Common neural signatures of psychedelics: Frequency-specific energy changes and repertoire expansion revealed using connectome-harmonic decomposition

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4

Common neural signatures of psychedelics: Frequency-specific energy changes and repertoire expansion revealed using connectome-harmonic decomposition

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Abstract

The search for the universal laws of human brain function is still on-going but progress is being made. Here we describe the novel concepts of connectome harmonics and connectome-harmonic decomposition, which can be used to characterize the brain activity associated with any mental state. We use this new frequency-specific language to describe the brain activity elicited by psilocybin and LSD and find remarkably similar effects in terms of increases in total energy and power, as well as frequency-specific energy changes and repertoire expansion. In addition, we find enhanced signatures of criticality suggesting that the brain dynamics tune toward criticality in both psychedelic elicited states. Overall, our findings provide new evidence for the remarkable ability of psychedelics to change the spatiotemporal dynamics of the human brain.

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Keywords

Connectome harmonics, Brain, Psychedelics, Psilocybin, LSD

1 INTRODUCTION

If you want to understand the secrets of the universe, think in terms of energy, frequency and vibration

Attributed to Nikola Tesla

Science has made spectacular progress in elucidating the fundamental laws of nature; generating elegant mathematical equations describing the detailed interactions between many of the forces governing the spatiotemporal distribution of matter and energy in the universe. Yet, one of the most exciting challenges remains, namely to understand the dynamical complexity of the human brain, and specifically how mental states arise through the complex interplay of structural and functional brain connectivity.

The invention of non-invasive neuroimaging techniques with ever more precise spatiotemporal information on human brain activity has given rise to a growing field of neuroscientific research, which is starting to bring about new fundamental insights into the brain dynamics of integration and segregation of information over time (Deco et al., 2015; Dehaene et al., 1998; Tononi et al., 1994). Here we focus on the important progress in using a promising mathematical framework (Atasoy et al., 2016) for decoding the brain activity in any mental state (whether awake, in deep sleep, under anesthesia, or in a psychedelic state) as a combination of harmonic brain modes (Atasoy et al., 2017, 2018). These harmonic brain modes can be determined as the harmonic modes of structural connectivity yielding fully synchronous neural activity patterns with different frequency oscillations. The complex spatiotemporal patterns of brain activity during a mental state can be expressed in terms of these elementary building blocks of brain activity, i.e., connectome harmonics, using a *connectome-harmonic decomposition*. More generally, the mathematical framework of connectome harmonics is directly related to the fundamental principle of harmonic patterns, which are ubiquitous in nature—emerging in physical, as well as biological phenomena ranging from acoustics, optics, electromagnetic interactions to morphogenesis (Atasoy et al., 2018).

Here, we used this mathematical framework to elucidate the brain activity in a special mental state, namely the altered states elicited by psychedelics, currently enjoying a renaissance in terms of scientific study (Sessa, 2012). Over millennia, people have been using psychedelics derived from indigenous plants including Peyote and the subspecies of the Psilocybin mushroom (Pollan, 2018; Whybrow, 1962). Often, these have been central to healing rituals but also to expand the mind. The scientific study of psychedelics started with the chemical characterization of mescaline in 1898 by Arthur Heffer and the synthesizing of LSD by Albert Hoffmann in 1938 (Hoffmann, 1980). Subsequent research in the 1950s and

1960s revealed the powerful potential of psychedelics to treat addiction and anxiety, but this research was eventually curtailed worldwide (Nichols, 2016). Yet, with the identification of the $5HT_{2A}$ receptor as a main target of LSD in the 1980s and the advent of brain imaging, the study of the brain correlates of psychedelics has slowly been gathering pace (Halberstadt, 2015; Kyzar et al., 2017). There is a clear need for a better understanding of the underlying mechanisms in order to potentially harness the power of psychedelics for treating brain disorder and for exploring the limits of consciousness.

In the following, we first describe the fundamental principles of harmonic patterns and the mathematical framework of connectome harmonics as brain states. We then review the existing literature on the neural correlates of psychedelics and finally discuss how the effect of psychedelics can be understood in this frequency-specific language of cortical activity, and can be studied in terms of different expressions of these harmonic brain states. Analogous to how different combinations of elementary particles form various atoms and molecules or combinations of musical notes comprise different melodies or even symphonies, connectome harmonics provide the elementary building blocks to express complex spatiotemporal patterns of neural activity. Here, we demonstrate how the expressions of these building blocks, the connectome harmonics, change in the psychedelic state. Furthermore, beyond reviewing the existing evidence on the LSD-induced changes in the expression of these harmonic brain states, we present new findings demonstrating common connectome-harmonic signatures of two different psychedelic substances, LSD and psilocybin. Finally, we discuss the implications of these findings in the context of deepening our understanding of mental states.

2 CONNECTOME HARMONICS AS BRAIN STATES

Brain states—elementary states of brain activity—have been an emerging concept in neuroscience over the last 2 decades (Atasoy et al., 2018; Cabral et al., 2017; Hansen et al., 2015; Hutchison et al., 2013; Robinson et al., 2016; Smith et al., 2012) (Fig. 1). Just like different combinations of musical notes create infinite many different pieces of music, may it be as simple as lullaby or as complex as a symphony, different combinations of elementary brain states can also give rise to an infinite number of possible variations of spatiotemporal patterns of brain activity (Atasoy et al., 2017). Recently, it has been shown that defining the brain states, i.e., the elementary building blocks of brain activity, as the harmonic modes of the human connectome, provides a new frequency-specific language for brain activity.

The definition of the brain states as the connectome harmonics; i.e., harmonic modes of the human connectome, is mainly motivated by the intrinsic relation between temporal oscillations and the spatial correlation patterns. Recent research has shown that the patterns of synchronous cortical activity emerging as the synchronization of different temporal frequencies can be estimated from the structural connectivity of the human brain via the mathematical framework of harmonic

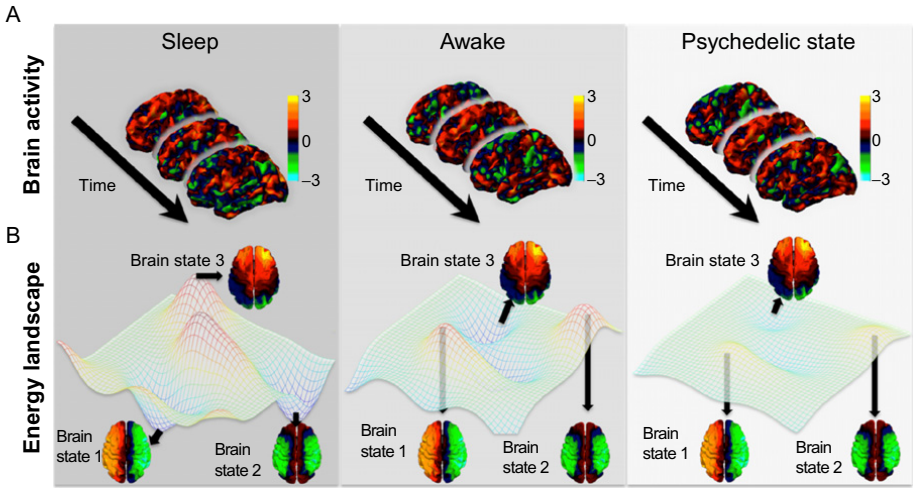

FIG. 1

Brain dynamics shown as (A) brain activity and (B) energy landscapes.

modes (Atasoy et al., 2016). Furthermore, supporting these propositions, biological mechanisms leading to the emergence of such harmonic patterns in macro-scale brain activity have also been demonstrated by various neurophysiological models (Atasoy et al., 2016; Nunez and Srinivasan, 2006; Robinson et al., 2016).

