criteria for selecting the most informative analysis are described in *Section S2.2.2*.

In total, out of the 34 studies on connectivity identified in our literature search, we performed a quantitative meta-analysis on $n = 12$ studies. Eleven other studies were eligible to be assessed by our meta-analysis algorithm; we excluded eight of these from the quantitative analysis to reduce bias for the reasons mentioned above, and three others did not report a matrix or map of all the significant connections that were determined in their analyses. The algorithm was unable to synthesise data from 11 other studies because they did not measure pairwise FC. We performed a qualitative review (*Section S5.2*) on these 11 studies plus the aforementioned 11 studies that we had omitted from the quantitative meta-analysis.

As shown in **Figure 5a**, the quantitative meta-analysis produced a 7x7 aggregate FC matrix, in which each entry represents the overall FC between the corresponding pair of Yeo networks. Positive entries represent increases in FC under psychedelics, and negative entries correspond to decreases under psychedelics. We also tested the significance of our results by comparing them to a null distribution formed from resting-state fMRI data collected by the Human Connectome Project (HCP) (Van Essen et al., 2013). We calculated the FC between randomly selected windows of the HCP BOLD timeseries and identified pairs of significantly correlated ROIs. Then, we computed the alignment between these pairs of ROIs and the Yeo networks. We repeated this process 1,000 times, generating a histogram of aggregate FC matrices that effectively constituted a null distribution.

According to our analysis, psychedelics significantly strengthened between-network connectivity. The only two decreases in between-network connectivity, which took place between the limbic network & somatomotor network (SMN) and between the limbic network & VAN, were insignificant. Within-network connectivity decreased in all networks except for the frontoparietal network (FPN). However, all reductions in within-network FC were deemed insignificant, whereas the increase in within-network FC for the FPN surpassed the threshold for statistical significance. The decrease in within-network FC was disproportionately greater (by at least 10x) for the visual network than for all other networks.

We compared the FC profiles of each psychedelic by running our meta-analysis algorithm on the datasets for each individual psychedelic: ayahuasca/DMT (ayahuasca: $n = 2$; DMT: $n = 1$), LSD ($n = 3$), and psilocybin ($n = 6$). The aggregate FC matrix of each psychedelic is shown in **Figure S4**. FC profiles were derived from the "total FC" – the connectivity between each network and all other networks – which was obtained by summing the aggregate FC matrix of each psychedelic across rows (**Figure 6**). All three of the psychedelics lowered FC in the visual network and default mode network (DMN) and generally elevated between-network FC. Intriguingly, ayahuasca/DMT disproportionately augmented FC between two "transmodal" or associative networks (FPN and DMN) & the two "unimodal" or sensory networks (visual and SMN), while strongly reducing FC within and between the two sensory networks; all other changes in FC were much

smaller. LSD dramatically increased FC between the visual network and all other networks, as well as FC within the SMN. Psilocybin amplified FC between the visual network and DMN over an order of magnitude more than between any other pair of networks, but this result is confounded by the fact that the ROIs in the psilocybin literature did not overlap much with the other Yeo networks; hence, these ROIs were essentially excluded by our meta-analysis algorithm.

Using permutation tests, we tried to identify methodological covariates that were significantly associated with the results, but none of the covariates were found to be significant.

Section 2.2.3. Entropy and criticality

The n = 12 fMRI studies on entropy and criticality in the psychedelic literature are very heterogeneous, employing a wide variety of measures on dissimilar variables of interest. A quantitative meta-analysis was extremely challenging, so we opted instead to perform a qualitative review of this literature.

Because of the *Entropic Brain Hypothesis*, many studies in the psychedelic neuroimaging literature have examined the effects of psychedelics on entropy in the brain. The father of information theory, Claude Shannon, defined (Shannon) entropy as the *breadth* of possible outcomes for a random variable (Shannon, 1948). If only a single outcome ever occurs with a probability of 1, then Shannon entropy is minimised at zero. Otherwise, if a broad range of outcomes can occur, each with low probability, then Shannon entropy will increase. Thus, in neuroscience, greater (Shannon) entropy refers broadly to an increase in the range of possible neural configurations. However, each study in the psychedelic literature measures a different type of neural configuration. Some assess the variance of intra-network synchrony, whereas others consider the diversity of connections to clusters of brain nodes. Therefore, while most studies demonstrate an increase in Shannon entropy under psychedelics (Carhart-Harris et al., 2014; Luppi et al., 2023; Tagliazucchi et al., 2014; Viol et al., 2017, 2019), none of them are measuring changes in entropy *of the same variable*.

Shannon entropy is closely related to compressibility, which three of the other studies (Ruffini et al., 2023; Singleton et al., 2022; Varley et al., 2020) examine. Indeed, a fundamental theorem in information theory, the Source Coding Theorem, states that entropy is a lower bound on the length of the optimal code for compressing data into a given set of symbols (e.g. a binary code of 0s and 1s) (Shannon, 1948). In the psychedelic literature, compressibility is measured as Lempel-Ziv complexity (LZc), which converges to the entropy rate when normalised (Ziv & Lempel, 1978). LZc determines the minimum number of unique substrings that are needed in order to decompose a string (Lempel & Ziv, 1976; Ziv & Lempel, 1977, 1978). For instance, if the string in question is a binary series of zeros and ones, then the LZ algorithm will compute the "building blocks" of binary patterns (e.g. "00101" and "1011") that comprise the entire string. If the string is a repeating sequence (e.g. "010101…"), then LZc will be minimised, as the string can be constructed by writing the same substring (in this case, "01") over and over again. If the string is completely random (e.g. independent flips of a fair coin), then LZc will be maximised, as the set of substrings that make up the entire string is infinitely large. All three fMRI studies on compressibility conclude that psychedelics increase LZc (that being said, Varley et al. (2020) only find significant differences for LSD, but not for psilocybin). This result is consistent with the findings of MEG studies on LZc under psychedelics (Mediano et al., 2020; Schartner et al., 2017; Timmermann et al., 2019).

The last of the three categories of entropy measures is sample entropy (Lebedev et al., 2016). Given that two sequences (e.g. BOLD timeseries) of length m are separated by a distance of less than r (distance may be measured by Pearson correlation or some other metric), sample entropy quantifies the probability that the

sequences will still be less than *r* units apart when they are extended by one sample, i.e. when their lengths are increased to $m + 1$. Lebedev et al. (2016) found a distributed pattern of LSD-induced increases in sample entropy across both unimodal and transmodal cortices.

As discussed in *Section 3.2.3*, the Entropic Brain Hypothesis claims that increasing entropy brings the brain closer to criticality. Three studies (Atasoy et al., 2017; Lord et al., 2019; Ruffini et al., 2023) have measured the effect of psychedelics on criticality. However, the association between entropy and criticality is far from straightforward. Entropy and criticality are two different statistical phenomena; while entropy describes the amount of variability or disorder in a system, criticality refers to behaviour exhibited when the so-called "order parameter" of a system undergoes a discontinuous "phase transition" as some other ambient property is modulated (Hesse & Gross, 2014). For example, the order parameter of water is its density, which decreases sharply as the temperature of the water (the ambient property) increases beyond 100° C. This results in a transition between the liquid and the gaseous phases of water. The "critical point" of a system can be roughly described as the threshold between order and disorder, as it is characterised in the Entropic Brain Hypothesis, but in complex, non-equilibrium systems like the brain, states above the critical point may not always be more disordered. Canonical models of criticality in physics, such as the Ising model, describe equilibrium systems, in which all microstates of a system are equally likely in the absence of perturbations. However, in the brain, some microstates may intrinsically be more likely than others; for instance, it may be inherently more probable for a neuron to be active than to be quiescent (Beggs & Timme, 2012). This may consequently predispose the system towards macrostates of greater order even past the critical point. Nevertheless, Ruffini et al. (2023) fit fMRI data on psychedelics to an Ising model and found that the fitted model surprisingly resembled empirical data. Unlike the other two studies on criticality under psychedelics, Ruffini et al. (2023) showed that psychedelics bring the brain away from criticality, since in the sober state, the brain is already above the critical point according to their model.

Critical systems are also characterised by power-law scaling, in which the size, duration, and other parameters L of events k are related by the power law $L(k) \propto k^{-\beta}$, where β is a constant corresponding to the "critical exponent" of the system. To show that psychedelics push the brain towards criticality, one study in the literature (Atasoy et al., 2017) showed that psychedelics improve the goodness of fit of brain activity to a power-law relationship. Brain activity was defined here in a unique manner: the "harmonics" of the connectome, or patterns of oscillations determined by the topology of structural connections in the brain. However, the technique used by the study – linear regression – has been shown to yield inaccurate estimates of power-law distributions, which usually disobey the assumptions of linear regression (Clauset et al., 2009).

The third study on criticality (Lord et al., 2019) does not assess power-law relationships in the brain, but instead measures the metastability of brain activity. Metastability is closely related to criticality; it describes a system in which states are locally stable yet are vulnerable to perturbations, resulting in frequent transitions between states. In particular, a metastable system that fluctuates between states of synchronisation and desynchronisation is poised at criticality. These fluctuations are typically measured with the Kuramoto order parameter, which quantifies the degree of synchrony between the phases of oscillators (Shanahan, 2010). The higher the variance of the Kuramoto order parameter, the more metastable the brain will be, since the oscillating BOLD timeseries will more strongly vary between states of synchronisation and desynchronisation.

What can we take away from this review, given that the entropy measures are so different? We argue that the aspect of the data that entropy is computed on – that is, the variable of interest – matters just as much

as, if not more than, the measure of entropy that is used. No two studies in the literature estimated Shannon entropy on the same random variable, which ranged from graph-theoretic properties to the variance of intra-network synchrony. Similarly, none of the studies computed criticality on the same property of brain activity/structure. In this literature, the results were always consistent – psychedelics increased entropy – despite the huge variation in the variable of interest. However, the statement that psychedelics increase entropy does not specify very much, as it does not indicate *which* feature of brain activity is undergoing these changes.

Section 2.3. Pharmacology

We performed two separate meta-analyses on the pharmacology of psychedelics. The first assessed the binding affinity (measured as K_i) of DMT, LSD, and psilocin for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_6, D_1, and D_2 receptors. We selected these receptors because there were available PET maps of them from a recent, state-of-the-art atlas of receptor profiles, which was created from data of thousands of human participants (Hansen et al., 2022). We also produced "pharmacology profiles" of each psychedelic, which represented the binding affinity of each psychedelic to neuronal receptors in each Yeo network. The second meta-analysis examined the GPCR-mediated functional activity (measured as EC_{50}) of DMT, LSD, and psilocin at the same six receptors.

Section 2.3.1. Affinity

We first present our meta-analysis of the binding affinity (K_i) values. Broadly speaking, affinity can be measured with at least two types of experiments: saturation experiments and competition experiments (Sykes et al., 2019). In saturation experiments, a radioactive label is attached to the drug of interest (for instance, radiolabeling LSD yields [^{3}H]-LSD) (Diab et al., 1971). Increasing concentrations of the radiolabeled drug are added while the concentration of the receptor of interest remains constant, and then the concentration of bound and free ligand are measured. The equilibrium dissociation constant (K_d) is the concentration of drug that is needed to bind to half of the receptors. On the other hand, in competition experiments, the drug of interest is not radiolabeled but instead competes with a different radiolabeled ligand that has a known K_d. The experimenter measures the concentration of drug at which it inhibits half of the binding of the radiolabeled ligand. This concentration is then converted into a K_i value.

We chose to conduct a meta-analysis on only the K_i data rather than the K_d data because, as far as we are aware, radioactive labels have only been attached to LSD in studies of binding affinity, but not to DMT or psilocin (the chemical that psilocybin gets metabolised into). Thus, there is disproportionately more K_d data on LSD than DMT and psilocin. However, we were able to find ample K_i data on DMT and psilocin.

To perform the meta-analysis, we constructed separate random-effects models for each psychedelic (DMT, LSD, and psilocin), each receptor, and each species (human and rat). In the main text, we report the results for the meta-analysis on human data, for which there were $n = 31$ studies (DMT: $n = 9$; LSD: $n = 23$; psilocin: $n = 8$). (Results of the meta-analysis on rat data, for which there were $n = 47$ studies, are shown in **Table S9**.) While we had hoped to include all drugs and receptors in a single model, the difference in variance between the affinities of LSD and the affinities of psilocin and DMT was so large that the results were highly unstable. Because we modeled each drug-receptor pair separately, we were unable to assess significant differences between drugs and between receptors.

It is worth noting that some receptors are much more extensively researched than others. For instance, there are only two studies about the affinity of LSD for 5-HT_6 in humans, whereas there are 20 studies about the affinity of LSD for 5-HT_{2A} in humans. We always performed a meta-analysis whenever there were at least three studies on the affinity or activity of a psychedelic for a particular receptor in a particular species; if there were only two studies, we proceeded with the meta-analysis so long as the two data points did not differ by at least one order of magnitude. If there was only one study, which was the case for several pairs of receptors and psychedelics (see the caption for **Figure 7**), we reported the data published in that study as opposed to the pooled value estimated by the model.

Pooled K_i values for human receptors are displayed in **Figure 7** (numerical data are given in **Table S8**). Note that K_i is inversely associated with affinity; the higher the K_i, the lower the affinity. LSD has at least one order of magnitude higher affinity for all the receptors than psilocin and DMT (**Figure 7a**). In particular, LSD binds with about 25-170 times higher affinity to dopamine receptors than psilocin and DMT; this result aligns with other reviews that have stated that LSD has some affinity for dopamine receptors, whereas DMT and psilocin do not (de Vos et al., 2021).

