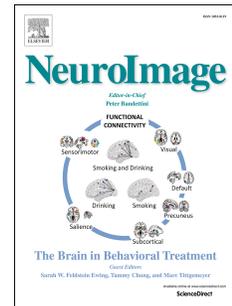


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Dynamic functional connectivity and brain metastability during altered states of consciousness

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Abstract

The scientific study of human consciousness has greatly benefited from the development of non-invasive brain imaging methods. The quest to identify the neural correlates of consciousness combined psychophysical experimentation with neuroimaging tools such as functional magnetic resonance imaging (fMRI) to map the changes in neural activity associated with conscious vs. unconscious percepts. Different neuroimaging methods have also been applied to characterize spontaneous brain activity fluctuations during altered states of consciousness, and to develop quantitative metrics for the level of consciousness. Most of these studies, however, have not explored the dynamic nature of the whole-brain imaging data provided by fMRI. A series of empirical and computational studies strongly suggests that the temporal fluctuations observed in this data present a non-trivial structure, and that this structure is compatible with the exploration of a discrete repertoire of states. In this review we focus on how dynamic neuroimaging can be used to address theoretical accounts of consciousness based on the hypothesis of a dynamic core, i.e. a constantly evolving and transiently stable set of coordinated neurons that constitute an integrated and differentiated physical substrate for each conscious experience. We review work exploring the possibility that metastability in brain dynamics leads to a repertoire of dynamic core states, and discuss how it might be modified during altered states of consciousness. This discussion prompts us to review neuroimaging

studies aimed to map the dynamic exploration of the repertoire of states as a function of consciousness. Complementary studies of the dynamic core hypothesis using perturbative methods are also discussed. Finally, we propose that a link between metastability in brain dynamics and the level of consciousness could pave the way towards a mechanistic understanding of altered states of consciousness using tools from dynamical systems theory and statistical physics.

Keywords: consciousness, neuroimaging, brain dynamics, fMRI, dynamic core, metastability

Introduction

The character, variety and intensity of the conscious content that constitutes our everyday experience represent some of the most puzzling questions faced by modern neuroscience. The ubiquity of consciousness in our first-person perspective of the world challenges a definition in terms of more primitive notions (Chalmers, 1995). Operationally, conscious content can be defined as information processing in the brain that is accompanied by subjective and reportable experience; in contrast, unconscious or subliminal information processing can influence cognition and behavior without reportability (Dehaene et al., 2006). Consciousness as a temporally extended brain state can be defined as a set of conditions in the brain that are compatible with conscious content (Bayne et al., 2016). Such conditions are modified during altered states of consciousness such as deep sleep, anesthesia or in disorders of consciousness (DOC). To answer the question as to whether the state and the content of consciousness can be fully dissociated, one must first find an empirical approach to investigate them independently. This is highly challenging by the very definition of both concepts, since the state of consciousness is defined precisely based on its capacity for sustaining conscious content. Current research is being carried out on the possible divergence between these concepts (see Bayne et al., 2016 for an example), but more studies are needed to settle this issue.

The contemporary recognition of consciousness as a neurobiological phenomenon requiring scientific explanation can be traced to the fundamental articles by Bachmann (Bachmann, 1984) and Crick & Koch (Crick & Koch, 1990). These articles proposed the search of neural correlates of consciousness, understood as the minimal set of neural events associated with a certain

conscious experience. These neural correlates should be informative of where and when physical events associated with consciousness occur in the brain. Decades of experimental efforts have been dedicated to mapping the brain areas involved in conscious experience, both in humans and in non-human primates (for extensive reviews see Mormann & Koch, 2007; Rees, 2013; Tononi & Koch, 2008; for possible future directions of research see Aru et al., 2012; Tsuchiya et al., 2015; Sandberg et al., 2016; Koch et al., 2016; for criticism of the concept of neural correlates of consciousness see Noë & Thompson, 2004). Most of these experiments were based on invasive electrophysiological recordings (in non-human primates) and on non-invasive methods such as electroencephalography (EEG), magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI), in combination with the psychophysical paradigm of minimal contrast between consciously perceived and subliminal stimuli (Dehaene & Changeux, 2011). It is now clear that consciousness involves a distributed network of regions encompassing higher order associative areas in the parietal cortex, as well as the frontal and pre-frontal cortex – even though experiments using “no report” paradigms challenge the involvement of the latter areas (see the references provided above).

A complementary approach to the neural correlates of consciousness consists in studying consciousness as a temporally extended state, and contrasting wakefulness vs. states of diminished consciousness. Following this approach, positron emission tomography (PET) studies revealed that metabolism in the thalamus, and in frontal and parietal areas is reduced during anesthesia induced by different agents (Alkire & Miller, 2005), as well as during deep non-rapid eye movement (NREM) sleep (Braun et al., 1997; Nofzinger et al., 2002; Tagliazucchi et al., 2013a), and during transient episodes of impaired consciousness associated with generalized spike and wave discharges in epilepsy (absence seizures; Blumenfeld, 2012). Brain metabolism is also impaired in patients suffering from DOC, which include unresponsive wakefulness syndrome (UWS) and the minimally conscious state (MCS) (Laureys et al., 2004).

fMRI recordings present improved temporal resolution over PET and can be used to study functional connectivity (FC) of spontaneous brain activity fluctuations (Fox & Raichle, 2007), understood as the degree of statistical covariance between blood-oxygen-level dependent (BOLD) signals recorded at different anatomical locations (Van Den Heuvel & Pol, 2010). The decoupling of fronto-parietal regions has been consistently reported for deep NREM sleep (Horowitz et al., 2009; Spormaker et al., 2010; Samann et al., 2011; Larson-Prior et al., 2011; Wu et al., 2012). The affected anatomical regions are found within the default mode network

(DMN) (Raichle, 2015), which has been implicated in consciousness of the self and the environment (Fernandez-Espejo et al., 2012; Spreng & Grady, 2010; Qin & Northoff, 2011). Changes in whole-brain FC measured using fMRI can be combined with machine learning algorithms for the automatic classification of levels of consciousness (Tagliazucchi et al., 2012a; Monti et al., 2013; Tagliazucchi & Laufs, 2014; Altmann et al., 2016). The successful application of such algorithms in DOC patients (Demertzi et al., 2015) illustrates the potential clinical relevance of neuroimaging methods in the scientific study of consciousness.