Mathematically, these harmonic patterns are computed via the eigen-decomposition of the Laplace operator Δ, which lies at the heart of theories of heat, light, sound, electricity, magnetism, gravitation, and fluid mechanics (Stewart, 1999):

$$\Delta\psi_k = \lambda_k\psi_k, \quad \text{with } 0 < \lambda_1 < \lambda_2 < \cdots, \tag{1}$$

where ψ_k denotes the harmonic pattern with the spatial wavenumber k and λ_k relates to the frequency of temporal oscillation.

Interestingly, harmonic patterns are ubiquitous in nature—e.g., standing wave patterns forming in sound-induced vibrations of a guitar string or a metallic plate (first demonstrated as complex sand patterns by Chladni, 1802), patterns of ion motion emerging from electromagnetic interactions (Britton et al., 2012; Roos, 2012), electron wave function of a free particle given by time-independent Schrödinger equation (Moon et al., 2008; Schrödinger, 1926), and even in patterns emerging in complex dynamical systems such as the reaction–diffusion models (Murray, 1988; Xu et al., 2001), thus providing a fundamental principle governing a multitude of physical and biological phenomena.

Let us focus on the example of standing waves emerging in resonance phenomena to gain insights into the harmonic patterns and temporal oscillations. Every physical system capable of vibrating, even a simple metal plate used in the experiments of Ernst Chladni, has a spectrum of *natural frequencies*, i.e., the preferred

frequencies at which the system tend to oscillate. If the system is excited at one of these natural frequencies, the resonance of the system with the incident natural frequency will lead to a dynamic stable state, called the *eigenmode* or the natural mode of vibration, where a standing wave self-organizes on the vibrating domain. In other words, the standing wave is formed and sustained by the oscillation of each spatial location with the same natural frequency and these oscillations are synchronized throughout the complete system; e.g., metal plate forming a fully synchronous mode of oscillation. In the resonance phenomenon, the shape of the standing wave is determined by the geometry of the underlying domain and the frequency of vibration. When the exciting natural frequency changes, the accompanying standing wave pattern will be automatically altered. This intrinsic relation between the spatial and temporal aspects of the resonance phenomenon is also reflected in the standing wave equation. Eq. (1), also known as the Helmholtz equation, which links the frequency of temporal oscillations (λ_k) to the spatial pattern of the standing wave (ψ_k) that is adapted to the particular geometry of the underlying domain. Notably, the solutions of the standing wave equation on a ring (one-dimensional domain with cyclic boundary conditions) correspond to sine and cosine functions with different frequencies, which also constitute the function basis of the well-known Fourier transform.

Remarkably, the extension of these harmonic patterns to the particular structural connectivity of the human brain, i.e., solutions of the Helmholtz equation on the human connectome—termed *connectome harmonics*—reveal the resting state networks of the human brain (Atasoy et al., 2016). This finding not only suggests that the same fundamental principles governing various natural phenomena may also underlie the cortical patterns of collective neural activity (Atasoy et al., 2016) but also provides a new harmonic language to describe any cortical activity pattern. The complete spectrum of connectome harmonics provides a new function basis, as different frequency harmonics are orthogonal. Furthermore, as the connectome harmonics are the eigenfunctions of the Laplacian (Δ) applied to the human connectome, by definition they provide the extension of the Fourier basis to the structural connectivity of the human brain. The same way any continuous signal can be represented as a combination of sine and cosines, any pattern of cortical activity can also be reconstructed from the set of connectome harmonics. Thus, the decomposition of cortical activity into the set of connectome harmonics yields its expression in a new, frequency-specific language.

In this review, we demonstrate how the expression of brain activity in this harmonic language reveals new insights into the effects of psychedelics. We first briefly review the existing findings on changes in brain activity in the psychedelic state. We show how these findings can be complemented by the results revealed by the connectome-harmonic decomposition to understand the effects of LSD, psilocybin, and other psychedelics in terms of changes in total power and energy as well as frequency-specific energy changes. Furthermore, we also describe how psilocybin and LSD give rise to increased repertoire and critical brain dynamics.

3 NEURAL CORRELATES OF PSYCHEDELICS

Psychedelics have an important place among pharmacological substances for their ability to profoundly alter both the state as well as the content of consciousness (Schartner et al., 2017). They can be found in nature, e.g., as psilocybin—the active compound of magic mushrooms; mescaline—a psychedelic alkaloid in peyote cactus; or ayahuasca—a brew combining *N*,*N*-dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOIs), but also synthesized as lysergic acid diethylamide (LSD), and 5-MeO DMT (Nichols, 2016). Their "mind-manifesting" effects have been associated with experiences of "vivid imaginations," "ego disintegration," or "feelings of supernatural" (Swanson, 2018). These cognitive "enhancements" have led some to consider such conscious experience as "elated" or "encompassing" level of consciousness (Schartner et al., 2017). Recent neuroimaging studies have focused on understanding the neural correlates (Carhart-Harris et al., 2012a; Palhano-Fontes et al., 2015) and mechanisms underlying the psychedelic state (Table 1), for they might enable new treatment possibilities in many neuropsychiatric diseases such as depression, anxiety, and addiction (Carhart-Harris et al., 2016a; Morgan et al., 2017; Reiche et al., 2018).

3.1 TIME: OSCILLATORY CORRELATES OF THE PSYCHEDELIC STATE

The decrease in oscillatory power has been consistently detected across broad range of frequencies in psychedelic state. In brief, the oscillatory power has been shown to decrease in the alpha and gamma-band EEG signal in ayahuasca-induced state (Schenberg et al., 2015), in low frequency fMRI signal and different frequency bands in MEG signal in LSD-induced state (Carhart-Harris et al., 2016c; Tagliazucchi et al., 2014), and in 1–100 Hz frequency band in MEG in psilocybin-induced state (Muthukumaraswamy et al., 2013). Interestingly, the decreases in oscillatory power have been mostly observed in the default mode network (DMN) and higher-order cognitive networks. Furthermore, signal-channel diversity has been found to increase in LSD, psilocybin, and ketamine-induced states (Schartner et al., 2017).