We also found large within-drug differences between receptors. Each of the psychedelics binds with one order of magnitude greater affinity to serotonin than dopamine receptors (**Figure 7b**). Differences within the serotonin receptors – in particular between 5-HT_{1A} and 5-HT_{2A}, two key drivers of psychedelic effects – were much smaller.

We ran further meta-regressions to determine whether any methodological covariates were significantly associated with the results. One radioligand ([^{3}H]-INB) and the choice of centrifugation or filtration for terminating the binding assay significantly influenced the reported affinity of LSD for 5-HT_{2A}. However, none of the methodological covariates for the affinity of other drug-receptor pairs met the threshold for statistical significance.

Finally, we performed sensitivity analyses to ensure that our results were consistent with studies that compared binding affinities across drugs. There were four studies in human receptors that measured affinities of at least two psychedelics (out of the three psychedelics of interest) for 5-HT_{1A} (Eshleman et al., 2014; Janowsky et al., 2014; Kozell et al., 2023; Pierce & Peroutka, 1989) and seven studies that did so for 5-HT_{2A} (Braden et al., 2006; Braden & Nichols, 2007; Eshleman et al., 2014; Janowsky et al., 2014; Kozell et al., 2023; Pierce & Peroutka, 1989; Sadzot et al., 1989). In line with our findings, all comparative studies on 5-HT_{1A} and 5-HT_{2A} found that DMT had much lower affinity than LSD for both receptors. One study showed that psilocin had lower affinity than DMT and LSD for 5-HT_{1A} (Kozell et al., 2023), which did not agree with our results; that being said, the standard error of the pooled affinity of psilocin for 5-HT_{1A} is very large. Two studies found that LSD > psilocin > DMT in affinity for 5-HT_{2A} (Braden & Nichols, 2007; Kozell et al., 2023), which was congruent with our results. Finally, our results were also consistent with the aggregate rank-ordering of affinities in studies that compared K_i within drugs, across receptors (DMT affinity: 5-HT_{1B} > 5-HT_{2A} > 5-HT_{1A}; LSD affinity: 5-HT_{1A} ≈ 5-HT_{2A} > 5-HT_6 > D_2 > D_1; psilocin affinity: 5-HT_{2A} > 5-HT_{1A} > D_2).

To relate the binding affinities to the neuroimaging and phenomenology of psychedelics, we first determined the expression of the six receptors in the Yeo networks. We derived this from Hansen et al. (2022), who averaged human PET data of the six receptors. Then, we defined the "phenomenology profile" as the weighted combination of the expression patterns, in which the weights were the inverse K_i of each psychedelic for the corresponding receptor (**Figure 8**). Because the pooled K_i values were orders of magnitude lower, i.e. affinity was much higher, for LSD than for DMT and psilocin, LSD's pharmacology

profile is much "higher." LSD's profile was "largest" in the SMN, VAN, DAN, and FPN, reflecting the high expression of 5-HT_{2A} and 5-HT_{1A} in those networks and the high affinity of LSD for those two receptors.

Section 2.3.2. Functional activity

Binding affinity is only one facet of the pharmacology of psychedelics. Another key aspect is their functional activity: the responses that they elicit in receptors after binding to them. While there are many ways to measure functional activity, we focused on GPCR signaling, as the signaling pathways that are uniquely modulated by psychedelics may explain why these substances induce hallucinations whereas drugs with equal affinity for the 5-HT_{2A} receptor do not (Gonzalez-Maeso & Sealfon, 2009; López-Giménez & González-Maeso, 2018).

5-HT_2 receptors (of which 5-HT_{2A} is one subtype) couple preferentially to a family of G proteins known as $G\alpha_{q/11}$, which activates the enzyme phospholipase C (PLC). This enzyme then catalyses the synthesis of the secondary messenger inositol triphosphate (IP_3, a species of inositol phosphate [IP]) , which subsequently leads to the release or "mobilisation" of calcium from the endoplasmic reticulum (López-Giménez & González-Maeso, 2018). β-arrestin proteins dampen G protein signaling by blocking the interaction between G proteins and the GPCR and removing the GPCR from the cell membrane, while also coupling GPCRs to signaling proteins without activating G proteins; thus, β-arrestin promotes alternative signaling pathways (Bohn & Schmid, 2010). Thus, functional GPCR assays on psychedelics have tended to focus on the three aspects of GPCR signaling described above: (1) IP formation, (2) calcium mobilisation, and (3) β-arrestin (specifically β-arrestin2) recruitment.

In total, our literature search identified n = 47 studies on functional activity at the six receptors whose affinities we analysed in *Section 2.3.1*. While we found studies on many types of assays in our literature search, the three GPCR assays mentioned above were the only ones that were performed at least once for each of the three psychedelics. Furthermore, these three assays were consistently conducted on the human 5-HT_{2A} receptor rather than the other receptors. Therefore, for the human data, we only performed a meta-analysis on studies of functional activity at the 5-HT_{2A} receptor, as measured by the above three assays. There were n = 26 such studies (DMT: n = 8; LSD: n = 20; psilocin: n = 6). For rat receptors, there was only enough data to run meta-analyses on IP formation assays of LSD at the 5-HT_{2A} receptor (n = 6 studies) and on cyclic AMP accumulation assays of LSD at the 5-HT_6 receptor (n = 4 studies). We report the results of the meta-analyses on rat data in **Table S11**.

We used random-effects models to perform our meta-analyses (results for human receptors shown in **Figure 9**; numerical data given in **Table S10**). Functional activity is measured as EC_{50}, which refers to the effective concentration of each psychedelic that is needed to induce 50% of the maximal functional response at the receptor. (Note that EC_{50} inversely corresponds to functional activity.) We performed meta-regressions to determine significant differences between drugs, as well as significant within-drug differences between assays. Between-drug comparisons showed that DMT elicited significantly less IP formation at the human 5-HT_{2A} receptor than psilocin and LSD. No significant differences between LSD and psilocin were found for any of the assays. Additionally, within-drug comparisons demonstrated that DMT induced significantly less IP formation than calcium mobilisation and β-arrestin2 recruitment. None of the methodological covariates that we identified *a priori* were significantly associated with the pooled EC_{50} values.

Finally, sensitivity analyses showed that the pooled functional activity in IP formation assays was consistent with the rank-ordering of functional activity in the four studies that directly compared IP

formation between drugs: LSD > psilocin > DMT (Braden & Nichols, 2007; Eshleman et al., 2014; Janowsky et al., 2014; Kozell et al., 2023). One study measured β-arrestin2 recruitment by both DMT and LSD and found, in agreement with our results, that the functional activity of DMT was multiple orders of magnitude lower than that of LSD (Pottie et al., 2020). However, our results were at odds with two studies that compared calcium mobilisation between psychedelics (Flanagan et al., 2021; Rickli et al., 2016).

Section 3. Discussion

Here we examine the effects of psychedelics at three levels: 1) the interaction of psychedelics with serotonin and dopamine receptors, in terms of both binding affinity and functional activity (pharmacology), 2) whole-brain activity, measured with fMRI as BOLD activation and functional connectivity (neuroimaging), and finally, 3) the subjective experience of the psychedelic trip (phenomenology). At each level, we performed a quantitative meta-analysis and computed the alignment between the results and the seven resting-state Yeo networks. The latter network analysis enabled us to directly compare the effects of three psychedelics – ayahuasca/DMT, LSD, and psilocybin – within and between levels.

Section 3.1. Unifying the levels of the hierarchy

For pharmacology, we conducted two meta-analyses: one of binding affinity and another of functional GPCR-mediated activity in assays of β-arrestin2 recruitment, calcium mobilisation, and IP formation. Our meta-analysis of affinity spanned six different serotonin and dopamine receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_6, D_1, and D_2). While our literature search on functional activity focused on the same receptors, we only presented the results for our meta-analysis on studies of 5-HT_{2A}, as there were too few studies of other receptors. LSD exhibited much higher affinity than DMT and psilocin for all receptors. Additionally, within-drug comparisons demonstrated that LSD and psilocin bind with higher affinity to 5-HT_{2A} and 5-HT_{1A} than all other receptors. (We may have observed the same result with DMT had there been more studies on the other serotonin receptors.) With regards to functional activity, LSD and psilocin induced significantly more IP formation than DMT, and within-drug comparisons showed that DMT elicited significantly less IP formation than β-arrestin2 recruitment and calcium mobilisation.

The whole-brain neuroimaging data consisted of three subsets of data: entropy, functional connectivity (FC), and BOLD activation. We did not conduct a meta-analysis of the entropy literature due to the heterogeneity of methods and instead opted for a qualitative review. To perform a meta-analysis on FC data, we essentially re-parcellated the published data into the Yeo networks and then calculated a weighted sum of the connections between Yeo networks. LSD strongly elevated FC between the visual network and the other networks, whereas ayahuasca/DMT increased FC most between transmodal networks (specifically, the FPN and DMN) and unimodal networks (i.e. SMN and visual). Our GingerALE meta-analysis of BOLD activation data showed that psilocybin and LSD alter activity in very different regions of cortex, but these results are likely spurious as they are strongly confounded by the different tasks that were performed in the psilocybin and LSD studies (see *Section 3.3*).

Finally, for the phenomenology literature, we conducted a meta-analysis of both the 5-dimensional and 11-dimensional versions of the Altered States of Consciousness (ASC) scale, a commonly-used questionnaire for measuring changes in subjective experience on psychedelics. LSD ranked significantly higher than psilocybin in "visionary restructuralisation," a dimension capturing the quality and intensity of visual hallucinations. It is surprising that we did not find any significant differences between DMT and the other

psychedelics, given that the phenomenology of DMT has many unique features, such as the "breakthrough" experience (John, 2018). This may be a byproduct of the small number of studies on 5D-ASC ratings of DMT (n = 3), or it may reveal that the ASC scale is insufficient for capturing the distinctive aspects of DMT phenomenology.

Directly comparing the pharmacology, neuroimaging, and phenomenology profiles of psychedelics (**Figure 10**) reveals a weak one-to-one relationship between the three levels of the hierarchy, which is unsurprising given the highly non-linear, complex, and reciprocal (Kringelbach et al., 2020) interactions between them. However, the results of the meta-analyses at each level may reveal some insights into the nature of these interactions.

On a superficial level, there do appear to be some direct correspondences between the phenomenology, neuroimaging, and pharmacology. Phenomenologically, we only found one significant difference between psychedelics: visionary restructuralisation was rated more highly for LSD than for psilocybin. Neurobiologically, LSD disproportionately enhanced connectivity between the visual network & all other networks, while very strongly reducing connectivity within the visual network. LSD's effect on FC between other networks was much weaker. While psilocybin dramatically increased FC between the visual network & DMN, its effect on FC between the visual network and other networks was much more muted; that being said, this result is confounded by the fact that it was difficult to assign individual Yeo networks to ROIs in the psilocybin literature, which tended to overlap with multiple networks.

Pharmacologically, LSD displays much higher affinity (by one to two orders of magnitude) for dopamine receptors than DMT and psilocin do. While the role of dopamine in the visual hallucinations induced by LSD has not yet been elucidated, the effect of dopamine on visual hallucinations in neurological diseases like Parkinson's and dementia with Lewy bodies (DLB), as well as in neuropsychiatric disorders like schizophrenia, has been researched more extensively; furthermore, the phenomenology of hallucinations in these disorders may be similar to that of psychedelics (Russo et al., 2019). It is well-established that schizophrenia induces hallucinations, albeit primarily auditory rather than visual, through dopaminergic pathways (Kuepper et al., 2012), and dopamine agonists for managing symptoms of Parkinson's produce visual hallucinations as side effects (Burghaus et al., 2012). However, treatment with antipsychotics that antagonise dopamine can alleviate visual hallucinations, although atypical antipsychotics that inhibit serotonin to a greater extent may be more effective at mitigating hallucinations (Sommer et al., 2012). DLB patients also exhibit greater binding of dopamine in thalamic nuclei (Piggott et al., 2007), and evidence from dopaminergic treatments in Parkinson's patients suggests that increased dopamine levels may reduce DMN activity (Krajcovicova et al., 2012). Taken together, these lines of evidence support a recent model of visual hallucinations in Parkinson's and DLB, in which hyperactivity of the thalamus upsets the balance between the DMN and the task-positive network (TPN, which includes the DAN and VAN) (Onofrj et al., 2019). Typically, the DMN and the TPN are anti-correlated (Fox et al., 2005); the TPN is engaged in maintaining and orienting attention to stimuli in the external environment, while the DMN updates the prior beliefs that inform the interpretation of those stimuli. In line with the RElaxed Beliefs Under pSychedelics (REBUS) hypothesis, which is discussed in *Section 3.2.3*, aberrant coupling between the DMN and TPN disrupts the normal process by which priors are updated on the basis of new information from the environment, resulting in hallucinations (Russo et al., 2019).

