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Opinion

A complex systems perspective on psychedelic brain action

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Recent findings suggesting the potential transdiagnostic efficacy of psychedelic-assisted therapy have fostered the need to deepen our understanding of psychedelic brain action. Functional neuroimaging investigations have found that psychedelics reduce the functional segregation of large-scale brain networks. However, beyond this general trend, findings have been largely inconsistent. We argue here that a perspective based on complexity science that foregrounds the distributed, interactional, and dynamic nature of brain function may render these inconsistencies intelligible. We propose that psychedelics induce a mode of brain function that is more dynamically flexible, diverse, integrated, and tuned for information sharing, consistent with greater criticality. This 'meta' perspective has the potential to unify past findings and guide intuitions toward compelling mechanistic models.

Highlights

Promising results from clinical trials have ignited a resurgence of scientific interest in serotonergic psychedelic compounds.

Functional neuroimaging investigations of acute psychedelic brain action have broadly revealed that they reduce integration within, and segregation between, most large-scale networks. However, spatially specific findings have shown poor convergence.

Complex systems approaches characterize the brain as a dynamically evolving system of interacting elements. In doing so, they abstract from localized patterns of activity and instead focus on the dynamical properties of the brain as a whole.

Drawing from complexity science, we propose a new 'meta' perspective in which psychedelics are catalysts of a distinct mode of brain functioning that is best characterized by dynamical whole-brain features rather than by region- or network-specific changes.

Reconciling inconsistencies within psychedelic neuroimaging with complexity science

Classic serotonergic psychedelics, such as lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT), are potent psychoactive drugs capable of inducing marked changes in subjective experience [1]. All of these compounds share serotonin 2A agonist properties, which account for most of their characteristic psychological effects [2,3]. Preliminary clinical trials suggest that psychedelic drug administration coupled with supportive psychotherapy has transdiagnostic efficacy in the treatment of mental health conditions, including depression, end-of-life distress, tobacco addiction, and alcoholism [4]. As clinical interest in psychedelics escalates, alongside a burgeoning billion-dollar 'psychedelic industry', the need for a deeper mechanistic understanding of their brain action is mounting.

Toward this end, the past decade has seen an emerging field of human psychedelic neuroimaging [5–7]. Given that much of this work has utilized fMRI or been inspired by its findings, here we place special focus on this modality. A popular way to interrogate the brain with fMRI is via analyses that characterize the brain as a set of large-scale networks that interact following the competing constraints of functional integration and segregation [8], typically operationalized as a balance between positive functional connectivity (FC) within or between regions/networks ('integration') and negligible or negative FC between networks ('segregation'). A common finding from analyses of 'resting-state' fMRI assessments of the acute psychedelic state is reduced functional integration within, and increased integration between, most (but not all) large-scale brain networks [7]. This is consistent with a global trend toward reduced functional network differentiation (i.e., distinct networks are less segregated), an effect we refer to as 'increased global integration' for simplicity. Preliminary findings suggest that postacute neural effects mirroring the acutely

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increased global integration found in healthy subjects are linked to reduced depression symptoms in patients with depression [9].

However, the consistency of the general trend toward global integration is in stark contrast to the heterogeneity of results pertaining to changes in specific brain regions or networks. Notably, minimal overlap has been found across drugs and data sets in terms of interactions between networks [10–15], discrepancies have been found with respect to the global integration of distinct regions [16–19], and network-specific effects (e.g., default mode network disintegration), while more consistent, have been found with pharmacologically distinct drugs [20–22], rendering their interpretation unclear. Overall, fMRI research has not yet been able to disambiguate the brain action of psychedelic drugs with respect to specific region- or network-wise changes.

Here, we contend that, as with neuroimaging findings in general (see [23]), the apparent inconsistencies of psychedelic neuroimaging research can be made intelligible by an alternative macroscale, complex systems perspective of psychedelic brain action. This perspective holds that the apparent inconsistency found in past work stems directly from the use of analytic approaches that are based on an outmoded 'locationist' conception of brain function that does not fully account for the overarching spatiotemporal context in which neural changes are embedded. We argue that a consistent picture of the brain action of psychedelics arises when existing findings are interpreted in light of emerging theoretical perspectives within 'complexity science', an interdisciplinary field that draws from statistical physics, graph/network theory, dynamical systems theory, and information theory [24] to characterize and analyze complex systems of dynamically interacting parts. When applied to an understanding of the brain, complexity science offers a well-suited perspective and toolbox for characterizing and measuring the distributed, interactive, and fundamentally dynamic nature of brain function [23,25,26].