3.2 SPACE: NETWORK CORRELATES OF THE PSYCHEDELIC STATE

From a spatial perspective, functional connectivity (FC) between important hub areas (medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)) within the DMN has been shown to decrease in the psilocybin-induced state (Carhart-Harris et al., 2012a) accompanied by increase in between-network FC of DMN and higher-order cognitive networks (Roseman et al., 2014). Importantly, this increase is pronounced in FC between DMN and task positive network (DMN's anti-correlated network) (Carhart-Harris et al., 2016c). In the LSD-induced state, FC increases have been observed predominantly within higher-associative cortices (matching with the default mode, salience, and fronto-parietal attention networks) and the thalamus. These networks have been further found to increase between-network FC with lower cognitive networks (visual, auditory, and somato-motor) (Carhart-Harris et al., 2016c;

Table 1 Neural Correlates of the Psychedelic State

Study	Psychedelic Induced State	Imaging Modality	Neural Correlates
Carhart-Harris et al. (2012a)	Psilocybin	fMRI	• Decrease in functional connectivity (FC) between mPFC and PCC (anterior–posterior regions of the DMN) • Decrease in activity of ACC and mPFC
Carhart-Harris et al. (2012b)	Psilocybin	fMRI	• Increase in FC between DMN and task positive network (TPN) whereas thalamo-cortical FC remained the same
Muthukumaraswamy et al. (2013)	Psilocybin	MEG	• Large decrease in oscillatory power within the DMN • Reduction in spontaneous oscillatory power 1–50 Hz frequency band in posterior association cortex and in 8–100 Hz frequency band in frontal association cortex
Roseman et al. (2014)	Psilocybin and MDMA	fMRI	• Increase in between-network FC among all resting state networks (RSNs) except between visual and sensorimotor networks • MDMA had a notably less marked effect on between-RSN FC
Tagliazucchi et al. (2014)	Psilocybin	fMRI	• Decrease in power spectrum exponent and oscillatory power in low frequency range (0.01–0.1 Hz) measured with fMRI within DMN, executive control, and dorsal attention networks • Increase in exploratory rate of DMN under psilocybin • Increase in Shannon entropy in the repertoire of functional connectivity patterns (left and right hippocampus, left and right ACC) and a wider repertoire of states under psilocybin
Palhano-Fontes et al. (2015)	Ayahuasca	fMRI	• Decrease in FC between PCC and precuneus, parts of the DMN • Increase in functional activity of DMN including posterior cingulate cortex (PCC)/precuneus and the medial prefrontal cortex (mPFC) • No significant change in FC between DMN and TPN
Schenberg et al. (2015)	Ayahuasca	EEG	• Decrease in oscillatory power in the alpha-band (8–13 Hz) at parieto-occipital cortex after 50 min from intake • Decrease in gamma power (30–100 Hz) in left centro-parietal-occipital, left fronto-temporal, and right frontal cortices between 75 and 125 min after intake
Tagliazucchi et al. (2016)	LSD	fMRI	• Global increase in FC throughout the cortex, in particular within high-level association cortices (partially overlapping with the default mode, salience, and fronto-parietal attention networks) and the thalamus • These cortices also have an increase in between-network FC to lower cognitive systems (VIS, AUD, and SM) • Increase in global integration

Continued

Table 1 Neural Correlates of the Psychedelic State—cont'd

Study	Psychedelic Induced State	Imaging Modality	Neural Correlates
Carhart-Harris et al. (2016b)	LSD	fMRI and MEG	• Decrease in within-network FC and signal variance in DMN, and various other resting state networks (RSNs) (medial and lateral visual, occipital pole, sensorimotor, parietal cortex, posterior opercular, dorsal attention, left and right fronto-parietal networks) • Increase in between-network FC between several lower and higher level cognitive networks • Decrease in oscillatory power in four frequency bands delta (1–4 Hz), theta (4–8 Hz), alpha (8–15 Hz), and beta (15–30 Hz)
Atasoy et al. (2017)	LSD	fMRI	• Frequency-specific changes in the energy, power, and repertoire of harmonic brain states • Increase in temporal correlation among the co-activation of various frequency-specific brain states • Tuning of brain dynamics further toward criticality under LSD revealed by power-law analysis
Petri et al. (2014)	Psilocybin	fMRI	Persistent homology and homological scaffold analysis: • Emergence of many low-stability and few persistent structures in the psilocybin-induced condition as opposed to placebo suggestive of increased functional "uncertainty" but at the same time retainment of stable structures unique to the psychedelic state
Schartner et al. (2017)	Psilocybin, LSD, and ketamine	MEG	• Qualitative increase in spontaneous signal diversity for all three psychedelics • Stronger significance for single channel Lempel–Ziv complexity suggesting temporal diversity is more prominent to spatial diversity • Occipital–parietal areas have increased single channel Lempel–Ziv in all three drugs
Deco et al. (2018)	LSD	fMRI and whole-brain models	Whole-brain computational modeling: • Global density distribution of $5HT_{2A}$ receptor applied to modulate the gain scaling parameter (proxy to the LSD high-affinity to $5HT_{2A}$ receptor in glutamatergic pyramidal cells) reflects the spatiotemporal dynamics of the data
Viol et al. (2017)	Ayahuasca	fMRI	• Shannon entropy of the degree distribution increases in ayahuasca-induced state • Local efficiency and integration increase while global integration and efficiency decrease under ayahuasca

Table representing literature on different psychedelic induced states and their neural correlates.

Tagliazucchi et al., 2014). Furthermore, graph theoretical measures have revealed increases in global integration under the effect of LSD (Tagliazucchi et al., 2014), while in the ayahuasca-induced state they have showed increased local and decreased global network integration (Viol et al., 2017).

Interestingly, diversity, as described by Shannon's entropy, has been observed to significantly increase in a group of regions with high signal variability (left and right hippocampus, left and right anterior cingulate cortex (ACC)) in the psilocybin-induced state (Tagliazucchi et al., 2014). An enlarged repertoire of possible FC patterns between these networks has also been found under the influence of psilocybin (Tagliazucchi et al., 2014). Ayahuasca-induced state diversity, again measured by Shannon's entropy but on the degree distribution, has been shown to increase globally (Viol et al., 2017). Furthermore, increased diversity in brain activity, measured by Lempel–Ziv complexity, has recently been reported in psilocybin, LSD, and ketamine-induced states (Schartner et al., 2017). Moreover, investigation of fMRI data via the harmonic brain states, defined by connectome harmonics (Atasoy et al., 2016), has shown frequency-specific changes and a repertoire expansion with increased cross-frequency correlations between these brain states suggestive of non-trivial re-organization under LSD (Atasoy et al., 2017). Similarly, another study investigating fMRI signal in psilocybin-induced state using algebraic topology has shown increased numbers of homological structures with low-stability accompanied by the emergence of new, stable homological structures in the brain's connectivity patterns, which are unique to the psychedelic state (Petri et al., 2014).

