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Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains

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ABSTRACT

Psychedelic drugs, such as psilocybin and LSD, represent unique tools for researchers investigating the neural origins of consciousness. Currently, the most compelling theories of how psychedelics exert their effects is by increasing the complexity of brain activity and moving the system towards a critical point between order and disorder, creating more dynamic and complex patterns of neural activity. While the concept of criticality is of central importance to this theory, few of the published studies on psychedelics investigate it directly, testing instead related measures such as algorithmic complexity or Shannon entropy. We propose using the fractal dimension of functional activity in the brain as a measure of complexity since findings from physics suggest that as a system organizes towards criticality, it tends to take on a fractal structure. We tested two different measures of fractal dimension, one spatial and one temporal, using fMRI data from volunteers under the influence of both LSD and psilocybin. The first was the fractal dimension of cortical functional connectivity networks and the second was the fractal dimension of BOLD time-series. In addition to the fractal measures, we used a well-established, non-fractal measure of signal complexity and show that they behave similarly. We were able to show that both psychedelic drugs significantly increased the fractal dimension of functional connectivity networks, and that LSD significantly increased the fractal dimension of BOLD signals, with psilocybin showing a non-significant trend in the same direction. With both LSD and psilocybin, we were able to localize changes in the fractal dimension of BOLD signals to brain areas assigned to the dorsal-attenion network. These results show that psychedelic drugs increase the fractal dimension of activity in the brain and we see this as an indicator that the changes in consciousness triggered by psychedelics are associated with evolution towards a critical zone.

Author summary

The unique state of consciousness produced by psychedelic drugs like LSD and psilocybin (the active component in magic mushrooms) are potentially useful tools for discovering how specific changes in the brain are related to differences in perception and thought patterns. Past research into the neuroscience of psychedelics has led to the proposal of a "general theory" of brain function and consciousness: the Entropic Brain Hypothesis proposes that consciousness emerges when the brain is sitting near a critical tipping point between order and chaos and that the mind-expanding elements of the psychedelic experience are caused by the brain moving closer to that critical transition point. Physicists have discovered that near this critical point, many different kinds of systems, from magnets to ecosystems, take on a distinct, fractal structure. Here, we used two measures of "fractal-quality" of brain activity, as seen in fMRI, to test whether the activity of the brain on psychedelics is "more fractal" than normal. We found evidence that this is the case and interpret that as supporting the theory that, psychedelic drugs are move the brain towards a more critical state. We also found that these measures behave similarly to a well established, non-fractal measure of signal complexity frequently used in previous studies of consciousness.

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1. Introduction

Since the turn of the century, there has been a renewal of interest in the science of serotonergic psychedelic drugs (LSD, psilocybin, mescaline, etc.), both in terms of possible medical applications of these drugs (Vollenweider and Kometer, 2010; Tupper et al., 2015), and what they might tell us about the relationship between activity in the brain and the phenomenological perception of consciousness (Andrew, 2015; Carhart-Harris, 2018). For those interested in the relationship between activity in the brain and consciousness, psychedelic drugs are particularly useful, as volunteers under the influence of a psychedelic are still able to report the nature of their experience and recall it even after returning to normal consciousness. This contrasts favourably with the other class of drugs commonly used to explore consciousness: anaesthetics, which by the very nature of their effects, make it difficult to gather first-person experiential data from a volunteer (Michael, 2005). The subjective experience of the psychedelic state is associated with radical alterations to both internal and external senses, including visual distortions, vivid, complex closed-eye imagery, alterations to the sense of self, emotional extremes of euphoria and anxiety, and in extreme cases, psychosis-like effects (Studerus et al., 2011). The psychedelic experience can also have profound personal, and even spiritual or religious character (Griffiths et al., 2006; Barrett and Griffiths, 2017), which has made them central to the religious practices of many cultures around the world (Evans Schultes et al., 2001).

Neuroimaging studies using fMRI and MEG have suggested that the experiential qualities of the psychedelic state can be explained, in part, by the effects these drugs have on the entropy of brain activity: a theory known as the Entropic Brain Hypothesis (EBH) (Carhart-Harris et al., 2014; Carhart-Harris, 2018). The EBH posits that during normal waking consciousness, activity in the brain is near, but slightly below, a critical zone between order and disorder, and that under the influence of psychedelic drugs the entropy of brain activity increases, bringing the system closer to the zone of criticality. In this context, 'criticality' refers to a zone between two qualitatively different states (a phase transition): the sub-critical state, which is comparatively inflexible, highly ordered and displays low entropy, while the super-critical state may be highly entropic, flexible, and disorganized. A canonical example of a critical phase transition is the heating of a magnet: at a critical temperature the magnet rapidly looses is magnetic properties (a hallmark of a globally organized, sub-critical state), as the atomic spins become disorganized (a high entropy, low-order super-critical state). The hypothesis that the brain operates in, or near, the critical zone is a much-discussed one (Beggs and Timme, 2012; John, 2019) and it is well-established that critical systems posses appealing information-processing properties, such a memory, communication, and maximized dynamic range (Cocchi et al., 2017). Near the critical point, as will be discussed late, systems tend to take on particular, highly stereotyped structures, including fractal character, which can serve as an indirect test of criticality.

Studies with psilocybin have found that the patterns of functional connectivity in the brain undergo dramatic reorganization, characterized primarily by the rapid emergence and dissolution of unstable communities of interacting brain regions that do not occur in normal waking consciousness (Petri et al., 2014). Similarly, under psilocybin, the repertoire of possible states functional connectivity networks can occupy is increased, which is interpreted as an increase in the entropy of the entire system (Tagliazucchi et al., 2014). Work on other psychedelics with pharmacology related to psilocybin has found similar results: under the influence of Ayahuasca, a psychedelic brew indigenous to the Amazon, the Shannon entropy of the degree distribution of functional connectivity networks is increased relative to normal consciousness (Viol et al., 2017) (encouragingly, the opposite effect has been shown under the conditions of sedation with propofol (Pappas et al., 2018)). Analysis of MEG data from volunteers under the influence of lysergic acid diethylamide (LSD) has shown an increase in the Lempel-Ziv complexity of the signals, which is thought to reflect increased complexity of activity in the brain (Schartner et al., 2017a). LSD has also been recently shown to alter the connectome harmonics of brain networks, in a manner that suggests an increase in the complexity of network harmonics describing brain activity (Atasoy et al., 2017). For a comprehensive review of the current state of psychedelic research into the EBH see *The Entropic Brain - Revisited* (Carhart-Harris, 2018).

While a core element of the EBH is the theory that the psychedelic experience moves the brain closer to the zone of criticality, many of the measures that have been tested so far do not address the phenomena of criticality directly. These measures usually test where the brain falls on a unidimensional axis of order vs. randomness. Lempel-Ziv complexity (Schartner et al., 2017a), nodal entropy (Viol et al., 2017; Pappas et al., 2018) and the entropy of possible states (Tagliazucchi et al., 2014), all describe a movement towards higher entropy, which is consistent with the entropic predictions of the EBH, but not necessarily informative about the relative proximity to the zone of criticality. In many of these analyses, a completely random system would score maximally high on complexity (for instance a completely random time-series would have a normalized Lempel-Ziv score of unity, which is the upper bound of the measure). While these analyses are interesting and have clearly been fruitful, they paint a limited picture of the brain as a complex system, and don't directly test the central thesis of the EBH. To date, the only study that has directly addressed the criticality aspect of the EBH is the study of LSD and connectome harmonics (Atasoy et al., 2017), although other studies have found evidence of scale-free, power-law behaviour generally thought to be indicative of critical phenomena (Muthukumaraswamy and Liley, 2018). We stress that entropy is not identical to randomness in all circumstances (it is entirely possible to have a highly structured system with higher entropy), but rather in this context, many of the measures, such as LZ_C monotonically increase with randomness. This is a useful, but limited understanding of "complexity", particularly in the context of critical systems, prompting our proposal of fractal dimension as an additional measure that can be related to critical processes. We also note (discussed below) that there are many ways to assess the complexity of a time-series which provide different information about system dynamics, and which can be successfully applied in human neuroimaging paradigms relevant to the quality of consciousness (Varley et al., 2020a). None of the measures discussed or reported here should be considered the archetypal measure of complexity (if such a thing is even possible, or desirable (Feldman and Crutchfield, 1998)), and each measure comes with strengths and weaknesses.

To address the relative lack of studies testing criticality directly, in this paper, we propose the fractal dimension of brain activity as a novel measure of complexity that provides insights into the criticality of the psychedelic state, as well as providing a measure of 'complexity' that is related to, but distinct from, the entropic measures described above.

Fractals are ubiquitous in nature and dramatic visualizations of colourful constructs like the Mandelbrot set have even permeated popular culture (Mandelbrot, 1983). Fractals are defined by the property of having a non-integer dimension, which can be naively thought of as how 'rough' or 'complex' the shape in question is, or slightly more formally, the extent to which it maintains symmetry across different scales (Falconer, 2003). In systems that display self-organizing criticality, as the system naturally evolves towards a critical point, its dynamic structure will tend to take on increasingly fractal character that can be described in terms of fractal dimension (Bak and TangKurt, 1987; Watanabe et al., 2015; Mizutaka, 2018), and in systems which can be 'tuned' to a critical state (such as the Ising model, which has been explored as a model of critical brain activity (Haimovici et al., 2013; Das et al., 2014; Abeyasinghe et al., 2018)), fractal structures emerge near the critical point (Stinchcombe, 1989). If, under the influence of a psychedelic, the brain is moving closer towards a state of criticality, as the EBH posits, then we might expect any fractal character in brain activity to become more pronounced. There is some evidence of a symmetrical effect when consciousness is lost: in states of sleep and drug-induced anaesthesia, the fractal dimension of brain activity drops significantly, with the exception of REM sleep, during which the fractal dimension rises again (Pereda

et al., 1998; Klonowski et al., 2005; Ferenets et al., 2006; Klonowski et al., 2010). As REM sleep is the state of sleep when the greatest quantity of phenomonological experience takes place (in the form of dreams), this suggests that the fractal dimension of brain activity is related to the 'quantity' of experiential consciousness available to an individual. Similarly, in rats, during ketamine-induced anaesthesia the fractal dimension of brain activity is significantly higher in key-brain regions associated with consciousness when compared with anaesthesia induced by other drugs (Sladjana Spasic et al., 2011), and as ketamine is known to induce vivid, dream-like states of consciousness at high doses (Paul and Galloon, 1975), which comports with the REM sleep finding. A recent study exploring the relationship between temporal and spatial fractal dimension and consciousness found that the fractal dimension was reliably reduced following loss of consciousness in sleep and sedation, proving a powerful means of intra-subject state discrimination (Ruiz de Miras et al., 2019). Temporal fractal dimension is also sensitive to subtler changes in cognition, including differentiating between internally and externally generated perceptions (Ibaáñez-Molina and Iglesias-Parro, 2014), attentional states (Bornas et al., 2013), and hypnosis (Solhjoo et al., 2005).