The experiments discussed above are informative of the anatomical regions involved in the emergence of conscious content and in the global level of consciousness; however, they generally fail to establish a link between these concepts and the dynamics of coordinated brain activity. Methods such as PET glucose consumption imaging, fMRI event-related designs and FC analyses provide a “static”, time-averaged picture of brain activity. However, it has been argued that consciousness is a dynamic process that involves the constant shaping and re-shaping of an irreducible, simultaneously integrated and differentiated set of regions termed the “dynamic core” (Tononi & Edelman, 1998), which suggests the adequacy of factoring the temporal dimension in the analysis of neuroimaging data. In recent years it has become increasingly clear that fMRI can identify spontaneous co-activation near its limit of temporal resolution, and that FC computed over relatively short temporal windows of time (from seconds to few minutes) can carry important neurobiological information (Chang & Glover, 2010; Allen et al., 2012; Hutchison et al., 2013a; Hutchison et al., 2013b; Calhoun et al., 2014). The neurobiological relevance of dynamic FC is supported by multimodal imaging studies linking transient FC changes to electrophysiological brain signals, both in humans and in animal models (Tagliazucchi et al., 2012b; Chang et al., 2013; Thompson et al., 2013; Keilholz, 2014; Tagliazucchi & Laufs, 2015; Thompson et al., 2015; Grooms et al., 2017). Furthermore, dynamic FC reflects ongoing cognition (Gonzalez-Castillo et al., 2015; Braun et al., 2015; Shine et al., 2016; Kucyi et al., 2017), the level of arousal (Chang et al., 2016; Wang et al., 2016) and mind-wandering (Kucyi & Davis, 2014; Mooneyham et al., 2017), and has also been implicated in certain neuropsychiatric diseases (Hutchison et al., 2013b; Calhoun et al., 2014).

This review is focused on how the analysis of the dynamics of coordinated brain activity measured with fMRI -and, to a lesser extent, with EEG and MEG- can be used to test the predictions of theoretical accounts of consciousness. We begin with a general discussion of models of consciousness, with special emphasis on the dynamic core hypothesis and the

information integration theory (IIT), and then establish a series of predictions on the behavior of the repertoire of possible brain configurations. Afterwards, we introduce the concept of metastable dynamics as a plausible way in which such a repertoire of brain configurations could emerge, and review empirical and computational studies supporting the existence of metastability in human brain dynamics. The rest of our article is devoted to the discussion of dynamic neuroimaging studies providing evidence of changes in the repertoire of brain configurations during altered states of consciousness. We also discuss the limitations of correlational studies and the use of perturbative approaches to reveal the narrowing of possible configurations during unconsciousness.

Phenomenology and theoretical models of consciousness

Moving forward from the more descriptive notion of neural correlates of consciousness, the formulation of theoretical models of consciousness aims towards a mechanistic explanation, i.e. knowing the “how” (mechanism) it should be possible to predict then “when” and “where” (Seth et al., 2007). While a number of mechanistic models have been formulated, our focus is on those based on the phenomenology of consciousness that were pioneered by Tononi & Edelman (Tononi & Edelman, 1998; Edelman & Tononi, 2000; Tononi, 2004). The discussion of these models is attractive from the viewpoint of our article since 1) they provide a quantitative formulation and 2) put restrictions on the dynamic behavior of neural activity as a function of the level of consciousness.

The phenomenology of consciousness is understood as a characterization of inner mental life, i.e. “what it feels like” to undergo different experiences, and of what features are common to all conscious experiences (Varela, 1996). Tononi & Edelman identified two key properties of each conscious experience from phenomenological considerations (Tononi & Edelman, 1998; Edelman & Tononi, 2000; Tononi, 2004). First, each conscious experience is highly informative, since it represents one instance among a vast repertoire of possibilities. This property is equivalent to stating that brain activity associated with consciousness must be highly differentiated, as opposed to dynamic behavior ruled by very strong interactions that give rise to a low number of collective modes of activity. This point can also be made using a cardinality argument: if different conscious experiences are associated with different physical states of the brain, the fact that the number of experiences is overwhelmingly large imposes an (at least)

equally large number of possible physical states. The second property stems from the observation that, at all times, each conscious experience is undecomposable into sub-parts that are consciously perceived independently of the whole (Cleeremans, 2003). For instance, while our nervous system can access the environment through different senses, when information from these senses is perceived consciously and simultaneously it is always fused into a unitary experience containing elements from all sensory modalities, as well as internally generated thought and cognition. This property prescribes that neural activity must be integrated, i.e. the activity from different sets of neurons associated with a certain content of consciousness must present a positive amount of mutual information.

It follows that competition must exist between the two properties postulated by Tononi & Edelman as key phenomenological aspects consciousness. Maximal differentiation can be achieved when all members of a system behave independently in the statistical sense, but this situation prevents integration. On the other hand, a high level of integration must reduce the global behavior of the system to a small repertoire of possible configurations. This competition can be quantified using the concept of neural complexity, which is based on the ratio between the statistical dependence within a given subset of the system, and the statistical dependence between that subset and the rest of the system (Tononi et al., 1994). Later formulations led to IIT and to the proposal of other quantitative metrics for the level of consciousness (Tononi, 2004).

An intuitive visualization of the notion of neural complexity is provided in the upper panel of **Figure 1**. Consider elements in a two-dimensional grid that can have a discrete number of states, for instance, pixels in a TV screen. TV static corresponds to a maximally differentiated state, since lack of statistical dependence between the elements results in a repertoire with the highest number of possible configurations (C). On the other extreme, the statistical dependence between the elements is very high and the repertoire is reduced (B). These two cases result in states of low neural complexity. In the balance between these two extremes, a state of higher neural complexity emerges (A), presenting a rich repertoire of highly integrated configurations. An analogous reasoning was followed by Boly and colleagues (Boly et al., 2015), who employed an experimental paradigm based on movies of different complexity (from random noise to actual movie scenes) and observed that differentiation of brain activity peaked with the stimulus of the highest complexity.

The dynamical evolution of a system in these three scenarios is illustrated in the lower panel of **Figure 1**. Circles represent elements of a system (e.g. neurons) and links between them indicate statistical dependence. The transient formation of highly integrated groups of neurons that are drawn from a large repertoire of possibilities constitutes the principal tenet of the dynamic core hypothesis put forward by Edelman & Tononi. According to this hypothesis, each conscious experience is associated with a transient assembly of neurons having the aforementioned properties, which are consistent with phenomenological considerations. These assemblies form and dissolve in a time scale of few hundreds of milliseconds, and engage different neurons depending on the nature of each conscious experience. Thus, according to this hypothesis, consciousness must be understood as a dynamic process instead of a physical event amenable to precise spatial and temporal localization (Le Van Quyen, 2000; Tononi & Edelman, 1998; Edelman & Tononi, 2000). Other neuroscientists have put forward models of neural computation bearing resemblance to the dynamic core hypothesis, such as the coordination dynamics theory by Kelso and colleagues (Bressler & Kelso, 2001), and Francisco Varela's proposal that "*For every cognitive act, there is a singular and specific large cell assembly that underlies its emergence and operation*" (Varela, 1979; Le Van Quyen, 2000). Implicit in the proposal made by Varela is a constantly shifting -but transiently stable- assembly of coordinated cells which could be identified with Tononi & Edelman's dynamic core.