The research on hallucinations in Parkinson's, DLB, and schizophrenia (1) highlights the potential role of dopamine in augmenting the visual hallucinations elicited by LSD and (2) dovetails well with the findings from our FC meta-analysis. Psychedelics strongly increase FC between the DMN & VAN, a key node of the

TPN; thus, our meta-analysis indicates, in line with the literature (Carhart-Harris et al., 2013), that psychedelics reduce the anti-correlations between the DMN & TPN. Additionally, our meta-analysis found that psychedelics enhance FC between the thalamus & all cortical networks (results not shown). Intriguingly, ayahuasca/DMT apparently elevates FC between the DMN & VAN much more than LSD does, yet according to our meta-analysis, its hallucinations are less intense than those of LSD. However, as mentioned above, this finding may not hold true as more studies are conducted and different scales are used to assess the subjective effects of DMT.

While LSD does display moderate affinity for dopamine receptors, the 5-HT_{2A} receptor plays a much more essential role in the hallucinogenic effects of not only LSD but also all other psychedelics. Blocking the receptor with a 5-HT_{2A} antagonist such as ketanserin has repeatedly been shown to attenuate or abolish the subjective experience in humans (Becker et al., 2023; Preller et al., 2017; Preller, Burt, et al., 2018; Vollenweider et al., 1998). In our meta-analysis, we find that LSD and psilocin bind with higher affinity to 5-HT_{2A} than to any of the other receptors we examined (the fact that we do not also find this for DMT may be attributable to the small number of studies). However, affinity for 5-HT_{2A} is not a sufficient condition for hallucinations. Lisuride, ergotamine, and other chemicals are 5-HT_{2A} agonists, but they do not induce psychedelic-type effects (González-Maeso et al., 2007).

The phenomenon of "biased agonism" may explain why only some 5-HT_{2A} agonists, i.e. psychedelics, result in profoundly altered states of consciousness. Biased agonists preferentially induce specific changes in the conformation of the receptors that they bind, whereas so-called "balanced" agonists are not selective for certain conformations (Hodavance et al., 2016). Once activated by a biased agonist, these particular conformations trigger a specific subset of downstream signaling pathways, thereby preventing alternative pathways from operating. It has been hypothesised that the hallucinogenic effects of psychedelics arise from their biased agonism at the 5-HT_{2A} receptor (Pottie et al., 2020). Like almost all other serotonin receptors, 5-HT_{2A} is a G-protein coupled receptor (GPCR), which canonically signals through G proteins; however, GPCRs also interact with another class of proteins, β-arrestin2, which not only desensitise GPCRs but also promote alternative signaling pathways that operate independently of G proteins (Jean-Charles et al., 2017). While psilocin is a balanced agonist with respect to β-arrestin2, LSD appears to preferentially recruit β-arrestin2 over G-protein signaling pathways (Schmitz & Roth, 2023). Furthermore, LSD does not appear to induce psychedelic-type behaviour, e.g. head twitches, in mice that do not have the gene for the β-arrestin2 gene (Rodriguiz et al., 2021). In our meta-analysis, we did not find any significant differences between β-arrestin2 recruitment and G-protein signaling (as measured by calcium mobilisation and IP formation) induced by LSD. Therefore, LSD does not appear to have biased agonism with respect to β-arrestin2. However, the small number studies on calcium mobilisation, together with the fact that the data reported by these studies spanned two orders of magnitude, may have prevented us from detecting significant differences. More research is needed to confirm whether LSD exhibits biased agonism.

In addition to β-arrestin2, psychedelics engage canonical G-protein signaling pathways. There are four families of G proteins – $G\alpha_q$, $G\alpha_s$, $G\alpha_{i/o}$, and $G\alpha_{12/13}$ – each of which initiates different signaling pathways. Different receptors are coupled to different G proteins and consequently to different signaling pathways. For instance, all the 5-HT_2 receptors are coupled to $G\alpha_q$, which eventually leads to IP formation and intracellular calcium mobilisation (Boczek et al., 2021). In our meta-analysis, we quantified the effects of psychedelics on not only β-arrestin2 recruitment but also IP formation and intracellular calcium mobilisation, which measure $G\alpha_q$ signaling by proxy. We found that calcium mobilisation was similar among all three psychedelics, but that DMT was significantly less active in IP assays than LSD and psilocin. IP formation is

a more immediate effect, and therefore perhaps a better indicator, of $G\alpha_q$ activation than calcium mobilisation. DMT's low activity in assays of $G\alpha_q$ signaling and β-arrestin2 recruitment may suggest that it elicits a third signaling pathway. Indeed, unlike the other psychedelics, DMT may bind to the sigma-1 receptor (Fontanilla et al., 2009; Szabo et al., 2016). This receptor is not a GPCR (Mercier et al., 2017), and there is limited evidence on its ability to recruit β-arrestin2 (Moreno et al., 2014).

While recent research has shown that a threshold level of $G\alpha_q$ is necessary for 5-HT_{2A} agonists to bring about hallucinogenic effects (Wallach et al., 2023), $G\alpha_q$ signaling may not be the only G-protein mechanism that mediates the hallucinations induced by psychedelics, as removing $G\alpha_q$ signaling in mice does not strongly reduce the behavioural effects of psychedelics (Garcia et al., 2007). Furthermore, DMT causes hallucinations even though it is less potent at activating $G\alpha_q$ signaling than the other psychedelics. Which other G-protein signaling pathways help to trigger hallucinations for both DMT and the other psychedelics? Like LSD, DMT binds to 5-HT_{1A} with roughly the same affinity that it agonises 5-HT_{2A}, as shown in our meta-analysis (psilocin has moderate affinity for 5-HT_{1A}, though its pooled K_i for 5-HT_{1A} is one order of magnitude higher than its pooled K_i for 5-HT_{2A}). Unlike 5-HT_{2A}, 5-HT_{1A} interacts with the $G\alpha_{i/o}$ family of G-proteins, which inhibit adenylyl cyclase and thereby decrease the conversion of ATP into cyclic AMP (Boczek et al., 2021). Thus, GPCR signaling at the 5-HT_{1A} receptor is inhibitory, whereas it is excitatory at the 5-HT_{2A} receptor. Furthermore, while both hallucinogenic and non-hallucinogenic 5-HT_{2A} agonists signal through the $G\alpha_q$ pathway, only the hallucinogenic agonists activate $G\alpha_{i/o}$ proteins as well (González-Maeso et al., 2007). While $G\alpha_{i/o}$ signaling by hallucinogens appears to be mediated by the 5-HT_{2A} receptor than the 5-HT_{1A} receptor, it is possible that 5-HT_{1A} plays a modulatory role in the hallucinogenic effects of psychedelics via $G\alpha_{i/o}$ signaling. In humans, the 5-HT_{1A} agonist buspirone reduces scores in the "oceanic boundlessness" and "visionary restructuralisation" dimensions of the 5D-ASC scale when co-administered with psilocybin, perhaps by competing with psilocybin for 5-HT_{1A} receptors (Pokorny et al., 2016). In mice, 5-HT_{1A} agonism mediates the behavioural effects of both 5-MeO-DMT and psilocybin (Halberstadt et al., 2011).

In summary, LSD's moderate agonism for dopamine receptors may be one mechanism that accounts for its enhanced visual hallucinations. However, while research has been conducted on the role of dopamine in visual hallucinations triggered by schizophrenia, Parkinson's, and DLB, more research is needed to elucidate the relationship between dopamine and LSD-induced hallucinations. The meta-analysis may also shed some light on the cellular signaling pathways that underlie the hallucinogenic properties of psychedelics. While we did not find evidence for biased agonism (with respect to β-arrestin2 recruitment) in any of three psychedelics, the shared affinity of psilocin and especially LSD and DMT for 5-HT_{1A} underscores the potential role of $G\alpha_{i/o}$ signaling in the hallucinogenic properties of these substances.

Section 3.2. Relating the results of the meta-analysis to the neuroimaging literature

Does the meta-analysis support or challenge the prevailing theories about the neuroscience of psychedelics? In this section, we answer this question by focusing on three major themes in the literature: the findings that psychedelics decrease activity and connectivity within the default mode network, that they disintegrate and desegregate brain networks, and that they relax the weighting of priors in the predictive coding hierarchy of the brain (REBUS).

Section 3.2.1. Psychedelics and the default mode network

One major finding in the literature, which has been consistently highlighted in review papers (Artin et al., 2021; DiVito & Leger, 2020; Fox et al., 2018; Nichols, 2016) and in the popular press (Pollan, 2018), is that psychedelics decrease activity and connectivity within the default mode network (DMN), a region that is generally implicated in self-awareness, self-reflection, and other self-referential cognitive processes (Davey et al., 2016; Davey & Harrison, 2018; Molnar-Szakacs & Uddin, 2013; Moran et al., 2013). This popular 'meme' likely has its origin in the first resting-state fMRI study of a psychedelic, where decreased blood flow, BOLD signal and altered FC were observed in a pattern of regions resembling the DMN (Carhart-Harris et al., 2012). Eleven years later, evidence continues to indicate that psychedelics potently affect the regularity of population brain activity in DMN regions (Timmermann et al., 2023). Since a commonly reported experience on psychedelics is the dissolution of the self, a phenomenon known as "ego death" (Moreton et al., 2020; Nour et al., 2016; Pahnke, 1969b), it would superficially make sense that psychedelics dysregulate the DMN. Many studies have found significant correlations between subjective ratings of ego dissolution and DMN disintegration (Atasoy et al., 2017; Barrett, Krimmel, et al., 2020; Luppi et al., 2021; Madsen et al., 2021; Palhano-Fontes et al., 2015; Pasquini et al., 2020; Roseman et al., 2014; Smigielski et al., 2019; Tagliazucchi et al., 2014, 2016), though other analyses did not find evidence for a relationship between the two (Lebedev et al., 2015; Müller, Dolder, et al., 2018).

However, claims of "de-activation" or worse, "shutting-off" of the DMN as signatures of psychedelic action are wrong and misleading. Other neuroimaging studies by Carhart-Harris et al. (2012, 2013, 2016) and Roseman et al. (2014) discovered that psychedelics affect the *connectivity* of the DMN, decreasing within-DMN FC ("disintegration") while increasing DMN coupling with other resting-state networks (RSNs) ("desegregation"). While these latter findings about RSN disintegration and desegregation have been replicated across time, DMN-specific deactivation has not, and the initial focus on the DMN now seems unjustified. In more recent work by Carhart-Harris and colleagues, greater emphasis has been placed on the dysregulation of spontaneous activity across the high-level transmodal cortex, of which the DMN is a part (Girn et al., 2023; Timmermann et al., 2023).

When we initially looked at the pairwise FC matrices from the studies that we included in the meta-analysis, we were surprised to find that the increases in within-DMN FC outnumbered the decreases. This result was mostly driven by three studies that performed whole-brain seed-to-seed FC analyses (Bedford et al., 2023; Dai et al., 2023; Timmermann et al., 2023). However, we subsequently discovered that many of the regions in these studies overlapped with other Yeo networks besides the DMN. When we excluded regions that overlapped less than ~65% with any single Yeo network, we confirmed that all three of the psychedelics decrease connectivity within the DMN.

While the literature shows evidence of a correlation between the disintegration of the DMN and the subjective effects of psychedelics, a causal relationship has not yet been established. (However, inspired by psychedelic research, a recent study discovered that ultrasound stimulation of the PCC, a key hub of the DMN, enhanced ego dissolution in experienced meditators (Sanguinetti et al,. forthcoming)). Several other drugs such as amphetamines and alcohol, as well as drug addiction in general, reduce within-DMN connectivity in humans (Schrantee et al., 2016; Weber et al., 2014; Zhang & Volkow, 2019), even though they typically do not lead to ego dissolution (Doss et al., 2020). These results illustrate that there may not be a simple one-to-one correspondence between the within-network connectivity of the DMN and ego integrity. Certain psychological states that exacerbate self-rumination, such as maladaptive self-focused attention, are *not* associated with hyperconnectivity in the DMN (Fang et al., 2022), and one study found that some tasks

requiring self-related judgments were associated with a *suppression* of within-DMN connectivity (van Buuren et al., 2010). That being said, a recent meta-analysis of 14 studies did endorse an association between rumination and the DMN (Zhou et al., 2020).

Section 3.2.2. Desegregation and disintegration under psychedelics

As discussed above, segregation is a term used to define the FC *between* brain regions; lower segregation (or greater desegregation) refers to greater FC between networks. Integration, on the other hand, denotes functional connectivity *within* a network. Carhart-Harris et al. (2016) found that LSD led to disintegration and desegregation not only for the DMN, as described above, but also for most of the RSNs that they examined. This finding has been independently confirmed in several other studies (Barrett, Doss, et al., 2020; Dai et al., 2023; Girn et al., 2022; Lebedev et al., 2015; Madsen et al., 2021; Müller, Dolder, et al., 2018; Roseman et al., 2014). In a review of three studies (Carhart-Harris et al., 2016; Müller, Dolder, et al., 2018; Roseman et al., 2014), Müller, Liechti, et al. (2018) found good convergence in reports of desegregation.

Our meta-analysis corroborates the desegregation and disintegration hypothesis. FC significantly increased between all non-identical pairs of brain networks; the two decreases (limbic & SMN, limbic & VAN) were both deemed insignificant. Within-network FC decreased for all networks except for the FPN. However, all reductions in within-network FC were insignificant. In this meta-analysis, we determined statistical significance by comparing the psychedelic literature to resting-state FC data collected by the Human Connectome Project in sober human participants. However, the HCP data does not reflect the heterogeneity of analysis methods in the psychedelic literature. Whereas we used a whole-brain seed-to-seed FC analysis of the HCP data, many of the studies in the psychedelic literature isolated specific seeds rather than examining the entire brain. Additionally, we applied a single parcellation (DK-80) to the HCP data, whereas multiple parcellations were used in the psychedelic literature. Thus, the insignificant result may reflect inconsistencies between our methods and the literature. Nevertheless, it does raise the intriguing possibility that reductions in within-network FC can sometimes be greater in sober resting-state than on psychedelics.

