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Psychedelics Disrupt the Functional Hierarchy of the Human Brain

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Abstract

Psychedelics, such as lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), and psilocybin, are hallucinogenic drugs that act on the 5-HT_{2A} receptor. Their effects can be analysed on three different levels: (1) phenomenology, or subjective experience, as psychedelics strongly alter a person's state of consciousness; (2) neuroimaging, using tools such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG); and (3) pharmacology, or their biochemical interactions with various receptors in the brain. In the last ten years, there has been a considerable rise in psychedelic research due to emerging evidence that they can be effective for treating a wide range of conditions, including depression, substance use disorder, end-of-life anxiety, and post-traumatic stress disorder (PTSD). A popular theory known as RElaxed Beliefs Under pSychedelics (REBUS) posits that psychedelics “flatten” the functional hierarchy of the brain; that is, they diminish the inhibitory effect of higher-order, associative cortical networks on lower-order, sensory networks. However, it is challenging to test REBUS because it proposes that psychedelics modify the weights of the prior beliefs, or “priors,” encoded in higher-order networks, yet there are no robust models that systematically link priors to the activity of these networks, as recorded by MEG or fMRI. Instead, it is more straightforward to measure hierarchy directly on the connectivity of these networks, without assuming that the connectivity instantiates priors.

My aims in this thesis are twofold. The first is to provide a comprehensive overview of the current landscape of scientific literature about the effects of psychedelics on healthy humans. In particular, I conduct systematic reviews and meta-analyses of the three levels of analysis mentioned earlier – phenomenology, neuroimaging, and pharmacology – across three different psychedelics (DMT, LSD, and psilocybin). I discover that there are highly nonlinear relationships both between drugs and also between levels of analysis. The second aim is to measure brain hierarchy under psychedelics with simple, empirically tractable methods. In particular, I discuss two different measures: irreversibility, or the asymmetry between sending and receiving neural signals; and trophic coherence, which decomposes networks into hierarchical levels. I apply these two measures to an existing MEG dataset of healthy human participants who were administered LSD. My analyses reveal that LSD decreases both irreversibility and trophic coherence, suggesting that LSD does indeed flatten the functional hierarchy of the brain. Furthermore, the spatial distribution of changes in irreversibility and hierarchical levels on LSD is consistent with the findings of the meta-analysis. In particular, the meta-analysis demonstrates that LSD, more than other psychedelics, alters the quality and intensity of visual hallucinations, while also elevating connectivity between the visual network and other brain networks. LSD reduces irreversibility and top-down hierarchical levels most in the regions of the brain that are involved in visual processing. Taken together, these results indicate that LSD diminishes the influence of visual network activity on hierarchically directed connectivity in the brain, which may explain the profound effects of LSD-induced visual hallucinations on higher-order cognitive processes such as a person's sense of self. Furthermore, this thesis constitutes the first attempt to measure the hierarchy of directed information flow in the brain under psychedelics. Future work could deploy the same methods to determine whether the flattening of hierarchy predicts the therapeutic response to psychedelics.

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Chapter 1. Introduction

Chapter 1.1. About psychedelics

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, or “phenomenology,” 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, I provide an introduction to the literature on the phenomenology, neuroimaging, and pharmacology of psychedelics. I also discuss the theory that psychedelics “flatten” the hierarchy of the brain, which I aim to test in this thesis.

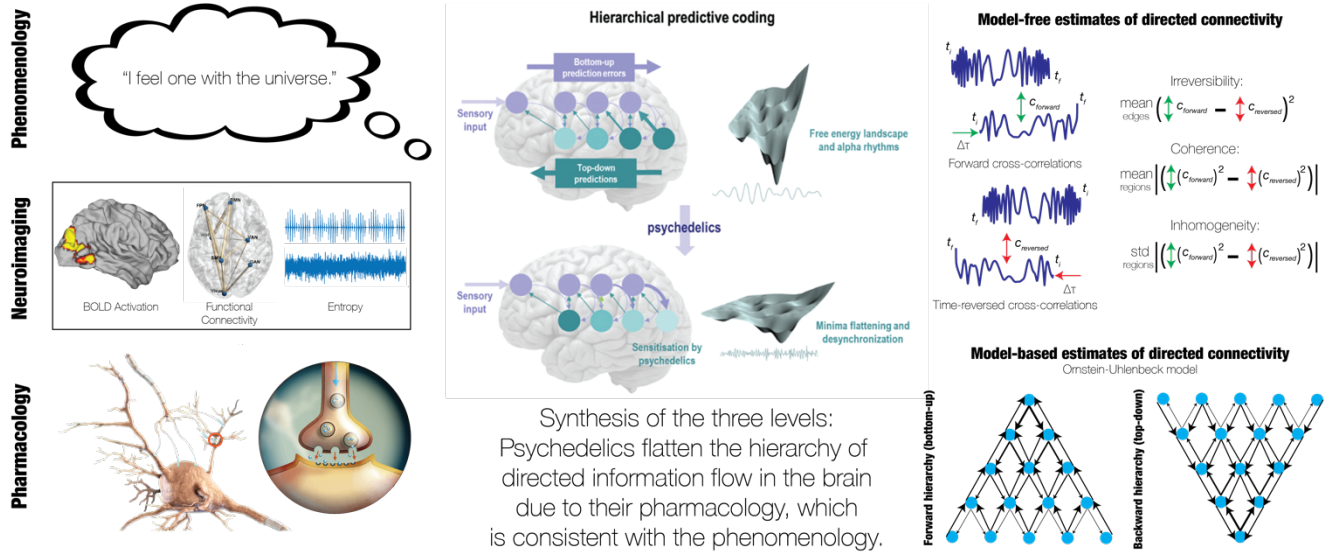


Figure 1.1. Overview of the thesis.

Psychedelics can be understood on three different levels of analysis: (1) phenomenology, captured by ratings of the subjective experience; (2) neuroimaging, captured by fMRI measures of BOLD activity, functional connectivity, and entropy; (3) pharmacology, captured by the affinity and functional activity of psychedelics at various receptors in the brain, especially the 5-HT_{2A} receptor. The RElaxed Beliefs Under pSychedelics (REBUS) framework is able to unify these three levels through a hierarchical predictive coding model of the brain (Carhart-Harris & Friston, 2019). Here, top-down expectations of the environment, or “priors,” are encoded by the activity of pyramidal neurons in deep layers of cortex, which are the same neurons in which the 5-HT_{2A} receptor tends to be expressed. Activation of the 5-HT_{2A} receptor by psychedelics decreases the weighting of the priors by increasing the sensitivity of deep-layer pyramidal neurons to bottom-up signals that convey differences between the priors and the actual sensory data about the environment. This results in amplified bottom-up excitation of deep-layer pyramidal neurons, as well as a reduction in top-down inhibition of regions that are lower in the cortical hierarchy. Consequently, psychedelics “flatten” the hierarchy of directed information flow in the brain; that is, they reduce the control of higher-order regions over lower-order regions, while enhancing the influence of the latter over the former. This suggests that the brain becomes more sensitive to the environment under psychedelics, which is consistent with phenomenological reports. We can measure the strength of hierarchy through two different approaches. In the first, hierarchy is approximated as the asymmetry of directed connectivity in MEG signals, or the difference between incoming and outgoing connections. These are estimated in a model-free manner with time-delayed correlations (cross-correlations). In the second approach, an Orstein-Uhlenbeck model is fitted to the MEG signals, which performs auto-regressions on the data to estimate an effective network of directed connections between brain regions. Using graph-theoretic techniques, I characterise the effects of psychedelics separately on the forward (bottom-up) hierarchy and backward (top-down) hierarchy. In particular, I identify changes in the hierarchical level of each brain region as well as the mean and standard deviation of differences between hierarchical levels, which, according to REBUS, are diminished by psychedelics.

Chapter 1.1.1. 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 to probe into the specific insights that psychedelic trips tend to occasion, such as awareness of previously repressed emotions (A. K. Davis, Barrett, So, 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, I performed a meta-analysis on both the 5D- and 11D-ASC scores of DMT, LSD, and psilocybin, as discussed in *Chapter 2*.

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).

Chapter 1.1.2. 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 ayahuasca, 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).

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. Therefore, I conducted a meta-analysis on the fMRI literature rather than the other modalities.

For the most part, fMRI studies on psychedelics assess three different metrics of brain activity: BOLD activation, connectivity, and entropy. (However, there are some studies that also applied various computational models to fMRI data on psychedelics, e.g., models of coupled neuronal-neurotransmitter dynamics and models that combined 5-HT_{2A} expression with population dynamics in the brain (Burt et al.,

2018; Deco, Cruzat, et al., 2018; Kringelbach et al., 2020).) 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. In *Chapter 3*, I discuss my meta-analysis on all three segments of the fMRI literature.

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).

Chapter 1.1.3. 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-HT₂) 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-HT₁ 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., 2007a; 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. In *Chapter 4*, I report the results of my quantitative meta-analysis of the affinity of DMT, LSD, and psilocin for four serotonin and two dopamine receptors in both humans and rats. Additionally, I conducted a quantitative meta-analysis of their activity at these receptors, as determined by the functional GPCR assays.

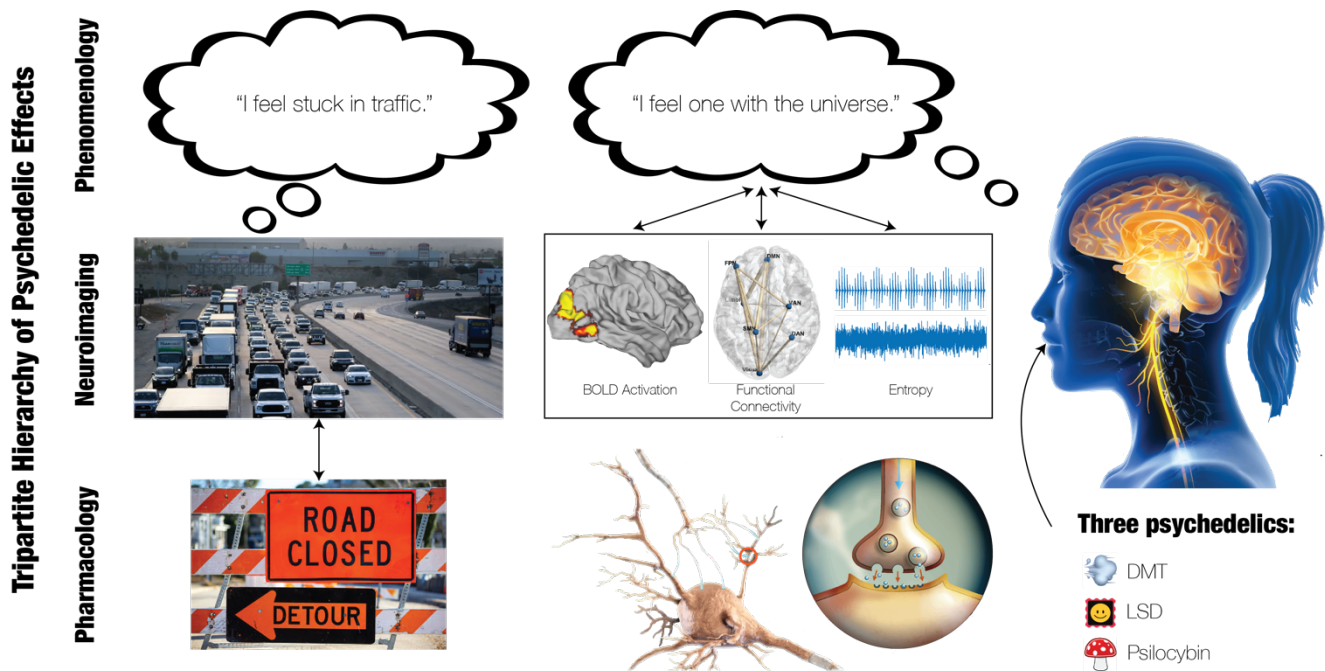


Figure 1.2. Overview of the three levels of analysis.

Psychedelics can be understood on three different levels: phenomenology (subjective experience), neuroimaging (fMRI), and pharmacology (the biochemical interactions of psychedelics with serotonergic and other receptors). By way of analogy, these three levels can be likened to traffic. Neural receptors can be thought of as traffic signs, rerouting the flow of traffic in the brain. Neuroimaging measures the traffic itself, or the flow of information. Finally, the traffic gives rise to a subjective experience. In Chapter 2, Chapter 3, and Chapter 4, I perform systematic reviews and meta-analyses on each level, comparing three different psychedelics within each level: N,N-DMT, LSD, and psilocybin.

Chapter 1.2. REBUS: A unifying framework?

As discussed above, psychedelics can be understood on three levels of analysis: phenomenology, neuroimaging, and pharmacology. However, it is difficult to relate these three levels together, due to the highly complex and nonlinear relationships that govern the effect of neural receptors on whole-brain activity, as well as the lack of knowledge about the neural mechanisms that encode subjective experience.

Nevertheless, an influential theory known as RElaxed Beliefs Under pSychedelics (REBUS) may be capable of unifying the three levels (Carhart-Harris & Friston, 2019). REBUS is based on the predictive coding framework, according to which the brain generates models that make top-down predictions about the world based on certain “priors” (or assumptions). The models are updated whenever those predictions are proven wrong by bottom-up “prediction errors,” which reflect discrepancies between the predictions and sensory evidence about the environment (Holmes & Nölte, 2019; Knill & Pouget, 2004; Seth & Friston, 2016). Both priors and prediction errors are weighted by their precision, which corresponds to confidence. Thus, when confidence in the priors is high, perception is dominated by the priors rather than by information from the environment. According to REBUS, depression, anxiety, and other psychiatric illnesses can be cast as disorders of overweighted priors that correspond, for instance, to negative beliefs such as “I am worthless” or “the world is terrible.” Furthermore, these beliefs do not get updated when new information from the environment arrives, so, for example, positive interactions with other people are unable to alter the symptoms of depression.

REBUS hypothesises that psychedelics relax the precision weighting of the priors. In other words, psychedelics loosen the suppressive influence of top-down predictions on the processing of bottom-up sensory information. Thus, psychedelics can be therapeutic because they reduce the control that strongly-held beliefs exert over sensory perception. Patients with depression can be freed from the oppression of pathological beliefs. 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; M. Johnson, 2019). Under REBUS, these new equilibria would correspond to novel beliefs.

According to REBUS, priors are encoded by layer V pyramidal neurons, which are the same neurons that express 5-HT_{2A} receptors on their apical dendrites (Aleksandrova & Phillips, 2021; Hamada et al., 1998; Jakab & Goldman-Rakic, 1998). Activating these receptors disinhibits layer V pyramidal neurons and increases their sensitivity to ascending prediction errors from lower layers of cortex. Furthermore, 5-HT_{2A} receptors are expressed most densely in layer V neurons within associative, “transmodal” networks such as the default mode network (DMN), which psychedelics strongly dysregulate according to neuroimaging studies (Atasoy et al., 2017; F. S. 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). Finally, disrupted activity and connectivity in these networks correlate with the intensity of certain subjective experiences on psychedelics, such as ego dissolution. Therefore, REBUS links the pharmacology, neuroimaging, and phenomenology of psychedelics.

However, it is extremely challenging to test REBUS because it is unclear how priors are instantiated in the brain, as well as how priors are related to the beliefs that are modified by psychedelics. It is much easier to evaluate the implications of REBUS for the hierarchy of directed connectivity in the brain. In particular, high precision-weighting of priors implies strong top-down inhibition from higher-order, associative networks, whereas relaxed priors (and increased precision-weighting of prediction errors) correspond to elevated bottom-up excitation from lower-order, sensory networks (R. L. Carhart-Harris & Friston, 2019; Rajpal et al., 2022). In other words, psychedelics “flatten” the hierarchy of directed connectivity by reducing the inhibitory control of higher-order regions over lower-order regions and amplifying the ability of the latter to influence the former.

Girn et al. (2022) provided evidence for a flattened hierarchy under psychedelics by using a nonlinear dimensionality reduction technique to uncover a “principal gradient” or axis of brain connectivity spanning unimodal and transmodal cortices. Based on fMRI data of human participants who were administered LSD or psilocybin, the study determined that psychedelics contracted or flattened the principal gradient, effectively implying more “cross-talk” or connectivity between the unimodal cortices at one end of the gradient and the transmodal cortices at the other end. This finding has now been replicated in an fMRI study on DMT (Timmermann et al., 2023). Other research has extracted “backward” (top-down) and “forward” (bottom-up) travelling waves from EEG data and demonstrated that DMT suppresses the former while elevating the latter (Alamia et al., 2020; Timmermann et al., 2023). Finally, psilocybin decreases directed information flow, as measured with Granger causality in MEG data, towards frontal regions of the brain and away from more posterior areas (Barnett et al., 2020).

In *Chapter 5* and *Chapter 6*, I put REBUS to the test by evaluating the effect of LSD on two different measures of hierarchy, which were estimated on MEG data. These measures are described in further detail below.

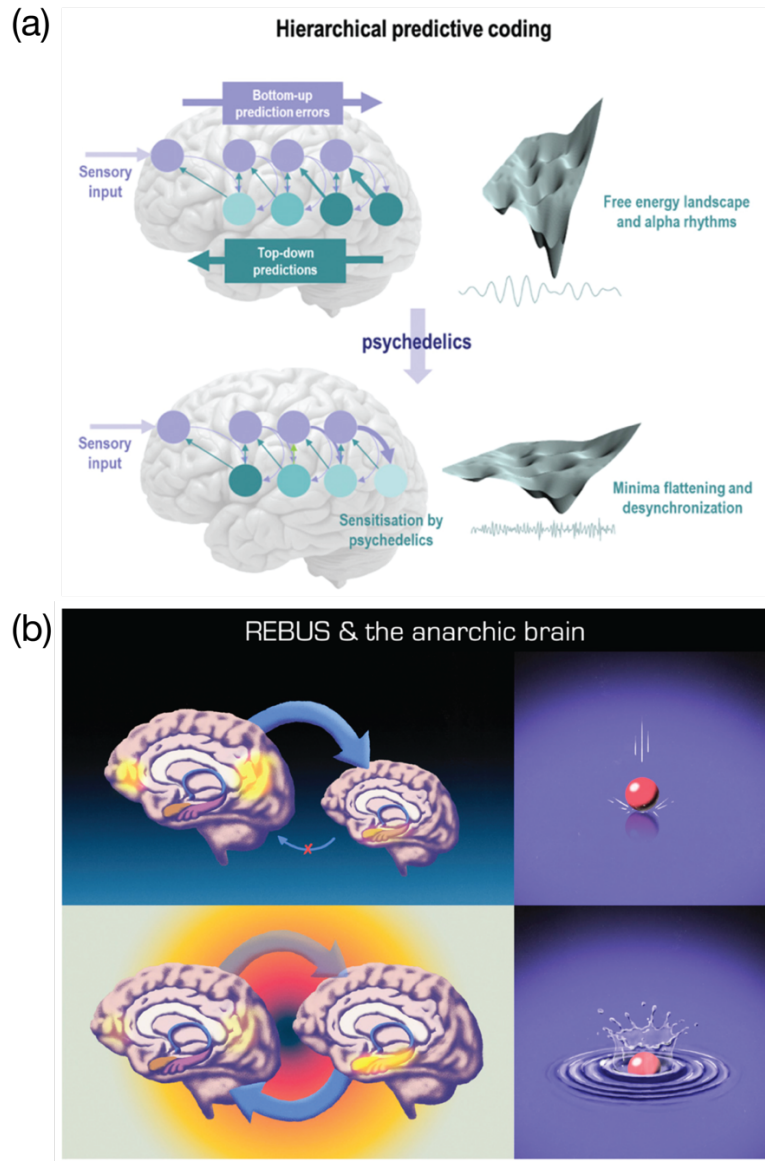


Figure 1.3. Schematic of the RELaxed Beliefs Under pSychedelics (REBUS) framework.

(a) REBUS claims that psychedelics decrease the precision-weighting of top-down priors, or expectations. Precision-weighting refers to the confidence in the priors. High precision-weighting of priors means that perception is dominated by the priors rather than bottom-up prediction errors. In other words, priors at higher-order levels of the hierarchy, which correspond to associative cortices, strongly inhibit bottom-up excitation from lower-order levels, which correspond to sensory cortices. By decreasing the precision-weighting of priors, psychedelics sensitise the higher-order regions to prediction errors ascending from the lower-order regions. This entails a “flatter” free energy landscape, in which the free energy corresponds to the amount of prediction error; in other words, because the brain is less confident about a particular expectation of the environment, it is willing to entertain or explore a wider set of expectations about reality. (b) The upper panel of this schematic illustrates a normal, sober state of consciousness, in which strongly weighted priors inhibit bottom-up excitation. Consequently, consciousness, which is represented by a pond on the right side of the image, is not affected very much by an external stimulus, which is represented by the red ball. The lower panel depicts the psychedelic state, in which top-down and bottom-up information flow become more balanced as ascending prediction errors have a greater ability to influence the states of higher-order neurons. Hence, consciousness is more affected by the environment. Images taken from Carhart-Harris & Friston (2019).

Chapter 1.3. Hierarchy

Chapter 1.3.1. Many meanings of hierarchy

Before defining the measures of hierarchy that I used, it is first worth qualifying that there are many meanings of the word hierarchy. Hilgetag & Goulas identify at least four major definitions of hierarchy in neuroscience: (1) a sequence of structural connections in the brain; (2) a gradient of features such as cortical thickness or neuron density; (3) a progression of scales from local (micro) to global (macro) organisation; and (4) forward and backward projections between different cortical layers (Hilgetag & Goulas, 2020). It is unclear whether a single dose of psychedelics can modify structural connectivity (definition 1), cortical thickness (definition 2), or the orientation of inter-laminar projections (definition 2), though chronic users of ayahuasca apparently have thinner posterior cingulate cortices (Bouso et al., 2015). Additionally, the principal gradient discussed in the previous subchapter is not a gradient in the same sense as described by Hilgetag & Goulas (definition 2); the former is an axis in which points that are close to each other are functionally connected, whereas the latter describes a smooth, gradual change in a parameter such as neuron density. An example of the local-to-global hierarchy (definition 3) is a hierarchical modular network, in which the brain is organised as a module of modules of modules. Multiple fMRI studies have shown that psychedelics decrease modularity (F. S. Barrett, Krimmel, et al., 2020; Tagliazucchi et al., 2016), but they have not established that psychedelics modify the *hierarchical* organisation of modularity. The forward and backward projections in definition (4) are structural and therefore unlikely to be modulated by psychedelics. Thus, to date, there are no studies on psychedelics that have measured aforementioned types of hierarchy. However, if forward and backward projections are defined in a functional manner, then MEG/EEG studies of forward and backward travelling waves, as well as other such studies of directed functional connectivity, do illuminate the effects of psychedelics on hierarchy.

I propose that REBUS can be tested by measuring the *directional asymmetry* of brain connectivity. In general, all hierarchies must exhibit directional asymmetry. The nodes at the top control the nodes in the rest of the hierarchy, but not the other way around. If the connections (edges) in the network reflect the relevant modes of control, then the difference between the weights of the top-down and bottom-up edges captures the overall strength of hierarchy. Thus, a strong hierarchy, as defined by REBUS, implies that top-down inhibition from higher-order regions and bottom-up excitation from lower-order regions are asymmetric; the former dominates the latter. REBUS implies that psychedelics increase the symmetry of directed information flow in the brain. In *Chapter 5* and *Chapter 6*, I apply two different measures of directional asymmetry to MEG data on psychedelics.

Chapter 1.3.2. Irreversibility

The first is the irreversibility of pairwise connections between regions of the brain, as measured with the INSIDEOUT algorithm. The irreversibility of the connectivity between a region A and a region B reflects the difference between connectivity from A to B and connectivity from B to A . Thus, irreversibility corresponds to the directedness of connectivity. When it was originally introduced in 2022, INSIDEOUT was used to measure irreversibility in three different states of consciousness among macaque monkeys: awake, sleep, and anesthesia (Deco et al., 2022). Sleep and anesthesia, except for ketamine-induced anesthesia, robustly increased reversibility relative to wakefulness; furthermore, changes in irreversibility more effectively differentiated between states of consciousness than undirected functional connectivity. (Irreversibility also distinguishes task-induced brain states better than undirected functional connectivity (Tewarie et al., 2023).) Accordingly, reversibility is significantly higher in patients with disorders of consciousness (G-Guzmán et al., 2023).

In *Chapter 5*, I measure the irreversibility of directed, time-delayed correlations between MEG amplitude envelopes, with the hypothesis that LSD increases reversibility. However, irreversibility is not a sufficient condition for hierarchy; a set of nodes with irreversible connections but a circular topology is non-hierarchical, as explained in *Chapter 5*. I also quantify two related measures that capture the asymmetry of directed connectivity, namely the mean (hierarchical coherence) and the standard deviation (hierarchical inhomogeneity) of the imbalance between incoming and outgoing connections. While irreversibility is computed on each connection, hierarchical coherence and inhomogeneity are measured for each brain region. Unlike irreversibility, hierarchical coherence and inhomogeneity are necessary and sufficient conditions for hierarchy; nodes with larger incoming-outgoing imbalances are situated higher in the hierarchy.

Chapter 1.3.3. Trophic coherence and hierarchical levels

In *Chapter 5*, I measure irreversibility and hierarchical coherence/inhomogeneity separately, but in *Chapter 6*, I discuss a framework, trophic coherence, that mathematically relates these two quantities and thereby decomposes networks into hierarchical levels. I then apply an extension of this framework that distinguishes between “forward” (bottom-up) and “backward” (top-down) hierarchical levels; information tends to flow *towards* nodes with a high forward hierarchical level, whereas information tends to flow *away* from nodes with a high backward hierarchical level. This framework enables us to measure the effect of psychedelics not only on the overall strength of hierarchy (the mean and standard deviation of differences between hierarchical levels), but also on the relative positions of brain regions within both the top-down and bottom-up hierarchy.

Chapter 1.3.4. Entropy production, entropy, and hierarchy

Recent pioneering work by my colleagues showed that the strength of hierarchy in a network determines the amount of entropy production in the dynamics that take place along the network (Nartallo-Kaluarachchi et al., 2024). Entropy production is equivalent to irreversibility, or the difference between the probability of transitioning from a state A to a state B and the probability of transitioning from B back to A . However, the finding that the directedness of network topology corresponds to the entropy production of network dynamics is not trivial, since entropy production is the irreversibility of *state* transitions but not necessarily the asymmetry of directed connections between *nodes*. In *Chapter 6*, I measure the hierarchical levels of an effective brain network, which was estimated in a way that also enables me to directly solve the amount of entropy production in the brain. My aim is to demonstrate that a flattened hierarchy of effective connectivity under LSD decreases entropy production in the brain. Previous work applying the OU model to fMRI data showed that wakefulness is associated with increased entropy production compared to deep sleep (Gilson et al., 2023).

This result appears to contradict the evidence that psychedelics increase entropy, which is one of the most consistent findings in the psychedelic neuroimaging literature. (A full account of all the definitions of entropy is given in *Appendix 3*.) However, entropy and entropy production are distinct concepts. Entropy production is equivalent to irreversibility, while entropy corresponds to the number of ways in which the microscopic states of a system can be arranged, given the macroscopic constraints of the system (e.g., constant energy, volume, number of particles, etc.). When entropy in an isolated system is maximised at equilibrium, entropy production must be zero because it is impossible for entropy to decrease over time within an isolated system, according to the Second Law of Thermodynamics. Thus, maximising entropy is consistent with minimising entropy production. Furthermore, all equilibria respect detailed balance; the probability of the transition from a state A to a state B is the same as the probability of the time-reversed transition from B back to A (G. N. Lewis, 1925). This is equivalent to the statement that all equilibria are fundamentally reversible in time. Indeed, maximal entropy implies that the system can be arranged into a maximally large number of states, which means that one state cannot be more likely than another. Therefore, the probability of transitioning towards any one state must be equal to the probability of transitioning away from it. Any breaking of detailed balance implies that entropy is being *produced* in the system (Carnot, 1824). Therefore, the irreversibility of brain activity directly corresponds to the rate of entropy production in the brain. This correspondence was explicitly formalised in Crookes' fluctuation theorem, which states that entropy production is exponentially related to the ratio between the probabilities of forward and reverse transitions (Crooks, 1998).

True reversibility only occurs when the brain is in equilibrium, where there is no macroscopic change in the system; that is, on net, neither energy nor matter flow into or out of the system. There is no such thing

as true equilibrium in any living being, for all biological systems require net inputs of energy in order to function; indeed, scientists dating as far back as Erwin Schrödinger have argued that the very essence of life is the persistent act of resisting the decay to thermodynamic equilibrium by maintaining low entropy (Schrodinger, 1944). The notion that psychedelics decrease entropy production (and increase entropy) seems to suggest that psychedelics bring the human brain closer to a state of death, when in fact consciousness becomes much richer and more vivid under the influence of these drugs.

Undoubtedly, psychedelics do not bring the brain into a state of true equilibrium, but they may increase the incidence of local and transient *statistical* equilibria. In statistical equilibrium, the probability distribution of the microscopic states of a system remains constant over time. That is, while individual particles in a system (e.g., molecules in a gas) may exhibit fluctuations in their states (e.g., velocities), the overall distribution does not change. In statistical non-equilibrium, there may be “pockets” of local or transient equilibria in which the probability distribution of a subset of states remains constant; for instance, the rates of forward and reverse reactions may temporarily become equal within a particular cellular process, leading to a stable concentration of molecules, while the rest of the cell is far from equilibrium (Ho, 2008). In the brain, local and transient equilibria could include periods of time in which the connectivity directed away from a region becomes equal to the connectivity directed towards the region, yielding a briefly stable concentration of, for instance, neurotransmitters exchanged between regions. Thus, the decrease in entropy production under psychedelics may imply greater symmetry in directed connectivity, precisely as I show in this thesis.

Chapter 1.4. Magnetoencephalography (MEG)

In *Chapter 5* and *Chapter 6*, I measure the effects of psychedelics on hierarchy in MEG data. While there are at least 30 original fMRI datasets on psychedelics, as discussed in the meta-analysis, there are only two MEG datasets in existence: one on psilocybin and the other on LSD (R. L. Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013). I chose to examine MEG rather than fMRI data because the former has much higher temporal resolution and is therefore better suited for capturing dynamics (Hall et al., 2014). MEG has revealed that resting-state networks activate on timescales that are as short as 200 milliseconds, which is typically one order of magnitude lower than one sample of an fMRI timeseries (A. P. Baker et al., 2014). Thus, MEG makes it possible to assess the evolution of directed connectivity and hierarchy over much faster timescales than fMRI. While EEG also has higher temporal resolution than fMRI, the EEG signal is much more distorted by the skull and cerebrospinal fluid than the MEG signal, and its spatial resolution is also worse than that of MEG (Singh, 2014).

Additionally, psychedelics are vasoconstrictors (Dyer & Gant, 1973), which significantly confounds the fMRI signal. Indeed, vasoconstriction reduces oxygen levels in blood and therefore diminishes the fMRI signal (Özbay et al., 2019), which indirectly measures brain activity via blood oxygenation (Hillman, 2014). Hence, fMRI studies may underestimate brain activity on psychedelics; reported activations could be lower and less extensive than they are in the actual brain. Studies showing that psychedelics decrease fMRI activity did not consider the contribution of vasoconstriction to the fMRI signal (R. L. Carhart-Harris, Erritzoe, et al., 2012). On the other hand, MEG is not susceptible to the effects of vasoconstriction because it measures an entirely different signal than fMRI does. Thus, MEG is a better tool than fMRI for capturing the neural correlates and mechanisms of psychedelics.

MEG captures the magnetic field generated by postsynaptic potentials (PSPs), which are generated when neurotransmitters, upon binding to the receptor of a postsynaptic neuron, cause ions to flow across the postsynaptic membrane (Velmurugan et al., 2014). PSPs can be thought of as the “inputs” into neurons, whereas action potentials, which fire after the neuron integrates hundreds to thousands of excitatory and inhibitory PSPs, are the outputs. The magnetic field associated with a single PSP is way too small to be detected; in fact, over 50,000 PSPs must occur simultaneously in order to generate a detectable field (P. C. Hansen et al., 2010). The magnetic field of each PSP is a dipole, and the PSPs must not only be synchronous but also parallel to each other in order for the dipoles to reinforce one another. Additionally, according to the right-hand rule, the magnetic dipole is perpendicular to the PSP, so MEG detects “tangential” dipoles that are perpendicular to the cortical surface, whereas radial dipoles, which are parallel to the cortical surface, do not contribute to the MEG signal. Because pyramidal neurons are not only parallel to each other but also perpendicular to the cortical surface, MEG mostly detects the PSP inputs into pyramidal neurons (da Silva, 2010).

Using MEG to estimate the activity of neural sources, rather than merely the activity recorded at the channels, is a fundamentally ill-posed problem because there are far more sources (up to tens of thousands) than there are channels (typically no more than 306). “Source reconstruction,” as it is called, requires not only a forward model, in which the magnetic field detected at a channel is determined as a function of the current at each source, but also a solution to the inverse problem, in which the activity at each source is a function of the recorded magnetic field at the channels. To construct a biologically plausible forward model, techniques such as the boundary element method and finite element method leverage structural MRIs of each participant’s brain to model the geometry of the head (Baillet et al., 2001). Furthermore, through coregistration, the coordinates of the MRI can be mapped to the coordinates of the head in the MEG coordinate system.

There are at least three popular solutions to the inverse problem. The first is the equivalent current dipole (ECD), which assumes that the recorded activity at each channel is generated by a very small number (typically no more than five) of localised, simultaneously active dipoles (Salmelin, 2010). While this assumption may hold true in simple experimental paradigms when an external stimulus is expected to evoke PSPs at only a small number of local brain regions, it clearly does not apply well to the resting state or altered states of consciousness, which likely affect very spatially distributed patterns of brain activity (Barttfeld et al., 2015; Boly et al., 2013; Dehaene & Changeux, 2011; Oizumi et al., 2014). The second family of solutions is distributed source imaging, in which the recorded activity is assumed to arise from thousands of neural sources, such as a set of vertices on the cortical surface. However, because the sources outnumber the channels by at least one order of magnitude, additional assumptions must be made in order to solve the inverse problem. One common assumption is the minimum norm estimate, i.e., that the solution should minimise the sum of squared currents (Matsuura & Okabe, 1995). On face, however, it is unclear why such an assumption would be true; certain conditions may maximise activity in a subset of brain regions, but such a distribution would not be observed under a solution that minimises activity across all regions. The final approach to source reconstruction is beamforming, in which spatial filters are constructed for every neural source (Van Veen & Buckley, 1988). These filters apply a weight to the contribution of each sensor to the overall output of the beamformer. A common method for optimising these weights is the linearly constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997). Here, the aim is to find the weights that minimise the variance of the beamformer output subject to the constraint that the gain for the output from the source is the identity matrix; in other words, the beamformer neither amplifies nor diminishes the signal from the source. Beamforming has several advantages over the other two source reconstruction techniques. In particular, it does not pre-specify the number of neural sources, it suppresses activity from irrelevant sources, and it does not minimise large contributions from individual sources (A. Baker, 2014; Hillebrand & Barnes, 2003).

In *Chapter 5* and *Chapter 6*, I apply LCMV beamforming to perform source reconstruction on a MEG dataset of 16 healthy human participants who were administered LSD. This dataset was previously acquired by my collaborators at Imperial College London (R. L. Carhart-Harris et al., 2016). Each participant was administered both LSD (75 micrograms) and placebo on two separate days, and they underwent four experimental conditions in each session: eyes-open resting-state, eyes-closed resting-state, listening to music, and watching a silent video.

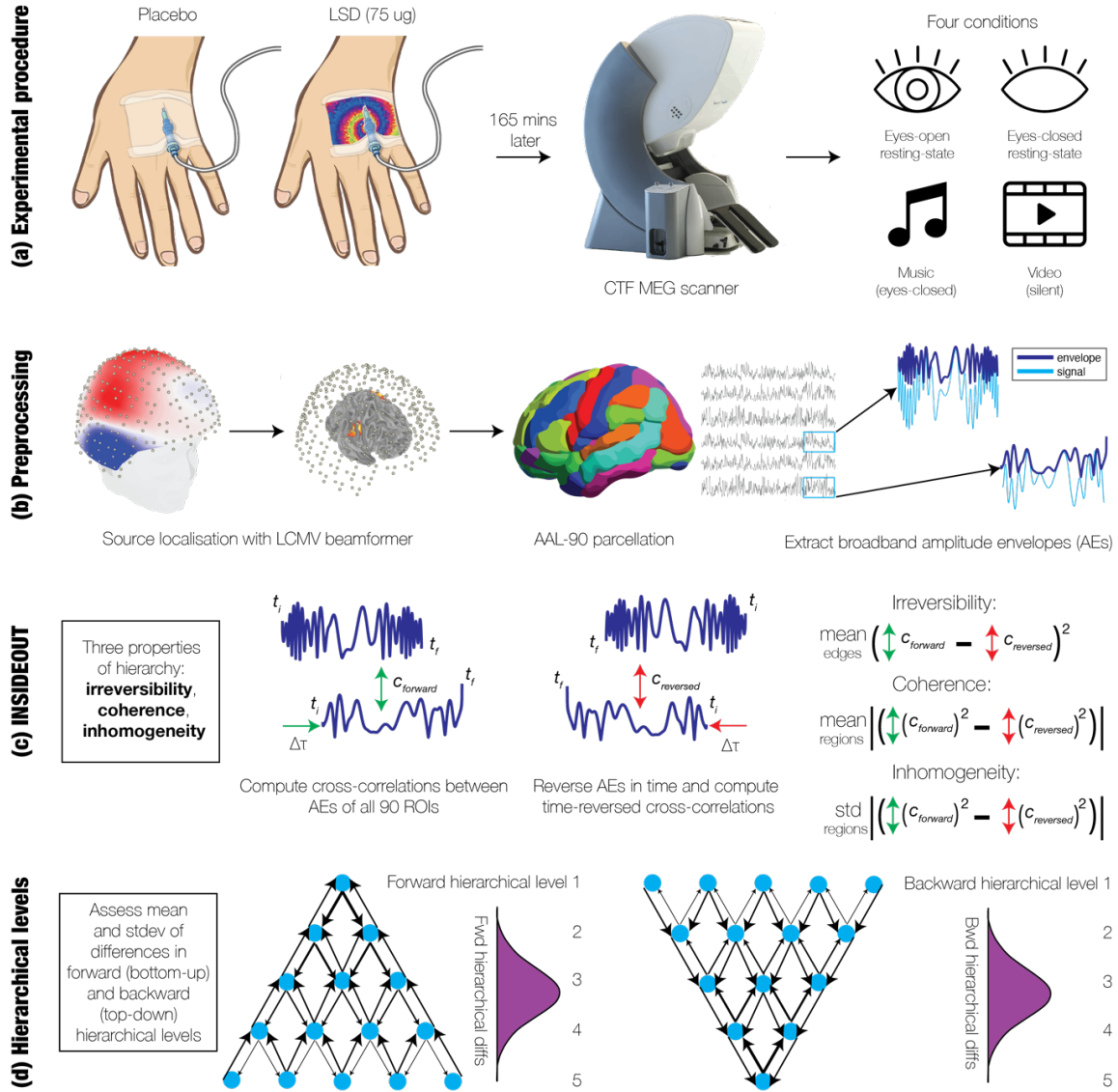


Figure 1.4. Overview of MEG data and analysis.

(a) Sixteen human participants were each administered placebo and 75 micrograms (μg) of LSD in two separate sessions (Carhart-Harris et al., 2016). Each session included four separate conditions: eyes-open resting-state, eyes-closed resting-state, listening to music with eyes closed, and watching a silent video. (b) The MEG data was preprocessed with methods described in a previous study (Mediano et al., 2024). Source localisation was performed using a linearly-constrained minimum variance (LCMV) beamformer. Broadband amplitude envelopes (AEs) were extracted via the Hilbert transform from 90 regional timeseries, which were parcellated with the Automated Anatomic Labelling (AAL) atlas. (c) I assessed three different properties of hierarchy – irreversibility, hierarchical coherence, and hierarchical inhomogeneity – based on the asymmetry in the connectivity between the forwards and time-reversed AEs. The irreversibility reflects the magnitude of the difference between connectivity from a region B to a region A and connectivity from A to B. Coherence and inhomogeneity are the mean and standard deviation of the incoming-outgoing asymmetry, i.e., the difference between the magnitude of incoming connections ($B \rightarrow A$) and the magnitude of outgoing connections ($A \rightarrow B$) at each region. (d) I estimated the forward (bottom-up) and backward (top-down) hierarchy of a network of effective connectivity under psychedelics. Regions with high forward or backward hierarchical levels correspond to regions that a lot of information flows towards and away from, respectively. We measure the effect of LSD on not only the forward and backward hierarchical levels, but also the mean and standard deviation of the differences between the forward and backward levels.

Chapter 1.5. Chapter summary

Psychedelics can be understood on three different levels of analysis: phenomenology, or subjective experience; neuroimaging; and pharmacology. *Chapter 2*, *Chapter 3*, and *Chapter 4* will present the results of my systematic review and meta-analysis of each level, in that order. Additionally, psychedelics are known to increase the entropy, or variability, of brain activity. Previous work has shown that entropy *production*, or irreversibility, reflects the strength of hierarchy in a network. In *Chapter 5* and *Chapter 6*, I test the theory that psychedelics flatten brain hierarchy and concomitantly the effects of these drugs on entropy production.

Chapter 2. Phenomenology Meta-Analysis

Chapter 2.1. Chapter abstract

Psychedelics are known to induce altered states of consciousness. Their effects on subjective experience have been measured using a variety of questionnaires, including the 5-dimensional and 11-dimensional Altered States of Consciousness scale (5D-ASC & 11D-ASC). Here, I performed a multilevel random-effects meta-analysis on the 5D- and 11D-ASC data. In the 5D case, LSD ranked significantly higher than psilocybin in the visionary restructuralisation (VR) dimension, which measures the intensity and quality of visual hallucinations, for both medium and high doses. LSD also received significantly higher scores in the oceanic boundlessness (OB) dimension, which characterises feelings of interconnectedness and unity on psychedelics. The 11D-ASC analysis revealed significant differences between LSD and psilocybin in VR and OB subscales, as well as one subscale of anxious ego dissolution (AED), for only medium doses.

Chapter 2.2. Literature search

We firstly performed a quantitative meta-analysis of studies that measured the subjective effects of DMT, LSD, and psilocybin using the 5-dimensional and 11-dimensional versions of the Altered States of Consciousness (ASC) scale. We focused on these scales because they are the most commonly-used questionnaires in the fMRI literature. We also qualitatively reviewed the studies that directly compared the phenomenology of DMT/ayahuasca, LSD, and psilocybin (*Section S3*).

We conducted our literature search of the ASC data in August 2023. We examined four databases: SCOPUS, Web of Science, the Altered States Database, and Google Scholar. There were two studies that we “independently discovered” from citations in the included papers; these studies did not appear on any of the databases. The Altered States Database (alteredstatesdb.org) is a publicly available website that displays data from several different questionnaires about a variety of altered states of consciousness (Prugger et al., 2022; Schmidt & Berkemeyer, 2018). It is not exhaustive, however, as we identified several ASC studies on psychedelics that were not included in the database. Search terms followed the format “<drug name> AND <scale name>”, where “drug name” was “LSD”, “psilocybin”, “DMT”, or “N,N-dimethyltryptamine” and “scale name” was “ASC”, “5D-ASC”, or “11D-ASC”. We excluded papers based on the following criteria:

1. Work that did not report any original experiments or analyses, such as literature reviews, commentaries and editorials.

2. Studies that did not examine one or more of three classical psychedelics: DMT, LSD, psilocybin. Note that we did not include studies on ayahuasca for this meta-analysis.
3. Studies that did not use the ASC scale.
4. Studies that did not report original ASC data.
5. Studies that were conducted in a clinical population of participants, such as depressed participants. Only studies on healthy human participants were included.
6. Studies in which the participants were meditators or learning meditation, as these participants may experience psychedelics in significantly different ways than non-meditators do.
7. Studies on extended DMT, a recently-developed experimental technique that prolongs the duration of the DMT trip (Luan et al., 2023).
8. Studies on microdosing, since the subjective effects of microdosing are often indistinguishable from those of placebo (Bershad et al., 2020).
9. Studies that reported data in unclear units.
10. Original studies that administered the ASC questionnaire to participants but did not publish any ASC data. This includes studies that measured and reported correlations between ASC results and other metrics, but did not actually report the ASC scores themselves.

A PRISMA flowchart of the literature search is shown in **Figure 2.1**. Our search yielded ***n* = 44 studies in total** (Becker et al., 2023; Bernasconi et al., 2014; Carbonaro et al., 2018; Carter, Burr, et al., 2005; Carter, Pettigrew, et al., 2005; Carter et al., 2007; Daumann et al., 2008; Duerler et al., 2020; Family et al., 2022; Gouzoulis-Mayfrank et al., 2005; Hasler et al., 2004; Holze et al., 2020, 2021, 2022; Kometer et al., 2012; Kraehenmann, Preller, et al., 2015; Kraehenmann et al., 2017; C. R. Lewis et al., 2017; Ley et al., 2023; Madsen et al., 2021; Mallaroni et al., 2023; Mason et al., 2020; McAlpine et al., 2023; F. Müller, Lenz, Dolder, Lang, et al., 2017; Ort et al., 2023; Pallavicini et al., 2021; Pokorny et al., 2016, 2017, 2020; Preller et al., 2016, 2017, 2020; Quednow et al., 2012; Schmid et al., 2015; A. Schmidt et al., 2012, 2018; Smigielski et al., 2020; Straumann et al., 2023; Timmermann et al., 2023; Umbricht et al., 2002; Vogt et al., 2023; Vollenweider et al., 2007; Wießner et al., 2023; Wittmann et al., 2007). These included ***n* = 21 studies on the 5D-ASC** and ***n* = 31 studies on the 11D-ASC**; there were *n* = 11 studies that administered both versions of the questionnaire. The 5D-ASC literature included *n* = 3 studies on DMT, *n* = 9 studies on LSD, and *n* = 12 studies on psilocybin. The 11D-ASC literature contained *n* = 3 studies on DMT, *n* = 12 studies on LSD, and *n* = 17 studies on psilocybin. Two studies of both versions of the scale gave both LSD and psilocybin to participants (Holze et al., 2022; Ley et al., 2023). Data from a total of 1,037 participants were examined in the meta-analyses (DMT: 111 participants; LSD: 394 participants; psilocybin: 592 participants). Two of the

5D-ASC studies on DMT measured subjective effects for only three of the dimensions, so the remaining two dimensions (auditory alterations and reduction of vigilance) were only examined by a single study (Vogt et al., 2023). Additionally, two of the 11D-ASC studies on DMT did not report standard errors (Pallavicini et al., 2021; Timmermann et al., 2023). In our meta-analyses, we pooled ASC scores by weighting each one by its inverse variance (squared standard error), so the standard errors were essential. We reached out to the authors for the standard errors but did not hear back. Since there was only one 11D-ASC study on DMT that did publish standard errors, we decided not to perform a meta-analysis of the 11D-ASC data on DMT.

Many studies reported numerical 5D- and 11D-ASC data. However, others merely displayed plots of the data. We chose not to email the authors for the numerical data, since it could be very time-consuming to wait for responses. Instead, we translated graphical data into numerical data by counting the number of pixels that corresponded to ASC scores. For instance, in a bar plot of ASC scores, the length of each bar in pixels would indicate the ASC score. By dividing this length by the length of the relevant axis, we obtained the numerical ASC data. While this technique is imprecise, we found that it generally succeeded when we tested it on studies for which numerical data existed.

In order to determine the neural correlates of the subjective effects of each psychedelic, which we did for the purpose of comparing phenomenology to neuroimaging and pharmacology, we conducted a separate literature search in SCOPUS and the Altered States Database. We identified three new studies from this search (Mueller et al., 2018; Northoff et al., 2005; Scheidegger et al., 2016).

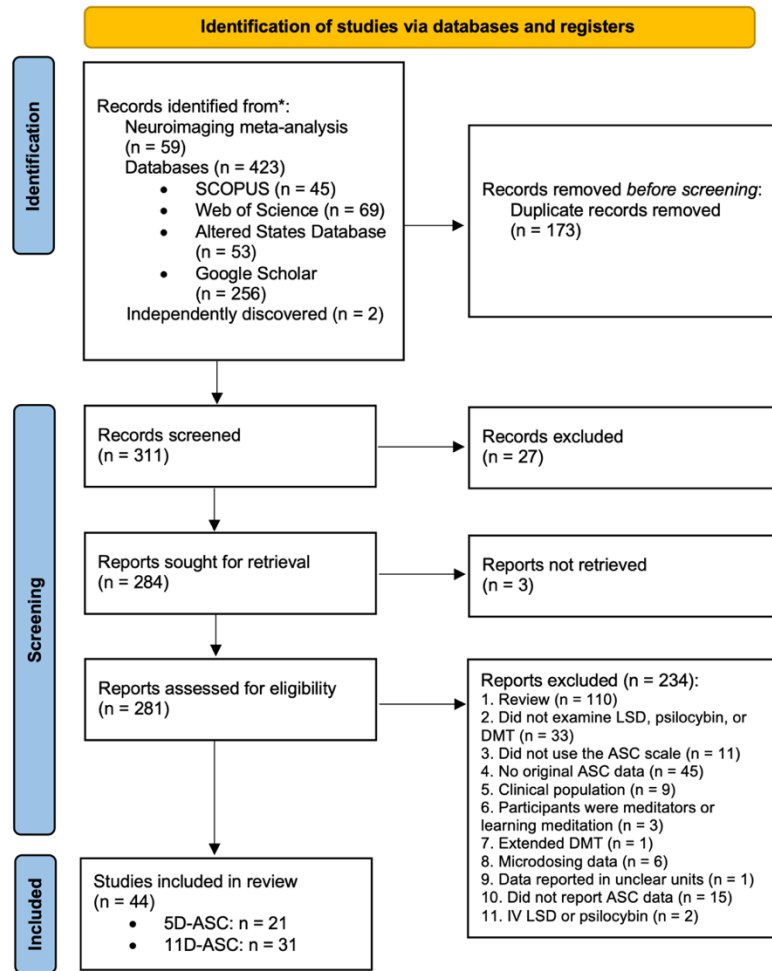


Figure 2.1. PRISMA flowchart for phenomenology literature search.

PRISMA is a set of guidelines for performing systematic reviews and meta-analyses. 21 5D-ASC and 31 11D-ASC studies were extracted from the literature search.

Chapter 2.3. Methods

There are two versions of the Altered States of Consciousness: one that measures five dimensions (5D) of consciousness and another that measures eleven dimensions (11D). While the eleven dimensions are subscales of the five dimensions, the two versions of the questionnaire do not have an equal number of questions, so the 11D data cannot be averaged across subscales to obtain 5D data. Therefore, we had to perform separate meta-analyses of the 5D- and 11D-ASC data.

In addition to measuring multiple subjective dimensions, ASC studies administered multiple doses of a psychedelic to the same group of participants, and a few also gave different psychedelics to the same group. Therefore, the ASC scores are not statistically independent from one another, which violates a core

assumption of a traditional meta-analysis. A three-level meta-analysis accounts for these statistical dependencies (Harrer et al., 2021). The three levels are: (1) the effect sizes, or ASC scores, of individual participants; (2) the pooled effect size, or overall ASC scores, of each dimension, dose, and drug; and (3) the pooled effect size of the whole study. Thus, in this model, multiple effect sizes can be nested within one study. The three-level model fits the data to the following formula (Assink & Wibbelink, 2016; Cheung, 2014):

$$\hat{\theta}_{ij} = \mu + \beta x_i + \zeta_{(2)ij} + \zeta_{(3)ij} + \epsilon_{ij} \quad (2.1)$$

where $\hat{\theta}_{ij}$ is an estimate of the true effect size i (ASC score) nested in study j , β is the regression weight of a predictor variable x , μ is the true (population) effect size, $\zeta_{(2)ij}$ is the within-study heterogeneity, $\zeta_{(3)ij}$ is the between-study heterogeneity, and finally ϵ_{ij} is the sampling error.

To account for the fact that not only effect sizes but also sampling errors within studies are correlated with each other, we specifically applied an extension of the three-level model known as the Correlated and Hierarchical Effects (CHE) model with Robust Variance Estimation (Hedges et al., 2010; Pustejovsky & Tipton, 2022; Tipton & Pustejovsky, 2015). Essentially, this technique estimates the true dependence structure (variance-covariance matrix) between effect sizes within the same study, given a known correlation coefficient ρ between those effect sizes. We assumed $\rho = 0.6$, as a previous meta-analysis recommended this correlation coefficient (Harrer et al., 2021); however, the choice of ρ was apparently arbitrary in this meta-analysis, and we did not run any sensitivity analyses to confirm that this ρ was appropriate. When the number of studies in a meta-analysis is small (under 40, which is the case for this meta-analysis), traditional variance estimators tend to be biased. We reduced the risk of bias by adjusting the estimated variance with bias-reduced linearisation (CR2 method) (Tipton & Pustejovsky, 2015).

In our model, effect sizes were pooled using the generic inverse variance method (see *Section S2.3*). Effect sizes for each dose, dimension, and drug were modeled as random effects nested within the study, which serves as a grouping variable and higher-level random effect. Within- and between-study heterogeneity were estimated with the restricted maximum-likelihood procedure. We applied the Knapp-Hartung method to adjust the standard errors of the β weights in order to provide more conservative estimates of the p -value (Knapp & Hartung, 2003). All of the above analyses were carried out with the *dmeter* package in R (Harrer et al., 2021).

DMT was administered intravenously in the phenomenological studies whereas LSD and psilocybin were administered orally (we excluded phenomenological studies that used IV LSD and psilocybin). IV administration yields different pharmacokinetics, which are known to influence the subjective experience of the drug (Luan et al., 2023; Vogt et al., 2023). Therefore, while we conducted meta-analyses of all three drugs,

we only examined significant differences between ASC ratings of LSD and psilocybin. Additionally, we only measured significance for similar doses of LSD and psilocybin. We assumed 20 mg psilocybin is equivalent to 0.01 mg LSD (Ley et al., 2023), and we defined low, medium, and high doses based on the literature (Carbonaro et al., 2018; Hasler et al., 2004; Vollenweider et al., 2007). A low dose is 8-14 mg psilocybin or 0.05-0.074 mg LSD, a medium dose is 15-21 mg psilocybin or 0.075-0.109 mg LSD, and a high dose is ≥ 22 mg psilocybin or ≥ 0.110 mg LSD. Any findings that corresponded to quantities of LSD or psilocybin that were below a low dose were excluded from the study, as many (though not all) of these doses were microdoses. Many phenomenological studies on psilocybin adjusted dosing based on the weight of the participant, whereas phenomenological studies on LSD tended to administer the same dose to all participants. To make the data consistent, we assumed an average weight of 70 kg for participants in the psilocybin studies. It is worth noting that, in the literature, a medium dose of LSD was almost always 0.010 mg, whereas a medium dose of psilocybin tended to be 0.215 mg/kg, which we considered to be equivalent to 15.05 mg. Therefore, the medium dose of LSD tended to be higher than the medium dose of psilocybin.

To model the influence of methodological covariates that may confound the results, we produced a third model in which we included timing (i.e. the length of time between the administration of the drug and of the questionnaire), the presence or absence of a task in the experiment, and the prior psychedelic use of the participants as extra predictor variables in addition to the interaction between dose, scale, and drug. To compare the fit of this “full” model and one of the “reduced” models (i.e. the second three-level model mentioned above), we examined the corrected Akaike’s information criterion (Akaike, 1998).

Later, we compare the phenomenology of psychedelics to the neuroimaging and pharmacology by measuring the “profile” of each level of description, which we defined as its neural correlates in the Yeo networks. In order to obtain the phenomenological profile of each psychedelic, we needed to define the neural correlates of their subjective effects. In general, we believe that subjective experience is encoded in a dynamic and flexible fashion across the whole brain, rather than in a static and specific subset of regions (Barttfeld et al., 2015; Boly et al., 2013; Dehaene & Changeux, 2011; Oizumi et al., 2014). Therefore, it is unlikely that the subjective experiences of psychedelics, which are extraordinarily rich and complex, correlate with a single configuration of Yeo networks. Nevertheless, the subjective profile that we have created in this paper provides a starting point for comparing the phenomenology with the neuroimaging and pharmacology.

We identified $n = 14$ studies that examined correlations between subjective effects and either fMRI activity or pairwise connectivity. We assigned a Yeo network to each region that was significantly correlated with an ASC dimension, based on the coordinates of the centroid of the region. For each of the five dimensions, we created a 7x1 vector of correlations between that dimension and the corresponding Yeo network. We averaged correlations whenever multiple regions belonged to the same Yeo network. The

phenomenology profile of each psychedelic was a weighted sum of the five 7x1 vectors, in which the weights were the pooled 5D-ASC scores for the corresponding dimension.

$$\mathbf{s}^{(p)} = \sum_{d=1}^5 w_d^{(p)} \mathbf{r}^{(d)} \quad (2.2)$$

where $\mathbf{s}^{(p)}$ is a 7x1 vector representing the phenomenology profile of each psychedelic p , w_d is the pooled 5D-ASC rating of each psychedelic for each subjective dimension d , and $\mathbf{r}^{(d)}$ is a 7x1 vector containing the correlations between the Yeo networks and the neural correlates of each dimension.

Section 2.4. Results

We performed a meta-analysis on the 5D- and 11D-ASC scores of DMT, LSD, and psilocybin. Our literature search identified $n = 44$ phenomenology studies that met the inclusion criteria, including 5 studies on DMT (5D-ASC: $n = 3$; 11D-ASC: $n = 3$), 14 studies on LSD (5D-ASC: $n = 9$; 11D-ASC: $n = 12$), and 25 studies on psilocybin (5D-ASC: $n = 12$; 11D-ASC: $n = 17$).

Pooled 5D-ASC scores for DMT, LSD, and psilocybin are shown in **Figure 2.2**. Between-drug differences for LSD and psilocybin are displayed in the left column of **Figure 2.2a-c**, and within-drug differences are displayed in the right column. At medium doses (LSD: 0.075-0.109 mg, psilocybin: 15-21 mg), 5D-ASC scores were significantly greater for LSD than psilocybin in the OB dimension ($p = 0.0283$), which corresponds to feelings of interconnectedness, and the VR dimension ($p = 0.0468$), which measures the quality and intensity of visual hallucinations. We also observed a significant difference between LSD and psilocybin in the VR dimension ($p = 0.0417$) at high doses (LSD: ≥ 0.010 mg, psilocybin: ≥ 22 mg). There were no significant differences at low doses (LSD: 0.050-0.074 mg, psilocybin: 8-14 mg).

Within-drug differences between the five subjective dimensions were quite similar. A clear separation can be seen between two groups of subjective categories: (1) OB, VR, RV, and (2) AA and AED. At medium doses, VR and OB scores were significantly higher than both AED and AA scores for both LSD and psilocybin. Intriguingly, RV scored higher than all other dimensions at low doses of psilocybin, but this comparison was not significant. For DMT, there were no significant differences between dimensions at high doses (≥ 16 mg bolus injection, followed by continuous infusion of 1 mg/min), but for low doses (10-15 mg bolus + 0.6-0.99 mg/min continuous infusion), AED ranked significantly lower than both OB and VR. (Note that only one study measured AA and RV scores for DMT (Vogt et al., 2023), so we did not perform a meta-analysis on these dimensions for DMT.)

The results of the 11D-ASC meta-analysis were not very consistent with those of the 5D-ASC meta-analysis (**Figure 2.3**). 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.