The hypothesis put forward by Tononi & Edelman predicts that loss of consciousness is associated with diminished neural complexity, which can result from a reduction in the repertoire of possible brain configurations (state B in **Figure 1**) or from an enlarged repertoire of states with a low level information integration (state C in **Figure 1**). A frequently cited example of the first possibility is loss of consciousness during epileptic seizures, when large portions of the cerebral cortex oscillate in bimodal fashion (Blumenfeld, 2012). On the other hand, certain dissociative anesthetics such as ketamine might act by disrupting information integration, thus leading to a brain state of abnormally high differentiation (Alkire et al., 2008, Sarasso et al., 2015). Graph analyses of brain activity measured with fMRI during deep sleep (Boly et al., 2012; Spormaker et al., 2012; Tagliazucchi et al., 2013b) and anesthesia (Monti et al., 2013) indicate increased network modularity compared to conscious wakefulness, which is suggestive of diminished cortical integration.

Another influential model is the global workspace theory proposed by Baars, Dehaene and Changeux (Baars, 1997; Dehaene & Changeux, 2003). According to this theory, incoming

sensory information competes for the access to a distributed set of cortical regions that “broadcast” this information, making it globally available for further processing. Such competition occurs in a “winner-takes-all” fashion and the winning stimulus non-linearly “ignites” the propagation of information to global workspace regions. This theory provides an explanation in terms of competitive dynamics to phenomena such as binocular rivalry, masking, the attentional blink, and others (Baars, 2002; Baars, 2005; Sergent & Dehaene, 2004, Del Cul et al., 2007). The approach followed by Baars, Dehaene and Changeux is in the direction of functionalism, i.e. conscious information access serves the role of allowing global information availability in the brain. This is in contrast to the view rooted on the phenomenology of consciousness adopted by Tononi & Edelman. The Global Workspace Theory is developed from a third-person functionalist perspective, since the theory fundamentals come from assigning a purported function to conscious access, and testing these fundamentals using different empirical paradigms. Thus, Baars, Dehaene and Changeux’s theory explains the phenomenon of consciousness as embedded within a network of causal relationships in the brain that give rise to human behavior. On the other hand, the postulates of Tononi & Edelman’s IIT (both in its original and current versions) are based on the phenomenology of the first-person perspective, i.e. on information readily available through introspection. So while IIT clearly makes predictions that are testable from the third-person perspective (as all scientific theories do) it is conceived from arguments based on the first-person point of view. On the other hand, the Global Workspace Theory rests upon a third-person perspective which does not explicitly rely on the phenomenology of the conscious experience, except at its simplest level (i.e. reporting seen vs. unseen percepts, for instance). The divergence between a third-person perspective functionalist account and a first-person perspective phenomenological account does not imply that both models of consciousness are mutually contradictory (Chalmers, 2013; Tagliacruzchi, 2017). For instance, the transient assembly of integrated regions that constitute the global workspace could be a manifestation of the dynamic core proposed by Tononi & Edelman (Baars et al., 2013; Tagliacruzchi, 2017).

In the following sections we will review neuroimaging work investigating the repertoire of possible brain configurations as a function of the level of consciousness. Before embarking on this discussion, however, a fundamental point remains to be addressed: to which degree is brain dynamics compatible with a discrete and finite repertoire of states or configurations? Much of the previous discussion relies on the assumption that such a repertoire exists and consists of the separate configurations that the dynamic core adapts during the succession of experiences

that make up the normal wakeful state. However, not all physical systems present dynamics that can be clustered into distinct and transiently stable states (think, for instance, of an oscillating vertical pendulum). Metastability is a property guaranteeing that a system will be attracted to certain states of quasi-equilibrium (metastable states) and therefore that the application of a clustering algorithm to the measured dynamics will approximately decompose them into a repertoire of “building blocks” (as we discuss below, the converse does not hold true, since a physical system could have a discrete repertoire of states without metastable dynamics). This property is present in many physical systems such as earthquakes and other geological phenomena (Jackson et al., 2004), spin glasses (Bray & Moore, 1980), proteins (Honeycutt & Thirumalai, 1990), polymers (Keller & Cheng, 1998), and certain classes of phase transitions (Kosterlitz & Thouless, 1973). In the next section we review theoretical and computational considerations, as well as empirical evidence, that strongly suggest the presence of metastability in brain dynamics.

Metastability and the repertoire of brain configurations

Consider a physical system and the minimum number of variables necessary for its description. The evolution of the state of the system can be conceptualized as a point moving in a space with a number of dimensions equal to that number of variables (the *phase space*). A classical pendulum, for instance, “lives” in a phase space of two dimensions, since it can be fully described by its vertical angle and its angular velocity. **Figure 2** illustrates these concepts in a system that can be described using three variables. The temporal evolution of these variables (**Figure 2A**) can be visualized as a trajectory in three-dimensional phase space (**Figure 2B**).

The phase space of a system is defined with respect to a certain spatial and temporal resolution. While the coarse-grain description of a pendulum in terms of two variables is a textbook example of classical mechanics, the dimensionality of the phase space is increased when accounting for macroscopic variables such as the rotation of the rope and the pendulum itself, the elasticity of different materials, air resistance and the associated dissipation of energy as heat, etc. In principle, the physical state of the system, including all microscopic variables (e.g. at the atomic and sub-atomic level) could be accommodated in a phase space of an extremely large number of dimensions.

The human brain, considered as a physical dynamical system, can also be described in terms of the temporal evolution of a point in a phase space of a dimensionality that depends on the spatio-temporal grain of description. Such description can include from relevant variables at the cellular level (e.g. conductances, ion concentrations, etc), to the firing of individual action potentials in networks of neurons, and to the generation of mass neural action as the summation of these action potentials over a macroscopic portion of brain matter. The spatio-temporal grain used to describe the brain is related to the experimental technique employed for its investigation. For instance, fMRI maps the temporal evolution of brain activity in a space of small dimensionality compared to a hypothetical technique capable of recording whole-brain electrical activity at a sub-millimeter scale.

The concept of metastability is best understood in terms of the dynamics of the system in phase space. A point of stability in phase space attracts the state of the system towards its coordinates whenever the state is at a certain portion of such space (the *basin of attraction*) (Ott, 2006). Complex non-linear dynamical systems such as the brain tend to be intrinsically unstable and to present points of quasi-equilibrium that transiently attract the dynamics (Tognoli & Kelso, 2014). Such points in phase-space are also termed the *metastable states* of the system, and the phenomenon of the dynamics traversing a series of such states is termed *metastability*.

It is very important to distinguish the concepts of multistability and metastability. Multistability refers to a system with a certain number of proper equilibrium points. In the absence of fluctuations (usually modeled as additive noise) a dissipative dynamical system will eventually converge towards an equilibrium point. It is widely believed that the human brain is an intrinsically unstable non-equilibrium system (Chialvo, 2010) and therefore computational models and data analysis methods assuming multistable dynamics are an approximation, albeit a very useful one in many situations. In particular, multistability presents a picture in which brain dynamics can “lock” into a number of discrete patterns. A simple example of a system showing multistable dynamics is the HKB model (Haken – Kelso – Bunz) (Haken et al., 1985) in which a single parameter (relating to the phase difference between oscillators) can potentially reach two points of stability before a parameter of the model crosses a critical value (i.e. before the dynamics undergo a bifurcation). In the presence of additive noise, the phase difference can alternate between both points of stability. In contrast, metastable dynamics do not unfold in the presence of true points of stability, and appear instead as the result of the opposing tendency of the dynamics towards coupling and independence. Dynamically, this tendency can be realized

by quasi-stable points (e.g. saddle node points) that are capable of attracting and repelling the dynamics along different manifolds (Kelso, 2012). Note that the competition of coupling and independent behavior endows metastable systems with a tension between integration and segregation which is reminiscent of the principles underlying IIT. Systems of several non-linearly coupled oscillators (e.g. Kuramoto model) exhibit these kind of dynamics for adequate choice of parameters (Shanahan, 2010). For further discussion on the differences between multistability and metastability we refer the reader to an article by Scott Kelso (Kelso, 2012).

