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Information parity increases on functional brain networks under influence of a psychedelic substance

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Supplementary material for this article is available [online](#)

Abstract

The physical basis of consciousness is one of the most intriguing open questions that contemporary science aims to solve. By approaching the brain as an interactive information system, complex network theory has greatly contributed to understand brain process in different states of mind. We study a non-ordinary state of mind by comparing resting-state functional brain networks of individuals in two different conditions: before and after the ingestion of the psychedelic brew Ayahuasca. In order to quantify the functional, statistical symmetries between brain region connectivity, we calculate the pairwise information parity of the functional brain networks. Unlike the usual approach to quantitative network analysis that considers only local or global scales, information parity instead quantifies pairwise statistical similarities over the entire network structure. We find an increase in the average information parity on brain networks of individuals under psychedelic influences. Notably, the information parity between regions from the limbic system and frontal cortex is consistently higher for all the individuals while under the psychedelic influence. These findings suggest that the resemblance of statistical influences between pair of brain regions activities tends to increase under Ayahuasca effects. This could be interpreted as a mechanism to maintain the network functional resilience.

1. Introduction

Understanding the relationship between mental states and brain activity is one of the most intricate challenges of neuroscience. Finding distinguishing features of the human brain mechanisms considering different states of mind seems to be a reliable approach toward unraveling the neural correlate of consciousness. In fact, several studies using neuroimaging data have shown consistent correlations between mental states and functional brain networks in humans [1–7]. Emergent behaviors on networked systems are determined by their topological structure. For instance, topological features such as quenched disorders and modularity are known to influence key aspects of criticality [8–10], which have been related to brain dynamics [11]. In this paper, we intend to shed light on the following questions: How is symmetry in the functional brain networks affected in different states of consciousness? Can we capture possible symmetry variations in individuals in psychedelic state of consciousness by quantifying the consonance of influences on brain networks?

To address this question, we evaluate the *information parity* [12] on functional brain networks of individuals in the ordinary state of mind and under the effects of a potent psychedelic substance. The information parity is a measure that estimates the similarity of influences on a pair of nodes considering their relative location in the network. The intuition behind this measure is that a node in a network influences and is influenced not only by its nearest neighbors but by the network structure as a whole. We assess the ‘topological profile’ of a node in terms of the whole network structure considered from the viewpoint of the referred node. This means a mapping of which nodes are in the nearest neighborhood, in the next-nearest neighborhood, and so on. We refer to the [13] for further clarification about topological profiles. For instance, in the case of networks in which the topology completely defines the node roles, nodes with the same topological profile would have exactly the same role. Information parity estimates the common information collected by a pair of nodes, while also taking into account their individual statistics [12]. In simple words, information parity quantifies how much information one can have about a node by knowing the topological profile of another node. From the information theory perspective, information parity is the excerpt of mutual information responsible for quantifying the statistical symmetry. Moreover, being a local measure (in the sense that it quantifies the consonance between a pair of node) that encapsulates global information, information parity can help map network structural resilience. The more nodes are distributed in such way to increase the network redundancy, the greater will be the network robustness and ultimately its resilience [14]. The information parity quantifies this topological redundancy.