As with the relationship between within-DMN connectivity and the phenomenology of psychedelics, there is a correlation between desegregation/disintegration and ego dissolution (Tagliazucchi et al., 2016), but there is no evidence for a *causal* link. There appear to be parallels between the conscious experience of interconnectedness and the "interconnectedness" of the brain on psychedelics, but further research is needed to demonstrate that the connection between the two is more than merely semantic.

Section 3.2.3. Entropic Brain Theory and Relaxed Beliefs Under Psychedelics

Much of the psychedelic neuroimaging research has been guided by the Entropic Brain Hypothesis (Carhart-Harris et al., 2014; Carhart-Harris, 2018), which proposed that the subjective effects of psychedelics, such as ego dissolution, are associated with increased levels of entropy in the brain. In our qualitative review of the literature on entropy under psychedelics, we found not only that measures of entropy were very different, but also that studies varied strongly in the *aspect of the data* that they measured. No two studies in the literature estimated Shannon entropy on the same random variable, which ranged from graph-theoretic properties to the variance of intra-network synchrony. In this literature, the results were always consistent – psychedelics increased entropy – despite the huge variation in the aspect of the data that was measured. However, the

statement that psychedelics increase entropy does not specify very much, as it does not indicate *which* feature of brain activity is undergoing these changes.

A subsequent theory called Relaxed Beliefs Under Psychedelics (REBUS) integrated EBH with the Bayesian brain hypothesis (Carhart-Harris & Friston, 2019). Broadly speaking, the Bayesian brain framework states that the brain generates models that make top-down predictions about the world based on certain priors (or "assumptions"). When those predictions are proven wrong by bottom-up information from the environment, the model updates its priors (Holmes & Nolte, 2019; Knill & Pouget, 2004; Seth & Friston, 2016). REBUS hypothesises that psychedelics relax the precision weighting of the priors, or, in other words, the confidence in the accuracy of the assumptions that shape the model. In other words, psychedelics loosen the suppressive influence of top-down predictions on the processing of bottom-up sensory information, such that strongly held beliefs will exert less control over the interpretation of "sense-data" from the environment. A similar idea called "neural annealing" compares psychedelics to metallurgy; in the same way that heating and then cooling down a metal enables it to recrystallise into new patterns, psychedelics also energise the brain in such a way that it can subsequently self-organise into new equilibria (Gómez-Emilsson, 2021; Johnson, 2019). Under REBUS, these new equilibria would correspond to novel beliefs.

EBH and REBUS make several concrete predictions about the effects of psychedelics on the brain, including some that can be tested with fMRI. Hypothesis **(1):** Psychedelics push neural systems closer to their "critical point," which is the border between ordered and disordered regimes (Carhart-Harris et al., 2014). Hypothesis **(2):** Psychedelics flatten the functional hierarchy of the brain by increasing bottom-up and decreasing top-down information flow (Carhart-Harris & Friston, 2019). (There are other hypotheses concerned with changes in connectivity within and between resting-state networks, but we already addressed these in previous sections.)

In our review of the entropy literature, we found support for some, but not all, of these hypotheses. Regarding hypothesis (1), two studies (Atasoy et al., 2017; Lord et al., 2019) showed that psychedelics enhanced criticality in the brain. However, they each tested different signatures of criticality. One of them, power-law scaling, is not a sufficient condition for criticality (Beggs & Timme, 2012); there are many ways to produce power-law distributions through an underlying process that does not exhibit criticality, such as multiplicative noise (Sornette, 1998). However, findings of elevated metastability under psychedelics may provide stronger evidence for the claim that these drugs bring the brain closer to criticality. Lord et al. (2019) found that psilocybin increases the standard deviation of the Kuramoto order parameter, which quantifies the degree of synchrony between the phases of regional BOLD timeseries. In other words, under psilocybin, brain regions fluctuate more between phases of synchronisation and desynchronisation. For a system of Kuramoto oscillators, these fluctuations are indicative of criticality (Shanahan, 2010). Finally, a third study in the literature found that the sober brain already rests above the critical point, and psychedelics bring the brain *farther* away from criticality (Ruffini et al., 2023).

In the literature, some support for hypothesis (2) comes from Girn et al. (2022), which found that psychedelics flatten the principal gradient of functional connectivity from unimodal (i.e. sensory) to transmodal (i.e. associative) cortices. In other words, unimodal regions are less functionally segregated from transmodal regions, suggesting that top-down and bottom-up information flow become less distinguishable from each other. Our meta-analysis of the FC dataset also revealed that psychedelics elevate connectivity between unimodal and transmodal networks, substantiating Girn's findings. Ayahuasca and DMT, unlike the other psychedelics, also strongly reduced FC within the unimodal networks. However, because our quantitative meta-analysis only included studies on undirected FC (which constituted the majority of the

literature), our results are unable to speak to the direction of information flow under psychedelics. In other words, it is unclear from our results whether psychedelics make information flow more top-down or bottom-up. The evidence for hypothesis (2) from studies on (directed) effective connectivity is more conclusive. For instance, Preller et al. (2019) models the EC of the cortico-striato-thalamo-cortical (CTSC) loop under LSD. If the orientation of information flow is defined by the direction of the loop, then LSD heightens bottom-up information flow, e.g. EC from the thalamus up to the cortex.

Section 3.3. Sources of heterogeneity in the neuroimaging literature

Conducting a meta-analysis of the literature on psychedelics is difficult due to the numerous inconsistencies between the methods used at each level of the hierarchy. In this meta-analysis, we performed meta-regressions and permutation tests to determine whether methodological covariates were significantly associated with our results. Additionally, the random-effects models that we used in the pharmacology and phenomenology meta-analyses enabled us to directly quantify heterogeneity using the I^2 statistic. Below, we discuss the sources of heterogeneity and the findings from our tests.

Section 3.3.1. Phenomenology

While the methods for assessing phenomenology via the 5D-ASC and 11D-ASC were more consistent than the methods for evaluating the other levels of the hierarchy, there were still some important differences between studies. Firstly, not all participants had the same level of experience with psychedelics. One might reasonably expect that more experienced psychedelic users might give lower scores to some dimensions of subjective experience, since the psychedelic trip is less novel and therefore perhaps less intense for them than for first-time users. Secondly, studies differed with respect to when they administered the ASC questionnaire to participants. The questionnaire was issued at the peak of the trip in some studies but at the end of the trip or the next day in other studies. Clearly, the timing of the questionnaire exerts an effect on the scores, especially since memories of trips can often become blurry very quickly (Healy, 2021). Thirdly, in some experiments, participants had to perform a task in addition to answering the ASC questionnaire. The specific nature of the task may predispose participants to certain subjective experiences; for instance, an experiment on time perception may lead participants to experience distortions in temporal awareness more strongly. Unfortunately, due to the wide variety of tasks in the literature, we did not have enough statistical power to determine whether ASC scores were significantly associated with specific tasks, but only to identify whether they were modulated by the presence or absence of a task.

Our meta-regression demonstrated that none of the above covariates – prior psychedelic use, timing of the questionnaire, and presence or absence of a task – significantly influenced either the pooled 5D- or 11D-ASC scores. In both cases, the model in which the covariates were included as regressors fit the data better than the model in which only the interaction between drug, scale, and dose was used to predict the pooled scores.

Among the three drugs, quantified heterogeneity was lowest for DMT's 5D-ASC scores; for the OB and AED dimensions, total I^2 was around 60%, which falls within the "may represent substantial heterogeneity" range according to Cochrane's Handbook for Systematic Reviews and Interventions (Deeks et al., 2019), and only 11% for the VR dimension ("not important" range). Total I^2 exceeded 75% ("considerable heterogeneity", the highest range) in all five dimensions for LSD and in three dimensions for psilocybin. For all dimensions and all drugs, heterogeneity was split equally between studies and within studies.

Section 3.3.2. Neuroimaging

All of the studies about the effects of psychedelics on BOLD activation are task-based. (We did find one study on resting-state BOLD activity under psilocybin (Carhart-Harris, Erritzoe, et al., 2012), but the data from this study was unavailable.) However, the range of tasks is very broad, including: (1) tasks on social behaviour/cognition (Duerler et al., 2020; Preller et al., 2016; Preller, Schilbach, et al., 2018), (2) on emotional processing (Barrett, Doss, et al., 2020; Kraehenmann, Preller, et al., 2015; Müller, Lenz, Dolder, Harder, et al., 2017), (3) on attention (Daumann et al., 2008, 2010; Duerler et al., 2021; Schmidt et al., 2018), (4) on music (Barrett et al., 2018; Kaelen et al., 2017; Preller et al., 2017), and (5) on mental imagery (de Araujo et al., 2011). These categories measure very different aspects of cognition and perception; furthermore, even within each category, there was considerable variability between tasks. For instance, in one of the tasks on social behaviour/cognition (Preller, Schilbach, et al., 2018), the authors measured the contrast between "self-initiated" social interaction and "other-initiated" social interaction based on the order in which pairs of participants looked at a particular object. Yet, in another social task (Duerler et al., 2020), participants rated the quality of various pieces of artwork and then re-ranked them after they were informed of the average ratings of other people; the task therefore assessed the effect of social pressure on subjective judgments. Clearly, these are two very different tasks.

Given the huge variation between the tasks in the BOLD activation dataset, as well as the small number of studies (n = 14 in total; n = 7 on LSD; n = 4 on psilocybin), it is remarkable that we were able to obtain any results from the GingerALE analysis, not only for the entire dataset but also for the LSD and psilocybin subsets. (Furthermore, the analysis corrected for multiple comparisons.) Nevertheless, it is likely that the results of the BOLD activation meta-analysis were biased by the types of tasks in the literature. For instance, among the four studies on BOLD activation under psilocybin, three used visual stimuli (Barrett, Doss, et al., 2020; Kraehenmann, Preller, et al., 2015; Preller et al., 2016). Unsurprisingly, the meta-analysis found that psilocybin, unlike LSD, was generally associated with changes in BOLD activity in the visual network. There were not enough studies to perform a meta-regression on the experimental stimuli, but nevertheless, it is safe to say that our finding may be an artefact of the tasks that happened to be used in the literature, rather than genuinely implying that psilocybin uniquely increases activity in the visual network. If future studies use stimuli that engage other sensory modalities, they may not show that psilocybin uniquely induces BOLD activation in the visual network.

One major impediment to the FC meta-analysis was the variety of parcellations used in the literature. Of the 12 studies that we included in our quantitative meta-analysis, only two used the same parcellation. Some parcellations had as few as seven regions, whereas other parcellations had as many as 112 regions. Even parcellations with an identical number of ROIs divided and labeled the regions differently. It challenging to directly compare the results from different parcellations, so in our meta-analysis, we effectively "re-parcellated" the published data into the Yeo networks. However, our results would be more robust if we applied the same parcellation to the raw data, a task that we hope to accomplish in the future.

Another major source of heterogeneity in the FC literature was the diversity of preprocessing techniques. In general, different preprocessing pipelines can lead to divergent, perhaps even contradictory, findings, even when they are performed on the same dataset (Bhagwat et al., 2021; Botvinik-Nezer et al., 2020; Bowring et al., 2022; Carp, 2012; Olszowy et al., 2019). For instance, Botvinik-Nezer et al. (2020) asked 70 independent research teams to test nine hypotheses regarding the same fMRI dataset, and they found not only that all of

the teams chose different pipelines, as was the case for independent researchers in the psychedelic neuroimaging literature, but also that the teams, on average, diverged significantly from one another in their conclusions. The study found that variation in spatial smoothing, motion correction methods, and choice of preprocessing software (e.g. FSL or SPM) contributed significantly to the inconsistent results. This finding is highly relevant for the psychedelic literature, which also shows large variability in the width of spatial smoothing kernels and preprocessing software. Additionally, different techniques for regressing out white matter may confound the results; one method used in the literature, aCompCor, has been shown to perform nearly three times better than another method, ANATICOR, since it results in fewer residual correlations between head motion and FC (Ciric et al., 2017). We conducted permutation tests to determine whether the pooled FC data was significantly associated with any of the above covariates. None of the covariates met the threshold for statistical significance, but the small number of studies may limit the robustness of our statistical tests.

One other preprocessing technique that has generated some contention within the field is global signal regression (GSR). While a minority of studies explicitly stated that they performed GSR (Avram et al., 2022; Barrett, Doss, et al., 2020; Preller, Burt, et al., 2018; Preller et al., 2020; Timmermann et al., 2023; Viol et al., 2017, 2019, 2023), it proved to be sufficiently controversial that Preller, Burt, et al. (2018) devoted a large part of their study to isolating its effects. Without GSR, global brain connectivity (GBC) significantly increased in associative cortices, whereas it decreased when GSR was applied. These results potentially suggest that the lack of GSR in most psychedelic neuroimaging studies could be distorting the results. However, there are several good reasons for avoiding GSR, especially the fact that it may introduce spurious anticorrelations into the data (Murphy et al., 2009; Murphy & Fox, 2017; Weissenbacher et al., 2009). Additionally, in contrast to Preller, Burt, et al. (2018), Avram et al. (2022) found that applying GSR actually erased the significant differences in FC between the salience network & thalamus, and Timmermann et al. (2023) showed that GSR did not have an effect on multiple measures of FC, including disintegration, desegregation, and global connectivity. Among the 12 studies that we included in our quantitative FC meta-analysis, there were too few that reported results with GSR for us to include GSR as a covariate in our tests.