Past research has found evidence that both the physical structure of the brain itself, and the patterns of activity measured by neuroimaging paradigms display pronounced fractal character (Ieva et al., 2014; Di Ieva et al., 2015). Changes to the fractal dimension of brain structures are associated with changes in cognition and clinically significant diagnoses, such as schizophrenia and obsessive-compulsive disorder (Ha et al., 2005), Alzheimer's disease (King et al., 2009), as well as characteristics such as intelligence (Kiho et al., 2006) and ageing (Mustafa et al., 2012). There is some preliminary evidence that cortical functional connectivity networks display fractal character, both during rest and tasks (Gallos et al., 2012a) and that this fractal character plays an important role in regulating how information is propagated through the brain (Gallos et al., 2012b).

To test the relationship between the fractal dimension of activity of brain and consciousness, we used fMRI data from subjects under the influence of either LSD or psilocybin, provided by the Psychedelic Research Group at Imperial College London (Carhart-Harris et al., 2012, 2016). From this data, we created 1000-node functional connectivity networks and performed a network-specific variation of the box-counting algorithm (Song et al., 2007) to extract the fractal dimension. We also used a second measure, the Higuchi fractal dimension (Higuchi, 1988), to test the temporal fractal dimension of BOLD time-series. These two measures capture two axes on which the complexity of brain activity might be measured: spacial (network fractal dimension) and temporal (Higuchi fractal dimension). If the psychedelic state is associated with a movement towards a critical zone associated with increased fractal character, we would expect to see this when examined on multiple measures, and so these two measures serve as internal validation for each-other. While the network fractal dimension is not spacial in the way, for example, a 2-dimensional box-counting analysis of activity at the cortical surface would be, it does return insight into how information processing may be distributed across multiple, spatially distinct brain regions. Previous work has shown that both of these measures are sensitive to changes in level of consciousness following traumatic or anoxic brain injury in patients with disorders of consciousness (Varley et al., 2020b). Both measures were reliably able to discriminate between healthy controls, those in a minimally conscious state, and those in a vegetative state, suggesting that they are sensitive to dynamics important for the maintenance of complex consciousness.

In addition to the measures of fractal dimension, we also implemented a Lempel-Ziv complexity.

(LZ_C) analysis, as described in (Schartner et al., 2015, 2017a, 2017b) as a check of validity. LZ_C has historically been used in temporally dense signals (EEG, MEG), although recent evidence suggests that it, and several other non-linear signal analysis tools are also applicable to fMRI BOLD signals (Varley et al., 2020a), and we hypothesize that the patterns observed in previous studies (increased complexity under psychedelics) should be apparent here as well.

2. Materials & methods

2.1. Ethics statement

The data analyzed here have been reported in previous studies (Carhart-Harris et al., 2012, 2016). Both studies described herein were approved by a UK National Health Service research ethics committee, and the researchers complied with all relevant regulations and ethical guidelines, including data privacy and participant informed consent.

2.2. Calculating network fractal dimension

When calculating the fractal dimension of a naturally occurring system, researchers commonly use a box-counting algorithm, which is an accessible and computationally tractable method that captures the distribution of elements across multiple scales (Falconer, 2003). Intuitively, the box-counting dimension defines the relationship between a measured quality of a shape in space, and the metric used to measure it. The canonical example is the question of how long the coastline of Britain is (Mandelbrot, 1967). If one wishes to measure the length of Britain's coast, they could estimate it by calculating the number of square boxes $N_B(l_B)$, of a given width l_B, that are necessary to tile the entire coastline. For very large values of l_B, $N_B(l_B)$ will be small, while as the value of l_B decreases, $N_B(l_B)$ will asymptotically approach some value. If the shape being tiled is a fractal, then:

$$N_B(l_B) \propto l_B^{-d_B} \tag{1}$$

Where d_B is the box-counting dimension. Algebraic manipulation shows that d_B can be extracted by linear regression in log-log space as:

$$\lim_{l_B \to 1} \frac{ln(N_B(l_B))}{ln(l_B)} \propto -d_B \tag{2}$$

A similar logic is used when calculating the box-counting dimension of a graph. For a graph $G = (V,E)$, a box with diameter l_B defines a set of nodes $B \subset V$ where for every pair of nodes v_i and v_j the distance between them $l_{ij} < l_B$. Here, the distance between two nodes v_i, v_j is the graph geodesic between the vertices: the number of edges in the shortest path between them. To quantify the fractal dimension of the functional connectivity networks, a box counting method, the Compact Box Burning algorithm (CBB) (Song et al., 2007), was used to find $N_B(l_B)$ for a range of integer l_B values 1.10. If G has fractal character, a plot of $ln(N_B(l_B))$ vs. $ln(l_B)$ should be roughly linear, with a slope of $-d_B$. If, during the iteration $ln(N_B(l_B)) = 0$, we stopped the iteration, as all subsequent boxes of size l_B will equal 0, which would bias the estimate of network fractal dimension. For a visualization of the linear regressions, see 5.

Unfortunately, because of the logarithmic relationship between box-size and fractal dimension, exponentially higher resolutions are required to achieve modest increases in the accuracy of the measured fractal dimension. Computational explorations, where a box-counting method is used to approximate a fractal dimension that has already been solved analytically, show that the box-counting dimension converges to the true dimension with excruciating slowness (Joosten et al., 2016), necessitating the highest-resolution parcellation that is computationally tractable.

It should be noted that there has been much discussion surrounding the appropriateness of this method for describing the presence (or absence) of power-laws in empirical data (Clauset et al., 2009). We chose the above-described method for a few reasons: the first was to remain as consistent as possible with the method used in previous analysis of the fractal dimension of human FC networks (Gallos et al., 2012a, 2012b), the second was because of the tractability of the analysis, and finally, the relatively small size of the network forced a limited range of box sizes l_B

(approximately a single order of magnitude), which precluded many of typical power-law fitting algorithms (Clauset et al., 2009). We stress that, given the ongoing discussion around the optimal way to find power-law relationships, the results reported here should not be interpreted as an unambiguous claim of incontrovertible proof that such a power-law relationship holds here - rather a preliminary result to establish the possibility that fractal topologies and brain dynamics may be related to the maintenance of consciousness.

The implementation of the CBB was provided as open-source code by the Mackse lab, and can be found at: http://www-levich.engr.ccny.cuny.edu/webpage/hmakse/software-and-data/

2.3. Calculating BOLD time-series fractal dimension

To calculate the temporal fractal dimension, we used the Higuchi method for calculating the self-similarity of a one-dimensional time-series, an algorithm widely used in EEG and MEG analysis (KesićSladjana and Spasić, 2016). The original method is recorded in detail in the original paper (Higuchi, 1988), but will be briefly described here. The algorithm takes in a time-series $X(t)$ with N individual samples, defined as:

$$X(t) = x_1, x_2, x_3, \ldots, x_N \tag{3}$$

In this case, every $X(t)$ corresponds to one Hilbert-transformed BOLD time-series $H(t)$ extracted from our functional brain scans (details below). Hilbert-transforming was chosen to be consistent with previously-reported studies of time-series complexity and consciousness (Schartner et al., 2015, 2017a, 2017b). From each time-series $X(t)$, we create a new time-series $X(t)_k^m$, defined as follows:

$$X(t)_k^m = x_m, x_{m+k}, x_{m+2k}, \ldots, x_{m+\left\lfloor \frac{N-m}{k} \right\rfloor k} \tag{4}$$

where $m = 1, 2, \ldots, k$.

For each time-series $X(t)_k^m$ in $k_1, k_2, \ldots k_{max}$, the length of that series, $L_m(k)$, is given by:

$$L_m(k) = \frac{\left(\sum_{i=1}^{\frac{N-m}{k}} |x_{im+k} - x_{(i-1)k}|\right) \frac{N-1}{\frac{N-m}{k} k}}{k} \tag{5}$$

We then define the average length of the series $\langle L(k) \rangle$, on the interval $[k, L_m(k)]$ as:

$$\langle L(k) \rangle = \sum_{m=1}^{k} \frac{L_i(k)}{k} \tag{6}$$

If our initial time-series $X(t)$ has fractal character, then $\langle L(k) \rangle \propto k^{-D}$. As with the procedure for calculating the network fractal dimension, the algorithm iterates through values of k from $1 \ldots k_{max}$ and calculates $ln(\langle L(k) \rangle)$ vs. $ln(k^{-1})$, extracting D by linear regression. The various values of k can be thought of as analogous to the various values of l_B used to calculate the network fractal dimension. The Higuchi algorithm requires a pre-defined k_{max} value as an input, along with the target time-series. This value is usually determined by sampling the results returned by different values of k_{max} and selecting a value based on the range of k_{max} where the fractal dimension is stable. For the psilocybin and LSD datasets, we sampled over a range of powers of two $(2, \ldots, 128)$. Due to the comparably small size of BOLD time-series (100 entries for the psilocybin dataset and 434 entries for the LSD dataset), the range of k_{max} values that our algorithm could process without returning an error was limited. We ultimately decided on $k_{max} = 64$ for the LSD dataset and $k_{max} = 32$ for the psilocybin dataset.

The implementation we used was from the PyEEG toolbox (Bao et al., 2011), downloaded from the Anaconda repository. Interestingly, the Higuchi fractal dimension algorithm can also be applied to two-dimensional images, such as histological photographs (Ahammer, 2011; Klonowski et al., 2013; Aliahmad et al., 2014). An interesting follow-up to this work might be to explore the distribution of instantaneous activations over a two-dimensional the cortical surface, thus providing another test of whether the spacial distribution of cortical activity follows a fractal pattern.

2.4. Lempel-Ziv complexity of temporal BOLD series

Lempel-Ziv complexity (LZ_C), is a commonly-used measure of signal complexity in consciousness studies (Schartner et al., 2015, 2017a; Schaefer et al., 2017). Lempel-Ziv complexity can be best thought of as a measure of the entropy rate of a signal, giving an estimate of the information-density per unit time (Amigó et al., 2004). Alternately, it can be understood as an upper-bound on the algorithmic complexity of a time-series based on how compressible it is (Ruffini, 2017a). The algorithm itself is sensitive the length of the signal being analyzed (Ruffini, 2017a), which we account for in the following analysis. The algorithm has been detailed elsewhere (see cited research), but in short, the LZ_C measures the "complexity" of a signal by quantifying the size of the dictionary necessary to reconstruct the signal in question.

For every ROI in our parcellated brain, the absolute value of the Hilbert-transformed time-series $F(t)$ is binarized according to the following procedure:

$$F_B(t_i) = \begin{cases} 1, & \text{if } F(t_i) \geq mean(F(t)) \\ 0, & \text{otherwise} \end{cases}$$

The resulting time-series are stacked into a binary matrix where every row corresponds to an ROI and every column is a time-point in the scan. The matrix is then flattened orthogonally to T, resulting in a vector on which the Lempel-Ziv analysis was performed.