In the present study, we detect a persistent increase in the average information parity for all individuals under the psychedelic influence. We find an increase of average information parity across all individuals, despite the variability in individual patterns. This suggests that regardless of the individual configuration that brain adopts under the psychedelic influence, it will choose a configuration that increases information parity on the functional networks. Previous works have pointed to an increase of flexibility in functional brain networks under Ayahuasca influence, which has been measured by an increase in entropy of the correlation map [15], the increase of diversity of influences [13], and the increase on entropy of connectivity distribution [3]. The present results lead us to hypothesize that the rise in entropy may be coordinated with an increase in redundancy, when pairs of nodes tend to gather more homologous information. Furthermore, we also detected that all individuals exhibit an increased information parity between the frontal cortex and regions of the limbic system, while changes in other regions vary for different individuals. This means that regarding the functional topology, the influences of the frontal regions and limbic regions on the whole networks become more similar. It has been suggested that frontal cortex regions are involved in top-down modulation of external attention and emotions [16–18], while the limbic regions as hippocampus and amygdala are involved in internal process as memory and emotions [19, 20]. Based on our results, we argue that the increase in the consonance between frontal and limbic regions could be related to an hierarchy flattening. A functional hierarchy disruption due to top-down modulation reduction while the human brain is under influence of a psychedelic substance was previously suggested by Alonso and collaborators [21] as we will explore in the Discussion section. Next, we briefly describe the method and then, report on the results. This is followed by a discussion of possible interpretations in the context of the quantitative neuroscience of psychedelics.

2. Methods

2.1. Neuroimaging data

The data used in the present analysis is the same of previously published studies [3, 13]. The reader can find carefully described details of their acquisition in [3]. In the following, we briefly summarize the essential information. The data consist of seven right-handed adults volunteers (≈ 31.3 years old, from 24 to 47 years) in absence of medication influence at least 3 months prior to the acquisition sessions. They were in abstinence from alcohol, caffeine and nicotine and had attested no psychiatric or neurological disorders (assessed by DSM-IV structured interview). All the volunteers were submitted twice to functional magnetic resonance image (fMRI) scanning: one before and the other 40 minutes after Ayahuasca intake. In both scanning sections, they were requested to remain in awake resting state, that is, lying down, with eyes closed, with the mind free for wandering [22]. Each volunteer ingested 120–200 ml (2.2 ml kg^{-1} of body weight) of Ayahuasca. The brew contained 0.8 mg ml^{-1} of DMT and 0.21 mg ml^{-1} of harmine. The data were preprocessed according to the following steps: slice-timing and head motion correction, and spatial smoothing (Gaussian kernel, FWHM = 5 mm). The samples were spatially normalized to the Montreal

Neurologic Institute (MNI152). It was calculated 9 regressors using a general linear model: 6 regressors to movement correction, 1 to white matter signal, 1 to cerebrospinal fluid and 1 to global signal.

2.2. Functional brain networks

In order to define the networks, we segmented the 3D brain images into 110 brain regions according to the Harvard–Oxford cortical and subcortical structural atlas (threshold of $\leq 25\%$, using FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). Due to technical limitations, 6 regions had to be excluded from the analysis. We extracted one time series from each region by computing the average within that region and applied a band-pass filter (≈ 0.03 – 0.07 Hz) using the maximum overlap wavelet transform. In our approach, the brain regions define the network nodes, and links are defined by the Pearson correlation between the wavelet coefficients, yielding a 104×104 correlation matrix. We obtain adjacency matrices A representing unweighted undirected networks by applying thresholds on the absolute value of the correlation matrices. That is if the values are larger than the threshold, the link A_{ij} is set to be 1, otherwise, it is defined to be 0. Since there is no solid method to estimate *a priori* the most appropriate threshold, to ensure the robustness of our analysis we evaluate a range of thresholds generating a set of networks with different densities for each sample and compare networks of the same density. The process of filtering the connectivity mapping according threshold allow us to detect intrinsic features of connective structure [10]. The threshold range was chosen according to the following rules: (i) The network must be of small-world type and connected, i.e. there must be at least one path connecting any pair of nodes. (ii) The network must be sparse enough so that it does not behave like a random network. In other words, the global efficiency [23] must be lower than its degree-preserving randomized version [24], and the local efficiency [23] must be higher than its randomized version. The average degrees of the networks that obey these criteria for the present dataset range from $24 \leq \langle k \rangle \leq 39$. The same procedure was used in [3, 13, 25, 26]. See [2, 3] for further details. In short, considering that information parity, as most of the network measurements, is sensible to network density, we were careful in comparing networks before and after Ayahuasca intake with the same densities.