The concepts of metastability and multistability can be better visualized assigning an *energy landscape* to the phase space of the system. The dynamics of the system evolve attracted towards points of minimum energy, which can be either local or global. After being transiently attracted towards a local point of minimum energy, an externally driven system can escape the basin of attraction and visit other equilibrium states. In a metastable system, points of minimum energy are replaced by points that only transiently attract the dynamics (e.g. saddle nodes, with more examples provided below). A very simple dynamical system illustrates this concept in **Figure 2C** (adapted from Tagliazucchi et al., 2016a). The ball at different times (t_1 , t_2 , t_0) represents the state of the system moving towards one of many states of equilibrium. If we assume that at these points the dynamics are unstable in a second dimension that is not visualized in the illustration, we can consider these points as representing metastable states. As the dynamics of the system linger around these metastable states, the concept of a *repertoire* of states or configurations can be introduced. Clustering the dynamics of the system in the phase space is bound to approximately reveal the presence of the metastable states. We note that different mechanisms exist capable of trapping the dynamics in certain parts of the phase space, such as attractor ruins (Kaneko & Tsuda, 2003), heteroclinic cycles (Rabinovich et al., 2008), and unstable attractors (Timme et al., 2002).

The series of examples provided in **Figure 2** also illustrate how the repertoire of states of the system depends on its energy landscape. Increasing the depth of the energy wells might reduce the repertoire of states visited by the system, as the external driving or endogenous fluctuations might not be sufficient to displace the state of the system from one metastable state to another. Alternatively, different metastable states can coalesce and disappear into a single global point of equilibrium, representing a drastic reduction in the repertoire of states of the system. Finally, it must be kept in mind that metastability could display hierarchical properties, i.e. certain regions of the phase space could transiently attract the dynamics of the system and within these

regions additional points of quasi-stability could exist. In the rightmost panel of **Figure 2C** the energy landscape of the system presents a barrier dividing the metastable states into two different groups, and a sufficiently strong external driving or endogenous fluctuation is required for the system to explore both sub-repertoires.

It has been observed by many authors that brain dynamics present features consistent with metastability (Friston, 1997; Werner, 2007; Chialvo, 2010; Bhowmik & Shanahan, 2013; Tognoli & Kelso, 2014; Hellyer et al., 2014; Hellyer et al., 2015; Deco & Kringelbach, 2016). The number and nature of metastable states in brain dynamics is most likely dependent on the spatial and temporal grain used for the description. For instance, Varela has proposed metastable dynamics at three different temporal scales: the scale of cellular rhythms (10 to 100 ms), the scale of large scale integration –relevant for the transitions between dynamic core configurations (100 – 300 ms) and the scale of long-range integration (> 1 s) (Varela, 1999). Le Van Quyen observes that different analytical techniques are required for the understanding of each temporal scale (spectral analysis, phase space analysis techniques, time series statistics, respectively) (Le Van Quyen, 2000). Following the example provided in the rightmost panel of **Figure 2**, a hierarchical dependence between these time scales is likely. The repertoire of dynamic core configurations (100 – 300 ms) could depend on the modulation of whole-brain excitability due to neurotransmitter release originating from subcortical structures such as those in the reticular activating system (RAS) (Moruzzi & Magoun, 1949). The human sleep cycle (Iber et al., 2007) could be conceptualized as a transition through a series of metastable states on a relatively slow temporal scale (changes in vigilance modulated by the aforementioned subcortical structures), with each one of these states presenting a different repertoire of possible brain configurations. According to the theory put forward by Tononi & Edelman, such repertoire should be reduced during deep sleep, a brain state characterized by diminished capacity for consciousness.

Electrophysiological experiments at different levels of spatial resolution provide evidence for metastability in brain dynamics, ranging from spiking activity in neural assemblies to the fluctuations in electrical potential recorded at the human scalp using EEG or MEG (Tognoli & Kelso, 2014). The application of clustering algorithms to the temporal sequence of scalp potentials has revealed a discrete set of *microstates*. These configurations are transiently stable and evolve in a temporal scale of few milliseconds, providing evidence for metastable large-scale dynamics (Koenig et al., 2002). **Figure 3A** provides an example of EEG signals at the

sensor level together with their clustering into four microstates, which appear in a certain temporal sequence throughout the experiment (the bottom panel shows the global field power colored in terms of the microstate that is present at each temporal segment). The transient formation and dissolution of large-scale networks in MEG data has also been shown at the source level (de Pasquale et al., 2010; Baker et al., 2014), which could be related to the aforementioned scalp microstates.

Imaging of spontaneous blood flow fluctuations using fMRI reveals a discrete set of coordinated brain regions overlapping with brain systems associated with relatively well-understood functions termed resting state networks (RSN) (Beckmann et al., 2005). **Figure 3B** shows the spatio-temporal evolution of activity within an axial slice of fMRI data, and the clustering of this activity into five spatial maps corresponding to visual, auditory, sensorimotor, default mode, control and dorsal attention RSN. Recent results establish that the temporal evolution of whole-brain activity measured with fMRI can be characterized as the exploration of a series of states associated with different RSN (Karahanoğlu and Van De Ville, 2015). Importantly, multimodal imaging experiments have revealed that RSN measured with fMRI and EEG microstates can be put into one-to-one correspondence, suggesting nested metastable dynamics at two different levels of temporal resolution (Britz et al., 2010). The correspondence between the repertoires of configurations observed at different temporal scales led Van de Ville and colleagues to suggest and evaluate the hypothesis that the sequence of EEG microstates presents scale-free or fractal properties (Van De Ville et al., 2010). This last example emphasizes that multimodal neuroimaging is of key importance to test the hypothesis of hierarchical multistability in brain dynamics. Unfortunately, the combination of different imaging techniques is fraught with complications involving the presence of undesired noise (Laufs, 2012). However, the combination of invasive and multimodal electrophysiological techniques (Zhang et al., 2007) with methods for measuring metabolism and neurotransmitter release in vivo (Watson et al., 2006), and to selectively manipulate the activity of individual cells (such as optogenetics) (Deisseroth, 2011) will be fundamental to probe the dynamical landscape of brain activity in different animal models.

Metastable dynamics in large-scale brain activity is also suggested by the observation that FC temporal fluctuations can be clustered into a set of *dynamic FC states* (Allen et al., 2012; Calhoun et al., 2014). The example shown in **Figure 3C** illustrates this procedure, starting from BOLD time series at each region in a given parcellation, and applying a windowed correlation

procedure to obtain a temporal sequence of dynamic FC matrices, which are aggregated across subjects and submitted to k-means clustering to reveal a discrete set of dynamic FC states.