Taken together, these findings are consistent with the entropic brain theory (Carhart-Harris et al., 2014), particular in its latest form (Carhart-Harris, 2018), which simply states that within upper and lower limits, the richness of content of brain activity within given states of consciousness, indices the subjective richness of that state. More broadly, these results also speak to an image of the psychedelic state in which brain function is altered across space and time manifesting in highly atypical complex brain dynamics. In this review, we propose a framework to unify these different dimensions by describing them through harmonic brain modes and their different combinations. We, further, demonstrate how complexity can arise from the self-organization of the harmonic brain modes.

3.3 NEUROPHYSIOLOGICAL CORRELATES OF THE PSYCHEDELIC STATE

Brain activity in resting state is known to organize into specific spatiotemporal networks (Biswal et al., 1995; Raichle et al., 2001). These patterns across time and space are thought to emerge from the spontaneous neural dynamics of the cortex governed by long-range (cortico-cortical) and short-range (intra-cortical) interactions constrained by the brain's white matter scaffold (Isaacson and Scanziani, 2011).

Structural long-distance connections have recently been mapped through novel diffusion spectrum imaging (DSI) techniques, tracking spread of water molecules along white matter axonal bundles, and thus have enabled to obtain a macroscopic

structural brain map—referred to as the human connectome (Hagmann, 2005; Sporns et al., 2005). This structural connectivity has demonstrated significant correspondence to resting state functional connectivity (Hagmann et al., 2008). When structural connectivity was incorporated as a constraint in whole-brain computational models, the resulting spontaneous activity has shown reproducible emergent dynamics related to the resting state functional connectivity patterns (Deco et al., 2009; Honey et al., 2007). Furthermore, such sophisticated models have allowed the investigation of complimentary features, necessary for the emergent brain dynamics, such as coupling strength and delays and noise (Cabral et al., 2014, 2017). Importantly, these whole-brain models can now be used to move beyond correlational neuroimaging to discovering causal mechanisms (Deco et al., 2017; Deco and Kringelbach, 2017), which has the potential to reveal new ways of rebalancing the brain in disease (Kringelbach et al., 2011; Saenger et al., 2017).

On the other hand, local dynamics arise from the unique interplay between two types of neural activity, that of the pyramidal (excitatory) neurons and GABAergic (inhibitory) interneurons. Although the cell classes are extremely heterogeneous in their morphology, physiology, and synaptic attributes, together they create recurrent networks responsible for many of the brain's computational processes (Markram et al., 2004; Mesulam, 1998). The network's organizational abilities lead to a well-defined local excitatory–inhibitory balance of roughly 80% excitatory to 20% inhibitory neurons. Theoretical models have shown more realistic emergent dynamics when learning rules for the maintenance of the excitatory–inhibitory balance were considered (Deco et al., 2014).

The specific excitatory–inhibitory balance is accepted to be one of the necessary conditions for normal functioning of the human brain associated with the awake conscious state (Chialvo, 2010; Lord et al., 2017). Mounting evidence has postulated a transition into an unconscious state to be accompanied by the alteration of this balance with more inhibition and/or less excitation (Brown et al., 2010; Tononi and Koch, 2008). On the contrary, the psychedelic-induced state of consciousness has been proposed to alter this balance toward increased cortical excitation (Glennon et al., 1984). On a pharmacological level, all psychedelic drugs are known to interact with serotonergic neuroreceptors (Carhart-Harris and Nutt, 2017; Halberstadt, 2015) and mainly act as agonists to the $5HT_{2A}$ receptor, thus resulting in increased $5HT_{2A}$ signaling (Glennon et al., 1984). In fact, in humans, many key subjective effects of psilocybin, LSD, and ayahuasca have been halted by the administration of potent $5HT_{2A}$ antagonists (Kometer et al., 2013; Kraehenmann et al., 2017; Valle et al., 2016). As the main density expression of the receptors, in mainly glutamatergic pyramidal neurons, is polysynaptic, the psychedelic drugs tend to depolarize the neurons through $5HT_{2A}$ receptor agonism driving increased cortical excitation, and thus altering the excitatory–inhibitory balance in favor of greater excitation. Indeed, this has been recently supported by a LSD study where positron-emission tomography (PET) maps of the $5HT_{2A}$ receptor informed neuronal whole-brain model has been shown to best describe the spatiotemporal dynamics of LSD-induced fMRI resting state activity (Deco et al., 2018). Although, the resulting

effects of psychedelic drugs might be largely to tip the balance to more excitation, it is to be noted that $5HT_{2A}$ receptors also depolarize GABAergic interneurons suggesting that further exploration of these complex interactions may be required (Andrade, 2011). It is also worth noting that all psychedelic drugs activate additional serotonergic neuroreceptors and act on additional neuromodulatory systems, which in turn may contribute to the overall quality of a psychedelic experience (Schmidt and Berkemeyer, 2018). Interestingly, the shift of the excitation/inhibition balance toward increased excitation has been shown to lead to a repertoire expansion of active harmonic brain states, connectome harmonics, using computational models (Atasoy et al., 2016) as well as by connectome-harmonic decomposition of the fMRI data acquired in the LSD-induced psychedelic state (Atasoy et al., 2017). As next we discuss these findings in more detail and demonstrate that these harmonic correlates of the LSD experience are also shared by the psilocybin-induced psychedelic state.

4 CONNECTOME-HARMONIC CORRELATES OF PSYCHEDELICS

By defining the connectome harmonics as the individual states (attractors) of brain dynamics, we investigate the dynamical characteristics of brain activity in terms of the repertoire of frequency-specific brain states (Atasoy et al., 2018). In order to estimate the contribution (ω_k^t) of each connectome harmonic (ψ_k) to brain activity at any given time t, we first project the volumetric fMRI data onto the cortical surface (Fig. 2C). Then we decompose the cortical activity pattern corresponding to each time point into the complete set of connectome harmonics ($[\psi_k]_{k=1}^N$) yielding the weight (the amount of contribution) (ω_k^t) of each of the harmonic brain states (ψ_k) to that particular pattern of cortical activity (ω_k^t) (Fig. 2D). Based on this contribution, we define the power of each harmonic brain state as the amplitude of this contribution ($|\omega_k^t|$) and the energy as a frequency-weighted version of the power ($|\omega_k^t|\lambda_k)^2$ with λ_k being the eigenvalue corresponding to the kth connectome harmonic ψ_k, which combines the contribution as well as the intrinsic energy of each harmonic brain state. By applying the connectome-harmonic decomposition to the fMRI data under LSD, psilocybin, and the corresponding placebo conditions, we explore the psychedelic induced energy and power changes in brain activity. Our findings on LSD have previously been published (Atasoy et al., 2017), where the acquisition and preprocessing are described in details. Further information on the acquisition and preprocessing of the psilocybin data can be found in Carhart-Harris and colleagues (2012a).