Applying this perspective to psychedelic brain action, we propose that the brain under psychedelics is best seen as entering a distinct mode of functioning, which can be characterized as being more dynamically flexible, diverse, and tuned for global information sharing, consistent, in complex systems language, with a maximally metastable regime that is tuned closer to criticality. Under this view, psychedelic administration, via 5-HT2A receptor agonism in association cortices, represents a perturbation that elicits a spatiotemporal trajectory of neural states that varies across, and within, individuals based on accompanying nonpharmacological conditions (i.e., 'set and setting' [27]). We hold that the idiosyncratic nature of this spatiotemporal trajectory can generate mixed and potentially contradictory neuroimaging results when observed at the region/network level or when averaging across time and individuals. This conceptualization of psychedelic action moves the focus of analysis from spatially specific patterns to the way in which patterns dynamically evolve and offers an interpretational framework that could help resolve previous inconsistencies and move the field toward greater consensus.

In what follows, we begin with a review of region/network-specific findings from fMRI investigations of the acute experience, highlighting inconsistencies in the field. We follow with a didactic overview of complex systems perspectives of brain function, alongside a review of empirical findings from studies applying complex systems analyses to psychedelic fMRI data sets. We end by detailing the above-mentioned theoretical framework of psychedelic brain action, which conceptualizes it as a shift in whole-brain/systems-level dynamic functioning. This theoretical framework is motivated by a range of findings and perspectives of brain

function independent of psychedelics and is proposed, in part, to inspire future empirical work with psychedelic data sets to more directly assess our claims and replicate preliminary findings to date.

Inconsistencies within region- and network-focused analyses of acute psychedelic neuroimaging data

'Resting-state' (i.e., task-free) fMRI investigations have arguably had the greatest impact on psychedelic neuroimaging, whether ultimately justified. Analyses applied to acute psychedelic fMRI data sets have largely focused on drug-induced changes to large-scale network FC (see Box 1 for an overview of common FC network approaches and their limitations). Unfortunately, as highlighted in a previous review [11], this work has yielded negligible consistency in the between-network interactions observed across both drugs and data sets of a given drug, and little evidence for psychedelic-specific effects in the within-network changes observed. One study directly juxtaposed the findings from three data sets, two with LSD [10,13] and one with psilocybin [12,28], which applied the same analytic protocol for network comparisons and did not find a single consistent change in between-network FC across the three data sets [10]. Relatively poor consistency was also found between these three data sets and a more recent psilocybin data set that applied similar analyses [14]. With respect to within-network changes, the most consistent finding with psychedelic data sets is reduced integration within visual, somatomotor, and default mode networks [10,12,14,15,29]. However, this same set of changes has been observed with other (mechanistically distinct) pharmacological

Box 1. Limitations of large-scale network approaches to resting-state fMRI

Resting-state fMRI investigations of the acute psychedelic experience have applied several distinct analytic approaches to characterize drug-induced changes in FC within and between large-scale networks. These include independent component analysis (ICA), seed-based FC, interregional FC, and the more recently developed leading eigenvector dynamics analysis (LEiDA) [114] (see [115] for an overview of resting-state network analytic approaches). While all serving as putative assessments of large-scale functional network organization, each of these approaches has their own statistical assumptions and idiosyncrasies, which preclude simple equivalency.

One point of distinction is of 'soft parcellations' versus 'hard parcellations'. ICA, seed-based FC, and LEiDA constitute soft parcellations in that they generate weighted network assignments, whereas interregional FC is typically used to generate hard parcellations with binary network assignments [116]. Another important factor is the degree of reliance on *a priori* maps or assignments. Although ICA does not in principle require *a priori* maps, it is common for ICA network estimation to involve a dual regression procedure in which *a priori* group-level network maps (typically from [117]) serve as spatial priors. Similarly, interregional FC methods typically take *a priori* region-to-network assignments from a widely used network parcellation (e.g., [116]) and compute the mean correlation of the regions constituting putative networks/network pairs. By contrast, seed-based FC and LEiDA approaches do not rely upon group-level network templates.