At high doses, there were no significant differences between LSD and psilocybin in any of the dimensions, and standard errors were very large for psilocybin in some dimensions, particularly in some OB and VR subscales. At medium doses, where standard errors tended to be lower, we observed that two of the OB subscales (experience of unity and insightfulness), one of the AED subscales (impaired control and cognition), and three of the VR subscales (complex imagery, audio-visual synaesthesia, and changed meaning of percepts) ranked significantly higher for LSD than psilocybin. In line with the 5D-ASC results, we did not find any significant differences between LSD and psilocybin at low doses. However, unlike the 5D-ASC analysis, the 11D-ASC analysis showed that psilocybin rated higher than LSD in most of the dimensions; that being said, standard errors were very high for both LSD and psilocybin, so our estimates are not reliable. For medium doses, within-drug comparisons for the 11D-ASC analysis generally aligned with those of the 5D-ASC analysis.

We did not find any significant relationship between the pooled 5D-ASC scores and three methodological covariates that were defined *a priori*: prior psychedelic use, the time that the questionnaire was administered relative to the drug, and the presence or absence of a task in the experiment. Additionally, there was significant residual heterogeneity in the pooled 5D- and 11D-ASC scores ($p < 0.0001$ in both cases). Unfortunately, we were unable to obtain reliable estimates of heterogeneity specifically attributable to within-study and between-study differences. For three of the 5D-ASC scales, we found evidence of significant publication bias with Egger’s regression test, which determines whether small studies report disproportionately high effect sizes (OB: $p = 0.0187$, AED: $p < 0.0001$, VR: $p = 0.6279$, AA: $p < 0.0001$, RV: $p = 0.6532$). The results of our risk-of-bias assessments for individual studies are shown in **Table 2.1**. Due to the moderate-to-serious risk of bias, significant residual heterogeneity, high probability of publication bias, and indirectness (some studies measured subjective effects while participants were performing a specific task, as opposed to during resting-state), our certainty in the body of phenomenological evidence is low.

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 neural correlates of their subjective effects. We performed a separate 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. The phenomenology profiles were defined by a weighted combination of the mean correlations between each ASC scale and each Yeo network, 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 2.4**). 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, but the tasks varied strongly in the literature. There need to be more studies that link whole-brain fMRI activity to ASC ratings before we can estimate the phenomenology profiles with confidence.

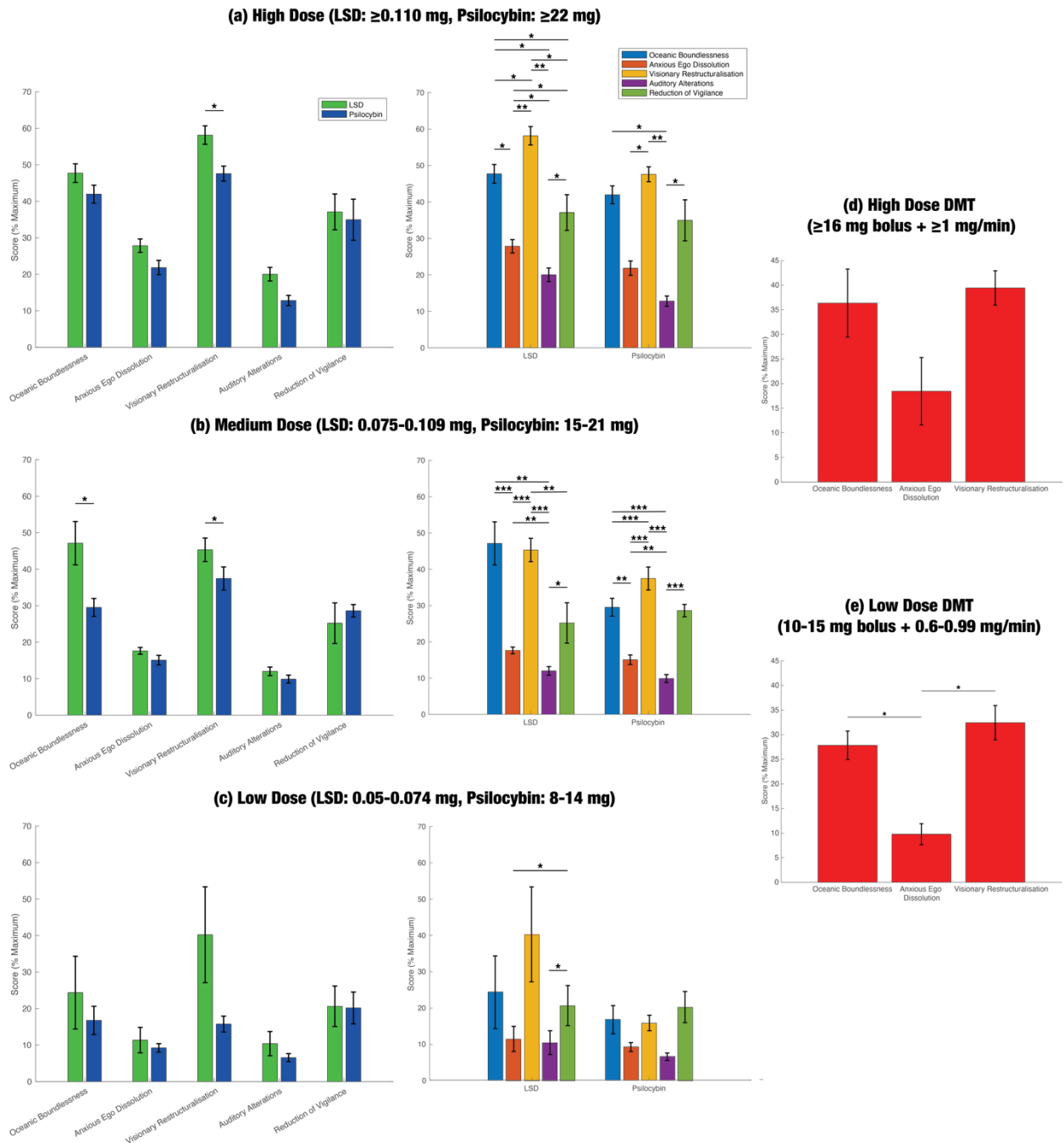
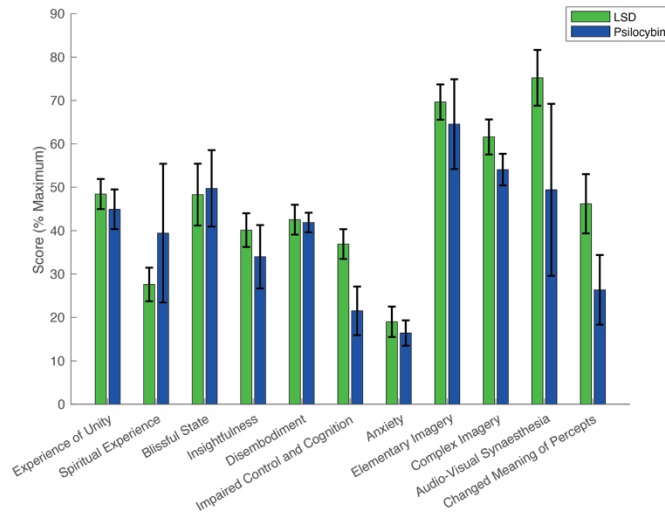


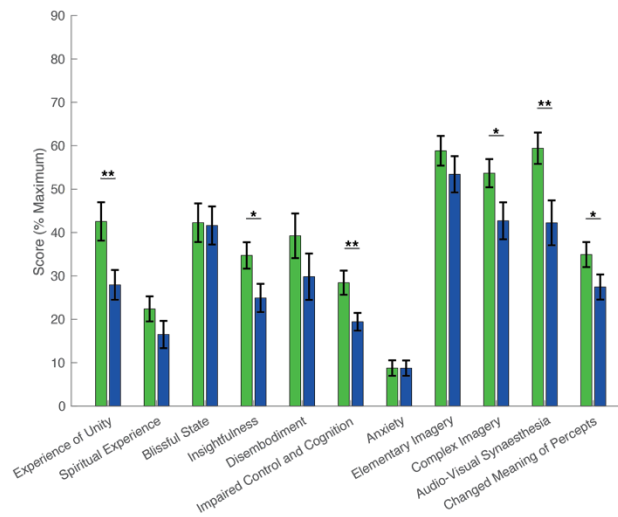
Figure 2.2. Meta-analysis of the 5-Dimensional Altered States of Consciousness (5D-ASC) data reveals only a few significant differences between psychedelics, but many more significant differences within psychedelics.

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. DMT was administered intravenously in phenomenological studies, whereas LSD and psilocybin were administered orally. Thus, DMT has different pharmacokinetics from LSD and psilocybin, which impacts the subjective experience, so we only compared significant between-drug differences for LSD and psilocybin. We only compared the two drugs for similar doses, assuming that 0.1 mg LSD = 20 mg psilocybin (Ley et al., 2023). (a-c, left column) Between-drug comparisons of pooled 5D-ASC scores for LSD and psilocybin. LSD almost always ranked higher than psilocybin, but differences only reached significance in the VR dimension for high and medium doses and in the OB dimension for medium dose. (a-c, right column) Within-drug comparisons for LSD and psilocybin. VR, OB, and RV received much higher scores than AED and AA. (d-e) Within-drug comparisons for DMT. At low doses, OB and VR ranked significantly higher than AED. Only one study measured ASC scores for the AA and RV dimensions on DMT, so we did not perform a meta-analysis on these dimensions for DMT. 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 2.2**. * < 0.05, ** < 0.01, *** < 0.001.

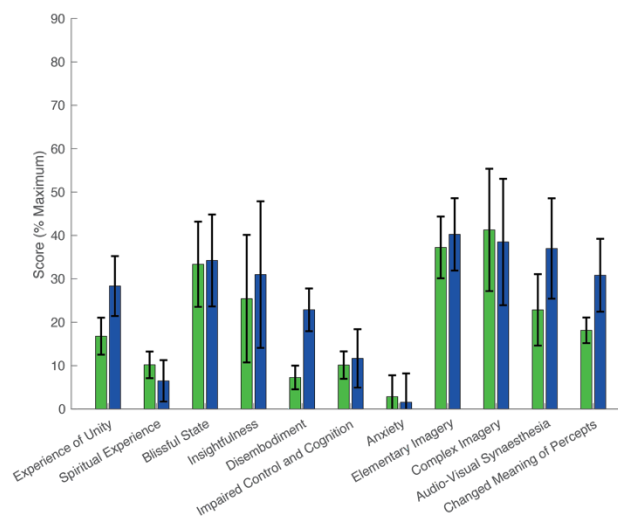
(a) High Dose (LSD: ≥ 0.110 mg, Psilocybin: ≥ 22 mg)



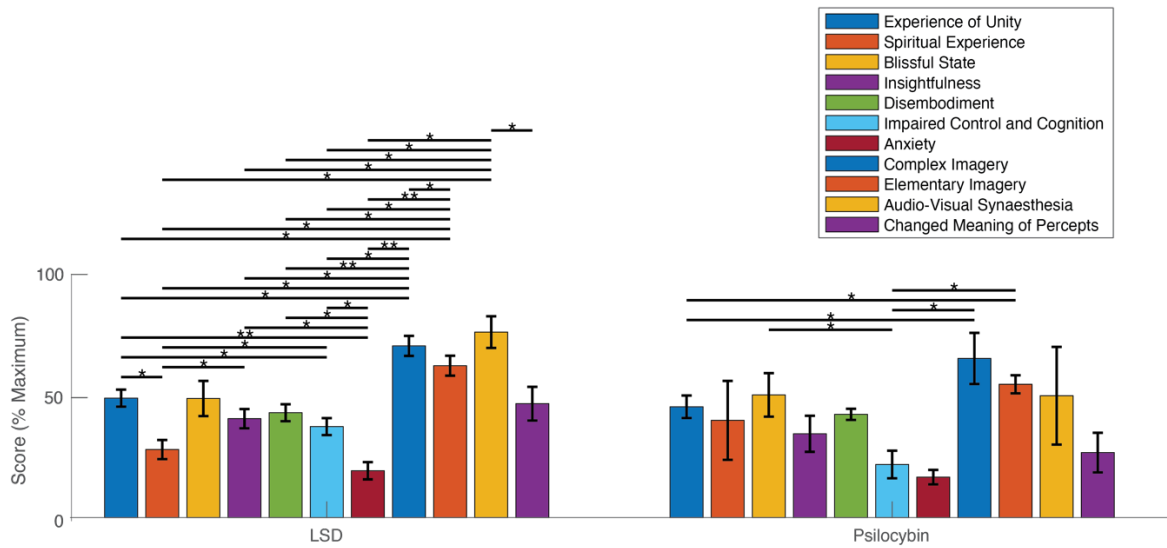
(b) Medium Dose (LSD: 0.075-0.109 mg, Psilocybin: 15-21 mg)



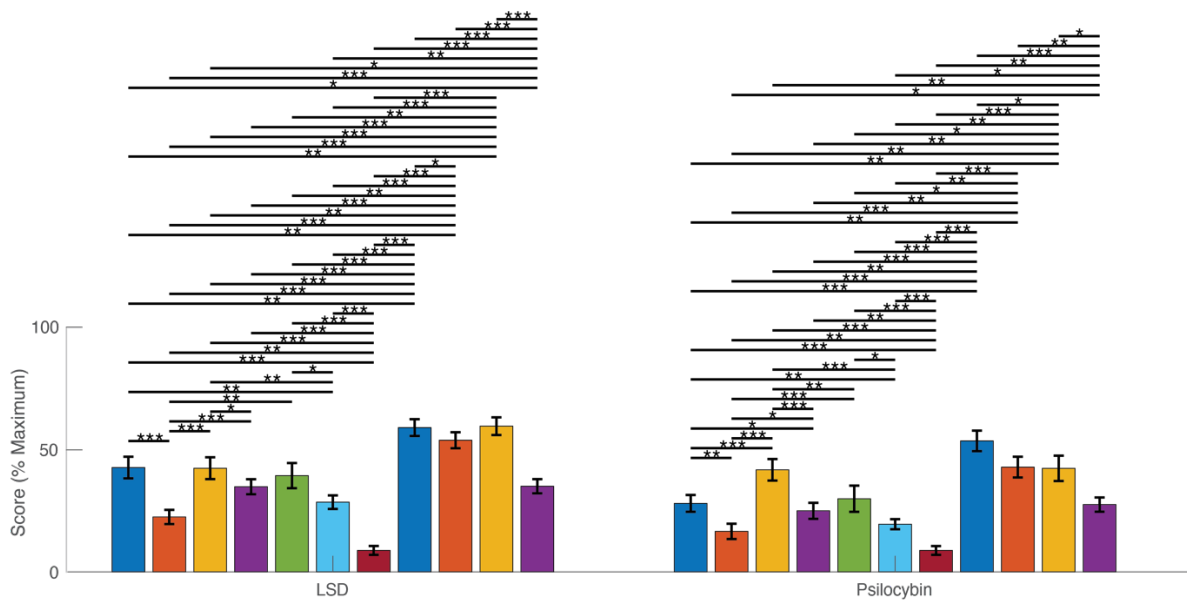
(c) Low Dose (LSD: 0.05-0.074 mg, Psilocybin: 8-14 mg)



(d) High Dose (LSD: ≥ 0.110 mg, Psilocybin: ≥ 22 mg)



(e) Medium Dose (LSD: 0.075-0.109 mg, Psilocybin: 15-21 mg)



(f) Low Dose (LSD: 0.05-0.074 mg, Psilocybin: 8-14 mg)

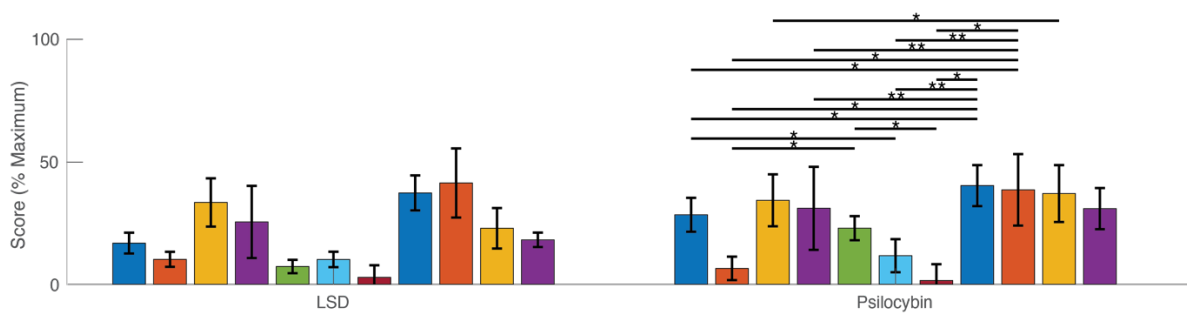


Figure 2.3. Meta-analysis of the 11-dimensional Altered States of Consciousness (11D-ASC) data shows more significant differences between psychedelics than the 5D-ASC analysis.

Our literature search identified 33 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 (LSD and psilocybin) on pooled 11D-ASC scores. Note that we could not include DMT in this meta-analysis as there was only one 11D-ASC study on DMT that reported standard errors. We only compared the two drugs for similar doses, assuming that 0.1 mg LSD = 20 mg psilocybin (Ley et al., 2023). (a-c) Between-drug comparisons of pooled 11D-ASC scores. LSD tended to rank higher than psilocybin in the subjective dimensions, except for low doses; however, there was only one study that gave LSD at a low dose (0.005 mg), so our estimates of significance may be unreliable. (d-f) Within-drug comparisons. Subscales of visionary restructuring (complex imagery, elementary imagery, audio-visual synaesthesia, changed meaning of percepts), tended to be significantly greater than subscales of anxious ego dissolution (disembodiment, impaired control and cognition, anxiety) and oceanic boundlessness (experience of unity, spiritual experience, blissful state, insightfulness). * < 0.05, ** < 0.01, *** < 0.001.

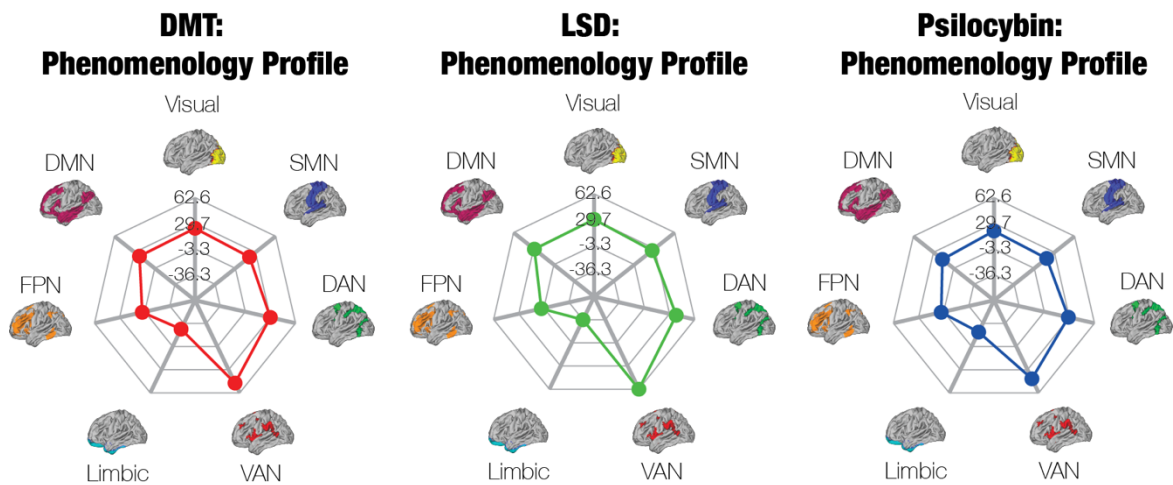


Figure 2.4. Phenomenology profiles of the psychedelics demonstrate broad similarity between the neural correlates of their phenomenology.

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.

Reference	Con	SP	CI	DII	MD	MO	SRR	Overall RoB
Becker et al. (2023)	M	L	L	L	L	M	L	M
Bernasconi et al. (2014)	M	L	L	L	L	S	L	S
Carbonaro et al. (2018)	M	L	L	L	L	L	L	M
Carter, Burr, et al. (2005)	M	L	L	L	L	M	L	M
Carter, Pettigrew, et al. (2005)	M	L	L	L	L	M	L	M
Carter et al. (2007)	M	L	L	L	L	M	L	M
Daumann et al. (2008)	S	L	L	L	L	M	L	S
Duerler et al. (2020)	S	L	L	L	L	M	L	S
Family et al. (2022)	M	L	L	L	L	M	L	M
Gouzoulis-Mayfrank et al. (2005)	M	L	L	L	L	M	L	M
Hasler et al. (2004)	L	L	L	L	L	M	L	M
Holze et al. (2020)	M	L	L	L	L	M	L	M
Holze et al. (2021)	M	L	L	L	L	M	L	M
Holze et al. (2022)	M	L	L	L	L	M	L	M
Kometer et al. (2012)	M	L	L	L	L	M	L	M
Kraehenmann, Preller, et al. (2015)	M	L	L	L	L	S	L	S
Kraehenmann et al. (2017)	M	L	L	L	L	M	L	M
Lewis et al. (2017)	M	L	L	L	L	S	L	S

Ley et al. (2023)	M	L	L	L	L	L	L	M
Madsen et al. (2021)	M	L	L	L	L	M	L	M
Mallaroni et al. (2023)	M	L	L	L	L	M	L	M
Mason et al. (2020)	M	L	L	L	L	M	L	M
McAlpine et al. (2023)	S	L	L	L	L	S	L	S
Müller, Lenz, Dolder, Lang, et al., 2017	M	L	L	L	L	S	L	S
Ort et al. (2023)	S	L	L	L	L	L	L	S
Pallavicini et al. (2021)	M	L	L	L	L	S	L	S
Pokorny et al. (2016)	S	L	L	L	L	M	L	S
Pokorny et al. (2017)	S	L	L	L	L	S	L	S
Pokorny et al. (2020)	S	L	L	L	L	M	L	S
Preller et al. (2016)	S	L	L	L	L	S	L	S
Preller et al. (2017)	M	L	L	L	L	M	L	M
Preller et al. (2020)	M	L	L	L	L	S	L	S
Quednow et al. (2012)	M	L	L	L	L	M	L	M
Schmid et al. (2015)	M	L	L	L	L	S	L	S
Schmidt et al. (2012)	S	L	L	L	L	M	L	S
Schmidt et al. (2018)	M	L	L	L	L	S	L	S
Smigielski et al. (2020)	S	L	L	L	L	S	L	S
Straumann et al. (2023)	M	L	L	L	L	M	L	M

Timmermann et al. (2023)	M	L	L	L	L	S	L	S
Umbricht et al. (2002)	S	L	L	L	L	S	L	S
Vogt et al. (2023)	M	L	L	L	L	M	L	M
Vollenweider et al. (2007)	M	L	L	L	L	M	L	M
Wießner et al. (2023)	M	L	L	L	L	S	L	S
Wittmann et al. (2007)	M	L	L	L	L	M	L	M

Table 2.1. Risk of bias for individual studies in the phenomenology literature

Using the ROBINS-I tool, we analysed risk of bias in seven domains: bias due to confounding (Con), bias in selection of participants into the study (SP), bias in classification of interventions (CI), bias due to deviations from intended interventions (DII), bias due to missing data (MD), bias in measurement of outcomes (MO), and bias in selection of the reported result (SRR). The overall risk of bias (RoB) is given in the rightmost column. L, M, and S refer to low, moderate, and serious risk of bias. Risk of bias was deemed low for all studies in the SP, CI, DII, MD, and SRR domains. Most studies received either an M or an S rating for the Con domain due either to confounding from the participants' levels of prior psychedelic use or failure to measure this characteristic, respectively. Many studies were rated M in the MO domain because it was possible for participants to guess the intervention (i.e., drug and, if applicable, dose level) that they had received. Some studies were rated S because they used a within-subjects, cross-over design in which the psychedelic and the placebo were the only two drugs that were administered. Participants who received a psychedelic in the first session were likely to know with certainty that they would get a placebo in the second session; thus, they may respond that they experienced zero effects along all dimensions of the ASC scale, whereas participants who received placebo in the first session may give low but non-zero responses for some dimensions. Overall RoB was either M or S for all studies.

Section 2.5. Discussion

Section 2.5.1. Comparing the results to the literature

We can verify the results of our meta-analysis by comparing them to the studies that measured ASC ratings of LSD and psilocybin in the same group of participants. Holze et al. (2022) gave a medium (15 mg) and a high (30 mg) dose of psilocybin, as well as a medium (0.01 mg) and a high (0.02 mg) dose of LSD, and then compared both 5D- and 11D-ASC scores. It is worth noting that the doses of psilocybin and LSD in this study are not equivalent, since 0.01 mg LSD = 20 mg psilocybin. When comparing 15 mg psilocybin to 0.01 mg LSD, mean 5D-ASC and 11D-ASC scores tended to be higher for LSD than psilocybin. However, the only differences that reached significance were in the OB and VR scales for the 5D-ASC analysis, and in the complex imagery and audio-visual synaesthesia subscales for the 11D-ASC analysis. In our meta-analysis, LSD and psilocybin were significantly different in both OB and VR ratings, and in complex imagery but not audio-visual synaesthesia ratings, at medium doses. Ley et al. (2023) compared the subjective effects of medium doses of LSD (0.01 mg) and psilocybin (20 mg). Here, the doses are equivalent, unlike in the previous study. The study found no significant differences between LSD and psilocybin in any of the dimensions, both in the 5D and 11D analyses. Therefore, the results of our meta-analysis are not entirely supported by studies that conducted direct comparisons between psychedelics.

Section 2.5.2. Sources of heterogeneity

The experimental procedures in the phenomenology literature were quite heterogeneous. 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.

Section 2.6. Chapter summary

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 common questionnaire for measuring changes in subjective experience on psychedelics. At both medium and high doses, LSD ranked significantly higher than psilocybin in “visionary restructuralisation,” a dimension capturing the quality and intensity of visual hallucinations. The VAN appears to be correlated with the phenomenology of all three psychedelics, but this result may be spurious due to the small number of studies that measured correlations between ASC ratings and fMRI activity. Nevertheless, there are reasons to think that the VAN may be uniquely implicated in the phenomenology of psychedelics. The VAN is responsible for orienting attention toward surprising objects or events (Vossel et al., 2014), and it is engaged during mismatch negativity (MMN), an event-related potential that is triggered when an unexpected stimulus is shown (Lee et al., 2017). Psychedelics diminish the MMN response while enhancing the neural response to familiar stimuli (Duerler et al., 2021; Timmermann et al., 2018), perhaps because these drugs engender profound feelings of childlike awe and wonder (Hendricks, 2018). This heightened predisposition towards subjective experiences of novelty may increase activity in the VAN.

Chapter 3. Functional Neuroimaging Meta-Analysis

Chapter 3.1. Chapter abstract

In the last ten years, fMRI studies have examined the neural correlates of psychedelic use in healthy humans, primarily capturing three measures of brain activity: BOLD activation, functional connectivity (FC), and entropy. Here, I attempted to perform a meta-analysis of the BOLD activation data using the GingerALE tool, which computes common clusters of BOLD activity across studies. Unfortunately, the analysis was strongly confounded by the experimental procedures in the literature, so the results are likely misleading. Next, I conducted a “vote-counting” meta-analysis on the FC data, which effectively tallied the pairs of Yeo networks that contained pairs of functionally connected regions in the literature. This meta-analysis supported the popular hypothesis that psychedelics disintegrate and desegregate brain networks; that is, they reduce FC within networks while elevating FC between networks. Finally, I decided to provide a qualitative review of the studies on entropy due to the heterogeneity of analysis methods in this segment of the literature. While all studies showed that psychedelics increase entropy, most of them estimated entropy on different measures of brain activity, rendering their findings difficult to unify.

Chapter 3.2. Literature search

We conducted our initial literature search of the fMRI studies in March 2022 and performed an update in May 2023. We searched four large databases: SCOPUS, Web of Science, psycINFO, and bioRxiv. Our search terms followed the structure: “<drug name> AND <neuroimaging term>”, where <drug name> was “psychedelics”, “LSD”, “psilocybin”, “DMT”, or “ayahuasca”, and <neuroimaging term> was “fMRI”, “MRI”, “functional magnetic resonance imaging”, or “neuroimaging”. We then excluded any reports that met the following criteria:

1. Works that did not report any original research, such as literature reviews, commentaries, and editorials.
2. Studies in which the experimental drug was not a classical psychedelic. We define a “classical psychedelic” as any drug whose primary mechanism of action is mediated by the 5-HT_{2A} receptor. This criterion excluded studies that investigated MDMA, cannabis/THC, and/or ketamine. We included studies on the following classical psychedelics: ayahuasca, DMT, LSD, and psilocybin.
3. Studies that did not collect any new fMRI data or run a novel analysis on existing fMRI data. This excluded studies that measured brain activity under psychedelics using MEG, EEG, PET,

structural MRI, or other techniques, as well as studies that gathered only behavioural or subjective data. Additionally, we excluded studies that conducted new measurements of correlations between subjective data and existing neuroimaging data, but did not analyse the neuroimaging data itself in an original way (Speth et al., 2016).

4. Studies that were conducted on non-human animals or on *in vitro* cell populations.
5. Studies whose results were not specific to psychedelics, including studies examining the neural correlates of hallucinogen, poly-drug, or general drug use/addiction (e.g. Butcher et al. (2021)).
6. Studies that investigated disorders caused by psychedelic use, such as palinopsia (Kawasaki & Purvin, 1996), cortical blindness (Bernhard & Ulrich, 2009), persistent visual hallucinations (Iaria et al., 2009), and more. Psychedelics rarely induce long-term neurological damage (Studerus et al., 2011), so we did not incorporate the neural correlates of these disorders into our meta-analysis.
7. Studies that were performed on participants from a clinical population, such as patients suffering from depression. Psychedelics may affect brain activity in depressed patients very differently than in healthy participants (Carhart-Harris et al., 2017).
8. Studies that primarily simulated brain activity under the influence of psychedelics, rather than measuring or analysing empirical neuroimaging data on psychedelics (Burt et al., 2021; Deco, Cruzat, et al., 2018; Kringelbach et al., 2020).
9. Studies that measured post-acute effects of psychedelics, i.e. brain activity after the psychedelic trip had already ended.
10. Studies on microdosing. Since the subjective effects of microdoses are often imperceptible, there is good reason to think that brain activity in response to a microdose would be significantly different than brain activity on a macrodose.

The flowchart in **Figure 3.1** summarises our literature search, which led us to identify ***n* = 58 studies in total**. We further divided the studies into three sections: studies on BOLD activation, on functional connectivity (FC), and on entropy. We included ***n* = 17 studies on BOLD activation** (Barrett, Doss, et al., 2020; Barrett et al., 2018; Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris, Leech, et al., 2012; Daumann et al., 2008, 2010; de Araujo et al., 2011; Duerler et al., 2020, 2021; Kaelen et al., 2017; Kraehenmann, Preller, et al., 2015; Müller, Lenz, Dolder, Harder, et al., 2017; Palhano-Fontes et al., 2015; Preller et al., 2016, 2017; Preller, Schilbach, et al., 2018; Schmidt et al., 2018), ***n* = 34 studies on connectivity** (Avram et al., 2022; Barrett, Doss, et al., 2020; Barrett, Krimmel, et al., 2020; Bedford et al., 2023; Carhart-Harris et al., 2013, 2016; Dai et al., 2023; de Araujo et al., 2011; Delli Pizzi et al., 2023; Gaddis et al., 2022; Girn et al., 2022;

Grimm et al., 2018; Jobst et al., 2021; Kaelen et al., 2016; Kraehenmann, Schmidt, et al., 2015; Lebedev et al., 2015; Lord et al., 2019; Luppi et al., 2021; Madsen et al., 2021; Mason et al., 2020, 2021; Müller et al., 2018; Müller, Lenz, Dolder, Lang, et al., 2017; Olsen et al., 2022; Palhano-Fontes et al., 2015; Petri et al., 2014; Preller, Burt, et al., 2018; Preller et al., 2019, 2020; Roseman et al., 2014, 2016; Tagliazucchi et al., 2014, 2016; Timmermann et al., 2023), **and $n = 12$ studies on entropy/criticality** (Atasoy et al., 2017; Carhart-Harris et al., 2014; Lebedev et al., 2015, 2016; Lord et al., 2019; Luppi et al., 2023; Ruffini et al., 2023; Singleton et al., 2022; Tagliazucchi et al., 2014; Varley et al., 2020; Viol et al., 2017, 2019, 2023). There was one study that did not fall neatly into any of the three categories (Viol et al., 2023).

We then sought the relevant data for each section. We did not require any data on entropy as we performed **a qualitative review of all $n = 12$ studies on entropy/criticality**. To conduct a meta-analysis on studies of BOLD activation, we used the stereotaxic coordinates in Montreal Neurological Institute (MNI) space of the brain regions that displayed significant changes in BOLD activation under psychedelics. We conducted **a quantitative meta-analysis on all $n = 17$ studies of BOLD activation**.

For the FC meta-analysis, we obtained either the coordinates or the spatial maps (in MNI space, at 2mm^3 resolution) of the brain areas that exhibited significant changes in connectivity (see **Table S7** for a comprehensive account of how we represented the data from each study). Our FC meta-analysis algorithm could only accommodate data from studies on pairwise FC, i.e. correlations between pairs of regions. However, there were 11 studies on connectivity that did not measure pairwise FC; instead, they examined global, structural indices of connectivity, such as modularity and GBC, or effective connectivity. We also excluded eight more studies of pairwise FC from the quantitative meta-analysis because they were redundant re-analyses of datasets that we had already included (see *Section S2.2.2*). Finally, we were unable to obtain data from three studies on pairwise FC, which were otherwise eligible for the quantitative meta-analysis. Thus, we conducted **a quantitative meta-analysis on $n = 12$ studies of FC** (F. S. Barrett, Krimmel, et al., 2020; Bedford et al., 2023; Dai et al., 2023; de Araujo et al., 2011; Gaddis et al., 2022; Grimm et al., 2018; Kaelen et al., 2016; Madsen et al., 2021; Mason et al., 2020; Palhano-Fontes et al., 2015; Roseman et al., 2014; Timmermann et al., 2023), and we performed **a qualitative review of $n = 22$ studies on connectivity** (Avram et al., 2022; Barrett, Doss, et al., 2020; Carhart-Harris et al., 2013, 2016; Delli Pizzi et al., 2023; Girn et al., 2022; Jobst et al., 2021; Kraehenmann, Schmidt, et al., 2015; Lebedev et al., 2015; Lord et al., 2019; Luppi et al., 2021; Mason et al., 2021; Müller et al., 2018; Müller, Lenz, Dolder, Lang, et al., 2017; Olsen et al., 2022; Petri et al., 2014; Preller, Burt, et al., 2018; Preller et al., 2019, 2020; Roseman et al., 2016; Tagliazucchi et al., 2014, 2016).

As shown in **Figure 3.2a**, there were three studies on both BOLD activation and connectivity (F. S. Barrett, Doss, et al., 2020; de Araujo et al., 2011; Palhano-Fontes et al., 2015), three on both entropy and

connectivity (Lebedev et al., 2015; L.-D. Lord et al., 2019; Tagliazucchi et al., 2014), and none on all three metrics of fMRI activity. (Arguably, Viol et al. (2017, 2019, 2023) could all be construed as studies of both entropy and connectivity since they applied graph theory to define functional brain networks and then measured entropy or information-theoretic metrics.)

Out of the 58 fMRI studies, only 22 produced primary datasets, so over half of the studies are secondary analyses (**Figure 3.2b**). There are disproportionately more secondary analyses of the primary datasets in Carhart-Harris, Erritzoe, et al. (2012) and Carhart-Harris et al. (2016) (9 of the former and 13 of the latter, not including secondary analyses of the MEG data in the latter) than of any other datasets. Across all primary datasets that we included in our qualitative reviews and quantitative meta-analyses, there were a total of 391 participants (DMT/ayahuasca: 52 participants; LSD: 148 participants; psilocybin: 191 participants). The meta-analysis of the BOLD activation literature included data from 258 participants, and the meta-analysis of the FC literature was performed on data from 237 participants.

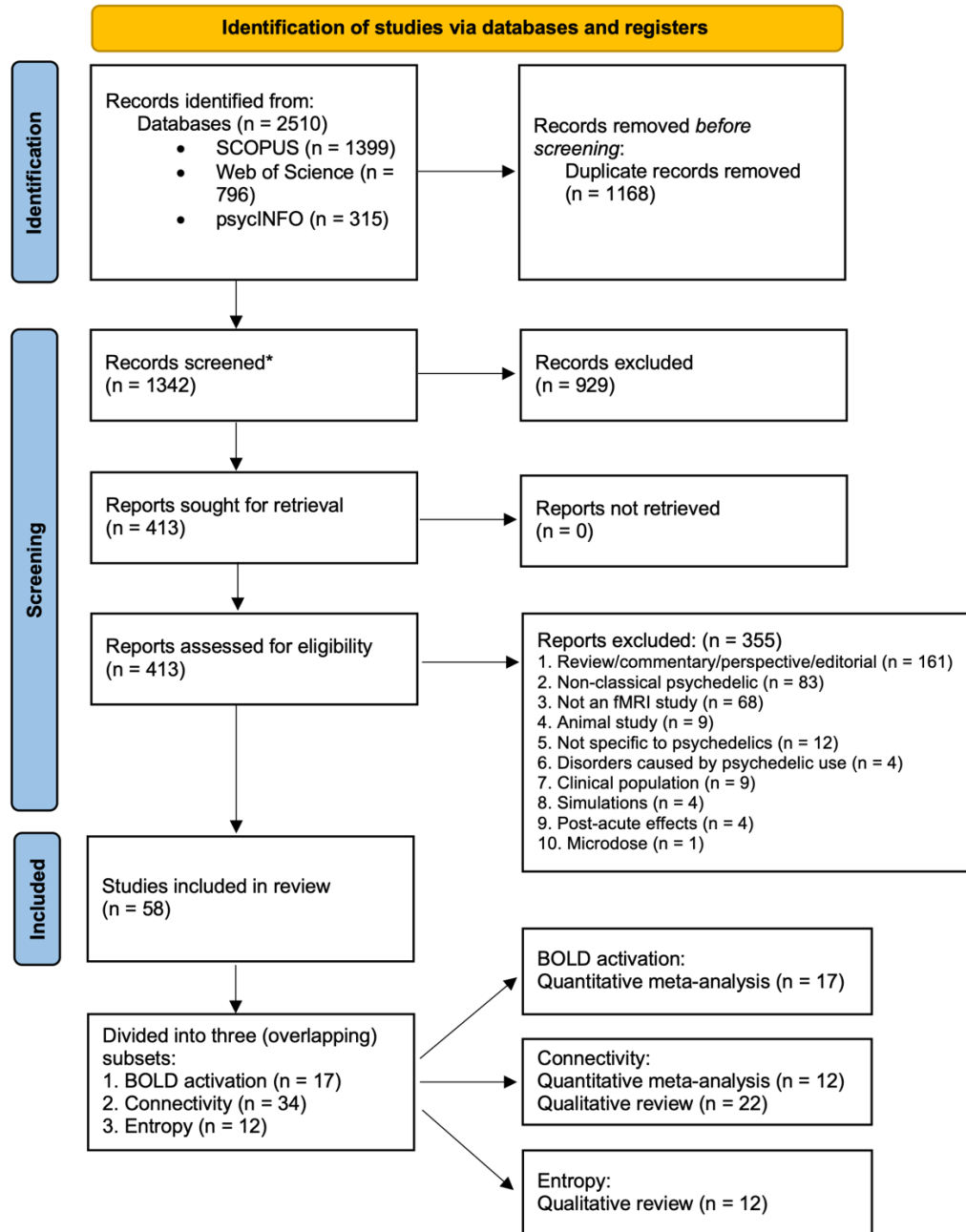


Figure 3.1. PRISMA flowchart for neuroimaging literature search.

PRISMA is a set of guidelines for performing systematic reviews and meta-analyses. 58 fMRI studies were identified, including 17 on BOLD activation, 34 on connectivity, and 12 on entropy.

(a)



(b)

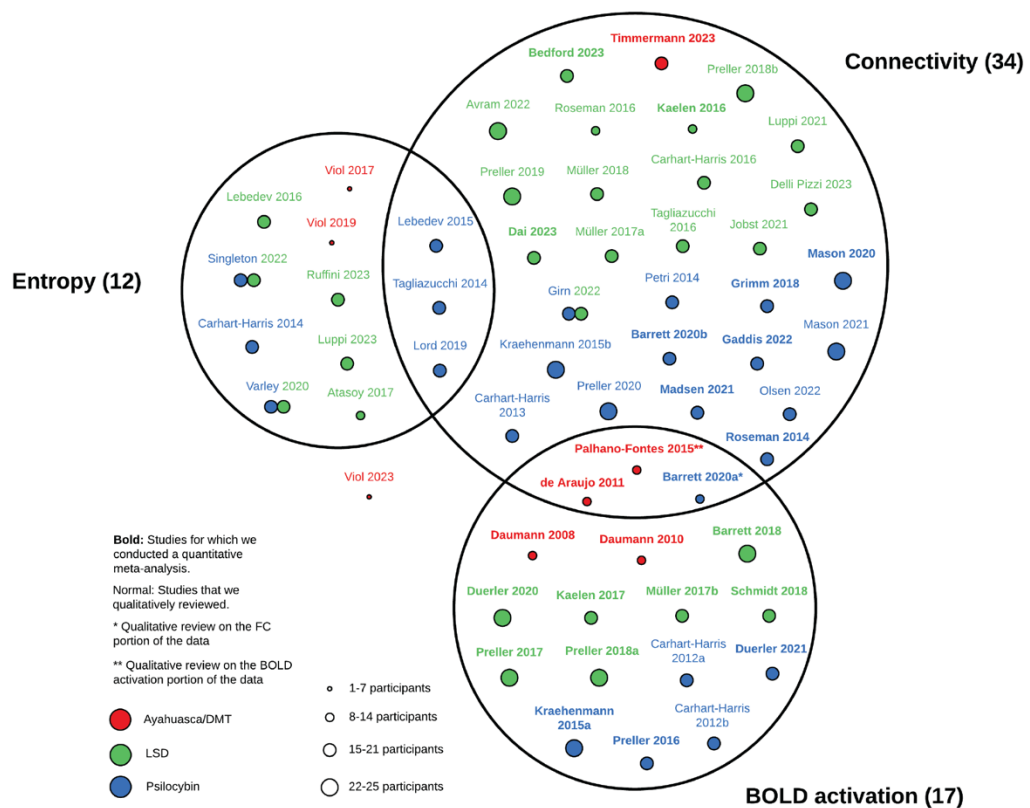


Figure 3.2. Overview of the fMRI literature on psychedelics.

(a) Primary datasets vs. secondary analyses. Primary datasets with at least one secondary analysis are depicted as large circles containing smaller circles. Clearly, the primary datasets in Carhart-Harris et al. (2016) and Carhart-Harris, Erritzoe, et al. (2012) were subjected to disproportionately more secondary analyses than any other primary datasets. (b) Venn diagram of the drugs, number of participants, and metric of brain activity (entropy, connectivity, or BOLD activation) analysed by each study. The size of the colored circles represents the number of participants in the study. We conducted a qualitative review of all the entropy studies, any FC and BOLD activation studies for which the data was unavailable, and any FC studies whose analysis methods were not suitable for our quantitative meta-analysis. Daumann et al. (2008, 2010) used DMT, whereas the remainder of the studies in the ayahuasca/DMT category measured the effects of ayahuasca on brain activity. Barrett 2020a refers to Barrett, Doss, et al. (2020); Barrett 2020b to Barrett, Krimmel, et al. (2020); Müller 2017a to Müller, Lenz, Dolder, Lang, et al. (2017) and Müller 2017b to Müller, Lenz, Dolder, Harder, et al. (2017); Preller 2018a to Preller, Schilbach, et al. (2018); Preller 2018b to Preller, Burt, et al. (2018); Carhart-Harris 2012a to Carhart-Harris, Erritzoe, et al. (2012); Carhart-Harris 2012b to Carhart-Harris, Leech, et al. (2012).

Chapter 3.3. Methods

Chapter 3.3.1. BOLD activation

We conducted our meta-analysis of BOLD activity by using a technique called GingerALE, which computes common clusters of BOLD activation across different studies (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2011). GingerALE takes in a list of the coordinates (in either MNI or Talairach space) of peak activations, or foci, from each study, and then it outputs the common clusters of activation in four steps. 1) GingerALE blurs the coordinates of the foci using a Full-Width Half-Maximum of a Gaussian function, whose size is determined by the number of subjects in each study, and then calculates a Modeled Activation (MA) map, which is formed from the union or maximum of the Gaussian of each focus. GingerALE then produces a spatial map of the ALE (activation likelihood estimate) statistic from the union of all the MA maps. 2) GingerALE calculates the null distribution of the ALE statistic based on a histogram of the number of voxels in each MA map, yielding a table of p -values corresponding to the probability that a particular MA map contains a certain number of voxels. 3) GingerALE thresholds the p -value of the ALE statistic using one of three possible methods: cluster-level family-wise error (FWE) inference, voxel-level FWE inference, or no correction. 4) GingerALE calculates the volume, bounds, weighted center, and coordinates of regions in the brain whose ALE statistic surpasses the threshold.

Our inputs into GingerALE were the MNI coordinates of peak BOLD activation for any contrast comparing brain activity in the placebo/baseline condition with brain activity under psychedelics. Therefore, if a study required participants to perform multiple tasks while they were on psychedelics, we included the coordinates of peak activity from all the tasks in our meta-analysis. Ideally, we would have differentiated the

results based on the type of task, for instance by performing a meta-regression (see *Section S2.1, S2.3*), but this was not possible because all the tasks were very different from each other (see *Section 3.3.2*).

Some studies administered not only placebo and psychedelics but also ketanserin, a 5-HT_{2A} antagonist that blocks many of the subjective effects of psychedelics (Vollenweider et al., 1998), and contrasted BOLD activation under the combination of ketanserin and psychedelics with activation under psychedelics alone. For studies that administered ketanserin, we only inputted the coordinates of regions that showed a significant difference between placebo and psychedelics, since the results of experiments involving ketanserin were often redundant.

Studies assessed statistical significance in different ways. Some studies used fairly stringent yet uncorrected p -value thresholds (typically $p < 0.001$), whereas others also corrected for multiple comparisons, usually by adjusting the threshold based on the family-wise error rate (FWER) and sometimes by applying small volume correction when the analysis was limited to specific ROIs. We only included the results that adjusted for multiple comparisons in our analysis.

As noted above, GingerALE also offers three different options for multiple corrections: cluster-level inference, FWER correction, and no correction. The best method is cluster-level inference. Uncorrected p -values obviously result in too many false positives when a large number of voxels in the brain are measured. Methods to correct for voxel-level FWER (i.e. Bonferroni correction) assume statistical independence between voxel-wise tests, yet voxels of the brain are often spatially correlated (Tierney et al., 2016). We applied a cluster-forming threshold of $p < 0.05$ and a cluster-level inference threshold of $p < 0.05$. (More stringent thresholds did not yield significant results.)

Chapter 3.3.2. Functional connectivity

In the FC literature, a wide range of parcellations are used to define regions of interest (ROIs). To perform a meta-analysis on studies of FC, we first needed to “re-parcellate” all of the data into the same reference parcellation. The reference parcellation that we chose was the seven resting-state Yeo networks, since we determined the profiles, or neural fingerprints, of the other hierarchical levels of analysis (phenomenology and pharmacology) based on these networks. Additionally, the Yeo networks are perhaps the most coarse-grained parcellation of the human brain. We conducted what amounted to a “vote-counting” meta-analysis (Bushman & Wang, 2009). Our algorithm determined the pair of Yeo networks that contained every pair of functionally connected ROIs in the literature. That is, we identified the Yeo networks that overlapped with the largest number of voxels in each ROI. If the pair of ROIs became more connected under psychedelics, then a “vote” was cast in favour of the corresponding Yeo networks; that is, the vote was counted as positive. If not, then a vote was cast against those Yeo networks; that is, the vote was counted as negative.

Studies that use parcellations with many seeds bias vote-counting FC meta-analyses because the number of significant connections is much higher, and hence these studies contribute much more to the aggregate FC. To avoid this bias, we weighted each study’s vote for a pair of networks by the total number of *possible* connections between those networks in the study. For instance, if a study used a parcellation with 11 regions in the DMN and 8 regions in the FPN, then there are $11 * 8 = 88$ possible connections between the DMN and FPN. If the study only found 22 significant connections between the DMN and the FPN, then the study would contribute a vote of $22/88 = 0.25$ to the aggregate DMN-FPN FC. This method substantially reduces the contribution of studies with large parcellations to the aggregate FC.

Our quantitative meta-analysis included any studies on pairwise FC, namely studies that performed one of the following analyses: seed-to-seed analysis; seed-to-voxel analysis; or component-to-component analysis, in which the components are identified through Independent Component Analysis (ICA). We qualitatively reviewed studies that conducted other types of FC analyses in *Section S5*.

Many of the FC studies were secondary analyses of preexisting datasets, or they performed multiple analyses of an original dataset, e.g. Timmermann et al. (2023), which conducted both seed-to-seed and ICA-based measurements of FC. To prevent bias from primary datasets that received more than one analysis, we selected the most informative analysis of each unique dataset, unless the secondary analysis addressed a part of the dataset that was not reported in the original publication. For instance, Kaelen et al. (2016) is an analysis of the music condition in the primary dataset collected by Carhart-Harris et al. (2016), which reported analyses of only the resting-state condition. Therefore, we included Kaelen et al. (2016) despite the fact that it was a secondary analysis. We defined the most informative analysis as the most spatially extensive, fine-grained one, i.e. the analysis that examined FC across the largest portion of the brain, using the parcellation with the highest number of ROIs. We further excluded secondary analyses in which the number of significant connections did not scale as expected with the size of the parcellation. In general, we expect the number of significant between-ROI connections to scale roughly quadratically with the parcellation size, since the number of possible connections is approximately the square of the number of regions in the parcellation. However, in Lebedev et al. (2015) and Luppi et al. (2021), the number of significant connections is smaller than the parcellation size. This effect likely occurred because both studies were the only ones to use the network-based statistic (NBS) to determine statistically significant connections. Unlike other techniques, NBS measures the size of interconnected “components” in brain networks, rather than assessing each possible connection individually (Zalesky et al., 2010). Since there are fewer components than pairwise connections, the number of significant connections determined by NBS is likely to be much lower than the number of significant connections uncovered by other techniques, such as mass-univariate *t*-tests. Thus, even though Lebedev et al. (2015) and Luppi et al. (2021) were both whole-brain secondary analyses that used

more fine-grained parcellations than other analyses did, we excluded them because their method for assessing statistical significance underestimated the number of significant connections, relative to the other techniques in the literature. **Table 3.1** gives a full account of all the primary datasets in the literature on pairwise FC, the secondary analyses, and the studies that we included in the FC meta-analysis.

What were the inputs into the meta-analysis? **Table 3.2** specifies the data that we inputted from each of the 12 studies. For seed-to-seed analyses, we obtained spatial maps of the seeds from the relevant parcellation or from the authors of the study, when special techniques were used to extract the seed (F. S. Barrett, Krimmel, et al., 2020). One seed-to-seed analysis measured FC between pairs of networks by averaging across the FC of 10mm-radius spheres constructed around the centroids of the constituent ROIs in those networks (Madsen et al., 2021). To incorporate the data from this study into the meta-analysis, we used the MarsBar toolkit (Brett et al., 2002) to generate 10mm-radius spheres around the coordinates of each ROI centroid, which were supplied by Madsen et al. (2021). For each network in Madsen et al. (2021), we determined the Yeo network that contained each of the constituent ROIs and then identified the mode, i.e. the Yeo network that overlapped with more of the constituent ROIs than any other Yeo network. FC between mode networks then contributed towards the aggregate FC matrix.

For seed-to-voxel analyses, we reached out to the authors for spatial maps of the voxels that displayed significant changes in FC with the corresponding seeds. When these maps were unavailable (Grimm et al., 2018), we created spheres around the reported peak coordinates of each significant cluster of voxels. The radius of each sphere corresponded to the size of the corresponding cluster. We then assigned each cluster to a Yeo network.

Finally, the three ICA-based analyses that we included in the meta-analysis (Gaddis et al., 2022; Mason et al., 2020; Roseman et al., 2014) found strong correlations between independent components and resting-state networks (RSNs) derived by Smith et al. (2009), or they directly back-projected those RSNs onto their participants' data through dual regression. In order to help unify the three studies, our inputs for all three studies were the RSNs defined by Smith et al. (2009), not the group ICs.

To compute the significance of our results, we compared our results to a surrogate dataset formed from the resting-state BOLD timeseries of 100 unrelated participants in the Human Connectome Project (HCP) (Van Essen et al., 2013). We parcellated this timeseries with the Schaefer-100 parcellation (Schaefer et al., 2018). To do this, we randomly sampled N subjects from the HCP data, and two length- T windows from each subject's BOLD data, where N and T are the average number of subjects and the average number of TRs, respectively, in the studies of FC under psychedelics. In each window, we calculated the Pearson correlation between the ROIs of the Schaefer-100 parcellation. The pairs of ROIs that were significantly correlated constituted the results of one surrogate study. (Note that we did not perform multiple comparisons

on the correlations, since otherwise there would have been no significant edges.) Since there are 12 studies of FC in our meta-analysis, we repeated the FC calculation 12 times, resulting in a “surrogate study set” of significantly connected ROIs. We then computed the aggregate FC matrix of this surrogate study set. We repeated this process 500 times, which produced a null distribution of values for each element of the aggregate FC matrix. If an element of the aggregate matrix for the psychedelic data was below the 2.5th percentile or above the 97.5th percentile of the null distribution, then it was deemed to be significant. Finally, the aggregate FC matrix was corrected for multiple comparisons with the Benjamini-Hochberg FDR procedure.

We stress that our method for performing an FC meta-analysis is novel and has not been validated elsewhere. Indeed, there are reasons to think that the surrogate method does not accurately assess statistical significance. When measuring resting-state FC in each surrogate study, we calculate the correlations between all pairs of ROIs in the Schaefer-100 parcellation. On the other hand, in the literature, many studies analyse connectivity between only a subset of the ROIs from the chosen parcellation.

While the FC meta-analysis was initially performed on the cortical Yeo networks, we later expanded the analysis to include eight subcortical regions from the Tian atlas – the hippocampus, amygdala, posterior thalamus, anterior thalamus, nucleus accumbens, globus pallidus, putamen, and caudate – plus cerebellum (Tian et al., 2020). Since the Schaefer-100 atlas only contains cortical regions, we used the Desikan-Killiany (DK-80) atlas, which includes 62 cortical and 18 subcortical regions, to parcellate the null distribution for the cortical + subcortical analysis (Deco et al., 2021; Desikan et al., 2006).

As we did in the phenomenology and pharmacology meta-analyses, we tried to identify methodological covariates that were significantly associated with the results. We identified eight potential covariates *a priori*: (1) the method used to regress out white matter from BOLD signal (in particular, whether anatomical Component-Based Noise Correction (aCompCor) was used); (2) whether or not the study performed scrubbing in order to correct for head motion; (3) whether or not the study preprocessed fMRI data with FSL; (4) whether or not the study used SPM for preprocessing; (5) whether or not the study administered psilocybin; (6) the route of administration (either oral or IV); (7) the width of the Gaussian kernel that was used to smooth the data; and (8) the time that the drug was administered, relative to the duration of the drug’s acute effects (7.5 hours for ayahuasca, 20 minutes for DMT, 10 hours for LSD, 5 hours for psilocybin). (1)-(5) are binary covariates, whereas (6)-(8) are continuous.

For binary covariates, we compared the aggregate FC matrices of studies that contained the covariate in question to those that did not, by taking the absolute value of the difference between each entry of the corresponding matrices. Then, we scrambled the labels of the covariates and re-compared the score matrices for the permuted data. We repeated this process approximately 500 times. Our analysis was hampered by the

small number of studies; there were fewer than 495 unique permutations when fewer than four studies exhibited a particular covariate. Thus, we could not determine whether the FC of psilocybin and LSD were significantly different from each other, as we only analysed three studies on the FC of LSD. We could only assess whether psilocybin's FC was significantly different from the rest of the FC dataset, as we included six studies on the FC of psilocybin. For continuous covariates, we assessed the significance of the correlation between each entry of each study's marginal contribution to the aggregate FC matrix and each study's value for the covariate in question. We adjusted for multiple comparisons with FDR for both types of covariates.

In addition to correcting for publication bias stemming from the large number of secondary analyses in the literature, as discussed above, I assessed risk of bias in individual studies using the ROBINS-I tool.

Finally, I obtained the FC profiles by first determining the aggregate FC matrix of each psychedelic. Then, we summed across the rows of the matrix (note that the matrix is symmetric, so the choice of row or column does not matter) and divided by the sum of all values in the matrix.

Chapter 3.3.3. Entropy

I performed a literature review of the studies about the effects of psychedelics on entropy.

Study in which primary dataset was first reported	Secondary analyses	Analysis included in the FC meta-analysis
Carhart-Harris, Erritzoe, et al. (2012)	Lebedev et al. (2015)	Roseman et al. (2014)
	Roseman et al. (2014)	
Carhart-Harris et al. (2016)	Carhart-Harris et al. (2016): seed-to-voxel analysis	Dai et al. (2023)
	Carhart-Harris et al. (2016): ICA-based analysis	
	Dai et al. (2023)	
	Luppi et al. (2021)	
	Tagliazucchi et al. (2014)	
Holze et al. (2020)*	Avram et al. (2022)	Bedford et al. (2023)**
	Bedford et al. (2023)**	
Mason et al. (2020)	Mason et al. (2021)	Mason et al. (2020)***
Müller, Lenz, Dolder, Lang, et al. (2017)	Bedford et al. (2023)**	Bedford et al. (2023)**
	Müller, Dolder, et al. (2018)	
	Müller, Lenz, Dolder, Lang, et al. (2017): thalamic seed-to-seed analysis	
	Müller, Lenz, Dolder, Lang, et al. (2017): seed-to-voxel analysis	
Timmermann et al. (2023)	Timmermann et al. (2023): seed-to-seed analysis	Timmermann et al. (2023): seed-to-seed analysis
	Timmermann et al. (2023): ICA-based analysis	

Table 3.1. Studies that were included in the meta-analysis, when there was more than one reported analysis of the corresponding dataset.

The existence of multiple studies on the same primary dataset biases the results of the FC meta-analysis. We only included one analysis of each unique dataset in the meta-analysis. This analysis was the one that spanned the largest portion of the brain and used the most fine-grained parcellation, as long as it did not apply the network-based statistic, which underestimates the number of significant connections relative to other techniques. *Holze et al. (2020) was not identified in the neuroimaging literature search because it did not report any fMRI data, though fMRI data was collected as part of the study. **Bedford et al. (2023) assessed data from both Avram et al. (2022) and Müller, Lenz, Dolder, Lang et al. (2017). ***The ICA-based analysis reported in Mason et al. (2021) is almost exactly the same as the one reported in Mason et al. (2020), except it additionally includes the salience network in its analysis.