Section 3.3.3. Pharmacology

While it may seem that the pharmacology data would have the least heterogeneity, due to the scale, precision, and objectivity of the measurements, we found substantial variation in the data, with reported affinity and functional activity values sometimes spanning two orders of magnitude for the same drug. For all drugs, I^2 exceeded 85% for all affinity (K_i) and activity (EC_{50}) values, with the exception of LSD's affinity for D_1 (I^2 = 52.9%).

In our meta-regressions on the affinity data, we examined the relationship between the results and the following five covariates, which were selected *a priori*: 1) the radioligand that the psychedelic competed with for the receptor of interest, 2) the concentration of radioligand, 3) the source of the receptor (i.e. whether it came from brain homogenates or it was cloned into cell lines; if the latter, the name of the cell line), 4) whether the competition binding assay was terminated with filtration or centrifugation (this was identified as an *a priori* covariate in previous meta-analyses of psychoactive drug affinities (McPartland et al., 2007)), and 5) the chemical that was used to define nonspecific binding. One radioligand ([^{3}H]-INB) and the choice of centrifugation or filtration significantly influenced the reported affinity of LSD for 5-HT_{2A}. However, none

of the methodological covariates for the affinity of other drug-receptor pairs met the threshold for statistical significance.

We selected different covariates for the functional activity data depending on the assay. For the studies on calcium mobilisation, we chose the following covariates: (1) the name of the cell line used in the study, (2) the device for detecting fluorescence, (3) the reagent used as the fluorescence indicator, and (4) the density (cells/well) at which the cells were seeded. We picked a single covariate for studies on β-arrestin2 recruitment: whether the study used a NanoBiT assay, which measures β-arrestin2 recruitment with bioluminescence (Reyes-Alcaraz et al., 2022), or a BRET assay, which quantifies resonant energy transfer between the luminescently-tagged GPCR and the fluorescently-tagged β-arrestin2 (Harikumar et al., 2017). We did not conduct meta-regressions for studies on IP formation because almost all of the studies used the same methods. None of the covariates for the calcium mobilisation and β-arrestin2 recruitment studies were significantly associated with the pooled EC_{50} values. However, all the covariates together (plus the drug) explained 100% of the heterogeneity in the calcium data and 96% of the heterogeneity in the β-arrestin2 data.

Section 3.4. Recommendations for future research

Our systematic review of the literature has revealed several knowledge gaps in the field of psychedelic neuroscience. Firstly, there is relatively little neuroimaging data on psychedelics. There are now more secondary analyses of the dataset of Carhart-Harris et al. (2016) than the number of participants (15) in that study (Doss, personal communication). Of the 58 studies that we included in the neuroimaging meta-analysis, fewer than half (22) collected original data. While the secondary analyses have offered new and compelling perspectives on brain activity under psychedelics, there need to be more replication studies in order to verify the findings from the primary datasets. Furthermore, as shown in **Figure S2a**, over a third of the studies that we identified in our literature search are secondary analyses of the same two primary datasets (Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris et al., 2016), which causes a considerable risk of bias. Ten of the 12 studies on entropy analyse data from these primary datasets, so it is not surprising that all of them conclude that psychedelics increase entropy. If the studies had measured entropy on different primary datasets, then the results may have been different. We acknowledge this bias in our qualitative review of the entropy literature, and we also account for it in our quantitative meta-analysis of the functional connectivity (FC) literature, where we only included one study on each unique dataset.

Secondly, we advise future studies to use the same preprocessing pipelines, when measuring the same metric of brain activity (BOLD activation, functional connectivity, and/or entropy). The studies in this body of literature applied very different preprocessing pipelines implemented on a range of software packages, and some of these pipelines involved many more data-cleaning processes than others. It is likely that the field would converge on more similar findings if it harmonised its preprocessing techniques, by, for instance, using the minimal pipeline recently implemented in FMRIPrep (Esteban et al., 2019).

Thirdly, future studies on functional connectivity should use the same parcellation to define ROIs. Due to the lack of a consistent parcellation in the literature, various studies have used the same labels to refer to different regions of the brain. The best parcellation to use in future research may be the Schaefer-232 or the Brainnetome-246 parcellation, which has been shown to yield the most "representative" brain networks (i.e. the ones with the lowest information-theoretic divergence from networks derived by other parcellations) (Luppi & Stamatakis, 2021).

Our meta-analysis was limited by the fact that it assessed the published data rather than the raw data. It is prohibitive, time-consuming, and sometimes impossible to obtain raw data; institutions are limited by data confidentiality agreements, have lost access to old data, or are unwilling to share data for other reasons. However, we urge future researchers to make data publicly available, pool together raw data on psychedelics from different institutions, preprocess and parcellate it identically, and then re-apply our meta-analysis pipeline. The subsequent findings would not be confounded by different methodological choices made by different labs and would more accurately reflect the common effects of psychedelics on brain activity.

Finally, we encourage researchers to develop tools for modelling the nonlinear relationships between the pharmacology, neuroimaging, and phenomenology of psychedelics, the three hierarchical levels of analysis that are at the heart of this meta-analysis. While some researchers have attempted to examine the associations between each level (Ballentine et al., 2022; Lawn et al., 2022), their techniques are model-free and only measure *correlations* between the effects of psychedelics, rather than elucidating the *causal mechanisms* that underpin them.

Recent whole-brain models have made significant advances in discovering these causal mechanisms (see Kringelbach & Deco (2020) for a general review of these models). Typically based on insights from statistical physics, whole-brain models consist of nodes that approximate local or mesoscopic neuronal dynamics through mean field models of coupled excitatory-inhibitory interactions (Deco et al., 2014; Honey et al., 2007) or Hopf models of bifurcations into and out of sustained oscillatory activity (Deco et al., 2017; Freyer et al., 2012), respectively. Crucially, whole-brain models have enabled researchers to identify the specific regions that should be stimulated in order to force transitions between different states of consciousness, such as from sleep to wakefulness (Deco et al., 2019). Whole-brain models have also been applied to psychedelics; in particular, the 5-HT_{2A} receptor density in each area of the brain was used to fit a mean field model of fMRI data on LSD, capturing the nonlinear interactions between connectivity and the distribution of 5-HT_{2A} receptors (Deco et al., 2018). This model was recently extended to determine the associations between global brain connectivity on LSD and categories of subjective experience (Burt et al., 2021). The model has also been applied to the relationship between neurotransmitters (namely, serotonin) and neuronal regions on psilocybin; in particular, Kringelbach et al. (2020) coupled a mean field model of each neuronal region to the release-and-reuptake dynamics of serotonin concentration. Importantly, this coupled neuronal-neurotransmitter model exhibited a better fit to the empirical FC than a model of solely the neuronal activity. Overall, whole-brain models display great promise for linking neurotransmitter release, which is partly determined by pharmacology, to the brain regions that causally mediate, rather than merely correlate with, the effects of psychedelics. Most recently, whole-brain models have also been combined with another cutting-edge method, turbulence, to determine the susceptibility of the brain to external stimuli under psychedelics (Cruzat et al., 2022).

Section 4. Conclusion

Whereas a previous meta-analysis only covered a subset of the fMRI literature on psychedelics (Castelhano et al., 2021), this is the first meta-analysis to evaluate not only all of the functional neuroimaging studies on psychedelics to date, but also the literature on their phenomenology and pharmacology. We assess and compare these three hierarchical levels of analysis – pharmacology, neuroimaging, and phenomenology – across three different classical psychedelics: DMT, LSD, and psilocybin. Thus, we performed comparisons not only between psychedelics, but also between the levels of the hierarchy.

We found that the different levels of the hierarchy exhibited a weak one-to-one correspondence with one another. This is not surprising, as the interactions between phenomenology, neuroimaging, and pharmacology are highly non-linear and complex. We encourage future research to develop tools for modelling these relationships in order to improve our scientific understanding of psychedelics.

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Code Availability
Code is available upon request by emailing the corresponding author: kenneth.shinozuka@psych.ox.ac.uk

Competing Interests Statement
The authors have no conflicts of interest to declare.

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Figures

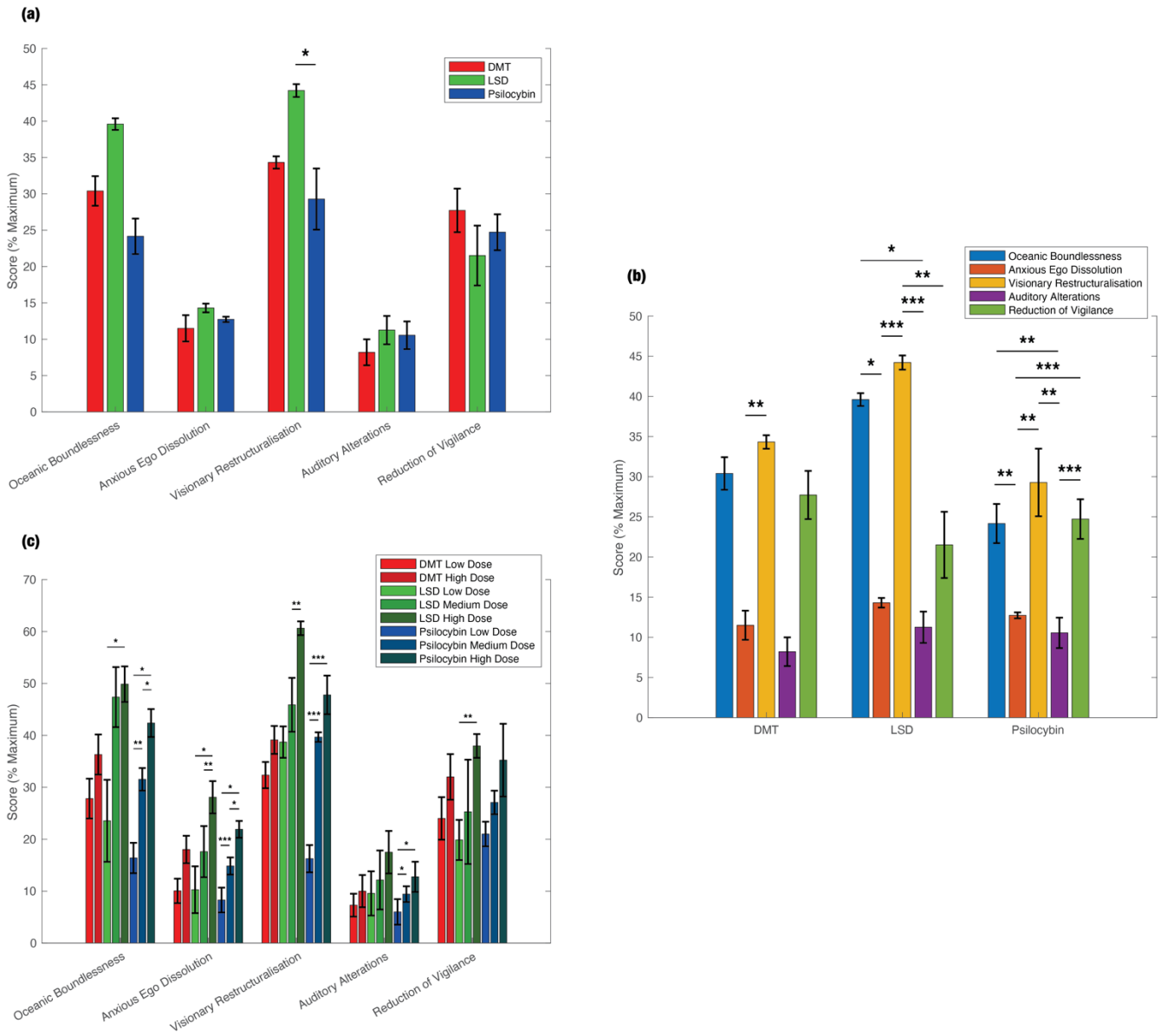


Figure 1. Meta-analysis of the 5-Dimensional Altered States of Consciousness (5D-ASC) data reveals only one significant difference between psychedelics, but many more significant differences within psychedelics. *The 5D-ASC is one of the most commonly-used scales for subjective reports of psychedelic experiences. It measures altered states of consciousness along five different dimensions: oceanic boundlessness (OB; a feeling of interconnectedness), anxious ego dissolution (AED), visionary restructuralisation (VR; the quality and intensity of visual hallucinations), auditory alterations (AA), and reduction of vigilance (RV). Our literature search identified 23 studies that reported 5D-ASC data. We performed a three-level random-effects meta-analysis, where the third level consisted of studies that reported multiple data points corresponding to different doses given to the same group of participants; this analysis thereby accounted for the lack of statistical independence among the inputs. Within-study and between-study heterogeneity were estimated with the restricted maximum likelihood procedure. Using a Correlated and Hierarchical Effects model to account for within-study correlations in sampling error, we performed meta-regressions to analyse the effect of dose and drug (DMT, LSD,*

or psilocybin) on pooled 5D-ASC scores. (a) Between-drug comparison of pooled 5D-ASC scores. LSD ranked higher than DMT and psilocybin in all five dimensions. (b) Within-drug comparison. VR, OB, and RV received much higher scores than AED and AA. (c) Within-drug, between-dose comparison. All scores increased with dose. Numerical data for the above figure are given in ***Table S1****. We also conducted a meta-analysis of the 11-dimensional ASC scale, which is also widely used in the literature; the results are displayed in* ***Figure S3*** *and* ***Table S2****.*