The Lempel-Ziv algorithm creates a dictionary D, which is the set of binary patterns that make up V and returns a value $LZ_C \propto |D|$. For every time-series $F_B(t) \in X$, a random time-series was created, by shuffling all the entries in $F(t)$. These were stacked into a binary matrix M_{rand}, with the same dimensions as M, however containing only noise. This random matrix was flattened and its LZ_C value calculated. As the randomness of a string increases, $LZ_C \to 1$, so this value was used to normalise the "true" value of LZ_C, which was divided by LZ_{Crand} to ensure all values were within a range $(0, 1)$.

In electro-physiological studies, LZ_C is commonly used in conjunction with HFD as a synergistic measure of complexity (e.g. (Gómez and Hornero, 2010; Akar et al., 2015; Husseen Al-Nuaimi et al., 2018)). While LZ_C and HFD often behave similarity (high HFD appears with high LZ_C and vice-versa), they index different elements of temporal dynamics: LZC provides an estimate of the algorithmic complexity and entropy rate of a binary (or otherwise-discretized time-series), while the HFD takes a renormalization-like approach to the distribution of values in the time-series. As far as we know, there has been no investigation into the analytic relationship between the measures, although, if such a relationship can be derived, this would provide significant insights into the analysis of complexity in time-series.

2.5. Data acquisition & preprocessing

Both the LSD data and the psilocybin data were provided by the Psychedelic Research Group at Imperial College London, having already been preprocessed according to their specifications (Carhart-Harris et al., 2012, 2016).

2.5.1. LSD data

The data acquisition protocols and preprocessing pipelines were described in detail in a previous paper (Carhart-Harris et al., 2016), so we will describe them in brief here. 20 healthy volunteers underwent two scans, 14 days apart. On one day they were given a placebo (10-mL saline) and on the other they were given an active dose of LSD (75 μg of LSD

in 10-mL saline). BOLD scanning consisted of three 7 min eyes closed resting state scans. The first and third scans were eyes-closed, resting state without any in-ear auditory stimulation (music), and these were what were used in this report.

Anatomical imaging was performed on a 3T GE HDx system (the same machine was used for both datasets). These were 3D fast spoiled gradient echo scans in an axial orientation, with field of view = 256 × 256 × 192 and matrix = 256 × 256 × 129 to yield 1 mm isotropic voxel resolution. TR/TE = 7.9/3.0 ms; inversion time = 450 ms; flip angle = 20°. BOLD-weighted fMRI data were acquired using a gradient echo planer imaging sequence, TR/TE = 2000/35 ms, FoV = 220 mm, 64 × 64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. Thirty five oblique axial slices were acquired in an interleaved fashion, each 3.4 mm thick with zero slice gap (3.4 mm isotropic voxels). The precise length of each of the two BOLD scans was 7:20 min (a third scan, recording during music listening was collected, but excluded from this analysis). One subject aborted the experiment due to anxiety and four others were excluded for excessive motion (measured in terms of frame-wise displacement).

The following pre-processing stages were performed: removal of the first three volumes, de-spiking (3dDespike, AFNI), slice time correction (3dTshift, AFNI), motion correction (3dvolreg, AFNI) by registering each volume to the volume most similar to all others, brain extraction (BET, FSL); 6 rigid body registration to anatomical scans, non-linear registration to 2 mm MNI brain (Symmetric Normalization (SyN), ANTS), scrubbing (FD = 0.4), spatial smoothing (FWHM) of 6 mm, band-pass filtering between [0.01 to 0.08] Hz, linear and quadratic de-trending (3dDetrend, AFNI), regressing out 9 nuisance regressors (all regressors were bandpass-filtered using the same range described above).

2.5.2. Psilocybin data

The data acquisition protocols and preprocessing pipelines were described in detail in a previous paper (Carhart-Harris et al., 2012), so we will describe them in brief here. Fifteen healthy volunteers were scanned. Anatomical and task-free resting state scans (each lasting 18 min) were taken. Solutions were infused manually over 60 s, beginning 6 min after the start of each functional scan. Subjects psilocybin (2 mg in 10-mL saline) in the active scan. In this study we used only the psilocybin-positive scan, comparing the pre-infusion condition to the post-infusion condition for control.

All imaging was performed on a 3T GE HDx system. For every functional scan, we obtained an initial 3D FSPGR scan in an axial orientation, with FoV = 256 × 256 × 192 and matrix = 256 × 256 × 192 to yield 1-mm isotropic voxel resolution (TR/TE = 7.9/3.0 ms; inversion time = 450 ms; flip angle = 20°). BOLD-weighted fMRI data were acquired using a gradient-echo EPI sequence, TR/TE 3000/35 ms, field-of-view = 192 mm, 64 × 64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. Fifty-three oblique-axial slices were acquired in an interleaved fashion, each 3 mm thick with zero slice gap (3 × 3 × 3-mm voxels). A total of 240 vol were acquired.

All data was preprocessed using the following pipeline: de-spiking, slice time correction, motion correction to best volume, brain extraction using the BET module in FSL, registration to anatomy (using FSL BBR), registration to 2 mm MNI (ANTS), scrubbing (FD = 0.4), smoothing with a 6 mm kernel, bandpass filtering [0.01–0.08 Hz], linear and quadratic detrending, regression of 6 motion regressors and 3 nuisance regressors (all of the regressors were not smoothed and were bandpassed with the same filters). At the suggestion of the original research team that provided the data, six volunteers were excluded from the analysis for excessive motion.

2.6. Formation of functional connectivity networks

BOLD time-series data were extracted from each brain in CONN (CONN is a collection of SPM/MATLAB scripts with a GUI designed for easy manipulation of fMRI, MEG, and EEG data. It is available at http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon, 2012) and the cerebral cortex was segmented into 1000 distinct ROIs, using the "Schaefer Local/Global 1000 Parcellation" (Schaefer et al., 2017) (https://github.com/ThomasYeoLab/CBIG/blob/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal/Parcellations/MNI/Schaefer2018_1000Parcels_7Networks_order_FSLMNI152_1mm.nii.gz) Due to the slow-convergence of Eq. (2), and the necessity of having a network with a wide enough diameter to accommodate a sufficiently wide range of box-sizes (if l_B is greater than or equal to the diameter of the network, then $N(l_B)$ is trivially one), we attempted to strike an optimal balance between network resolution and computational tractability.

Every time-series $F(t)$ was first transformed by taking the norm of the Hilbert transform of each time-series, to ensure an analytic signal and keep the signals consistent with the Higuchi fractal dimension analysis.

$$H(t) = |Hilbert(F(t))| \tag{7}$$

Pearson Correlation was chosen largely due to its wide use in the field and ease of interpretation. While more exotic, nonlinear similarity functions exist (normalized mutual information, information-based similarity, etc), for a prospective study of this sort, use of a well-characterized, linear function was appropriate, although future studies might explore the effect of different functions on large network topology. The resulting time-series $H(t)$ was then correlated against every other time-series, using the Pearson Correlation, forming a matrix M such that:

$$M_{ij} = \rho\big(H_i(t), H_j(t)\big) \tag{8}$$

No significance testing was done (every ρ was included, regardless of whether it met some arbitrary α value or not), because significance filtering would result in an uneven distribution of edges and degrees between graphs that may have effected the analysis. Due to the high thresholding, the vast majority of weak, or potentially spurious connections were likely removed anyway. The correlation matrix has a series of ones that run down the diagonal, corresponding the correlation between each timeseries and itself which, if treated directly as a graph adjacency matrix, would produce a graph where each node had exactly one self-loop in addition to all its other connections. To correct for this, the matrices were filtered to remove self-loops by turning the diagonal of ones to zeros, ensuring simple graphs:

$$M_{ij} = \begin{cases} 0, & \text{if } i = j \\ M_{ij}, & \text{otherwise} \end{cases} \tag{9}$$

Finally, the matrices were binarized with a 95% threshold, such that:

$$M_{ij} = \begin{cases} 1, & \text{if } M_{ij} \geq P_{95} \\ 0, & \text{otherwise} \end{cases} \tag{10}$$

The thresholding procedure was passed over all entries in the matrix, regardless of whether they were positive or negative, and any surviving edges became ones. The practical effect of such stringent thresholding is that only positive values survived, and including the negative values drove down the minimum edge weight that survived thresholding, resulting in a marginally less sparse network than what might have occurred if negative values had been thrown out prior to thresholding. While binarization does throw out information, the CBB algorithm that we used does not factor edge weight into whether two nodes constitute members of the same box. A 95% threshold was chosen based on the findings of Gallos et al. (2012b), who showed that functional connectivity networks only display fractal character at high thresholds (see Introduction). All surviving values $M_{ij} < 0 \mapsto 0$. The results could then be treated as adjacency matrices defining functional connectivity graphs, where each row M_i and column M_j corresponds to an ROI in the initial cortical parcellation, and the connectivity between all nodes is given by Eq. (3). To see samples of the binarized adjacency matrices, and the associated graphs see Fig. 1.