2.3. Information parity

Given a network $G(V, E)$, in which V is a set of N nodes and E is the set of their undirected and unweighted links. The network is represented by the adjacency matrix A defined 1 for a pair (i, j) of connected nodes and 0, otherwise. The probability $p_i(r)$ of find a node at r links of distance from the node i and the probability $p_{ij}(r)$ of find a node at the same r distance from the nodes i and j are respectively defined as following:

$$p_i(r) = \frac{1}{N-1} \sum_{\substack{k \in V \\ k \neq i}} \delta(D_{ik}, r), \quad (1)$$

and

$$p_{ij}(r) = \frac{1}{N-2} \sum_{\substack{k \in V \\ k \neq i, j}} \delta(D_{ik}, r) \delta(D_{jk}, r), \quad (2)$$

where $\delta(\cdot, \cdot)$ denotes the Kronecker delta and D_{ik} the geodesic distance between the node i and the node k [12]. That is, the matrix $\{D_{ik}\}_{i,k=1,\dots,N}$ is defined by the shortest path length between all pair of nodes. The information parity [12] between a pair of nodes (i, j) is defined as:

$$I_{ij} = \sum_{r=1}^{r_{\max}} p_{ij}(r) \log \frac{p_{i,j}(r)}{p_i(r)p_j(r)}, \quad (3)$$

in which r are integer in the interval $1 \leq r \leq r_{\max}$, in with $r_{\max}$ is the maximum neighborhood radius of the nodes [12, 13]. Examples of information parity mapping of simple networks can be seen in the supplementary material.

3. Results

In this section, we report the detected changes when we compared the functional brain networks before and after Ayahuasca intake. Figure 1(a) shows the average information parity for each subject before (purple) and after Ayahuasca intake (green). Each boxplot depicts the information parity of a set of networks with different average degree ($24 \leq \langle k \rangle \leq 39$), generated from the same correlation matrix. The threshold range