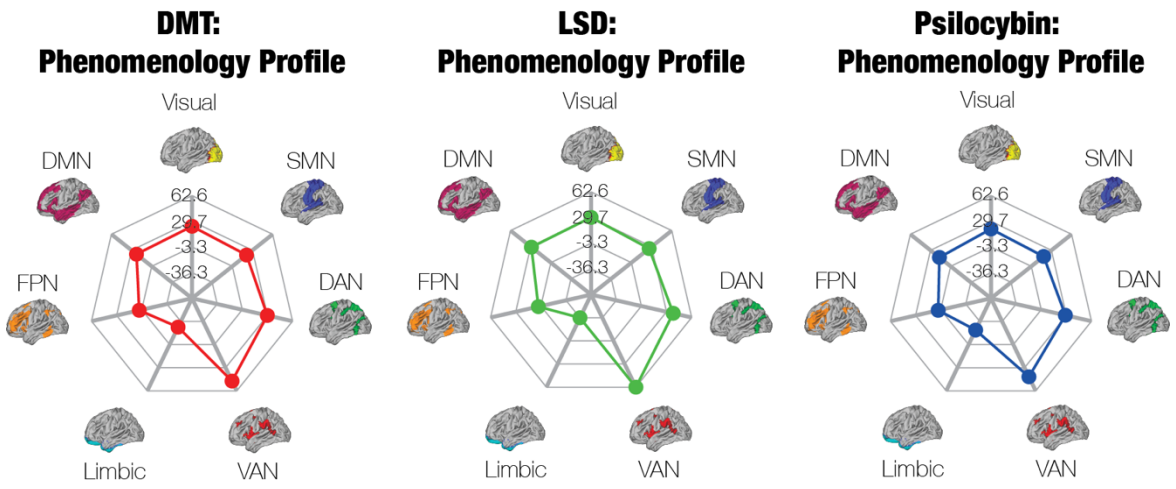


Figure 2. Phenomenology profiles of the psychedelics demonstrate broad similarity between the neural correlates of their phenomenology. *We identified 14 studies that measured correlations between ASC ratings and fMRI activity or pairwise connectivity, including three studies on ketamine. We determined the Yeo network that contained each brain region that exhibited a significant correlation, and then we averaged across the correlations associated with each Yeo network, resulting in the mean correlation between each Yeo network and each ASC scale. The phenomenology profiles were defined by a weighted combination of the mean correlations for each ASC scale, in which the weights were the pooled ASC ratings of each psychedelic for the corresponding scale. Because the pooled ASC ratings are similar across psychedelics, the phenomenology profiles are very alike one another as well. However, the lack of data on the neural correlates of the ASC ratings limits our confidence in the validity of these profiles.*

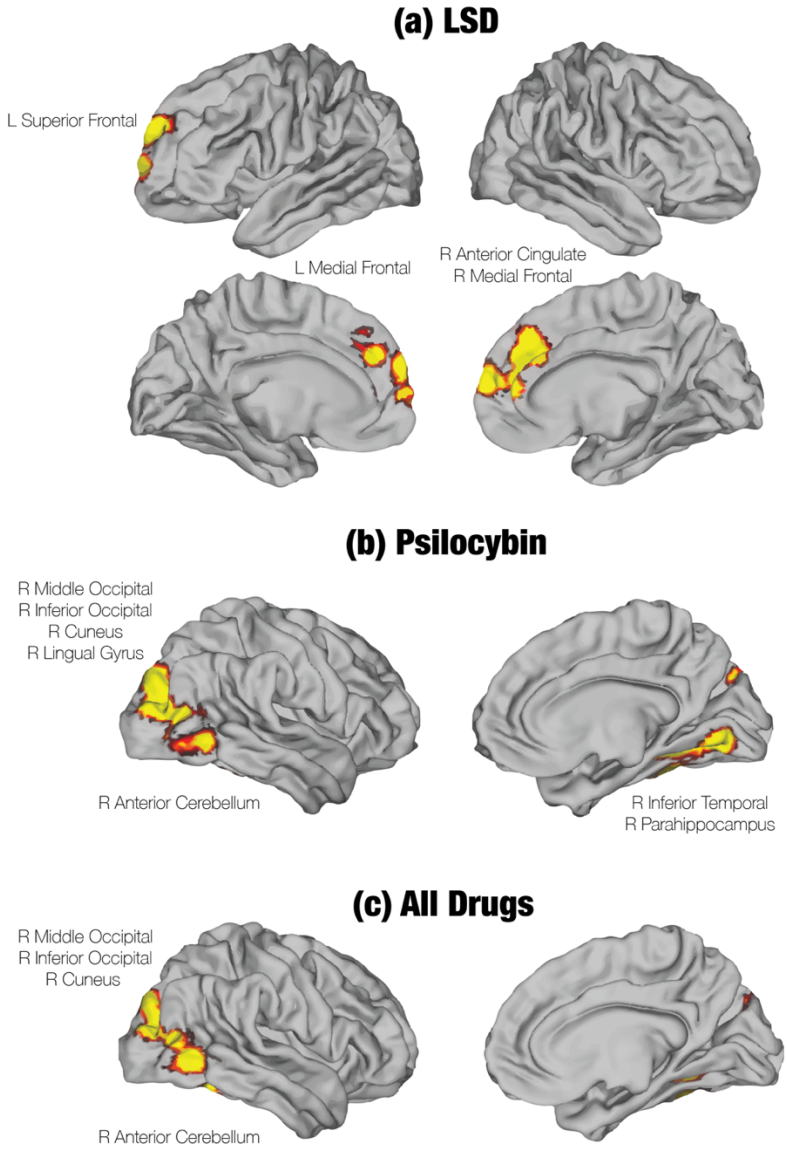


Figure 3. Meta-analysis of BOLD activation data yields distinct neural correlates for LSD and psilocybin. *We identified 17 studies on BOLD activation under psychedelics, three of which did not report the requisite data for our analysis. We performed a GingerALE meta-analysis on the entire BOLD activation dataset, which consisted entirely of task-based data (n = 14); on the LSD subset of the data (n = 7); and on the psilocybin subset (n = 4). GingerALE takes in a list of the coordinates of peak BOLD activations across all studies and computes the activation likelihood estimate (ALE) statistic from the union of Gaussian distributions centred around each set of coordinates. In each analysis, we thresholded the ALE statistic via cluster-level inference (p < 0.05) at a cluster-forming threshold of 0.05 (1000 threshold permutations). Each image shows the contiguous non-zero regions of the spatial map of statistically significant ALE values. Note that the tasks were very different, ranging from social to motor inhibition tasks, and the results are likely confounded by the experimental stimuli used in the studies. For instance, three of the four psilocybin studies used visual stimuli, which may explain the unique activations in the visual cortex for psilocybin.*

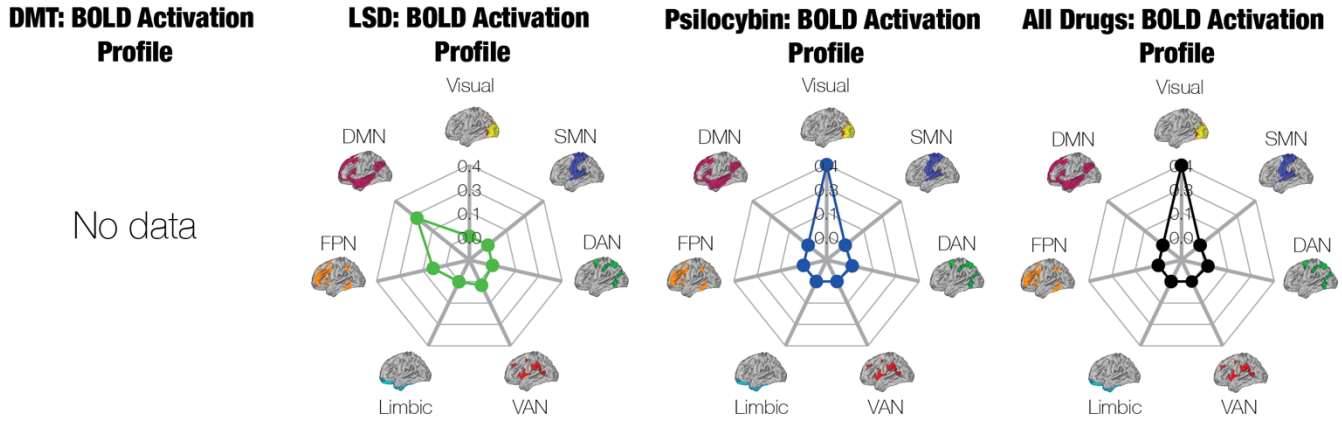


Figure 4. BOLD activation profiles of each psychedelic show very different patterns in the Yeo networks. *This figure shows the alignment between the Yeo networks and the cluster images produced by the GingerALE analysis for each dataset. (Prior to normalising them by the size of each Yeo network, the numbers in each profile range from 0 to 1, with 1 representing complete overlap between a Yeo network and the corresponding cluster image.) LSD and psilocybin exhibit different profiles of BOLD activation, with LSD predominantly affecting BOLD activity in the DMN and psilocybin almost exclusively altering activity in the visual network. However, these results are strongly confounded by the methods of the studies. In particular, three of the four psilocybin studies displayed visual stimuli to participants. Clearly, the peak coordinates of BOLD activation from the psilocybin dataset contributed more to the overall clusters of activity, across all psychedelics, than the LSD dataset.*

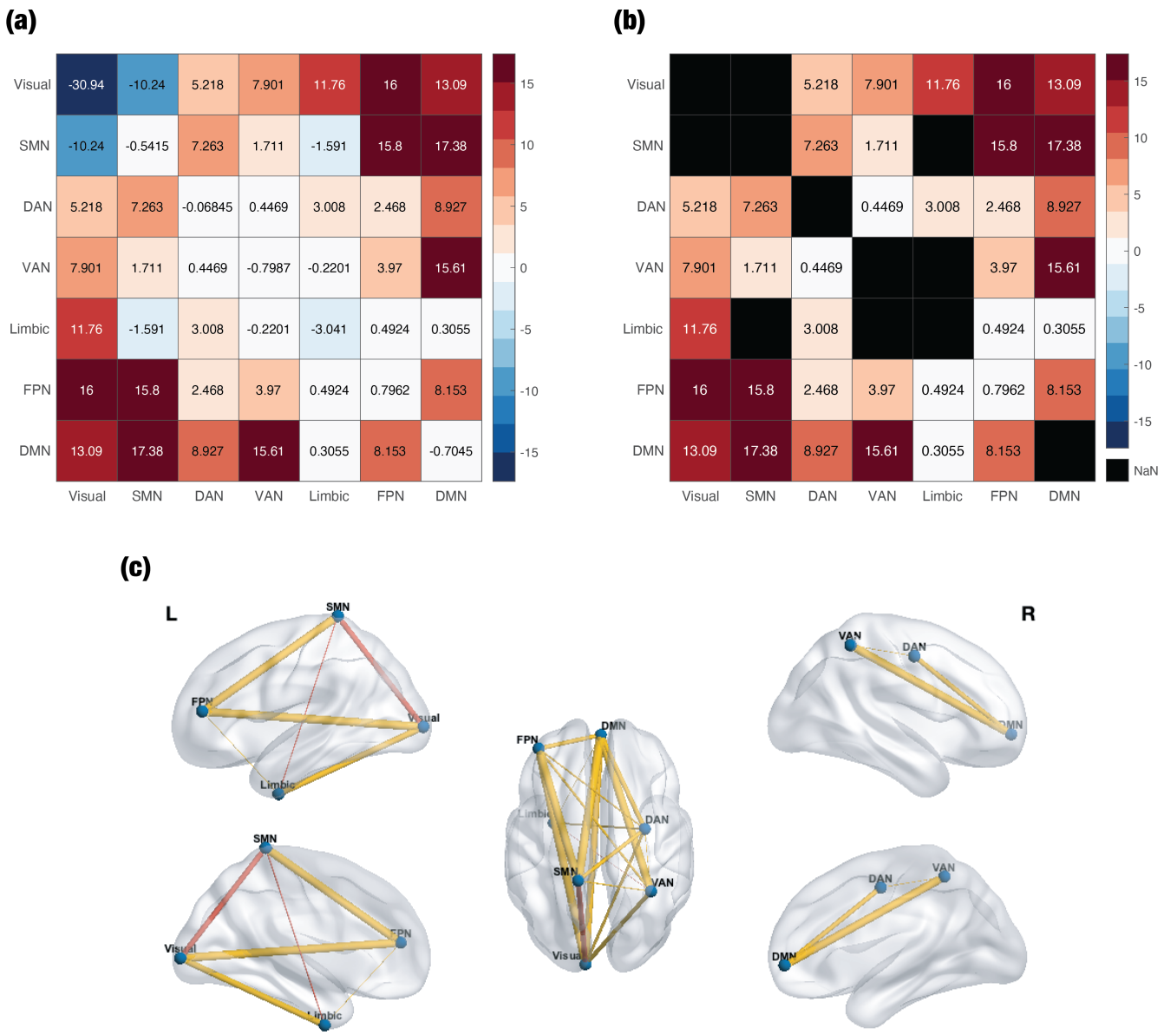


Figure 5. Meta-analysis of the functional connectivity (FC) data indicates increases in between-network connectivity and decreases in within-network connectivity. *To perform a meta-analysis on the FC data, we determined the Yeo networks that contained each pair of functionally connected regions of interest (ROIs) in the literature and then performed a weighted sum of the number of significant connections between Yeo networks. We included n = 12 studies in this meta-analysis, after excluding studies that did not measure pairwise FC and secondary analyses of identical datasets. (a) Aggregate FC matrix, in which each entry contains the overall connectivity between a pair of Yeo networks. (b) Blacked-out values are statistically insignificant (p > 0.05) with respect to a null distribution formed from resting-state Human Connectome Project data. (c) A rendering of the statistically significant FC scores on the surface of the brain. Insignificant edges are red, and significant edges are yellow. Images produced through the BrainNet Viewer (Xia et al., 2013).*