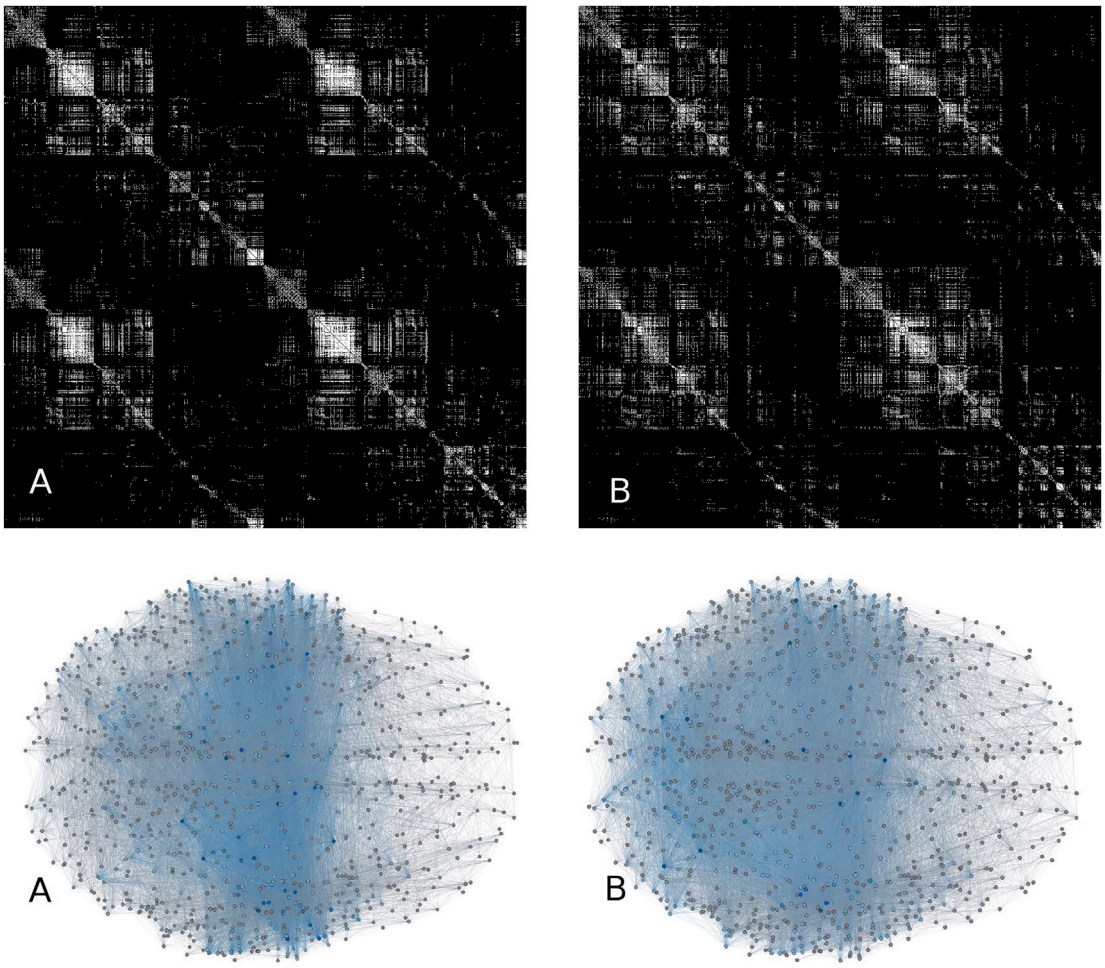


Fig. 1. Whole-brain functional connectivity networks and matrices.
Two binarized, 1000-ROI adjacency matrices from a single, randomly chosen subject, and their associated functional connectivity graphs (A ↦ A, etc). In the adjacency matrices, every pixel represents an edge between two nodes: if the pixel is white, the edge exists, if black, the edge does not exist. A is the functional connectivity matrix from the placebo condition, B is the matrix from the LSD condition. While the differences in fractal character are not intuitively obvious upon visual inspection, subtle differences in the distribution of connections can be seen.

When the corresponding networks are constructed, differences in gross-scale connectivity can be seen, although, as with the matrices, a change in fractal structure is not intuitively obvious. The networks are constructed using axial projections of the 3-dimensional atlas: each node is roughly at the centroid of it's associated ROI.

2.6.1. *Specific-network analysis*

To localize changes in the complexity of brain activity, individual ROIs were grouped into networks, using the mapping proposed by Yeo et al. (2011). We used the 1000 ROI parcellation with seven networks: default mode network, somato-motor network, visual network, dorsal-attenion network, ventral-attenion network, limbic network, and fronto-parietal control network. For each of the 1000 ROIs in the Schaefer Local/Global parcellation, the mapping by Yeo et al. (2011) provides an assignment of that node to one of the seven listed networks. After assigning each individual time-series to a network, we can then explore statistics (HFD, LZ_C) in these smaller subsets of the system, instead of aggregating over all 1000 nodes. This gives us a sense of how LSD and psilocybin effect disparate brain systems. For visualization of the assignment of nodes to these networks see Fig. 2. We then used the Higuchi fractal dimension method described above on each subset of regions to get a measure of the average time-series fractal dimension of each network.

2.6.2. *Statistical analysis*

All analysis was carried out using the Python 3.6 programming language in the Spyder IDE (https://github.com/spyder-ide/spyder), using the packages provided by the Anaconda distribution (https://www.anaconda.com/download). All packages were in the most up-to-date version, with the exception of NetworkX: due to compatibility issues with the CBB code, NetworkX v. 0.36 was used. Packages used include NumPy (van der Walt et al., 2011), SciPy (Jones et al., 2001), and NetworkX (Hagberg et al., 2008). NetworkX was used for the implementation of the CBB algorithm, NumPy was used for manipulation of adjacency matrices and arrays, SciPy was used for statistical analysis, primarily using the SciPy.Stats module. Unless otherwise specified, all the significance tests are non-parametric: given the small sample sizes and heterogeneous populations, normal distributions were not assumed. Wilcoxon Signed Rank test was used to compare drug conditions against their respective control conditions. To correct for multiple comparisons within a single analyses (eg. assessing HFD for LSD and psilocybin, at both the global and network levels), we used the Benjamini-Hochberg procedure with an FDR of 5% for all tests within a single analysis.

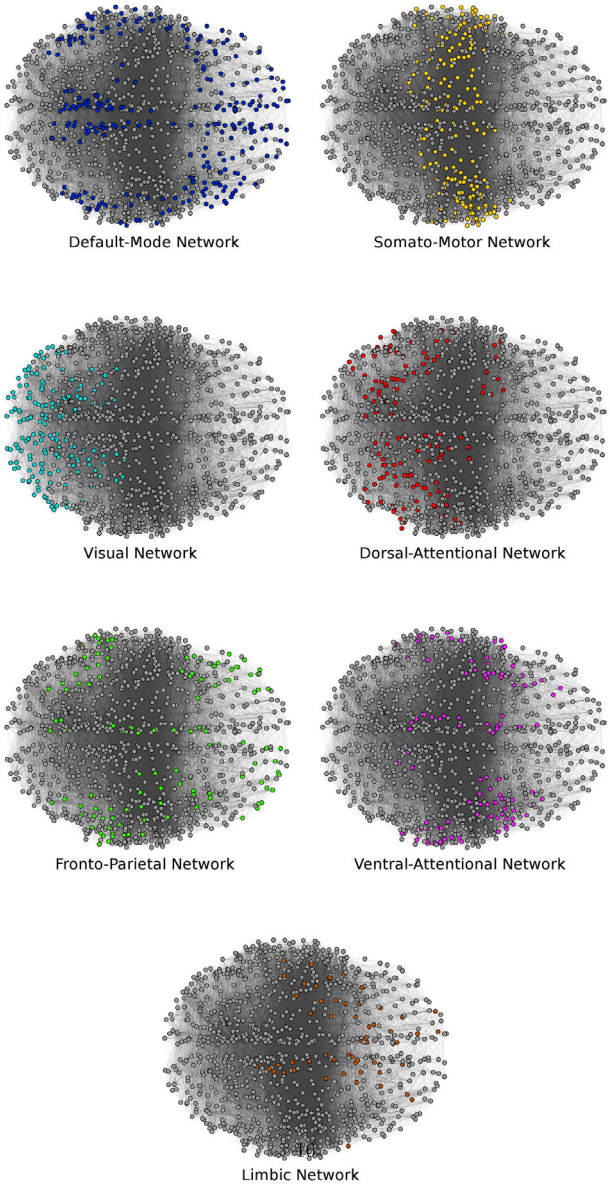


Fig. 2. Assignment of nodes to canonical networks.
A visualization of how the 1000-node functional connectivity networks were parcellated into seven different brain regions, following the mapping described by Yeo et al. (Yeo et al., 2011; Schaefer et al., 2017), The specific map file is available from GitHub at https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal/.

3. Results

3.1. LSD & psilocybin network fractal dimension

The Wilcoxon signed-rank test found significant differences, when corrected with the Benjamini-Hochberg procedure with an FDR of 5% (BenjaminiYosef, 1995), between LSD and placebo conditions (H(4), p-value = 0.001), and between the pre-infusion and post-infusion psilocybin conditions (H(6), p-value = 0.05). The mean fractal dimensions for the LSD condition was 3.37 ± 0.15, and for the associated placebo condition it was 2.939 ± 0.29. For psilocybin the mean fractal dimension was 3.52 ± 0.049, and for control it was 3.277 ± 0.372. For a plot of the relative fractal dimensions, see Fig. 3. For a visualization for how the fractal dimension was calculated by linear regression for LSD see 4A and for Psilocybin, see Fig. 4B. For visualization of all box-counting plots, see Figs. 5 and 6.

These results are consistent with the EBH, which posits that the properties of criticality will increase during psychedelic states (Carhart-Harris et al., 2014). These results are also consistent with the hypothesis that the changes in brain activity induced by LSD are very similar to the changes induced by psilocybin, which is unsurprising given their shared serotonergic pharmacology and the phenomenological similarities between the associated experiences. The difference in base-line fractal dimension [between LSD and psilocybin] is intriguing: we had expected it to be consistent across both datasets, as normal waking consciousness is presumably similar among volunteers in both datasets. We tentatively hypothesize that it may be a result of differences in data acquisition and processing specifications. It may be, however, that the base-line fractal dimension of BOLD signals is not as consistent between populations as we had assumed, and this may be an interesting future direction of exploration.

3.2. LSD & psilocybin BOLD time-series fractal dimension

The Wilcoxon signed-rank test, when corrected with the Benjamini-Hochberg procedure with an FDR of 5%, found significant differences between the Higuchi fractal dimension of the LSD time-series and placebo time-series (H(3) p-value = 0.001), but not between the pre-infusion and post-infusion psilocybin time-series. The mean network fractal dimension for the LSD-condition time-series was 0.91 ± 0.005 and for the placebo condition it was 0.9 ± 0.006. For the post-infusion psilocybin condition, the mean network fractal dimension of the BOLD time-series was 1.03 ± 0.015, while for the pre-infusion condition it was 1.02 ± 0.009. For visualization of the global Higuchi fractal dimension for the LSD versus control conditions, see Fig. 7A, and for visualization of the global Higuchi fractal dimension for the psilocybin versus control conditions, see Fig. 7B.

In the LSD condition, we found a non-significant, positive correlation between the network fractal dimension and the temporal fractal dimension ($\rho = 0.26$, p-value = n.s.), but no meaningful correlation between both measures in the psilocybin condition ($\rho < 0.1$). In the LSD condition, this correlation was destroyed by truncating the BOLD time-series, as described previously.

These results suggest that, at least for the LSD condition, the activity of the brain tends towards increased fractal character in the temporal as well as spatial dimension. This is consistent with the EBH and serves as validation of the network fractal dimension results reported above. The difference between the averages between the two non-drug conditions (placebo condition of the LSD dataset, and the pre-infusion condition of the psilocybin dataset) are most likely explained by the significant difference in the lengths of scans and number of time-points the algorithm was fed. To test this, we re-ran the Higuchi fractal dimension analysis on LSD signals that had been truncated to be the same length as the psilocybin time-series (100 samples), and found that there was no longer a significant difference between the drug and control conditions. We take this as evidence that the lack of significant difference between psilocybin and control conditions cannot be attributed to the drug directly but rather, may be reflective of a fundamental limitation in the utility of the Higuchi algorithm when working with sparse datasets.