We note that these examples constitute indirect evidence of metastability in brain dynamics. The literature abounds in examples of the neurophysiological relevance of both EEG microstates and fMRI dynamic FC states, establishing links to behavior, cognition, arousal, and a spectrum of neuropsychiatric pathologies (see Lehmann et al., 2009 and Calhoun et al., 2014). In spite of this relevance, it must be emphasized that the application of clustering algorithms to continuous data is, by definition, bound to produce a discrete set of patterns. For instance, it has been called into question whether fMRI dynamic FC states are a manifestation of metastability or they arise as an artifact intrinsic to the clustering procedure (Laumann et al., 2016).

Further evidence for metastability in brain dynamics comes from behavioral experiments pioneered by the group of Scott Kelso (Kelso, 1984). Also, computational simulation studies performed at different spatial and temporal grain provide evidence for metastable dynamics, and emphasize a key role for reentrant cortico-thalamic dynamics, i.e. ongoing signaling between separate neuronal groups in a reciprocal and recursive fashion over cortico-cortical, and cortico-thalamic connections (Lumer et al., 1997; Deco & Kringelbach, 2016). At small spatial scales, the formation of metastable neuronal groups can be traced to the interplay between spike time dependent plasticity and conduction delays (Izhikevich et al., 2004). Metastability is an emergent property of physical systems presenting a form of behavior termed *criticality* (Chialvo, 2010). Beyond metastability, systems at criticality present a number of idiosyncratic features that have been corroborated experimentally in the brain, such as scale-free spatial and temporal bursts of activity (Linkenkaer-Hansen et al., 2001; Beggs & Plenz, 2003; Tagliazucchi et al., 2012c; Shriki et al., 2013; Scott et al., 2014), divergence of correlation length and finite size scaling (Fraiman & Chialvo, 2012; Haimovici et al., 2014) (see “Conclusions and future directions” for further discussion on criticality).

Assessing the repertoire of brain configurations during different states of consciousness is important to validate or refute the theoretical predictions of the models of consciousness previously introduced in this article. Given the extremely high dimensionality of the phase space associated with brain dynamics (even adopting a macroscopic description), an indirect approach combining the dynamic imaging of brain activity fluctuations with the application of clustering algorithms of variable grain is required to investigate the repertoire of possible configurations of

the system. In the next sessions we review and discuss empirical efforts based on this perspective.

Studies based on fMRI co-activation patterns

Spontaneous co-activation patterns (CAPs) are defined as sets of voxels becoming simultaneously activated within the temporal resolution of the fMRI acquisition sequence. CAPs can be efficiently derived from a representation of the data in terms of a spatio-temporal point-process (Tagliazucchi et al., 2016b). This approach identifies time points associated with a threshold crossing of the normalized BOLD signal. The selected time points can later be used to construct conditional rate maps, or clustered to produce spatiotemporal CAPs. Both methods have been successfully applied to uncover the well-known RSN (Beckmann et al., 2005). In principle, the clustering of CAPs could be capitalized to derive a discrete set of states that are visited over time by the brain, and to investigate whether such repertoire is changed during different states of consciousness. However, so far only three studies have capitalized on this procedure.

Two studies have used the point process method to investigate how loss of consciousness affects the degree of information sharing between brain regions. Amico and colleagues examined whether propofol anesthesia altered the CAPs of a nodal area in the DMN (Amico et al., 2014). Their findings suggest that, although core connections are preserved under anesthesia, integration between the DMN and other areas of the brain (such as the auditory or motor cortices) is diminished. Similarly, Liang and colleagues used a rodent model to probe the effects of isoflurane on CAPs of both the infralimbic cortex and primary somatosensory cortex (Liang et al., 2015). They reported an overall decrease of connectivity strength during anesthesia, and showed that drops are more pronounced for cognitive and emotional processing regions. Overall, these results are consistent with the hypothesis that communication between brain areas is disrupted during reduced states of consciousness. However, the loss of integration observed during unconscious states seems to vary between brain regions. For example, it has been suggested that higher order regions are affected first during a gradual disruption of dynamic functional connectivity (Liang et al., 2015). Likewise, connectivity between anatomically-linked areas may remain unaffected during anesthesia (Barttfeld et al., 2015; Tagliazucchi et al., 2016c).

A more recent study in rats used the point process method to directly examine the dynamical repertoire of brain states under propofol sedation (Hudetz et al., 2015). Adding temporal variance estimations to the analysis, the authors quantified the number of threshold crossings on the whole brain or on specified regions of interest as a function of time, and compared the results between high and low sedation states. The data showed fewer threshold crossings when rats received high doses of propofol compared to the low dose condition. Given the decreased variance in the observed CAPs under propofol, this finding suggests loss of differentiation in the repertoire of states visited by the brain at the voxel resolution. Concerning this work, it must be noted that a recent article from the same group employed 64-contact microelectrode arrays in the primary visual cortex of rats under increasing levels of desflurane anesthesia, and could not observe a reduction in the repertoire of brain configurations as determined using CAPs (Hudetz et al., 2016). The authors speculate that this contradicting result could be due to the analysis being performed at a finer spatial grain, or due to the fact that activity was recorded from sensory areas.

The interpretation of the available evidence may be somewhat limited by the fact that all three studies used anesthesia to alter consciousness levels. Consequently, the data might reflect specific aspects of the drugs not directly related to their effects on consciousness. To surpass this limitation, future work using the point process method should study other states of diminished consciousness, such as subjects during deep sleep or DOC patients. It is also important to establish a link between CAPs and recordings of electrophysiological activity, given the seemingly contradictory results observed using fMRI and microelectrode arrays.

Studies based on fMRI dynamic functional connectivity

Dynamic FC is a promising tool to investigate neurophysiological signals measured with fMRI in a way that does not disregard the temporal dimension of the data (Hutchison et al., 2013b). The dynamic analysis of FC is relatively recent compared to the first observations of non-trivial resting state FC between distant anatomical regions (Biswal et al., 1995), and presents the advantage of allowing an assessment of dynamic coordination between brain networks, and the identification of recurring states (dynamic FC states) that could be associated to points of metastability of whole-brain brain dynamics at a macroscopic resolution (Calhoun et al., 2014). As already mentioned in the introduction, different methods have been proposed to estimate dynamic FC from BOLD signals recorded in humans and animals; each presenting a number of

advantages as well as potential issues (Leonardi & Van De Ville, 2015; Hindriks et al., 2016; Laumann et al., 2016). The work of Hindriks et al. is of particular relevance since it employs simulations to show that dynamic FC cannot be properly estimated in single experimental runs lasting less than 10 minutes. However, this problem can be attenuated by averaging the results over a considerable number of sessions and/or subjects, increasing the duration of the scanning sessions, and using regularized versions of linear correlation that are capable of more robust estimations over relatively short time windows (see Barttfeld et al., 2015 for an example). Thus, all dynamic FC studies reported in this review must be evaluated in light of these potential limitations. In the next paragraphs we focus on articles assessing the repertoire of dynamic FC states during different states of consciousness.