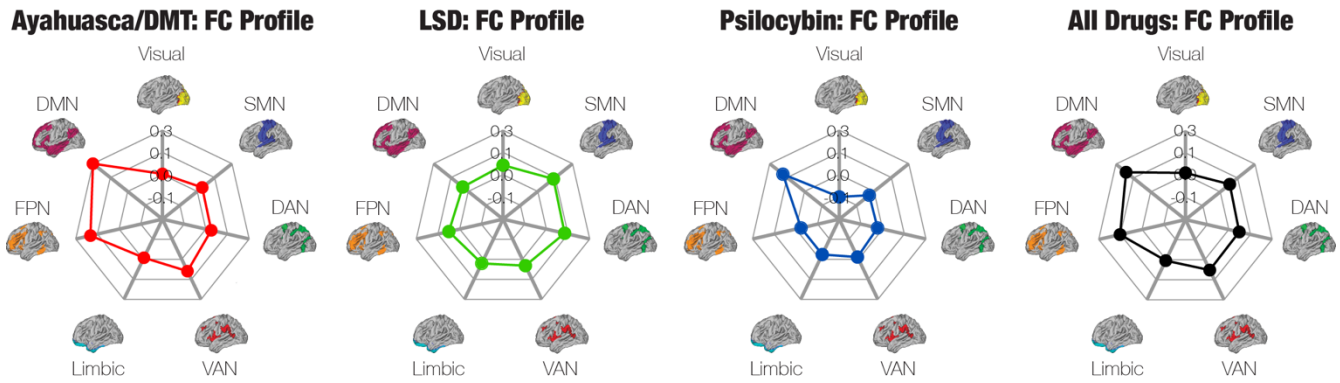
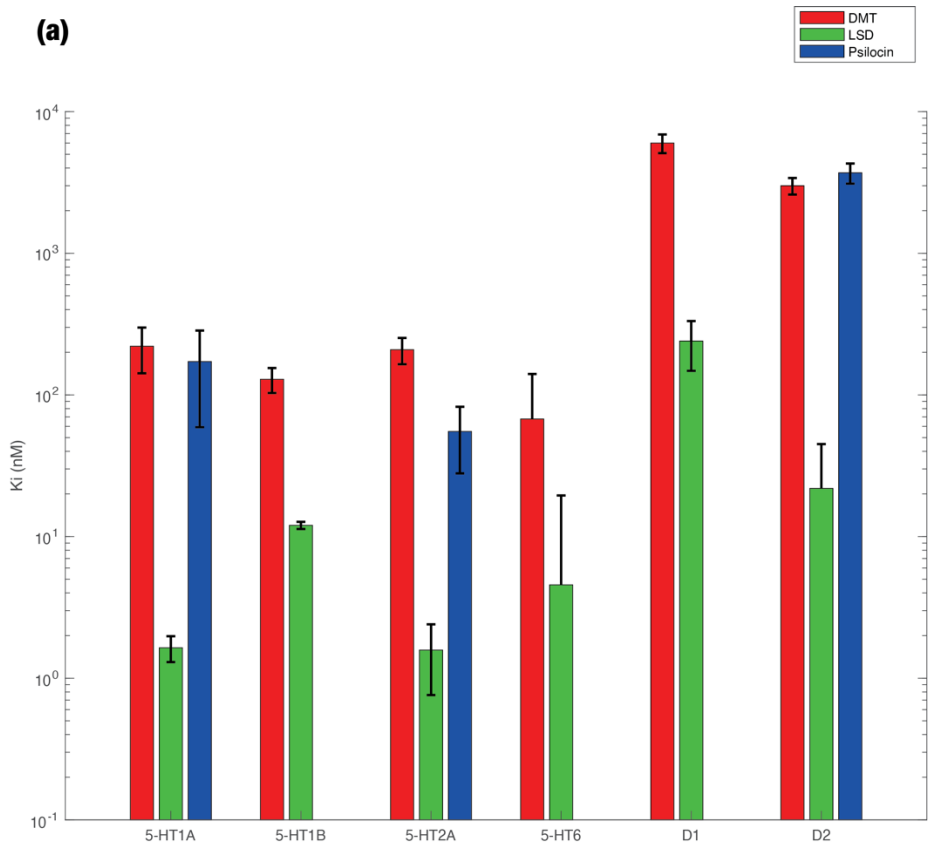


Figure 6. Functional connectivity (FC) profiles show unique FC patterns for each psychedelic. *Out of the n = 12 studies that we examined in our quantitative FC meta-analysis, n = 3 were studies on ayahuasca/DMT (ayahuasca: n = 2; DMT: n = 1), n = 3 on LSD, and n = 6 on psilocybin. Each FC profile contains the total FC of each network, which was obtained by taking the normalised sum of the rows of the corresponding aggregate FC matrices, including insignificant values. (The units of the profiles are arbitrary.) The psychedelics display distinct FC profiles; for instance, ayahuasca and DMT increase total FC for the DMN more strongly than for other networks, whereas LSD elevates FC more for the SMN and DAN than for other networks.*


(a)
DMT
LSD
Psilocin
Ki (nM)
10^4
10^3
10^2
10^1
10^0
10^{-1}
5-HT1A
5-HT1B
5-HT2A
5-HT6
D1
D2

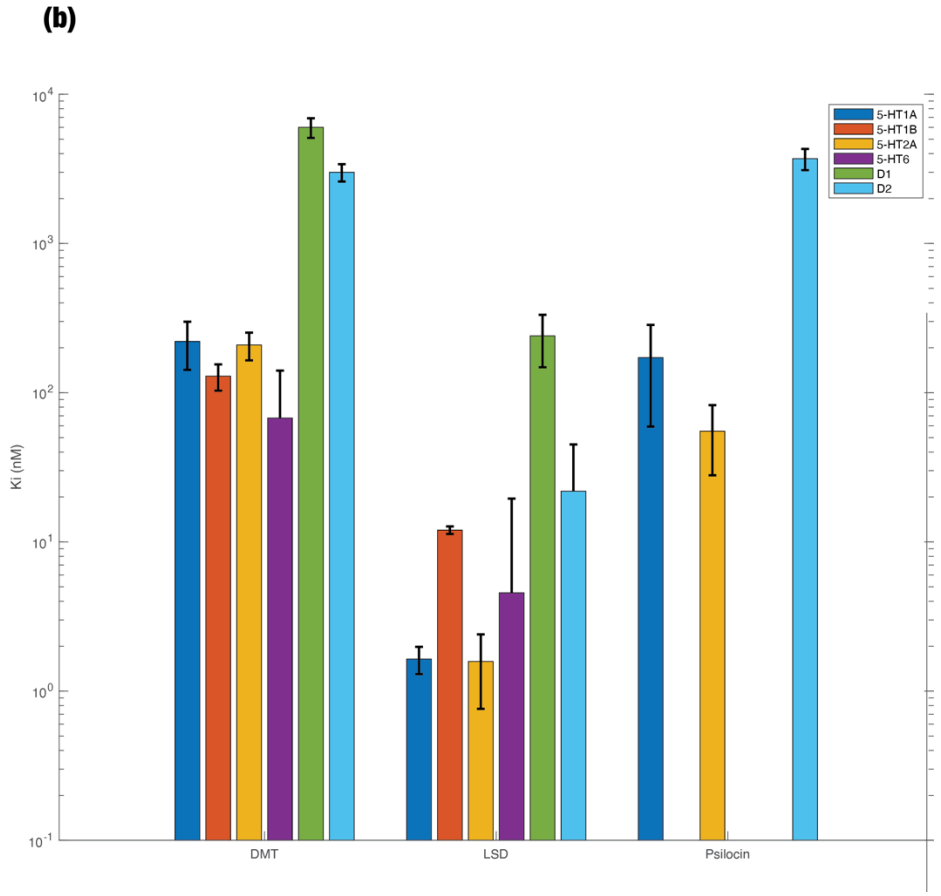

(b)
5-HT1A
5-HT1B
5-HT2A
5-HT6
D1
D2
Ki (nM)
10^4
10^3
10^2
10^1
10^0
10^{-1}
DMT
LSD
Psilocin

Figure 7. Meta-analysis of binding affinities demonstrates that LSD binds with much higher affinity to six human receptors than DMT and psilocin. *These receptors include 5-HT_{1A} (5-HT = serotonin), 5-HT_{1B}, 5-HT_{2A}, 5-HT_6, D_1 (D = dopamine), and D_2. We selected these receptors because there are averaged PET maps of them in a recent atlas derived from data of over a thousand human participants (Hansen et al., 2022); these maps enabled us to relate the spatial expression of these receptors to the other levels of the hierarchy – that is, to the distribution of FC and BOLD activation patterns across the brain, as well as to the phenomenology profile of each psychedelic. Our literature search identified n = 70 studies on the affinities, measured as K_i, of psychedelics for the aforementioned six receptors, including n = 16 studies on DMT, n = 57 studies on LSD, and n = 9 studies on psilocin. Because the standard errors of DMT and psilocin were orders of magnitude higher than that of LSD, we could not construct a single model for all three drugs, which prevented us from calculating significant differences between psychedelics. Instead we created separate random-effects models for each psychedelic, receptor, and species (human, rat, or mouse), in which we weighted the K_i values by their inverse variance and estimated heterogeneity with the restricted maximum likelihood procedure. Here, we present only the results for the human data. (a) Between-drug comparison of binding affinities. For all recepetors, LSD has orders of magnitude higher affinity (note that K_i is inversely associated with affinity) than DMT and psilocin. (b) Within-drug comparison. Each of the three psychedelics has much less affinity for the dopamine receptors than the serotonin receptors, whereas differences between 5-HT_{1A} and 5-HT_{2A} were much smaller. Note that there is only one reported K_i value for DMT w.r.t. (with respect to) 5-HT_{1B}, 5-HT_6, D_1, and D_2 in humans; for LSD w.r.t. 5-HT_{1B}; and for psilocin w.r.t. D_2. For these drug-assay pairs, we display the value and standard error that was reported in the studies themselves, not the value and standard error outputted by the model. N.D. means no data.*