3.2.1. Localizing time-series fractal dimension to sub-networks

To take advantage of the fact that the Higuchi method of calculating fractal dimension works on one time-series at a time, we were able to test whether any specific sub-networks of the brain displayed any changes in the fractal-dimension of the associated time-series. For the psilocybin condition, only one significant difference in the fractal dimension of BOLD time-series was found: the fractal dimension increased in the dorsal attenion network, at the edge of significance (H(6), p-value = 0.05). In light of our suspicion that the psilocybin time-series are too short for meaningful Higuchi analysis, we strongly feel that these results

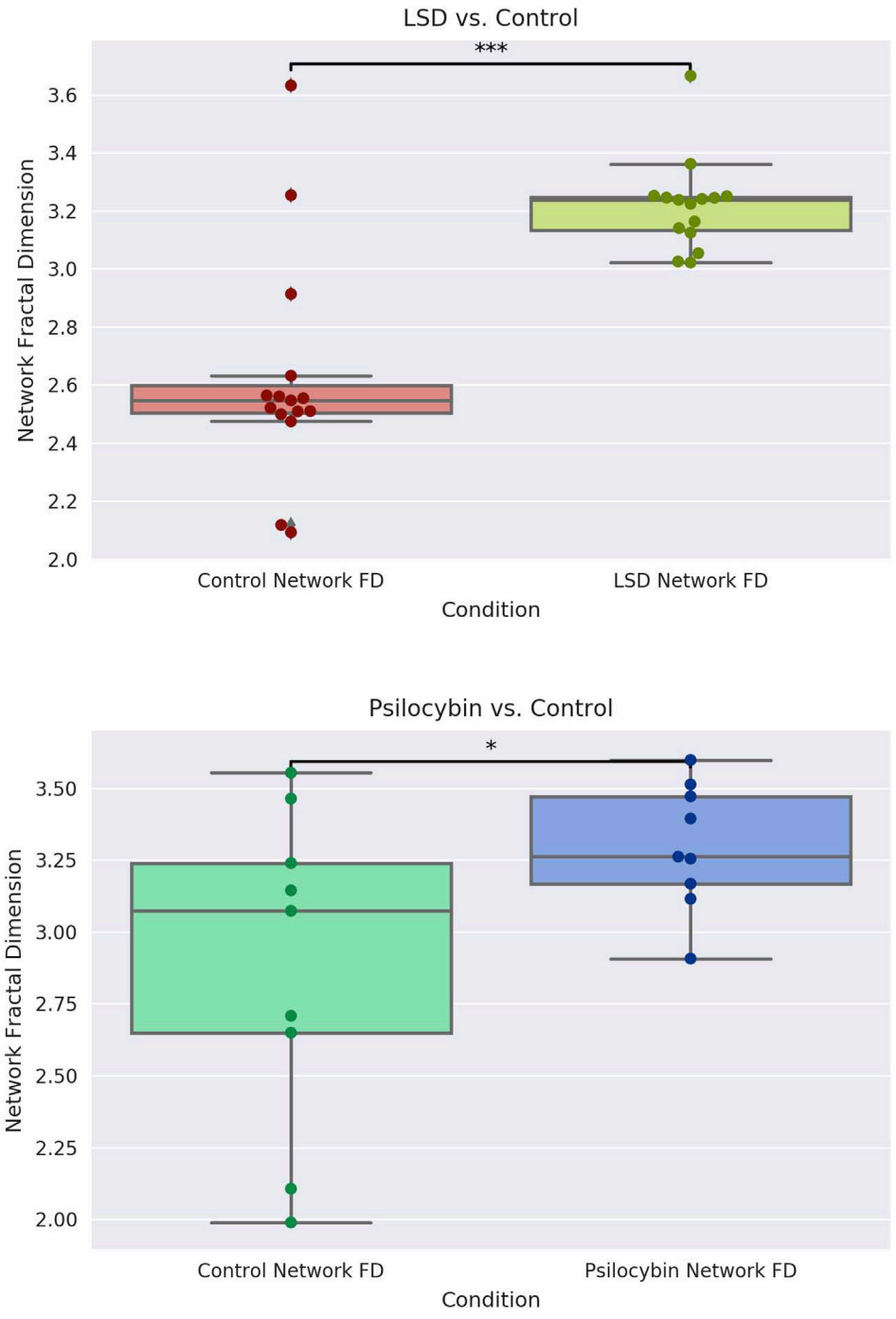


Fig. 3. Network fractal dimension.
Swarm and box plots of the network fractal dimensions for the two psychedelic drugs tested. Note that both psychedelic conditions show less variability compared to their respective controls.*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

should be replicated, using either longer fMRI scans, or, ideally, MEG or EEG data. For a table of the Higuchi fractal dimensions for each network tested in the psilocybin condition, see Table 1.

For the LSD condition, compared to the placebo condition, we found significant increases in fractal dimension under LSD in the fronto-parietal network (H(4), p-value = 0.001), in the dorsal-attenion network (H(0), p-value = 0.0005), and the visual network (H(4), p-value = 0.001). For a table of the Higuchi fractal dimensions for each network tested in the LSD condition, see Table 2.

The significant increase in the dorsal-attenion network in both the LSD and psilocybin conditions suggests that this finding may be more robust than the increases in the fronto-parietal network or visual network that appear to be unique to LSD. An increase in the complexity of activity in the visual system under LSD is somewhat unsurprising, although why this did not appear in psilocybin is unclear (under the psilocybin condition the mean complexity in the visual system did increase relative to the pre-infusion condition, although this was not significant).

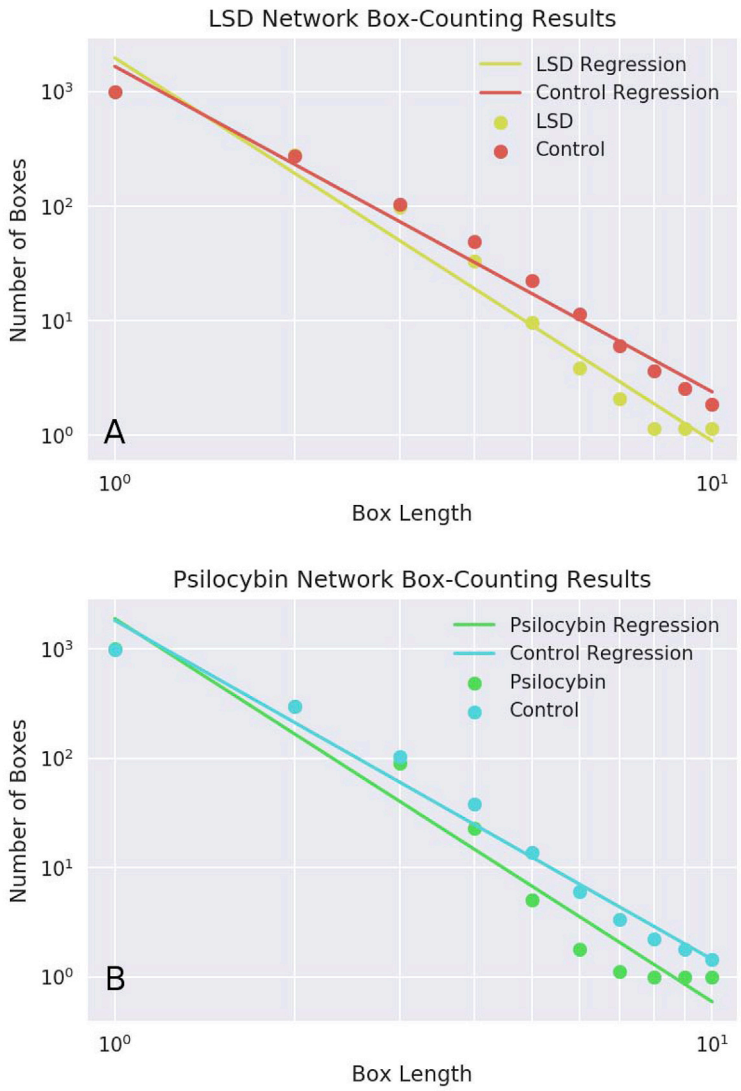


Fig. 4. Log-log regression of box length vs. number of boxes to tile the network.
Here is the derivation of the fractal dimension for the LSD and psilocybin tests. For a range of integer-valued box-lengths ({1,2,…,10}), the minimum number of boxes of that length necessary to tile a 1000-ROI functional connectivity measure is calculated. If the log-transformed values display a linear relationship, that is evidence of a power-law distribution, and the slope characterizes the dimension of the network. Here, each point is th the average number of boxes across all subjects (n = 15) in that condition, for each box length. A steeper slope corresponds to a higher fractal dimension, which is associated with a more complex system. For this plot, we took all data points into account when calculating the average, for visualization purposes. See the Methods section for a discussion on how individual network fractal dimensions were calculated.
Note the log-log axes.

Log-log regression of box length vs. number of boxes to tile the network.

3.3. LSD & psilocybin BOLD Lempel-Ziv complexity

The Wilcoxon signed-rank test found significant differences in the LZ_C between the LSD time-series and the placebo timeseries (H(1), p-value = 0.001), but not between the pre- and post-infusion psilocybin conditions. The mean complexity of the LSD condition was 0.95 ± 0.004, while the control condition had a mean complexity of 0.93 ± 0.01. The psilocybin condition had a mean complexity of 0.96 ± 0.01, while the pre-infusion condition had a mean complexity of 0.95 ± 0.02. For visualization of these results, see Fig. 8.

In the LSD condition, we found significant correlations between the LZ_C and both the network fractal dimension ($\rho = 0.68$, p-value < 0.0001) and Higuchi fractal dimension ($\rho = 0.62$, p-value = 0.0003), for visualization see Fig. 9. In the psilocybin condition we found positive, non-significant correlations between the LZ_C and the network fractal dimension ($\rho = 0.16$, p-value = n.s.) and the Higuchi fractal dimension ($\rho = 0.25$, p-value = n.s.), visualization not shown. The finding that both measures correlate better with Lempel-Ziv complexity than they do with each-other is interesting and a potential area of further exploration.

Unlike the Higuchi fractal dimension measure, truncating the LSD condition to 100 TRs did not abolish the significant difference between the drug and placebo conditions (H(0), p-value = 0.001). The significance of this is unclear, although it suggests that the LZ_C measure may be more "robust" when compared to the fractal dimension measure, at least where temporally sparse signals such as BOLD are concerned.