Functional Connectivity Study and Method	Inputs
de Araujo et al. (2011): seed-to-seed analysis	1. Spatial maps of specific seeds from the Brodmann areas
Barrett, Krimmel, et al. (2020): seed-to-seed analysis	1. Spatial maps of left and right claustrum seeds, obtained from the authors 2. Networks of 10mm-radius spheres around coordinates of network seeds in the Power atlas
Bedford et al. (2023): seed-to-seed analysis	1. Spatial maps of seeds extracted from the Harvard-Oxford atlas
Dai et al. (2023): seed-to-seed analysis	2. Spatial maps of seeds extracted from the HCP-ICA atlas
Gaddis et al. (2022): ICA	1. Cortical: spatial maps of template group ICs from Smith et al. (2009)*; thalamic: template group ICs obtained from author
Grimm et al. (2018): seed-to-voxel analysis	1. Spatial maps of the right amygdala seed, extracted from the AAL atlas 2. 10mm-radius spheres around the coordinates of voxels that had peak FC with the seed
Kaelen et al. (2016): seed-to-voxel analysis	1. Spatial map of the parahippocampus seed, extracted from the Harvard-Oxford atlas 2. Spatial map of voxels that had peak FC with the seed, obtained from the authors
Madsen et al. (2021): seed-to-seed analysis	1. Networks of 10mm-radius spheres around coordinates of network seeds in the Raichle atlas
Mason et al. (2020/21): ICA	1. Spatial maps of template group ICs from Smith et al. (2009)*
Palhano-Fontes et al. (2015): seed-to-voxel analysis (not DMN-TPN orthogonality test)	1. 10mm-radius spheres around coordinates of PCC and mPFC seeds 2. 10mm-radius spheres around the coordinates of voxels that had peak FC with the seed
Roseman et al. (2014): ICA	1. Spatial maps of template group ICs from Smith et al. (2009)**
Timmermann et al. (2023): seed-to-seed analysis	1. Spatial maps of seeds extracted from the Schaefer-100 atlas and subcortical seeds in the AAL atlas

Table 3.2. Summary of inputs into the FC meta-analysis.

*Our scoring algorithm compared data from three kinds of studies: seed-to-seed, seed-to-voxel, and ICA-based analyses. For seed-to-seed studies, we obtained spatial maps of the seeds, either from the relevant parcellation or from the authors themselves. For seed-to-voxel studies, we tried to obtain spatial maps of the clusters of voxels that were significantly connected to the seeds; when this was not possible, we constructed spheres around the MNI coordinates of the clusters, where the radius of the sphere varied depending on the size of the cluster. For ICA-based studies, we used spatial maps of group independent components (ICs). In some ICA-based studies, group ICs were either *cross-correlated with template ICs from Smith et al. (2009); others **used those template ICs for dual regression/ back-projection into subject-specific spatial IC maps. Thus, to run the meta-analysis on the ICA-based analyses, we used the template ICs from Smith et al. (2009).*

Chapter 3.4. Results

Chapter 3.4.1. BOLD activation

We identified $n = 17$ studies on BOLD activation that fit our inclusion criteria. Three of the studies did not report the coordinates of peak BOLD activity. 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 3.3**). 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 3.3; Figure 3.3a**). 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 3.4; Figure 3.3b**). 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 3.5; Figure 3.3c**).

Figure 3.4 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 (F. S. Barrett, Doss, et al., 2020; Duerler et al., 2021; Krachenmann, 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 similarities in experimental procedures more than they reveal the genuine

neural correlates of psilocybin. When I submitted the neuroimaging meta-analysis for publication, I did not include the results of the BOLD activation analysis due to concerns that they would be misleading.

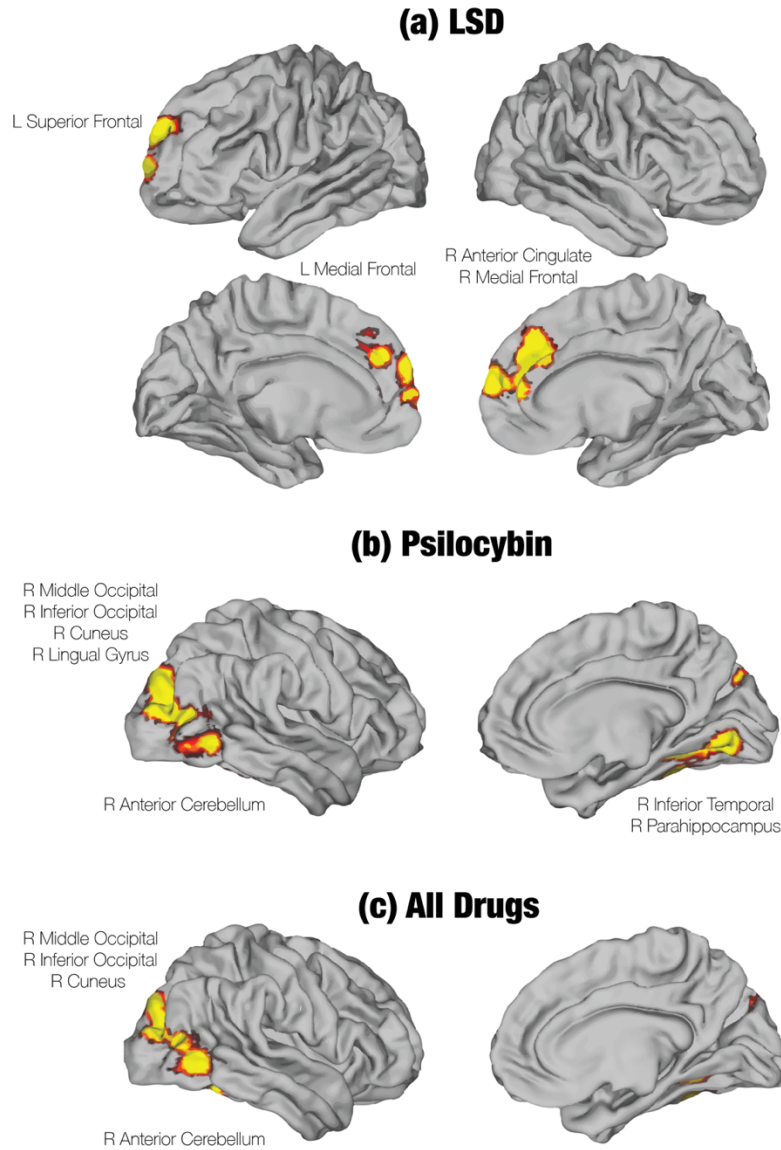


Figure 3.3. Meta-analysis of BOLD activation data yields distinct neural correlates for LSD and psilocybin.

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.

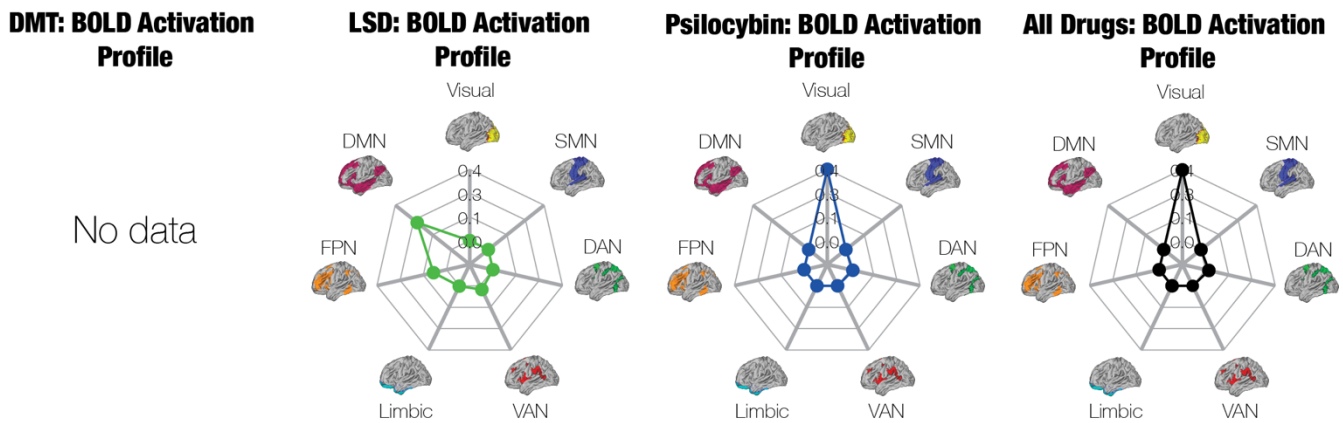


Figure 3.4. BOLD activation profiles of each psychedelic show very different patterns in the Yeo networks.

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.

Cluster #	x	y	z	ALE	Label
1	2	58	16	0.01156	L Medial Frontal Gyrus (BA 9)
1	2	34	38	0.00899	L Medial Frontal Gyrus (BA 8)
1	-14	56	30	0.00899	L Superior Frontal Gyrus (BA 9)
1	-10	62	26	0.00892	L Superior Frontal Gyrus (BA 9)
1	4	46	10	0.00854	R Anterior Cingulate (BA 32)
1	6	30	30	0.00853	R Cingulate Gyrus (BA 32)
1	-12	64	6	0.00849	L Medial Frontal Gyrus (BA 10)
1	8	38	28	0.00824	R Medial Frontal Gyrus (BA 9)
1	14	42	16	0.00822	R Anterior Cingulate (BA 32)
1	-2	42	28	0.00731	L Medial Frontal Gyrus (BA 9)

Table 3.3. Results of GingerALE analysis on the BOLD activation studies using LSD ($n = 7$).

The analysis was thresholded via cluster-level FWE ($p < 0.05$) at a cluster-forming threshold of 0.05 (1000 threshold permutations). Abbreviations and column labels are the same as in **Table 3.1**.

Cluster #	x	y	z	ALE	Label
1	18	-68	-6	0.01597	R Lingual Gyrus (BA 19)
1	38	-72	10	0.01527	N/A
1	22	-84	34	0.01448	R Cuneus (BA 18)
1	38	-74	-2	0.01445	R Lingual Gyrus (BA 18)
1	34	-48	-8	0.01286	R Parahippocampal Gyrus (BA 19)
1	28	-88	18	0.00901	R Middle Occipital Gyrus (BA 18)
1	42	-64	-2	0.00886	R Inferior Temporal Gyrus
1	36	-86	16	0.00878	R Middle Occipital Gyrus (BA 19)
1	26	-82	24	0.00870	R Cuneus (BA 18)
1	30	-60	-30	0.00731	R Anterior Cerebellum
1	34	-50	-22	0.00722	R Anterior Cerebellum, Culmen

Table 3.4. Results of GingerALE analysis on the BOLD activation studies using psilocybin ($n = 4$).

The analysis was thresholded via cluster-level FWE ($p < 0.05$) at a cluster-forming threshold of 0.05 (1000 threshold permutations). Abbreviations and column labels are the same as in **Table 3.1**.

Cluster #	x	y	z	ALE	Label
1	40	-72	10	0.01804	R Middle Occipital Gyrus (BA 19)
1	40	-74	-2	0.01584	R Inferior Occipital Gyrus (BA 19)
1	22	-84	34	0.01459	R Cuneus (BA 18)
1	44	-64	0	0.01438	R Middle Occipital Gyrus (BA 37)
1	34	-48	-8	0.01300	R Parahippocampal Gyrus (BA 19)
1	34	-52	-26	0.00985	R Anterior Cerebellum, Culmen
1	28	-88	18	0.00900	R Middle Occipital Gyrus (BA 18)
1	26	-82	24	0.00889	R Cuneus (BA 18)
1	36	-86	16	0.00878	R Middle Occipital Gyrus (BA 19)
1	30	-60	-30	0.00804	R Anterior Cerebellum
1	42	-56	-20	0.00782	R Anterior Cerebellum, Culmen

Table 3.5. Results of GingerALE analysis on the entire BOLD activation dataset ($n = 14$).

The analysis was thresholded via cluster-level FWE ($p < 0.05$) at a cluster-forming threshold of 0.05 (1000 threshold permutations). The analysis identified a single cluster of meta-analytic BOLD activations, consisting of 11 peaks. Columns 1-3 are comprised of the x , y , and z MNI coordinates of the weighted centre of mass of the cluster; column 4 contains the maximum ALE value of each peak; column 5 consists of the anatomical label assigned by the Talairach Daemon to the coordinates in columns 1-3. R = right; BA = Brodmann's Area. All listed peak coordinates are located in gray matter. Abbreviations and column labels are the same as in **Table 3.1**.

Chapter 3.4.2. Quantitative meta-analysis of functional connectivity data

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 (*Appendix 1*) on these 11 studies plus the aforementioned 11 studies that we had omitted from the quantitative meta-analysis.

As shown in **Figure 3.6**, 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 500 times, generating a histogram of aggregate FC matrices that effectively constituted a null distribution (**Figure 3.5**).

Psychedelics significantly strengthened between-network connectivity across most pairs of networks. Within-network connectivity significantly decreased in the visual network, VAN, and default mode network (DMN), yet significantly increased in the dorsal attention network (DAN) and frontoparietal network (FPN). Connectivity between the limbic network and other networks was generally deemed insignificant, likely due to the small size of this network in the Yeo parcellation and therefore low number of seed regions in the literature that predominantly overlap with it.

In addition to aggregating FC across all psychedelics, we performed our analysis separately on each individual psychedelic (**Figure 3.7**). All three of the psychedelics significantly reduced the within-network FC of the visual network while generally elevating between-network FC. Intriguingly, LSD significantly increased FC within the DMN, but this is largely due to a high number of significant connections that were identified in a single study (Bedford et al., 2023) between regions that are typically not considered to be core elements of the DMN yet are nevertheless classified by the Yeo parcellation as regions within the DMN, such as the frontal pole and inferior frontal gyrus (Liu et al., 2023; Martín-Signes et al., 2021; Rai et al., 2021). LSD significantly elevated FC between the limbic network and visual network, as well as between the limbic network and FPN, whereas FC between the limbic network and all other networks was insignificant for ayahuasca/DMT and psilocybin. Ayahuasca/DMT was the only psychedelic to significantly reduce FC

between the visual network and SMN, as well as between the visual network and FPN. Thus, only ayahuasca/DMT was associated with negative total FC of the visual network (sum of FC between the visual network and all other networks), while total FC of the VAN was negative for only psilocybin, though this result was driven by the findings of just a single study (F. S. Barrett, Krimmel, et al., 2020) (**Figure 3.8**).

Figures 3.9-3.11 display the results of our meta-analysis on the FC of subcortical regions. Because several studies did not measure subcortical FC, most of the subcortical-to-subcortical and subcortical-to-cortical edges in the aggregate FC matrix are insignificant. Nevertheless, the significant edges indicate that psychedelics elevate connectivity from two regions in the subcortex – the anterior thalamus and cerebellum – to cortex, as well as from the anterior thalamus to some other subcortical structures. Compared to the other psychedelics, LSD vastly elevated the FC between the anterior thalamus and both the cortex and subcortex.

Finally, there was no significant association between our results and any of the methodological covariates in the literature that we identified *a priori*: the width of the Gaussian kernel used to smooth the data, the use of FSL or SPM, the technique used to regress out white matter, the use of scrubbing to correct head motion, and route (oral or intravenous) and relative timing of drug administration. The results of our risk-of-bias assessment for individual studies is shown in **Table 3.6**. Because of the moderate-to-serious risk of bias, our certainty in the body of FC literature is low.

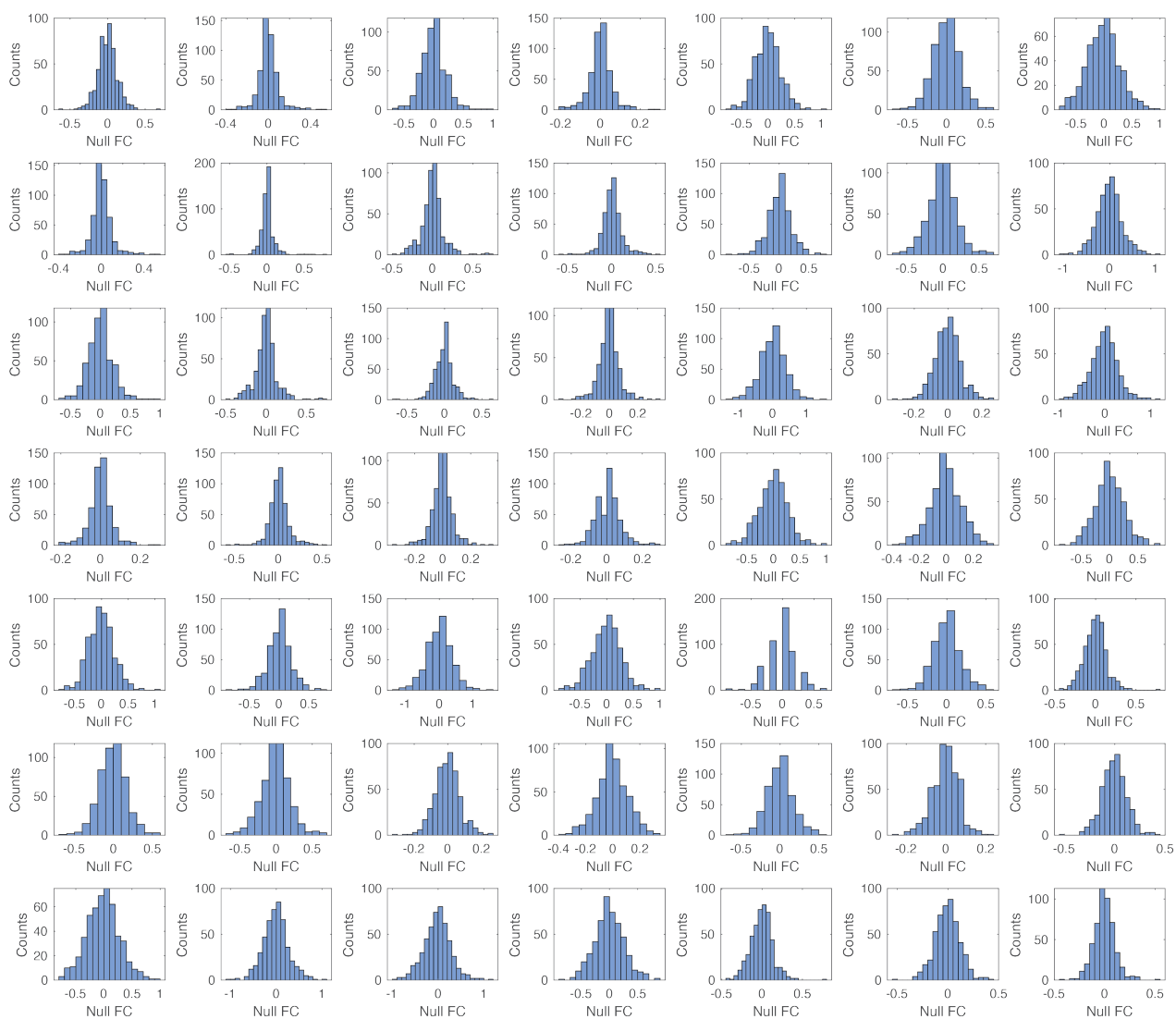
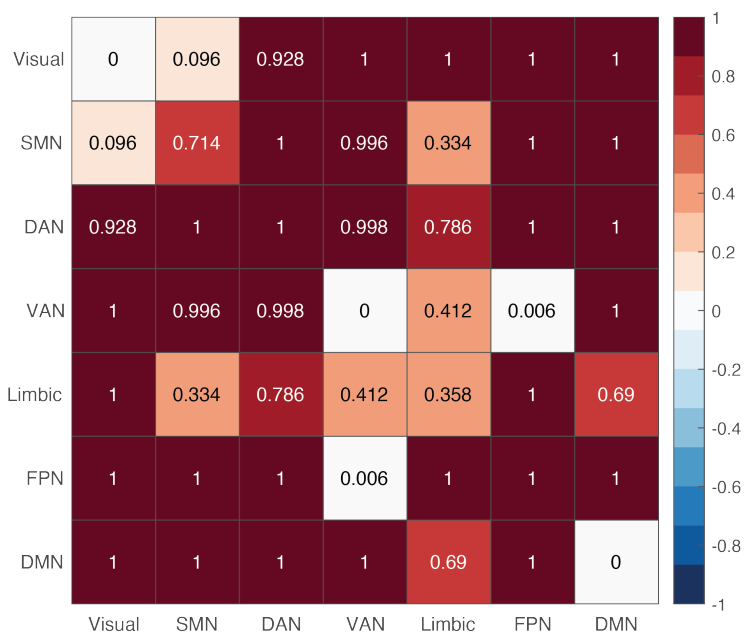
(a)**(b)**

Figure 3.5. Null distribution of functional connectivity (FC).

Null distribution was formed by measuring functional connectivity in resting-state fMRI data collected by the Human Connectome Project (HCP) in 100 unrelated, healthy, sober individuals. The data was parcellated with the Schaefer-100 atlas. The FC meta-analysis algorithm was repeatedly applied to randomly chosen subjects and windows of data, resulting in a “surrogate study set.” (a) We formed 500 surrogate study sets and produced a null distribution of each element of the aggregate FC matrix. (b) We determined the percentile of each element of the true aggregate FC matrix within the null distribution. If an entry of the true aggregate FC matrix was below the 2.5th percentile or above the 97.5th percentile of the corresponding entry in the null distribution, then it was deemed significant (so long as it also survived multiple comparisons.)

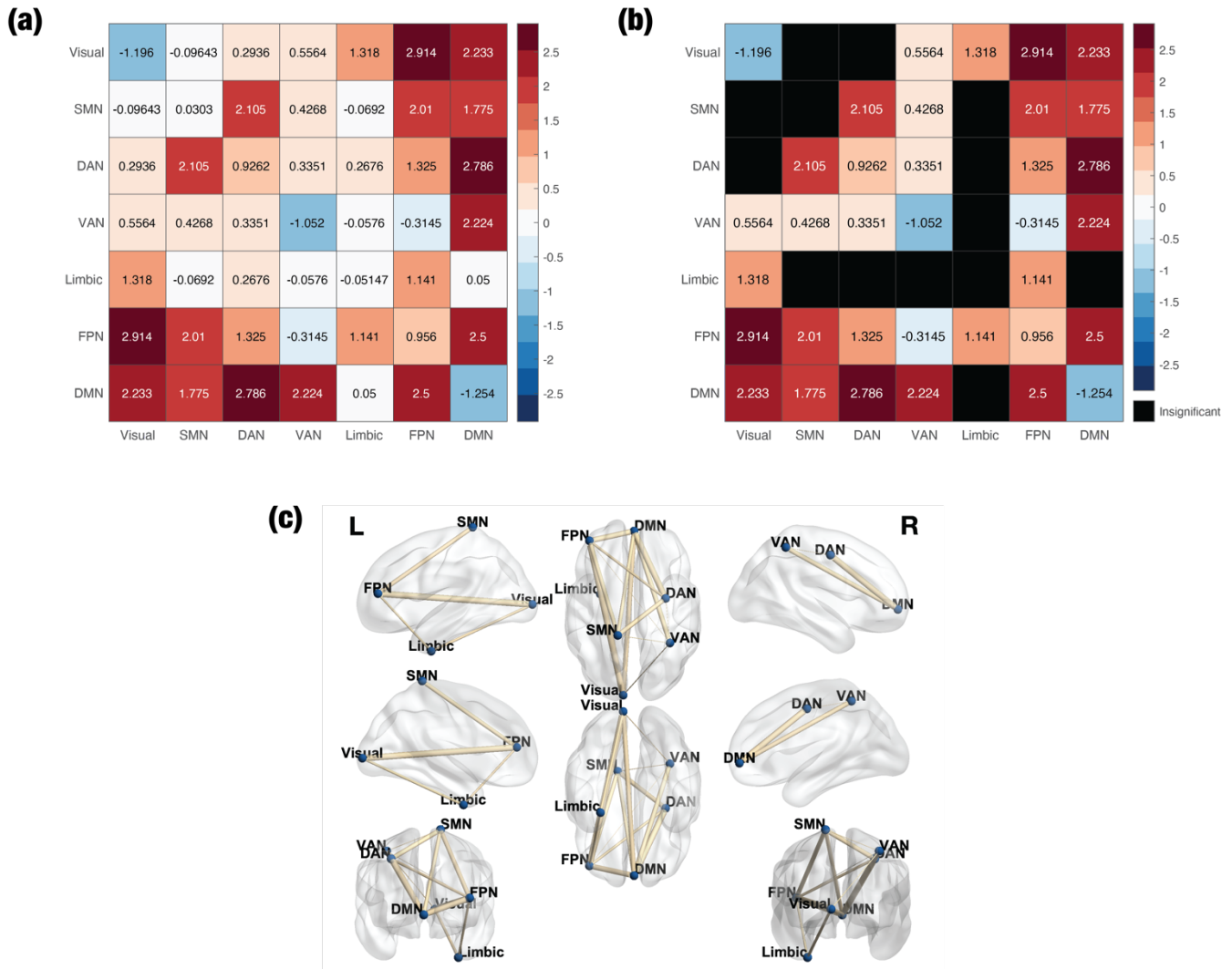
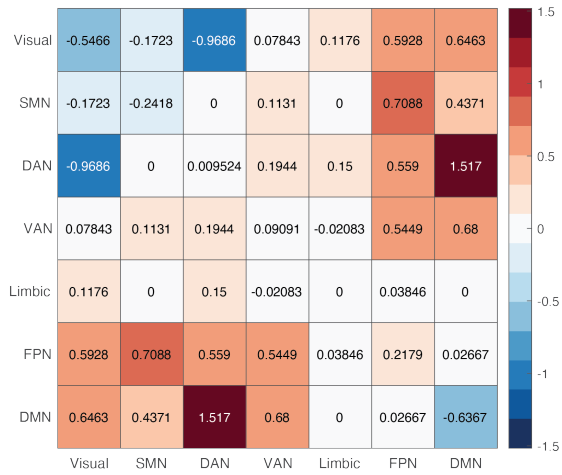


Figure 3.6. Meta-analysis of the functional connectivity (FC) data indicates increases that psychedelics potentially increase between-network connectivity.

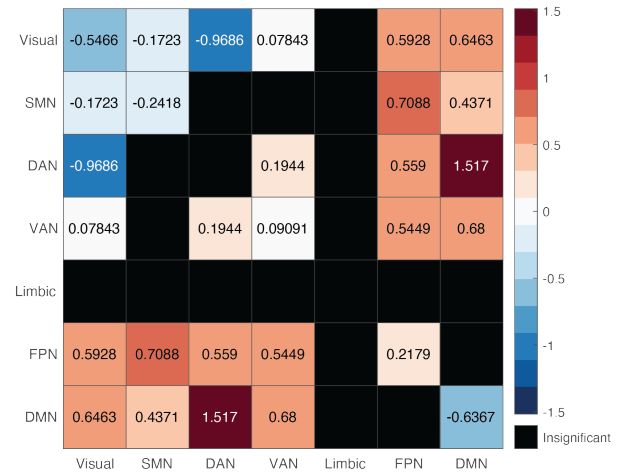
To perform a meta-analysis on the FC data, we determined the Yeo networks that contained each pair of functionally connected regions of interest (ROIs) in the literature and then performed a weighted sum of the number of significant connections between Yeo networks. We included $n = 12$ studies in this meta-analysis, after excluding studies that did not measure pairwise FC and secondary analyses of identical datasets. (a) The aggregate FC matrix shows the overall connectivity between pairs of Yeo networks. Units are arbitrary. (b) Several connections were deemed to be insignificant relative to a null distribution that was formed from an independent resting-state fMRI dataset collected by the Human Connectome Project. (c) A rendering of (b) on the surface of the brain, created with the BrainNet Viewer (Xia et al., 2013).

Ayahuasca/DMT

(a)



(b)

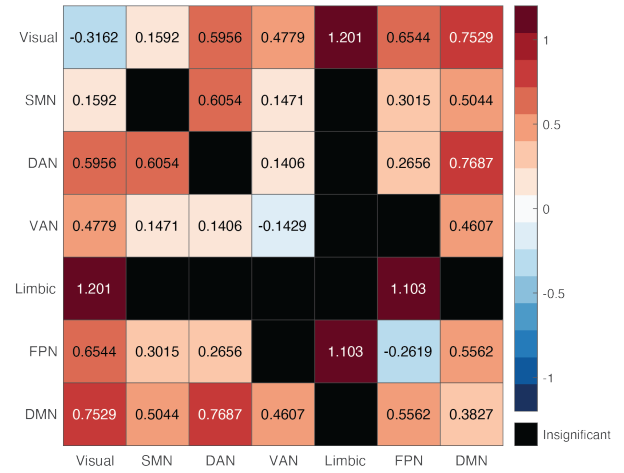


LSD

(c)

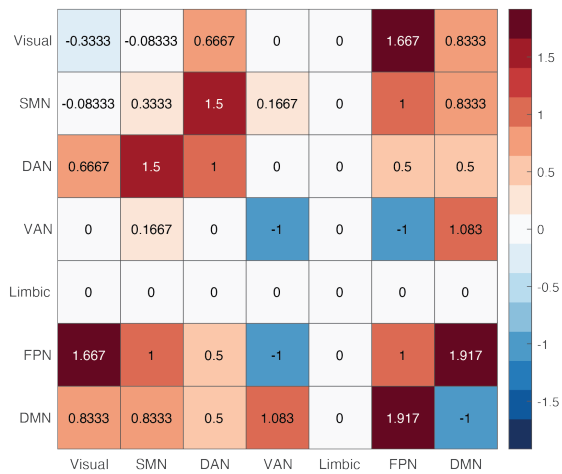


(d)



Psilocybin

(e)



(f)

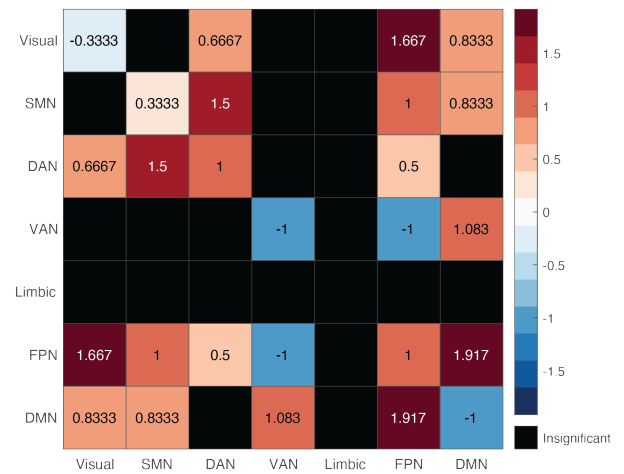


Figure 3.7. Results of FC meta-analysis for each classic psychedelic.

Whereas **Figure 3.6** displays the aggregate FC matrix across all three psychedelics, here we show the aggregate FC matrix that was computed on each individual psychedelic. Units are arbitrary. The left column displays all of the aggregate FC values, including insignificant edges, whereas the right column shows only significant entries. All psychedelics significantly disintegrate the visual network and generally increase between-network FC, with a couple of exceptions for ayahuasca/DMT and psilocybin.

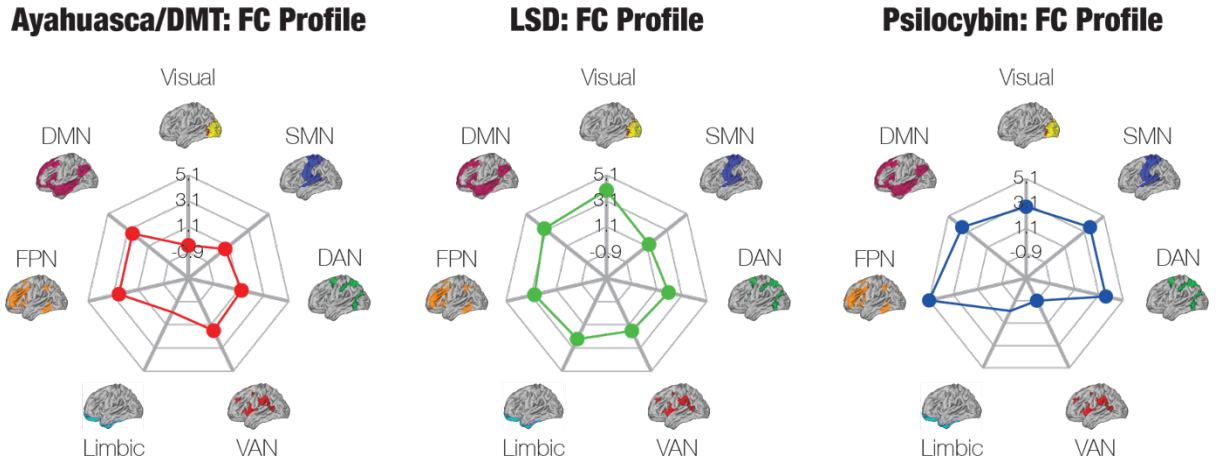


Figure 3.8. FC profiles show unique patterns for each psychedelic.

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 sum of the rows of the corresponding aggregate FC matrices (**Figure 3.7**). Units are arbitrary. The psychedelics display distinct FC profiles; for instance, LSD strongly elevates the total FC of the limbic network, whereas FC between the limbic network and all other networks was insignificant for ayahuasca/DMT and psilocybin (hence there is no point on the limbic network for the respective spider plots).

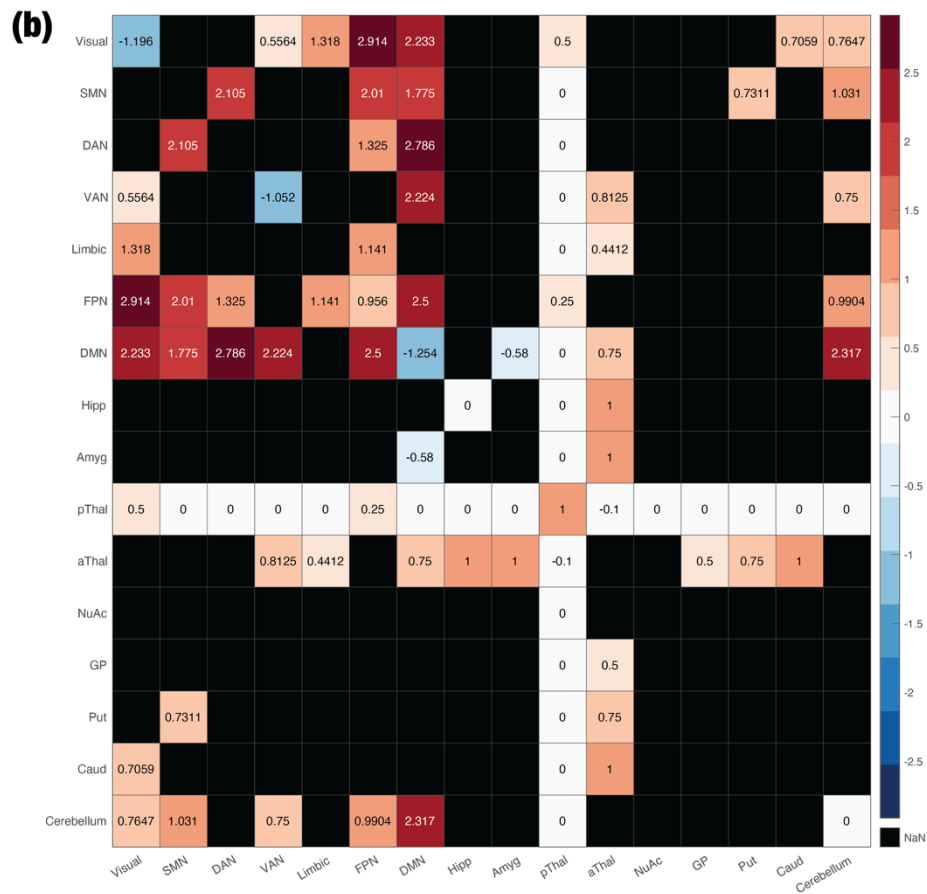
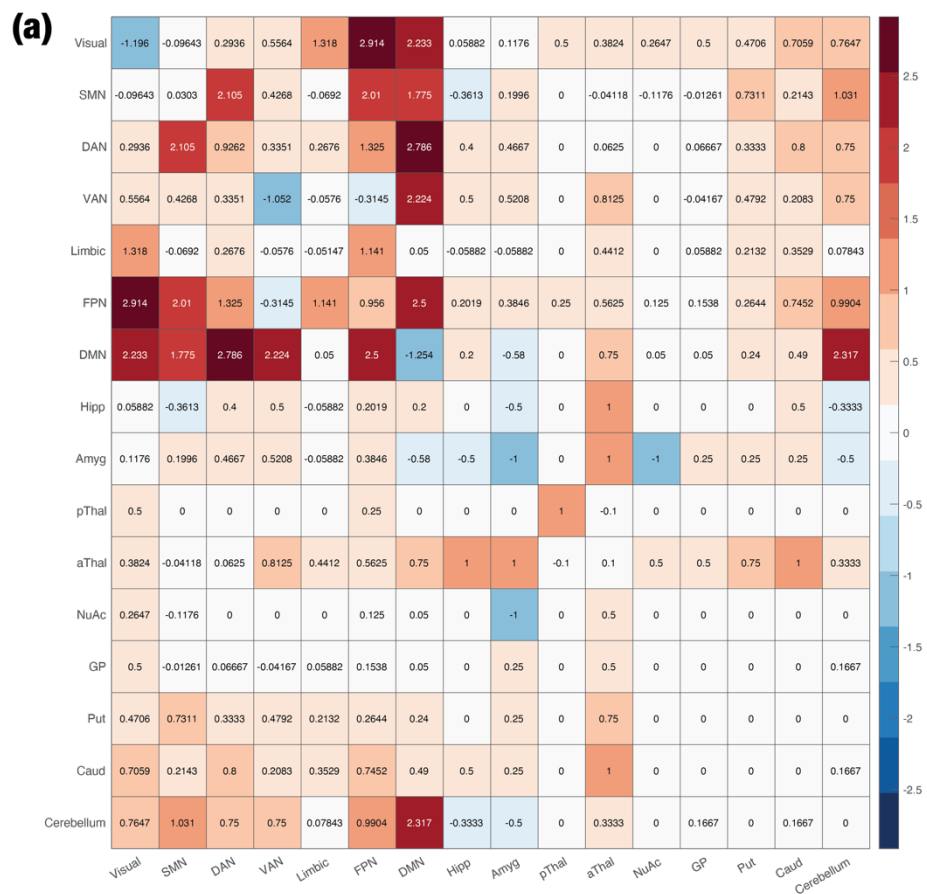


Figure 3.9. Aggregate FC matrix with subcortical regions included.

(a) We measured the aggregate FC matrix using the Tian parcellation, which defines eight subcortical regions: hippocampus (Hipp), posterior thalamus (pThal), anterior thalamus (aThal), nucleus accumbens (NuAc), globus pallidus (GP), putamen (Put), caudate (Caud), and cerebellum (Tian et al., 2020). Units are arbitrary. Note that the cortical portion of this matrix is the same as **Figure 3.6a**. (b) The statistical significance of this matrix was determined relative to a null distribution formed from resting-state HCP data. Unlike in the cortical case, the resting-state HCP data was parcellated here with the Desikan-Killiany (DK-80) atlas, which includes subcortical regions. (Due to the change in parcellation, the null distribution of the cortical FC is also altered.) FC between most pairs of subcortical regions, as well as between subcortex and cortex, was generally deemed insignificant, likely due to a lack of subcortical FC analyses in the literature. The increased connectivity between the anterior thalamus and cortex, as well as between the cerebellum and cortex, stand out as exceptions.

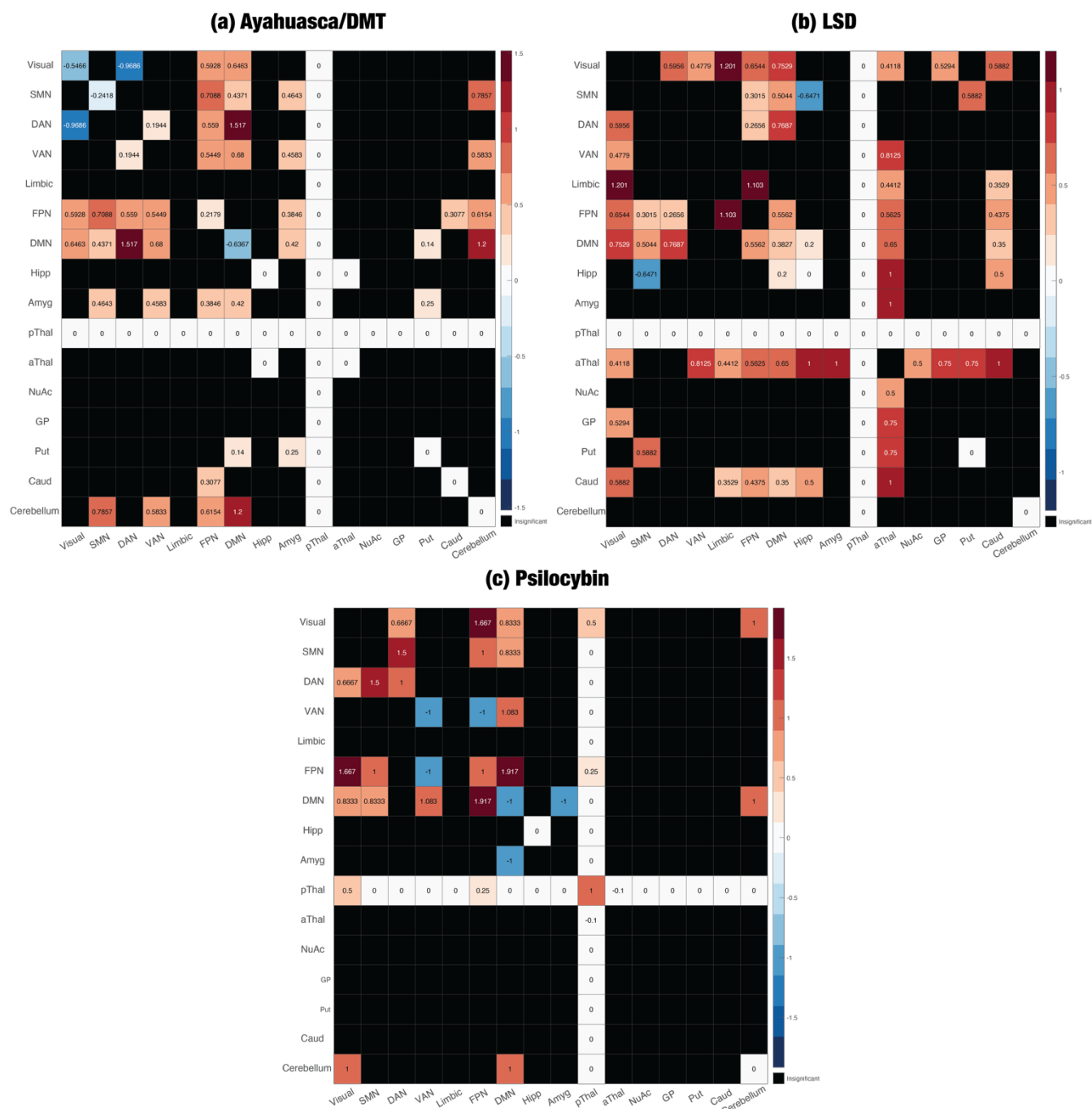
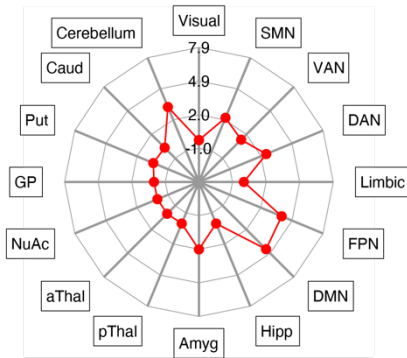


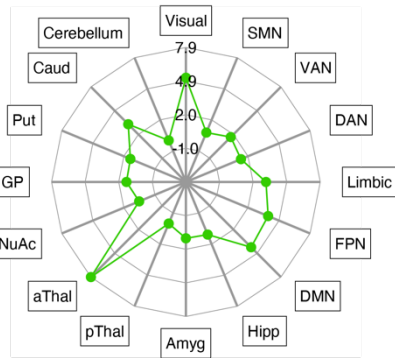
Figure 3.10. Aggregate FC matrices for each psychedelic, with subcortical regions included.

FC between subcortical regions, as well as FC between cortical and subcortical regions, tended to be insignificant for each psychedelic, especially psilocybin. Units are arbitrary. LSD significantly elevated the FC of the anterior thalamus, both to the subcortex and to the cortex.

Ayahuasca/DMT:
Subcortical+Cortical FC Profile



LSD:
Subcortical+Cortical FC Profile



Psilocybin:
Subcortical+Cortical FC Profile

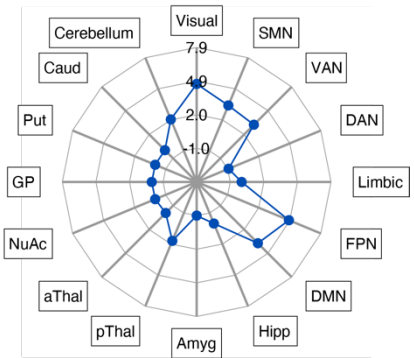


Figure 3.11. FC profiles with subcortical regions included.

We summed across the columns of each of the matrices in **Figure 3.10** to obtain the corresponding spider plots. Units are arbitrary. Compared to the other psychedelics, LSD much more strongly elevated the total FC of the anterior thalamus and, to a lesser extent, the caudate, even though there was only a single study on the effects of LSD on subcortical FC. Ayahuasca/DMT enhanced the total FC of the amygdala and cerebellum, but psilocybin had a negligible effect on subcortical FC, likely due to the lack of subcortical analyses of psilocybin.

Reference	Con	SP	CI	DII	MD	MO	SRR	Overall RoB
Barrett, Krimmel, et al. (2020)	M	L	L	L	L	M	L	M
Bedford et al. (2023)	M	L	L	L	L	L	L	M
Dai et al. (2023)	M	L	L	L	L	M	L	M
de Araujo et al. (2011)	S	L	L	L	L	M	L	S
Gaddis et al. (2022)	M	L	L	L	L	M	L	M
Grimm et al. (2018)	S	L	L	L	L	L	L	S
Kaelen et al. (2016)	M	L	L	L	L	M	L	M
Madsen et al. (2021)	M	L	L	L	L	M	L	M
Mason et al. (2020)	M	L	L	L	M	L	L	M
Palhano-Fontes et al. (2015)	M	L	L	L	L	M	L	M
Roseman et al. (2014)	M	L	L	L	L	M	L	M
Timmermann et al. (2023)	L	L	L	L	L	M	L	M

Table 3.6. Risk of bias for individual studies in the neuroimaging literature.

Using the ROBINS-I tool, we analysed risk of bias in seven domains: bias due to confounding (Con), bias in selection of participants into the study (SP), bias in classification of interventions (CI), bias due to deviations from intended interventions (DII), bias due to missing data (MD), bias in measurement of outcomes (MO), and bias in selection of the reported result (SRR). The overall risk of bias (RoB) is given in the rightmost column. L, M, and S refer to low, moderate, and serious risk of bias. Risk of bias was deemed low for all studies in the SP, CI, DII, and SRR domains. One study used a between-subjects design and excluded more subjects in the psilocybin group than the placebo group due to head motion, so it was assigned a moderate risk of bias in the MD domain (Mason et al., 2020). Psychedelics are known to be vasoconstrictors (Dyer & Gant, 1973), which may influence the fMRI signal (Özbay et al., 2019). None of the studies explicitly controlled

for vasoconstriction, but it is also unclear how to feasibly measure neural vasoconstriction in a study with humans, so most studies were assigned a moderate risk of bias in the Con domain. Timmermann et al. (2023) received an L rating in this domain because it measured EEG and fMRI simultaneously, and EEG signal is less susceptible to vascular changes than fMRI. Studies that did not report the results of head motion analyses, which are known to strongly confound fMRI measurements (Makowski et al., 2019), were given an S rating in the Con domain. Studies that were not double-blind were deemed to have moderate risk of bias in the MO domain. In this case, the outcome assessors were aware of whether participants received a psychedelic or placebo, but this likely did not have a significant effect on the measurement outcomes. Overall risk of bias was moderate for 10/12 studies and serious for 2/12 studies.

Chapter 3.4.3. 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., 2022a; 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; L.-D. 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 (L.-D. 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.

Another problem is that ten of the twelve studies measured entropy on the same two primary datasets (Carhart-Harris, Erritzoe, et al., 2012; Carhart-Harris et al., 2016), which could explain why they all arrived at similar conclusions despite differences in methods. A recent study applied all twelve of the entropy measures in the literature to an independent cohort of 28 participants who were administered psilocybin (McCulloch et al., 2023). (The study is still a pre-print, so we did not officially include it in our review.) Psilocybin did not have a significant effect on seven of these measures, suggesting that the results from the literature may not generalise to other datasets. Additionally, the measures did not correlate well with each other. The study highlights the need for more primary data and replication studies in the field of psychedelic neuroimaging.

Chapter 3.5. Discussion

Chapter 3.5.1. 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 potentially 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; F. S. 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; F. 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”). Our neuroimaging meta-analysis confirms that psychedelics significantly decrease connectivity within the DMN while significantly elevating its connectivity with all other networks. Furthermore, the reduction in within-network FC was greater for the DMN than for any other network, though it was not that much larger than that of the visual network. Although we found that LSD increased within-DMN FC, this result is likely attributable to connectivity between regions that are not key hubs of the DMN. Our phenomenology meta-analysis revealed that all psychedelics induced positive experiences of depersonalisation and derealisation, as captured by the oceanic boundlessness dimension of the 5D-ASC scale; these experiences are related to the feeling of ego death.

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 (Lyu et al., 2023). (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 (B. Lord et al., 2024)). 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 (H.-X. Zhou et al., 2020).

Chapter 3.5.2. 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 (F. S. Barrett, Doss, et al., 2020; Dai et al., 2023; Girn et al., 2022; Lebedev et al., 2015; Madsen et al., 2021; F. 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. A recent study, which was published after my meta-analysis was completed, utilised a novel longitudinal precision functional mapping approach, in which participants were scanned 18 times before, during, and after psilocybin administration (Siegel et al., 2024). It also reported massive decreases in anticorrelations between networks (desegregation), as well as in correlations within networks (disintegration).

Our meta-analysis corroborates the desegregation hypothesis and provides mixed support for the disintegration hypothesis. Psychedelics significantly elevated FC between all non-identical pairs of brain

networks except the FPN and VAN. Within-network FC significantly decreased for the visual network, VAN, and DMN, yet it significantly increased for the DAN and FPN. The reduction in within-VAN FC and amplification of within-DAN FC may be consistent with the behavioural neurophysiology and phenomenology of psychedelics, respectively. Broadly speaking, the VAN redirects attention to salient stimuli, whereas the DAN is responsible for sustaining attention (Vossel et al., 2014). In agreement with the VAN FC results, there is some evidence, albeit mixed, that psychedelics reduce mismatch negativity, or the brain's response to surprising stimuli (Duerler et al., 2021; Heekeren et al., 2008; Timmermann et al., 2018), though the MMN is primarily generated by regions outside the VAN (Garrido et al., 2009). Whereas closed-eyes mental imagery tends to be very fleeting when people are sober, it is often much more stable and vivid on psychedelics (Dittrich, 1998; Komater & Vollenweider, 2018; Studerus et al., 2010). We speculate that this increase in stability could be attributed to a vast enhancement of the ability to freely allocate attentional resources on psychedelics, as has been proposed in the past (Lyon, 2023). That is, external stimuli typically demand attention, which limits the brain's capacity to freely allocate attention to spontaneously generated, closed-eyes mental imagery. Psychedelics may reduce the competition between external stimuli and closed-eyes mental imagery for sustained attention, which could explain an increase in the within-network FC of the DAN. Intriguingly, ayahuasca and DMT are the only psychedelics to reduce FC between the visual network and the DAN. This could be consistent with the fact that only ayahuasca and DMT appear to give rise to *open-eye* “breakthrough” experiences, which feature extraordinarily rich and realistic visual hallucinations (Komater & Vollenweider, 2018). Indeed, the loss of connectivity from the visual network, and consequently of visual input from the environment, may make it possible to sustain attention on complex visual hallucinations even while the eyes are open.

Meanwhile, increases in connectivity within the FPN could account for the therapeutic effects of psychedelics. The FPN is a network that initiates and flexibly adjusts cognitive control in response to feedback from the environment (Marek & Dosenbach, 2018). Depression compromises executive control and cognitive flexibility (Gabrys et al., 2018; Kraft et al., 2023); hence, it reduces FC within the FPN (Alexopoulos et al., 2012; Hwang et al., 2015). Psilocybin has shown promise for treating depression (A. K. Davis, Barrett, May, et al., 2021; Goodwin et al., 2022; Raison et al., 2023; Tabaac et al., 2024; Von Rotz et al., 2023), and while this meta-analysis was only conducted on data from healthy participants, our finding that psychedelics elevate within-FPN FC may still be able to explain their antidepressant effects.

The significant increases in within-FPN and within-DAN FC indicate that the effects of psychedelics on within-network FC are more nuanced than total disintegration across the whole brain. Furthermore, the explanatory power of desegregation and disintegration remains unclear. While there is a correlation between desegregation/disintegration and the subjective experience of ego dissolution (Tagliazucchi et al., 2016),

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.

Chapter 3.5.3. Sources of heterogeneity

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 (F. S. Barrett, Doss, et al., 2020; Kraehenmann, Preller, et al., 2015; F. Müller, Lenz, Dolder, Harder, et al., 2017), (3) on attention (Daumann et al., 2008, 2010; Duerler et al., 2021; A. Schmidt et al., 2018), (4) on music (F. S. 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 (F. S. 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; F. S. 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.

Finally, it is worth noting that a recent systematic review of the neuroimaging literature on psychedelics concluded that it was not possible to perform a meta-analysis due to the heterogeneity of the studies, as well as other methodological concerns (Linguiti et al., 2023). Overall, we agree that it is challenging to perform a standard meta-analysis on the psychedelic neuroimaging literature. However, several steps were taken in our analysis to overcome the concerns that Linguiti and colleagues raised. Unlike Linguiti and colleagues, we separated studies on functional connectivity from studies on entropy and BOLD activation. As stated above, the BOLD activation studies subjected participants to such a wide variety of tasks that it was impossible to conduct a meta-analysis on this segment of the literature. However, almost all of the functional connectivity studies that we included in our meta-analysis conducted resting-state recordings. Linguiti and colleagues correctly note that, even among the resting-state recordings, there experimental procedures and analysis methods are very heterogeneous. We ran subgroup analyses to confirm that these covariates, such as route of administration (oral or intravenous), timing of drug administration relative to the duration of the drug's acute effects, and various preprocessing techniques, did not impact the results of our meta-analysis. Linguiti and colleagues also observed that there is a high sample overlap in the published neuroimaging studies; that is, there are many studies that reused or re-analysed data from previously published research. In our meta-analysis, we ensured that we included only one analysis of each unique dataset in the literature. Because of this and other exclusion criteria, we entered data from only 12 studies into our quantitative meta-analysis, whereas Linguiti and colleagues included 91 studies. We do agree with Linguiti and colleagues that at least one of our included studies failed to adequately control for Type I error (Kaelen et al., 2016) and that at least another one did not sufficiently report head motion correction (Grimm et al., 2018). Nevertheless, overall, we believe that there is enough consistency among some studies in the neuroimaging literature to conduct a meaningful meta-analysis.

Chapter 3.6. Chapter summary

In this chapter I performed a meta-analysis of existing whole-brain neuroimaging data, which consisted of three subsets of data: entropy, functional connectivity (FC), and BOLD activation. Neuroimaging meta-analyses have many potential pitfalls but can be useful for discovering general principles. In order to perform a meta-analysis on FC data, I essentially re-parcellated the published data into the Yeo networks and then

calculated a weighted sum of the connections between Yeo networks. I found different signatures between the different classic psychedelics. 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). In addition, a voxel-based GingerALE meta-analysis of BOLD activation data showed that psilocybin and LSD alter activity in very different regions of cortex. However, these results are likely spurious since they are strongly confounded by the different tasks that were performed in the psilocybin and LSD studies. We did not conduct a meta-analysis of the entropy literature due to the heterogeneity of methods and instead opted for a qualitative review, which illustrated that definitions of entropy vary widely between studies. Overall, the results highlighted large differences between the neural correlates of LSD, psilocybin, and ayahuasca/DMT.

Chapter 4. Pharmacology Meta-Analysis

Chapter 4.1. Chapter abstract

Studies on the pharmacology of psychedelics have elucidated their interactions with serotonergic and other receptors in the brain. On the one hand, studies of affinity measure the strength with which psychedelics bind to these receptors. On the other hand, studies of functional activity quantify the effects of psychedelics on cellular signaling after binding to receptors. Here, I performed random-effects meta-analyses on the affinity and activity literature. There were no significant differences between psychedelics in their affinity for the 5-HT_{2A}, 5-HT_{2C}, or D₂ receptors, relative to the 5-HT_{1A} receptor. LSD elicited significantly more relative activity than DMT and psilocin via the inositol phosphate pathway, but not via other pathways such as calcium mobilisation and β -arrestin2 recruitment. While the results seem to suggest that psychedelics share a similar pharmacological profile, the heterogeneity of the data limits our confidence in the findings.

Chapter 4.2. Literature search

We conducted two separate meta-analyses on the pharmacology of psychedelics: one on the selective affinities of psychedelics for three G protein-coupled receptors (GPCRs) – 5-HT_{2A}, 5-HT_{2C}, and D₂, relative to 5-HT_{1A} – and another on the functional activity of psychedelics, as measured by assays on GPCR-mediated signaling.

We performed our literature searches in May-August 2023. We searched the following four databases: SCOPUS; Web of Science; the National Institute of Mental Health’s Psychoactive Drug Screening Program (PDSP) K_i Database; and ChEMBL, the “chemogenomic” database of the European Bioinformatics Institute, which is part of the European Molecular Biology Laboratory (EMBL). The PDSP K_i Database (pdsp.unc.edu/databases/pdsp.php) is an online resource that contains nearly 100,000 published affinity (K_i) values for a very large number of chemicals and receptors (Roth et al., 2000). ChEMBL contains a wide variety of data on the chemistry, bioactivity, and genomics of more than 2.2 million compounds, including not only affinity (K_i and K_d) and functional activity (EC₅₀) values but also information on chemical structures, molecular properties, absorption, metabolism, toxicity, and more (Davies et al., 2015; Mendez et al., 2019). Neither the PDSP K_i Database nor the ChEMBL Database is comprehensive, as we found many studies on affinity and functional activity that were not included in the databases. Finally, there were three studies that we found through citations in articles that we had already included, but were not listed in any of the above databases.

We applied the following search terms for the literature search on binding affinities: <drug name> and “receptor affinity”, <drug name> AND “inhibitory constant” OR K_i , <drug name> AND “binding affinity”, <drug name> AND <receptor name> and affinity, where <drug name> was “DMT”, “LSD”, or “psilocin”, and <receptor name> was “5-HT_{1A}”, “5-HT_{1B}”, “5-HT_{2A}”, “5-HT₆”, “D₁”, or “D₂”. For the literature search on functional activity, we used a single search term: <drug name> AND EC₅₀ OR potency OR “functional assay”, where <drug name> was “DMT”, “LSD AND ‘lysergic acid diethylamide’”, or “psilocin”. We excluded studies that met the following criteria:

1. Works that did not report any original research, such as literature reviews, commentaries, and editorials.
2. Studies that did not measure the binding affinities of DMT, LSD, or psilocin. Note that we excluded data on ayahuasca and psilocybin. A metabolite of psilocybin, psilocin is the main pharmacologically active substance in magic mushrooms (Passie et al., 2002).
3. Studies that did not examine the following receptors: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT₆, D₁, and D₂. We selected these receptors because there were available PET maps of them from a recent, state-of-the-art atlas of receptors, which was created with data from thousands of human participants (J. Y. Hansen et al., 2022). Note that the atlas also includes PET maps of the serotonin and dopamine transporters [SERT and DAT, respectively], but we excluded these receptors from our literature searches because the NIMH PDSP does not report any affinity with the classical psychedelics.
4. Affinity studies that did not measure K_i or functional activity studies that did not measure GPCR-mediated signaling. While affinities are often measured as K_d (dissociation constant) in pharmacology, studies on K_d typically require a radionuclide to be attached to the drug of interest, in order to radioactively label the drug’s interaction with the relevant receptor. Therefore, we only included K_i data in the binding affinity meta-analysis. We focused on GPCR functional assays because GPCR-mediated signaling appears to be a key mechanism underlying the hallucinogenic effects of psychedelics (López-Giménez & González-Maeso, 2018). Thus, GPCR functional assays bore the most relevance to our research aim, which was to link the pharmacology of psychedelics with their phenomenology and neuroimaging. The datapoint of interest in functional GPCR assays was the EC₅₀ value, or the effective concentration of drug that produces 50% of the maximal functional response.
5. Studies that did not report original K_i or EC₅₀ data.
6. Studies that performed original measurements of K_i and EC₅₀, but did not publish the results.