A last notable point of distinction is that all of these approaches, with the exception of LEiDA, are based on time-averaged associations that do not directly account for temporal dynamics. This is important given that the brain exhibits functionally meaningful transient states that are obscured by session-level averaging [118]. Collectively, these differences in statistical assumptions and conception of network definition render comparisons of results across techniques nontrivial. In addition, we point out that the use of *a priori* templates and assignments from subjects during normal waking consciousness may limit network estimation in the psychedelic state, given that psychedelics potently alter brain network organization.

Furthermore, a notable limitation of network approaches in general is the often-minimal acknowledgment of individual differences in functional neuroanatomy and interregional functional organization. A core assumption underlying standard group-level network FC analyses is that the spatial topography of a given region and/or network is consistent across individuals. However, this is untenable given that studies have revealed that the spatial topography of both regions and large-scale networks can significantly vary across and within individuals in a manner that confounds FC estimates and covaries with a variety of cognitive, neuropsychological, trait, and clinical measures [119–122]. In tandem, this work further highlights the significant limitations intrinsic to standard group-level and time-averaged approaches to functional network analysis. These limitations may be even more pertinent in the context of a pharmacological manipulation, such as psychedelic drug administration, which elicits highly variable subjective effects.

interventions, including the serotonin reuptake inhibitor (SSRI) sertraline [22], atypical hallucinogen *Salvia divinorum* [21], and entactogen MDMA [20], rendering the relationship of these changes to psychedelic-specific effects unclear.

An important limitation of the above network-based approaches is that they are either univariate (within network) or bivariate (between network), rather than considering more distributed multivariate dependencies. Therefore, a potential solution might be to take the whole-brain spatial (and temporal) average FC of a given region or voxel. This approach, referred to as global FC or global brain connectivity, has been applied to data sets across three independent research groups, spanning LSD [17–19], psilocybin [16,19,30], and DMT [127]. Strikingly, nearly diametrically opposite effects were found when comparing results found in psychedelic data sets collected at Imperial College London (ICL) versus those collected at the University of Zurich (UZH). In particular, both ICL data sets exhibited significantly increased global FC in transmodal association regions spanning default mode and frontoparietal networks [18,19], whereas the two UZH data sets found minimal changes to transmodal regions and instead found significantly increased global FC in somatomotor and visual regions [16,17]. Subsequent analyses have suggested that this discrepancy is not a result of divergences in the denoising pipeline alone [19]. Therefore, this approach has also failed to yield consistent findings across subjects and data sets.

One potentially convergent spatially specific finding in psychedelic neuroimaging is altered thalamocortical FC [5,31]. Specifically, several investigations have found increased FC between the thalamus and sensorimotor regions following psychedelic administration [10,17,18,32]. Importantly, however, this result is nonspecific to psychedelics and was recently found across each of LSD, d-amphetamine, and MDMA in a single sample [33]**.** A recent study also found evidence that this increase might be an artifact of averaging over heterogeneous thalamic subdivisions, many of which in isolation exhibit reduced thalamocortical FC [34]. Preclinical work has also questioned the central involvement of the thalamus in the action of psychedelics [35], and *in vivo* PET imaging in humans has found that 5-HT2AR expression is relatively low in this structure [36]. More research is needed to identify the reliability and fine-grained spatial specificity of thalamocortical changes under psychedelics.

Complex systems perspectives of brain function and psychedelic brain action

The findings reviewed above appear to defy straightforward unification into compelling mechanistic models of psychedelic action. Although these discrepancies may reflect, in part, small sample sizes, non-neural artefacts, and differences in the analytic/denoising pipeline, we posit that this heterogeneity of findings may be a meaningful feature, and not a bug, of psychedelic brain action. Furthermore, the effort to identify the canonical 'neural correlates' of the psychedelic state can be thought of as the persistence of a 'locationist' approach to brain function, which assumes that focal one-to-one mappings exist between given regions or networks and specific psychological processes. While this approach has proven fruitful in advancing our understanding of lower-level brain processes (e.g., basic sensorimotor processing), there is a large line of theoretical and empirical research highlighting its limitations when assessing higher-level integrative functions of the brain [37–40].

An alternative theoretical framework to properly situate and develop the view that psychedelics induce alterations in fundamental properties of global brain function is offered by complexity science, a discipline that abstracts away from properties regarding the individual parts of a given system (e.g., brain regions or networks), and instead focuses on the systems-level dynamic and relational properties that arise when parts spatiotemporally interact [24]. Within this approach, the brain is viewed as a dynamically evolving complex system of interacting components,

situating it in the same space as a variety of other complex systems, from weather systems to economies to ecosystems [23,41].