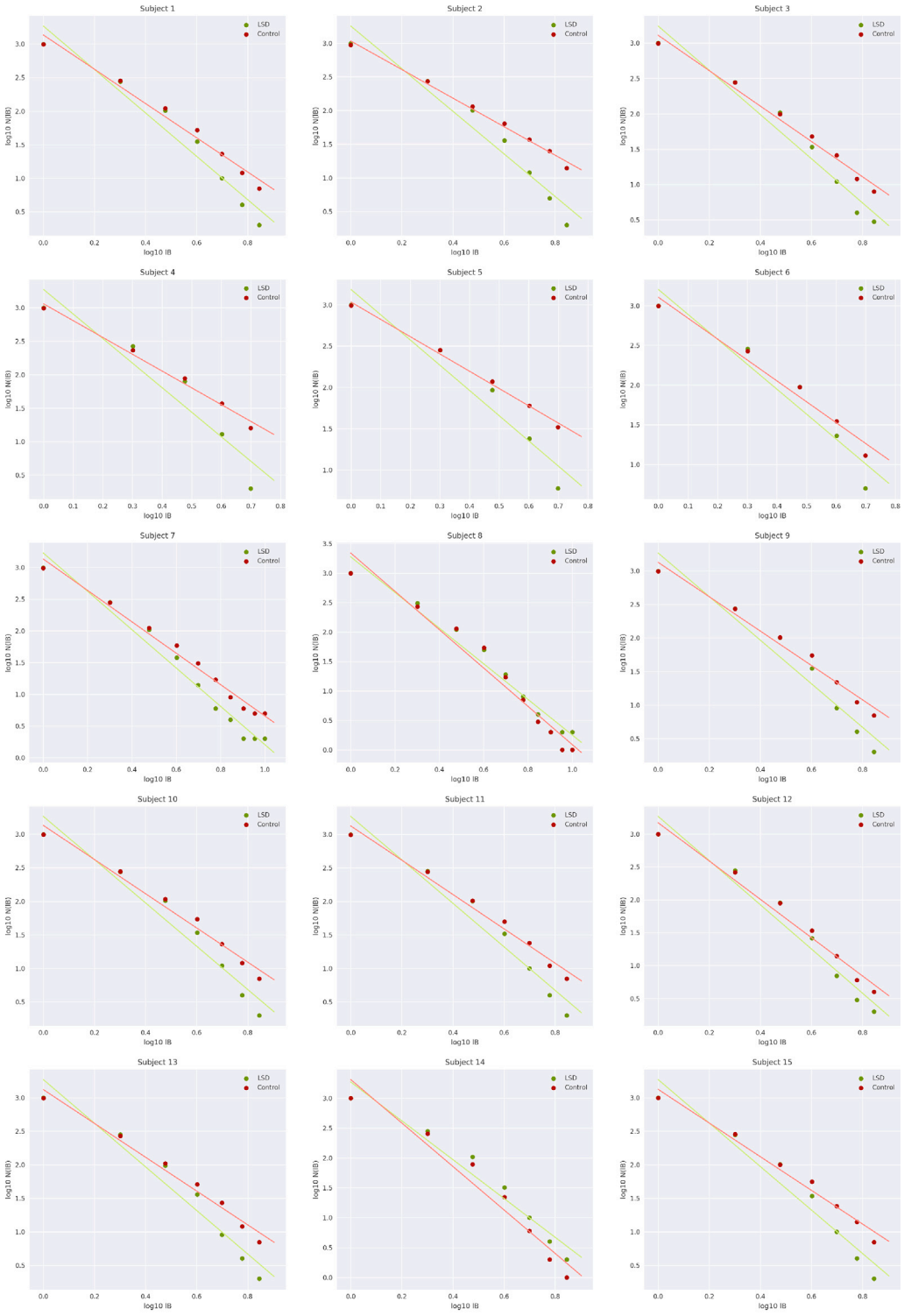
3.3.1. Localizing time-series complexity to sub-networks

In the LSD condition, we found significant increases in the LZ_C in several networks, including the fronto-pariental network (H(5), p-value = 0.002), somato-motor network (H(0), p-value = 0.001), ventral-attenion network (H(23), p-value = 0.04), dorsal-attenion network (H(15), p-value = 0.01), and the visual network (H(0), p-value = 0.001). All networks showed higher complexity in the LSD condition relative to the placebo condition. In the psilocybin condition, all networks had higher complexity relative to controls as well, although none reached the level of statistical significance (although ventral- and dorsal-attenion networks approached significance).

These results are consistent with the results from the Higuchi fractal dimension analysis, although the LZ_C algorithm found more significant differences. In the LSD condition, both analysis found significant increases in the fronto-parietal network, the dorsal-attenion network, and the visual network.

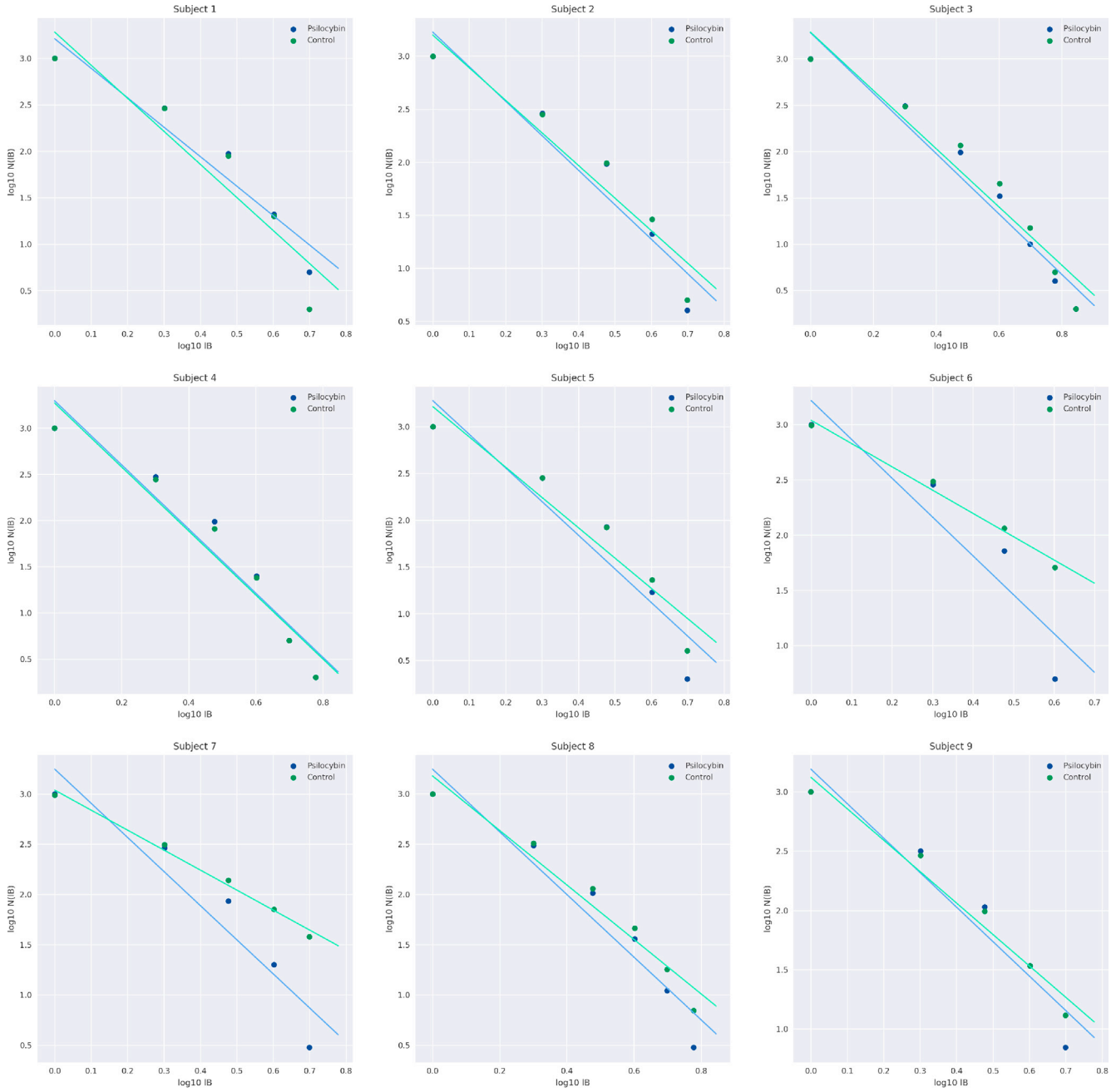
4. Discussion

Here, we report that, using a Compact-Box Burning algorithm (Song



CBB plots for LSD

Fig. 5. CBB plots for LSD. The compact box-burning results for each of the 15 subjects under the influence of LSD vs. control.



CBB plots for psilocybin

Fig. 6. CBB plots for psilocybin. The compact box-burning results for each of the 8 subjects under the influence of psilocybin vs. control.

et al., 2007), the fractal dimension of high-resolution cortical functional connectivity networks is increased under the influence of both psilocybin and LSD, both serotonergic psychedelic compounds, and that the fractal dimension of the BOLD time-series is increased by LSD, but not psilocybin. Furthermore, for both LSD and psilocybin, we were able to show a significant increase in the fractal dimension of the BOLD time-series in the brain regions generally thought to make up the dorsal-attenion network. These results suggest that psychedelic drugs increase the fractal character of brain activity in both temporal (as measured by Higuchi fractal dimension), and spatial domains (as measured by the Compact-Box burning algorithm). This is in keeping with the predictions of the Entropic Brain Hypothesis (EBH), which hypothesizes that the level and quality of consciousness changes as the brain evolves towards the zone of criticality, between distinct phases (Carhart-Harris et al., 2014; Carhart-Harris, 2018). Our results using the well-established LZ_C algorithm also line up nicely with other attempts to quantify the