The pioneering work of Hutchison first established the presence of dynamic FC in a group of anesthetized primates, but did not examine in detail the effects of anesthesia on dynamic FC states (Hutchison et al., 2013a). Posterior work by the same group clustered the dynamic FC data into a discrete number of states and computed the dwelling time in each state as a function of isoflurane level (**Figure 4A**) (Hutchison, 2014). This analysis led to two important results providing empirical support to the theory put forward by Tononi & Edelman: 1) the repertoire of dynamic FC states was gradually reduced for high levels of isoflurane anesthesia (**Figure 4B**, left) and 2) the stability of the states was increased, leading to an inverse correlation between the number of transitions between states and the level of isoflurane anesthesia (**Figure 4B**, right). These results should be interpreted with caution since the unconscious states induced by isoflurane were not compared with a conscious state (such as wakefulness). Interestingly, the incremental reduction of the repertoire of brain states while maintaining unresponsiveness suggests either that: 1) the level of consciousness is graded even though from the experimenter's point of view the animals remain unresponsive throughout all isoflurane levels or 2) beyond a certain critical point, consciousness is lost regardless of a further reduction in the repertoire of potential brain states. Also, the observation of increased stability of large-scale dynamics associated with loss of consciousness is consistent with the analysis of electrophysiological data performed by Solovey and colleagues (Solovey et al., 2015).

It is instructive to contrast these results to those reported under the influence of psilocybin (a 5-HT_{2A} agonist psychedelic; Nichols, 2016) using similar analytical techniques. Tagliazucchi and colleagues investigated all 64 possible FC motifs between four regions of interest (bilateral anterior cingulate cortex and hippocampus) (Tagliazucchi et al., 2014). As in the work by

Hutchison and colleagues, dynamic FC was obtained using windowed correlations. A symbolization procedure was applied to the dynamic FC motifs and the entropy of the resulting sequences was estimated, leading to the observation of increased entropy levels under psilocybin vs. a suitable placebo condition. Furthermore, the repertoire of dynamic FC motifs was enhanced after psilocybin infusion. These results go in the opposite direction to those reported by Hutchison and colleagues, and resonate with the hypothesis that psychedelics lead to a state of “enhanced” consciousness (Carhart-Harris et al., 2014). Further results obtained analyzing MEG time series from subjects under psilocybin, LSD and ketamine add support to this hypothesis (Schartner et al., 2017). How results from this and other altered states of consciousness fit within the theoretical framework of the information integration theory and the dynamic core hypothesis remains to be investigated.

The repertoire of dynamic FC states under propofol anesthesia in primates was investigated using fMRI by Bartfeld and colleagues (Bartfeld et al., 2015). While seemingly non-trivial FC patterns were not lost under anesthesia, this work elegantly established that those dynamic FC states that were most prevalent under unconsciousness presented a striking resemblance to the large-scale network of underlying anatomical connections. In other words, the changes in the conformation of the repertoire of states during unconsciousness was consistent with a reduction of FC to a structural backbone that might support non-trivial activity fluctuations as a homeostatic process, even in the absence of meaningful conscious content and cognition. In contrast, the repertoire of states measured during conscious wakefulness was ampler and transcended these anatomical constraints. This result was independently replicated for human deep sleep (Tagliazucchi et al., 2016c), and for rats under isoflurane anesthesia (Ma et al., 2017). In this last study, windowed correlations were obtained and clustered into five dynamic FC states, and the expression of the state bearing the highest resemblance to anatomical connectivity was found to be higher during deep sedation vs. conscious wakefulness.

The work of Kafashan et al. investigated dynamic FC in humans under sevoflurane anesthesia, finding a number of connectivity motifs that were preserved from conscious wakefulness to deep sedation (Kafashan et al., 2016). These were associated with within-RSN interactions, which are known to parallel anatomical constraints (Bartfeld et al., 2015). Note that they could also reflect some form of residual consciousness, but further work is needed to tackle this question. Importantly, the study also found that FC variability was reduced. This reduction in the variability of dynamic FC is consistent with work mentioned in the previous section based on the

computation of CAPs (Hudetz et al., 2015), and indicates reduced levels of differentiation, as predicted by the information integration theory.

Perturbational methods to assess the repertoire of possible brain configurations

In the previous sections of this review we discussed how the notion of metastable brain dynamics naturally accounts for the notion of a discrete repertoire of brain configurations, and how such repertoire can be estimated by applying different clustering methods to brain activity and connectivity. The reviewed articles consistently reported loss of consciousness linked to diminished levels of differentiation/integration, and to a reduction in the repertoire of brain configurations visited over time.

A limitation inherent to the analysis of spontaneous fluctuations of brain activity is that inferences can be drawn on the repertoire of brain configurations visited over time, but not on the repertoire of *potential* configurations. Consider the second and third panels of **Figure 2C**. Both deepening energy wells and the loss of points of metastability might lead to a reduced repertoire of states visited over time. The disambiguation between these alternatives requires the application of an external perturbation to the system, capable of driving its state out of stable points towards the exploration of other possible configurations

The seminal work of Massimini and colleagues combined EEG and transcranial magnetic stimulation to investigate the dynamic behavior of electrophysiological activity after a brief and focused perturbation, both during conscious wakefulness and NREM sleep (Massimini et al., 2005). This technique disentangles effective or causal interactions from functional connectivity (which is based on correlational analyses), and it is useful to investigate the result of externally forcing the system towards the exploration of its repertoire of potential states. The application of a brief TMS pulse during wakefulness led to sustained waves of activity presenting a high level of spatial differentiation. The site of peak activity was displaced between premotor and prefrontal brain areas after the pulse, and in some subjects it also involved the motor and the posterior parietal cortex. In contrast, activity elicited by an identical pulse delivered during NREM sleep did not propagate to brain areas distant from the stimulation site. This result suggests that either the actual repertoire of possible brain states is diminished, or a more powerful external perturbation is required to displace the dynamics towards other points of metastability. Interestingly, recent work shows that intrinsic perturbations (i.e. sufficiently large

endogenous fluctuations) could be of use to reveal a reduction in the repertoire of potential states during unconsciousness (Deco et al., 2017).

Further studies observed similar results in response to a focal TMS pulse delivered during other states of unconsciousness, including different types of anesthetic drugs (Sarasso et al., 2015) and in DOC patients (Casarotto et al., 2016). It has been shown that a single numerical quantity (the *perturbation complexity index*) can be derived from the activity patterns observed after the pulse, and that this index can reliably distinguish between states of unconsciousness vs. conscious wakefulness, REM sleep and locked-in patients (Casali et al., 2013). Interestingly, the divergence in the activity elicited during conscious vs. unconscious states appears after 150 ms, corresponding to a time scale compatible with the hypothesized metastability of the dynamic core. Taken together, these articles suggest that unconsciousness is not only related to a diminished repertoire of realized states, but also to a reduction in the repertoire of potential states of the system.