7. Studies that did not specify the receptor subtype, e.g. studies on 5-HT₁ binding affinity that did not indicate whether they were measuring affinity for 5-HT_{1A}, 5-HT_{1B}, or one of the other subtypes of the 5-HT₁ family. We separated data from different receptor subtypes, so we did not wish to conflate them. Some older studies were published at a time when the receptor subtypes had not been discovered yet. However, we did include binding affinity studies on 5-HT₁ and 5-HT₂ if the radioligand, i.e. the radioactive chemical that competes with the drug for the receptor, used in the study has been shown to selectively bind to specific receptor subtypes. For instance, the radioligand [³H]-8-OH-DPAT is quite selective for the 5-HT_{1A} subtype (Hjorth et al., 1982), whereas the radioligand [³H]-5-HT is not (K. L. Davis et al., 2002).
8. Studies that did not examine human receptors.
9. Affinity studies that did not measure K_i for 5-HT_{1A}, which we chose to be the reference receptor for the selectivity meta-analysis.
10. Studies that did not specify the source of receptor (e.g. whether the receptor was cloned or extracted from brain homogenates) or the species of the animal from which the receptor was derived.

A flowchart of the pharmacology literature search is shown in **Figure 4.1**. We identified **$n = 28$ studies in total**. These included **$n = 14$ studies on selectivity** (Chadeayne et al., 2020; Erkizia-Santamaría et al., 2022; Eshleman et al., 2014, 2018; Glatfelter et al., 2022; Halberstadt et al., 2020; Janowsky et al., 2014; Keiser et al., 2009; Kozell et al., 2023; Luethi et al., 2018, 2019; Pierce & Peroutka, 1989; Rickli et al., 2015, 2016), as well as **$n = 18$ studies on functional activity** (Braden & Nichols, 2007; Cimadevila et al., 2020; Cussac et al., 2008; Eshleman et al., 2014, 2018; Gatch et al., 2011; Glatfelter et al., 2022; Halberstadt et al., 2020; Janowsky et al., 2014; Keiser et al., 2009; A. K. Klein et al., 2021; Kozell et al., 2023; Newton et al., 1996; Porter et al., 1999; Pottie, Cannaert, et al., 2020; Pottie, Dedeker, et al., 2020; Schmitz et al., 2022; Sherwood et al., 2020).

All pK_i (negative logarithm of K_i) and pEC_{50} (negative logarithm of EC_{50}) values were transformed into K_i and EC_{50} for the selectivity and functional activity analyses, respectively. While the majority of studies reported standard errors (SEM), some published standard deviations (SD) instead but did not explicitly state the number of corresponding experiments, which is needed in order to transform SD into SEM. In these cases, we inferred the number of experiments from other assays performed in the study.

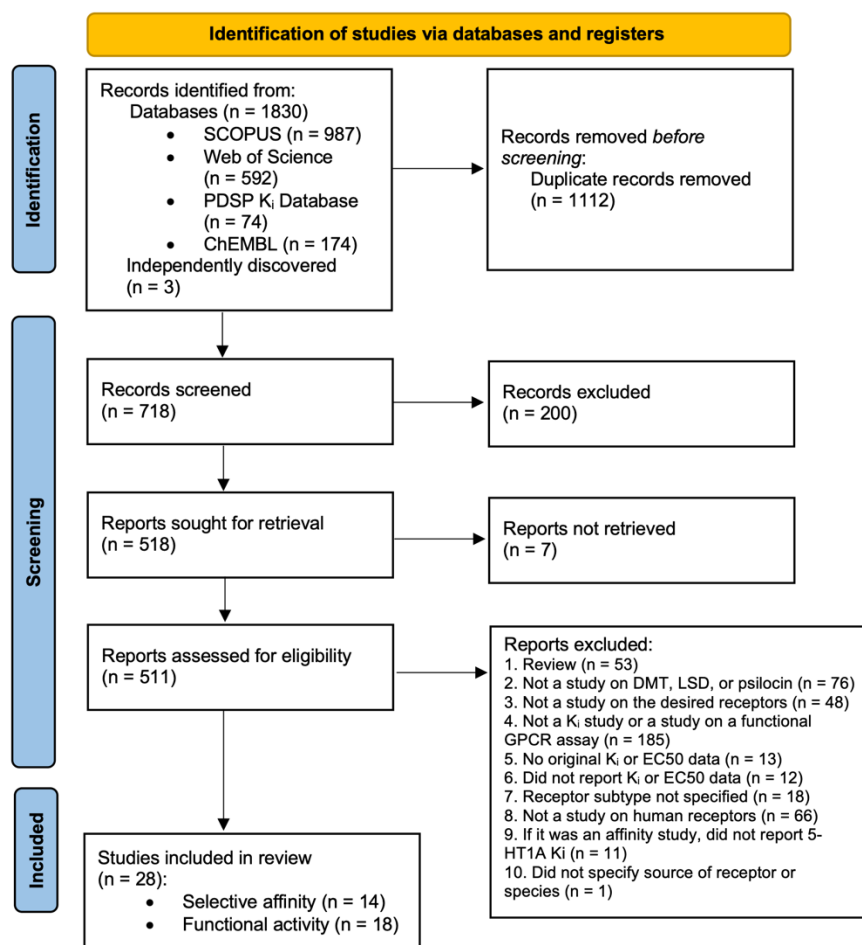


Figure 4.1. PRISMA flowchart for pharmacology literature search.

PRISMA is a set of guidelines for performing systematic reviews and meta-analyses. 28 pharmacology studies were identified, including 14 on affinity and 18 on functional activity.

Chapter 4.3. Methods

We performed two meta-analyses of the pharmacology literature. To synthesise the data on binding affinity, we analysed selectivity, measured as the ratio of the K_i for the three receptors of interest (5-HT_{2A}, 5-HT_{2C}, and D₂) relative to the K_i for 5-HT_{1A}. We also performed a supplementary analysis on selectivity relative to 5-HT_{2A}. K_i refers to the inhibition constant, which reflects the concentration of a drug that is needed to inhibit the binding of another ligand, for instance a radioactively-labeled ligand (radioligand), to the receptor of interest; it is inversely related to binding affinity (Sykes et al., 2019). We decided to analyse selectivity rather than absolute K_i because the latter is biased by the potency of the drug. Since LSD is much more

potent than DMT and psilocin, the meta-analysis would simply reveal that LSD has higher affinity for all receptors if we were to examine the absolute K_i instead.

To analyse the data on functional activity, we pooled relative activity values, defined as $\Delta\log(E_{\max}/EC_{50})$. When a drug is a partial, rather than full, agonist at a receptor, estimates of functional activity are affected in a nonlinear manner by the sensitivity of the assay (Kenakin, 2017). The sensitivity of can increase or decrease, for instance, based on whether the cells in the assay overexpress the receptor of interest or express it at endogenous levels. One solution is to compare the relative activity, defined as $\Delta\log(E_{\max}/EC_{50})$ (Kenakin et al., 2011). $E_{\max}$ is the maximal response elicited by the drug of interest, relative to a reference ligand, and EC_{50} is the concentration of drug that is needed to bring about 50% of the maximal response. The log of the ratio between these two quantities is measured both for the drug of interest and a reference ligand, and the relative activity is then defined as the difference. Because activity is quantified relative to the reference ligand, this measure of relative activity essentially cancels out differences in assay sensitivity (Kenakin, 2017). Thus, there is no need to regress out differences in assays, such as the cell line, in a meta-analysis.

All GPCR functional assays, at least in humans, were performed on cloned cell lines. The majority of affinity studies were also conducted on cloned cell lines, and a handful of affinity studies carried out their experiments on brain homogenates. While some of the latter studies reported multiple data points, since they measured affinity for multiple drugs or receptors, we treated the data points in these studies as statistically independent from one another, as it was not apparent that the homogenates were extracted from the same brain. Thus, we chose not to perform a multilevel meta-analysis as we did for the phenomenology literature.

Instead, for both the affinity and activity meta-analyses, we constructed random-effects models, which, unlike fixed-effects models, assume that true effect sizes (K_i and EC_{50}) are not uniform across studies once sampling errors are accounted for (Hedges & Vevea, 1998). Rather, the true effect sizes exist along a distribution with an overall mean μ . The true effect size of a particular study k deviates from the mean μ of all true effect sizes by an error ζ_k , and the actual effect size of one study deviates from its true effect size by the sampling error ϵ_k . Therefore, the random-effects model is:

$$\hat{\theta}_k = \mu + \beta x_k + \zeta_k + \epsilon_k \quad (4.1)$$

where $\hat{\theta}_k$ is the actual effect size of study k , x is a predictor, and β is its weight.

We chose random-effects models over fixed-effects models due to the large heterogeneity that we observed in the data. In order to account for ζ_k , we must estimate the variance of the distribution of true effect sizes, known as τ^2 (Harrer et al., 2021). There are several well-validated estimators of τ^2 ; we chose the restricted maximum likelihood procedure, which has been shown to outperform other estimators for

continuous data like ours (Veroniki et al., 2016). Once τ^2 has been estimated, we can calculate a weight for each data point:

$$w_k^* = \frac{1}{s_k^2 + \tau^2} \quad (4.2)$$

where s is the square of the standard error. Then, the pooled effect size is calculated as follows, in what is known as the generic inverse variance method:

$$\hat{\theta} = \frac{\sum_{k=1}^K \hat{\theta}_k w_k^*}{\sum_{k=1}^K w_k^*} \quad (4.3)$$

For both the selectivity and functional activity analyses, we initially modeled the drugs as the sole covariates. We applied the Knapp-Hartung adjustment to produce more conservative estimates of variance in the β -weight of the predictor (Knapp & Hartung, 2003). However, we stress that the range of variances was still quite large, and the number of studies on each assay and each psychedelic was small. Therefore, our estimates of p -values may not be reliable.

For just the selectivity analysis, we created another model in which we included the radioligand as an additional covariate, since the radioligand is known to influence the K_i estimate. To compare the fit of this “full” model to the fit of the “reduced” models (i.e. the model where only the drugs were covariates), we examined the corrected Akaike’s information criterion (Akaike, 1998). Because relative activity already accounts for all possible differences in assay protocols, we did not model any additional covariates for the functional activity analysis.

In order to obtain the pharmacology profile of psychedelics, we needed to identify the neural substrate of their pharmacology in the human brain. We based the pharmacology profile on the binding affinity data, rather than the functional activity data, because it was unclear how to combine data about the three different cellular signaling pathways. We defined the pharmacology profile as a weighted combination of the overall receptor density in each Yeo network, weighted by the selectivity of the psychedelics:

$$\mathbf{h}^{(p)} = \sum_{r=1}^2 S_r^{(p)} \mathbf{l}^{(r)} \quad (4.4)$$

where $S_r^{(p)}$ is the selectivity of a psychedelic p for a receptor r , relative to the 5-HT_{1A} receptor; $\mathbf{l}^{(r)}$ is a 7x1 vector containing the total expression level of each receptor in each Yeo network; and $\mathbf{h}^{(p)}$ is a 7x1 vector representing the pharmacology profile of each psychedelic.

To determine $\mathbf{l}^{(r)}$, we took human PET maps of 5-HT_{2A} and D₂ from Hansen et al. (2022), which itself obtained and in some cases averaged maps from previous literature. (Unfortunately, there was no map of the 5-HT_{2C} receptor in this atlas.) The 5-HT_{2A} map was taken from Beliveau et al. (2017) and the D₂ map was averaged from data by Sandiego et al. (2015) and C. T. Smith et al. (2019). The 5-HT_{2A} study used the [¹¹C]-CIMBI-5 PET radiotracer, and both D₂ studies used the [¹¹C]-FLB457 PET radiotracer. Hansen and

colleagues parcellated these maps with the Schaefer-200 atlas. We then performed min-max normalisation on the maps, which turned the lowest value of receptor expression into 0 and the highest into 1. To obtain $\mathbf{I}^{(r)}$, we then summed the normalised values of receptor expression across all regions belonging to each Yeo network.

We also constructed subcortical pharmacology profiles based on subcortical maps of 5-HT_{2A} (Beliveau et al., 2017) and D₂ receptor expression (Malén et al., 2022). Because the subcortical D₂ map used a different radiotracer, [¹¹C]-raclopride, than the cortical map, we kept the cortical and subcortical pharmacology profiles separate.

Chapter 4.4. Results

Chapter 4.4.1. Affinity

Our literature search identified $n = 14$ studies on selectivity, including $n = 6$ studies on DMT, $n = 9$ studies on LSD, and $n = 5$ studies on psilocin. We performed a random-effects meta-analysis with the drugs as covariates. Pooled selectivity values are displayed in **Figure 4.2a**. We found no significant between-drug differences in selectivity for any of the receptors – 5-HT_{2A}, 5-HT_{2C}, and D₂ – relative to the 5-HT_{1A} receptor. Standard errors were very large for all of the pooled selectivity values, and heterogeneity was very high for the 5-HT_{2A} selectivity data ($I^2 = 93.69\%$) and for the 5-HT_{2C} selectivity data ($I^2 = 99.14\%$). Nevertheless, it is clear that all drugs display less selectivity for D₂ than they do for 5-HT_{2C} and 5-HT_{2A}. Each individual drug is more selective for 5-HT_{2A} than 5-HT_{1A}. DMT and psilocin are about as equally selective for 5-HT_{2C} as they are for 5-HT_{1A}, but LSD is much less selective for 5-HT_{2C} than for 5-HT_{1A}.

We constructed another random-effects model in which both the drug and the radioligand for the receptor of interest were included as covariates; we refer to this as the “full” model and the previous one as the “reduced” model. For 5-HT_{2A}, the use of the radioligands [³H]-ketanserin ($p = 0.0141$) and [³H]-spiperone ($p = 0.0271$) significantly influenced the pooled selectivity estimates. Use of [³H]-mesulgerine ($p = 0.0292$), but not [³H]-ketanserin ($p = 0.0872$), significantly affected our estimates of selectivity for 5-HT_{2C}. According to the corrected Akaike’s information criterion, the full model performed significantly better than the reduced model for 5-HT_{2A} selectivity ($p < 0.0001$), whereas the reverse was true for 5-HT_{2C} selectivity ($p = 0.0024$).

We assessed publication bias due to small study effects and found significant evidence for bias in the 5-HT_{2A} ($p = 0.0001$) and 5-HT_{2C} ($p = 0.0004$) affinity data. (There were not enough studies on D₂ affinity to measure bias.) Due to the large imprecision of the results and high probability of publication bias, our certainty in the body of evidence about selectivity is low.

However, when selectivity was measured relative to the 5-HT_{2A} receptor, there were significant between-drug differences (**Figure 4.4**). (Note that there were three additional studies, one for DMT and two for LSD.) In particular, DMT was significantly more selective for the 5-HT_{2C} receptor than both LSD ($p = 0.001$) and psilocin ($p = 0.0035$). In addition, selectivity for the D₂ receptor was significantly higher for DMT than for psilocin ($p = 0.001$). Heterogeneity was once again high for the 5-HT_{2C} selectivity data ($I^2 = 98.56\%$) and for the 5-HT_{1A} selectivity ($I^2 = 99.91\%$). Surprisingly, there was no evidence for small-study bias in either the 5-HT_{1A} ($p = 0.1683$) or the 5-HT_{2C} case ($p = 0.3604$).

To relate the selective affinities to the neuroimaging and phenomenology of psychedelics, we first determined the expression of the 5-HT_{2A} and D₂ receptors in the Yeo networks, based on an atlas of PET maps (J. Y. Hansen et al., 2022) (unfortunately, this did not include maps of the 5-HT_{2C} receptor). Then, we defined the “pharmacology profile” as the weighted combination of the expression patterns, in which the weights were the selectivity of each psychedelic for the corresponding receptor (**Figure 4.3**). The PET atlas indicates that 5-HT_{2A} receptor density is around two orders of magnitude higher than that of D₂ receptor density, so the pharmacology profile predominantly reflects selectivity for 5-HT_{2A}. Because psilocin’s selectivity for 5-HT_{2A} is greater than that of LSD and DMT, psilocin has the “largest” pharmacology profile. 5-HT_{2A} is expressed more in transmodal networks than the visual network; thus, selectivity for 5-HT_{2A} may affect brain activity the most in these networks.

Chapter 4.4.2. Functional activity

We found $n = 18$ relevant studies on functional activity, including $n = 6$ studies on DMT, $n = 13$ studies on LSD, and $n = 6$ studies on psilocin. We performed a random-effects meta-analysis, with the drugs as covariates. For the IP formation and calcium mobilisation assays, the reference ligand was serotonin; for the β -arrestin2 recruitment assays, the reference ligand was chosen to be mescaline, as this was the only reference ligand used in experiments on all three psychedelics. The pooled relative activity values indicate that LSD induces significantly more IP formation than DMT ($p < 0.0001$) and psilocin ($p = 0.0002$) (**Figure 4.2b**). Additionally, DMT elicits significantly more IP formation than psilocin ($p = 0.0203$). There were no significant between-drug differences for the other two pathways. Heterogeneity was very high for all three pathways (IP formation: $I^2 = 95.35\%$, calcium mobilisation: $I^2 = 92.66\%$, β -arrestin2 recruitment: $I^2 = 91.05\%$).

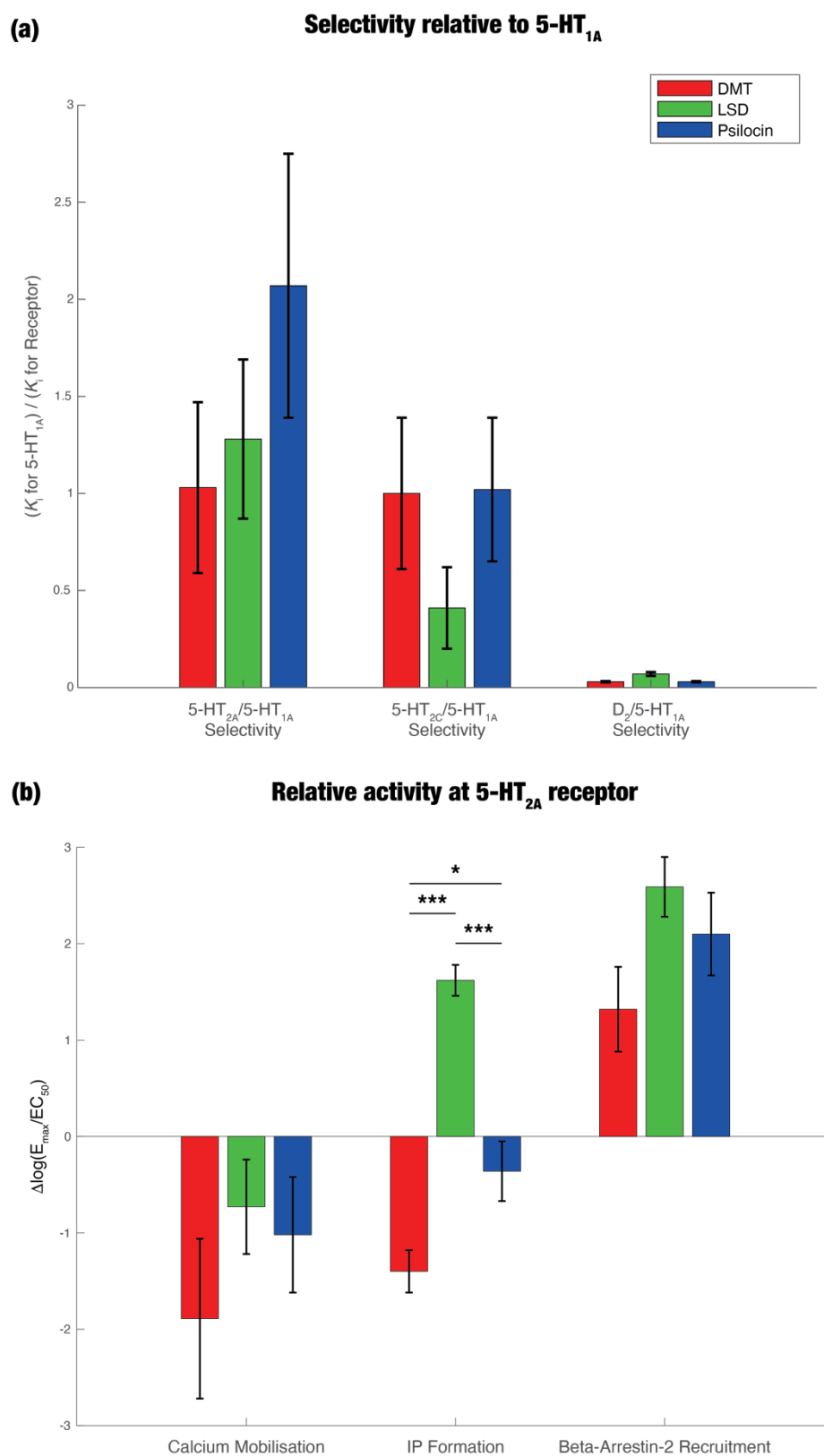


Figure 4.2. Pharmacology meta-analysis reveals that there are no significant differences in selectivity between psychedelics and that LSD induces significantly higher relative activity at the inositol phosphate (IP) formation pathway.

For both the selectivity and relative activity data, we created random-effects models that modeled between-study variance, with drugs included as covariates. (a) Selectivity is the ratio between the binding affinity (measured as K_i) for a receptor of interest and the affinity for a reference receptor. We measured selectivity for three different receptors, 5-HT_{2A}, 5-HT_{2C}, and D₂, relative to 5-HT_{1A}. Our literature search identified $n = 14$ studies on selectivity, including $n = 6$ studies on DMT, $n = 9$ studies on LSD, and $n = 5$ studies on psilocin. We did not find any significant between-drug differences in selectivity for any of the three receptors. (b) Relative activity is $\Delta\log(E_{\max}/EC_{50})$, where $E_{\max}$ is the maximal effect of the drug relative to a reference ligand and EC_{50} is the concentration needed to elicit 50% of the maximal response. The log of the ratio is measured for both the drug and the reference ligand, and then the difference is taken (Kenakin, 2017). We found $n = 18$ studies on functional activity, including $n = 6$ studies on DMT, $n = 13$ studies on LSD, and $n = 6$ studies on psilocin. We measured relative activity at three different signaling pathways: calcium mobilisation, IP formation, and β -arrestin2 recruitment. IP formation was the only pathway that exhibited any significant between-drug differences; LSD elicited significantly higher activity than both DMT and psilocin.

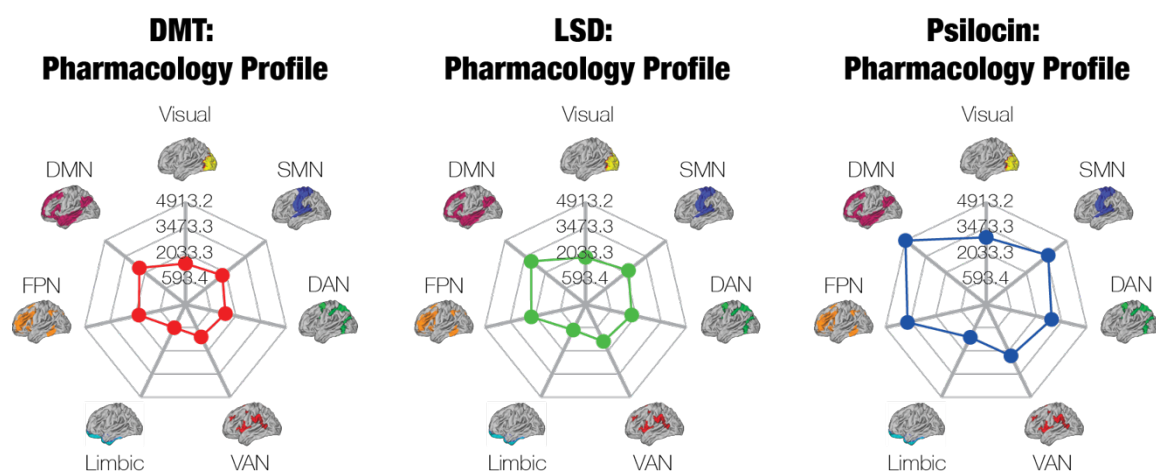


Figure 4.3. Pharmacology profiles reveal that psilocin binds with (insignificantly) higher specificity to the 5-HT_{2A} receptor than DMT and LSD do.

Based on an available PET atlas of the 5-HT_{2A} and D₂ receptors (Hansen et al., 2022), we created the pharmacology profile of each psychedelic. The profiles show the expression of those two receptors in the Yeo networks, weighted by the selectivity of the corresponding psychedelics for those receptors. Units are arbitrary. Because the selectivity for 5-HT_{2A} is two orders of magnitude higher than the selectivity for D₂, the profiles are dominated by 5-HT_{2A} receptor expression. Since psilocin has the most selectivity for 5-HT_{2A} (relative to 5-HT_{1A}), followed by LSD then DMT, psilocin's pharmacology profile is the "largest."

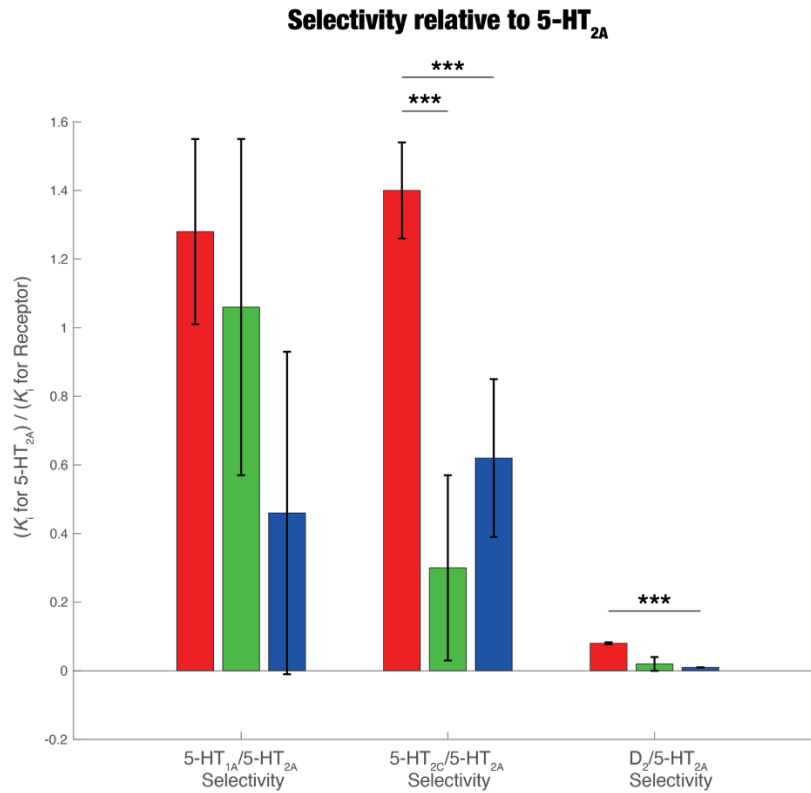


Figure 4.4. While there were no significant between-drug differences in selectivity relative to the 5-HT_{1A} receptor, there are significant differences relative to the 5-HT_{2A} receptor.

We created random-effects models that modeled between-study variance. DMT was significantly more selective for the 5-HT_{2C} receptor than LSD and psilocin. Additionally, DMT exhibited significantly higher selectivity for the D₂ receptor than psilocin. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Chapter 4.5. Discussion

Chapter 4.5.1. Comparing the results to the literature

The results of the affinity meta-analysis aligned well with studies that performed direct comparisons of selectivity between different psychedelics (Eshleman et al., 2014; Janowsky et al., 2014; Kozell et al., 2023; Pierce & Peroutka, 1989; Rickli et al., 2016). In line with our findings, all of these studies showed that LSD is more selective than DMT for 5-HT_{2A}, relative to 5-HT_{1A}. Two studies also observed that psilocin is more selective than LSD for 5-HT_{2A} (Kozell et al., 2023; Rickli et al., 2016). Our meta-analysis demonstrated that DMT is more selective than LSD for 5-HT_{2C}, a conclusion that is supported by three of four studies (Eshleman et al., 2014; Janowsky et al., 2014; Kozell et al., 2023).

Our findings about functional activity were also congruent with studies that measured the effect of multiple psychedelics on IP formation at the 5-HT_{2A} receptor (Braden & Nichols, 2007; Eshleman et al.,

2014; Janowsky et al., 2014; Kozell et al., 2023). We found that LSD's relative activity at this pathway was significantly greater than that of psilocin, which was in turn significantly larger than that of DMT. All four studies showed that LSD had higher relative activity at this pathway than DMT. Two studies also reported that psilocin's relative activity was lower than that of LSD, but larger than that of DMT (Braden & Nichols, 2007; Kozell et al., 2023).

Chapter 4.5.2. Sources of heterogeneity

We observed very high levels of heterogeneity for both the affinity and functional activity literature. For the affinity studies, we were able to identify reasons for this heterogeneity: the choice of radioligand significantly influenced our pooled estimates of selectivity for 5-HT_{2A} and 5-HT_{2C}. This is not surprising, given that differences in radioligand properties, including selectivity, the degree of cooperativity between the radioligand and ligand of interest, and association and dissociation rates, are known to influence estimates of K_i values (Bosma et al., 2019; Hulme & Trevethick, 2010). Unfortunately, the variability in radioligands was too high for us to conduct a separate meta-analysis for each radioligand type.

Furthermore, affinity and activity are fundamentally linked quantities, for two reasons (Strange, 2008). Firstly, since serotonin and dopamine receptors are both GPCRs, GPCR agonists, such as psychedelics, bind not only to the receptor but also to G proteins; hence, measurements of affinity will be biased by the extent to which the agonist activates G proteins (De Lean et al., 1980). Secondly, binding induces a conformational change to the receptor, which in turn stabilises a partially active state of the receptor without even coupling to G proteins (Colquhoun, 1998; Strange, 1999).

Hence, in addition to performing a meta-analysis on affinity, we also analysed the functional activity of psychedelics. We sought a measure of activity that was minimally biased: one that was not very susceptible to confounding influences. Classical receptor theory indicates that activity ratios (ΔEC_{50} , where EC_{50} is the concentration of drug that is needed to bring about 50% of the maximal response) are unbiased by experimental conditions, such as the density of the receptor of interest in the corresponding assay (Kenakin et al., 2012). However, when a drug is a partial, rather than full, agonist at a receptor, there is a nonlinear relationship between receptor density and activity ratios (Kenakin, 2017). One solution is to compare the relative activity, defined as $\Delta \log(E_{\max}/EC_{50})$ (Kenakin et al., 2011), where $E_{\max}$ is the maximal response elicited by the drug of interest relative to a reference ligand. Normalising the activity ratio by $E_{\max}$ essentially “cancels out” the effect of receptor density, as well as the sensitivity of the assay in general, on activity estimates, resulting in a minimally biased measure of receptor agonism (Kenakin, 2017).

Chapter 4.5.3. The role of the 5-HT_{2A} receptor

More than any other receptor, 5-HT_{2A} plays an essential role in the hallucinogenic effects of not only LSD but also all other psychedelics. Blocking the 5-HT_{2A} receptor with an antagonist such as ketanserin has repeatedly been shown to attenuate or abolish the subjective experience in humans (Becker et al., 2023; Preller, Burt, et al., 2018; Preller et al., 2017; Vollenweider et al., 1998). In our meta-analysis, we find that all three psychedelics bind with greater affinity to 5-HT_{2A} than to another receptor, 5-HT_{1A}, which may mediate some of the hallucinogenic properties of psychedelics (see below). 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., 2007a).

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, Dedeker, 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 (Rodríguez 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-HT₂ 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., 2007a). 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 restructuration” 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, 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.

Chapter 4.6. Chapter summary

Here, we conducted two meta-analyses on the pharmacology of psychedelics. The first assessed selectivity, or binding affinity relative to the 5-HT_{1A} receptor, and the other examined relative functional activity. There were no significant differences between psychedelics in selectivity for the 5-HT_{2A}, 5-HT_{2C}, or D₂ receptors relative to the 5-HT_{1A} receptor. Compared to DMT and psilocin, LSD elicited significantly more relative activity in IP formation assays. We did not observe any significant between-drug differences for the calcium mobilisation and β -arrestin2 recruitment assays.

Chapter 5. LSD flattens the hierarchy of directed information flow in fast, whole-brain dynamics

Chapter 5.1. Chapter abstract

The REBUS theory posits that psychedelics flatten the hierarchical structure of the generative model underpinning perception. However, REBUS is difficult to test. Here, we propose a simple definition of hierarchy based on the imbalance between sending and receiving brain signals, as determined by directed functional connectivity. In particular, we characterise three properties of the hierarchy: irreversibility, as defined the directional asymmetry of all pairwise connections; hierarchical coherence, or the mean directed connectivity at each region; and hierarchical inhomogeneity, or the standard deviation of directed connectivity across regions. We measure each of these properties in an MEG dataset of 16 healthy human participants who were administered the psychedelic lysergic acid diethylamide (LSD). Under multiple experimental conditions, LSD decreases all three properties, when averaged across time. Furthermore, LSD constrains the dynamics of each property, suggesting that the brain exhibits a reduced repertoire of hierarchical configurations across time. Taken together, these results indicate that LSD diminishes the hierarchy of directed connectivity in the brain by increasing the symmetry between senders and receivers of neural signals.

Chapter 5.2. Introduction

As stated in *Chapter 1*, REBUS (RElaxed Beliefs Under pSychedelics) hypothesises that psychedelics “flatten” hierarchical information processing in the brain (R. L. Carhart-Harris & Friston, 2019). Normally, strongly-weighted top-down prior beliefs encoded in transmodal (associative) cortices constrain the influence of bottom-up signals from unimodal (sensory) cortices, such that prediction errors encoded in those signals cannot modify the priors themselves (Holmes & Nolte, 2019; Knill & Pouget, 2004; Seth & Friston, 2016). According to REBUS, psychedelics decrease the weighting of priors, such that huge prediction errors stemming from intense hallucinations have the capacity to revise deep-seated priors that may correspond to fundamental beliefs about identity, baseline emotional states, and so on. However, it is difficult to identify the priors that encode the subjective effects of psychedelics and even more challenging to pinpoint the underlying neural mechanisms with coarse-grained imaging techniques like fMRI and MEG. Consequently, researchers have recently used measures of functional connectivity (FC) to determine the effects of psychedelics on hierarchical information processing. For instance, Girn and colleagues identified a principal

gradient of FC spanning higher-order (transmodal) and lower-order (unimodal) brain regions and found that LSD and psilocybin cause this gradient to contract (Girn et al., 2022).

This approach used undirected FC to determine functional connectivity. However, hierarchies are inherently directional; nodes at the top of the hierarchy control nodes at the bottom, but not the other way around. This implies that hierarchies exhibit asymmetries in the direction of connectivity. That is, higher-order nodes only send *or* receive signals, whereas lower-order nodes both send *and* receive signals. Therefore, we can simply define hierarchy as the imbalance between sending and receiving signals. Based on this definition, we can distinguish three different characteristics of hierarchies: irreversibility, hierarchical coherence, and hierarchical inhomogeneity.

Here, we quantified these three characteristics in a previously-acquired MEG data of 16 healthy human participants who were administered a psychoactive dose of LSD (Carhart-Harris et al., 2016). To measure irreversibility, we applied a technique known as INSIDEOUT, which determines the temporal irreversibility of brain timeseries: the difference between “forwards” directed connectivity (e.g., from a region A to a region B) and time-reversed directed connectivity (e.g., from B to A), averaged across all pairs of regions (Deco et al., 2022). Directed connectivity is defined by time-delayed correlations. We used the same correlations to determine the absolute value of the mean of the incoming (positive) and outgoing (negative) connections originating from or terminating at each region. Hierarchical coherence and inhomogeneity are the mean and standard deviation of this value across regions.

In physics, reversible dynamics occur whenever a system is in a state of equilibrium, in which no entropy is being produced (Seifert, 2005). In equilibrium, the principle of detailed balance states that the probability of any transition between states is equal to the probability of the reversed transition (G. N. Lewis, 1925). For instance, particles moving in random or “Brownian” motion exist in a state of thermal equilibrium. The probability that a particle moves in one direction is balanced with the probability that it moves in the opposite direction. In this reversible system, there is no arrow of time. However, if someone were to impose a temperature gradient on the particles, the system would be taken out of equilibrium; the particles would tend to move irreversibly towards the cooler region, and they would produce entropy by distributing thermal energy more evenly in the medium. Breaking detailed balance yields a local arrow of time, including in biological systems (Battle et al., 2016; Gnesotto et al., 2018).

Chapter 5.3. Methods

Chapter 5.3.1. Data acquisition

The data was acquired in a previous study (Carhart-Harris et al., 2016), and the experimental protocol is described in detail in the supplementary materials therein. Each participant underwent two scanning sessions, one in which they received placebo and another in which they received 75 μ g of intravenously administered LSD. After a 60-minute period of acclimatisation, participants were scanned with magnetic resonance imaging (MRI) for about 60 minutes; the results of the MRI scans are not discussed in this analysis but have been discussed extensively in other publications (Atasoy et al., 2017; Girn et al., 2022; Jobst et al., 2021; Kaelen et al., 2016, 2017; Lebedev et al., 2016; Luppi et al., 2021; Roseman et al., 2016; Singleton et al., 2022b; Tagliazucchi et al., 2016; Varley et al., 2020). Then, approximately 165 minutes after the LSD was administered, the participants were recorded with a CTF 275-gradiometer MEG machine, though four of the sensors were turned off because of excessive sensor noise. During the MEG recording, participants were subjected to four conditions: eyes-open resting-state (referred to in the paper as “Open”), eyes-closed resting-state (“Closed”), listening to music with eyes closed (“Music”), and watching a silent nature documentary (“Video”). Each scan lasted approximately seven minutes. There were two scans associated with each of the Open and Closed conditions and one scan for each of the Music and Video conditions. We randomly selected one Open and one Closed scan per subject.

Chapter 5.3.2. Data preprocessing and source reconstruction

Preprocessing of the data has also been described elsewhere (Mediano et al., 2024). Data was recorded at 600 Hz; high- and low-pass filtered at 1 Hz and 100 Hz, respectively; segmented into epochs of 2 seconds in length, such that epochs with pronounced artifacts could be removed completely (the length of two seconds was chosen such that theta-band activity could be measured in our analyses, as explained below); and, in this study, downsampled to 200 Hz. Epochs with large ocular, muscular, cardiac, and line noise artefacts were eliminated first manually, by visual inspection, and then automatically with various algorithms, including ICA. Of the original 20 participants, three were excluded from the data analysis because they either failed to complete both scanning sessions (placebo and LSD) or because their movement artefacts were too large. Additionally, one participant failed to complete all four conditions; they were missing data from the music condition. Therefore, we analysed data from 16 participants.

To perform source reconstruction, a template consisting of the centroids of the 90 regions of interest (ROIs) in the AAL parcellation was inversely warped to each subject’s native-space anatomical MRI. (These 90 ROIs span the whole brain, including subcortical regions, with the exception of the cerebellum.) A linearly constrained minimum variance (LCMV) beamformer was applied to the inversely-warped template, with the regularization parameter set to 5% of the average of the diagonal elements of the sensor covariance matrix (Van Veen et al., 1997). In the Main Text, we present the results of our broadband analysis, and we report

the frequency-specific analysis in the Supplementary Materials. For the latter, we bandpass filtered the data into four frequency bands of interest: theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-48 Hz) (note that we filtered the data after beamforming). We omitted the delta band because the data was segmented into 2-second epochs, so one epoch could be the same length as a single, low-frequency delta cycle. We applied symmetric orthogonalisation to remove spurious zero-lag correlations from the filtered data (Colclough et al., 2015), and then we obtained the amplitude envelopes of the signal from the Hilbert transform.

Chapter 5.3.3. Irreversibility of hierarchy: INSIDEOUT

Here, we used a technique called INSIDEOUT to measure the irreversibility of directed connectivity: the squared difference between the cross-correlations of the forwards and reversed amplitude envelope timeseries of all pairs of brain regions (Tewarie et al., 2023). As we will see later on, irreversibility is the same as the asymmetry of directed connectivity, that is, the asymmetry of the cross-correlation function.

In general, the cross-correlation between two timeseries x and y is the correlation between x and y when y is shifted in time relative to x by a constant interval or “lag” τ . Therefore, for a particular τ , the cross-correlations of the forwards and time-reversed timeseries are:

$$c^f(\tau) = \text{corr}(x(t), y(t + \tau)) \quad (5.1)$$

$$c^r(\tau) = \text{corr}(x^r(t), y^r(t + \tau)) \quad (5.2)$$

If the system is reversible, then the delay τ will not induce temporal asymmetry in the correlation. Because it takes time for signals to travel from one region of the brain to another, and therefore for those regions to become correlated with each other, the value of τ that maximises the cross-correlation in MEG captures the speed of signal propagation for postsynaptic potentials (Mizuno-Matsumoto et al., 2002, 2005). Therefore, for the correct τ , the difference in forwards and reversed cross-correlations may indicate the irreversibility of the transmission of postsynaptic potentials in the brain.

We computed the cross-correlations between the demeaned amplitude envelopes of all pairs of the 90 brain regions, for all possible values of τ . To calculate the cross-correlations, we used the function `xcorr` in MATLAB 2023b, with the timeseries normalized such that autocorrelations at zero lag equal 1 (scaleopt was set to ‘normalized’). We measured cross-correlations separately for each epoch, and there were 400 samples in each epoch; thus, there were 399 possible values of τ , if τ is restricted to positive values only.

We measured $c^f(\tau)$ and $c^r(\tau)$ on the amplitude envelopes of all pairs of the 90 brain regions in the AAL parcellation, resulting in 90×90 $C^f(\tau)$ and $C^r(\tau)$ matrices for each epoch. We then calculated the irreversibility matrix, $R(\tau)$, as the squared difference between each element of $C^f(\tau)$ and $C^r(\tau)$:

$$R(\tau) = \left(C^f(\tau) - C^r(\tau) \right)^{\circ 2} \quad (5.3)$$

where $\circ 2$ denotes element-wise squaring of $C^f(\tau) - C^r(\tau)$.

We also calculated the irreversibility $R_{\text{region}}(\tau)$ for each region:

$$R_{\text{region}}(\tau) = \left(C_{\text{region},*}^f(\tau) - C_{\text{region},*}^r(\tau) \right)^{\circ 2} \quad (5.4)$$

where $C_{\text{region},*}^f(\tau)$ ($C_{\text{region},*}^r(\tau)$) denotes the row of $C^f(\tau)$ ($C^r(\tau)$) that contains the forward (time-reversed) cross-correlations between the given region and all other regions.

It is worth noting that the regional irreversibility does not indicate the positions of regions within the hierarchy. Highly irreversible connections could either be strongly directed outwards or inwards; our method doesn't specify the direction. Therefore, an area with large regional irreversibility may be a strong recipient rather than transmitter of information, so these regions would be at the bottom of the hierarchy under the assumption that regions with more top-down (outgoing) connections should be ranked more highly. However, this assumption is not always accepted in analyses of hierarchy (Moutsinas et al., 2021).

In order to reduce noise, we thresholded $R(\tau)$ and $R_{\text{region}}(\tau)$ by their 95th percentile values, resulting in $R^{\text{thres}}(\tau)$ and $R_{\text{region}}^{\text{thres}}(\tau)$, respectively. The choice of the 95th percentile was arbitrary. We also reran our computation of irreversibility without thresholding. The results agreed with the thresholded analysis; we found significant differences in irreversibility between LSD and placebo across all four of the conditions (results not shown).

Finally, we took the mean of $R^{\text{thres}}(\tau)$ and $R_{\text{region}}^{\text{thres}}(\tau)$, resulting in scalar values of irreversibility $r(\tau)$ and $r_{\text{region}}(\tau)$ for each epoch, respectively. We then averaged these values across all epochs, yielding the final value of irreversibility.

It is worth noting that irreversibility is equivalent to directional asymmetry; that is, the irreversibility of the connection between a timeseries x and y is the same as the squared difference between the connectivity from x to y and the connectivity from y to x . In other words,

$$\text{corr}(x^r(t), y^r(t + \tau)) = \text{corr}(x(t - \tau), y(t)) \quad (5.5)$$

This is true because the cross correlation of the reverse timeseries in the forward direction is equivalent to the cross correlation of the original timeseries, with one timeseries shifted backwards in time. Furthermore, $\text{corr}(x(t - \tau), y(t))$ is simply the correlation of x and y when y is shifted forward in time relative to x , i.e.

the cross-correlation of y with respect to x . Therefore, irreversibility is equal to the squared difference between the cross-correlation of x with respect to y and the cross-correlation of y with respect to x . For this reason, we equate irreversibility with directional asymmetry, or simply irreversibility.

For this reason, $C^r(\tau)$ is simply equal to the transpose of $C^f(\tau)$. Therefore, Equation 1 could be re-expressed as:

$$R(\tau) = (C^f(\tau) - C^f(\tau)^T)^2 \quad (5.6)$$

Chapter 5.3.4. Choosing τ and statistical testing

The value of a cross-correlation, and therefore the value of irreversibility, depends on the choice of τ . We applied three different methods for choosing τ . In the first one, we did not identify a specific, optimal τ , but instead we computed irreversibility across all 399 values of τ . We then integrated the area under the irreversibility vs. τ curve to obtain a measure of “total” irreversibility. We also determined the τ that maximises irreversibility in each dataset and observed whether that value of τ is significantly different between drugs and conditions. In the second approach, we averaged the irreversibility results across both drugs, all conditions, and all participants (in other words, across all datasets). Then, we selected the τ that yielded the highest mean irreversibility. Finally, in the third approach, we used stratified cross-validation and permutation testing to identify the τ that was associated with the greatest difference in irreversibility between placebo and LSD. We partitioned all datasets into eight counter-balanced folds consisting of 16 datasets each, such that the first eight datasets in each fold were placebo datasets and the latter eight were LSD datasets. In each cross-validation loop, we randomly selected seven folds to be training folds and one fold to be the testing fold. Over all eight cross-validation loops, each fold was used for testing exactly once. We concatenated the placebo and LSD datasets across all training folds and determined the τ that was associated with the highest absolute difference between the means of irreversibility for the placebo and LSD datasets. We then calculated the difference of means for this τ in the testing fold. After all eight cross-validation loops had been completed, we selected the τ (τ_{optimal}) corresponding to the highest difference of means across all eight testing folds. We then computed the irreversibility associated with τ_{optimal} in all of the datasets. To assess the significance of this result, we used permutation testing.

In summary, with Approach 1, we measured irreversibility for a range of τ , whereas with Approach 2, we did so for a single value of τ . However, unlike in Approach 3, this single value of τ was not necessarily the τ that maximised the separability between the irreversibility of the placebo and LSD datasets. In the main text, we report the results of Approach 3 since it was the method that aligned most with our aims; it identified the strongest differences in irreversibility between the placebo and LSD datasets. We discuss the results of

the other approaches in the Supplementary Materials. For all subsequent measures – ranking irreversibility by condition, frequency-specific irreversibility, regional irreversibility, imbalance of directed connectivity, etc. – we used the τ derived from Approach 3.

In Approach 1, we applied cluster-based permutation testing separately to each condition in order to determine clusters of τ for which irreversibility is significantly different between LSD and placebo (Maris & Oostenveld, 2007). In this method, we cluster values of τ for which the difference in irreversibility exceeds $t = 1.75$ (which corresponds to $p = 0.05$ for 16 participants), sum t -values within clusters of temporally adjacent supra-threshold t -values, and identify the largest such sum. We then permuted the data 10,000 times to obtain a null distribution of cluster test statistics.

In Approaches 2 and 3, once τ was selected, we performed a two-way repeated-measures Analysis of Variance (ANOVA) in which the two within-subject factors were drug and condition. We used a battery of tests to determine whether the distribution of irreversibility at the selected τ met the condition of approximate normality (Öner & Kocakoç, 2017). For both approaches, the distribution of irreversibility was approximately normal according to at least two tests. (These were two different methods – Limiting Form (Facchinetti, 2009) and Marsaglia Method (Marsaglia et al., 2003) – for performing the Kolmogorov-Smirnov Normality Test, which assesses the distance between an empirical distribution function and a Normal cumulative distribution function.) While the placebo results passed almost all of the normality tests for the τ selected in Approach 2 and all of the normality tests for that of Approach 3, the LSD results failed the majority (but not all) of the normality tests in the Open condition for both Approaches 2 and 3. Compared to those of Approach 2, the LSD results of Approach 3 passed more normality tests for the Closed and Music conditions.

After conducting the ANOVAs, we performed multiple comparison testing with Tukey’s Honestly Significant Difference (HSD) procedure. We applied the two-way repeated measures ANOVA and post-hoc Tukey’s test to most other measures aside from mean irreversibility. Whenever we needed to compare a measure between LSD and placebo in specific regions, e.g. for regional irreversibility, we used a three-way repeated measures ANOVA, in which region was a third within-subject factor.

Chapter 5.3.5. Hierarchical coherence and inhomogeneity

Time-delayed correlations define an incoming (e.g., $B \rightarrow A$) and an outgoing (e.g., $A \rightarrow B$) component in each connection in the brain. Irreversibility identifies the connections with the highest squared difference between their incoming and outgoing components. Here, we measured a separate aspect of hierarchy: the difference between the magnitudes of the strongest incoming and outgoing connections at each region. If

the strongest incoming connections are greater in magnitude than the strongest outgoing connections, or vice versa, then the region exhibits imbalanced connectivity. However, if these two sets of connections are equal in magnitude, then connectivity is balanced at the region in question.

In *Section 2.3*, we defined $C^f(\tau)$ and $C^r(\tau)$ in each epoch of data. Here, we concatenated $C_{\text{region},*}^f(\tau)^{\circ 2}$ and $C_{\text{region},*}^r(\tau)^{\circ 2}$ into a single vector; note that these quantities represent the magnitude of the incoming and outgoing connections at each region:

$$C_{\text{region}}^{\text{all}} = \begin{bmatrix} C_{\text{region},*}^f(\tau)^{\circ 2} \\ C_{\text{region},*}^r(\tau)^{\circ 2} \end{bmatrix} \quad (5.7)$$

We then thresholded this vector by its 95th percentile, made all outgoing connections that survived thresholding negative, and took the mean of the resulting vector. We refer to this quantity as A_{region} , the incoming-outgoing asymmetry at each region:

$$A_{\text{region}} = \overline{C_{\text{region}}^{\text{all,thres}}} \quad (5.8)$$

Then, we average A_{region} across epochs. The mean of this quantity across regions is the hierarchical coherence, and the standard deviation is the hierarchical inhomogeneity.

Chapter 5.3.6. Dynamical analysis

We wanted to understand how the functional hierarchy evolves over time, both under placebo and under LSD. To do so, we performed a recurrence network analysis on the irreversibility, hierarchical coherence, and hierarchical inhomogeneity.

First, we conducted a sliding-window analysis in which we computed the irreversibility, hierarchical coherence, and hierarchical inhomogeneity in 0.25-second windows of data, with 80% overlap between windows. This results in three 1D timeseries, one for each hierarchy metric. Secondly, we performed a time-delay embedding of each timeseries; that is, we embedded each timeseries in a lower-dimensional phase space, in which each dimension d represents the centrality at lag $(d-1) * \tau_{\text{RNoptimal}}$. This phase space captures temporal dependencies in the centrality timeseries, which is assumed to have regular patterns that re-occur at multiples of $\tau_{\text{RNoptimal}}$. (Note that $\tau_{\text{RNoptimal}}$ is distinct from the τ described elsewhere in this paper.) We determined $\tau_{\text{RNoptimal}}$ by computing the mutual information between the timeseries at time t and the timeseries at time $t+1$ for values of τ_{RN} ranging from 1 sample to half the length of the timeseries (Wallot & Mønster, 2018). We then selected $\tau_{\text{RNoptimal}}$ as the value of τ_{RN} that corresponded to the first minimum of the function relating τ_{RN} to mutual information; at this point, the timeseries shifted by τ_{RN} is similar enough to the

unshifted timeseries that the embedding reflects genuine temporal dependencies in the data, but not so similar that the shifted timeseries is effectively redundant with the original timeseries.

Next, we determined the dimensionality m_{optimal} of the phase space based on the False Nearest Neighbours (FNN) criterion (Wallot & Mønster, 2018). When m is too low, many points in the phase space will cluster next to each other, resulting in “false neighbours” that yield false estimates of similarity. For values of m ranging from 1 to 10, we calculated the distance between neighbouring points in dimension m and again in dimension $m + 1$. If the distance in dimension $m + 1$ was more than twice as high as the distance in dimension m , then the points are considered false neighbours in dimension m . We selected m_{optimal} as the value of m that minimised the number of false neighbours. Analyses for determining $\tau_{\text{RNoptimal}}$ and m_{optimal} were conducted using the Cross Recurrence Plot (CRP) toolbox provided by the Toolboxes for Complex Systems (TOCSY) (Marwan et al., 2007).

Having optimised τ and m , we were prepared to construct the recurrence network, which identifies centrality dynamics that the brain recurrently exhibits. The recurrence network R is a $T \times T$ matrix with the following elements (Varley & Sporns, 2021):

$$R_{ij} = \Theta(\epsilon - \|X_i, X_j\|) \quad (5.9)$$

where X_i, X_j are timepoints i and j in the timeseries X , ϵ is a threshold on their distance in phase space, and Θ is the Heaviside function, which transforms $\epsilon - \|X_i, X_j\|$ into 1 if it is greater than 0, and 0, if it is less than zero. In other words, if the distance between two timepoints in the phase space is less than the threshold, then those timepoints are not connected in the recurrence network, but if the distance is greater than the threshold, then they are connected. To obtain the distance threshold ϵ , we used Eroglu’s method (Eroglu et al., 2014). That is, incrementally increasing binary thresholds are applied to the matrix until the matrix becomes connected, as evaluated by the sign of the second eigenvalue of the matrix. Note that a separate recurrence network is obtained for each of the three hierarchy metrics.

Finally, once the recurrence network was constructed, we assessed the recurrency of the hierarchy metrics by measuring the recurrence rate, or edge density, of the network. If the edge density is high, then the distance between points in the phase space is low, indicating that the dynamics of the corresponding metric are similar over time.

Because the hierarchy metrics are estimated in relatively small (1-second) sliding windows, they are subject to sampling variability; that is, the values of the metrics may vary a lot between windows. We sought to establish that differences in the recurrence rate between conditions are due to the actual dynamics of the hierarchy metrics and not properties of the timeseries that are affected by sampling variability, such as the cross-correlation function. Therefore, we performed coherent phase-randomization on the timeseries; that

is, we shuffled the phases of each timeseries in a manner that preserved the cross-correlation function. Coherent phase-randomization was accomplished by computing the cross-spectral density matrix (the Fourier Transform of which is the cross-correlation function), generating random phases for each frequency component, applying these random phases to the Cholesky-decomposed cross-spectral density matrix, and performing an inverse Fast Fourier Transform to obtain the surrogate timeseries. We compared the recurrence rate of each hierarchy matrix between the surrogate placebo and LSD timeseries, in each condition. Then, we determined whether the statistical significance of the difference between placebo and LSD was higher than for the original, non-shuffled timeseries.

Chapter 5.3.7. Random forest classifier

We wished to determine whether irreversibility, hierarchical coherence, and/or hierarchical inhomogeneity distinguish LSD and placebo more than other metrics of FC: undirected FC and (forward) cross-correlations. To obtain undirected FC, we measured the mean Pearson correlation coefficient between the orthogonalized amplitude envelopes of the timeseries of all 90 regions. We computed the mean cross-correlation across all pairs of regions at the value of τ that maximally distinguished placebo and LSD, which was determined via the same cross-validation approach described in *Section 2.3.1*. This τ was a single sample (0.005 seconds), which is different from the τ that was optimized for the hierarchy metrics (0.225 seconds).

We then trained a random forest algorithm with bootstrap aggregation (or “bagging”) to classify LSD and placebo based on undirected FC, cross-correlations, and the three hierarchy metrics. In this method, many random subsets of training data are selected with replacement (Breiman, 1996). These subsets are then used to train a classification tree, which optimizes a series of decision points, or thresholds, for splitting the values of the training features in order to estimate the correct label of the training data. In our case, there were two labels, “placebo” or “drug,” and four features, which corresponded to the four conditions. For each classification tree, random forest classifiers choose a random subset of features at each decision point and then identify the feature that optimally splits the training data (Breiman, 2001). Once trained, each classification tree produces a “vote” on the correct label of the validation data. By default, `fitcensemble` trains 100 classification trees and then outputs the majority vote of all the trees. We executed `fitcensemble` 100 times, each time with a different training and validation set. In each iteration, 80% of the data was partitioned into the training set, and the remaining 20% was partitioned into the validation set.

To evaluate the performance of the classifiers, we computed the area under the Receiver Operating Characteristic (ROC) curve. We then performed Wilcoxon signed-rank tests (with FDR correction) to assess significant differences between the area under the ROC curves for the classifier trained on regional irreversibility and for the classifiers trained on the other FC metrics.

Because the classifiers were trained using a value of τ that was chosen *a priori*, the classifiers may not generalize well. Therefore, we trained a second set of classifiers in which the value of τ was chosen in a manner that minimized generalization error. In particular, we pursued a nested cross-validation approach, in which the outer loop applied holdout cross-validation (80% train, 20% test) as before and the inner loop used 5-fold cross-validation to optimize τ . The inner loop iterates through values of τ ranging from 1 sample (0.005 seconds) to 100 samples (0.5 seconds) and trains a classifier on each τ . The value of τ that maximizes the area under the ROC curve is passed to the outer loop, which then trains a classifier on this τ . The performance of the classifier and statistical significance are assessed as before.

Chapter 5.3.8. Correlation between serotonin receptor expression and regional irreversibility

As mentioned above (*Section 2.3*), we calculated irreversibility within each region of the brain, in addition to computing it across the entire brain. Since the binding of psychedelics to the 5-HT_{2A} (serotonin-2A) receptor is known to mediate their hallucinogenic effects, we measured the correlation between regional irreversibility and 5-HT_{2A} receptor expression. To quantify spatial patterns of 5-HT_{2A} receptor expression, we used three existing PET maps (Beliveau et al., 2017; Savli et al., 2012; Talbot et al., 2012) and one average of those maps (J. Y. Hansen et al., 2022). We hypothesised that 5-HT_{2A} receptor expression would be more strongly associated with regional irreversibility than that of other serotonin receptors, which may not be essential for the characteristic behavioral effects of psychedelics. Therefore, we also correlated regional irreversibility with 5-HT_{1A} and 5-HT_{1B} receptor expression, using existing PET maps (Beliveau et al., 2017; Gallezot et al., 2010; J. Y. Hansen et al., 2022; Savli et al., 2012).

To determine the serotonin receptor expression in each AAL region, we averaged serotonin expression across all of the voxels within each region, so long as the grey matter at the voxel exceeded the mean grey matter across all voxels (Blaiotta et al., 2016). We measured the significance of the correlations by shuffling the serotonin receptor maps 1,000 times in a way that preserved their spatial autocorrelation (Burt et al., 2020). In this method, shuffled maps are smoothed using a kernel-weighted sum of the k nearest neighbours of each region, in which the kernel decays exponentially with distance. The algorithm identifies the value of k that minimizes the difference between the variogram (variance as a function of distance, which quantifies spatial autocorrelation) of the shuffled and empirical maps. The empirical map is then compared to a null distribution formed from the shuffled maps that were smoothed with the optimal value of k .