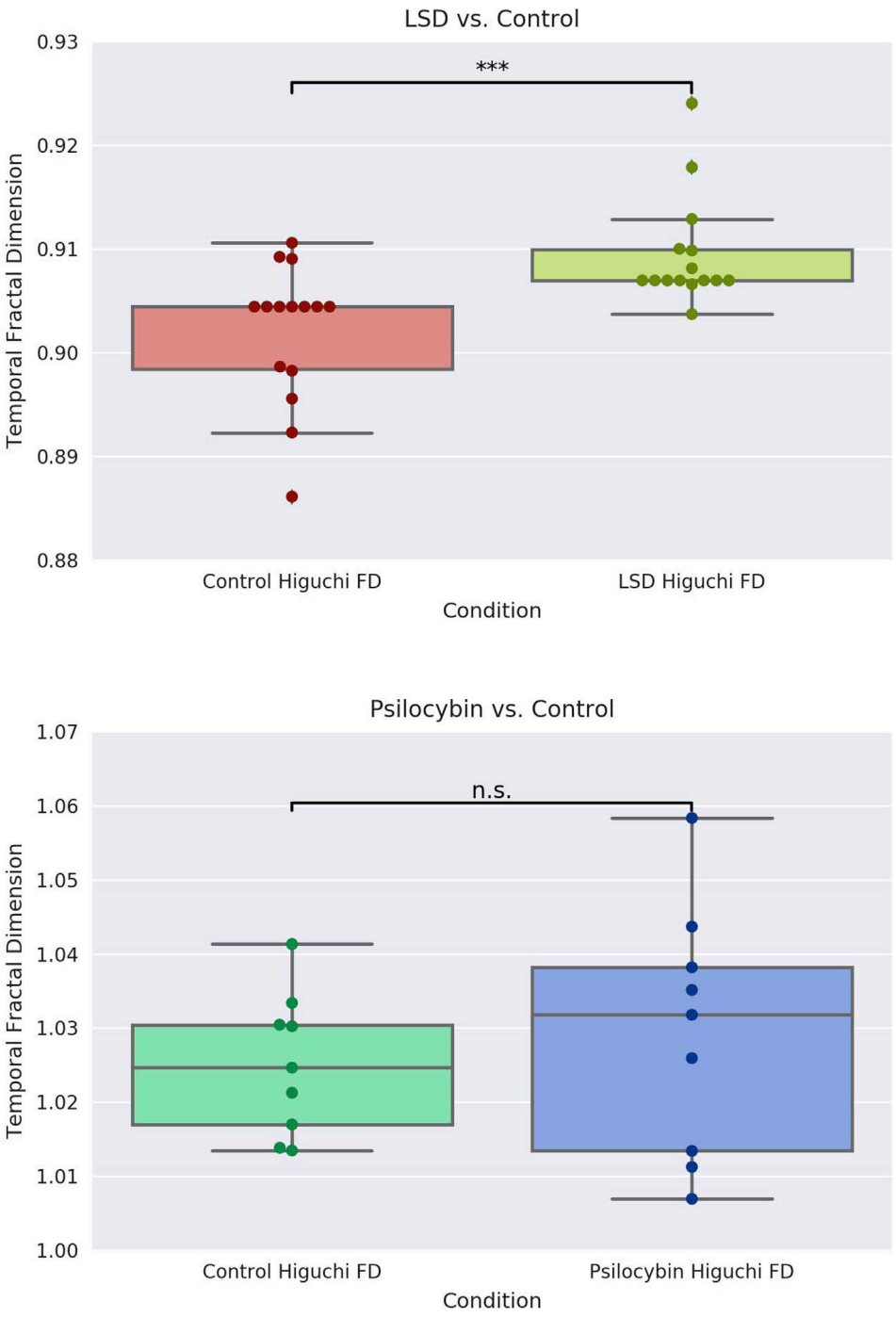


Fig. 7. Whole-brain Higuchi fractal dimension results.
The average Higuchi fractal dimension of BOLD time-series from every one of the 1000 ROIs used in the Network Fractal Dimension section. Plot A corresponds to the LSD vs. LSD Control condition, Plot B corresponds to the Psilocybin vs. Psilocybin Control condition. For each time-series, the fractal dimension was calculated using a $k_{max} = 64$. While the effect size is small in absolute terms, given the small range that the fractal dimension of a time-series usually falls, it remains highly significant.

Whole-brain Higuchi fractal dimension results.

complexity of brain activity under psychedelics, which have generally reported increases in entropy relative to an unaltered baseline (Tagliazucchi et al., 2014; Petri et al., 2014; Lebedev et al., 2016; Schartner et al., 2017a; Viol et al., 2017), as well as being consistent with the temporal and spatial fractal dimension measures discussed here. These results may also be significant for theories of consciousness beyond the EBH, such as Integrated Information Theory (IIT) (Tononi, 2008; Tononi et al., 2016), and the so-called algorithmic information theory of consciousness (KT) (Ruffini, 2017b). Modelling work has found that integrated information peaks near the critical phase transition in an Ising model (Khajehabdollahi et al., 2019), and empirical analysis of dissociated organotypic neural cultures has found that criticality maximizes multi-scale complexity of neural activity (Timme et al., 2016). These findings are arguably most relevant for KT, which explicitly proposes that information dynamics in the brain are organized into an entropic, but hierarchically modular structure characterized by both high entropy rate (high Lempel-Ziv complexity) and fractal character (Ruffini, 2017b). Both sets of results reported here are consistent with these predictions. Under KT, a relative change in the entropy rate and fractal character of brain data suggests a restructuring of the information dynamics the brain uses to model it's environment, which is consistent with the perceptual changes experienced under psychedelics.

Table 1
Higuchi fractal dimension during psilocybin.
Highuchi fractal dimension of BOLD time-series from specific sub-networks in the Psilocybin vs. Control condition* $p \leq 0.05$ **$p \leq 0.01$ ***$p \leq 0.005$.

Sub-Network	Condition	BOLD Fractal Dimension	*p*-Value
Default-Mode Network	Control	1.023 ± 0.016	W(14)
	Psilocybin	1.032 ± 0.017	$p = 0.31$
Limbic Network	Control	1.034 ± 0.017	W(13)
	Psilocybin	1.044 ± 0.014	$p = 0.26$
Fronto-Parietal Network	Control	1.022 ± 0.021	W(17)
	Psilocybin	1.03 ± 0.018	$p = 0.51$
Somato-Motor Network	Control	1.031 ± 0.017	W(21)
	Psilocybin	1.028 ± 0.016	$p = 0.86$
Ventral-Attentional Network	Control	1.031 ± 0.018	W(21)
	Psilocybin	1.033 ± 0.02	$p = 0.86$
Dorsal-Attentional Network *	Control	1.013 ± 0.023	W(6)
	Psilocybin	1.027 ± 0.024	$p = 0.05$
Visual Network	Control	1.024 ± 0.025	W(17)
	Psilocybin	1.021 ± 0.027	$p = 0.51$

Table 2
Higuchi fractal dimension during LSD.
Highuchi fractal dimension of BOLD time-series from specific sub-networks in the LSD vs. Control condition* $p \leq 0.05$ **$p \leq 0.01$ ***$p \leq 0.005$.

Sub-Network	Condition	BOLD Fractal Dimension	*p*-Value
Default-Mode Network	LSD	0.906 ± 0.008	W(54)
	Control	0.905 ± 0.006	$p = 0.73$
Limbic Network	LSD	0.915 ± 0.006	W(57)
	Control	0.913 ± 0.009	$p = 0.86$
Fronto-Parietal Network ***	LSD	0.911 ± 0.009	W(4)
	Control	0.9 ± 0.001	$p = 0.001$
Somato-Motor Network	LSD	0.909 ± 0.006	W(45)
	Control	0.9 ± 0.012	$p = 0.39$
Ventral-Attentional Network	LSD	0.911 ± 0.007	W(58)
	Control	0.911 ± 0.007	$p = 0.9$
Dorsal Attentional Network ***	LSD	0.907 ± 0.009	W(0)
	Control	0.894 ± 0.007	0.0006
Visual Network ***	LSD	0.913 ± 0.003	W(4)
	Control	0.897 ± 0.013	$p = 0.001$

While the theoretical implications for these results in the context of the EBH are interesting on their own, we also try to ground these results in the current literature concerning the neurobiology of psychedelic drugs. All serotonergic psychedelics (eg: LSD, mescaline, psilocybin) share agonist activity at the 5-HT2A receptor (David, 2016), a metabotropic serotonin receptor known to be involved in modulating a variety of behaviours. While the 5-HT2Ar is widely expressed in the CNS, a specific population localized to Layer V pyramidal cells in the neocortex is both necessary and sufficient to induce psychedelic effects (González-Maeso et al., 2007). These Layer V pyramidal neurons serve as 'outputs' from one region of the cortex to another (Nelson, 2008), and the 5-HT2Ar acts as an excitatory receptor, decreasing polarization and increasing the probability that a given neuron will fire (Andrade, 2011; AvesarAllan, 2012). This suggests a primitive model of 5-HT2Ar's role in neural information processing: on Layer V pyramidal neurons, the 5-HT2Ar serves as a kind of 'information gate'. When a psychedelic is introduced to the brain, it binds to the 5-HT2Ar, exciting the associated pyramidal neuron and decreasing the threshold required to successfully transmit information through the neuron. During normal waking consciousness, areas of the brain that are physically connected by Layer V pyramidal neurons may not be functionally connected because the signal threshold required to trigger an action potential is too high but when a psychedelic is introduced, that threshold goes down allowing novel patterns of information flow to occur. This perspective also recalls the branching process: (AlavaKent, 2009): in this case, increasing the probability of a pyramidal neuron firing may be analogous to increasing the branching ratio σ, which, if σ is normally sub-critical, would bring the process closer to the critical value of σ_c. As networks with fractal topology are related to the trees generated by critical branching processes (Goh et al., 2006), this may be a fruitful area to explore further. It should also be remembered that both LSD and psilocybin act as effective agonists at a range of receptors, beyond the 5-HT2Ar (which has been the primary receptor of interest). LSD, for instance, also has affinity for dopamine receptors thought to regulate psychotic behaviours (Marona-Lewicka et al., 2005) and both psilocybin and LSD also have high affinity for the 5-HT1Ar, which is thought to also be significant for understanding the effects of psychedelics (Carhart-Harris and Nutt, 2017). Furthermore, different neurotransmitter systems co-regulate each-other (for instance, connections between adrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe nuclei (Pasquier et al., 1977; Morgane and Jacobs, 1979)), and so the effects of psychedelic drugs are likely to rely on multiple systems, including the serotonergic, dopaminergic, noradrengeric, and histaminergic systems (for review see (Halberstadt and Geyer, 2011)). Future work combining fMRI and PET maps of cortical receptor densities (eg. the CIMBI database (Knudsen et al., 2016; Vincent et al., 2017)) will help to explain how these systems interact.

It is difficult to interpret the increase in the fractal dimension of the BOLD time-series in the dorsal-attenion network. This network is generally thought to be involved in a variety of processes related to visual processing of the environment, such as attending to the orientation of objects in space, visual feature-based attention, and biasing visual perception in response to cues (Vossel et al., 2014). It was originally proposed to be involved with top-down, conscious allocation of attention to environmental objects (CorbettaGordon and Shulman, 2002). Human studies with psilocybin have found that exposure to the psychedelic reduces attenion tracking ability, and the proposed mechanism given was that psilocybin reduced the ability of the brain to filter out irrelevant or distracting stimuli (Carter et al., 2005). This is consistent with findings that psychedelics attenuate sensory-gating functions in a manner reminiscent of patients with schizophrenia (Riba et al., 2002; Vollenweider et al., 2007).

The finding that LSD increased the fractal dimension of BOLD signals in the fronto-parietal network is consistent with previous findings that global increases in the functional connectivity density induced by LSD overlap with brain regions commonly assigned to the FP network (Tagliazucchi et al., 2016). We did not, however find significant changes in the complexity of signals from nodes commonly assigned to the Default Mode Network (DMN), which ran counter to our initial hypothesis. Many neuroimaging studies of psilocybin and LSD have found associations between changes in DMN activity and the phenomonology of the psychedelic experience (Carhart-Harris et al., 2012, 2016; Tagliazucchi et al., 2016; Wall, 2017). We hypothesize that this discrepancy might be explained by the sheer number of nodes assigned to the DMN (212 nodes in total): because the signal from every node was weighted equally, it is possible that peripheral nodes assigned to the DMN by our parcellation may not have been significantly effected, thus obscuring a real effect only present in a subset of DMN nodes. Validation with a smaller atlas or more conservative assignment of nodes may yet find an effect in the DMN (although a smaller atlas would preclude the NFD analysis).