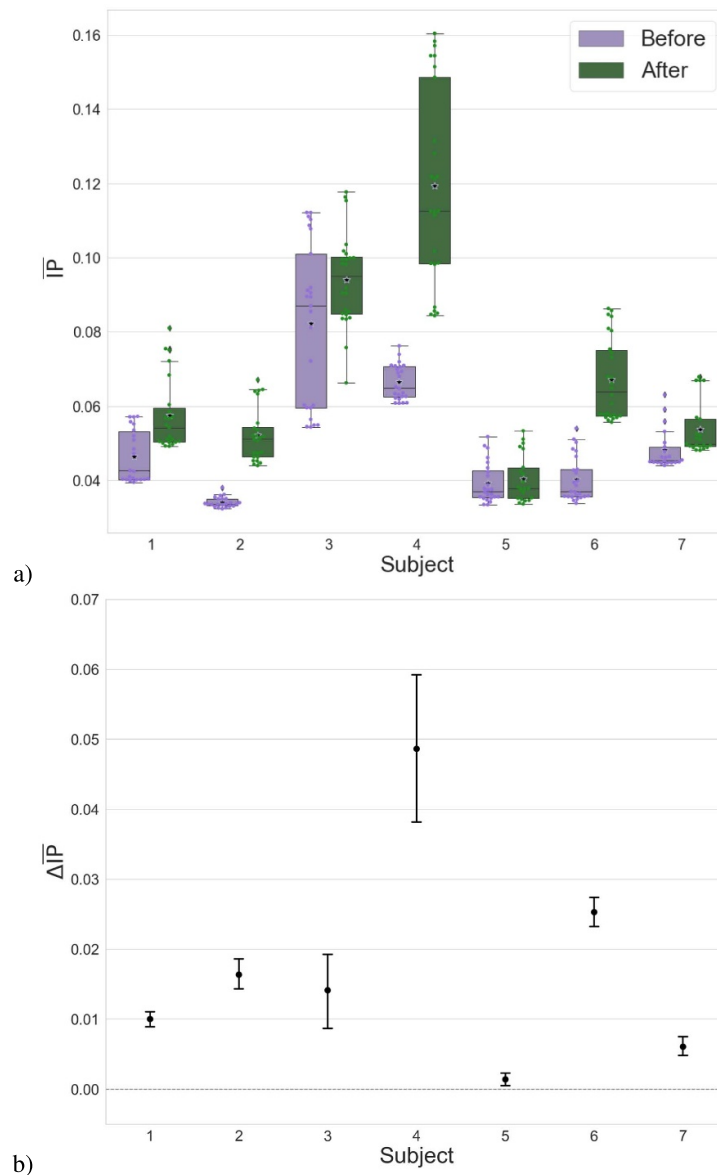
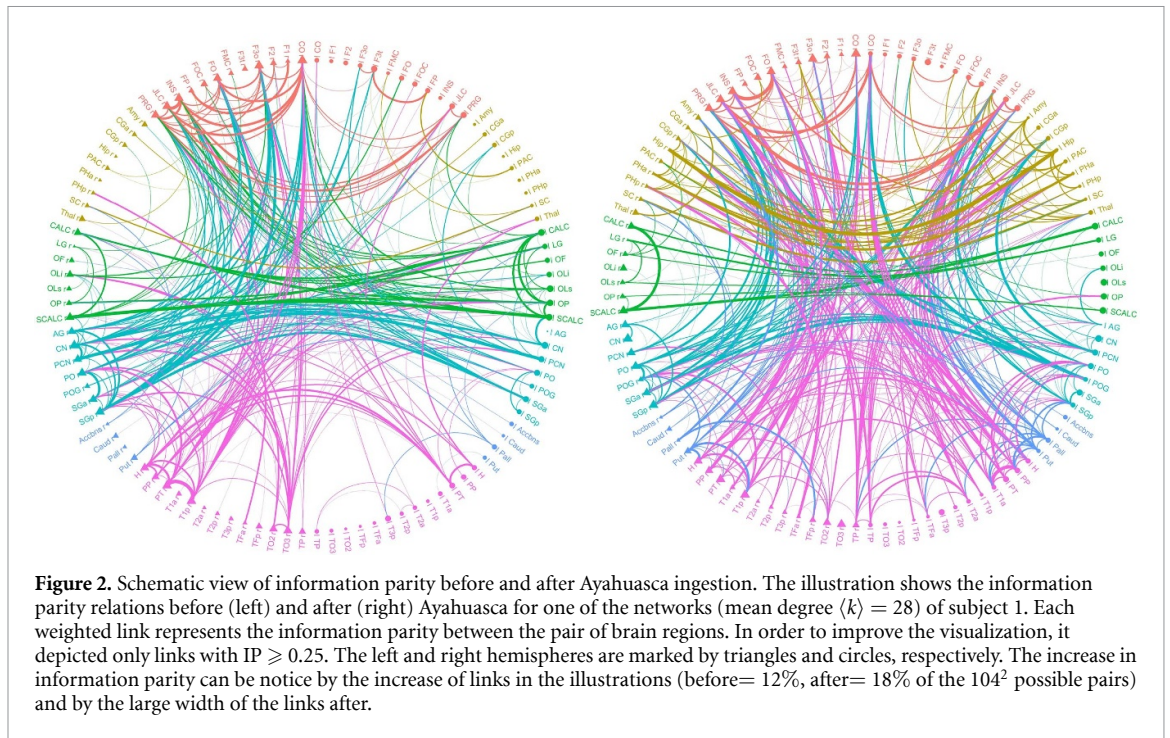