Chapter 5.3.9. Comparison of regional irreversibility with other measures of hierarchy

We compared regional irreversibility with well-established measures of hierarchy, namely the T1w-T2w ratio (Burt et al., 2018) and the principal gradient of functional connectivity (Margulies et al., 2016). The value of the T1w-T2w ratio in each region of the Schaefer-800 parcellation was previously measured (Bazinet et al., 2023) based on MRI data from the Human Connectome Project (Van Essen et al., 2013). Volumetric images of the principal gradient were obtained from the original publication. Values of the principal gradient in each AAL region were determined through the same method that mapped serotonin receptor expression to AAL areas in the previous subsection. To “re-parcellate” the T1w-T2w ratios into the AAL-90 parcellation, we identified the AAL region that contained the centroid of each area in the Schaefer-800 parcellation. T1w-T2w ratios were averaged across all the Schaefer-800 centroids contained within each AAL-90 area, so long as the centroid was above the same grey matter threshold described in the previous subsection.

We correlated changes in regional irreversibility under LSD₂ with the T1w-T2w ratio and the principal gradient. The significance of the correlation was determined with respect to a null distribution that preserved spatial autocorrelation, as described in the previous subsection.

Chapter 5.3.10. Hidden Markov Model

Because INSIDEOUT indirectly estimates entropy production, we sought to confirm our results with a method that more directly measures entropy production in the brain by comparing forwards transition probabilities to time-reversed transition probabilities. To do so, we trained a Hidden Markov Model (HMM) on the data. The HMM makes two assumptions: 1) brain states obey Markovian dynamics, i.e. the state at the current timepoint only depends on the state at the previous timepoint; 2) data in each state is drawn from a probabilistic observation model (A. P. Baker et al., 2014). Each type of HMM is defined by a unique observation distribution. Here, we extracted eight brain states defined based on MEG power, as well as a transition probability matrix that enabled us to quantify entropy production. (We chose eight states because this number of states has previously been used when extracting resting-state networks from MEG data (A. P. Baker et al., 2014).)

In this study, we used the time-delay embedded HMM (TDE-HMM), in which the observation model is a multivariate Normal distribution with zero mean and a covariance matrix defined over a time-delay embedding of the data (Vidaurre, Hunt, et al., 2018). This embedding transforms the data from a samples x regions matrix to a samples x (regions * lags) matrix. For dimensionality reduction, principal components analysis is then applied to the embedded data. We chose the TDE-HMM for two reasons. Firstly, the TDE-HMM is optimal for whole-brain analysis; other HMMs like the multivariate autoregressive model (HMM-MAR) require a large number of parameters (i.e. autoregressive coefficients) when modelling many regions,

potentially resulting in overfitting (Vidaurre et al., 2016; Vidaurre, Hunt, et al., 2018). Secondly, because the covariance matrix of the observation model in the TDE-HMM is essentially constructed from the cross-correlations of the data, the states identified by the TDE-HMM may be more similar to the networks formed from the cross-correlations computed by INSIDEOUT than the states identified by other types of HMMs.

Following Vidaurre, Hunt, et al. (2018), we set the maximum length of the lags in the embedding to 15 samples = 75 milliseconds and the number of principal components to $90 * 2 = 180$. (Ninety is the number of regions in our parcellation.) We trained the HMM using the HMM-MAR MATLAB toolbox. In order to speed up computation and save memory, the toolbox performs stochastic variational Bayesian inference to obtain states (Vidaurre, Abey Suriya, et al., 2018). In other words, each iteration of inference is performed on only a subset or batch of subjects rather than the entire dataset. We set the batch size to three subjects to further expedite computation, which may have resulted in noisy estimates.

Once the TDE-HMM was trained, we extracted transition probability matrices for the placebo and LSD data. We then computed entropy production (EP) as the Kullback-Leibler (KL) divergence between forwards (from state i to state j) and time-reversed transition probabilities (from state j to state i):

$$EP = \sum_{ij} P_{ij} \log_2 \frac{P_{ij}}{P_{ji}} \quad (5.10)$$

This yields two scalar values of entropy production, one for all of the placebo data and one for all of the LSD data. In order to perform tests of statistical significance, we estimated subject-specific state time courses and then we calculated entropy production for each dataset.

Chapter 5.4. Results

Chapter 5.4.1. Broadband irreversibility under LSD

In order to compute irreversibility, we needed to determine the length of the delay, or τ , to use when calculating cross-correlations between pairs of brain regions. First, we calculated irreversibility across all possible values of τ . At all τ except for the two or three smallest values of τ , placebo was more irreversible in each of the four conditions: Open, Closed, Music, Video (**Figure 5.1**). Cluster-based permutation testing revealed in each condition a single cluster of τ values spanning from $\tau = 0.02$ to $\tau = 1.985$ - 1.995 seconds for which LSD was significantly more reversible than placebo ($p_{\text{Open}} = 0.0002$, $p_{\text{Closed}} = 0.0001$, $p_{\text{Music}} = 0.0001$, $p_{\text{Video}} = 0.001$). We also found that the τ maximising irreversibility was significantly lower on LSD in all four conditions ($p_{\text{Open}} = 0.0009$, $p_{\text{Closed}} = 0.0044$, $p_{\text{Music}} = 0.0214$; $p_{\text{Video}} = 0.0012$) (**Figure 5.2**). Intriguingly, across all four conditions, the variance across participants of the τ that maximised irreversibility was much greater in LSD than in placebo; for instance, this value of τ ranged from 0.025 to 0.08 seconds on LSD in the Open

condition, whereas it was 16 for every participant on placebo in the same condition. Additionally, using the numerical trapezoidal method, we integrated the τ vs irreversibility function to obtain a measure of “total irreversibility” across all τ . LSD was significantly more reversible in all four conditions ($p_{\text{Open}} = 1.07 * 10^{-5}$, $p_{\text{Closed}} = 1.17 * 10^{-5}$, $p_{\text{Music}} = 2.26 * 10^{-6}$, $p_{\text{Video}} = 0.0023$) (**Figure 5.3**).

We used two other methods to identify a single value of τ for computing irreversibility. In the first, we determined the τ that maximised irreversibility across all conditions, drugs, and participants. This “orthogonal contrast” approach yielded $\tau = 0.12$ seconds. At this τ , LSD was even more significantly reversible than placebo in all four conditions ($p_{\text{Open}} = 6.77 * 10^{-7}$, $p_{\text{Closed}} = 8.25 * 10^{-6}$, $p_{\text{Music}} = 1.32 * 10^{-6}$, $p_{\text{Video}} = 0.0026$) (**Figure 5.4**).

The other approach employed cross-validation and permutation testing to select the τ that maximised the *difference* in irreversibility between placebo and LSD. (For most of the subsequent analyses, we used the τ that we derived from this approach. However, we doubt that we would have obtained significantly different results for the other analyses if we had opted for the orthogonal contrast approach, as irreversibility was consistently higher in placebo across all values of τ .) The cross-validation approach returned $\tau = 0.225$ seconds. At this value of τ , the difference between LSD and placebo was actually smaller than it was when we used orthogonal contrast to define τ . Nevertheless, the decrease in irreversibility was highly significant across all conditions ($p_{\text{Open}} = 1.25 * 10^{-6}$, $p_{\text{Closed}} = 1.72 * 10^{-5}$, $p_{\text{Music}} = 1.62 * 10^{-6}$, $p_{\text{Video}} = 0.0032$) (**Figure 5.5a**). For most of the subsequent analyses, we used the τ that we derived from the cross-validation approach. Our goal in this study was to identify differences in irreversibility between placebo and LSD, so the cross-validation method was the one that aligned most with our aims. However, we doubt that we would have observed significantly different results for the other analyses if we had opted for the orthogonal contrast approach, as irreversibility was consistently higher in placebo across all values of τ .

Under placebo, the conditions in which participants’ eyes were closed (Music and Closed) induced greater irreversibility than the conditions in which eyes were open (Video and Open) (**Figure 5.5b**). However, under LSD, Video was associated with significantly higher irreversibility than Closed.

In addition to taking the mean of irreversibility across all pairs of regions, we measured the irreversibility of each region. Regions in the occipital cortex consistently rank the highest in irreversibility across all conditions, even those in which the participants’ eyes are closed (i.e., Closed and Music) (**Figure 5.5c**). In the Open, Closed, and Music conditions, all or nearly all (≥ 85) of the regions exhibit significantly reduced irreversibility on LSD compared to placebo. In the Video condition, 74 out of 90 regions had significantly less irreversible timeseries; the insignificant regions were primarily parietal. In none of the conditions did any

of the regions have significantly more irreversibility on LSD compared to placebo. There is a robust anteroposterior gradient of changes in regional irreversibility in both hemispheres, although it is more pronounced in the right hemisphere.

We also measured the frequency-specific effects of LSD on irreversibility. We band-pass filtered the MEG signal to four canonical frequency bands: theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), gamma (30-48 Hz). We used cross-validation to determine the optimal τ for each frequency band. The alpha and beta results were consistent with those of our broadband analysis, but the theta and gamma bands were not (**Figure 5.6**). LSD significantly increased irreversibility in all four of the conditions for both theta ($p_{\text{Open}} = 0.0043$, $p_{\text{Closed}} = 0.0002$, $p_{\text{Music}} < 2.22 * 10^{-6}$, $p_{\text{Video}} = 0.0002$) and in three conditions for gamma ($p_{\text{Open}} = 0.0002$, $p_{\text{Closed}} = 4.10 * 10^{-5}$, $p_{\text{Music}} = 0.0006$, $p_{\text{Video}} = 0.2078$). However, in the theta band, LSD is more irreversible than placebo for values of τ ranging from 0.005 seconds to at least 0.25 seconds. Then, placebo is more irreversible than LSD until τ is at least 0.625 seconds. Since 0.25 seconds is the length of one 4Hz theta cycle, these results may indicate that there is greater asymmetry in within-cycle connectivity on LSD and larger asymmetry in between-cycle connectivity on placebo.

One problem with time-delayed correlations is that they do not control for confounding influences. There could be a strong correlation between a region A and a region B even if there were no causal relationship between the two, so long as there is a region C that is driving activity in both. Partial time-delayed correlations between any two timeseries provide a solution to this limitation by regressing out all other regions. With this approach, we still found that LSD significantly reduces irreversibility across all four conditions ($p_{\text{Open}} < 0.0001$, $p_{\text{Closed}} < 0.0001$, $p_{\text{Music}} < 0.0001$, $p_{\text{Video}} = 0.004$) (**Figure 5.7**).

Irreversibility (All Values of τ)

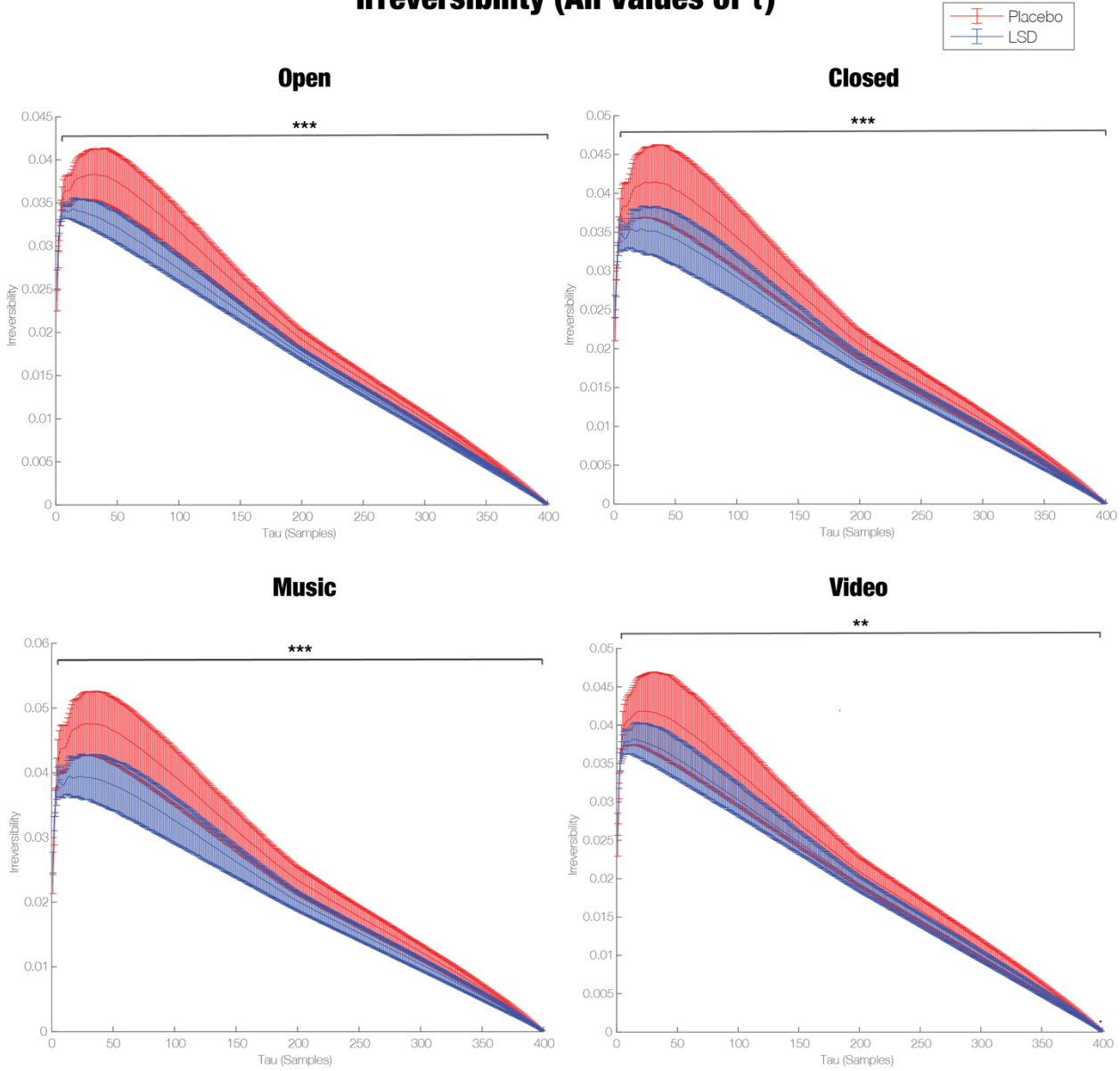


Figure 5.1. LSD reduces irreversibility across all values of τ .

Irreversibility is calculated as mean of the top 5% of squared differences between forwards and time-reversed cross-correlations of regional MEG amplitude envelopes. Cross-correlations are correlations shifted by an interval τ . We first computed irreversibility across all possible values of τ . (Since we executed INSIDEOUT on each epoch of data, which consisted of 400 samples (2 seconds), there were 399 possible values of τ .) We used cluster-based permutation testing to identify the values of τ that were associated with significant differences in irreversibility between LSD and placebo. Across nearly all values of τ , LSD was significantly more reversible than placebo in all four of the conditions. LSD was insignificantly more irreversible than placebo only at values of τ ranging from 1-3 samples (0.005-0.015 seconds). *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

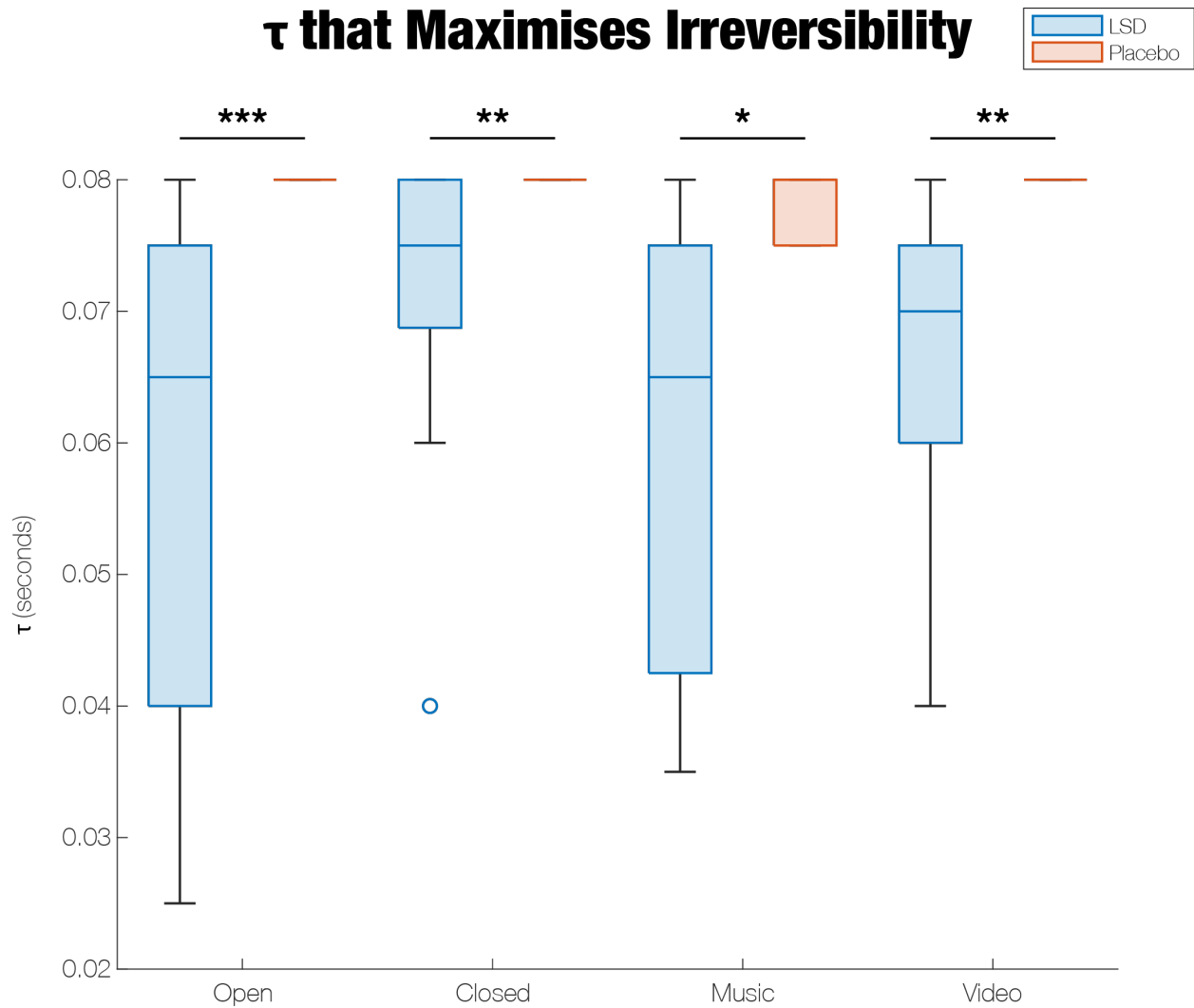


Figure 5.2. LSD increases the spread of the values of τ that maximise irreversibility.

As shown in **Figure 5.1**, irreversibility peaks at a single value of τ . In the Open, Closed, and Video conditions, the τ that yielded the peak value of irreversibility was the same across all participants under placebo ($\tau = 0.12$ seconds). However, under LSD, participants exhibited a significantly lower and much wider range of τ values that maximised irreversibility. If τ reflects the length of time that it takes regions to propagate signals to one another, these results perhaps suggest that there is greater inter-subject variability in the speed of connectivity under LSD. An alternative explanation is that connectivity becomes more local for some participants than others, thereby shortening their τ by a greater amount. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Total Irreversibility

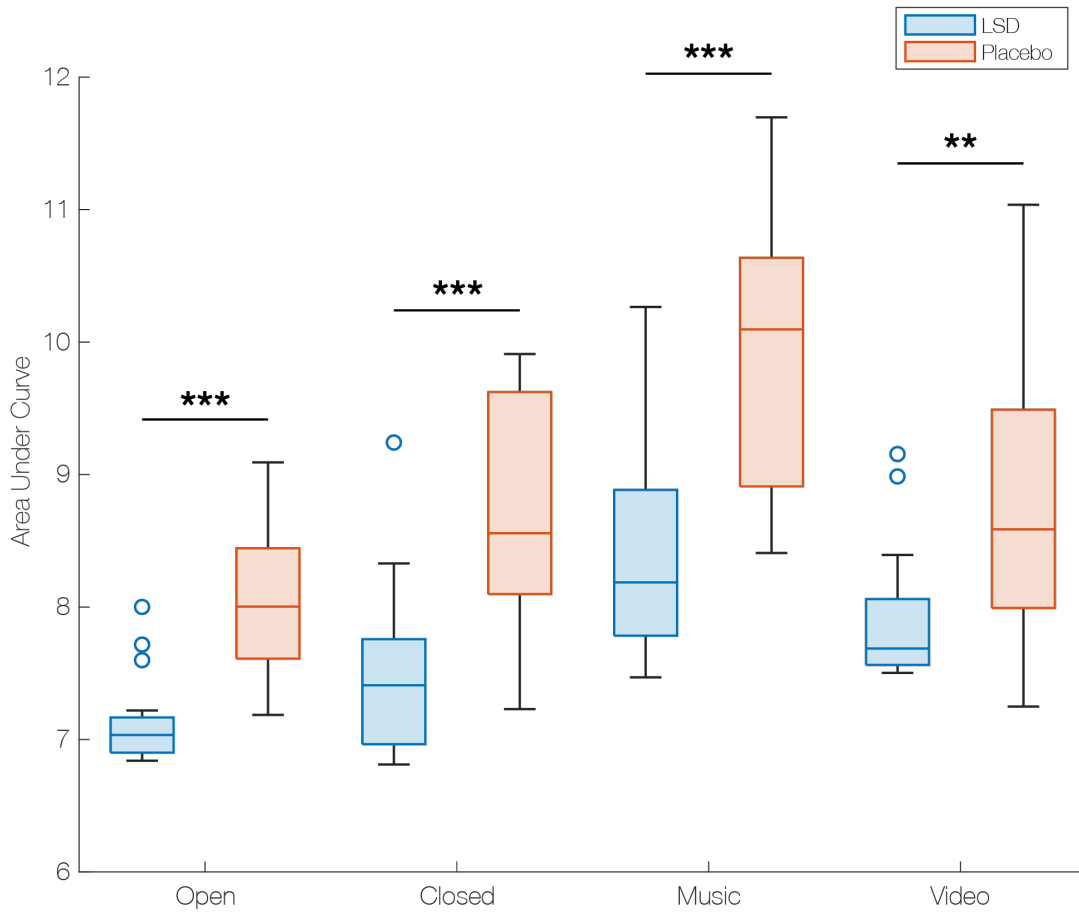


Figure 5.3. LSD decreases the “total” amount of irreversibility across all τ .

We integrated the value of irreversibility across all possible values of τ (0.005-1.995 seconds) by computing the area under the τ vs irreversibility curve (Figure 5.2). In line with our main result, LSD is significantly more reversible than placebo across all four conditions. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Irreversibility: Orthogonal Contrast ($\tau = 0.12s$)

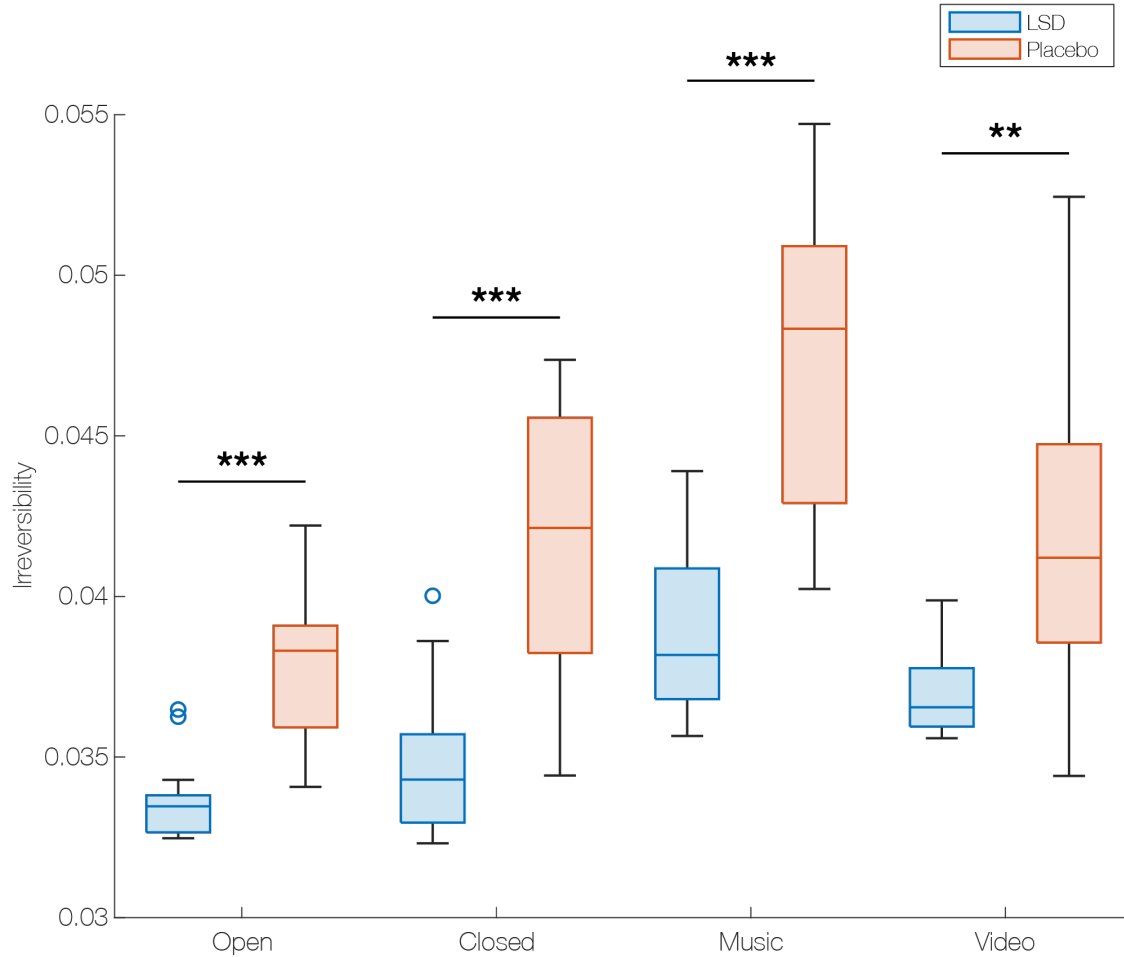


Figure 5.4. Using a different approach for selecting τ , we still find that the LSD data is significantly more reversible than the placebo data.

We used two different methods to identify a specific τ for conducting subsequent analyses. (Using a single τ expedited the analyses.) The results from the first method, which uses cross-validation to find the τ that maximally distinguishes LSD and placebo, are described in the main text. The second method, which we refer to as the orthogonal contrast technique, identifies the τ that maximises the mean irreversibility across all datasets. The cross-validation approach yielded $\tau = 0.225$ seconds, whereas the orthogonal contrast approach yielded $\tau = 0.12$ seconds. The results achieved with $\tau = 0.12$ were very similar to those that we obtained with $\tau = 0.225$. LSD was significantly more reversible across all four conditions. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

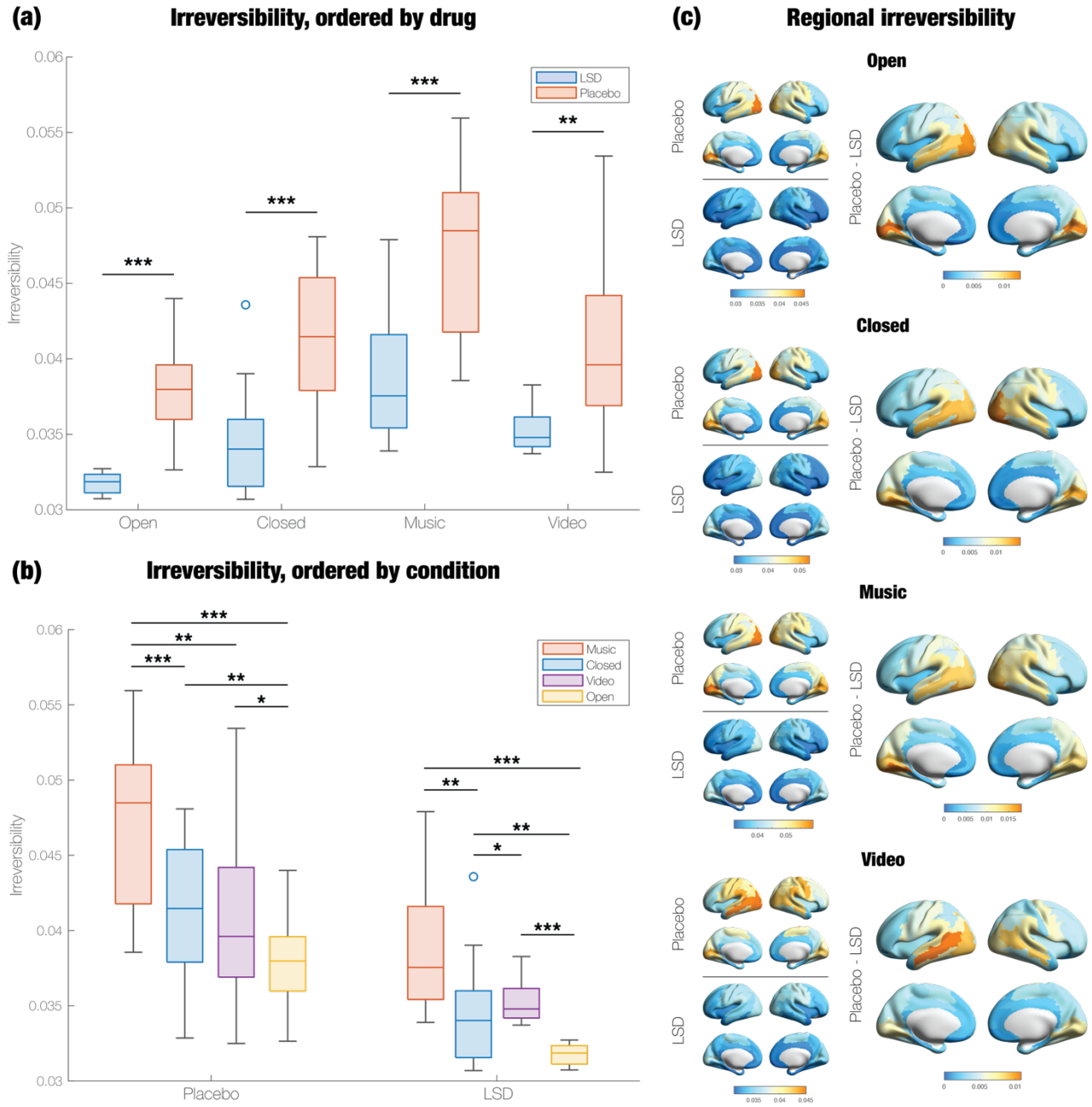


Figure 5.5. LSD makes broadband MEG signals significantly less directed (more reversible) across conditions.

Using a cross-validation approach, we selected the value of the time-lag ($\tau = 0.225$ seconds) that maximised the difference between irreversibility under LSD and irreversibility under placebo. We then computed the mean irreversibility across all pairs of regions at $\tau = 0.225$ seconds. (a) MEG signals under LSD were significantly more reversible than under placebo, in all four conditions. (b) Under LSD but not placebo, brain activity in the Video condition is significantly more irreversible than activity in the Closed condition. (c) In addition to taking the mean across regions, we measured the irreversibility of each region. For each condition, we show the regional irreversibility under placebo and under LSD, as well as regions that display significant differences between placebo and LSD. Regional irreversibility follows an anteroposterior gradient; across conditions, it tends to be highest in occipital areas and lowest in frontal areas. Orange values correspond to larger differences and blue values to smaller differences. Most differences were significant, across conditions. Units are arbitrary. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Irreversibility (Frequency-Specific)

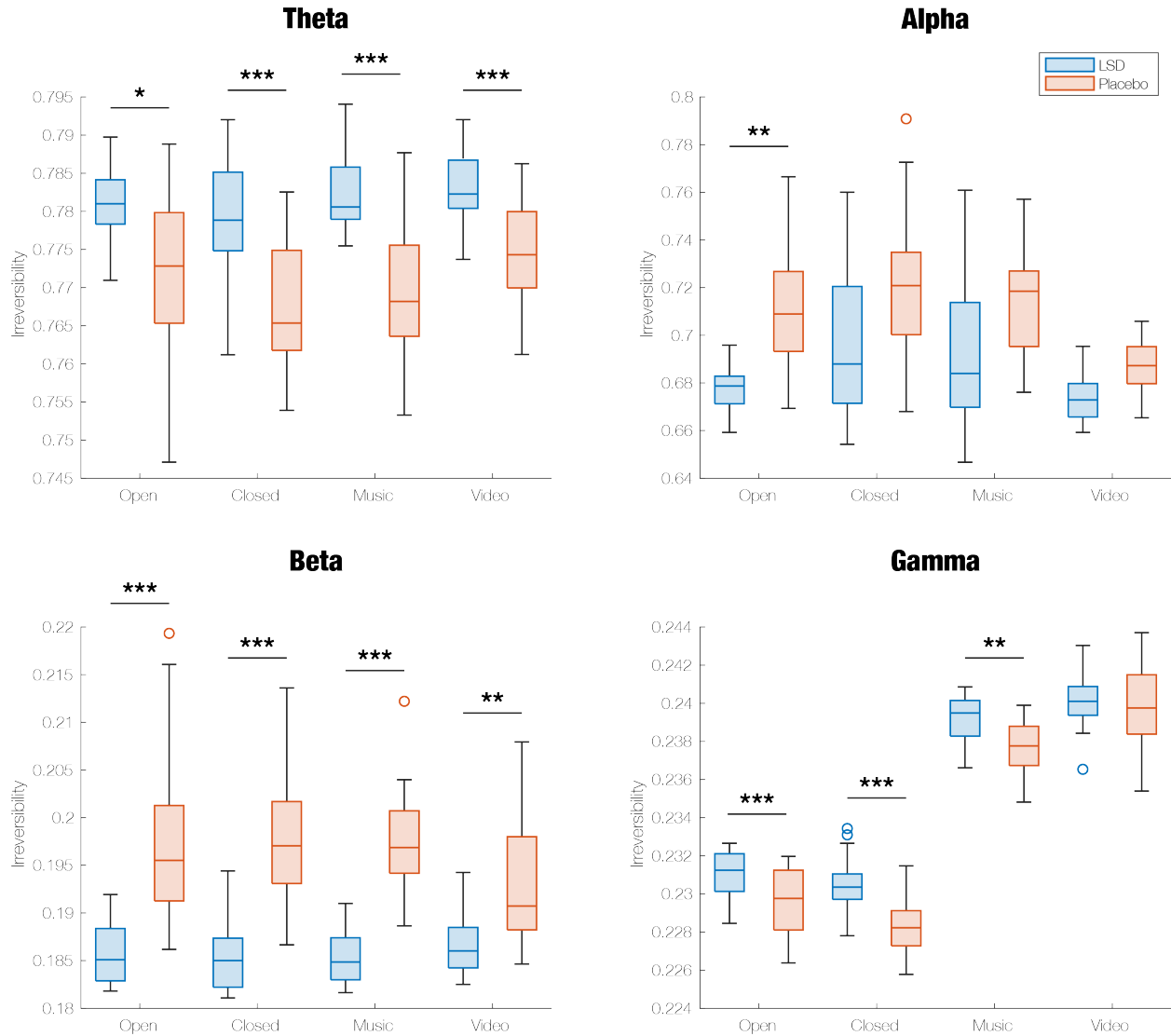


Figure 5.6. LSD is more reversible than placebo in the alpha and beta bands, but not in the theta and gamma bands.

After obtaining results for the broadband data, we bandpass-filtered the MEG timeseries into four frequency bands: theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-48 Hz). (We chose not to analyse the delta band because each epoch of data in each dataset was only two seconds long, which is equivalent to one or two low-frequency delta cycles.) In alpha and beta, LSD was more reversible than placebo, although this effect was only significant in the eyes-open condition in the alpha band. However, the theta and gamma results showed the opposite effect. That being said, in the theta band, LSD only ranked higher than placebo in irreversibility at certain values of τ . In particular, the irreversibility of LSD was greater than that of placebo for τ under 0.25 seconds, but smaller for τ between 0.25 and 0.625 seconds. Since 0.25 seconds is the length of one 4Hz theta cycle, these results may indicate that there is greater asymmetry in within-cycle connectivity on LSD and larger asymmetry in between-cycle connectivity on placebo.

Irreversibility: Partial Cross-Correlations

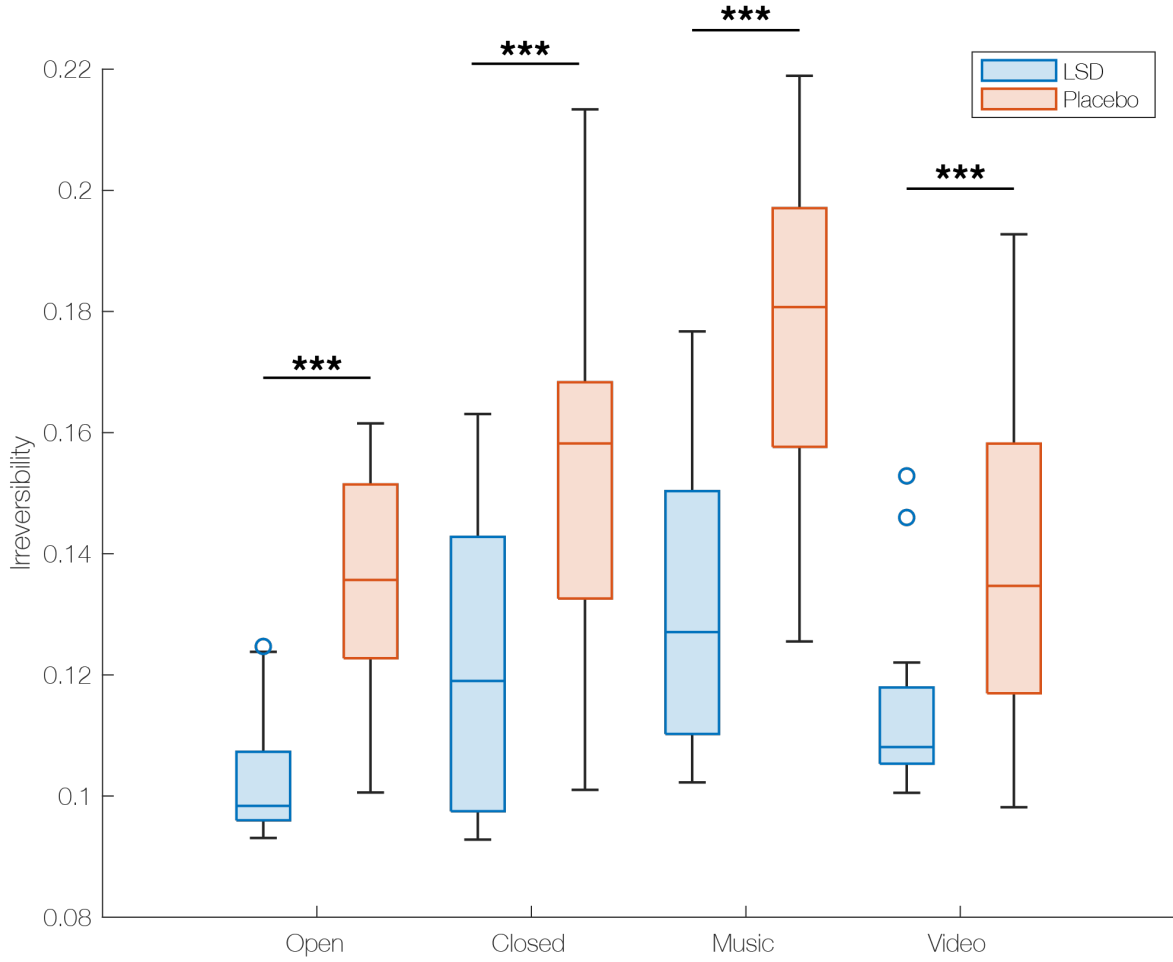


Figure 5.7. LSD significantly decreases irreversibility even with respect to partial cross-correlations rather than ordinary cross-correlations.

One limitation of the ordinary pairwise cross-correlations implemented in INSIDEOUT is that they do not control for confounding influences from other regions. This limitation can be resolved with partial cross-correlations. Here, timeseries were shifted by the same τ used in the main text (0.225 seconds). Then, each pair of timeseries was regressed against all other timeseries, and the correlation between the residuals was computed. Across all four conditions, irreversibility was still significantly lower on LSD when we used this method. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Chapter 5.4.2. LSD decreases hierarchical coherence and inhomogeneity

Irreversibility captures the connections that exhibit the largest differences between their incoming component and outgoing component. Here, we measured the difference in magnitude between the strongest incoming and outgoing connections at each region. While this incoming-outgoing asymmetry appears to be similar to irreversibility, **Figure 5.8a** illustrates toy models in which these two quantities diverge from each other. In particular, the direction of connectivity between the top node and bottom right node changes between network (1) and (2), such that the top node only has incoming connections in network (2); however, the irreversibility of all the connections remains the same in both networks.

Figure 5.8b illustrates significant differences in the incoming-outgoing asymmetry between placebo and LSD. LSD significantly decreases the asymmetry across all regions, under all four experimental conditions. The spatial distribution of these asymmetry values is nearly identical to that of regional irreversibility; the asymmetry tends to be highest in occipital and temporal cortices and lowest in frontal cortices. Thus, incoming-outgoing asymmetry and irreversibility typically do not diverge from each other.

We define hierarchical coherence and inhomogeneity as the mean and standard deviation of the incoming-outgoing asymmetry across regions, respectively. As shown in **Figure 5.8c-f**, LSD significantly reduces both hierarchical coherence ($p_{\text{Open}} = 6.43 * 10^{-6}$, $p_{\text{Closed}} = 0.0002$, $p_{\text{Music}} = 1.02 * 10^{-5}$, $p_{\text{Video}} = 0.0062$) and hierarchical inhomogeneity ($p_{\text{Open}} = 7.43 * 10^{-6}$, $p_{\text{Closed}} = 0.0139$, $p_{\text{Music}} = 0.0003$, $p_{\text{Video}} = 0.0121$) in all four conditions. Under both placebo and LSD, brain activity was more coherent and inhomogeneous in the eyes-closed conditions (Music and Closed) than the eyes-open conditions (Video and Open), though the difference between Closed and Open for both hierarchy metrics was significant only on LSD.

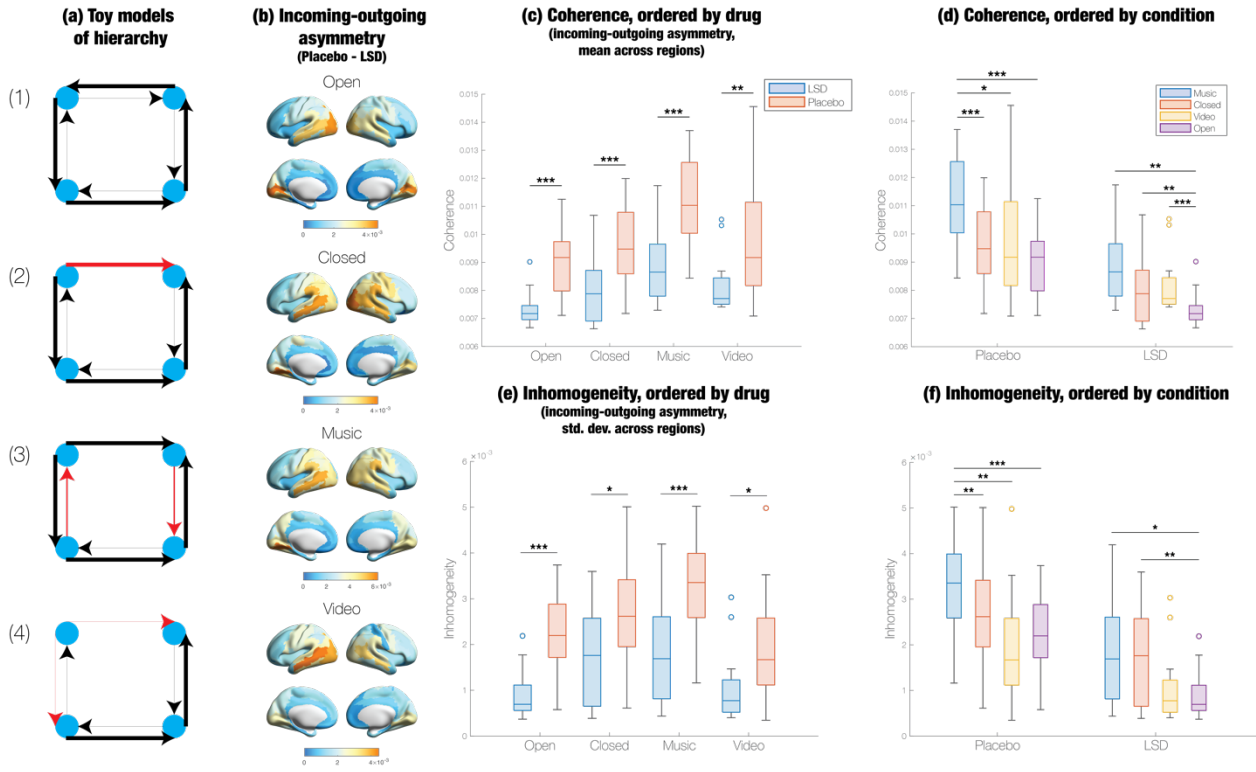


Figure 5.8. LSD significantly reduces coherence and inhomogeneity across conditions.

(a) Toy model (1) is completely non-hierarchical because each node is receiving the same amount of information that it is sending; the total weights of the incoming and outgoing connections are equally strong for all nodes. By altering the direction of a single edge (shown in red), model (2) is more hierarchical because the incoming and outgoing connections are now imbalanced for the upper left and upper right nodes. Its hierarchical coherence and inhomogeneity – mean and standard deviation of the incoming-outgoing asymmetry, respectively – are higher than model (1). Model (3) has higher hierarchical coherence but lower hierarchical inhomogeneity than (2) because the red edges grow larger in magnitude. Conversely, model (4) has lower hierarchical coherence but higher hierarchical inhomogeneity than (3) because the weights of the red edges decrease. Both coherence and inhomogeneity are required for hierarchy; therefore, both models (3) and (4) are less hierarchical than model (2). (b) The incoming-outgoing asymmetry is significantly higher under placebo in most regions; furthermore, the spatial topography of the incoming-outgoing asymmetry is very similar to that of regional irreversibility. Units of incoming-outgoing asymmetry are arbitrary. (c) In all four conditions, LSD significantly reduces coherence. (d) Under LSD but not placebo, coherence is significantly higher in the Closed condition than in the Open condition. (e) Inhomogeneity significantly decreases under LSD in all four conditions. (f) As with coherence, inhomogeneity is significantly greater in Closed compared to Open, but only under LSD. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Chapter 5.4.3. The measures of hierarchy dynamically reconstitute themselves over time

The above analyses were static, so we performed a dynamical analysis to determine how the three hierarchy metrics evolve over time. First, we computed each metric in overlapping sliding windows of 1-second length.

Figure 5.9a shows the irreversibility timeseries in one condition (Open) for a particular participant, under

both placebo and LSD. To inspect the dynamics, we performed a time-delay embedding of the irreversibility timeseries, which is a common procedure for extracting latent dynamical variables (Takens, 1981; Varley & Sporns, 2021). Each embedding dimension d represents the metric at time $(d - 1) * \tau_{\text{RN}}$ (**Figure 5.9b**). (Note that τ_{RN} is distinct from the τ determined in *Section 3.1*.) It is clear that points in the time-delay embedding are closer together under LSD than under placebo, suggesting that the dynamics of irreversibility are more similar on LSD compared to placebo. To quantify the similarity of the dynamics, we constructed a recurrence network, in which timepoints in the centrality timeseries are connected by an edge if their distance in the time-delay embedding is below a certain threshold. In the recurrence networks displayed in **Figure 5.9c**, the density of edges, or recurrence rate, is evidently much higher under LSD for this particular participant.

To ensure that differences in recurrence rate between placebo and LSD were attributable to actual changes in dynamics rather than fluctuations in cross-correlations that arise by chance from sampling variability, we first generated surrogate timeseries in which we randomized the phases in a coherent manner, thereby disrupting the dynamics but preserving the cross-correlation function. Under this “static null,” LSD’s recurrence rate was significantly higher than that of placebo in only the eyes-open conditions ($p_{\text{Open}} = 0.0009$, $p_{\text{Closed}} = 0.5035$, $p_{\text{Music}} = 0.1427$, $p_{\text{Video}} = 0.0008$). However, for the true timeseries, the recurrence rate on LSD was significantly greater than that of placebo in all four conditions ($p_{\text{Open}} = 0.0001$, $p_{\text{Closed}} = 0.0185$, $p_{\text{Music}} = 0.0032$, $p_{\text{Video}} = 0.0416$) (**Figure 5.9d**). Furthermore, the p -values for the eyes-open conditions were lower for the actual timeseries than for the surrogate timeseries, suggesting that LSD-induced changes in recurrence rate genuinely reflect differences in dynamics.

When we repeat the above steps for the other two hierarchy metrics, we find that LSD significantly increases the recurrence rate under all conditions (hierarchical coherence, non-surrogate: $p_{\text{Open}} = 0.0013$, $p_{\text{Closed}} = 0.0002$, $p_{\text{Music}} < 0.0001$, $p_{\text{Video}} = 0.0352$; hierarchical inhomogeneity, non-surrogate: $p_{\text{Open}} < 0.0001$, $p_{\text{Closed}} = 0.0030$, $p_{\text{Music}} = 0.0007$, $p_{\text{Video}} = 0.0012$) (**Figure 5.9e-f**). Yet for the surrogate timeseries, hierarchical coherence exhibited lower p -values in the Video condition, as did hierarchical inhomogeneity in both the Closed and Video conditions (hierarchical coherence, surrogate: $p_{\text{Open}} = 0.0013$, $p_{\text{Closed}} = 0.0491$, $p_{\text{Music}} = 0.0026$, $p_{\text{Video}} = 0.0047$; hierarchical inhomogeneity, surrogate: $p_{\text{Open}} = 0.0009$, $p_{\text{Closed}} = 0.0025$, $p_{\text{Music}} = 0.0039$, $p_{\text{Video}} = 0.0118$). Hence, in these conditions, sampling variability may be the cause of apparent differences in the dynamics of hierarchical coherence and inhomogeneity.

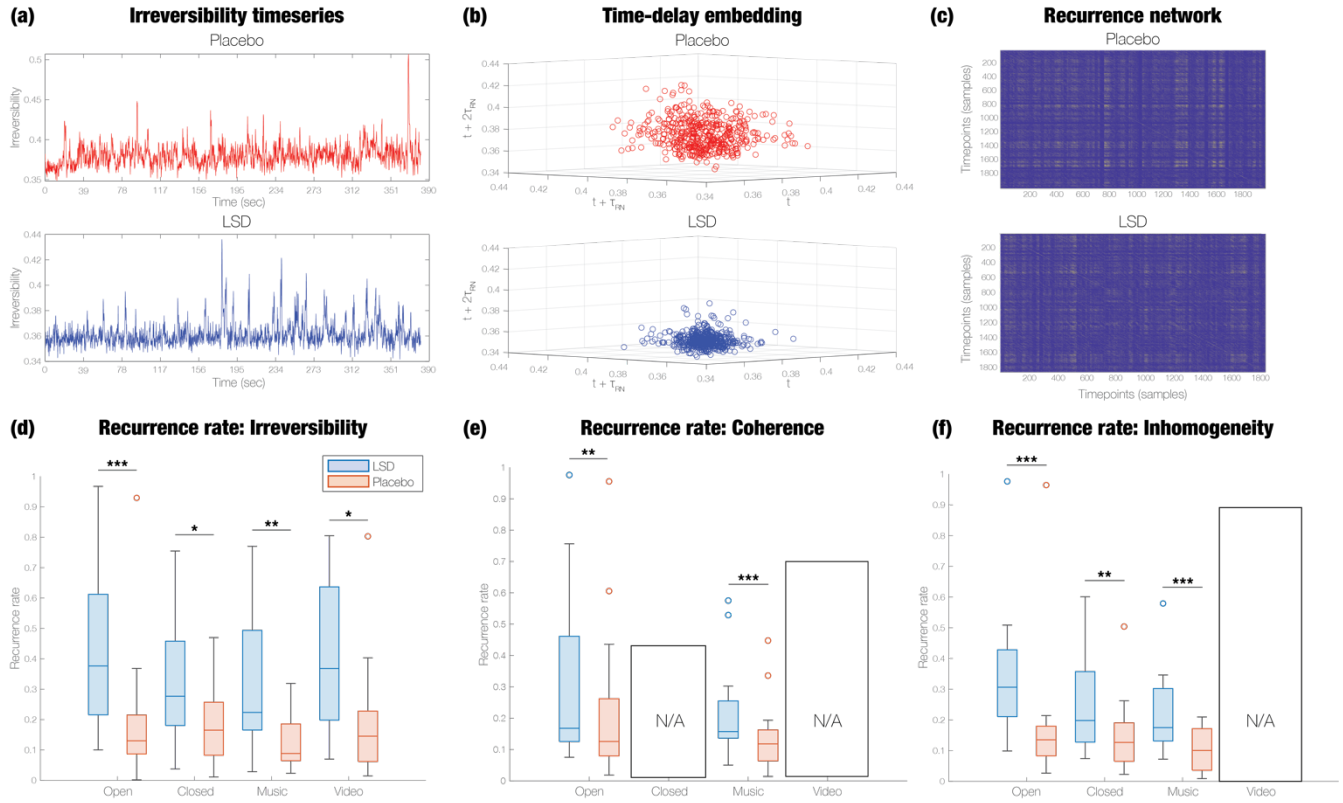


Figure 5.9. LSD constrains the dynamical repertoire of irreversibility, coherence, and inhomogeneity.

(a) We first performed a sliding-window analysis of each hierarchy metric in overlapping 1-second windows of data. Here, we display the irreversibility timeseries for one participant in the Open condition, under both placebo and LSD. (b) We conducted a time-delay embedding of each timeseries, where each dimension corresponds to the value of the metric across successive intervals of time. We show a 3-dimensional embedding of the same timeseries displayed in (a). LSD clearly reduces the density of points in the embedding. (c) We created a recurrence network, in which timepoints are connected by an edge if their distance in the embedding is below a certain threshold. Yellow entries correspond to the presence of an edge, and blue to the absence of an edge. Clearly, there are many more edges in the placebo recurrence network than the LSD recurrence network. (d-f) Across all participants, LSD significantly increases the recurrence rate of irreversibility, coherence, and inhomogeneity. Conditions marked with N/A are conditions in which the statistical significance of the difference between LSD and placebo was lower (higher p -value) for the actual timeseries than for surrogate timeseries. These surrogates were essentially “static nulls” in which the dynamics were disrupted but the cross-correlation was preserved through coherent phase-randomization. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Chapter 5.4.4. Irreversibility distinguishes LSD and placebo more than other measures of functional connectivity and hierarchy

How do the three hierarchy metrics compare to other measures of functional connectivity (FC), such as undirected FC and cross-correlations? To answer this question, we first measured the effects of LSD on the latter two measures. Over all conditions, LSD significantly reduced each metric, both when averaged across regions and within all or most regions (**Figure 5.10**). Furthermore, the spatial topographies of regional changes in undirected FC and forward cross-correlations were strikingly similar to those of regional

irreversibility. They were lowest in frontal cortices and highest in occipital and temporal regions, though decreases in undirected FC were more pronounced in occipital cortices, compared to irreversibility.

Yet despite the similarity between the topographies of irreversibility, forwards cross-correlations, and undirected FC, mean irreversibility differentiates LSD and placebo much more than the mean of either of these metrics. We trained random forest classifiers to distinguish placebo from LSD data based on regional irreversibility or one of these other metrics of FC. The classifier trained on irreversibility significantly outperformed the classifiers trained on cross-correlations and undirected FC, in addition to those trained on the other two hierarchy metrics (**Figure 5.11**).

We also tested a second set of classifiers in which the selection of τ was incorporated into the cross-validation training scheme, rather than being determined *a priori*. For the forward cross-correlations and the hierarchy metrics, this method yielded a broad range of optimized τ values across training runs (minimum: 0.005 seconds; maximum: 0.5 seconds). While the performance of the forward cross-correlation classifier improved with this scheme, the irreversibility classifier still significantly outperformed all the other classifiers (**Figure 5.12**).

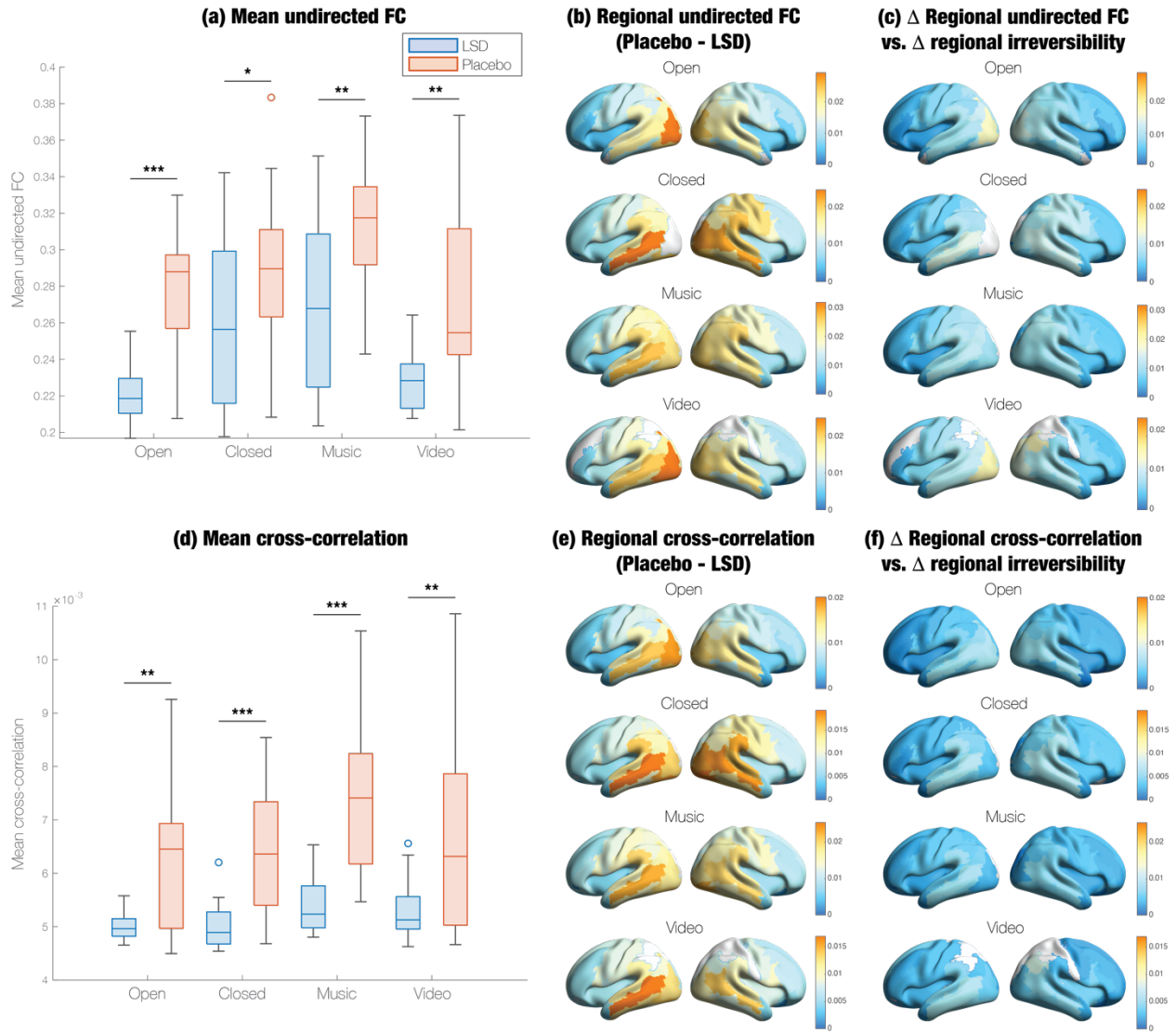


Figure 5.10. LSD's effect on regional irreversibility is highly similar to its effect on undirected functional connectivity and cross-correlations.