Finally, the increased complexity of BOLD signals in the visual network under LSD is interesting. It has already been established that LSD alters functional connectivity of visual cortices in humans (Roseman et al., 2016), and EEG analysis of LSD users post-experience has found alterations to the coherence of signals in visual areas thought to be associated with the experience of hallucinations (Abraham and Duffy, 2001). It has been suggested that the qualitative nature of psychedelic imagery may be informative about the structure and layout of the visual system (Bressloff et al., 2002), and so we propose that this may be a particularly fruitful avenue of psychedelic research going forward.

This study has several limitations that are worth considering. The first is the comparatively small size of the psilocybin sample ($n = 9$), which

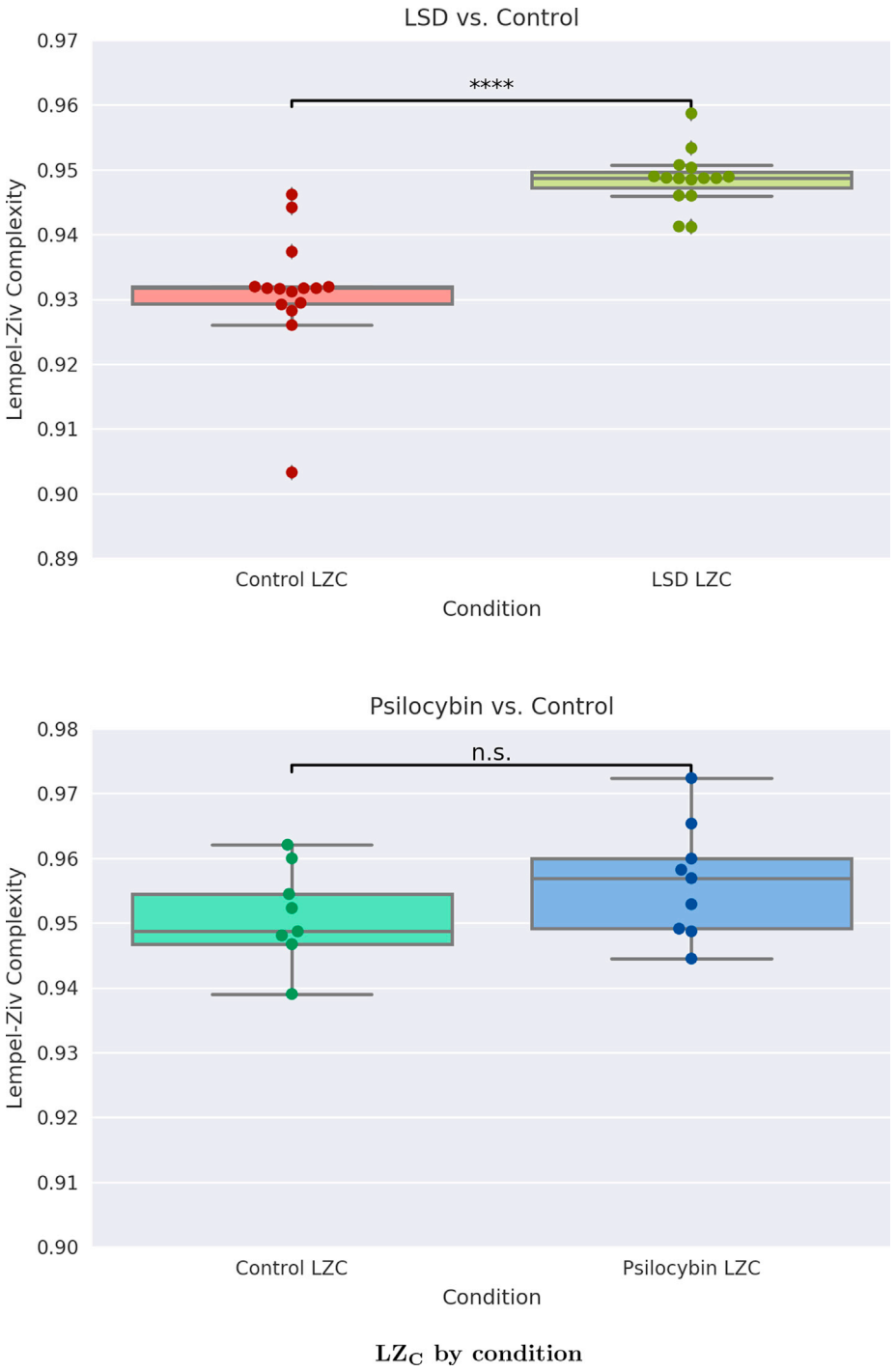


Fig. 8. LZ_C by condition.
The average LZ_C of BOLD time-series. Plot A corresponds to the LSD vs. Control condition, Plot B corresponds to the Psilocybin vs. Control condition.

means that it is harder to trust the replicability of the present findings than if the sample had been larger. Second, the Higuchi fractal dimension is not frequently used on BOLD signals, as the number of samples in each time-series is far lower than it is for EEG or MEG, resulting in a less robust analysis. In the case of psilocybin, the time-series may be so too short too produce Higuchi fractal dimension values of any reliability. In light of this, replication with EEG or MEG data should be a priority before these results are considered strong. Simultaneous EEG-fMRI recordings under a psychedelic would be particularly informative as it would enable us to test the relationship between fractal dimension recorded across modalities. Third, the parcellation resolution used here (1000 ROIs), which is considerably larger than many commonly-used parcellations is still smaller than would be desired for a truly comprehensive analysis of fractal dimension of functional connectivity networks, and so future analysis with a higher resolution cortical parcellation is needed. Given the complexity of the brain as a system, it is unlikely that a single exponent appropriately captures the extent of multi-scale dynamics playing out, both under psychedelics or under normal circumstances. In the future, a multi-fractal analysis would almost certainly provide a richer portrait of brain dynamics, although the limitations inherent in fMRI data made such an analysis infeasible for this study. Future research projects, possibly combining multi-modal imaging paradigms such as

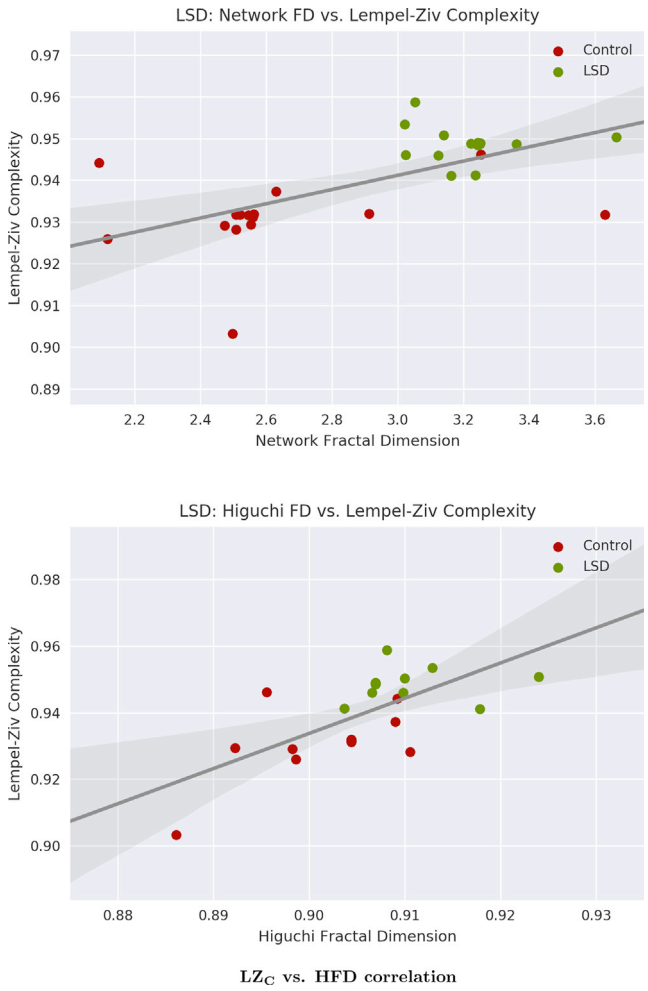


Fig. 9. LZ_C vs. HFD correlation.
The correlations between the LZ_C of BOLD signals and the network fractal dimension (upper, $\rho = 0.68$, p-value < 0.0001), and the Higuchi temporal fractal dimension (lower, $\rho = 0.62$, p-value $= 0.0003$).

MEG and fMRI may be able to explore this further. Future studies comparing different psychedelics, like LSD and psilocybin, should also strive to ensure some kind of dose-equivalence: given the nature of the datasets, it was not possible to ensure that the subjective intensities of the LSD and psilocybin experiences volunteers underwent was equivalent, and this may be reflected in the differences in results. To control for this, it would be valuable to have a universal, standardized measure of subjective experience such as the ASC questionnaire (Matthias, 2017), with graded doses for a variety of drugs, such as psilocybin, LSD, mescaline, etc. This would allow researchers the ability to more fully explore the commonalities, and differences between individual psychedelic compounds.

6. Conclusions

In this study we report that, under the influence of two serotonergic psychedelics: LSD and psilocybin, the fractal dimension of cortical functional connectivity networks is significantly increased. Under LSD, the fractal dimension of BOLD time-series is also significantly increased, while psilocybin shows a non-significant increase as well. These results are in line with previously published research suggesting that psychedelics increase the complexity of brain activity, and the specific measures used here may be a particularly useful tool for understanding how consciousness changes as the brain approaches criticality. We were able to show that, under both LSD and psilocybin, the fractal dimension of BOLD time-series from regions assigned to the dorsal-attenion network was increased. In addition, we show that these results are largely consistent with a different, non-fractal measure of complexity, Lempel-Ziv compressibility, which has been widely used in the field previously. These findings show that psychedelics increase the fractal dimension of brain activity in both spatial and temporal domains and have implications for the study of consciousness and the neurobiology the psychedelic experience.

Data and code statement

The raw.csv data files are available as supplementary material for this publication. Individual scripts can be acquired by contacting the author, or, in the case of code that was provided by a 3rd party, by following the citations in the paper.

Declaration of competing interest

The authors report no personal or financial conflicts of interest related to the research reported herein.

CRediT authorship contribution statement

Thomas F. Varley: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Robin Carhart-Harris:** Data curation, Investigation, Writing - review & editing. **Leor Roseman:** Data curation, Writing - review & editing. **David K. Menon:** Supervision, Writing - review & editing. **Emmanuel A. Stamatakis:** Conceptualization, Investigation, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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