Figure 1. Information parity increases after Ayahuasca intake. The boxplot in (a) shows the average information parity before (purple) and after (green) Ayahuasca. Each point represents the average over all pairs of nodes for networks with different mean average ($24 \leq \langle k \rangle \leq 39$). The stars mark the mean value across all networks from each sample. The plot in (b) depicts the average of the information parity divergence ($\Delta IP = IP_{\text{after}} - IP_{\text{before}}$) between networks with the same density. Note that the information parity increases for all the subjects (p-value = 0.006, t-test, testing the hypothesis *no difference*). It means that, on average, pair of nodes share more similar nodal profile. In other words, statistically, they influence and are influenced by the whole functional structure in a resembling way.

was defined to ensure that the networks are connected, but not too dense so as to exhibit the behavior of a random network as defined in [3]. Each dot represents the average information parity for one network. Note that, on average, the network's information parity increases for all subjects after Ayahuasca intake. Figure 1(b) shows the difference between information parity after and before Ayahuasca intake ($\Delta IP = IP_{\text{after}} - IP_{\text{before}}$) comparing networks with the same average degree. The comparisons for all subjects resulted in positive differences independent of the network density.

A schematic view of information parity increase can be observed in figure 2. It illustrates the information parity between the brain regions for one network sample before and one after Ayahuasca intake for one of the subjects (both computed from network with average degree, $\langle k \rangle = 28$). The dots represent the brain regions, and the links represent the information parity between the nodes. One can observe clear differences on the information parity patterns. Although the average information parity increases for all subjects, the patterns of changes vary considerable for each subject. As there is a wider variation across subjects, we recommend that the reader not draw conclusions based on observations of particular links.



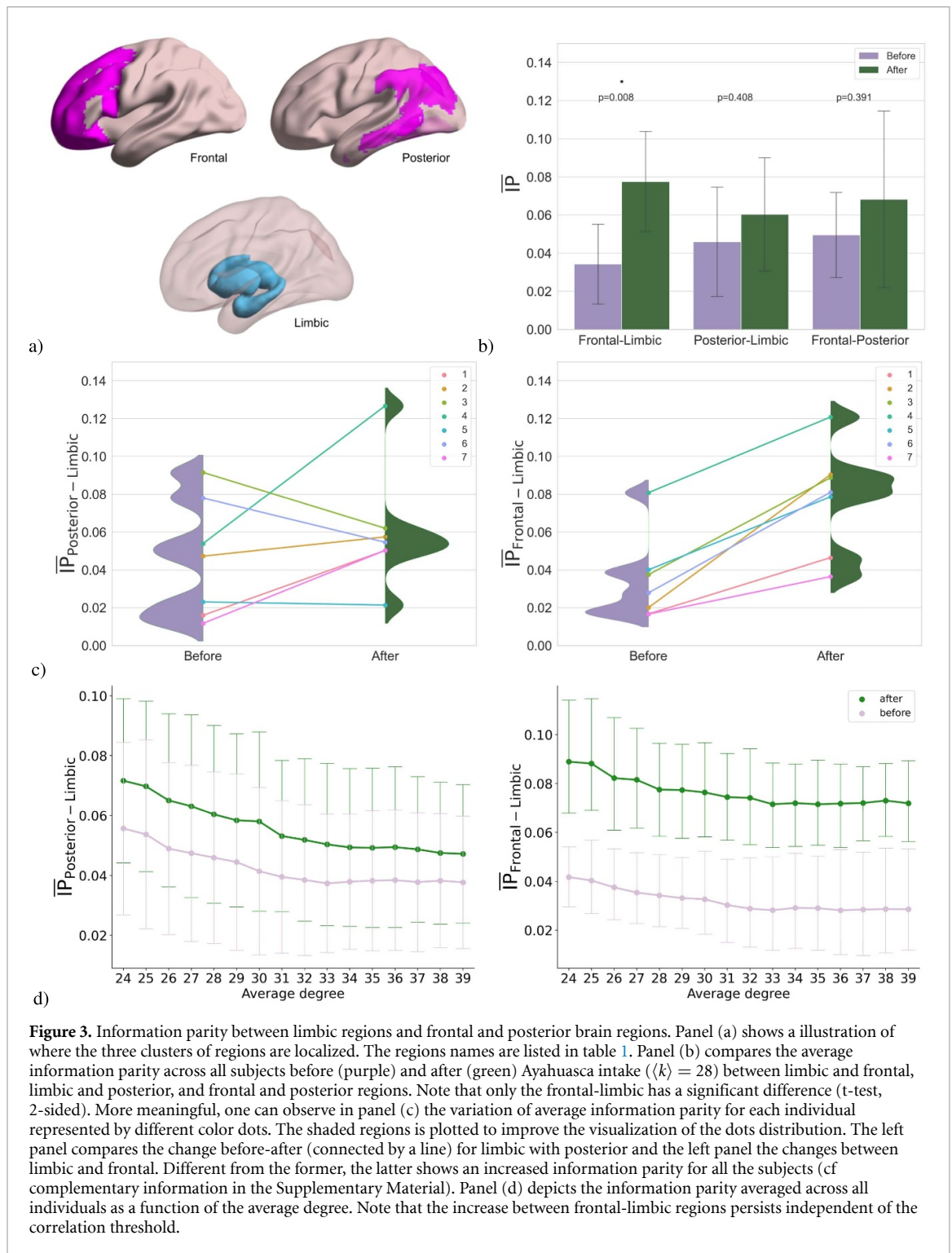
Next, we investigate if the information parity between a large set of the brain regions would change consistently under the influence of Ayahuasca. Guided by the literature, we focus our study on the relations between regions from posterior and frontal cortex [27] with subcortical regions of limbic system. The limbic structure considered here includes hippocampus, amygdala, and other regions that could play a role in memory retrieval psychedelic experiences. A sketch of the brain regions locations are presented in colorful shading in figure 3(a). The precise regions are listed in table 1.