The left column (a, d) shows the mean across regions of each metric, the middle column (b, e) the regions that significantly differed in each metric between placebo and LSD, and the right column (c, f) the difference between regional changes in each metric and regional changes in irreversibility on LSD. Orange colours represent large changes and blue colours denote small changes. Each metric, both within nearly all regions and when averaged across regions, was significantly lower on LSD than placebo, in all four conditions. The spatial topographies of undirected FC (c) and time-forwards cross-correlations (f) are very similar to those of regional irreversibility.

Classification Performance

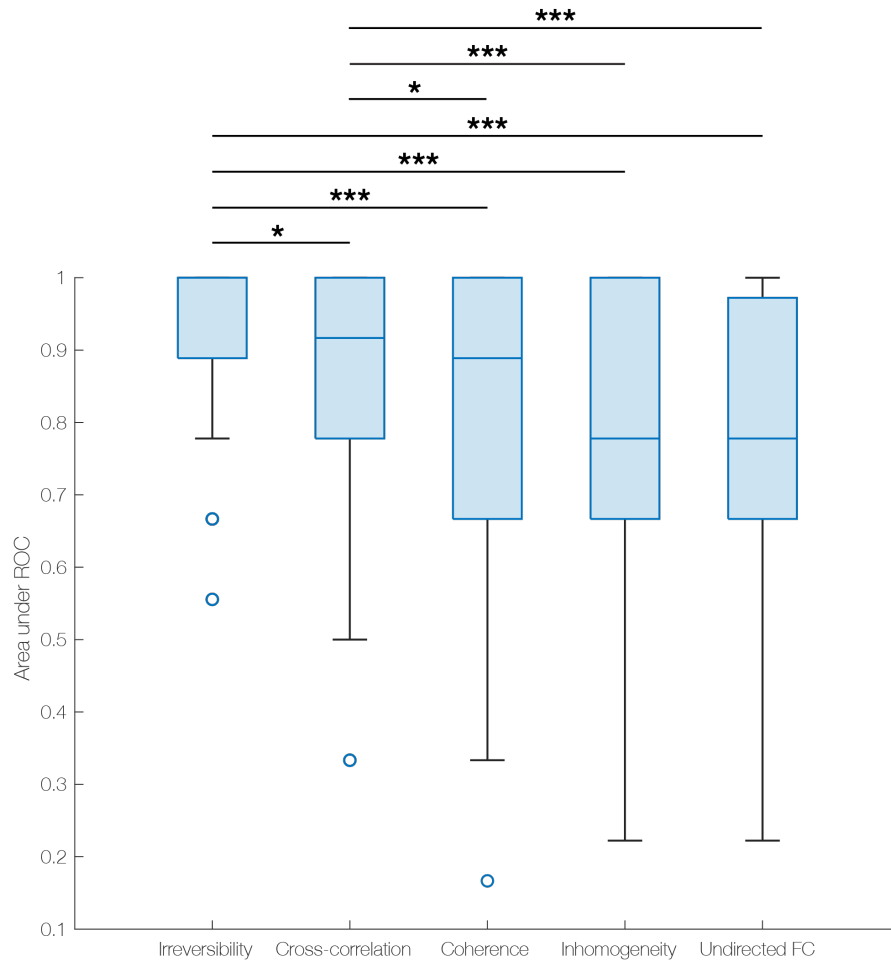


Figure 5.11. Regional irreversibility distinguishes LSD and placebo better than other metrics of functional connectivity.

We quantified the effect of LSD on two different metrics of functional connectivity (FC): undirected FC (Pearson correlation) and cross-correlations (measured only in the forward direction). The results of this analysis are shown in **Figure 5.10**. We then trained a random forest classifier to distinguish between LSD and placebo on the basis of undirected FC, cross-correlations, and the three hierarchy metrics introduced in this paper. Classification accuracy was significantly higher for the classifier trained on irreversibility, compared to all other classifiers.

Classification Performance with Nested Cross-Validation of τ

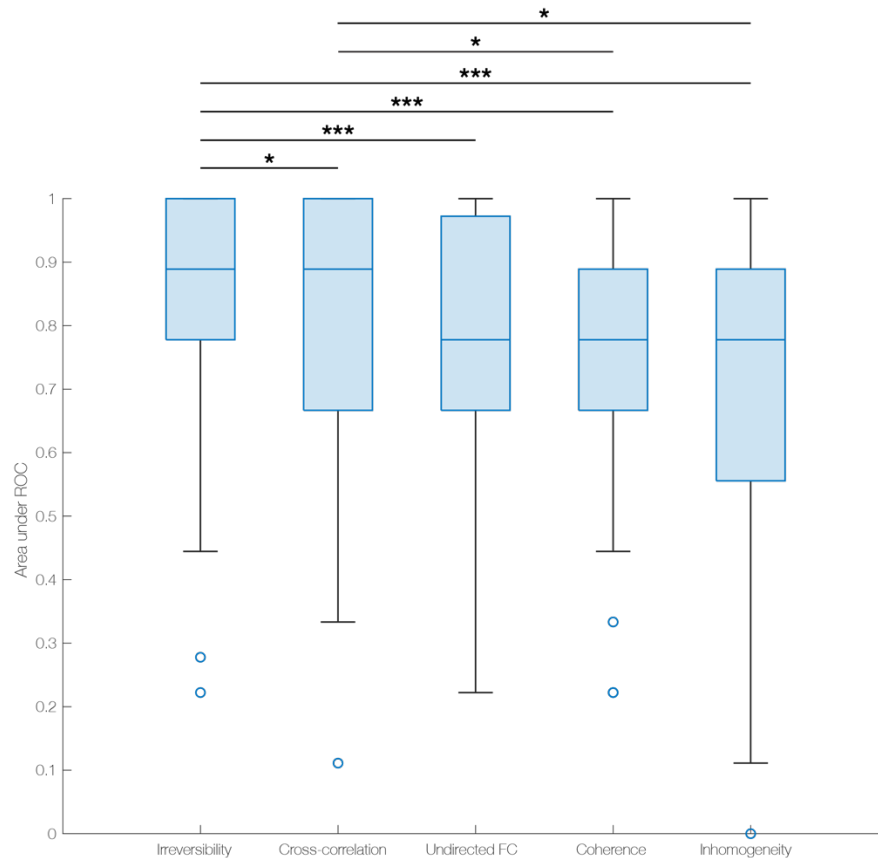


Figure 5.12. Irreversibility continues to outperform traditional measures of functional connectivity in classification performance, even when τ is not determined a priori.

A nested cross-validation approach was used to determine the optimal τ for distinguishing placebo and LSD in each run of training, whereas previously τ was selected before training. The performance of the cross-correlation classifier improves considerably under this training scheme, but not enough to outperform the irreversibility classifier, which still exhibits significantly higher accuracy than any of the other classifiers. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Chapter 5.4.5. Regional irreversibility does not correlate with serotonin receptor expression

Because the hallucinogenic effects of psychedelics are attributed to their interaction with the 5-HT_{2A} receptor (Vollenweider et al., 1998), we hypothesised that the spatial patterns of changes in regional irreversibility would be correlated with 5-HT_{2A} receptor expression. However, 5-HT_{2A} receptor expression was not significantly correlated with the difference between regional irreversibility under placebo and LSD, in any of the conditions ($p_{\text{Open}} = 0.9560$, $p_{\text{Closed}} = 0.9020$, $p_{\text{Music}} = 0.9560$, $p_{\text{Video}} = 0.8100$) (**Figure 5.13a-b**).

We also anticipated that the difference in regional irreversibility between placebo and LSD would be correlated more with 5-HT_{2A} receptor expression than with 5-HT_{1A} or 5-HT_{1B} expression, as these receptors

do not seem to play as essential of a role in mediating the hallucinogenic effects of psychedelics in humans (Nichols, 2016). While 5-HT_{1A} and 5-HT_{1B} receptor density correlate negatively with regional irreversibility, these correlations were surprisingly more significant than those of 5-HT_{2A} (5-HT_{1A}: $p_{\text{Open}} = 0.213$, $p_{\text{Closed}} = 0.215$, $p_{\text{Music}} = 0.2258$, $p_{\text{Video}} = 0.25$; 5-HT_{1B}: $p_{\text{Open}} = 0.336$, $p_{\text{Closed}} = 0.318$, $p_{\text{Music}} = 0.334$, $p_{\text{Video}} = 0.436$) (**Figure 5.13c-f**).

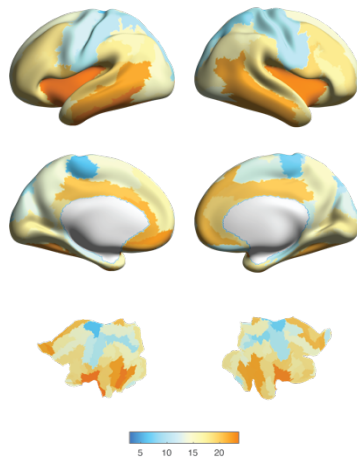
Chapter 5.4.6. Regional irreversibility is inversely correlated with traditional measures of hierarchy

Finally, we compared regional irreversibility to two well-established measures of hierarchy, namely the ratio between signal intensities of T1-weighted and T2-weighted MRI images and the principal gradient of functional connectivity. The T1w-T2w ratio exhibits an inverse relationship with hierarchy in the human cortex because it is high in the primary sensory cortex and low in associative regions (Burt et al., 2018). LSD-induced changes in regional irreversibility in the eyes-open condition were significantly and positively correlated with T1w-T2w ratio ($p = 0.008$).

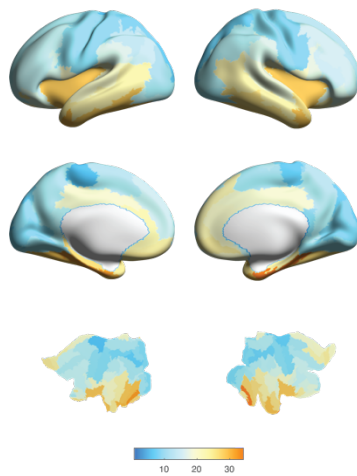
The principal gradient is the axis that accounts for maximum variance in (undirected) functional connectivity patterns across the human cerebral cortex (Margulies et al., 2016). On the negative end of the axis are primary and unimodal sensory and motor cortices, whereas the positive end contains regions in the default mode network. Thus, unlike the T1w-T2w ratio, the principal gradient is positively related to hierarchy. There was a negative yet insignificant correlation between drug-induced alterations in regional irreversibility in the eyes-open condition and the principal gradient ($p = 0.136$).

PET Maps of Receptor Expression (Beliveau Atlas)

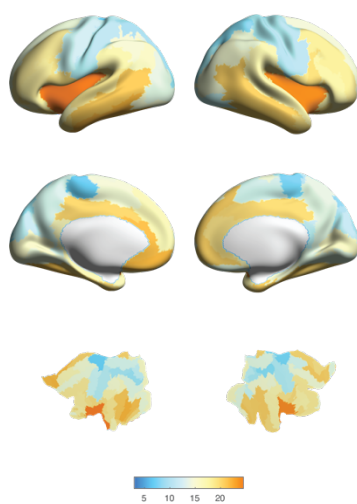
(a) 5-HT_{2A}



(c) 5-HT_{1A}

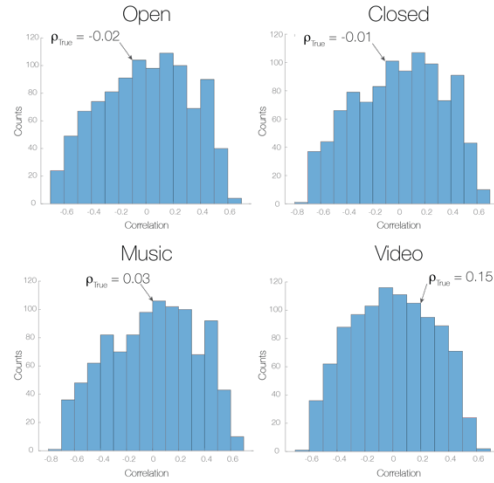


(e) 5-HT_{1B}

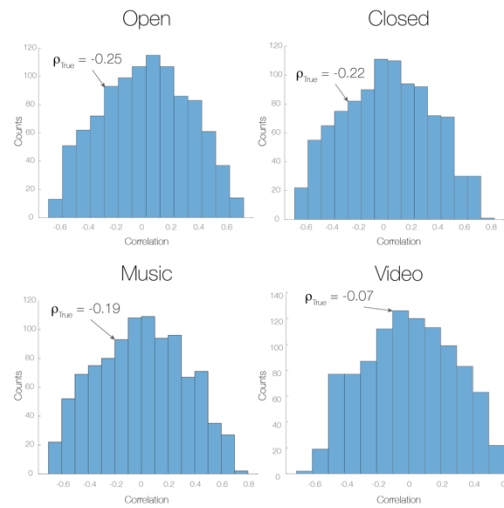


Correlation between Receptor Expression and Regional Irreversibility

(b) 5-HT_{2A}



(d) 5-HT_{1A}



(f) 5-HT_{1B}

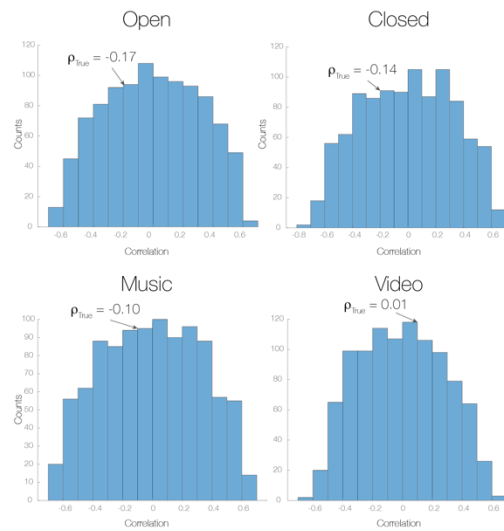


Figure 5.13. 5-HT_{2A} concentration does not correlate with changes in regional irreversibility under LSD.

LSD's agonism of the 5-HT_{2A} receptor is crucial for its hallucinogenic and behavioural effects; if the receptor is blocked, then participants do not experience the "trip" (González-Maeso et al., 2007b; Vollenweider et al., 1998). (a) Using PET data on 5-HT_{2A} receptor expression in the human brain (Beliveau et al., 2017), we quantified the average concentration of the 5-HT_{2A} receptor in each region of the AAL-90 parcellation, weighted by the probability that each voxel in each region was in grey matter. (Note: we also used other PET atlases, such as the Savli and Hansen atlases, and achieved similar results.) (b) We then correlated differences in regional irreversibility between LSD and placebo with the average regional concentration of 5-HT_{2A} receptors, and we determined the significance of this correlation with respect to a permutation of the 5-HT_{2A} distribution that preserved its spatial autocorrelation. There was virtually no correlation in any of the four conditions. (c) and (e) show the regional density of the 5-HT_{1A} and 5-HT_{1B} receptor, respectively, based on the same PET maps. (d) and (f) display the correlation between the density maps and regional irreversibility, with respect to the null distribution. While the correlation was negative for both receptors in all four conditions, it was surprisingly more significant than the correlation of 5-HT_{2A} receptor density.

Chapter 5.4.6. Effect of LSD on a more direct measure of entropy production

To confirm our results with a more direct method of estimating entropy production, we trained a time-delay embedded Hidden Markov Model (HMM) on the concatenated data of all subjects, which estimated eight states of brain activity. Based on the probability matrices describing the transitions between these eight states, we determined that LSD reduced entropy production by approximately 34%, from 1.89 to 1.25 (arbitrary units). Entropy production is a single number for the placebo and LSD data, which means that it is impossible to perform a test of statistical significance on these results. We therefore re-inferred subject-specific states and their corresponding transition probability matrices. However, the main effect of drug on entropy production was insignificant. This null finding may be attributed to the noisy stochastic estimation of HMM states, given the low number of subjects that we included in each batch in order to expedite training.

Chapter 5.5. Discussion

Chapter 5.5.1. Psychedelics and hierarchy

Here, we aimed to produce a simple method for testing the hypothesis that psychedelics flatten the hierarchy of the brain (R. L. Carhart-Harris & Friston, 2019). We argue that hierarchies are characterised by at least three properties: irreversibility, hierarchical coherence, and hierarchical inhomogeneity. Broadly speaking, any hierarchy must exhibit unidirectional information flow; information tends to flow either towards or away from the higher-order components. If information were to flow in both directions, the higher-order components would not regulate the activity of lower-order ones, thereby diminishing the strength of the hierarchy. Our finding that LSD significantly reduces the asymmetry of directed connectivity is consistent with previous MEG studies, which showed that LSD and psilocybin reduce other measures of directed connectivity like Granger causality across the whole brain (Barnett et al., 2020). While there have been an

abundance of studies on undirected functional connectivity under psychedelics (F. S. Barrett, Doss, et al., 2020; F. S. Barrett, Krimmel, et al., 2020; Bedford et al., 2023; R. L. Carhart-Harris et al., 2016; Dai et al., 2023; Gaddis et al., 2022; Grimm et al., 2018; Madsen et al., 2021; Mason et al., 2020; Palhano-Fontes et al., 2015; Pallavicini et al., 2019; Roseman et al., 2014; Timmermann et al., 2023), there have been relatively few studies on directed functional connectivity by comparison (Barnett et al., 2020; de Araujo et al., 2011). The fact that irreversibility distinguishes placebo and LSD better than undirected measures, according to our random forest analyses, suggests that irreversibility may be a more specific biomarker of psychedelics.

However, irreversibility does not always imply hierarchy. For instance, in network (1) of the toy models shown in **Figure 5.9a**, all three of the connections are highly irreversible, yet the network is not hierarchical at all, since information flows towards and away from all nodes equally. However, network (2) is more hierarchical because one of the connections (shown in red) flips direction, such that the top right node receives more information than it transmits, and vice versa for the top left node. Network (2) has higher hierarchical coherence and inhomogeneity than network (1) because there is a non-zero asymmetry between incoming and outgoing connections at these two nodes. Furthermore, non-zero coherence or inhomogeneity always entails irreversibility. We propose that both hierarchical coherence and inhomogeneity are necessary for hierarchy. For example, network (3) exhibits increased hierarchical coherence but decreased inhomogeneity relative to network (2), and network (4) higher hierarchical inhomogeneity but lower coherence compared to network (2). Yet both are evidently less hierarchical than network (2). In network (2), the top left node is predominantly a transmitter of information, whereas the top right is predominantly a receiver. However, the top left node receives more and the top right node transmits more in network (3), whereas the top left node transmits less and the top right node receives less in network (4). The significant decreases in not only irreversibility but also hierarchical coherence and inhomogeneity under LSD lend strong support to REBUS' claim that psychedelics diminish hierarchy.

While these toy models illustrate instances in which irreversibility and the incoming-outgoing asymmetry dissociate from each other, they exhibit very similar spatial patterns in empirical data. In other words, although it is theoretically possible for brain regions to become more irreversible and also more balanced in its incoming and outgoing connections, this never appears to occur in the data at hand.

Our assumption that hierarchies must exhibit asymmetry between incoming and outgoing connectivity is equivalent to the statement that hierarchies must contain acyclic information flow, a definition that is made explicit in measures of flow hierarchy (Luo & Magee, 2011). Here, the strength of hierarchy corresponds to the proportion of edges that do not participate in cycles.

Another established measure of hierarchy defines hierarchical coherence in a similar way. So-called “trophic coherence” is the normalised difference between “trophic levels,” or levels of the hierarchy, which

are determined based on both the imbalance between incoming and outgoing connections and the topology of the network (specifically, the graph Laplacian) (MacKay et al., 2020). However, trophic coherence can only be measured on a non-negative network, whereas the time-delayed correlations that we measured in this study can be negative. In the future, we hope to use a whole-brain modelling approach to extract an effective, non-negative network from the same dataset, so that we can subsequently quantify trophic coherence (Jobst et al., 2017; Kringelbach et al., 2023; Kringelbach & Deco, 2020).

A recent graph-theoretic framework that generalises trophic coherence bears even greater resemblance to our definition of hierarchy (Moutsinas et al., 2021). Here, the “democracy coefficient” of a network is defined based on the mean of the incoming and outgoing connections between hierarchical levels, and the “hierarchical incoherence” on the standard deviation of the same connections. Similar to trophic coherence, hierarchical levels are identified by solving a linear equation relating the graph Laplacian to the in- and out-degree of the network. Like ours, this framework acknowledges that both the mean and the standard deviation of imbalance between incoming and outgoing connections characterise the strength of a hierarchy.

So far, the notions of hierarchy that we have considered are statistical or functional rather than anatomical. In general, anatomical hierarchies do not align with functional hierarchies (Silvanto, 2015; Zeki, 2018). However, the rank-ordering of irreversibility is congruent with the anatomical hierarchy of cortical visual regions, which spans from the primary visual cortex (V1) to areas that are connected to the dorsal and ventral visual processing streams (e.g., the frontal eye field [FEF]) (Felleman & Van Essen, 1991). In the Open, Closed, and Music conditions, the calcarine, which contains V1 (Galetta, 2014), is either the most or the second most irreversible region. The cuneus and lingual gyrus, which encompass V2, V3, and V4 (Palejwala et al., 2021), are more reversible, followed by the precentral gyrus, which contains a portion of the FEF (El-Baba & Schury, 2024). In the Video condition, the middle temporal gyrus, which contains V5, is more irreversible than the calcarine; this is consistent with the fact that V5 controls motion perception (Zeki, 2015).

The direction of the hierarchy defined in this study appears to contradict the traditional direction of visual hierarchies; here, V1 is at the top, whereas V1 is usually at or near the bottom. Our analysis is agnostic about whether regions that transmit or receive information are higher or lower in the hierarchy; rather, it places regions with the highest asymmetry in directed connectivity at the top of the hierarchy. It turns out that the brain areas with the largest asymmetry, i.e., visual areas, transmit more information than they receive.

Hence, regional irreversibility is inversely correlated with conventional measures of hierarchy. We found a significant and positive association between regional irreversibility and the T1w-T2w ratio, which is itself inversely related to hierarchy. The T1w-T2w ratio is larger in regions with high myelin content, which is negatively correlated with dendritic spine density, dendritic arborization, and cell size (Glasser et al., 2014).

The strong relationship between regional irreversibility and the T1w-T2w map suggests that asymmetries in directed connectivity may correspond to variations in cortical microstructure that account for the complexity of intracortical circuits.

Finally, we also show that the brain “explores” a broader repertoire of hierarchical dynamics under placebo than LSD. While previous studies showed that LSD expands the repertoire of functional connectivity motifs (Atasoy et al., 2017; R. Carhart-Harris et al., 2014; Tagliazucchi et al., 2014), they averaged connectivity over time and therefore did not consider dynamics. Studies that investigated dynamics either found no differences between psychedelics and placebo or did not explicitly measure the dynamics of hierarchy (Luppi et al., 2021; Timmermann et al., 2023). To our knowledge, this is the first study that assessed the effect of psychedelics on the dynamics of hierarchy. Our finding suggests that hierarchy is not static but rather changes over time, yet LSD constrains the evolution of the hierarchy to a smaller subset of dynamics. A fundamental theorem in the study of dynamical systems, Takens’ Embedding Theorem, states that, under certain conditions, this subset is equivalent to the attractor set of the hierarchy (Takens, 1981). It is not clear whether these conditions are met, especially since the dynamics do not appear to be very smooth, but nonetheless our finding raises the intriguing possibility that psychedelics restrain the attractor landscape rather than enlarging it.

Chapter 5.5.2. Entropy, entropy production, and the arrow of time

Ever since Carhart-Harris formulated the Entropic Brain Hypothesis, which claims that the altered state of consciousness on psychedelics corresponds to a brain state of elevated entropy (Carhart-Harris et al., 2014), a number of studies in fMRI, MEG, and EEG have investigated the effect of psychedelics on entropy (Alonso et al., 2015; Lebedev et al., 2015, 2016; Mediano et al., 2024; Ruffini et al., 2023; Schartner et al., 2017; Singleton et al., 2022b; Tagliazucchi et al., 2014; Timmermann et al., 2019, 2023; Varley et al., 2020; Viol et al., 2017, 2019, 2023). Virtually all of them have demonstrated that psychedelics are associated with heightened entropy, though most of them define entropy on different variables. (In fact, a study on a new dataset found that psilocybin did not have a significant effect on seven of the 12 entropy measures in the literature, though this study examined relationships between entropy and plasma psilocin level unlike previous research (McCulloch et al., 2023)).

This study is the first one to show that LSD decreases irreversibility, which is equivalent to entropy production. Our main finding of reduced entropy production on LSD appears to contradict the abundance of evidence in the literature that psychedelics increase entropy. However, this contradiction is resolved by distinguishing entropy *production* from entropy. Entropy refers to the variability of the states of a system, and it is maximised in equilibrium; that is, the system is capable of existing in a maximally large number of states.

(For instance, once a drop of ink has diffused in a tank of water and reached equilibrium, the ink has maximised its probability of being located at any position in the tank.) Due to the Second Law of Thermodynamics, total entropy never decreases over time. Thus, once entropy has reached its maximum in equilibrium, it cannot do anything other than remain constant. Entropy is maximal while entropy production is minimal (zero).

Furthermore, entropy production, unlike entropy, is the same as irreversibility. The Crooks fluctuation theorem in physics demonstrates that entropy production is exponentially related to irreversibility, i.e. the ratio between the forward and time-reversed transition probabilities, when the dynamics of the system are Markovian (the state at each timepoint only depends on the state at the previous timepoint) (Crooks, 1998). Our measure of entropy production, INSIDEOUT, does not quantify the probability of forward and backward trajectories of brain activity; instead, INSIDEOUT only computes the time-delayed correlations between forward and backward timeseries. In the future, we aim to use the Ornstein-Uhlenbeck model, which analytically derives entropy production and has recently been applied to fMRI timeseries (Gilson et al., 2023), to directly obtain the amount of entropy production in the same dataset.

Outside of equilibrium, entropy and entropy production may also change in opposite directions. For instance, MEG studies have found that psychedelics increase Lempel-Ziv complexity (LZc) (Mediano et al., 2024; Schartner et al., 2017; Timmermann et al., 2019), which is known to be an efficient estimator of entropy rate, or the amount of uncertainty about the value of the next sample in a data timeseries (Ziv & Lempel, 1978). LZc is highest in reversible systems, in which the state that the system will transition to at the next timepoint is maximally uncertain. (For instance, in a cyclic and reversible system, it is equally probable that information will flow clockwise or counterclockwise at the next timepoint.) Intriguingly, a recent study that analysed the same primary dataset showed that LZc is higher in eyes-open conditions than eyes-closed conditions, under both placebo and LSD (Mediano et al., 2024). On the other hand, we demonstrated that irreversibility is higher in eyes-closed conditions than eyes-open conditions. Indeed, when irreversibility is higher, uncertainty about the direction of information flow is lower, and hence LZc will decrease.

Chapter 5.5.3. Limitations

While we have shown here that psychedelic use is associated with directedness of brain connectivity, we have not yet demonstrated causality. REBUS proposes that the flattened hierarchy gives rise to both the altered states of consciousness and therapeutic effects of psychedelics, but we have not provided evidence that the subjective experience of psychedelics is mediated by the three hierarchical metrics that we investigated.

Additionally, we measured the three properties of hierarchy in all brain regions, yet a smaller subset of latent features or brain regions likely controls directed connectivity (Cai et al., 2021; Taghia et al., 2018; Vidaurre,

Abeyesuriya, et al., 2018). While we averaged across the top 5% of values in each data epoch to compute the hierarchical properties, we would ideally apply a more principled method for reducing dimensionality and noise, such as reduced rank regression (MacDowell et al., 2023).

Thirdly, increases in our hierarchy-related measures may not always correspond to increases in the strength of hierarchy. For instance, consider a network with horizontal (within-layer) and vertical (between-layer) connections. The hierarchical flow of information is vertical in this network; information tends to flow upwards towards a small set of higher-order nodes. According to our framework, perturbing the imbalance of a node by altering its horizontal connectivity would have the same effect on the hierarchy as changing its vertical connectivity would. However, in reality, only the vertical connectivity modulates the strength of hierarchy in this network.

Finally, we did not rank brain regions according to their positions within the hierarchy. Our methods do not determine whether a region has more incoming than outgoing connections (or vice versa), only whether there is an asymmetry in the direction of connectivity. Future research should apply techniques that are capable of assigning hierarchical levels to brain regions based on the extent of their top-down control over the rest of the brain (Mackay et al., 2020; Moutsinas et al., 2021).

Chapter 5.6. Chapter summary

Here, we measured temporal irreversibility, a property of hierarchical networks that corresponds to the directedness of connectivity, in the amplitude envelopes of MEG data acquired from healthy human participants under the influence of LSD. Our main finding is that LSD makes broadband neural signals more reversible across multiple conditions: eyes-open resting-state, eyes-closed resting-state, listening to music, and watching a silent video. We also found that LSD significantly decreases two other properties of hierarchy: hierarchical coherence and inhomogeneity, or the mean and standard deviation of the asymmetry between incoming and outgoing connections. LSD constrains the dynamics of irreversibility, hierarchical coherence, and hierarchical inhomogeneity. While the spatial topography of changes in irreversibility on LSD is similar to that of other FC metrics, such as undirected FC and cross-correlations, random forest algorithms classify placebo and LSD more accurately when trained on irreversibility.

Chapter 6. Diminished hierarchy of effective connectivity on LSD reduces entropy production in the brain

Chapter 6.1. Chapter abstract

In the previous chapter, I demonstrated that psychedelics increase the reversibility of pairwise, directed connections between brain regions. Previous work has shown that entropy production, or irreversibility, increases for hierarchical networks (Nartallo-Kaluarachchi et al., 2024). However, irreversibility, as measured with INSIDEOUT, is not a direct measure of entropy production. Here, I analytically determine that LSD significantly reduces entropy production by fitting an Ornstein-Uhlenbeck (OU) model to MEG data. Furthermore, fitting the model yields an estimate of the brain's effective network, which can be decomposed into hierarchical levels with the trophic coherence framework. LSD significantly reduces the standard deviation of the differences between hierarchical levels, confirming that decreases in entropy production correspond to a flattening of hierarchy.

Chapter 6.2. Introduction

As discussed in *Chapter 5*, irreversibility does not always imply hierarchy. In particular, a system with a circular flow of information between its nodes will be highly irreversible yet not hierarchical at all, since all nodes are receiving and transmitting information equally. This insight motivated my decision to measure another parameter, “hierarchical coherence,” which is the asymmetry between incoming and outgoing connections at each brain region, averaged across regions. In the circular system described above, irreversibility is high but hierarchical coherence is zero.

However, hierarchical coherence is an imperfect measure of hierarchy, as the imbalance between incoming and outgoing connections could increase in a system without necessarily affecting the strength of hierarchy. **Figure 6.1a** illustrates a toy model in which the incoming connection at a node is increased, but it is not clear that the hierarchy consequently becomes stronger. A different, well-validated measure essentially uses both the incoming-outgoing asymmetry at each node *and* the irreversibility across all edges to identify the “trophic” or hierarchical levels of all regions, as well as to compute a global measure of hierarchical directedness or “trophic coherence” (MacKay et al., 2020). Hierarchical coherence, as defined in the previous chapter, does not partition the network into hierarchical levels. Thus, the benefits of this new method are twofold. Firstly, trophic coherence is more robust than hierarchical coherence. Secondly, trophic levels enable us to identify the levels at which brain regions are situated within the hierarchy.

Additionally, previous unpublished work by Nartallo-Kaluarachchi and colleagues demonstrated that entropy production correlates much more poorly with irreversibility, as estimated with INSIDEOUT, than with other measures of directedness. However, entropy production can be directly measured for an Ornstein-Uhlenbeck (OU) process, a linear model that assumes that the system in question, if left unperturbed, decays exponentially quickly towards a non-equilibrium steady-state characterised by a Gaussian distribution (Godrèche & Luck, 2018). “Non-equilibrium steady-state” means that the probability distribution of states does not change over time, but entropy is nevertheless being produced. An example of this is a system exhibiting a circular flow of information, in which the transition probabilities along the flow are not necessarily uniform (**Figure 6.1b**).

While the assumptions of the OU model may not be biologically plausible – the brain may not ever decay to a steady-state – entropy production, as estimated by the OU model on fMRI data, does robustly correlate with a person’s level of consciousness (Gilson et al., 2023). That is, significantly more entropy is being produced during wakefulness than during deep sleep.

Here, we fit the OU model to the same MEG dataset on LSD that was analysed in *Chapter 5* (R. L. Carhart-Harris et al., 2016). This yields an exact estimate of entropy production under LSD, and the strength of hierarchy in the network fitted by the model can subsequently be measured with trophic coherence.

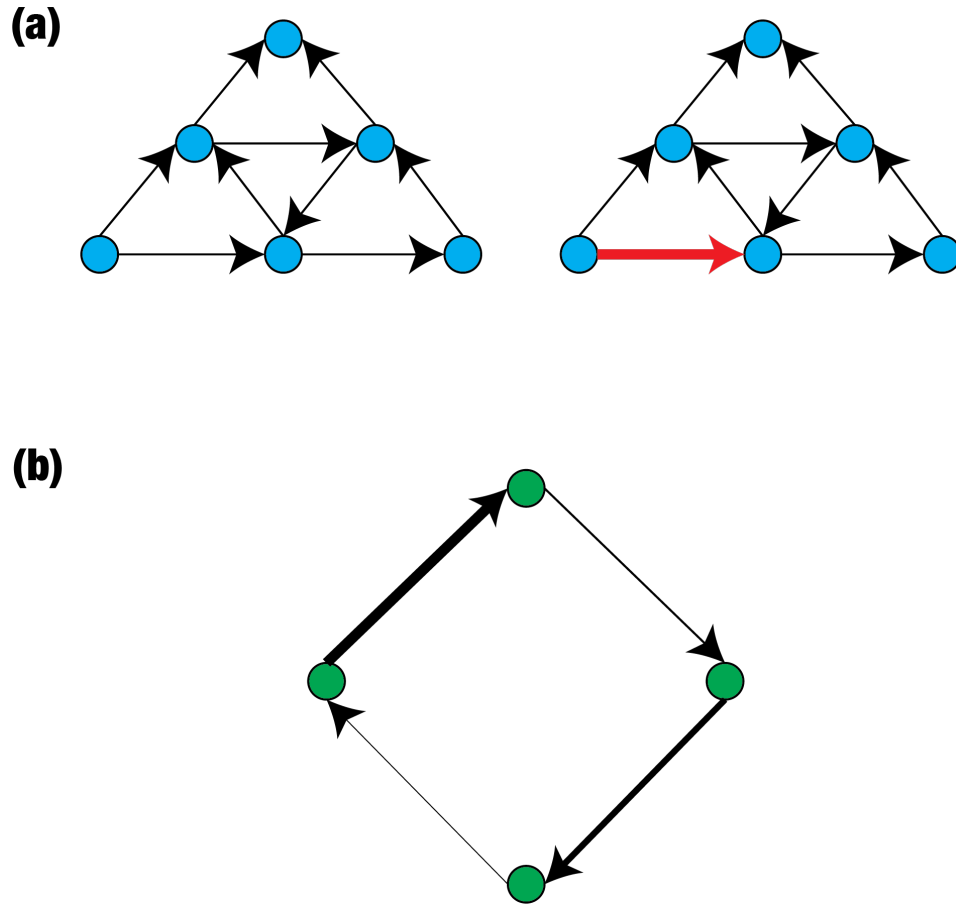


Figure 6.1. Toy models of hierarchy.

(a) The edge shown in red is five times stronger in the right network compared to the left network. Hence, the central node in the lowest layer of the hierarchy becomes more imbalanced. However, the overall network does not seem to become more hierarchical as a result. (b) Example of a hierarchical, non-equilibrium steady-state. Due to the imbalanced flows between the states of the system (represented by the green circles), the system is both not in equilibrium (i.e., irreversible) and hierarchical.

Chapter 6.3. Methods

Chapter 6.3.1. Data acquisition, preprocessing, and source reconstruction

Data acquisition, preprocessing, and source reconstruction are exactly the same as described previously in Chapter 5.3.1 and Chapter 5.3.2. None of the preprocessing or source reconstruction parameters were modified for the OU analysis. We fitted the OU model to the amplitude envelopes of broadband MEG data.

Chapter 6.3.2. The multivariate Ornstein-Uhlenbeck (OU) model

The multivariate OU model is essentially a linear model of brain activity; the formula of the model and all other formulas associated with the methods in this Chapter are given explicitly in Appendix 2. The model has

two components: a deterministic component that describes a linear change in brain activity over time, as well as a stochastic component that describes random fluctuations in brain activity. The deterministic component predicts that the brain decays rapidly to its mean (such a process is described as mean-reverting), whereas the stochastic component ensures that the brain remains in a non-equilibrium state due to fluctuations around the mean. The entropy production is the extent to which the system resists equilibrium due to the stochastic forces. An analytical derivation of the entropy production of the OU model was established by Godrèche & Luck (2018).

To solve entropy production, I fit an order-1 autoregressive model (AR(1) model) to the MEG amplitude envelope timeseries, in which the MEG timeseries at timepoint $t + 45$ is determined as a linear function of the timeseries at t . (Note that we select a time-lag of 45 samples rather than the traditional time-lag of 1 sample in order to ensure consistency with the same time-lag that was used when applying INSIDEOUT in the previous Chapter. While this time-lag results in a worse estimate of the effective network, it is mathematically valid because it is essentially coarse-graining the timescale with which the continuous OU process is being discretised, and the timescale is arbitrary.) The resulting coefficient matrix solves the deterministic component of the model, whereas the covariance of the residuals yields the stochastic component.

Our second goal is to measure trophic coherence on the effective network of directed connections between brain regions. While the coefficient matrix of the AR(1) model is asymmetric and therefore directed, it is not a network *per se*, since self-interactions (interactions between regions and themselves) can affect the dynamics of the network. Thus, I apply a network-constrained variant of the OU model, which was originally introduced by (Schwarze & Porter, 2021). Here, self-interactions are set to zero, and the dynamics are therefore constrained to the edges of a network. Another key difference between the network-constrained OU and the generalised OU is that noise is independently applied to each region of the network in the former, whereas different regions can receive different combinations of noise in the latter. To solve for the network, we perform non-negative least squares optimisation on the timeseries, which constrains the resulting network to strictly non-negative weights. (Trophic coherence can only be solved on networks with exclusively non-negative weights.)

Chapter 6.3.3. Trophic levels and coherence

As mentioned earlier, trophic coherence is determined based on the imbalance between incoming and outgoing connectivity at each node in a directed network, as well as the topology of the network, which is given by the “graph Laplacian.” This is equivalent to the difference between the degree matrix and a diagonal

matrix containing the total weights of all the connections of each node, and the asymmetry between the network and its transpose. Note that this latter quantity is identical to the square root of irreversibility.

The trophic levels can then be determined by solving a linear equation relating each node's imbalance to the graph Laplacian. The trophic coherence is essentially the average weighted difference between trophic levels. It is maximised at 1 when the difference between levels is maximised (also at 1) and minimised at 0 when there are no differences between any of the levels.

Chapter 6.3.4. Hierarchical levels and differences

Based on similar principles, a slightly more recent framework developed the notions of hierarchical levels, in which the “forward” hierarchical levels are defined based on the degrees and graph Laplacians of the incoming connections and the “backward” hierarchical levels are determined based on the degrees and graph Laplacians of the outgoing connections. The mean and standard deviation of the differences between the forward hierarchical levels and backward hierarchical levels reflect the strength of the corresponding hierarchies. Note that the standard deviation of the hierarchical differences is analogous to the trophic coherence.

Trophic levels only model bottom-up activity in the network, i.e., activity directed away from sources (regions with primarily outward edges) and toward sinks (regions with primarily inward edges). However, Moutsinas and colleagues consider both bottom-up and top-down activity in the network by incorporating both “forward” and “backward” hierarchical differences (HD) into their framework. Increases in bottom-up directedness do not necessarily imply decreases in top-down directedness, since, as elucidated by Moutsinas and colleagues, the two types of directedness relate to two different sets of matrices. Additionally, the trophic levels do not have a unique solution in Mackay's framework, though a unique solution can be forced by arbitrarily setting the trophic level of one region in each connected component to zero or some other constant. In Moutsinas' framework, a unique solution is guaranteed by searching for the hierarchical levels with the smallest Euclidean norm, among the set of all possible solutions. Finally, in a strongly connected component, where every region is reachable from every other region, the imbalance vector may be close to zero, which will cause the trophic levels of the regions within the component to be nearly identical to each other. Therefore, MacKay's solution cannot differentiate between the trophic levels of nodes within the same strongly connected component (Moutsinas et al., 2021). However, Moutsinas' framework uses the in- and out-degree of the network, which are typically not close to zero and therefore not susceptible to the same problem.

For these reasons, I measured hierarchical levels rather than trophic levels. (I introduced Mackay's framework as a steppingstone to Moutsinas' work, which is more comprehensible in light of the former.) In

particular, I compute the forward hierarchical levels, the backward hierarchical levels, the weighted mean of the forward HD, the standard deviation of the forward HD, the weighted mean of the backward HD, and the standard deviation of the backward HD.

Chapter 6.3.5. Statistical analyses

For Φ and all of the scalar hierarchical metrics, I fit a linear mixed-effects model with drug and condition as fixed effects and subjects as random effects. Region was included as an additional fixed effect for the forward and backward hierarchical levels. In all the models, Satterthwaite’s method was used to approximate the effective degrees of freedom for F -tests of fixed effects. I performed exploratory post-hoc Tukey’s tests for multiple comparisons, even when there was no significant interaction effect.

Additionally, Φ and all the scalar hierarchical metrics were measured both with and without normalising the MEG timeseries. The MEG timeseries on LSD have a much smaller standard deviation, so we wanted to ensure that changes in entropy production and hierarchical levels were not simply attributable to differences in scale between the datasets.

Chapter 6.4. Results

Chapter 6.4.1. LSD significantly reduces entropy production

My analysis revealed a significant main effect of drug on entropy production ($F_{1,105} = 48.94, p < 0.0001$) and a significant main effect of condition ($F_{3,105} = 136.50, p < 0.0001$), but an insignificant interaction effect between drug and condition ($F_{3,105} = 1.11, p = 0.3456$). In particular, LSD was associated with significantly lower entropy production than placebo (**Figure 6.2a**). Exploratory post-hoc tests identified a significant difference between LSD and placebo for all four of the conditions ($p_{\text{Open}} < 0.0081, p_{\text{Closed}} = 0.0024, p_{\text{Music}} < 0.0001, p_{\text{Video}} = 0.0023$). Under both placebo and LSD, the two stimulus conditions, Music and Video, both caused significantly more entropy production than each of the two resting-state conditions, Open and Closed (**Figure 6.2b**). Music produced significantly more entropy than Video on placebo but not on LSD.

However, it is worth noting that this effect only held when we used a time-lag of 45 samples (0.225 seconds) to perform an autoregression on the data. When we used the traditional time-lag of just 1 sample (0.005 seconds), there was a significant increase in entropy production on LSD ($F_{1,105} = 5.1824, p = 0.0249$), albeit still no significant interaction effect between drug and condition ($F_{3,105} = 1.7540, p = 0.1605$) and no significant main effect of condition ($F_{3,105} = 2.1601, p = 0.0971$). Exploratory post-hoc tests demonstrated that LSD induces significantly more entropy production than placebo in the Closed condition ($p_{\text{Closed}} = 0.0053$), but not in the other conditions ($p_{\text{Open}} = 0.8538, p_{\text{Music}} = 0.1514, p_{\text{Video}} = 0.6596$). The disparity between

the results associated with the different time-lags is consistent with INSIDEOUT, where we observed that LSD significantly increases irreversibility at a time-lag of 1 sample but significantly decreases irreversibility for time-lags of greater than 4 samples.

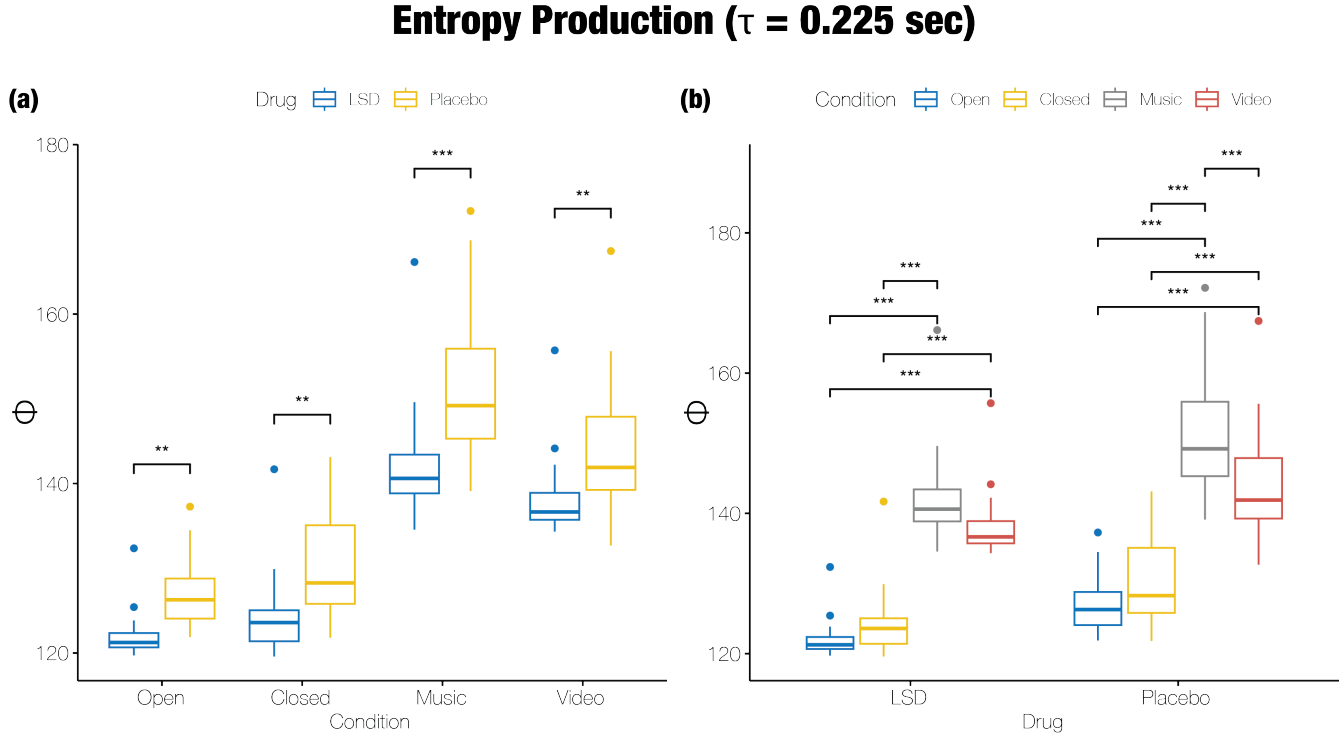


Figure 6.2. LSD significantly decreases entropy production (Φ) across all experimental conditions.

Φ was determined by fitting a generalised multivariate Ornstein-Uhlenbeck (OU) model to the amplitude envelopes of the MEG data. The model assumes that the brain decays to a non-equilibrium steady-state, in which entropy is produced by stochastic Gaussian fluctuations. (a) groups the data by drug, whereas (b) groups the data by condition. It is clear from (b) that the stimulus conditions, Music and Video, induce much more entropy production than the resting-state conditions, Open and Closed, under both placebo and LSD.

Chapter 6.4.2. LSD significantly decreases both the mean and standard deviation of forward and backward HD

As stated above, we identified both forward and backward HD, corresponding to bottom-up and top-down connectivity, respectively, from the effective network that was fitted to the OU model. LSD significantly reduced the mean of forward HD ($F_{1,105} = 35.8240$, $p < 0.0001$), though there was an insignificant interaction effect between drug and condition (**Figure 6.3a**). According to exploratory post-hoc tests, mean forward HD was lower under LSD in all four conditions ($p_{\text{Open}} = 0.0298$, $p_{\text{Closed}} = 0.0194$, $p_{\text{Music}} = 0.0028$, $p_{\text{Video}} < 0.0001$). The standard deviation of forward HD was also significantly decreased on LSD ($F_{1,105} = 25.9748$, $p < 0.0001$), though there was no significant interaction effect between drug and condition (**Figure 6.3b**).

Exploratory post-hoc tests demonstrated that the decrease was significant for the Open, Music, and Video conditions and trending towards significance for the Closed condition ($p_{\text{Open}} = 0.0186$, $p_{\text{Closed}} = 0.0634$, $p_{\text{Music}} = 0.0065$, $p_{\text{Video}} = 0.0021$).

LSD also significantly lowered the mean of backward HD ($F_{1,105} = 25.0757$, $p < 0.0001$), though the between-drug differences in only the Open and Video conditions reached statistical significance ($p_{\text{Open}} = 0.0007$, $p_{\text{Closed}} = 0.0519$, $p_{\text{Music}} = 0.0621$, $p_{\text{Video}} = 0.0088$) (**Figure 6.3c**). The same main effect of LSD was observed for the standard deviation of backward HD ($F_{1,105} = 10.0555$, $p = 0.0020$), but only the Open condition was significantly different between LSD and placebo ($p_{\text{Open}} = 0.0035$, $p_{\text{Closed}} = 0.1709$, $p_{\text{Music}} = 0.7094$, $p_{\text{Video}} = 0.1132$) (**Figure 6.3d**).

Hierarchical Differences (HD)

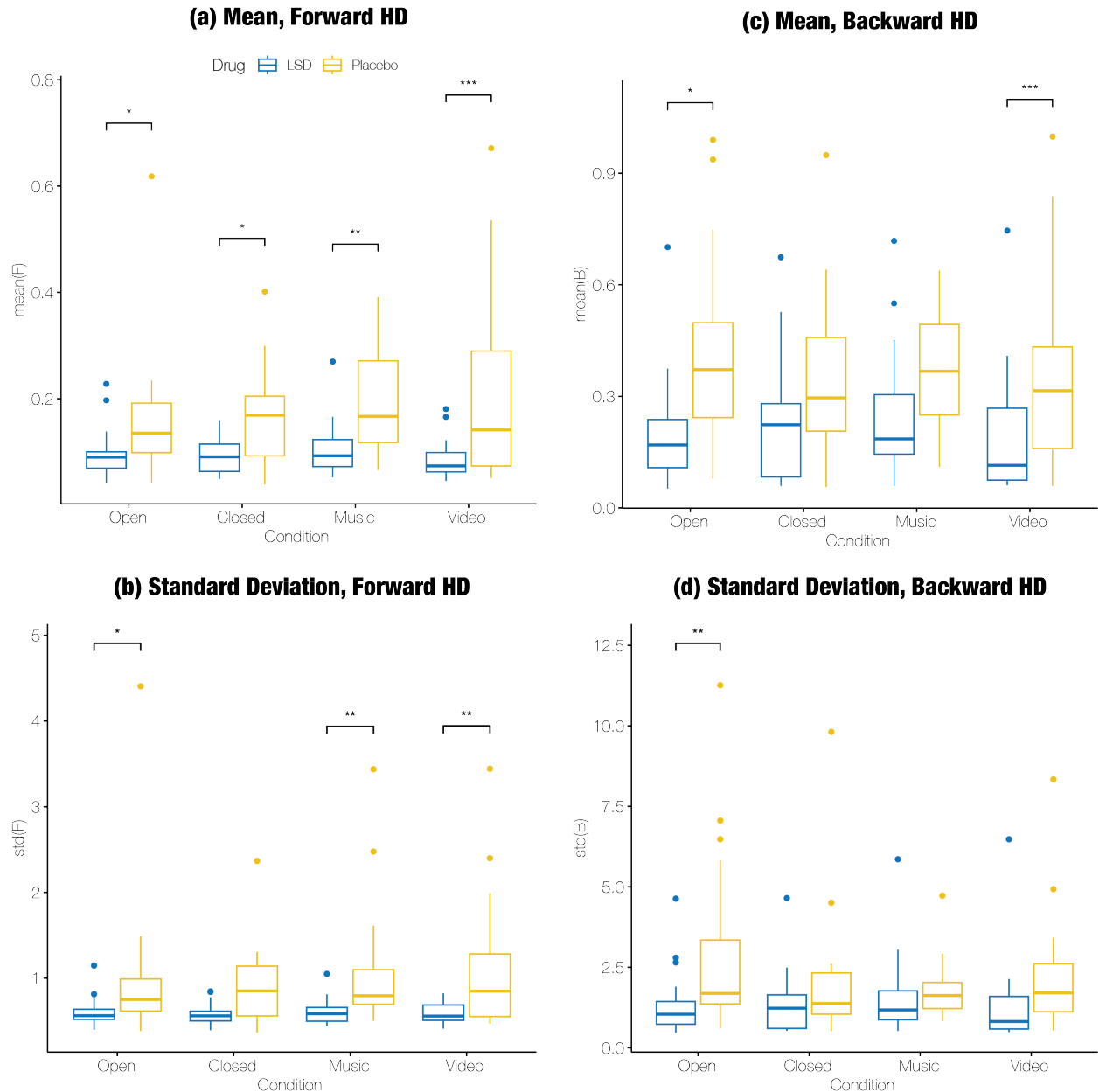


Figure 6.3. LSD significantly reduces both the mean and standard deviation of both forward and backward hierarchical differences (HD).

The hierarchical level of a region reflects the extent to which that region causes imbalances in the connectivity of other regions. Regions with high forward hierarchical levels “pull” incoming connectivity toward themselves, away from other regions. On the other hand, regions with large backward hierarchical levels “push” outgoing connectivity away from themselves, toward other regions. HD are the differences between the hierarchical levels of each pair of regions. The mean HD is the average separation between levels, weighted by the strength of the corresponding edges in the network, and the standard deviation of the HD is the spread of this separation.

Chapter 6.4.3. LSD reduces the forward hierarchical levels of non-visual regions and backward hierarchical levels of visual regions

For the forward hierarchical levels, we identified a significant main effect of drug ($F_{1,10785} = 545.1460, p < 0.0001$), condition ($F_{3,10785} = 2.7211, p = 0.0428$), and region ($F_{89,10785} = 2.0970, p < 0.0001$), as well as a significant drug by region interaction ($F_{89,10785} = 1.5936, p = 0.0003$). Post-hoc tests showed that between-drug differences in forward hierarchical levels of regions varied by the experimental condition, despite no significant interaction effect between region, drug, and condition (**Figure 6.4; Figure 6.5**). All significant regional differences were decreases on LSD. Across conditions, the regions that exhibited significant reductions in forward hierarchical levels spanned a distributed set of cortical networks. These predominantly encompassed the SMN, FPN, DMN, and limbic network for the Open and Closed conditions. This set of networks expanded to include the VAN for both the Music and Video conditions. With the exception of the fusiform gyrus, which is involved in higher-order visual processing such as face recognition (Kanwisher & Yovel, 2006), the visual network was conspicuously absent from the Open, Closed, and Music conditions. Only in the Video condition did lower-order areas in the visual network, such as the Left Calcarine Fissure, where the primary visual cortex (V1) is located, and the Right Cuneus, significantly differ between LSD and placebo.

LSD also significantly lowered the backward hierarchical levels (**Figure 6.6; Figure 6.7**). There was a significant main effect of drug ($F_{1,10785} = 108.0319, p < 0.0001$), condition ($F_{3,10785} = 23.2628, p < 0.0001$), and region ($F_{89,10785} = 11.1835, p < 0.0001$), in addition to a significant drug by condition interaction ($F_{3,10785} = 18.2440, p < 0.0001$) and a significant drug by region interaction ($F_{89,10785} = 1.6444, p = 0.0001$). Unlike for the forward hierarchical levels, the visual network comprised the majority of the regions that exhibited significant decreases in backward hierarchical levels in the Closed and Music conditions, as well as a plurality in the Open and Video conditions. These regions were primarily lower-order areas that contain parts of V1-V3, such as the Left and Right Calcarine Fissure, the Right Cuneus, the Left Lingual Gyrus, as well as other areas involved in colour processing such as the Left and Right Inferior Occipital Gyrus (Allison et al., 1993). Intriguingly, in the Video condition, there were three regions that showed significant reductions in both forward and backward hierarchical levels, namely the Right Precentral Gyrus, Right Cuneus, and Right Precuneus. A handful of regions underwent a significant increase in backward hierarchical levels under LSD, including the Left Middle Occipital Gyrus in the Open condition, the Left Fusiform Gyrus and Right Angular Gyrus in the Closed condition, and the Right Fusiform Gyrus and Left and Right Inferior Parietal Gyrus in the Music condition.

Forward Hierarchical Levels (HL)

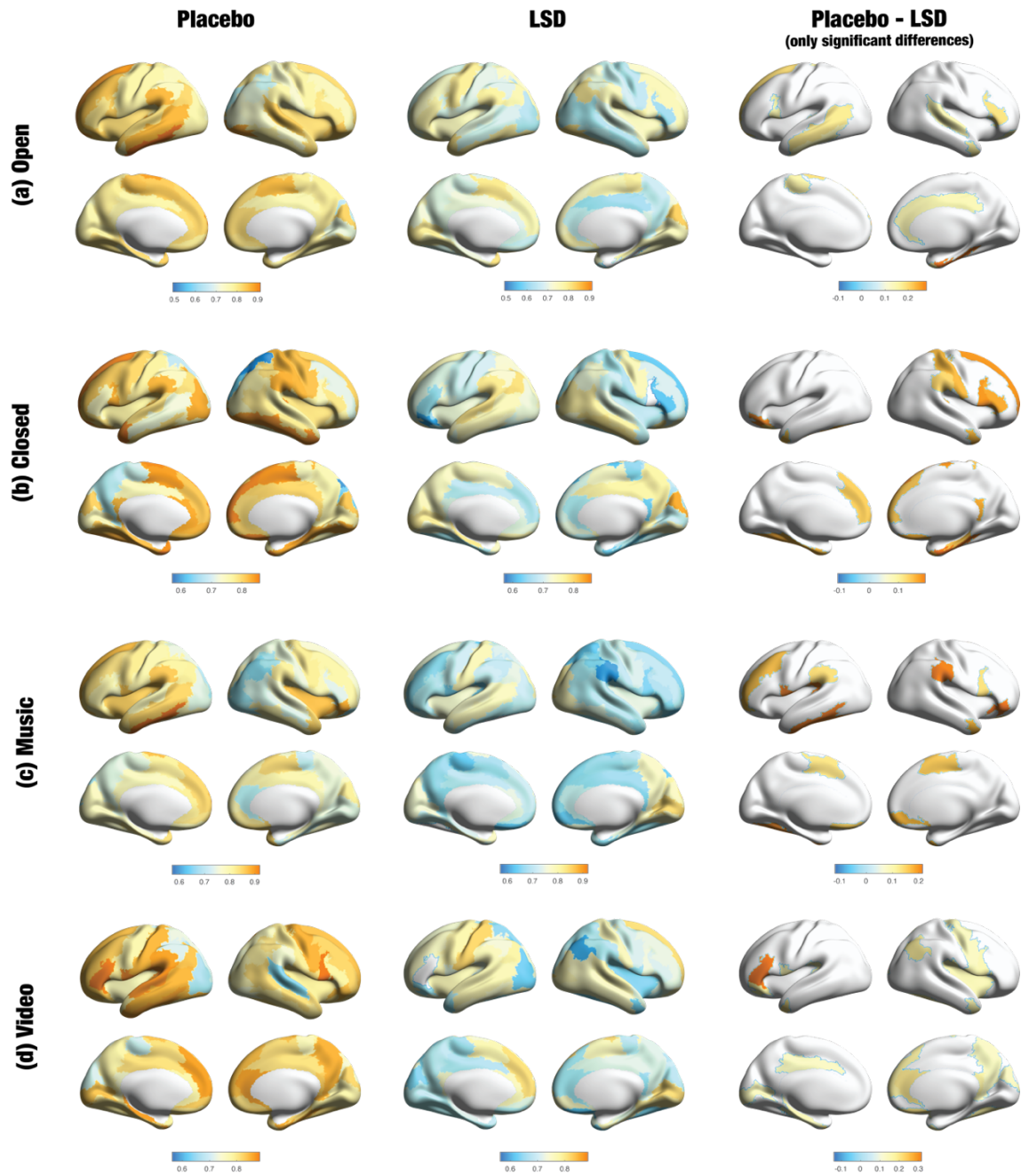


Figure 6.4. LSD significantly lowers the forward hierarchical levels (HL) of regions in associative networks and the somatomotor network.