4.1 PSYCHEDELIC INDUCED ENERGY AND POWER CHANGES IN BRAIN ACTIVITY

First, we consider the complete connectome-harmonic spectrum and estimate the total energy and total power of all harmonic brain states for each condition. This analysis reveals that the LSD-induced psychedelic state leads to a significant increase in the total power and total energy of brain activity compared to the placebo condition

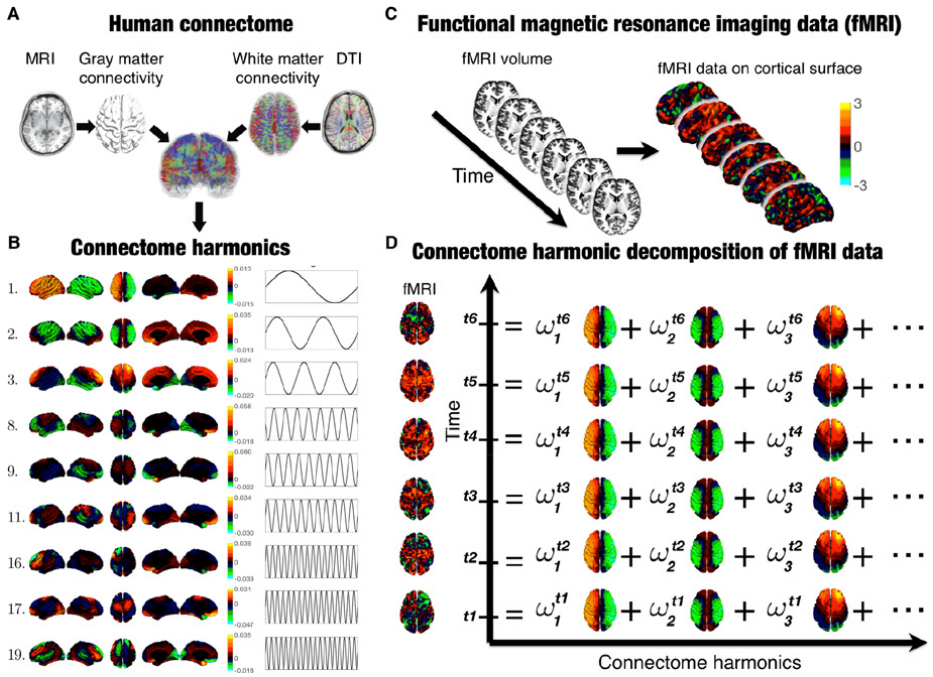

FIG. 2

Connectome harmonics and connectome-harmonic decomposition of fMRI data. (A) High-resolution (20 K vertices) representation of the human connectome is created by reconstructing the gray matter cortical surface from magnetic resonance imaging (MRI) data and combining this gray matter connectivity with the white matter thalamo-cortical fiber traced from the diffusion tensor imaging (DTI) data. (B) Connectome harmonics are estimated as the eigenvectors of the graph Laplacian applied to the human connectome as shown in (A). The cortical patterns of connectome harmonics become increasingly more complex for increasing wave number (shown from top to bottom). (C) Functional magnetic resonance imaging (fMRI) data represented on the cortical surface, as spatial patterns changing over time. (D) Connectome-harmonic decomposition of the fMRI data is performed by projecting the cortical activity pattern at each time point on the set of connectome harmonics and by estimating the contribution (ω_k^t) of each of the harmonics ψ_k for each time point t.

in both, the eyes closed resting state as well as the same condition but with additional music listening (Fig. 3A and B). Furthermore, the LSD-induced energy increase also becomes evident in the changes in the probability distribution of different energy states (of overall brain activity), in terms of a shift of the most-probable energy states toward high-energy values (Fig. 3C).

Remarkably, in line with the LSD-induced psychedelic state, our results also demonstrate a significant increase in the total power and total energy of brain activity under the effect of psilocybin compared to the placebo condition (Fig. 3D and E). Once again, this energy increase is also confirmed by the shift of the most-likely energy states toward high energies, as seen in the probability distribution of different