In the bar plot of figure 3(b), we compare the average information parity between the limbic and frontal, limbic and posterior. In addition we compare frontal and posterior regions to serve as a control. The only consistent changes for all individuals are the increase of information parity between frontal and limbic regions. The details of the changes for each individual can be observed in figure 3(c). Note that the information parity between the limbic and frontal regions increases for all subjects, while the information parity between the limbic and posterior regions may increase or decrease, depending on the subject. Details about the frontal–posterior can be found in the supplementary material.

4. Discussion

Humans have at all times used psychedelics to deliberately manipulate the state of consciousness. Recently, psychedelic substances have been assigned a central importance in neuroscience not only for its therapeutic potential [28–30], but also because it allow us to explore the neural correlate of consciousness. Psychedelics substances affect the brain functions in a non-straightforward way. Therefore new analytical tools are needed in order to understand it from network theory point of view.

Recent studies have shown that under psychedelic influence the brain functions become less constrained as indicated by increasing entropy in different aspects of brain activity [1, 3, 13, 15, 31]. Along the increase on entropy, previous results have indicated an increase in network segregation after Ayahuasca intake characterized by an increase of local efficiency, clustering coefficient, and geodesic distances and a decrease of global efficiency [3]. Similar results were reported for individuals under the psychedelic substance lysergic acid diethylamide effects [32]. Together, they suggest that, on average, the brain regions tend to have a less restrictive influence from overall brain network. Indeed, the average geodesic entropy, that is, the entropy of the individual topological profiles of the nodes, is higher after Ayahuasca intake [13]. This means that the nodes have a greater diversity of influences. In this context, the increase in the average information parity could indicate that, although the overall influence on brain regions' activity tends to be less constrained, there is an increase in the redundancy of pairwise topological profiles. In other words, concerning the topological symmetry, the functional influences shared by a pair of regions are more similar. Redundancy



plays an important role for the robustness of networks and ultimately to restore a perturbed network, which is also called *resilience*. For instance, redundancy could guarantee the proper functioning of the network while it recovers via a node or link based mechanism of self-healing [33, 34]. In this light, information parity can be helpful to monitor such a process. Based on the results reported here, we hypothesize that the release on the constraints does not results in a network deterioration, instead, the functional networks reorganize itself in a way that the disruption in the hierarchy [3] does not affect its resilience, since, at least, the pairwise informational redundancy increases.