Conclusions and future directions

In this article we reviewed the current literature on dynamic FC changes during different states of consciousness, under the theoretical framework of the information integration theory and the dynamic core hypothesis. These theoretical considerations lead to the concept of a repertoire of states that is modified as a function of the level of consciousness. We discussed how the concept of metastability and metastable states naturally endows the system with a (possibly hierarchical) repertoire of states at different spatial and temporal grain. Finally, we reviewed relevant papers in the literature that corroborate the hypothesis that loss of consciousness is related to diminished differentiation (i.e. reduced repertoire of states) or diminished integration.

The relationship between the concepts of metastability and criticality suggests that the physical laws governing systems undergoing critical phase transitions could be relevant to understand the complexity of brain activity underlying conscious brain states. The literature supports the notion that the healthy human brain operates at or near a critical point (Chialvo, 2010). In a self-organized complex non-linear system such as the brain, at the critical state we observe properties related to the coexistence of integration and differentiation which are fundamental to the information integration theory (Chialvo et al., 2008; Tagliazucchi et al., 2016a; Tagliazucchi, 2017). Near the second order phase transition, the brain exhibits long-range correlations both in

space (Barttfeld, 2015; Beckmann et al., 2005) and time (He, 2011; Maxim et al., 2005), thus allowing the units of the system to be highly integrated. In addition, at the critical point, neuronal activity is able to explore a wide variety of locally stable or metastable states (Werner, 2007), and so the repertoire of possible brain configurations increases (i.e. the system is highly differentiated). Finally, critical systems present a maximal sensitivity to external stimuli (i.e. divergence of the susceptibility) which could explain the differences in cortical reactivity measured during different states of consciousness (Massimini et al., 2005; Tagliazucchi et al., 2016b). In accordance, some studies suggest a displacement from the critical point during states of diminished consciousness (Priesemann et al., 2013; Scott et al., 2014; Tagliazucchi et al., 2016a). As already speculated by G. Werner, this link might imply that the tools of statistical mechanics could lead to the postulates of the information integration theory via a route radically different from phenomenological considerations (Werner, 2013). It must be noted that (as mentioned in the “Metastability and the repertoire of brain configurations” section) metastability and criticality are not equivalent concepts, since metastable (but not critical) dynamical systems exist.

While fMRI studies are generally concordant with theoretical predictions, certain divergences are manifest in the results from electrophysiological recordings. These differences highlight the need for a multimodal approach capable of exploring the repertoire of states in the phase space of the system at different spatial and temporal resolutions and, if possible, link them through the concepts of scale-invariance and renormalization (Werner, 2013).

An important role is to be played by semi-empirical computational studies incorporating realistic brain anatomical connectivity and fitted to functional patterns measured with different neuroimaging techniques. The tractability of relatively simple mathematical models can be used to reveal the effects of loss of consciousness on brain metastability (see for instance Hudetz et al., 2014, and Jobst et al., 2017). Computational models can also be employed to infer the effects of external perturbations on human brain dynamics (including some of difficult experimental realizability) as a function of the level of consciousness, thus complementing empirical studies based on combined EEG and TMS (Deco et al., 2015).

In summary, while the concept of fMRI dynamic FC has sustained considerable criticism, a wealth of experimental reports across different states of consciousness lends support to the possibility that temporal fluctuations in BOLD FC reflect neurobiological changes of functional

relevance. Whether a multimodal investigation of unconscious brain states across a range of spatial and temporal scales is concordant with results from fMRI studies is perhaps the most pressing issue that must be addressed by future research in the field.

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ACCEPTED MANUSCRIPT

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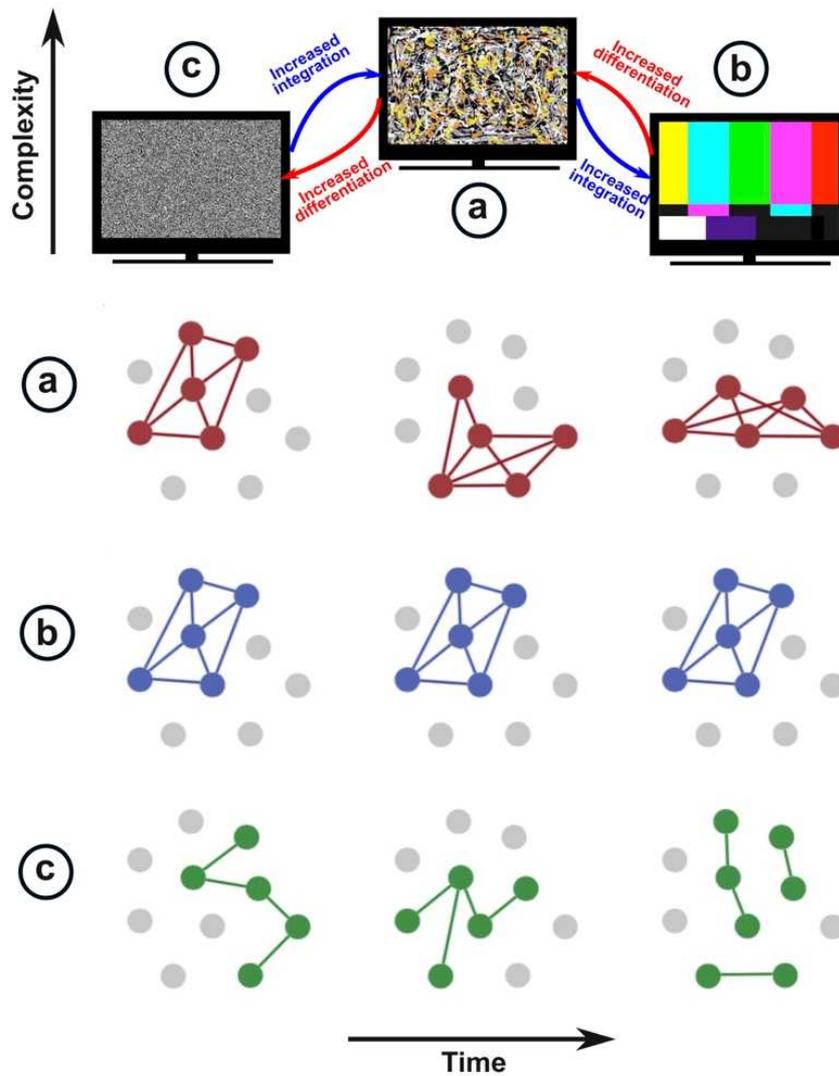
Figures

Figure 1: Upper panel: an analogy between integration/differentiation in neural systems and patterns in a bidimensional array of pixels in a screen. A high level of differentiation leads to a typical pattern of “TV static”. While the number of such patterns is very high, each pixel behaves independently of all others, thus lacking integration (A). At the other extreme, very high integration reduces the number of possible configurations to a few geometric patterns (B). In the middle, a balance between integration and differentiation leads to patterns of the highest complexity (C). Bottom panel: temporally evolving assemblies of neurons that present different levels of integration/differentiation, put in correspondence with the conceptual examples in the upper panel. Each circle represents a neuron and colored lines and circles represent transient coordinated assemblies. Example (A) shows a highly integrated “dynamic core” that shifts through many different configurations, (B) also shows a highly integrated set of neurons lacking differentiation, and (C) illustrates the behavior of assemblies lacking integration.