As has been argued previously [23], we believe that, by examining systems-level and temporally sensitive metrics, this characterization is less prone to inconsistency compared with those that focus on time-averaged focal patterns. In addition, by explicitly examining spatially distributed patterns, it avoids problems concerning false negatives that are imposed by thresholding practices in standard fMRI mass-univariate analyses, which localize specific clusters of peak differences rather than distributed patterns of co-recruitment [23,42]. Importantly, this characterization of the brain is consistent with a large body of theoretical and empirical work highlighting the distributed, dynamic, and interactional nature of neural processing [23,25,40–45]. To study the dynamic and relational properties of complex systems, complexity science draws predominantly from dynamical systems theory and information theory (Box 2). Next, before outlining our complex systems-based theoretical framework of psychedelic brain action, we review complex systems empirical findings with respect to both general brain function and psychedelics.

The brain is a self-organizing complex system (see Figure 1 for a didactic visualization) that operates in a tension between functional integration and segregation [46]. Complex systems analyses applied to acute psychedelic fMRI data sets, consistent with network-based analyses, have revealed a shift in this balance toward greater global functional integration. One study, in a reanalysis of a previously collected psilocybin data set [28], analyzed the dynamics of instantaneous blood oxygen-level dependent (BOLD) phase-locking patterns following psilocybin administration and found that a network-independent, globally coherent substate increased in its probability of occurrence relative to placebo [47]. Another study, in a parallel publication alongside [13], computed modularity [a graph theoretic metric quantifying the relative decomposability of a

Box 2. Different characterizations of dynamics offered by complexity science

One way to characterize the dynamics of a complex system such as the brain is via the lens of dynamical systems theory. This describes the temporal evolution of a system as a trajectory within the space of all possible states of the system, usually called a 'phase space'. Such trajectories are often modeled as following differential equations on a *N*-dimensional phase space, where *N* corresponds to the number of degrees of freedom of the system (e.g., number of brain regions). Areas within a given phase space that trajectories tend to move toward are referred to as 'attractors', whereas regions that trajectories move away from are 'repellors'. Different types of attractor exist depending on their dynamical properties [24], including single-point attractors, periodic cycles, and strange attractors. Therefore, from the perspective of dynamical systems theory, the brain is thought to carry out cognitive, perceptual, and emotional processes via multifocal brain-wide processing that unfolds along temporally extended trajectories spanning a constrained set of attractors [23,25].

A complementary way to investigate dynamics is by describing them in terms of their statistical properties via concepts derived from information theory. While in its inception, information theory was focused on engineering problems involving communication and signaling, more modern applications leverage information-theoretic quantities as general tools for reasoning about models involving randomness [123]. In this case, the language of probability theory is used to describe the evolution of a system as the unfolding of a stochastic process. Importantly, by interpreting probabilities as characterizations of states of limited knowledge (e.g., less knowledge implies more randomness), one reaches a natural duality between the methods and approaches of statistical physics, which focuses on the study of disordered systems, and statistical inference, which deals with the usage of data to learn about hypotheses [124]. This opens the door to study dynamics of complex systems in terms of information storage, transfer, and processing, which often have a statistical physics counterpart, a view known as 'information dynamics' [125]. One example is the notion of 'entropy', which in different scenarios can be used to quantify uncertainty, information, disorder, or heat, and which has been shown to be highly relevant to psychedelic brain action [25–28,65–69], reviewed below.

Most approaches to investigate dynamical complexity are rooted in either information theory or dynamical systems perspectives, two disciplines with very different aims and toolkits. This apparent dichotomy often forces researchers to choose between two diverging sets of tools and explanations [126]. Nonetheless, despite the apparent differences, it is worth keeping in mind that these two disciplines provide different means that can be used for reaching the same goal: to disambiguate and better understand different types of dynamical phenomenon.