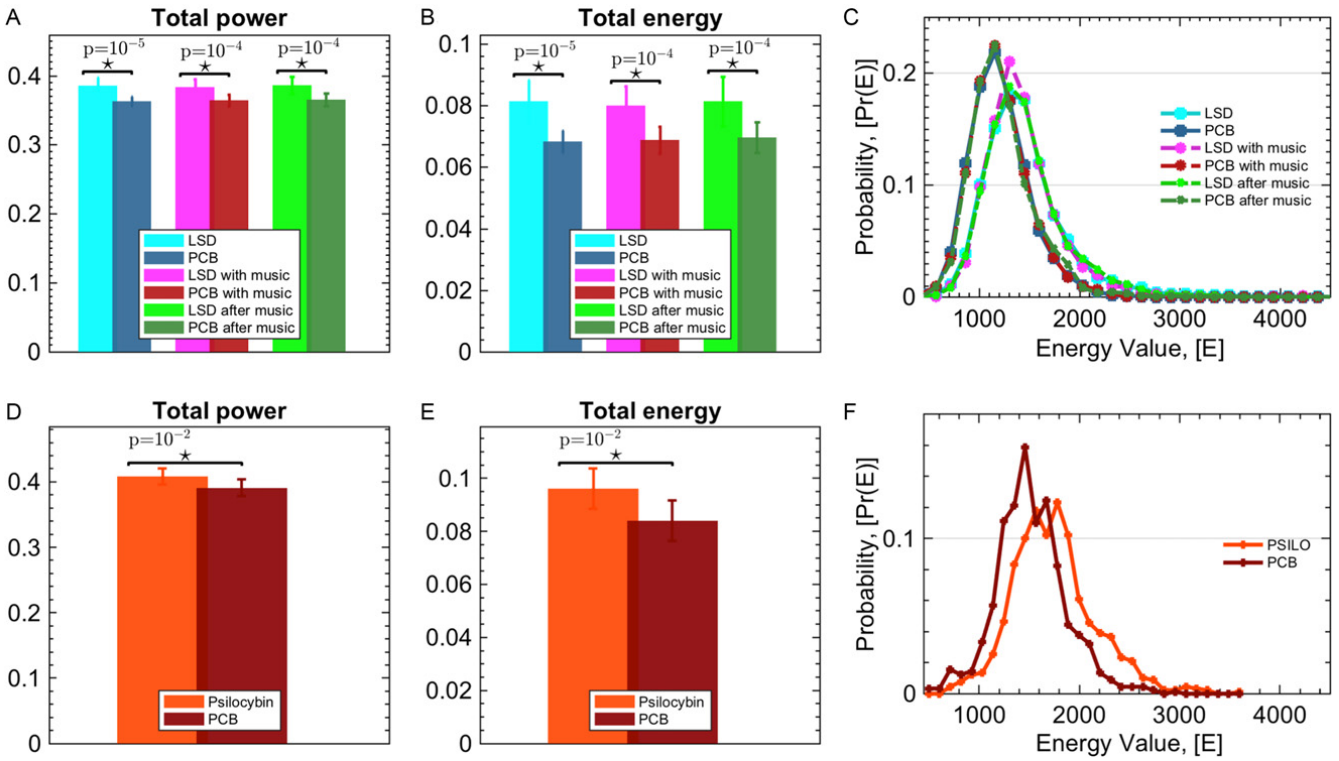

FIG. 3

Energy and power changes in psychedelic state. (A) Total power and (B) total energy of all connectome harmonics under the effect of LSD and placebo in resting state, while listening to music, in the after music condition. (C) Probability of observing certain energy states under the effect of LSD and placebo in all three conditions (rest, music, and after music). (D) Total power and (E) total energy of all connectome harmonics under the effect of psilocybin and placebo. (F) Probability of observing certain energy states under the effect of psilocybin and placebo in all three conditions (rest, music, and after music).

energy states (Fig. 3F). In all four comparisons, (LSD, corresponding placebo condition (PCB), LSD with music, PCB with music, LSD after music, PCB after music, psilocybin, and PCB), we find a significant increase in both, energy and power in the psychedelic state in the standard resting state as well as in the music listening condition (Fig. 3A, B, D, and E). Overall, these findings clearly show that both the LSD and psilocybin-induced psychedelic states lead to increased power and energy of brain activity.

4.2 FREQUENCY-SPECIFIC ENERGY CHANGES IN BRAIN ACTIVITY IN THE PSYCHEDELIC STATE

Next, we explored which connectome-harmonic brain states contribute to the observed total energy increase. We focused on frequency-specific alterations induced by the psychedelic state. To this end, we divided the spectrum of all harmonic brain states (limited by the number of nodes of the human connectome, 20,484 in this study) into frequency-specific bins (15 in this study) and compute the total energy within each bin. A comparison between the LSD- (or psilocybin)-induced psychedelic state to the corresponding placebo condition revealed that LSD as well as psilocybin alter brain activity in a frequency-specific manner. In particular, we found that the energy of a narrow range of low frequency connectome harmonics was suppressed ($k \in [1, \ldots, 10^2]$), while the energy of a broad range of high frequency connectome harmonics increased ($k \in [10^2, \ldots, 10^4]$) under the influence of LSD as well as psilocybin (Fig. 4). These results demonstrate that LSD actually altered brain activity in a frequency-selective manner and it activates rather higher frequency brain states. These findings suggest that both psychedelics, LSD and psilocybin, alter brain activity in a frequency-specific manner, by deactivating a specific low frequency range and activating a broader high frequency range of connectome harmonics.

4.3 PSYCHEDELIC INDUCED EXPANSION OF CONNECTOME-HARMONIC REPERTOIRE

Next, we investigated the changes in the connectome-harmonic repertoire by quantifying the size of the repertoire of the active brain states. To this end, we estimated the probability of activation of harmonic brain states without distinguishing between different harmonics or different time points. Fig. 5 shows the probability of observing a particular weight in the connectome-harmonic decomposition. Note that this weight (ω_k^t) is defined as the dot product between the cortical activity pattern at a given point in time and a particular connectome harmonic, and thus can take positive as well as negative values. The power of a connectome harmonic at a certain point in time is defined as the absolute value of this weight ($|\omega_k^t|$). As shown in Fig. 5A and B, in both psychedelic states, induced by LSD or by psilocybin, we observed that the probability of a connectome-harmonic being silent ($\Pr(\overline{\alpha}) = 0$), i.e., not active, decreased under the effect of LSD as well as psilocybin compared to placebo conditions, whereas the probability of strong contributions (see Fig. 5, tails of the

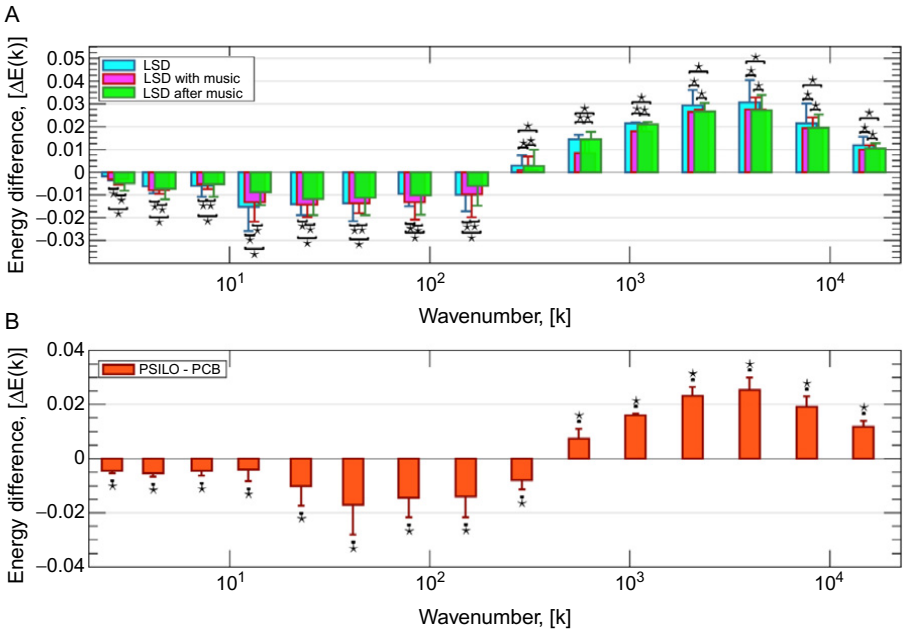

FIG. 4

Frequency-specific energy changes in the psychedelic state. (A) Energy changes of connectome harmonics between placebo and LSD conditions. (B) Energy changes of connectome harmonics between placebo and psilocybin conditions.

Panel (A) is reproduced with permission from Atasoy, S., Roseman, L., Kaelen, M., Kringelbach, M. L., Deco, G., Carhart-Harris, R., 2017. Critical brain dynamics under LSD revealed by connectome-specific harmonic decomposition. Sci. Rep. 7, 17661.

distribution) slightly increased. These findings reveal that both, LSD as well as psilocybin, lead to an expansion of the repertoire of active connectome-harmonic brain states leading to the emergence of more complex brain dynamics.