By comparing the placebo and LSD columns, it is clear that LSD reduces both the forward HL and the spread of the forward HL; the distance between small HLs and large HLs is lower on LSD. For the Open, Closed, and Music conditions, significant decreases in forward HLs (orange colours) took place in all brain networks except the dorsal attention network and the visual network, suggesting that regions in primarily higher-order, associative networks, as well as the somatomotor network, receive fewer incoming connections under LSD. (Note that, for the placebo and LSD columns, the colour bars are the same within each condition.)

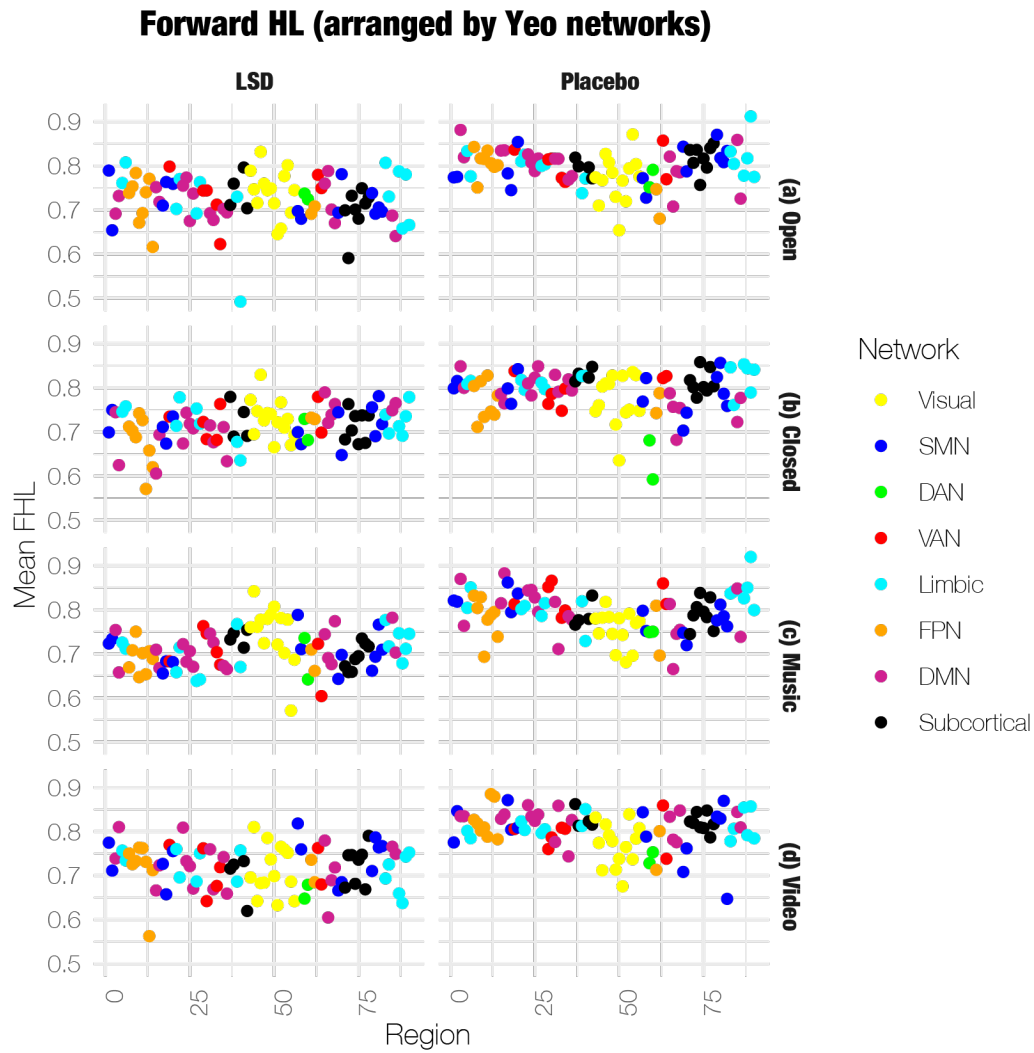


Figure 6.5. *Alternative representation of Figure 6.4, in which each region is coloured according to the Yeo network that it is part of.*

The forward hierarchical levels evidently decrease on LSD across networks, except for the visual network, whose hierarchical levels are relatively similar between drugs except in the Video condition. On both placebo and LSD, there is no single Yeo network that clearly rests above or below the others in the forward hierarchy.

Backward Hierarchical Levels (HL)

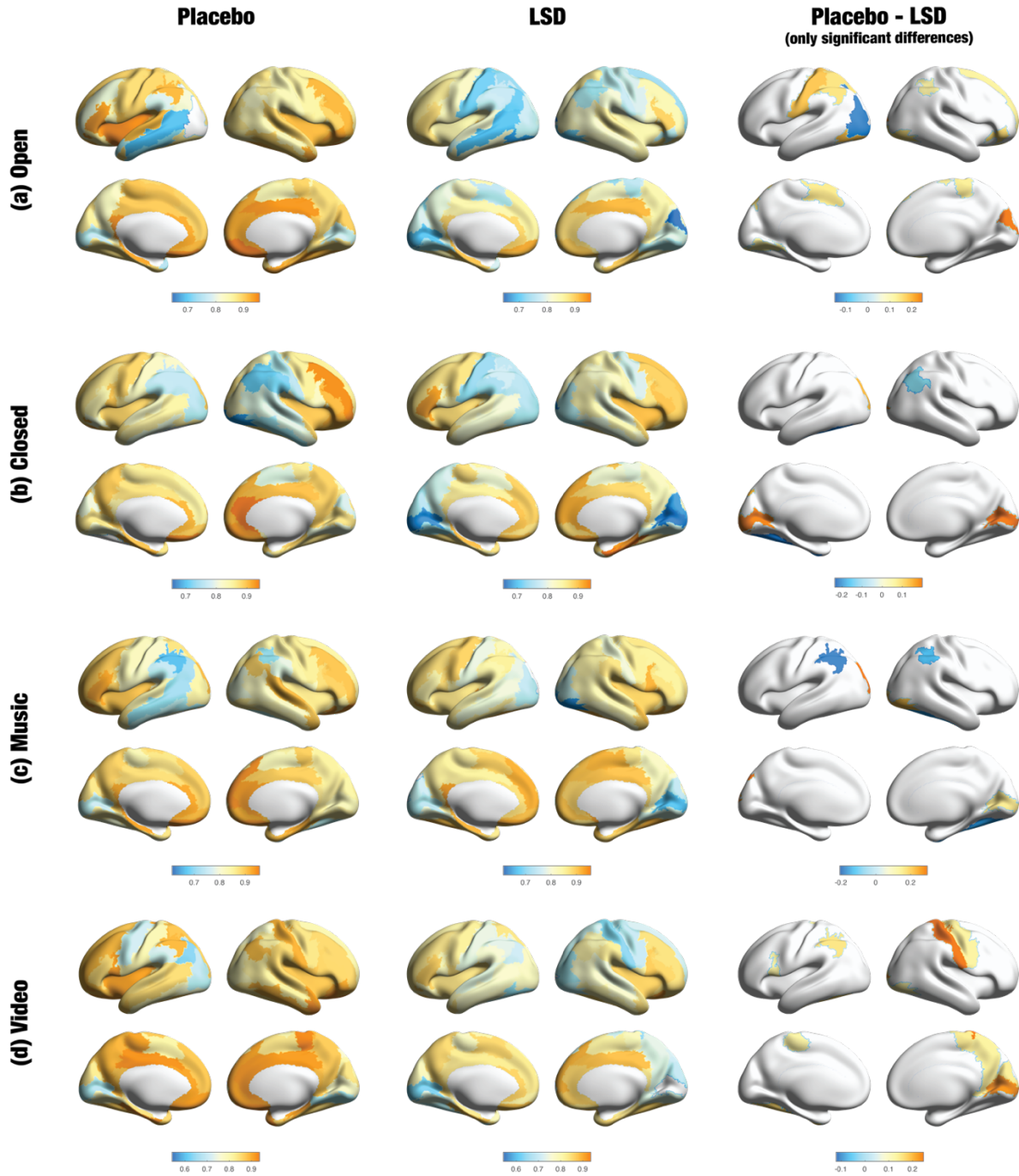


Figure 6.6. Significant reductions in backward hierarchical levels (HL) on LSD primarily occur in regions within the visual network.

Decreases in backward HL are less apparent than in forward HL, particularly for the Closed and Music conditions. Whereas LSD significantly affected forward HL in all networks except the visual network, LSD predominantly reduced backward HL in only the visual network (orange colours). Some significant increases in backward HL (coloured in blue, right column) were observed in parietal and occipital regions.

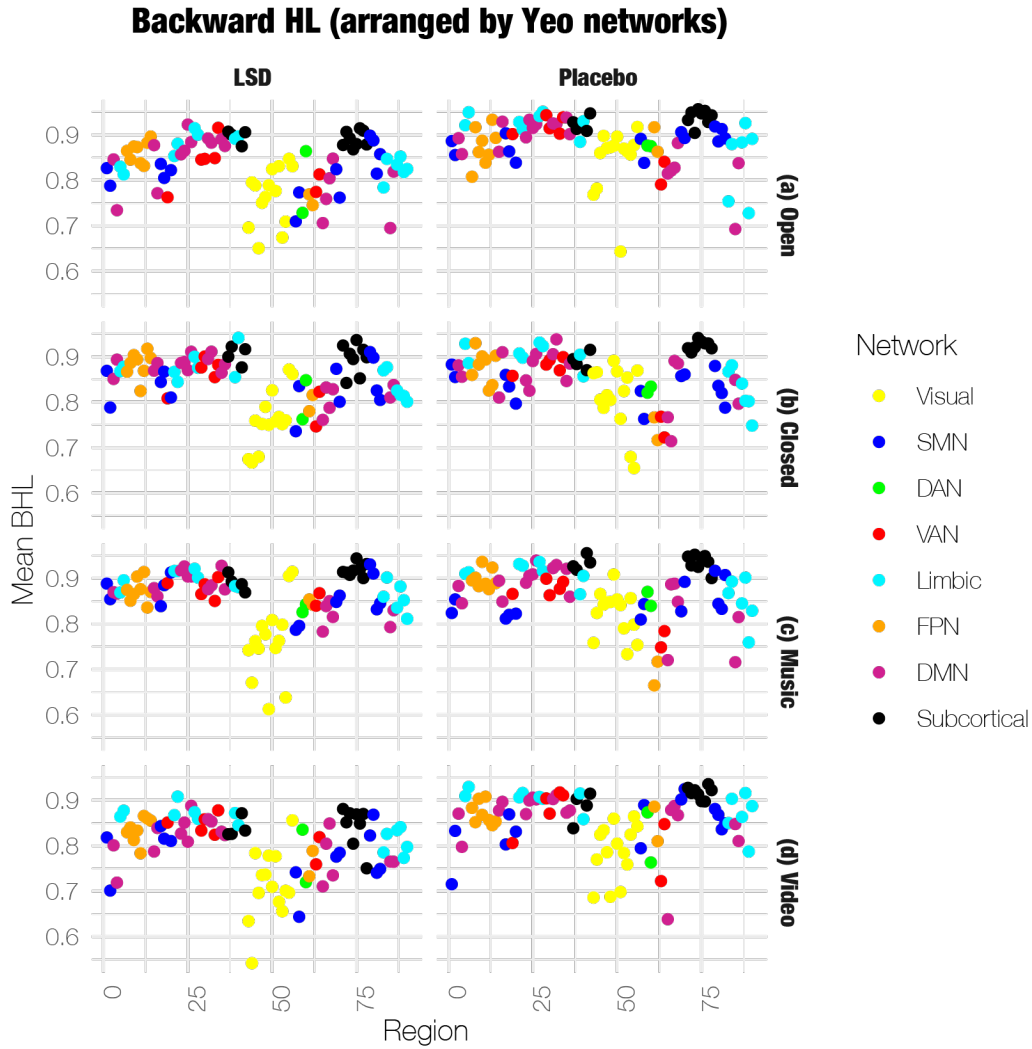


Figure 6.7. *Alternative representation of Figure 6.6, in which each region is coloured according to the Yeo network that it is part of.*

Unlike with the forward HL, there are some networks that have much lower backward HL than others under both placebo and LSD. In both drug conditions, these regions belong to multiple different networks, though the visual network appears to have the lowest backward HL. The network with the largest decrease in backward HL under LSD is the visual network. Intriguingly, subcortical regions always rank very highly in the backward hierarchy.

Chapter 6.5. Discussion

Chapter 6.5.1. Consistencies between entropy production and irreversibility

Unlike INSIDEOUT, which is an indirect measure of entropy production, the model presented in this chapter, the OU process, analytically solves the amount of entropy production in the brain. The OU process assumes that macro-scale brain activity is linear and decays to a non-equilibrium, Gaussian steady-state. The decay is deterministic, whereas the steady-state Gaussian fluctuations are stochastic and produce entropy.

(Without the Gaussian fluctuations, the brain would be in equilibrium.) By exploiting the properties of Gaussian distributions, the model precisely defines irreversibility based on the divergences between the deterministic and stochastic dynamics. The entropy production Φ is then a function of the irreversibility, deterministic decay, and stochastic fluctuations.

My application of the model to MEG data on LSD revealed that the drug significantly reduces entropy production across all four experimental conditions. This result agrees with INSIDEOUT, with which I found that LSD significantly decreases irreversibility across conditions. Furthermore, fitting the OU model shows that LSD only reduces entropy production when a time-lag of 45 samples (0.225 seconds) is used to estimate the deterministic aspect of brain activity, whereas a time-lag of 1 sample (0.005 seconds) yields a significant increase in entropy production on LSD for the Open and Closed conditions. Similarly, with INSIDEOUT, LSD increases irreversibility at time-lags lower than 4 samples (0.02 seconds). At low time-lags, MEG timeseries are dominated by autocorrelations, which may yield biased estimates of entropy production (Dean & Dunsmuir, 2016).

INSIDEOUT and the OU model do diverge in at least one key respect. Applying INSIDEOUT revealed that the eyes-closed conditions (Closed and Music) were more irreversible than the eyes-open conditions (Open and Video) under placebo. (On LSD, Music was still the most irreversible, but Video became significantly more irreversible than Closed.) In the OU model, the *stimulus* conditions (Music and Video) clearly produced much more entropy than the resting-state conditions (Open and Closed), under both placebo and LSD. This suggests that visual perception constrains the irreversibility of brain activity, whereas lack of sensory stimulation constrains entropy production. It is known that higher-order networks, such as the VAN, decrease their connectivity with the visual network and increase their connectivity with other associative networks when eyes are closed, relative to when eyes are open (Agcaoglu et al., 2019; Han et al., 2023). In other words, feedback connectivity from higher-order networks to the visual network may be stronger when the eyes are open, thereby balancing out feedforward connectivity from the visual network and reducing irreversibility. On the other hand, entropy production in the OU model is determined by spontaneous, stochastic fluctuations that cause the brain to depart from constant activity. Spontaneous fluctuations correlate with the ability to detect external stimuli (Schölvinck et al., 2012) and encode the brain's prior expectations about stimuli in the environment (Berkes et al., 2011). Thus, spontaneous fluctuations are likely to be higher during stimulus presentation than during resting-state, which leads to greater entropy production (Northoff et al., 2023).

Chapter 6.5.2. Consistencies between measures of hierarchy

Because irreversibility, as measured with INSIDEOUT, does not always reflect the strength of hierarchy, I defined two novel measures in *Chapter 5* that are better estimators of hierarchy, namely hierarchical coherence and inhomogeneity. These are the mean and standard deviation of the imbalance between incoming and outgoing connections at each region. Hierarchical coherence and inhomogeneity are similar to the mean and standard deviation of forward/backward hierarchical differences, as estimated in this Chapter. Hierarchical coherence/inhomogeneity and irreversibility were presented as separate metrics in *Chapter 5*, whereas the work in this Chapter goes a step further by explicitly linking them together. In particular, hierarchical levels are solved through equations that relate the Laplacian to the imbalance between incoming and outgoing connections at each region (Mackay et al., 2020). The Laplacian is a matrix that subtracts the degrees of the network from its irreversibility. The squared mean of the imbalance vector is essentially the same as hierarchical coherence, while the standard deviation is essentially identical to hierarchical inhomogeneity. In other words, the hierarchical levels are optimised such that the differences between them, weighted by the irreversibility across all edges, closely matches the incoming-outgoing imbalance at each node. Therefore, there is a direct correspondence between the quantities in this framework and the metrics of hierarchy that I applied and developed in *Chapter 5*. My observation that LSD significantly decreases the mean and standard deviation of both the forward and backward hierarchical differences is consistent with the previous finding that LSD significantly reduces hierarchical coherence and inhomogeneity.

However, whereas hierarchical coherence and inhomogeneity were significantly lower in all conditions on LSD, between-drug differences for the mean and standard deviation of backward hierarchical differences were only significant for some of the conditions (Open and Video for the former, Open only for the latter). Open and Video are the two eyes-open conditions, and the regions that exhibited significant reductions in hierarchical levels were primarily in the visual network. Understandably, the decreases of these regions tended to be greater for the eyes-open conditions (particularly Open) than for the eyes-closed conditions. LSD significantly altered the hierarchical levels of more frontal regions in the Open condition compared to the Video condition, perhaps due to increased mind-wandering during the resting-state compared to passive video-watching. These frontal regions are situated higher in the backward hierarchy, which could explain why only the Open condition significantly lowered the standard deviation of backward hierarchical differences.

Another key difference between hierarchical coherence/inhomogeneity and the metrics of hierarchy presented in this Chapter is that the former do not distinguish between bottom-up and top-down connectivity. Hierarchical coherence and inhomogeneity only reflect the (unsigned) magnitude of the imbalance between incoming and outgoing connectivity. If this value is reduced for a particular region, it is

unclear whether that decrease is attributable to a change in incoming or outgoing connections or both. However, forward and backward hierarchical differences specify different directions of connectivity. Hence, we observe that a very different set of regions exhibit significant alterations in backward hierarchical levels, compared to forward hierarchical levels. In particular, under LSD, backward hierarchical levels are predominantly decreased for areas in the visual network, whereas forward hierarchical levels are lowered for all other networks. In other words, visual regions transmit fewer outgoing connections, while regions in higher-order networks receive fewer incoming connections.

While the result regarding the visual network may appear to be inconsistent with multiple studies demonstrating that the acute psychedelic state enhances connectivity between visual areas and the whole brain (R. L. Carhart-Harris et al., 2013, 2016; Dai et al., 2023; Madsen et al., 2021; Mason et al., 2020; F. Müller, Lenz, Dolder, Lang, et al., 2017; F. Müller, Dolder, et al., 2018; Preller, Burt, et al., 2018; Preller et al., 2020; Roseman et al., 2014; Timmermann et al., 2023), these studies only examined *undirected* functional connectivity. Undirected FC yields opposite results than directed FC; according to one study, LSD increases undirected FC while decreasing directed FC, as measured with Granger causality (Barnett et al., 2020). A handful of studies have applied other directed measures, namely dynamic causal modelling (Bedford et al., 2023; Kaelen et al., 2016; Kraehenmann, Schmidt, et al., 2015) and travelling waves (Alamia et al., 2020; Timmermann et al., 2023), to assess connectivity between the visual network and other brain areas. Only one of the DCM studies modelled connectivity across the whole brain rather than selecting a handful of regions (Bedford et al., 2023). It reported that LSD significantly decreased effective connectivity between occipital regions, while it apparently increased effective connectivity from frontal areas toward occipital cortices. This finding is consistent with decreased backward hierarchical levels, yet no significant change in forward hierarchical levels, among areas in the visual network.

The travelling waves approach is particularly relevant to this Chapter because it extracts waves travelling from the posterior side to the anterior side of the brain (forward waves) and from the anterior side to the posterior side (backward waves). Both studies measuring travelling waves under DMT showed that the drug significantly enhances the power of forward waves while diminishing the power of backward waves. While this result substantiates REBUS' hypothesis, it is incongruent with my findings, as explained in more detail below.

Chapter 6.5.3. Implications for REBUS

The findings in this Chapter regarding hierarchy both support and challenge REBUS. On the one hand, reductions in the mean and standard deviation of forward and backward hierarchical differences is consistent with REBUS' claim that psychedelics flatten brain hierarchy. On the other hand, the observation that LSD

decreases outgoing connections from visual areas and provides evidence against REBUS' hypothesis about the direction of information flow under psychedelics. In particular, REBUS proposes that psychedelics “liberate” or amplify bottom-up information flow while subduing the inhibitory effect of top-down information flow (Carhart-Harris & Friston, 2019). Augmenting bottom-up information flow would imply that LSD enhances the forward hierarchical levels of higher-order regions. Suppressing top-down information flow would entail a decrease in the backward hierarchical levels of higher-order regions. These effects on the hierarchical levels would be consistent with the finding that DMT enhances and inhibits forward and backward travelling waves, respectively (Alamia et al., 2020; Timmermann et al., 2023).

However, I found that LSD *diminishes* the forward hierarchical levels of associative networks and backward hierarchical levels in the visual network. Lower backward hierarchical levels among visual areas imply that less information flows *away* from those areas. Lower forward hierarchical levels among higher-order areas indicate that less information flows *towards* those areas. The most parsimonious explanation of these results, taken together, is that LSD reduces the information flow from visual areas towards higher-order regions, rather than elevating it as REBUS hypothesises. There is not enough evidence to make conclusions about the effect of LSD on top-down connectivity, i.e., from associative networks to visual areas.

This result does not directly refute REBUS but rather refines its core argument. REBUS is predicated on the predictive coding model of the brain; this claims that top-down, “descending” predictions about the environment are updated based on a combination of prior beliefs, or “priors,” and bottom-up, “ascending” prediction errors, or sensory information that clashes with the predictions (Picard & Friston, 2014). Both the priors and the sensory information are weighted by their precision, which corresponds to confidence (K. Friston et al., 2011). When the precision-weighting of sensory information is low, then perception reflects the priors.

Let us assume that the feedforward information flow estimated through our model reflects the ascending prediction errors. (Admittedly, this may be an incorrect assumption because our model does not explicitly link bottom-up connectivity to prediction errors and top-down connectivity to predictions.) Weakened feedforward connections suggest that visual areas may provide attenuated prediction error signals to higher-order regions, thereby compromising their ability to update their predictions in light of new sensory data.

This explains three phenomena in psychedelics. Firstly, decoupling of predictions from prediction errors plausibly causes hallucinations on psychedelics; indeed, a dampening of normal prediction error signaling gives rise to hallucinations in conditions such as schizophrenia (Horga et al., 2014; McCleery et al., 2018; Nazimek et al., 2012; Northoff & Qin, 2011). Rather than adjusting their perception to match their sensory inputs, schizophrenic patients perceive their priors about the environment. According to REBUS, psychedelic hallucinations modify the precision-weighting of priors rather than the prediction errors (R. L.

Carhart-Harris & Friston, 2019; Rajpal et al., 2022), yet a reduction in the precision-weighting of prediction errors would be more consistent with the decreased feedforward information flow.

Secondly, psychedelics are known to attenuate mismatch negativity (MMN), or the brain’s response to deviant stimuli after a series of identical stimuli are presented (Duerler et al., 2021; Timmermann et al., 2018; Umbricht et al., 2003). Psychedelics also impair the ability to adapt to the environment, as observed in very simple “Go/No-Go” paradigms in which people have to adapt their actions (i.e., pressing a button) according to the instructions of the task (i.e., “press” or “do not press” the button) (A. Schmidt et al., 2018). Both of these phenomena suggest that psychedelics diminish prediction error signaling. The MMN is thought to directly encode the amount of prediction error when the unexpected, deviant stimulus is shown (Fong et al., 2020; Kirihara et al., 2020). Failure to adapt indicates an inability to act in a manner that resolves prediction errors, which raises the possibility that the prediction errors failed to reach or influence the top-down predictions (Marko et al., 2012). Diminished feedforward information flow from sensory and motor areas could be the mechanism that leads to impaired prediction error signaling, giving rise to blunted mismatch negativity and adaptation.

Thirdly, some of the experiences that characterise the altered state of consciousness on psychedelics could be recast as abnormal prediction error signaling. For instance, psychedelics lead to feelings of radical interconnectedness, which arise from a blurring of the boundary between self and other (Buchborn et al., 2023). Recent research has demonstrated that neural circuits in the brain encode different sets of sensory prediction errors for different people, and furthermore that the agent-specificity of these circuits can adapt to changes in social context (Ereira et al., 2018, 2020). In particular, when two people share similar experiences, the circuits encoding self-attributed prediction errors and those encoding other-attributed prediction errors overlap to a greater extent (Ereira et al., 2020). I speculate that psychedelics may cause total overlap between these circuits by maximising the uncertainty, or minimising the precision-weighting, of the agent (self or other) to which prediction errors can be attributed. Weaker feedforward connections may result in weaker signals of – and therefore greater ambiguity about – whether prediction errors are internally or externally generated.

Chapter 6.6. Chapter summary

Here, I fit a model for which entropy production can be exactly derived. In this model, entropy production reflects the extent to which the brain diverges from equilibrium due to stochastic Gaussian fluctuations. In line with the INSIDEOUT results, I observe that LSD significantly decreases entropy production. Furthermore, in agreement with previous work demonstrating that entropy production is driven by the directedness of brain connectivity (Nartallo-Kaluarachchi et al., 2024), the network fitted by the model is

significantly less hierarchical under LSD. Previous work only examined the relationship between entropy production and bottom-up connectivity, whereas here I demonstrate that LSD significantly reduces both top-down connectivity and bottom-up connectivity. Whereas the regions that exhibited decreases in forward hierarchical levels extended across a range of higher-order, transmodal networks, as well as the SMN, the regions with lower backward hierarchical levels on LSD were primarily in the visual network. That is, the visual network transmits fewer outgoing connections on LSD, while transmodal networks receive information through a smaller number of incoming connections.

Chapter 7. Conclusion

Chapter 7.1. Grand summary

The research presented in this thesis has two aims: (1) to systematically review and meta-analyse the literature about psychedelics, on three levels of analysis: phenomenology, neuroimaging, and pharmacology; (2) to test the ability of a leading framework, RELaxed Beliefs Under pSychedelics (REBUS), to unify these three levels of analysis (R. L. Carhart-Harris & Friston, 2019).

My work on the first aim has two main takeaways. Firstly, there are large between-drug differences within some levels but not others. At the level of neuroimaging, DMT, LSD, and psilocybin exhibit distinct functional connectivity profiles; DMT and psilocybin affect FC more in the DMN than other networks, whereas LSD displays a more homogeneous FC profile. LSD increases connectivity between the visual network and other networks, but massively reduces FC within the visual network.

However, at the level of pharmacology, I discovered no significant differences between psychedelics in their relative binding affinity for the 5-HT_{2A}, 5-HT_{2C}, and D₂ receptors, though LSD did differ significantly from DMT and psilocybin in another measure of pharmacology, namely functional activity at the inositol phosphate formation pathway. The lack of significant differences may be attributed to the large between-study variability in binding affinity data.

Similarly, there were also relatively few significant differences in ratings of phenomenology. While LSD was generally associated with higher ratings than psilocybin on all five dimensions of subjective experience measured by the 5D-ASC scale, these comparisons only reached significance in the visionary restructuralisation (VR) dimension for medium and high doses and in the oceanic boundlessness (OB) dimension for medium doses. (VR corresponds to the quality and intensity of visual hallucinations, whereas OB captures feelings of unity and spiritual insight.) The “phenomenology profiles” of the three psychedelics – the set of brain networks that encode their subjective experiences – are nearly identical.

Thus, the phenomenology and pharmacology of DMT, LSD, and psilocybin are relatively similar, but the fMRI data is more varied across psychedelics. The classical psychedelics share similar pharmacological profiles – they all bind to the 5-HT_{2A} receptor as their primary mechanism of action – so it is unsurprising that the pharmacology meta-analysis revealed few significant differences. Additionally, when administered LSD and placebo in double-blind experiments, participants are unable to tell the difference between the two based on their subjective experiences of the drugs (Ley et al., 2023). However, the fMRI data is notoriously variable across experiments, with few consistent findings other than desegregation (enhanced between-network connectivity) and disintegration (reduced within-network connectivity) (Girn et al., 2023). Additionally, fMRI captures brain activity continuously, whereas phenomenological ratings and

pharmacological assays are static. More studies with larger sample sizes are needed to confirm that LSD decreases within-network FC more than psilocybin and DMT/ayahuasca, as we found in this meta-analysis. Analyses of MEG data on LSD and psilocybin do substantiate the conclusions of the neuroimaging meta-analysis; specifically, LSD strongly increases undirected FC within the occipital cortex, whereas psilocybin diminishes it, though both of these results are statistically insignificant (Barnett et al., 2020).

How could the phenomenology and pharmacology profiles of the three psychedelics be similar, while the neuroimaging profiles are different across drugs? While the psychedelics may not be significantly different in their affinities for the 5-HT_{2A} receptor, they may trigger distinct signalling pathways. In fact, our finding that LSD induces significantly more IP formation, a marker of G_q signalling, than DMT and psilocin at the 5-HT_{2A} receptor provides evidence for this claim. The relationship between these signalling pathways, which take place at the cellular level in the brain, and whole-brain fMRI recordings is extremely complex, but it is certainly plausible that different pathways can lead to divergent patterns of resting-state network connectivity, even when the drugs share similar affinities for the same receptor. Why do distinct FC patterns give rise to nearly identical phenomenology profiles? My explanation for this is that the current questionnaires do not ask nuanced questions about the subjective experience of psychedelics. They probe participants about very abstract, generalised categories of experience like the ego and the boundary between self and other. If participants had to pay attention to more subtle aspects of subjective experience, like the precise geometric forms of the visual hallucinations, then they may be able to notice a stronger difference between LSD and psilocybin. With improved questionnaires, I expect we will see greater distinctions between the phenomenology profiles of the three psychedelics. Regardless of whether the scales are improved, there are fundamental limitations to phenomenological reports: people may use the same words to refer to very different subjective phenomena, and there is no standardised method of rating experiences. For instance, one person's "10/10" euphoria on psychedelics may actually be the same intensity as another person's "5/10" experience. It is also possible that experiences on the various psychedelics are so diverse across individuals that they are, in fact, phenomenologically indistinguishable at the population level.

The second main takeaway from the meta-analyses is that there are highly non-linear relationships between levels, within each psychedelic. As shown in **Figure 7.1**, there is no one-to-one correlation between the pharmacology, neuroimaging, and phenomenology of each drug. This is not a surprising result. The mechanisms that link these three levels of analysis are likely very complex and interconnected; there is no single receptor or network in the brain that encodes just one type of subjective experience, for example. Conscious experiences are encoded in very dynamic, flexible, and distributed patterns of brain activity (Barttfeld et al., 2015; Boly et al., 2013; Dehaene & Changeux, 2011; Oizumi et al., 2014), which is itself orchestrated in part by the activation of countless receptors in a constant state of flux (Raichle, 2015). The

challenges of bridging the three levels of analysis highlights the urgent need to develop better models for relating the phenomenology, neuroimaging, and pharmacology of psychedelics. While a handful of researchers have attempted to draw comparisons 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.

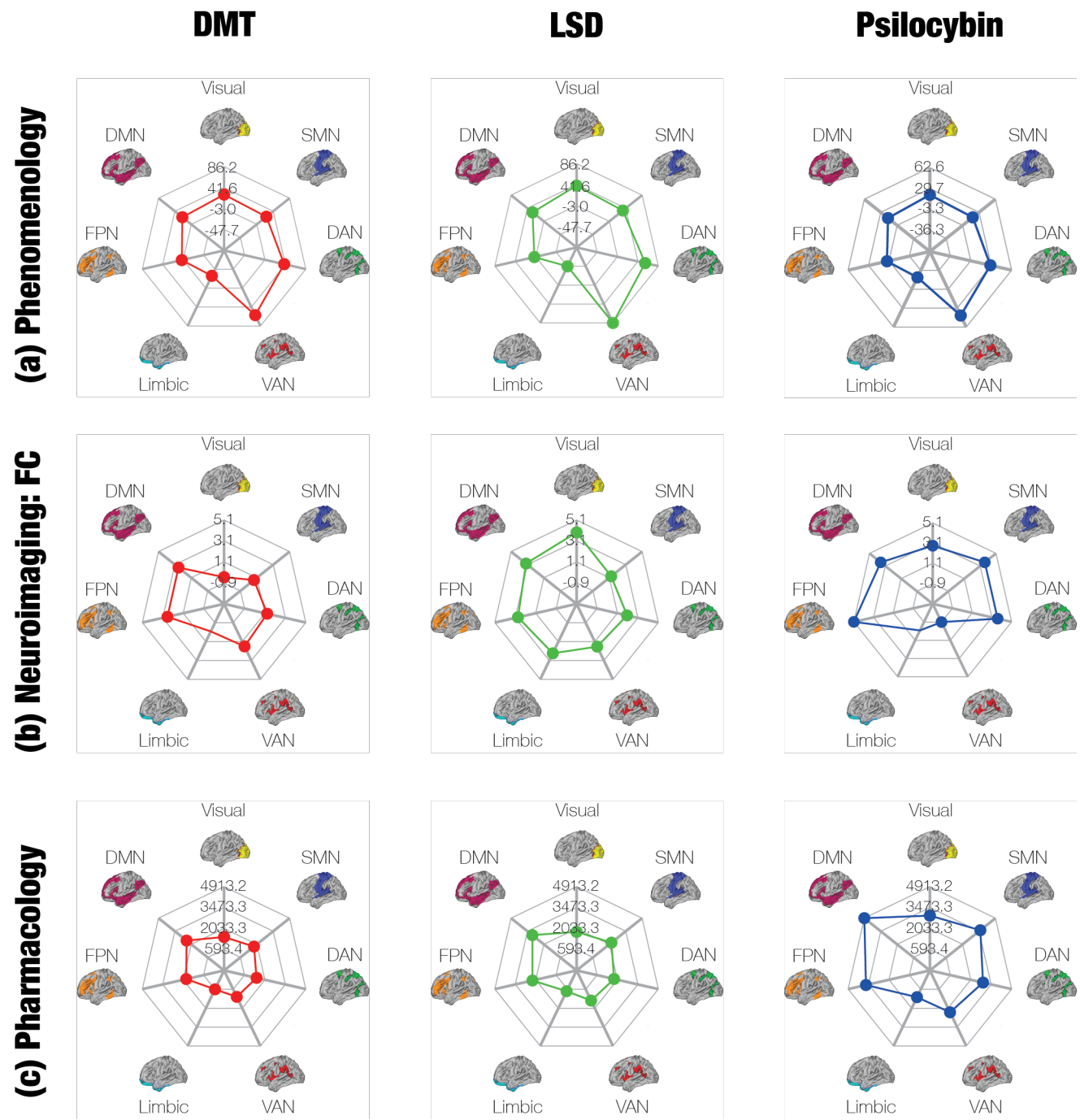


Figure 7.1. Our multi-level analysis of psychedelic effects highlights the nonlinear relationship between their pharmacology, neuroimaging, and phenomenology.

The effects of psychedelics form a tripartite hierarchy, consisting of subjective experience (a, phenomenology), functional connectivity (b, neuroimaging), and their selective affinity for receptors (c, pharmacology). 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 aggregate FC between each network and other networks, and (c) the distribution of each receptor, weighted by each psychedelic's selectivity for that receptor. 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 both DMT and ayahuasca in our FC meta-analysis, but only on DMT for the other meta-analyses. We examined data on psilocin in our pharmacology meta-analysis and on psilocybin in both of the other meta-analyses.

Non-invasive brain stimulation is needed to establish causal mechanisms, since it can modulate activity in specific regions of the brain. For instance, suppose one hypothesises that reduced connectivity within the temporoparietal junction (TPJ) gives rise to the subjective experience of interconnectedness. (This is a plausible hypothesis, given that the TPJ encodes the boundary between self and other (Northoff et al., 2006; Quesque & Brass, 2019)). To verify that aberrant connectivity within the TPJ actually causes this experience rather than merely correlating with it, one could apply TMS over the TPJ either during the acute effects of a psychedelic, to determine whether the TMS potentiates the subjective experience, or afterwards, to ascertain whether the TMS is able to revive the experience. So far, only one study has applied TMS to date while participants were experiencing the acute effects of a psychedelic, and it did find that certain categories of subjective experience were associated with TMS-induced changes in EEG power within particular brain regions (Ort et al., 2023).

Perhaps the most compelling framework for synthesising the three levels of analysis is RELaxed Beliefs Under pSychedelics (REBUS) (R. L. Carhart-Harris & Friston, 2019). REBUS is predicated on the predictive coding model of the brain, which posits that perception can be modelled as a hierarchical Bayesian process. In other words, higher-level regions make top-down predictions about lower-level regions, which are formed through a combination of priors – predictions made in the absence of input from lower regions – and prediction errors encoded by the lower-level regions (Rajpal et al., 2022; Teufel et al., 2013). When there is high confidence in the priors and low confidence in the sensory data, the “precision-weighting” of the priors increases, and perception is informed more by priors than by information from the environment. REBUS proposes that the highest-level priors in the human brain encode important beliefs, such as the views that a person maintains about their “ego” or sense of self. Certain psychiatric conditions like depression can cause the precision of these high-level priors to be pathologically overweighted; consequently, patients with these conditions rigidly hold negative beliefs about themselves. REBUS claims that psychedelics decrease the

precision-weighting of these priors, effectively liberating people from these beliefs and enabling them to see the world from a new perspective.

REBUS speculates that psychedelics modify the precision-weighting of priors by binding to the 5-HT_{2A} receptor, which is typically located on the apical dendrites of layer V pyramidal neurons (Aleksandrova & Phillips, 2021; Hamada et al., 1998; Jakab & Goldman-Rakic, 1998). The prevalence of the 5-HT_{2A} receptor in this deep layer of cortex supports REBUS, since top-down predictions are thought to be implemented in the brain via feedback connections originating from deep layers (Bonaiuto et al., 2018; Haarsma et al., 2022). Thus, strong activation of the 5-HT_{2A} receptor by psychedelics may disrupt these top-down predictions and the corresponding priors. 5-HT_{2A} is expressed most densely in high-level, associative networks such as the DMN (Beliveau et al., 2017); hence, one of the hallmark effects of psychedelics is that they “disintegrate” or decrease connectivity within these networks while also “desegregating” or enhancing connectivity between these networks and sensory brain regions (R. L. Carhart-Harris et al., 2013, 2016; R. L. Carhart-Harris, Leech, et al., 2012; Roseman et al., 2014). Because the DMN putatively mediates self-related cognition (Zhou et al., 2020), disrupting the DMN may lead to the experience of ego dissolution on psychedelics (Atasoy et al., 2017; F. S. 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). That being said, the mechanisms underlying ego death are likely much more complex than loss of connectivity within one large-scale network, since self-rumination or self-related judgments are not always associated with increases in DMN activity (Doss et al., 2020; Fang et al., 2022; van Buuren et al., 2010).

Thus, REBUS links the pharmacology, neuroimaging, and phenomenology of psychedelics; binding and subsequent activation of the 5-HT_{2A} receptor alters predictive coding, affecting functional connectivity most within higher-order, associative networks and thereby altering higher-order cognition and consciousness in a profound manner. Yet REBUS has not been formally tested in the literature, in part because it is very challenging to empirically verify that activation of the 5-HT_{2A} receptor modifies the precision-weighting of priors, let alone the priors that are relevant for the phenomenology or therapeutic value of psychedelics. A recent study showed that decreasing the precision-weighting of priors in a hierarchical Bayesian model recapitulates the empirically-observed effects of psychedelics on Lempel-Ziv complexity and transfer entropy (Rajpal et al., 2022). This study only fit the model to MEG data from V1 in the placebo condition, but it is certainly possible to fit the model to whole-brain MEG recordings under both placebo and drug conditions. Ostensibly, one could then directly test REBUS by measuring the effects of the psychedelic on precision-weighting of priors. (This is a project I would love to conduct in the future.) However, it would be challenging to interpret the results. According to this model, each prior would be the weight of the linear relationships between the past activity of a single higher-order brain region and its future activity. There is no evidence

that the priors correspond to the psychological beliefs that are relaxed under psychedelics; I am very sceptical that any model, especially one as simple as the system of two equations proposed by Rajpal and colleagues, could capture psychological phenomena that are as wildly complex as belief updating on psychedelics. None of the subjective experiences that characterise psychedelics, such as ego death, have actually been defined formally in a Bayesian framework.

The key insight of REBUS is that psychedelics flatten *hierarchical* information processing in the brain. Relaxing the precision-weighting of priors implies that higher-level networks update their activity more based on the prediction errors encoded by lower-level networks. Consequently, psychedelics enhance bottom-up connectivity and lower top-down inhibition, which implies that lower-order, sensory regions ascend in the brain's functional hierarchy while higher-order, associative regions descend. In other words, the hierarchy contracts; psychedelics should decrease the variance of the differences between hierarchical levels and potentially the mean as well.

Moving beyond meta-analyses, in *Chapter 5*, I indirectly tested REBUS' hypothesis about hierarchy by examining the irreversibility, or directedness, of MEG timeseries on LSD, as well as the hierarchical coherence and inhomogeneity. All three can be construed as measures of the strength of hierarchy; irreversibility represents the *pairwise* imbalance between incoming and outgoing connections, whereas hierarchical coherence and inhomogeneity are the mean and standard deviation of the imbalance between incoming and outgoing connections *at each region*. The underlying assumption is that more hierarchical networks exhibit larger imbalances between incoming and outgoing connections. We find that LSD significantly reduces all three measures of hierarchy, across multiple experimental conditions (eyes-open resting-state, eyes-closed resting-state, listening to music, and watching a video).

Chapter 6 presents the results of a more direct test on the hypothesis that psychedelics flatten brain hierarchy. Namely, I apply a framework that explicitly decomposes the brain into hierarchical levels by essentially relating irreversibility to hierarchical coherence and inhomogeneity. Thus, whereas irreversibility, hierarchical coherence, and hierarchical inhomogeneity were considered as separate concepts in *Chapter 5*, the framework in *Chapter 6* unifies them together. *Chapter 6* also considers the hierarchy of forward connectivity to be distinct from the hierarchy of backward connectivity. This overcomes one of the weaknesses of the approach in *Chapter 5*, which did not differentiate between bottom-up and top-down connectivity. Measuring hierarchical coherence and inhomogeneity in the brain yields the observation that visual areas are the highest regions in the hierarchy, whereas they are normally considered to be the lowest. However, hierarchical coherence and inhomogeneity primarily capture bottom-up connectivity in the brain; visual areas have many outgoing connections toward other regions but relatively few incoming connections. By examining both forward and backward hierarchies in *Chapter 6*, I was able to assess the effect of LSD on

the direction of information flow in the brain. LSD significantly decreased the backward hierarchical levels of visual areas and the forward hierarchical levels of non-visual areas, indicating reduced information flow from the former to the latter. Additionally, LSD significantly reduced the mean and standard deviation of both forward and backward hierarchical differences. These results substantiate REBUS' proposition that LSD flattens hierarchy and decreases top-down information flow, but they do not support its claim that LSD enhances bottom-up information flow.

Prior MEG analyses of the same dataset also suggest that LSD does not elevate bottom-up information flow. In particular, LSD universally and significantly decreases Granger causality, or directed information flow, between all pairs of brain networks, especially from occipital regions to higher-order networks (Barnett et al., 2020). In a predictive coding framework, diminished bottom-up information flow implies that prediction error signalling is dampened. This is consistent with experiences of visual hallucinations on LSD. In particular, hallucinations may result from the failure of visual regions to convey information about the environment (i.e., prediction errors) to higher-order networks, a view that is consistent with some explanations of auditory hallucinations in schizophrenia (Horga et al., 2014; McCleery et al., 2018; Nazimek et al., 2012; Northoff & Qin, 2011). Additionally, psychedelics diminish the amplitude of the mismatch negativity response, or the EEG signal that encodes prediction errors (Duerler et al., 2021; Timmermann et al., 2018; Umbricht et al., 2003). Elevated prediction error signalling, as REBUS proposes, would not only be inconsistent with the results of the studies on mismatch negativity under psychedelics, but would also falsely imply that perception becomes more veridical – that is, perception more accurately represents the environment – under psychedelics. For instance, pareidolia, a common hallucination on psychedelics in which faces are seen within plants, clouds, and other inanimate objects, could be explained as an experience in which the brain neglects prediction errors about the environment.

The research in this thesis has also elucidated the mysterious relationship between entropy and psychedelic use. Ever since Robin Carhart-Harris' influential Entropic Brain Hypothesis was published in 2014 (Carhart-Harris et al., 2014), many researchers have investigated the effect of psychedelics on entropy, specifically Shannon entropy (see *Appendix 3* for a comprehensive account of the various definitions of entropy). EBH's core assumption is that the richness of experience corresponds to the “richness” or complexity of brain signals, which can be measured with entropy. However, this assumption has not been put to the test, though most studies have endorsed a positive correlation between psychedelic use and various measures of brain entropy. Recent research has demonstrated that the amount of hierarchy in a network drives the amount of entropy that is produced by the dynamics along the network, since entropy production is equivalent to the amount of irreversibility (Nartallo-Kaluarachchi et al., 2024). In *Chapter 5* and *Chapter 6*,

we confirm this finding by showing that LSD-induced decreases in two different measures of entropy production correspond to reductions in the strength of hierarchy.

Chapter 7.2. Other ways of unifying phenomenology, neuroimaging, and pharmacology

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). 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) (Onofri 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 REBUS hypothesis, 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). Connectivity between the producer of dopamine in the brain, the ventral tegmental area, and the DMN mediates consciousness, potentially suggesting that the dopaminergic action of LSD may play a role in facilitating altered states of consciousness (Spindler et al., 2021).

In summary, the literature suggests that anti-correlations between the DMN and the TPN give rise to hallucinations. 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. Furthermore, LSD's moderate agonism for dopamine receptors may be one mechanism that accounts for its enhanced visual hallucinations. However, more research is needed to elucidate the contribution of dopamine to LSD-induced hallucinations above and beyond 5-HT_{2A}, which is the key driver of the altered state of consciousness.

Chapter 7.3. Relationship between meta-analysis and hierarchy findings

As discussed above, a consistent result in the meta-analysis is that LSD is more visual than psilocybin, both phenomenologically and neurobiologically. That is, LSD-induced hallucinations are more visually complex and intense, and LSD appears to modify the connectivity of the visual network more than other psychedelics. My analysis of hierarchy seems to yield similar results. In *Chapter 5*, I demonstrated that LSD affects irreversibility and the incoming-outgoing imbalance more in the visual cortex than in other areas, especially in the eyes-open and eyes-closed resting-state conditions. As shown in *Chapter 6*, LSD significantly alters the backward hierarchical levels of visual regions.

However, the *direction* of LSD's effect on the visual cortex does not appear to be consistent between the hierarchy analysis and the neuroimaging meta-analysis. The latter revealed that LSD enhances functional connectivity between the visual network and other networks. Yet the former indicated that LSD reduces the directedness of connectivity for the visual network, while also diminishing information flow away from the visual network. However, unlike the measures of connectivity in the hierarchy analysis, those that we reviewed in the neuroimaging meta-analysis were almost entirely undirected. That is, they capture instantaneous relationships between brain timeseries, which may not be the same as relationships that are shifted in time. Indeed, as stated in *Chapter 6*, undirected and directed measures of FC appear to give opposite results in psychedelic research. A study that applied both in the same MEG dataset on LSD determined that LSD elevates undirected FC, as measured with mutual information, while suppressing directed FC, as measured with Granger causality (Barnett et al., 2020). Additionally, even if directed FC were to increase under psychedelics, the hierarchy of directed connectivity may not necessarily become stronger. For instance, a set of edges within a cyclical (i.e., non-hierarchical) network is still completely non-hierarchical even if all

the edges become more directed. Finally, increases in undirected FC may correspond to a rise in reciprocal FC; for instance, if the undirected FC between the DMN and the visual network goes up, it could be the case that the connectivity from the DMN to the visual network and the connectivity in the reverse direction both rise by a similar amount. Then, the connectivity between the two networks would be more reversible, and the strength of hierarchy would decrease. The work in this thesis makes a substantial, novel contribution to the field by elucidating the effect of psychedelics on the direction of information flow, which traditional, undirected measures are fundamentally unable to capture.

Chapter 7.4. The relevance of hierarchy for therapeutic applications of psychedelics

In the last decade, psychedelic therapy has boasted impressive results in clinical trials. Outside of my DPhil, I co-authored a series of comprehensive reviews about the efficacy of seven different psychedelics for treating depression, generalised anxiety disorder and end-of-life anxiety, substance use disorders, and post-traumatic stress disorder (PTSD). For instance, 71% of participants no longer met the diagnostic criteria for PTSD after just three sessions of 3,4-methylenedioxymethamphetamine (MDMA, more commonly known as “ecstasy”) along with concurrent therapy (Mitchell et al., 2023). Heavy drinking days were nearly 14% less common among participants who received two sessions of psilocybin-assisted therapy for alcohol use disorder (Bogenschutz et al., 2022). A single dose of ayahuasca caused remission in 36% of participants with treatment-resistant depression (Palhano-Fontes et al., 2019). In a small pilot study, two doses of psilocybin, in conjunction with therapy, caused 80% of tobacco-addicted participants to quit smoking (M. W. Johnson et al., 2014). One major, unique advantage of psychedelics is that they only require a small number of doses in order to cause immediate effects that can last for years (Agin-Liebes et al., 2020; M. W. Johnson et al., 2017; Reckweg et al., 2022). On the other hand, existing medications such as selective serotonin reuptake inhibitors (SSRIs) must be taken on a daily basis before patients become consciously aware of changes in their mood, potentially because SSRIs operate on unconscious, negative biases in attention, appraisal, and memory in the early phases of treatment (Harmer & Cowen, 2013). Additionally, SSRIs are associated with a number of adverse side effects, including sexual dysfunction, fatigue, weight gain, liver toxicity, irregular heart rhythms (QTc prolongation), insomnia, tremor, and apathy (Kelly et al., 2008; Oliva et al., 2021; S.-M. Wang et al., 2018; S. Zhou et al., 2023).

REBUS proposes that decreased precision-weighting of priors underlies not only the phenomenological but also the therapeutic effects of psychedelics (R. L. Carhart-Harris & Friston, 2019). It assumes that pathologically overweighted priors lead to psychiatric disorders, an idea that has received support in theoretical research on depression (L. F. Barrett et al., 2016; Clark et al., 2018; Haarsma et al., 2021; Kube & Rozenkrantz, 2021). However, there are inherent difficulties in tracing psychiatric symptoms to the precision-

weighting of priors with non-invasive human neuroimaging data. Two models would be needed: one that relates psychiatric symptoms to specific sets of precision weights and another that maps brain activity onto precision weights. Even if the first model were possible, there are likely many-to-one mappings from precision weights to noisy, coarse-grained timeseries like MEG, which could contain many interactions between the underlying predictive coding mechanisms on multiple spatial and temporal timescales.

According to REBUS, a direct implication of decreased precision-weighting of priors is diminished top-down inhibition (corresponding to reduced precision of higher-order predictions about lower-order regions) and amplified bottom-up excitation (corresponding to increased precision of lower-order prediction errors) (Rajpal et al., 2022). Rather than modelling the effects of psychedelics on precision-weighting of priors with MEG data, it would be much more straightforward to simply measure their effects on directed (bottom-up or top-down) information flow. This is precisely the approach that I chose for my thesis. Because the MEG datasets were collected on healthy participants, I have not yet established that flattened hierarchy is a mechanism for the therapeutic effects of psychedelics. However, forthcoming work by my colleagues has applied similar methods to fMRI data on psilocybin for depression and shown that the degree to which the hierarchy is flattened predicts the therapeutic response (Deco et al., in press). Furthermore, escitalopram flattened hierarchy to less of an extent than psilocybin did.

While there needs to be more research on the relationship between hierarchy and the therapeutic efficacy of psychedelics, there is emerging evidence that brain hierarchy is impaired in psychiatric conditions. For instance, subthreshold depression significantly alters the position of key nodes of the DMN in the cortical hierarchy, which was defined by performing a gradient analysis of fMRI data (Yin et al., 2024). The same analysis technique showed that suicidal ideation in patients with major depressive disorder (MDD) increases the hierarchical level of the DMN (Shiwei et al., 2023). Separate graph-theoretic techniques have revealed that MDD lowers the hippocampus while raising the amygdala within the hierarchy of the connectome (Jacob et al., 2022).

Of particular relevance for this thesis is the role that top-down and bottom-up information flow play in the brain hierarchies that underpin psychiatric conditions such as depression. Multiple studies have implicated the medial prefrontal cortex (mPFC) in top-down processing due to its role in planning for the future, decision-making, and reward learning (Bechara et al., 2000; LeDuke et al., 2023; Sharot et al., 2007). Depression hyperactivates the mPFC while inhibiting dopaminergic neurons in the ventral tegmental area that perform bottom-up reward processing (Anderson et al., 2020; Hare & Duman, 2020; Pizzagalli & Roberts, 2022; Schultz, 2002). At least in rodent models, adverse social experiences increase the top-down inhibition of serotonin neurons in the dorsal raphe nucleus by the ventromedial PFC (vmPFC), resulting in avoidant behaviour (Challis & Berton, 2015). In humans, depression also dysregulates the top-down control

of the vmPFC over connectivity between the left ventrolateral PFC and amygdala while participants are effortfully enhancing or suppressing their emotional response to a stimulus (Johnstone et al., 2007). Additionally, depression impairs the ability of the dorsolateral prefrontal cortex to perform top-down regulation on bottom-up emotional processing within the limbic system (Disner et al., 2011; Suslow et al., 2010; Warren et al., 2015). Top-down regulation of the limbic system by the pregenual anterior cingulate cortex is similarly disrupted by depression (Godlewska & Harmer, 2021). Interventions such as cognitive behavioural therapy are hypothesised to restore healthy top-down control by the executive and dorsal attention networks (Godlewska & Harmer, 2021).

In summary, depression impairs the hierarchy of directed information flow in the brain by compromising the balance between top-down control and bottom-up excitation. Psychedelics may treat depression by restoring the ability of higher-order networks to properly regulate lower-order regions in the hierarchy. Flattening the hierarchy drives the brain into a more fluid state in which it can reorganise its connectivity; pathological top-down connections are impaired, giving the brain the opportunity to forge new pathways for regulating bottom-up sensory processing. Future work should examine the links between hierarchy flattening at the whole-brain level and findings that psychedelics reopen the critical period of learning by elevating metaplasticity, which has been investigated on the cellular level (Nardou et al., 2019, 2023).

Chapter 7.5. Hierarchy and consciousness

According to the Global Workspace Theory, consciousness is mediated by a small, higher-order brain network, the global workspace, which integrates and broadcast information from a much larger number of lower-order brain regions that are devoted to specialised processing of various sensory, motor and attentional operations (Baars, 2017; Dehaene et al., 1998). In other words, the global workspace *orchestrates* the hierarchy of brain function that underlies consciousness.

There is emerging evidence that normal, resting-state consciousness is associated with hierarchical brain function. The same methods that were used in this thesis have revealed that disorders of consciousness and lack of consciousness, i.e., anaesthesia and deep sleep, induce less hierarchical – that is, more reversible – brain activity (Deco et al., 2022; G-Guzmán et al., 2023; Gilson et al., 2023). Furthermore, irreversibility distinguishes brain activity under anaesthesia, deep sleep, and wakefulness much better than traditional, undirected functional connectivity methods (Deco et al., 2022), a result that has since been replicated with task-based data (Tewarie et al., 2023) and with the LSD dataset analysed in *Chapter 5*. Other studies have used different techniques to compute irreversibility, such as deep learning networks that are trained to classify whether a timeseries is forward or reversed in time (Deco et al., 2023). An application of this method to electrocorticography recordings in non-human primates revealed that forward and reversed timeseries are

much more distinguishable during wakefulness than during deep sleep and ketamine-induced anaesthesia; in other words, wakefulness is more irreversible than the latter two states of consciousness (de la Fuente et al., 2023).

Furthermore, anaesthetics may induce a loss of consciousness by disrupting the hierarchical structure of the global workspace. For instance, despite having very different mechanisms of action at a pharmacological level, propofol, sevoflurane, and ketamine all reduce functional connectivity between two key nodes of the global workspace, the prefrontal cortex and posterior parietal cortices (Bonhomme et al., 2016; Boveroux et al., 2010; Mashour et al., 2020; Palanca et al., 2015). Intriguingly, segregation between nodes of the global workspace leads to loss of consciousness even when lower-order sensory processing is kept intact (Warnaby et al., 2016). Meanwhile, aberrant increases in connectivity between the PCC and motor/somatomotor networks during propofol sedation may suggest that anaesthesia disrupts the ability of higher-order nodes to regulate sensory regions (Stamatakis et al., 2010). A recent information-theoretic approach to the global workspace found that general anaesthesia and disorders of consciousness impair the ability of “gateway” regions, primarily situated in the DMN, to synergistically integrate information from specialised modules in the brain (Luppi et al., 2024). This is consistent with previous research demonstrating that unconsciousness reduces global functional connectivity and diversity in posterior regions of the DMN (Luppi et al., 2019).

In the opposite direction, stimulation of global workspace hubs, such as the dorsolateral prefrontal cortex (DLPFC), may restore awareness to patients who suffer from disorders of consciousness (DoC), such as minimally conscious states (Thibaut et al., 2014, 2015). Cholinergic stimulation of the mPFC, which, as mentioned in the previous subchapter, is a key locus of top-down control within the brain, can reinstate wakefulness in anaesthetised rats even when general anaesthesia is continuously being applied (Pal et al., 2018). Fascinatingly, stimulation of the DLPFC during rapid eye movement (REM) sleep increases the probability of entering into a lucid dream (Stumbrys et al., 2013).

While these studies illustrate the importance of certain higher-order brain regions for maintaining consciousness, they do not necessarily demonstrate that the global workspace is hierarchically organised *per se*. The hierarchical structure of the global workspace has been studied through “intrinsic ignition,” which is measured based on the number of areas that a particular brain region co-activates with when it is in a high-amplitude state. (Deco & Kringelbach, 2017). Then, the hierarchy is determined based on the distribution of the intrinsic ignition across all nodes; a flat distribution indicates that the brain is not hierarchical, whereas a linear decrease in intrinsic ignition across regions implies that the brain exhibits a strong, uniform-graded hierarchy. Under various forms of anaesthesia, the hierarchy of the monkey brain becomes more uniform across regions, suggesting that there are fewer regions with especially strong top-down influence over the rest of the brain (Signorelli et al., 2021). Furthermore, the flattening of this hierarchy correlates with the loss

of emergence in brain activity, or the degree to which macroscopic features of brain activity predict the futures of individual regions above and beyond the pasts of those regions (Luppi, Mediano, et al., 2023). Propofol anaesthesia also flattens the hierarchy in the sense that it almost exclusively reduces feedforward effective connectivity, according to DCM analyses of EEG data (Sanders et al., 2018), and diminishes transfer entropy, a measure of directed connectivity, between different (hierarchical) layers of the visual cortex in rodents (Hudetz et al., 2020).