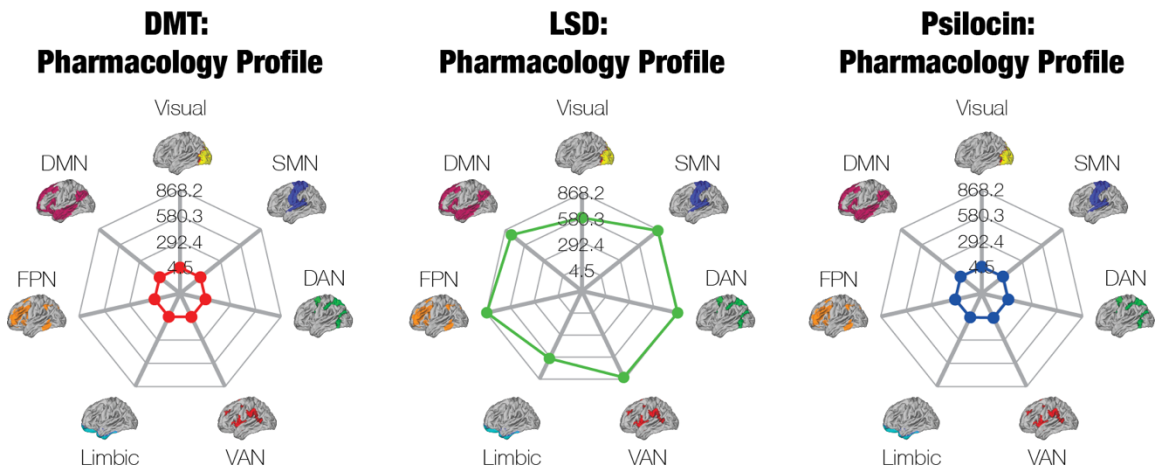
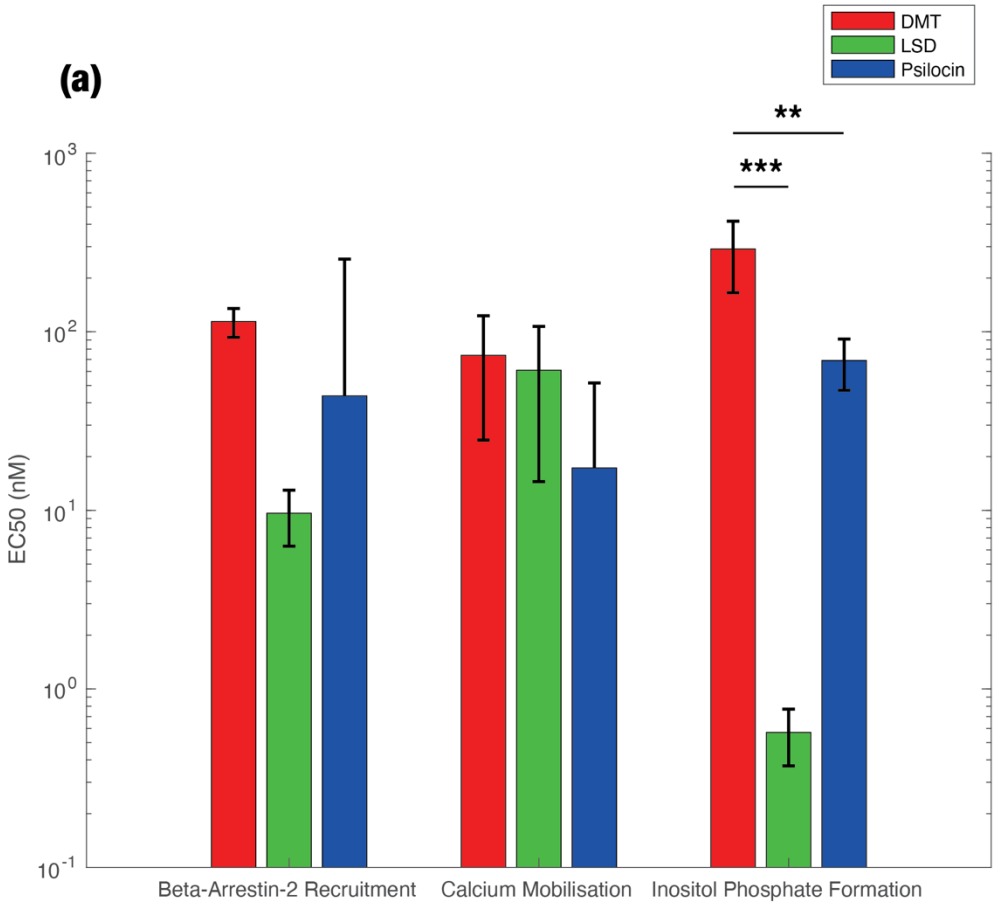


Figure 8. The pharmacology profile of LSD is much more extensive than that of DMT and psilocin *. The pharmacology profile of a psychedelic in a specific Yeo network is equivalent to the sum, across all receptors, of the product of its affinity for each receptor (inverse of pooled K_i values; see* ***Figure 7****) and the expression of that receptor in the Yeo network, which was quantified by Hansen et al. (2022) using averaged data from multiple PET maps of human brains. The profiles are derived from the following six receptors mapped by Hansen et al. (2022): 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_6, D_1, and D_2. Because LSD has orders of magnitude higher affinity (lower K_i) for all of these receptors than DMT and psilocin, its pharmacology profile is much more extensive. LSD's profile was largest in the SMN, VAN, DAN, and FPN, reflecting the high expression of 5-HT_{2A} and 5-HT_{1A} in those networks and the high affinity of LSD for those two receptors. The pharmacology profile for all drugs is the average across DMT, LSD, and psilocin.*


(a)
DMT
LSD
Psilocin
**
***
EC50 (nM)
10^3
10^2
10^1
10^0
10^{-1}
Beta-Arrestin-2 Recruitment
Calcium Mobilisation
Inositol Phosphate Formation

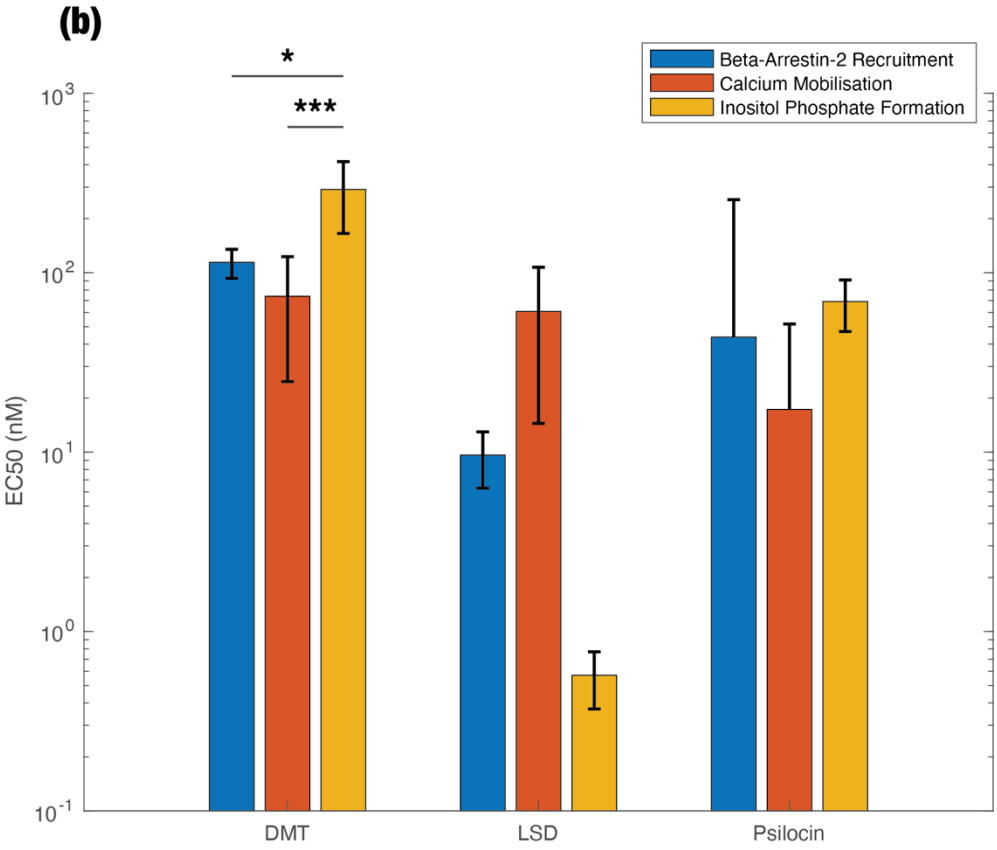

(b)
Beta-Arrestin-2 Recruitment
Calcium Mobilisation
Inositol Phosphate Formation
*
***
EC50 (nM)
10^3
10^2
10^1
10^0
10^{-1}
DMT
LSD
Psilocin

Figure 9. Meta-analysis of functional GPCR assays on the human 5-HT$_{2A}$ receptor reveals that DMT activates a signature of Gα$_q$ signaling significantly less than LSD and psilocin do. *We identified n = 47 studies on functional activity, including n = 12 studies on DMT, n = 38 studies on LSD, and n= 9 studies on psilocin. We specifically searched for studies that examined functional activity by measuring the effects of psychedelics on GPCR signaling in either human or rat versions of the six receptors listed in* ***Figure 8****. In studies on human receptors, GPCR signaling was primarily measured through three types of assays: (1) β-arrestin2 recruitment, (2) calcium mobilisation, and (3) inositol phosphate (IP) formation. The latter two assays are measures of Gα$_q$ signaling, while β-arrestin2 recruitment activates signaling pathways that are independent of G-proteins. While there were other types of assays in the literature, there were too few studies on each to conduct comparisons across psychedelics. Because there were not enough assays on other receptors, we only conducted meta-analyses (via random-effects models) on the activity of each psychedelic at the human and rat 5-HT$_{2A}$ receptor, in which we weighted the activities by their inverse variance and estimated heterogeneity with the REML procedure. Here, we present only the results for the human data. We performed meta-regressions to determine significant differences between the activities of various drugs as measured by the same assay, as well as significant differences between the activity of the same drug as measured by various assays. (a) Between-drug comparisons of functional activity, measured as the effective concentration needed to elicit 50% of the maximal functional response (EC$_{50}$). Note that EC$_{50}$ is inversely associated with activity. DMT induced significantly less activity via IP formation and β-arrestin2 recruitment than LSD and psilocin. (b) Within-drug comparisons of functional activity. There were no significant within-drug differences between different assays. Note that there is only one reported EC$_{50}$ value for DMT in β-arrestin2 recruitment assays and for psilocin in inositol phosphate (IP) formation assays. For these drug-assay pairs, we display the value and standard error that was reported in the studies themselves, not the value and standard error outputted by the model.*

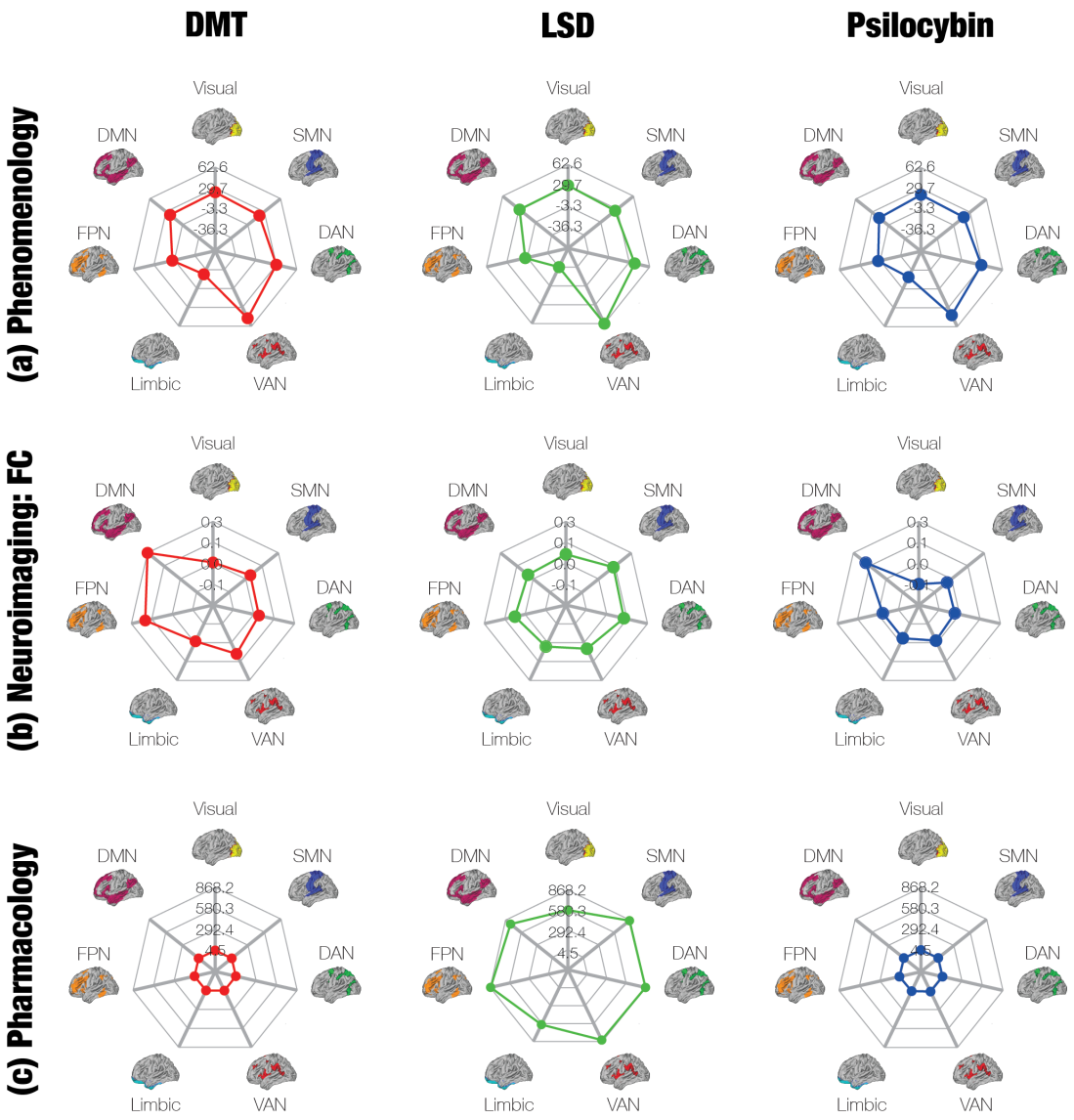


Figure 10. The hierarchy of psychedelic effects highlights the nonlinear relationship between pharmacology, neuroimaging, and phenomenology. *The effects of psychedelics form a tripartite hierarchy, consisting of subjective experience (a, phenomenology), functional connectivity (b, neuroimaging), and their affinity for receptors (c, pharmacology). (Note: we omitted the BOLD activation results because they were strongly confounded by experimental stimuli.) Here, we show the neural correlates of each level of the hierarchy in the seven Yeo networks. In brief, each profile was derived from (a) neural correlates of the subjective dimensions of the ASC scale; (b) summing the FC between each network and other networks; and (c) multiplying the affinities with each receptor's density in each Yeo network. Clearly, there is a very weak correspondence between the different levels of the hierarchy, revealing the highly non-linear relationship between phenomenology, neuroimaging, and pharmacology. Note: we analysed data on DMT in our phenomenology and pharmacology meta-analyses and data on both DMT and ayahuasca in our FC meta-analysis. We examined data on psilocin in our pharmacology meta-analysis and on psilocybin in all other meta-analyses.*