4.4 PSYCHEDELIC INDUCED CHANGES IN WHOLE-BRAIN CRITICALITY

Interestingly, an increased diversity of the repertoire and the emergence of complex dynamics are typically observed in complex systems when they approach criticality; the transition between an ordered and a less ordered regime. Criticality has been compared to "the constantly shifting battle zone between stagnation and anarchy, the one place where a complex system can be spontaneous adaptive and alive" (Waldrop, 1992). Just like at the transition zone between stagnation (order) and anarchy (chaos), complex behavior with novelty naturally emerges in complex systems at criticality. At criticality, at the balancing point between order and chaos, a complex system has enough stability to sustain itself and enough freedom to exhibit a novel pattern of behavior. Thus, criticality is said to be "the one place where life has enough stability to sustain itself and enough creativity to deserve the name of

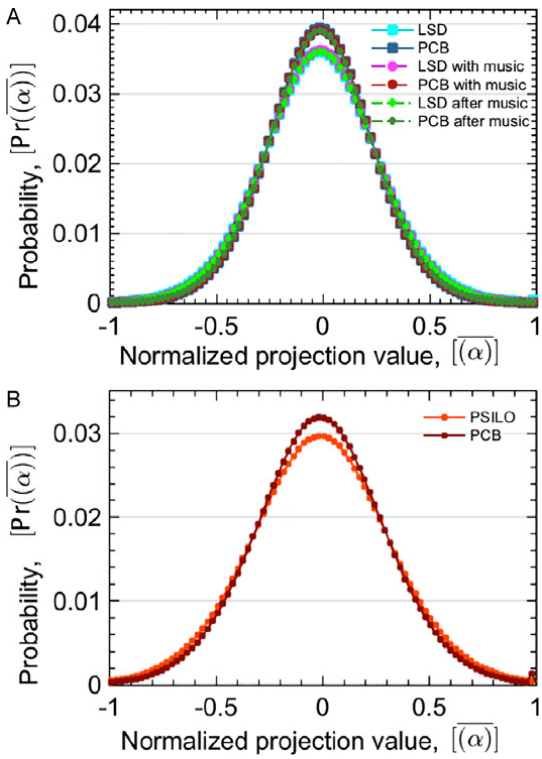

FIG. 5

Repertoire expansion observed in (A) LSD compared to placebo (B) psilocybin compared to placebo.

life" (Waldrop, 1992). Perhaps similar observations about the nature of criticality inspired Allan Turing to pose his famous question about machines:

> *Another simile would be an atomic pile of less than critical size: an injected idea is to correspond to a neutron entering the pile from without. Each such neutron will cause a certain disturbance which eventually dies away. If, however, the size of the pile is sufficiently increased, the disturbance caused by such an incoming neutron will very likely go on and on increasing until the whole pile is destroyed. Is there a corresponding phenomenon for minds, and is there one for machines? There does seem to be one for the human mind. The majority of them seems to be subcritical, i.e., to correspond in this analogy to piles of subcritical size. An idea presented to such a mind will on average give rise to less than one idea in reply. A smallish proportion are supercritical. An idea presented to such a mind may give rise to a whole "theory" consisting of secondary, tertiary and more remote ideas. (…) Adhering to this analogy we ask, "Can a machine be made to be supercritical?"* [(Turing, 1950), as cited in Brochini et al. (2016)]

These ideas not only led Turing to question the possibility of machine consciousness but also provided the first discussion about the idea that criticality in the brain could describe the human and animal mind in terms of subcritical, critical, and supercritical branching of thought processes (Turing, 1950), which later gave rise to the critical brain hypothesis (Chialvo, 2010; Hesse and Gross, 2014). This hypothesis predicts that brain (or certain networks within) function near phase transitions, i.e., near criticality, as it enhances information processing capabilities (Beggs, 2008; Kinouchi and Copelli, 2006; Shew and Plenz, 2013). Following Alan Turing's ideas, Herz and Hopfield's discovery about the mathematical parallels between the models of self-organized criticality (SOC) of earthquakes and those describing the networks of integrate-and-fire neurons, pointed out that the brain could also exhibit SOC, which has now found significant experimental support (Beggs and Plenz, 2003; Chialvo, 2010; Hesse and Gross, 2014; Marković and Gros, 2014). It has also been proposed that criticality may provide a signature of healthy neural systems (Massobrio et al., 2015) (Fig. 6).

Any complex system near criticality exhibits certain characteristics, which are now recognized as the signatures of criticality. The main characteristic signature of criticality is the emergence of power-laws in the relations and fluctuations of different observables. Although the existence of power-laws has been demonstrated exhaustively in terms of neural avalanches, the link between criticality and brain states has yet received limited attention in the neuroscience literature. In our recent study, we have demonstrated that the connectome-harmonic decomposition of the fMRI data has revealed that all power–frequency relations of harmonic brain states follow power-laws (Atasoy et al., 2017). Fig. 6A illustrates that the mean power of different frequency connectome harmonics (indicated as the wavenumber k) plotted over the whole connectome-harmonic spectrum for LSD vs. placebo conditions in all three fMRI sessions, i.e., resting state, music, and after music conditions (Atasoy et al., 2017), whereas Fig. 6B illustrates the same power–frequency relation for placebo and psilocybin conditions. Notably, the distributions in both conditions LSD (or psilocybin) and placebo follow power-laws (Fig. 6), which suggest that resting state brain dynamics reside close enough to criticality that its signatures, such as the emergence of power-laws, are already observable. However, both psychedelic substances, LSD as well as psilocybin, lead to alterations in power-law characteristics compared to the placebo condition. In particular, both conditions, LSD and psilocybin, yield a significant change in the power-law exponent (Fig. 6C and D), which is attributable to the combined effect of increased activity of high frequency and decreased activity of low frequency connectome harmonics. Furthermore, the error of fit of the power-law to the distribution of the data points significantly decreases in both LSD as well as in psilocybin condition (Fig. 6E and F), which illustrates enhanced signatures of criticality and suggests that the brain dynamics tune toward criticality in both, LSD and psilocybin-induced psychedelic states.