Taken together, these studies suggest that consciousness depends on hierarchically organised brain function. The fact that psychedelics and conditions that diminish conscious awareness, such as DoC, anesthesia, and sleep, both flatten the hierarchy of directed information flow in the brain may seem puzzling because the former arguably “raise” consciousness while the latter do the opposite. However, there is little basis for the claim that psychedelics induce a “higher” state of consciousness, given that various aspects of cognition and other functional capacities of consciousness are impaired by psychedelics (Bayne & Carter, 2018). Rather, psychedelics reorganise consciousness such that higher-order concepts such as identity, sense of space and time, and the boundary between self and other are massively disrupted due to profound distortions in sensory perception. This altered, but not necessarily higher, state of consciousness likely corresponds to a state of the brain in which higher-order brain networks that subserve cognition are unable to regulate lower-order, sensory regions in the way that they usually do.

A recent framework identified the brain regions that constitute the global workspace as the intersection of “functional rich clubs” (FRICs) across seven different tasks and the resting state (Deco et al., 2021). These FRICs are defined as subsets of regions that maximise the difference between incoming and outgoing normalised directed transfer entropy (NDTE), a measure of the information that the past of a timeseries X encodes about the future of a timeseries Y , above and beyond the past of Y . (Note that NDTE is essentially the information-theoretic equivalent of Granger causality (Barnett et al., 2009).) According to the NDTE framework, the global workspace comprises the left precuneus, left nucleus accumbens, left posterior cingulate, left putamen, left and right isthmus cingulate, right hippocampus, and right amygdala. The global workspace bears no similarity to the generalised hierarchical levels (GHL) that were determined in *Chapter 6*. (GHL is half of the difference between the forward and backward hierarchical levels.) All eight of the global workspace regions are below the median GHL.

There are three major reasons why the GHL and the global workspace do not correspond to each other. Firstly, GHL only captures linear relationships between the past and future of pairs of timeseries; it does not condition those relationships on the past of one of those timeseries. Secondly, the FRICs framework defines hierarchy based simply on the difference between incoming and outgoing NDTE, whereas GHL integrates both the incoming-outgoing asymmetry of each region and the topology of the entire network in order to

determine hierarchical levels. Thirdly, the global workspace was measured on both active task and resting-state fMRI data, whereas GHL was computed on MEG data from only resting-state and passive stimulus conditions.

This final consideration highlights an important point regarding consciousness, namely that consciousness has nothing to do with task performance. The set of FRICs that are invariant across task and resting-state are certainly important for orchestrating the hierarchy of brain function, but in order to arrive at any conclusions about consciousness, the FRICs must be measured in different states of consciousness. That is, the FRICs that are relevant for consciousness are better defined as the set that remains invariant across normal wakefulness and altered states of consciousness. Likewise, changes in FRICs across different states of consciousness, e.g., psychedelics, reflect the neural mechanisms of those states. My findings in *Chapter 6* illustrate that altering consciousness with LSD diminishes the role of visual regions in orchestrating the hierarchy of top-down connectivity, as well as the orchestration of bottom-up connectivity by non-visual areas.

Below, I will present my own views on consciousness; note that these are mainly speculations, hence the sparsity of references. I believe that consciousness is not inherently hierarchical; the primary function of consciousness is not necessarily top-down regulation of bottom-up sensory processes. Rather, consciousness non-hierarchically integrates sensory perception with a large number of memories that are each laden with an emotional tone. According to a teaching of the Buddha called *Paticca-samupadda*, the emotional tone of any experience is defined by two polarities: craving (*tanha*) and aversion (*dukkha*) (Bhikkhu, 2011). Craving is the urge to cling to things that are pleasurable, whereas aversion is the urge to avoid things that cause pain. Craving and aversion are fundamentally embodied; they elicit plans to move towards or away from the pleasurable or painful object in the environment. Sometimes, these plans can materialise into overt action (e.g., backing away from a poisonous plant) but are typically much more subtle; aversion may manifest as a sensation of withdrawal in some part of the body, whereas craving may be experienced as a tightening within the body. Consciousness is therefore not just the sensory perception of the environment, but instead the embodied experience of the environment's emotional tone, which is itself shaped by learned associations with many, many past experiences. The inextricable intertwining of emotional tone, memory, embodied cognition, and sensory perception yields an emergent “vibe,” which is unique to conscious beings and not to entities that merely perceive. In conscious humans, craving and aversion are not only felt towards events that are happening in the present, but also towards past and possible future experiences. Furthermore, thoughts enable the mind to express vibes in concepts and words, which are then unified across time into coherent narratives.

However, most of the time, embodied experience is so subtle and fleeting that attention is not drawn towards it. (I view attention as a “vector” of consciousness, one that decides where awareness goes.) I believe that brain function is hierarchical in the “default” state of consciousness – normal, sober wakefulness – because attention is directed towards only a small subset of all the experiences that are taking place within consciousness. Specifically, for most people, attention is focused on maintaining and reinforcing mental narratives. While consciousness itself is essentially egalitarian – none of the threads of experience are intrinsically more important than others – attention forms a hierarchy of experience by biasing awareness towards certain mental narratives. In the case of certain psychiatric conditions like depression, the persistent direction of attention towards negative narratives (e.g., “I am worthless” or “the world is a terrible place”) becomes pathological. The other threads of conscious experience – embodiment, memory, emotional tone, and sensory perception – are neglected, not only in depressed but also healthy people. Attention thereby becomes a “reducing valve” on consciousness.

Psychedelics enable people to discern the “micro-motions” of craving and aversion within the body by massively amplifying a person’s sensitivity to the vibes of the environment. That is, the emotional tone of the environment is felt much more profoundly than it usually is because psychedelics significantly increase the “attentional gain” on (i.e., draw attention towards) their experiences of craving and aversion, which is felt in an oscillatory manner. For instance, when a person enters a crowded place on psychedelics, all the learned associations about the spatial layout of the place, the expressions and movements of the people there, and so on are manifested in oscillating, somatic experiences of craving and aversion, which are normally suppressed by attention.

The flattening of brain hierarchy under psychedelics essentially distributes attention more equally to all the threads of conscious experience. Attention is drawn away from higher-order narratives about the self, where it is normally and disproportionately focused, and towards the emotional tone of the environment and its impact on somatic awareness. This implies a relaxation of top-down processes, i.e., higher-order narratives about the self, as well as certain bottom-up processes like visual perception, which generally dominate perception. However, psychedelics may elevate the sensitivity of not only brain regions but also other parts of the autonomic nervous system that process interoceptive signals from the body. The latter includes the vagus nerve, a very long cranial nerve that relay sensations felt in the heart, lungs, abdomen, digestive tract, and other organs, as well as sensations in the skin and muscles, to the lower brainstem. Additionally, pathways from the insula to the vagus nerve stimulate somatic processes such as digestion, thereby implicating the insula in the processing of interoceptive information (Levinthal & Strick, 2020). Future work should examine directed, bottom-up connectivity from the vagus nerve to the insula under psychedelics in order to measure the effects of these drugs on interoception.

Enhanced interoception may also affect entropy production. In particular, poor interoception could imply that signals from the body are being rapidly *dissipated* by the brain; that is, the brain ignores information from the body, and neural activity related to interoceptive signals is quickly dampened and fails to spread to other areas of the brain. In subtypes of certain conditions like depression, this rapid dissipation occurs for more or less all interoceptive signals, leading to an overall feeling of numbness with respect to the body. Dissipation is equivalent to entropy production; it is the loss of energy to the environment that occurs as the result of an irreversible process. For instance, when a car tire brakes on a road, heat is irreversibly dissipated via friction. The faster that the tire brakes, the more that friction is generated, and consequently dissipation increases. Similarly, oscillations that are quickly dampened due to friction or other resistance will dissipate more energy than oscillations which slowly die out (Goldbeter, 2018). Thus, dissipation and entropy production would be high if neural oscillations encoding the state of the body immediately subside and are not propagated to other regions of the brain. The fact that psychedelics decrease entropy production could mean that the insula and other brain regions suppress fewer of the bottom-up interoceptive signals carried forward by the vagus nerve and other components of the autonomic nervous system.

In summary, one of the leading theories of consciousness, the Global Workspace Theory, suggests that consciousness is hierarchically orchestrated by a small number of regions that constitute the so-called global workspace. This theory is supported by empirical evidence demonstrating that connectivity within the global workspace leads to loss of consciousness. The function of the global workspace is to integrate and broadcast information from many lower-order, local processors in the brain. My personal view is that the global workspace is predisposed towards incorporating information that pertains to a limited number of mental narratives, which perpetuate core beliefs of the self. Thus, attention is predominantly allocated towards these narratives and not to the multitude of other experiences that comprise consciousness, namely the subtle cravings and aversions that are elicited by the environment through a vast constellation of learned associations between emotions and external stimuli. Psychedelics flatten the hierarchy of the brain in the sense that they spread attention out more equally among the large number of experiences within consciousness. Hence, people who take psychedelics become much more aware of the effects of the environment on their feelings of craving and aversion, especially the oscillatory manner in which they manifest in the body.

Chapter 7.6. Moving Beyond REBUS

REBUS' central proposal is that psychedelics relax rigid beliefs, which are defined as statistical priors, but there is plenty of evidence that psychedelics can sometimes strengthen beliefs as well. For instance, someone who struggles with substance use disorder may believe on some level that they need to break their addictive

behaviours, yet that belief is dominated by an urge to take drugs. When used in a therapeutic context, psychedelics may bolster the already present belief that the participant needs to quit their addiction.

These ideas are echoed in Adam Safron's ALtered Beliefs Under pSychedelics (ALBUS) framework (Safron, 2020). ALBUS is a combination of REBUS and SEBUS (StrEngthened Beliefs Under pSychedelics). Safron argues that every intentional action, whether imaginative planning or goal-oriented cognition, requires the formation and strengthening of prior expectations. Thus, abiding by the intention to change one's behaviours, particularly when those behaviours are deeply ingrained, demands an increase in the precision-weighting of priors. REBUS' proposal that psychedelics only reduce the precision-weighting of priors implies that these drugs essentially make people more uncertain about their beliefs, since precision corresponds to confidence. However, a crucial psychological outcome of psychedelic therapy is that it motivates people to become more confident in their intentions and achieve greater clarity.

Safron also states that sensory hallucinations on psychedelics are likely a result of strengthened priors, which is consistent with previous theoretical research on non-psychedelic hallucinations (Corlett et al., 2019). For instance, as stated above, the experience of seeing faces in trees, a common hallucination on psychedelics, is likely mediated by a strengthened prior corresponding to face perception, while prediction errors conveying sensory data about trees are being suppressed. These hallucinations provide evidence against REBUS, which claims that psychedelics enhance rather than diminish the ability of prediction errors to influence the activity of neurons that encode priors.

Safron does not claim that psychedelics only increase the precision-weighting of priors. Rather, psychedelics cause a complex combination of strengthened and relaxed priors. Such an account seems much more plausible and holistic than REBUS, which appears to only paint half the picture of the psychedelic experience. If every deep-layer pyramidal neuron in the cortex encodes a prior, then there are potentially up to billions of priors (Y. Wang et al., 2018). It is exceedingly unlikely that precision-weighting will decrease in all of them on psychedelics. REBUS is uninformative because it does not predict the *pattern* of precision weights that psychedelics modify; it only provides the general direction in which these weights change.

Chapter 7.7. Future work

I encourage researchers to develop tools for modelling the nonlinear relationships between the pharmacology, neuroimaging, and phenomenology of psychedelics. The field must move beyond correlations, which are uninformative, and shed light on the interconnected web of *causal* mechanisms that link these three levels together.

Recent whole-brain models have made significant advances in discovering these causal mechanisms (see Kringelbach & Deco (2020) for a general review). 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). 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, Cruzat, 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).

While this thesis is one of the first bodies of work to illuminate the effects of psychedelics on brain hierarchy, the methods do suffer from several limitations. Firstly, they may result in poor estimates of hierarchical connectivity. Forward and backward hierarchies in *Chapter 6* were determined based on an effective network, which was essentially constructed from an autoregression on the data. However, the edges in this network only capture simple, linear dependencies in the data. The same is true of INSIDEOUT, which determines irreversibility based on time-shifted correlations, though we did observe a correlation between irreversibility and the hierarchy of visual cortex. Fundamentally, these linear dependencies are *statistical*, whereas other notions of hierarchy are *anatomical*. Future work should consider more accurate methods of inferring anatomical hierarchies based on whole-brain neuroimaging data.

Secondly, because the effective network only reflects these linear relationships, the biological meaning of the edges is very ambiguous. The “information flow” from one region to another is more or less just a correlation of timeseries; structural connectivity, neurotransmitter flux, and receptor activation are not incorporated into the model. The whole-brain models described above hold great promise for improving estimates of connectivity based on the actual biology of the human brain.

Thirdly, and finally, our model for entropy production in *Chapter 6* is based on flawed assumptions. It implies that the brain decays to a non-equilibrium, Gaussian steady state. Here, the intrinsic, resting-state fluctuations of the brain can essentially be modelled as a white noise process. Yet there is an abundance of evidence that these fluctuations are not random but instead organised into structured patterns, namely resting-state networks that exhibit ordered, “metastable” transitions (Deco et al., 2017; Deco & Kringelbach, 2016; Lyu et al., 2022; Northoff et al., 2020; Vidaurre et al., 2017; Vidaurre, Hunt, et al., 2018). However, the benefit of assuming white-noise fluctuations is that it enables us to analytically calculate entropy production in non-equilibrium states such as brain activity. Future work should develop more biologically plausible models of entropy production that account for the structured nature of noise in the human brain.

Despite these limitations, the methods described in this thesis hold tremendous promise for elucidating the neural mechanisms of psychedelics, which are very poorly understood. The meta-analysis presented in *Chapters 2-4* highlights the importance of relating the phenomenology, neuroimaging, and pharmacology of psychedelics, which have thus far mostly been researched in isolation or through inadequate correlational studies. The popular REBUS hypothesis, which is that psychedelics decrease the precision-weighting of priors, is very challenging to test, due to the difficulty of meaningfully linking priors to psychological variables of interest based on coarse-grained, non-invasive human brain data. However, there is emerging evidence that multiple psychedelics alter top-down and bottom-up information flow in the brain; for instance, LSD and psilocybin enhance the connectivity between lower-order and higher-order networks (Girn et al., 2022).

Top-down and bottom-up information flow imply that there is a hierarchy of directed connectivity in the brain, and it is now increasingly accepted in neuroscience that this hierarchy plays a crucial role in regulating numerous cognitive and psychological functions, as well as consciousness (Kringelbach, Perl, et al., 2024). Disruption of the hierarchy can lead to various neuropsychiatric disorders and even loss of consciousness. However, there are no studies to date that have explicitly measured the hierarchy of directed connectivity under psychedelics. This thesis is the first body of work to decompose brain data on psychedelics into hierarchical levels and quantify the degree of separation between them. Applying the same methods to data on clinical populations receiving psychedelic therapy may shed light on both the pathological characteristics of hierarchy during disease and how psychedelics exert their therapeutic effects by reconfiguring the hierarchy.

Are psychedelics poised to revolutionise psychiatry? They have exhibited unprecedentedly large effect sizes for treating a variety of conditions, including depression, end-of-life and generalised anxiety disorder, PTSD, and substance use disorders. For instance, whereas existing treatments only lead at most 35% of tobacco users to give up smoking, two doses of psilocybin-assisted therapy were sufficient to cause 80% of participants to completely abstain from smoking for at least six months (M. W. Johnson et al., 2014).

Psychedelics can also be therapeutic for the general population; as the psychedelic advocate Bob Jesse once said, these drugs can lead to the “betterment of well people” (Gandy, 2019).

Indeed, even healthy people struggle with bouts of existential anxiety and perhaps even terror, feelings of deep isolation, and so on. Doubt about our purpose in life is the essence of a “crisis of meaning,” which happens not only on an individual but also on a collective, societal level (Schnell et al., 2018). In other words, most people are surviving but not thriving. Psychedelics are essential tools for thriving (Kringelbach, Vuust, et al., 2024); they can spark a sense of expansive connectedness, rekindle childlike feelings of awe and wonder, and inspire earnest conviction in the ultimate preciousness of life. Double-blind experiments on healthy humans found that 67% of participants rated their psilocybin session as the single most meaningful or among the top five most meaningful experiences of their lives (Griffiths et al., 2006).

However, psychedelics can certainly be misused. When they are taken without proper supervision at chaotic settings such as festivals and raves, psychedelics are not necessarily therapeutic and can in fact trigger “bad trips”: intense feelings of anxiety, despair, and paranoia that seem to last forever. (One of my favourite song lyrics, from “Drugs with Friends” by the band Car Seat Headrest, goes: “Last Friday, I took acid and mushrooms / I did not transcend; I felt like a walking piece of sh*t.”) There are many rock and roll musicians and other celebrities who have abused psychedelics and experienced ego inflation rather than ego death.

Additionally, the evidence base for the therapeutic efficacy of psychedelics is still small. There are fewer than five double-blind, randomised controlled trials for several psychedelics, such as LSD. Better-studied psychedelics, such as psilocybin, exhibited very large remission rates (>50%) in studies with fewer than 60 participants (R. Carhart-Harris et al., 2021; A. K. Davis, Barrett, May, et al., 2021; Von Rotz et al., 2023), but when sample size was increased to more than 100 participants, remission rates from depression dropped substantially to 25-29% (Goodwin et al., 2022; Raison et al., 2023). Recently, the FDA rejected MDMA therapy for PTSD despite two promising Phase 3 clinical trials, due to lack of safety data, concerns about double-blinding, and ethical issues pertaining to underreporting of adverse outcomes and sexual abuse of a small number of participants (Kupperschmidt, 2024). While there are small studies ($N = 18$) demonstrating that psilocybin on its own can lead to long-lasting improvements in wellbeing (Griffiths et al., 2011), there is no large-scale research indicating that psychedelics can lead to flourishing at the population level, especially when psychedelics are not used in controlled settings.

The key to experiencing lasting, positive change from psychedelics is proper integration of the trip. Otherwise, any supposedly life-changing insights from the trip will simply be lost, and the user will revert to their same old habits once the effects of the drug have subsided. In most of the ongoing clinical trials on psychedelics, integration is administered via therapy or a more minimal form of “psychological support,” in which therapists create a space in which participants feel comfortable to discuss and reflect on their trip

(Goodwin et al., 2022). The prevailing view in clinical research is that psychedelics only play a supporting role in therapy, though of course psychedelics can be vastly more effective than therapy on its own (M. W. Johnson et al., 2014; Mitchell et al., 2023).

Future work should investigate the neural mechanisms of the synergy between therapy and psychedelic use. No studies to date have compared brain activity under psychedelics plus therapy with brain activity under psychedelics alone. The measures described in this thesis, together with whole-brain modelling, could provide valuable insights into the role that therapy plays in the restructuring of the brain's hierarchy after the acute effects of the drug have ended. There is an urgent need for this research given that states like Oregon have already legalised psilocybin-assisted therapy for the general population, including people who are not diagnosed with any mental health conditions (E. Klein, 2021).

Could it be true that psychedelics, when deployed in the appropriate context and integrated properly, will elicit a brief experience of genuine flourishing? It is naïve to think that psychedelics by themselves will lead to world peace and heal all the suffering in the world, as some psychedelic evangelists like Timothy Leary appeared to believe. Yet we can be cautiously optimistic that psychedelics, when taken in controlled settings, may foster a renewed sense of connection with the self and the outside world. Time will tell whether these psychological changes can heal the symptoms of depression and other psychiatric conditions more effectively than the existing treatments.

Appendix 1. Qualitative review of other studies about the effects of psychedelics on functional connectivity

The algorithm that we developed to analyse the FC literature could only incorporate data from studies on pairwise FC. There are other measures in the literature that do not compute pairwise FC, such as global brain connectivity (GBC), which defines the FC between voxels and the whole-brain timeseries, or graph-theoretic metrics (e.g. modularity), which quantify global, structural properties of FC. Additionally, our algorithm only analyses undirected connectivity in the brain, so it cannot accommodate studies of effective connectivity.

In this subsection, we will first summarise the findings of the studies that *did* measure pairwise, undirected connectivity but either did not make their data available or were excluded from the meta-analysis in order to mitigate bias. Then, we will discuss the studies that did not compute pairwise, undirected connectivity.

Three of these studies would have been included in the meta-analysis had they provided the necessary data. Carhart-Harris et al. (2013) used ICA to identify 11 RSNs, including the anterior DMN (aDMN). Through linear regression, they calculated the FC between the aDMN and each other RSN. They discovered that psilocybin increased FC between the aDMN and the salience network, right frontoparietal network (FPN), the auditory network, and the dorsal attention network (DAN). They also performed a seed-to-voxel analysis in which they measured the FC between a seed in the ventromedial prefrontal cortex (vmPFC) and every other voxel in the brain. They defined the set of voxels that had positive correlations with the vmPFC as the DMN and the negatively correlated voxels as the task-positive network (TPN). Linear regression revealed that the FC between the DMN and the TPN grew larger under psilocybin.

Roseman et al. (2016) identified patches in the visual cortex (specifically, V1 and V3) that were “retinotopically specific,” that is, patches that were uniquely responsive to stimuli presented along the horizontal or vertical meridians. Then, through linear regression, they determined the “retinotopic coordination” under LSD: the difference between the FC of patches with congruent retinotopic specificity (e.g. horizontally-activated patches in V1 and horizontally-activated patches in V3) and the FC of patches with incongruent retinotopic specificity (e.g. horizontally-activated patches in V1 and vertically-activated patches in V3). Retinotopic coordination was greater under LSD than under placebo.

Finally, Barrett, Doss, et al. (2020) computed the Pearson correlation coefficient between the resting-state timeseries of each ROI in the 268-node Shen parcellation (Shen et al., 2013) and found that FC increased overall under psilocybin, although changes in FC did not exhibit any discernible patterns at the network level.

In our meta-analysis, we showed that psychedelics increased FC between the DMN & both the DAN and ventral attention network (VAN), two networks that are commonly associated with the TPN (Seeley et al., 2007), therefore corroborating the findings of Carhart-Harris et al. (2013). The meta-analysis does not

examine any data about retinotopic coordination; we found that FC within the visual network decreased under psychedelics, but the relationship between retinotopic coordination and FC within the visual network is unclear. In agreement with Barrett, Doss, et al. (2020), we demonstrated that psilocybin, as well as other psychedelics, generally increased FC.

Our results were generally consistent with the findings of the other eight studies that would have been eligible for the meta-analysis. Of the five that focused on cortical FC, two measured whole-brain resting-state network FC with ICA and reported widespread disintegration and desegregation, i.e. reduced within-network FC and elevated between-network FC (Carhart-Harris et al., 2016; Müller et al., 2018). We also showed significant desegregation for all pairs of non-identical brain networks and disintegration, albeit insignificant, for all networks except the FPN. Lebedev et al. (2015) reported a correlation between ego death and salience network disintegration on psilocybin; according to our meta-analysis, the VAN, which is often referred to interchangeably with the salience network, became less connected to itself under psychedelics. In agreement with our findings, Luppi et al. (2021) determined that time-averaged FC globally increased under LSD. Finally, Mason et al. (2021) reported a nearly identical analysis to the one in Mason et al. (2020).

The remaining studies on non-pairwise or directed connectivity used the following methods: graph-theoretic analyses (7 studies), global brain connectivity (6), dynamic causal modelling (4), gradient-based analyses (2), Leading Eigenvector Dynamical Analysis (2), Perturbational Integration Latency Index (1), and local correlation (1).

Seven studies measure the effects of psychedelics on FC with graph-theoretic metrics. A graph is a network structure consisting of nodes and the edges connecting them. When applied to neuroscience, graphs typically describe patterns of FC, in which nodes are ROIs and edges represent the strength (or the mere presence) of connection between ROIs. There are five graph-theoretic properties or structures that are measured in the literature.

The first and most common one is the participation coefficient, which is used in four of the seven studies. The participation coefficient algorithm first divides the brain into modules, which are more connected within themselves than they are with regions outside themselves (Rubinov & Sporns, 2010). The participation coefficient then quantifies the extent to which regions are more connected with other regions in the same module than they are with regions in other modules. Two studies find that psilocybin and LSD reduce modularity in the FPN and in frontal and midline regions, respectively (F. S. Barrett, Krimmel, et al., 2020; Tagliazucchi et al., 2016). The third study divided windows of the BOLD timeseries into predominantly integrated and segregated sub-states, as determined by the degree of modularity in each window (Luppi et al., 2021). Intriguingly, the study only revealed significant differences under LSD in the *segregated* rather than the integrated sub-state. Lebedev et al. (2015) quantified the diversity of connections between brain regions

and modules, which, in the anterior parahippocampal cortex, negatively correlated with subjective ratings of ego death on LSD. (Note that this metric of diversity is actually a measure of Shannon entropy, as discussed in *Section 2.2.3*.)

Lebedev et al. (2015) also measured the effect of LSD on another graph-theoretic measure known as the within-network clustering coefficient. The within-network clustering coefficient reflects the proportion of fully connected triplets (sets of three nodes in which each node is connected to both of the others) in the set of all possible triplets in a network (Masuda et al., 2018). The study showed that the decrease in the clustering coefficient of the salience network under LSD correlated with the subjective experience of ego death. On the other hand, Viol et al. (2017) discovered an increase in clustering coefficients under ayahuasca; the divergent findings may be attributable to differences in the thresholding techniques that were applied to define edges.

Petri et al. (2014) identified persistence homological scaffolds in the graph structure of the partial correlation matrix of the brain. These scaffolds (Edelsbrunner et al., 2002) consist of cycles or “holes” that appear and disappear in the graph as edges are added one-by-one; additionally, cycles are weighted based on their persistence, or the length of time between their appearance and disappearance. Under psilocybin, edges in the graph participate in much more persistent cycles, suggesting more stable connectivity between different cortical regions. Furthermore, the homological scaffolds revealed that connections between modules became stronger and much more pervasive.

Viol et al. (2017) measured changes in a whole host of graph-theoretic metrics under ayahuasca, including the Shannon entropy of the node degrees, geodesic distance, global and local efficiency, and, as already mentioned, clustering coefficients. The degree refers to the number of other nodes to which a particular node is connected, geodesic distance to the shortest path between two nodes, and efficiency to the inverse of the harmonic mean of geodesic distances, either across the entire graph (global) or within subgraphs (local). Shannon entropy of node degree, geodesic distance, and local efficiency all grew larger under ayahuasca, whereas global efficiency grew smaller. (Viol et al. (2019) subsequently found that ayahuasca also elevates the Shannon entropy of geodesic distance.) These results suggest that regions within individual subnetworks become more directly connected on ayahuasca, whereas regions in separate subnetworks become less directly connected. This appears to contradict the aforementioned findings of decreased modularity under psilocybin.

To the extent that decreases in modularity correspond to increases in between-network FC, the results of our meta-analysis do agree with the findings of diminished modularity in the literature. In agreement with the findings of decreased clustering coefficients within the salience network in Lebedev et al. (2015), the meta-analysis revealed that the within-network connectivity of the VAN, which is often equated with the

salience network, decreases under psychedelics. It is difficult to relate our findings of increased between-network FC and decreased within-network FC on ayahuasca/DMT to the results of Viol et al. (2017, 2019), since changes in FC do not necessarily imply alterations to the geodesic distances between nodes. We cannot know for sure whether our meta-analysis substantiates or negates any of the above findings until we conduct a graph-theoretic analysis on our results, which we leave as a task for a future project.

The six studies on global brain connectivity (GBC), also referred to in the literature as “global correlation” (GCOR), measured the averaged Fisher-transformed Pearson correlation coefficient either between each voxel and a 64-component whole-brain time course (Madsen et al., 2021; F. Müller, Lenz, Dolder, Lang, et al., 2017) or between each grayordinate and every other grayordinate in the brain (Preller, Burt, et al., 2018; Preller et al., 2020; Tagliazucchi et al., 2016). (A grayordinate is a gray matter coordinate that is specified by a surface vertex in Connectome Workbench.) Madsen et al. (2021) demonstrated increases in GCOR in regions within the DAN and ECN under psilocybin, while Müller, Lenz, Dolder, Lang, et al. (2017) found that LSD amplified GCOR in subcortical areas spanning the thalamus, caudate, putamen, and pallidum. According to Tagliazucchi et al. (2016), LSD heightened GBC in association cortices. Preller, Burt, et al. (2018) reported opposite findings: if GSR was applied, GBC was higher in sensory and somatomotor areas under LSD, yet lower in subcortical areas and regions involved in associative networks. Preller et al. (2020) reported similar results for psilocybin. Finally, Delli Pizzi et al. (2023) measured the intrinsic connectivity contrast (ICC), which is the root-mean square of GBC, and correlated the results with maps of receptor density. They determined that ICC increased in areas rich in 5-HT_{2A} receptors and poor in 5-HT_{1A} receptors.

We showed that between-network connectivity of the FPN (which is often called the ECN) and DAN both grew larger under psychedelics. Unlike in Preller, Burt, et al. (2018) and in Preller et al. (2020), associative areas (the VAN, DAN, FPN, and DMN) become more connected to other networks in our analysis, though we do find that the visual network and SMN increase in connectivity with other networks. That being said, while their results may overlap, pairwise brain-network analysis cannot be equated with global brain connectivity analysis.

The results of Delli Pizzi et al. (2023) are especially pertinent to this meta-analysis because they sought to integrate the neuroimaging and pharmacology of psychedelics. Our own analysis showed that the 5-HT_{1A} receptor is expressed most in the DAN, whereas the 5-HT_{2A} receptor is densest in the VAN and FPN. Our meta-analysis somewhat corroborates Delli Pizzi et al. (2023), as we found significant decreases in FC within the DAN but an insignificant increase in FC within the FPN.

Studies on dynamic causal modelling (DCM) (Bedford et al., 2023; Kaelen et al., 2016; Kraehenmann, Schmidt, et al., 2015; Preller et al., 2019), unlike all the others, measure effective connectivity (EC) rather

than functional connectivity. FC is fundamentally different from EC; the former analyses correlations between the activity of brain regions, whereas the latter models the simplest brain circuit that explains the data (Stephan & Friston, 2010). The circuit includes intrinsic connections (between an ROI and itself), bilinear extrinsic connections (between ROIs), the driving inputs that affect the intrinsic connections, and the modulatory effects of the experiment on the strength of the extrinsic connections (K. J. Friston et al., 2003). Once they have been specified, these causal factors entail a model space, in which each model is defined by a particular set of driving inputs and modulatory effects. Bayesian model selection (BMS) is then used to identify the model that best explains the data.

Kaelen et al. (2016) measured brain activity in response to music while participants were on LSD. The ROIs in the DCM of that study are the parahippocampus (PH), which is involved in regulating emotional responses to music (Baumgartner et al., 2006; Gosselin et al., 2006; Koelsch, 2014), and the visual cortex (VC), which is activated when the PH is stimulated externally (Barbeau et al., 2005). BMS revealed that, in the model with the highest evidence, music and LSD weakened the intrinsic connections of the two ROIs, whereas the interaction effect between them positively modulated the connection from the PH to the VC.

Kraehenmann, Schmidt, et al. (2015) sought to determine the changes in connectivity that mediate the amygdala's decreased response to emotionally charged images under psilocybin. Their ROIs are the amygdala; visual cortex 1 (V1), which is driven by the images; and the lateral prefrontal cortex (IPFC), which regulates the amygdala's reaction to emotionally salient stimuli (Aznar & Klein, 2013; Hahn et al., 2011). They found that, in the optimal model, threatening stimuli modulated both bottom-up ($V1 \rightarrow \text{amygdala} \rightarrow \text{IPFC}$) and top-down ($\text{IPFC} \rightarrow \text{amygdala} \rightarrow V1$) connections, and furthermore that the interaction between threatening stimuli and psilocybin negatively modulated the connectivity from the amygdala to V1.

Preller et al. (2019) ran a spectral DCM (K. J. Friston et al., 2014), which, unlike the DCM used in the other two studies, is advantageous for modelling resting-state fMRI data. In the spectral DCM, the intrinsic and extrinsic connectivity between ROIs is modulated not by the experiment (e.g. tasks or stimuli) but rather by stochastic fluctuations. A Parametric Empirical Bayes (PEB) model then estimates the effect of between-subject differences (in this case, the placebo vs. LSD condition) on within-subject connections. Preller et al. (2019) measured the effect of LSD on the cortico-striatal-thalamo-cortical (CSTC) loop, which is comprised of ROIs in the PCC, thalamus, ventral striatum (VS), and the superior temporal gyrus (STG). The study found that, relative to placebo, LSD increased connectivity from the PCC to the VS and from the thalamus to the VS, while decreasing connectivity from the thalamus to the STG, from the VS to the PCC, from the VS to the thalamus, from the VS to the STG, and from the PCC to itself.

Finally, Bedford et al. (2023) applied another type of DCM known as regression DCM (rDCM), which is also useful for modeling resting-state fMRI. Whereas normal DCM requires the *a priori* selection of a handful

of brain regions in which to measure connectivity, rDCM enables connectivity estimates across the entire brain by recasting DCM as a linear regression in the frequency domain (Bedford et al., 2023). Connections between individual regions and themselves are assumed to be inhibitory. Bedford et al. (2023) showed that LSD elevated EC between regions and reduced self-inhibition, except in occipital and subcortical regions.

Because the DCM-based studies all have different aims and they do not model the same modulatory effects and driving inputs, it is difficult to perform a meta-analysis on them. Even if their methods were consistent with one another, our meta-analysis algorithm does not incorporate any information about modulatory effects and driving effects. Nevertheless, we can still compare the results of our meta-analysis to the conclusions of these studies about connectivity between specific pairs of ROIs. As already noted, however, the FC score matrix computed in our meta-analysis is symmetric and therefore does not contain any information about the directionality of connections between brain networks, whereas the EC measured in DCMs is inherently directional. In Preller et al. (2019), the sign (positive or negative) of PCC-VS and thalamus-VS connectivity depends on the direction of connectivity, so it is meaningless to compare our undirected results to theirs. However, we can corroborate the findings of Bedford et al. (2023), as we also found that psychedelics elevate between-network FC.

Fundamentally different than FC approaches that assess correlations between discrete ROIs or networks, the gradient-based methods in Girn et al. (2022) and Atasoy et al. (2017) identify axes of connectivity that span multiple regions of the brain. Our meta-analysis algorithm cannot accommodate these studies either, as the algorithm spatially localises patterns of FC to the Yeo networks.

Girn et al. (2022) computed the similarity between the global FC pattern (as measured by the Pearson correlation coefficient) of each of the 10,000 vertices in each cortical surface. They then applied diffusion map embedding to a similarity (covariance) matrix, resulting in a “gradient space”; vertices with lower (higher) gradient values had fewer (more) global connections. Unimodal and transmodal regions of cortex were defined as the set of vertices with lower-percentile and higher-percentile gradient values, respectively. On both LSD and psilocybin, unimodal and transmodal regions became more correlated with each other, whereas within-unimodal and within-transmodal connectivity declined. In the meta-analysis, we also found higher FC between unimodal and transmodal regions under psychedelics, as well as a reduction in FC within unimodal regions under ayahuasca/DMT.

On the other hand, Atasoy et al. (2017) defined gradients of connectivity based on the harmonics of the connectome, which are patterns of coactivation that each have a characteristic spatial frequency and are constrained by the graph structure of white matter tracts in the brain. Each such pattern is associated with a certain amount of power (strength of activation) and energy (strength of activation scaled by the characteristic frequency). LSD elevated the power and energy of the harmonics, especially the energy of high-

frequency harmonics; expanded the repertoire of connectome harmonics that contribute to the overall state of brain activity; and reduced cross-frequency correlations, especially among low-frequency harmonics. It is difficult to relate these findings to the results of the meta-analysis due to the spectral content of the data; there is no information about the *frequency* of brain network activation in the meta-analysis.

Leading Eigenvector Dynamical Analysis (LEIDA) identifies the leading eigenvector of the BOLD phase-locking matrix, which reflects a dominant global pattern of connectivity in the brain. Each region's BOLD phase is then projected onto the leading eigenvector. *K*-means clustering on these projections reveal brain states, e.g. resting-state networks, that are recurrently visited over time. Lord et al. (2019) discovered that psilocybin decreased the probability of occurrence of a phase-locking state that strongly resembled the FPN and increased the probability of occurrence of a phase-locking state that reflects global coherence. Olsen et al. (2022) showed that psilocybin reduced the occurrence and dwell time of a brain state characterised by connectivity between the lateral frontoparietal (part of the FPN) and medial parietal-cingulate (part of the DMN) cortices. To the extent that phase-locking reflects FC as defined by most other studies in the literature, our meta-analysis support neither of the above findings. According to our results, both within-network FC for the FPN and FPN-DMN FC increased, though between-network FC generally grew larger.

The last two analysis methods were each performed by only one study, so there was not enough data to execute the meta-analysis algorithm on them. (The algorithm would not have been able to accommodate the results from these studies anyway.)

Jobst et al. (2021) computed changes in the Perturbational Integration Latency Index (PILI) under LSD. They used a whole-brain model to perturb the supercritical Hopf bifurcation parameter of brain regions (Deco, Cabral, et al., 2018), resulting in patterns of global synchronisation and desynchronisation. Then, they compared the integration of brain activity, which was quantified as the overall amount of phase-locking, before and after perturbation. Changes in integration therefore served as a measure of the recovery of brain dynamics to the baseline state. Under LSD, brain dynamics, especially in the limbic network, visual network, and DMN, were perturbed farther away from their baseline state and also took longer to recover than under placebo. While there is no corollary to this finding in the results of our meta-analysis, they do substantiate another conclusion in the study, which is that the baseline state of brain dynamics is more integrated under LSD than under placebo. In other words, the brain exhibits greater global FC, as we show through increased between-network FC in the meta-analysis.

The local correlation (LCOR) analysis in Madsen et al. (2021) measures a weighted average of the Pearson correlation coefficient between the timeseries of each voxel and neighbouring voxels. Psilocybin

decreased LCOR in regions within the DMN, ECN, and visual cortex. If LCOR can be likened to a measure of within-network connectivity, then our meta-analysis supports these results, although within-network connectivity for the FPN, which is equated with the ECN, does increase.

Appendix 2. Formulas associated with methods in Chapter 6

The multivariate OU model is described by the following **Equation A2.1**:

$$\frac{d\mathbf{x}(t)}{dt} = -\mathbf{B}\mathbf{x}(t) + \boldsymbol{\eta}(t) \quad (\text{A2.1})$$

where $\mathbf{x}(t)$ is the multivariate timeseries (here, multivariate means multiple regions of the brain), $\mathbf{B}$ is a “friction matrix,” and $\boldsymbol{\eta}$ is white noise with the covariance matrix $\mathbf{D}$:

$$\langle \boldsymbol{\eta}(t)\boldsymbol{\eta}^T(t') \rangle = 2\mathbf{D}\delta(t - t') \quad (\text{A2.2})$$

$\mathbf{B}$ is a so-called friction matrix because the OU model’s core assumption is that, if the real parts of all of the eigenvalues of $-\mathbf{B}$ are negative, then the system will decay exponentially quickly to a Gaussian non-equilibrium steady state with mean $\mathbf{x} = \mathbf{0}$ and covariance $\mathbf{S}$:

$$\mathbf{S} = \lim_{t \rightarrow \infty} \langle \mathbf{x}(t)\mathbf{x}^T(t) \rangle \quad (\text{A2.3})$$

The smaller the eigenvalues of $-\mathbf{B}$ are in magnitude, the slower the system will decay to the steady-state; in other words, the “friction” on the decay is higher, hence the name of the matrix.

Equation A1.1 is a Langevin equation because it describes the evolution of the system in terms of a deterministic force, which is dictated by $\mathbf{B}$, and a stochastic or random force, which is determined by $\boldsymbol{\eta}$. If it were not for $\boldsymbol{\eta}$, the system would eventually decay to an equilibrium ($\frac{d\mathbf{x}(t)}{dt} = 0$) rather than a non-equilibrium steady-state. The entropy production is the extent to which the system resists equilibrium due to the stochastic forces.

Godrèche & Luck (2018) analytically derived the entropy production of the OU model:

$$\Phi = -\text{Tr}(\mathbf{D}^{-1}\mathbf{B}\mathbf{Q}) \quad (\text{A2.4})$$

where Φ is the entropy production rate and $\mathbf{Q} = \mathbf{B}\mathbf{S} - \mathbf{D}$. Because $\mathbf{S}$ obeys the following differential equation (see Godrèche & Luck (2018) for details):

$$\frac{d\mathbf{S}(t)}{dt} = 2\mathbf{D} - \mathbf{B}\mathbf{S}(t) - \mathbf{S}(t)\mathbf{B}^T \quad (\text{A2.5})$$

and $\frac{d\mathbf{S}(t)}{dt} = \mathbf{0}$ at the steady state:

$$\mathbf{B}\mathbf{S} + \mathbf{S}\mathbf{B}^T = 2\mathbf{D} \quad (\text{A2.6})$$

at the steady state. As first demonstrated by (Lax, 1960), reversibility would imply that:

$$\mathbf{B}\mathbf{D} = \mathbf{D}\mathbf{B}^T \quad (\text{A2.7})$$

and consequently:

$$\mathbf{B}\mathbf{S} = \mathbf{D} \quad (\text{A2.8})$$

Then:

$$\mathbf{Q} = \mathbf{B}\mathbf{S} - \mathbf{D} \quad (\text{A2.9})$$

parametrises the amount of irreversibility in the system. I refer the reader to Godrèche & Luck (2018) for further details on the derivation of Φ .

In order to measure Φ , we need to fit $\mathbf{B}$ and $\mathbf{D}$. We accomplish this with least-squares regression, which first requires that we discretise $\mathbf{x}(t)$ as follows:

$$\mathbf{x}(t_{i+1}) = [\mathbf{I} - \Delta t \mathbf{B}] \mathbf{x}(t_i) + \mathbf{A} \boldsymbol{\eta}_i \quad (\text{A2.10})$$

where $\mathbf{A}\mathbf{A}^T = 2\mathbf{D}$ and $\boldsymbol{\eta}_i$ is white noise with mean 0 and variance Δt . We then solve the following optimisation problem:

$$\min \|\mathbf{X}_{1:T} - (\mathbf{I} - \Delta t \mathbf{B}) \mathbf{X}_{0:T-1}\|^2 \quad (\text{A2.11})$$

where $\mathbf{X}_{1:T}$ and $\mathbf{X}_{0:T-1}$ are N regions $\times$ T timepoints matrices representing the evolution of $\mathbf{x}(t)$ from timepoint 1 to T and from timepoint 0 to $T-1$. The coefficient matrix yielded by the optimisation is then divided by $-\Delta t$ to obtain $\mathbf{B}$, and the covariances of the residuals are divided by $2\Delta t$ to obtain $\mathbf{D}$. I computed Φ in each epoch of data and averaged across epochs to obtain a final estimate of Φ for each dataset.

Our second goal is to measure trophic coherence on the network of directed connections between brain regions. While $\mathbf{B}$ is an asymmetric matrix and therefore “directed,” it is not a network *per se*, since self-interactions (interactions between regions and themselves) can affect the dynamics of the network. Thus, we apply a network-constrained variant of the OU model, which was originally introduced by (Schwarze & Porter, 2021). Here, self-interactions are set to zero, and the dynamics are therefore constrained to the edges of a network:

$$\frac{d\mathbf{x}(t)}{dt} = (\mathbf{W} - \mathbf{I})\mathbf{x}(t) + \mathbf{v}(t) \quad (\text{A2.12})$$

where the noise term $\mathbf{v}(t)$ has the covariance matrix $\sigma\mathbf{I}$:

$$\langle \mathbf{v}(t) \mathbf{v}^T(t') \rangle = 2\sigma\mathbf{I}\delta(t - t') \quad (\text{A2.13})$$

Note the following correspondences between the generalised (network-unconstrained) and network-constrained OU models:

$$-\mathbf{B} = \mathbf{W} - \mathbf{I} \quad (\text{A2.14})$$

$$\mathbf{D} = \sigma\mathbf{I} \quad (\text{A2.15})$$

Another key difference between the network-constrained OU and the generalised OU is that noise is independently applied to each region of the network in the former, whereas different regions can receive different combinations of noise in the latter.

To solve for $\mathbf{W}$, the network on which we will later measure trophic coherence, we first need to discretise $\mathbf{x}(t)$ as follows:

$$\mathbf{x}(t_{i+1}) = [\mathbf{I} + \Delta t(\mathbf{W} - \mathbf{I})]\mathbf{x}(t_i) + \mathbf{\Gamma}\boldsymbol{\zeta}_i \quad (\text{A2.16})$$

where $\mathbf{\Gamma}\mathbf{\Gamma}^T = 2\sigma\mathbf{I}$ and $\boldsymbol{\zeta}_i$ is white noise with mean 0 and variance Δt . Note that this discretisation can be re-expressed as:

$$\mathbf{x}(t_{i+1}) = [(1 - \Delta t)\mathbf{I} + \Delta t\mathbf{W}]\mathbf{x}(t_i) + \mathbf{\Gamma}\boldsymbol{\zeta}_i \quad (\text{A2.17})$$

Then we can solve the non-negative least squares optimisation problem, which constrains $\mathbf{W}$ to strictly non-negative weights:

$$\min_{\mathbf{W}: \mathbf{W}_{ij} \geq 0} \|\mathbf{X}_{1:T} - ((1 - \Delta t)\mathbf{I} + \Delta t\mathbf{W})\mathbf{X}_{0:T-1}\|^2 \quad (\text{A2.18})$$

The coefficient matrix that results from solving the optimisation is then divided by Δt to obtain $\mathbf{W}$, for which we measure trophic coherence.

I made two adaptations to the multivariate OU model. Firstly, in order to examine consistencies between models, I used the same time-lag in the OU model that I did in INSIDEOUT, i.e., $\tau = 45$ samples (0.225 seconds). This recasts the least squares optimisation problem for solving $\mathbf{B}$:

$$\min \|\mathbf{X}_{45:T} - (\mathbf{I} - \Delta t\mathbf{B})\mathbf{X}_{0:T-45-1}\|^2 \quad (\text{A2.19})$$

and also the non-negative least squares optimisation problem for solving $\mathbf{W}$:

$$\min_{\mathbf{W}: \mathbf{W}_{ij} \geq 0} \|\mathbf{X}_{45:T} - ((1 - \Delta t)\mathbf{I} + \Delta t\mathbf{W})\mathbf{X}_{0:T-45-1}\|^2 \quad (\text{A2.20})$$

While this time-lag results in a worse estimate of $\mathbf{B}$ and $\mathbf{W}$, it is mathematically valid because it is essentially coarse-graining the timescale with which the continuous OU process is being discretised, and the timescale is arbitrary.

Secondly, I $\mathbf{z}$ -scored each row (each region's timeseries) in $\mathbf{X}$, since I observed that the MEG timeseries have much lower standard deviation under LSD compared to placebo. Z-scoring standardises data in such a way that the mean becomes 0 and the standard deviation becomes 1. However, this does interfere with the calculation of Φ because it turns all the diagonal elements of $\mathbf{S}$ – all the steady-state variances – to 1, if the model fits the data. $\mathbf{S}$ affects Φ by altering $\mathbf{Q} = \mathbf{B}\mathbf{S} - \mathbf{D}$. I also measured Φ without $\mathbf{z}$ -scoring $\mathbf{X}$.

As mentioned earlier, trophic coherence is determined based on the imbalance between incoming and outgoing at each node in a directed network $\mathbf{W}$, as well as the topology of the network. The imbalance at each node n is:

$$v_n = w_n^{\text{in}} - w_n^{\text{out}} \quad (\text{A2.21})$$

where w_n^{in} are the weights of the incoming connections at n and w_n^{out} are the weights of the outgoing connections. The other quantity that is necessary for computing trophic coherence is the graph Laplacian:

$$\mathbf{L} = \mathbf{D} - \mathbf{W} - \mathbf{W}^T \quad (\text{A2.22})$$

where $\mathbf{D}$ is the “degree” matrix, a diagonal matrix in which the diagonal elements reflect the weights of all the connections at each node. $\mathbf{W} \neq \mathbf{W}^T$ for a directed network, so $\mathbf{W} - \mathbf{W}^T$ contains the difference between each connection (e.g., node $i \rightarrow j$) and its reversed counterpart (e.g., node $j \rightarrow i$); it is therefore identical to the square root of irreversibility.

The trophic levels $\mathbf{t}$ can then be determined by solving the linear equation:

$$\mathbf{L}\mathbf{t} = \mathbf{v} \quad (\text{A2.23})$$

Furthermore, the trophic incoherence $\mathbf{C}$ is:

$$\mathbf{C} = \sqrt{1 - \min_{\mathbf{t}} \frac{\sum_{i,j} w_{ij}(t_j - t_i - 1)^2}{\sum_{i,j} w_{ij}}} \quad (\text{A2.24})$$

Trophic coherence is maximised at 1 when the difference between levels is maximised (also at 1) and minimised at 0 when there are no differences between any of the levels. Thus, trophic coherence corresponds to the strength of hierarchy.

Based on similar principles, a slightly more recent framework developed the notions of hierarchical levels, where the “forward” hierarchical levels, $\mathbf{g}$, are defined as (Moutsinas et al., 2021):

$$\mathbf{g} = \underset{\mathbf{x} \in \mathbf{T}}{\operatorname{argmin}} \|\mathbf{x}\|_2 \quad (\text{A2.25})$$

where:

$$\mathbf{T} = \underset{\mathbf{x} \in \mathbb{R}^n}{\operatorname{argmin}} \|\mathbf{M}\mathbf{x} - \mathbf{d}\|_2 \quad (\text{A2.26})$$

with $\mathbf{M}$ being the transpose of the *in-degree* Laplacian matrix of the input network $\mathbf{W}$ and $\mathbf{d}$ being the in-degrees of all the nodes. That is,

$$\mathbf{M} = (\mathbf{D}^{\text{in}} - \mathbf{W})^T \quad (\text{A2.27})$$

where $\mathbf{D}^{\text{in}}$ is a diagonal matrix comprised of the in-degrees of all the nodes.

Similarly, the “backward” hierarchical levels, $\mathbf{y}$, are defined as follows:

$$\mathbf{y} = \underset{\mathbf{x} \in \mathbf{S}}{\operatorname{argmin}} \|\mathbf{x}\|_2 \quad (\text{A2.28})$$

where:

$$\mathbf{S} = \underset{\mathbf{x} \in \mathbb{R}^n}{\operatorname{argmin}} \|\mathbf{\Lambda}\mathbf{x} - \boldsymbol{\delta}\|_2 \quad (\text{A2.29})$$

with $\mathbf{\Lambda}$ being the *out-degree* Laplacian matrix of $\mathbf{W}$ and $\boldsymbol{\delta}$ being the out-degrees of all the nodes. That is,

$$\mathbf{\Lambda} = \mathbf{D}^{\text{out}} - \mathbf{W} \quad (\text{A2.30})$$

where $\mathbf{D}^{\text{out}}$ is a diagonal matrix comprised of the in-degrees of all the nodes.

Then, the “overall” hierarchical levels, $\mathbf{h}$, are defined as:

$$\mathbf{h} = \frac{1}{2}(\mathbf{g} - \boldsymbol{\gamma}) \quad (\text{A2.31})$$

We can then consider the forward hierarchical differences (HD), $\mathbf{F}$:

$$\mathbf{F} = \{g_j - g_i | W_{ij} > 0, i, j \in \mathbf{W}\} \quad (\text{A2.32})$$

The weighted mean of $\mathbf{F}$ corresponds to the average difference in the forward hierarchical levels:

$$\text{mean}(\mathbf{F}) = \frac{\sum_{i,j} w_{ij}(g_j - g_i)}{\sum_{i,j} w_{ij}} \quad (\text{A2.33})$$

and the standard deviation of $\mathbf{F}$ is the standard deviation of the differences in forward hierarchical levels:

$$\text{std}(\mathbf{F}) = \sqrt{\frac{\sum_{i,j} w_{ij}(g_j - g_i)^2}{\sum_{i,j} w_{ij}} - (\text{mean}(\mathbf{F}))^2} \quad (\text{A2.34})$$

Note that the latter quantity is analogous to the trophic coherence.

We can also consider the backward HD and their corresponding weighted mean and standard deviation:

$$\mathbf{B} = \{\gamma_i - \gamma_j | W_{ij} > 0, i, j \in \mathbf{W}\} \quad (\text{A2.35})$$

$$\text{mean}(\mathbf{B}) = \frac{\sum_{i,j} w_{ij}(\gamma_i - \gamma_j)}{\sum_{i,j} w_{ij}} \quad (\text{A2.36})$$

$$\text{std}(\mathbf{B}) = \sqrt{\frac{\sum_{i,j} w_{ij}(\gamma_i - \gamma_j)^2}{\sum_{i,j} w_{ij}} - (\text{mean}(\mathbf{B}))^2} \quad (\text{A2.37})$$

Appendix 3. Definitions of entropy

Throughout this thesis, I have discussed various techniques for measuring entropy, starting with the neuroimaging meta-analysis (*Chapter 3*), in which I reviewed all the fMRI studies that have examined entropic brain activity under psychedelics. In *Chapter 5* and *Chapter 6*, I measure entropy production, which is identical to irreversibility, in order to assess the effects of psychedelics on hierarchy. Entropy is a concept that appears to be defined differently in multiple branches of physics, such as classical thermodynamics, statistical mechanics, and information theory, but as we shall see below, they are all equivalent.

The concept of entropy originates from Rudolf Clausius (Clausius, 2009). In particular, Clausius noticed that, for a reversible heat engine, the ratio between the heat input and the rejected heat is equal to the ratio between the absolute temperatures of the high and low temperature reservoirs. That is,

$$\frac{Q_H}{Q_L} = \frac{T_H}{T_L} \rightarrow \frac{Q_H}{T_H} = \frac{Q_L}{T_L} \quad (\text{A3.1})$$

However, for an irreversible heat engine,

$$\frac{Q_H}{T_H} < \frac{Q_L}{T_L} \rightarrow \frac{Q_H}{T_H} - \frac{Q_L}{T_L} < 0 \quad (\text{A3.2})$$

In other words, the ratio between the heat transferred in a process and the temperature of the surroundings must always increase over time. Clausius defined entropy, S , as the continuous integral of the ratio between the heat transferred and the temperature of the surroundings. The Clausius inequality of 1855 states that, for a heat engine or any other thermodynamic system exchanging heat with its surroundings, entropy in the past must always be less than or equal to entropy in the future:

$$-\oint dS = \oint \frac{\delta Q}{T} \leq 0 \quad (\text{A3.3})$$

With this inequality, Clausius became the first person to rigorously define the Second Law of Thermodynamics. The inequality essentially states that heat spontaneously flows from hotter to colder bodies, but never the other way around; consequently, entropy must always increase over time.

Clausius' entropy was only formulated for classical thermodynamic systems, which are defined by macroscopic properties such as heat and temperature. The project of statistical mechanics was to explain these macroscopic variables in terms of the collective, statistical properties of ensembles or collections of many microscopic states (e.g., the velocities of individual properties). In the 1870s, Boltzmann defined the entropy of an ideal gas in terms of the number of microstates, Ω , that collectively have the macroscopic energy, E , of the gas (Sharp & Matschinsky, 2015). **Boltzmann's entropy** was later recast by Max Planck into the following form:

$$S(E) = k_B \ln \Omega(E) \quad (\text{A3.4})$$

where k_B is Boltzmann's constant. In other words, the larger the number of possible ways in which the gas can distribute its energy among its particles, the higher the entropy. Hence, a gas in which all the particles are initially located in one corner of a container has much lower entropy than a gas in which all the particles later spread out, simply because there are many more ways to distribute energy in the latter arrangement than in the former.

Furthermore, as the number of particles increases, it becomes extremely unlikely for the gas to spontaneously return to the arrangement in which all of the particles are bunched together, since the microstates in the scattered distribution of particles exponentially outnumber the microstates in the initial distribution. In just 1 mole of gas, there are already 10^{23} particles; thus, if it is equally probable for each particle to be at any location in the volume V of gas, there are $V^{10^{23}}$ more microstates in the scattered distribution than the initial distribution. This staggeringly large number ensures that the gas tends towards the more entropic (scattered) distribution. Thus, in statistical mechanics, the Second Law of Thermodynamics is essentially a consequence of large numbers of particles; more entropic distributions are vastly, vastly more numerous and therefore much, much more probable than less entropic ones.

How is Boltzmann's entropy related to Clausius' entropy? It turns out that they are exactly equivalent given that:

$$\frac{1}{T} = \frac{\partial S}{\partial E} \quad (\text{A3.5})$$

Integrating both sides over $dQ = dE$, we recover Clausius' entropy. While this may seem like an odd way of defining entropy, it actually accords with our commonplace notions of temperature, namely that heat flows from hotter to colder temperatures. Indeed, consider a system with two energies, E_1 and E_2 , at slightly different temperatures, T_1 and T_2 . Conservation of energy ensures that $\delta E_1 = -\delta E_2$. Therefore,

$$\begin{aligned} \delta S &= \frac{\partial S_1(E_1)}{\partial E} \delta E_1 + \frac{\partial S_2(E_2)}{\partial E} \delta E_2 \\ &= \left(\frac{\partial S_1(E_1)}{\partial E} - \frac{\partial S_2(E_2)}{\partial E} \right) \delta E_1 \\ &= \left(\frac{1}{T_1} - \frac{1}{T_2} \right) \delta E_1 \end{aligned} \quad (\text{A3.6})$$

Because $\delta S > 0$ due to the Second Law of Thermodynamics, $T_1 > T_2$ implies that $\delta E_1 < 0$, and therefore energy or heat passes from the hotter to the colder system.

Boltzmann's entropy, as stated above, refers to systems that have a fixed energy E . However, most equilibrium systems do not in fact have a fixed energy but instead fluctuate between different energies. To define entropy in this case, we can first calculate the entropy of many identical copies of the system and then divide by the number of copies W to obtain the entropy of the single system. When there are many identical

copies, the number of systems with energy n is equal to $p(n)W$. The total number of states across all possible energies Ω is simply the number of ways to arrange $p(n)W$ systems into energy n , across all n :

$$\Omega = \frac{W!}{\prod_n (p(n)W)!} \quad (\text{A3.7})$$

Based on Stirling's approximation,

$$\log W! = W \log W - W + 1 \quad (\text{A3.8})$$

Therefore,

$$S = k_B \log \Omega = k_B \log \frac{W!}{\prod_n (p(n)W)!} \quad (\text{A3.9})$$

simplifies to:

$$S = -k_B W \sum_n p(n) \log p(n) \quad (\text{A3.10})$$

And for the entropy of a single system, as stated above, we simply divide by W :

$$S = -k_B \sum_n p(n) \log p(n) \quad (\text{A3.11})$$

This is Josiah Willard **Gibbs' entropy**. It turns out to be completely identical in form to a separate definition of entropy that was created in an entirely different context, namely information theory. In the 1940s, the father of information theory, Claude Shannon, sought to determine the theoretical bounds on the probability of error when transmitting information over a channel. His Source Coding Theorem of 1948 proved that information can be compressed with negligible risk of information loss, or error, and furthermore that **Shannon entropy** is the lower bound on the number of bits of information in this compression (Shannon, 1948). The Shannon entropy is defined as follows:

$$S = -\sum_x p(x) \log p(x) \quad (\text{A3.12})$$

which is clearly the same as Gibbs' entropy, up to a factor of k_B .

Clausius' and Boltzmann's entropy were both defined for equilibrium systems, yet biological systems such as the brain are clearly far from equilibrium. While Gibbs' entropy does generalise to non-equilibrium systems, it is in practice extremely challenging to determine the different probabilities of all the various microstates. Fluctuation theorems in statistical mechanics have made it possible to quantify the change in entropy, or entropy production, in a non-equilibrium process. In particular, **Crooks' fluctuation theorem** of 1998 states (Crooks, 1998):

$$\frac{P_{\text{forward}}(W)}{P_{\text{reverse}}(-W)} = e^{\Delta S/k_B} \quad (\text{A3.13})$$

where $P_{\text{forward}}(W)$ is the probability of absorbing work W if the process at hand is run forwards in time, and $P_{\text{reverse}}(-W)$ is the probability of doing work $-W$ if the process is run backwards in time.

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