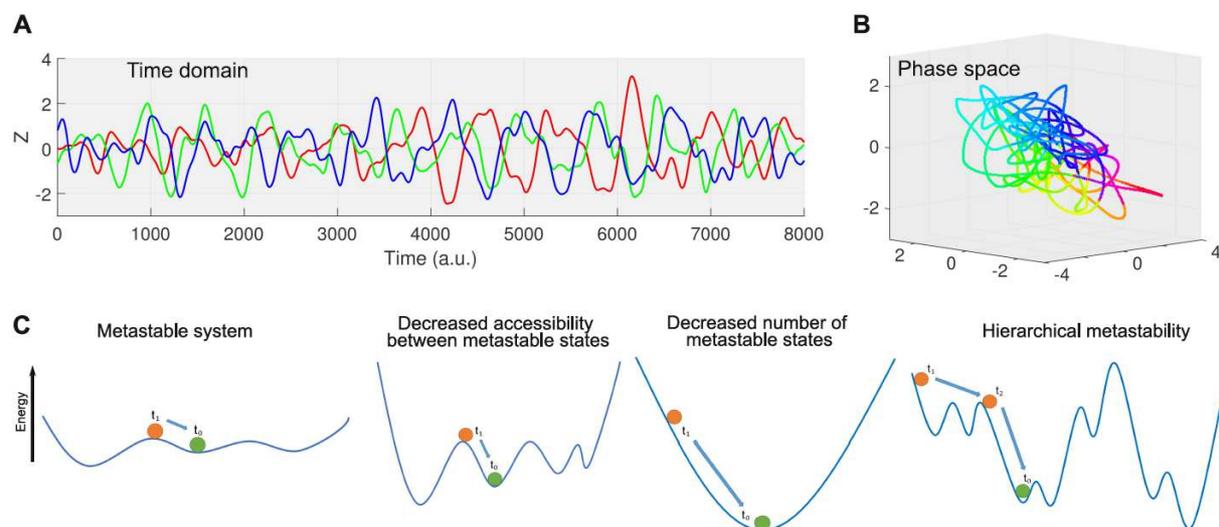


Figure 2: The concepts of phase space and metastability. A) The temporal evolution of the variables that describe a physical system with three degrees of freedom. B) A representation of these variables in a three-dimensional phase space. Each point of this space corresponds to a particular state of the system. C) Points of metastability in energy landscapes with different properties: deep wells separated by high energy barriers (“decreased accessibility between metastable states”), a landscape with only one equilibrium point (“decreased number of metastable states”), and a landscape with two sets of metastable states separated by a high energy barrier (“hierarchical metastability”). A second dimension along which the dynamics are unstable is assumed at the bottom of the wells (but not visualized in the illustration)

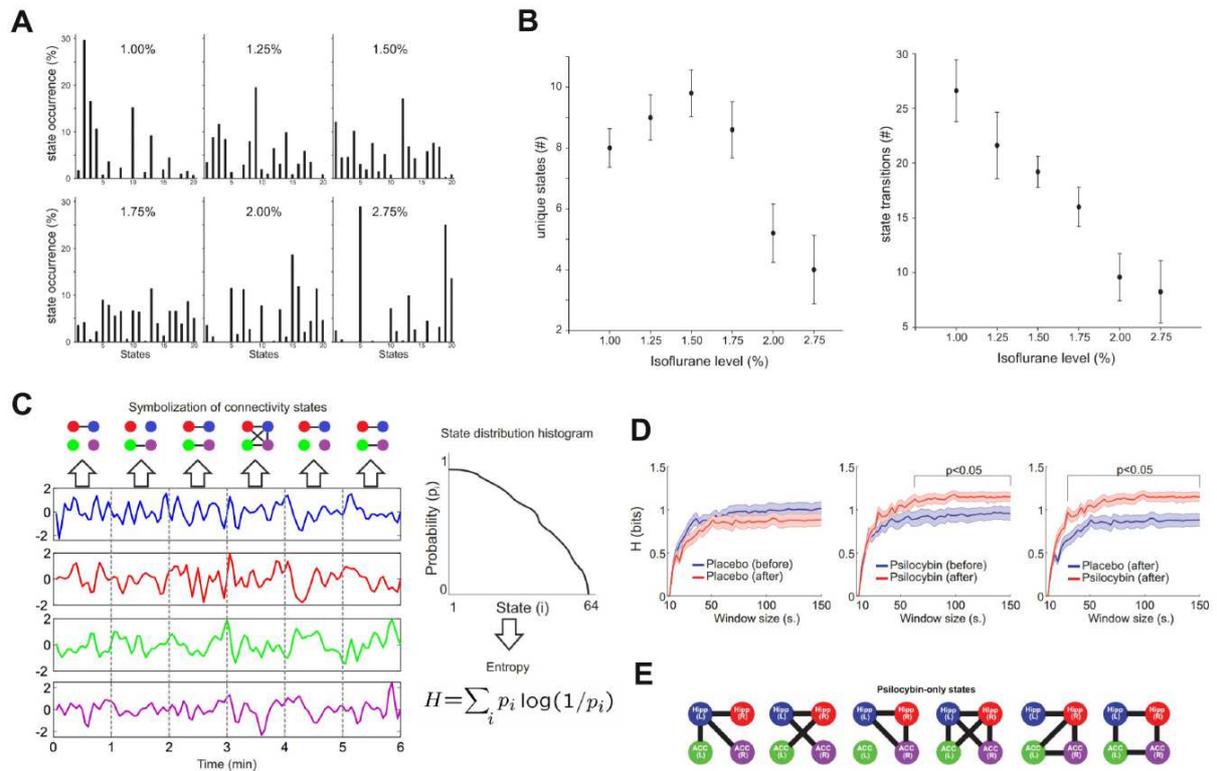


Figure 4: Changes in the repertoire of dynamic FC during loss of consciousness and after the infusion of a serotonergic psychedelic (psilocybin). A) Histograms showing the dwelling time in different dynamic FC states as a function of isoflurane level. B) The data in these histograms can be used to show that the number of unique dynamic FC states decreases as a function of isoflurane level (left), together with the number of transition between states (right). This suggests a diminished repertoire of more stable states under isoflurane anesthesia. Both panels reproduced with permission from Hutchison et al., 2014. C) The procedure followed to extract dynamic FC states between a restricted set of anatomical regions (bilateral anterior cingulate cortex and hippocampus). The small number of regions allows avoiding a clustering procedure, since all 64 possible motifs can be exhaustively listed. A symbolization procedure leads to the computation of the entropy of the motif sequences, and to the observation that (for most window sizes used to compute FC) the infusion of psilocybin leads to higher levels of entropy (panel D). Furthermore, certain states appear only in the repertoire of the psilocybin condition (panel E). Both panels reproduced with permission from Tagliazucchi et al., 2014.