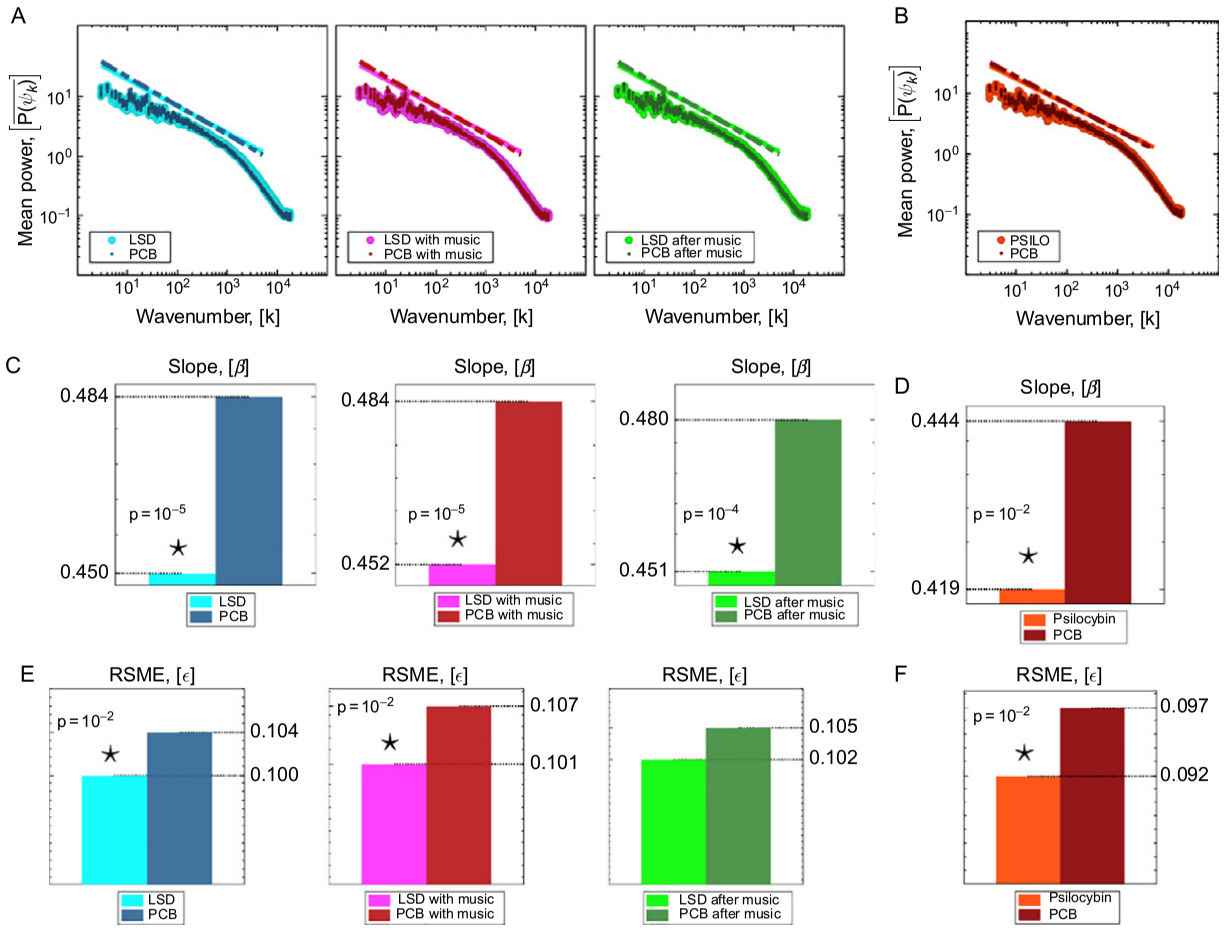

FIG. 6

Whole-brain criticality in the psychedelic state. (A) Power-laws emerging in the power vs. frequency relations (shown as wavenumber of connectome harmonics) under LSD vs. placebo in all three conditions (from left to right resting state, during music, after music) and under (B) psilocybin and placebo conditions. (C) Changes in the power-law exponent (slope) under LSD vs. placebo and (D) under psilocybin vs. placebo. (E) Changes in the error of fit of the power-laws under psilocybin vs. placebo and (F) under psilocybin vs. placebo.

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5 CONCLUSIONS

Our results clearly demonstrate that there are common signatures for the brain states elicited by LSD and psilocybin in terms of increases in total energy and power, as well as frequency-specific energy changes and repertoire expansion of harmonic brain states. We were able to show this using the novel concepts of connectome harmonics and connectome-harmonic decomposition, which have proven useful for characterizing the brain activity associated with any mental state including wakefulness, sleep- and anesthesia-induced loss of consciousness, and psychedelic states (Atasoy et al., 2018).

Besides the link between connectome harmonics and temporal oscillations as discussed in this work, these harmonic brain states have been also shown to naturally self-organize from the interplay between neural excitation and inhibition (Atasoy et al., 2016). This intrinsic link between connectome harmonics and neurophysiology and temporal oscillations (Atasoy et al., 2016) renders them uniquely suitable to be defined as the elementary brain modes composing the complex spatiotemporal patterns of brain activity. Similar to how musical notes are constituents of a complex musical piece, these harmonic brain modes defined as connectome harmonics yield the frequency-specific building blocks of cortical activity.

Given the demonstrated potential of psychedelics for treating certain psychiatric disorders, such as depression, addiction, and post-traumatic stress disorder, as well as for exploring the limits of consciousness, we used these methods for further characterizing the brain states elicited by psychedelics. Intriguingly, in addition to the changes in energy and power, we also found enhanced signatures of criticality associated with both psychedelic substances, LSD and psilocybin, which suggest that the brain dynamics may tune toward criticality in psychedelic elicited states as previously hypothesized (Carhart-Harris et al., 2014).

Interestingly, cross-frequency correlations have been found to increase for a broad, high frequency range of the connectome harmonic spectrum under LSD (Atasoy et al., 2017), suggesting increased communication between different frequencies. These findings indicate a re-organization rather than a random or chaotic activation during psychedelics. Using the metaphor of musical notes (connectome harmonics) composing a complex musical piece (brain activity), we find that during the psychedelic experience, the brain is not playing random musical notes, but rather perhaps expanding its repertoire of harmonic states in a complex and non-random fashion, similar to how improvising jazz musicians would generate a complex musical piece spontaneously (Limb et al., 2008, Vuust and Kringelbach, 2018).

In terms of therapeutic potential, music has shown to have considerable influence over the psychedelic experience and has even been proposed to act as a "hidden therapist" (Kaelen et al., 2018). In general, music has the power to move us through dance and emotion and can perhaps best be understood within a predictive coding framework (Vuust and Kringelbach, 2010; Vuust et al., 2018). As such, the close

links between connectome harmonics and music can potentially offer deeper insights into this process and perhaps generate novel ways of "singing the mind electric," to turn a phrase from Walt Whitman.

More generally, the framework of elementary harmonic brain modes offers a unifying perspective and explanatory framework revealing new ways to describe mental states in precise terms. The proposed mathematical framework links the spatial patterns of correlated neural activity, not only to the temporal oscillations characteristic of human brain activity but also to brain anatomy and neurophysiology (Atasoy et al., 2018). But even more, this framework utilized here to gain insights into the neural correlates of the psychedelic state, goes beyond enabling a new dimension of tools for decomposing complex patterns of neural activity into their elementary building blocks, by also providing a fundamental principle linking space and time in neural dynamics through harmonic waves—a phenomenon ubiquitous in nature.

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