The cluster of regions defined here as limbic system is traditionally associated with processes as learning, emotions, memory, reward mechanisms, and impulses control, among others. The frontal cortex has been

Table 1. List of regions considered the three clusters of brain regions compared in the figure 3. The regions were defined according to the Harvard–Oxford cortical and subcortical structural atlas (threshold of 25%, using FMRIB Software Library, www.fmrib.ox.ac.uk/fsl).

Frontal cortex	Frontal pole R/L
	Superior frontal gyrus R/L
	Middle frontal gyrus R/L
	Inferior frontal gyrus pars opercularis R/L
	Frontal region juxtapositional lobule cortex R/L
	Paracingulate gyrus R/L
	Cingulate gyrus, anterior division R/L
	Frontal orbital cortex R/L
	Frontal operculum cortex R/L
Posterior cortex	Middle temporal gyrus, posterior division R/L
	Middle temporal gyrus, temporooccipital part R/L
	Supramarginal gyrus, anterior division R/L
	Supramarginal gyrus, posterior division R/L
	Angular gyrus R/L
	Lateral occipital cortex, superior division R/L
	Lingual gyrus R/L
	Temporal fusiform cortex, posterior division R/L
	Temporal occipital fusiform cortex R/L
	Occipital fusiform gyrus R/L
Limbic system	Parahippocampal gyrus, anterior division R/L
	Thalamus R/L
	Caudate R/L
	Putamen R/L
	Pallidum R/L
	Hippocampus R/L
	Amygdala R/L
	Accumbens R/L

associated to top-down modulation [16], which consists in a high-level processing that modulate low-level processing such memory retrieval [35], emotions control [36] to cite some. Furthermore, it has been recently hypothesized that top-down control is reduced under Ayahuasca influence, due to a reduction of transfer entropy from frontal regions to other brain regions [21]. The reduction of constraints from frontal regions under psychedelic influences allow an increase of bottom-up information flow, characterized by a increased influence of low-level sensory cortices [21]. The increase in the information parity between the frontal cortex and limbic regions corroborate with the hypothesis of functional hierarchy disruption under psychedelic influences [21]. In fact, our results suggest that, from a statistical point of view, the frontal cortex and limbic system have a more comparable influence on the whole brain in the psychedelic state than in the normal state.

The present work greatly adds to the knowledge about the effect of psychedelics on brain networks. The method is compatible to previously analysis and suitable to integrate the analytical framework for evaluate brain functions in different consciousness states. However, one should consider the limitation of the data: (i) the number of individuals are small, which does not allow us to rely on traditional statistical tests well established in the field of neuroscience; (ii) our experimental design did not include a placebo group; (iii) for the local analysis, we choose the clusters of regions based on neuroscience literature instead perform a systematic network's modular inspection; (iv) to avoid misleading conclusions given the limited size of the data, we did not perform a detailed analysis for each brain region. Hence, in order have a more conclusive picture of changes on the brain functions in non ordinary state of consciousness, we recommend a replication of the analysis performed here, alongside to the previous analysis [3, 13, 15], for a large group of individuals. It invites investigations for other altered states of consciousness as well. We are convinced that this analytical framework can yield significant insights to the understand of the neural basis of consciousness.

Ethical statement

The experimental procedure for data collection was approved by the Ethics and Research Committee of the University of São Paulo at Ribeirão Preto (Process Number 14 672/2006).

Data availability statement

The data that support the findings of this study are openly available at the following URL/DOI: <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/28619>.

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