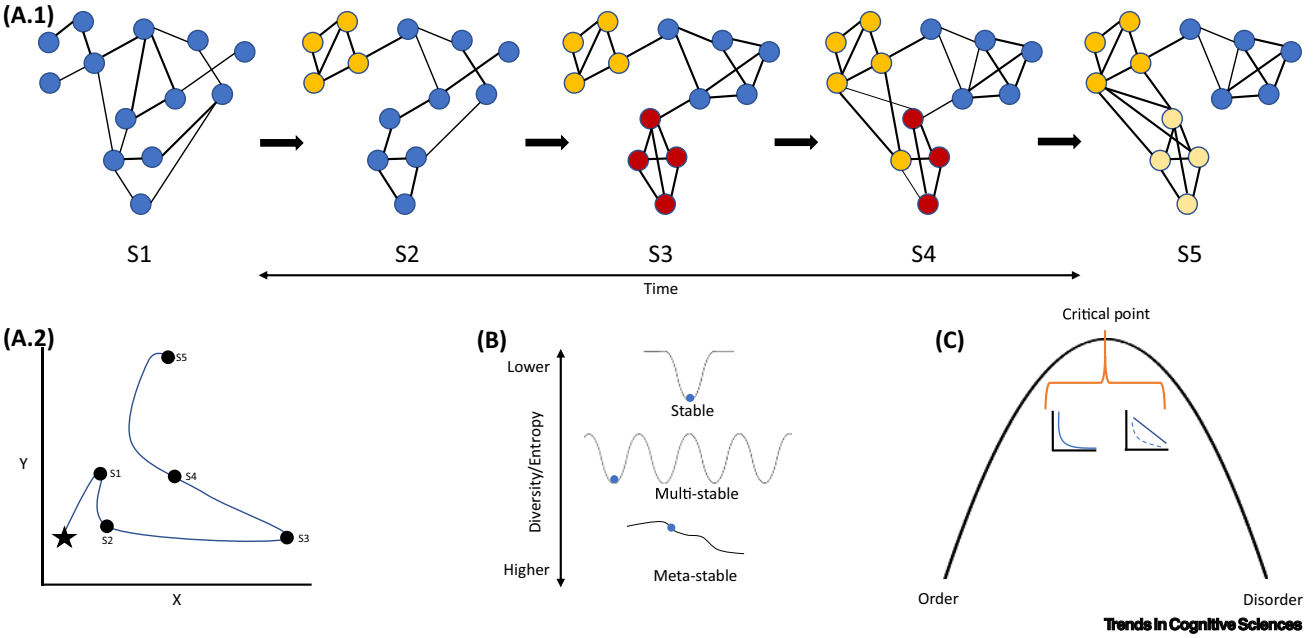

Figure 1. Schematics of core complex systems concepts. Note: these visualizations are for didactic purposes only and are not meant to represent empirical data. (A.1) A toy example of the self-organizing activity of a complex system over time. Local nonlinear interactions aggregate to give rise to macroscale structure, as most evident in S3 and S5. Colors indicate modules/(sub)networks. The yellow network in S5 exhibits hierarchical structure, because it includes two nested subsystems within it. (A.2) A simplified 2D phase diagram visualizing A.1 as a trajectory in phase space. The star indicates the initial conditions. (B) A visualization of different attractor landscapes. Each basin represents an attractor, and the ball represents the current state of the system. Stable regimes are associated with a single deep attractor in which the system gets stuck, with low diversity/entropy of dynamics. Multistable regimes are associated with multiple deep attractors, which the system may move between at a high energy cost, with medium-low diversity/entropy of dynamics. Meta-stable regimes are associated with multiple shallow 'saddle-point' attractors, wherein movement into a given attractor necessitates immediate movement toward another with minimal energy cost, with high diversity/entropy of dynamics. (C) A toy visualization of dynamical criticality. The curve represents continuous movement from order to disorder, with the 'critical' point occurring at the halfway point. Systems located at the critical point exhibit unique properties, including power law distributions (left inset) and slow recovery from perturbation (right inset), as shown by the dashed line compared with the solid line.

network (e.g., the brain as a whole) into distinct subnetworks] and found that, relative to placebo, LSD reduced modularity across the majority of edge densities examined [18]. Notably, decreased modularity was also found in postacute data following psilocybin therapy for depression, an effect that correlated with reductions in depression symptoms [9]. Complementing these empirical investigations, Jobst *et al.* applied a computational modeling approach to the above-mentioned LSD data set and found that the optimal value for the 'global coupling parameter' of whole-brain FC was significantly higher when modeling LSD data relative to placebo [48].

Self-organizing complex systems with an integration–segregation balance also feature the emergence of hierarchical structure. In the human brain, there is evidence for a macroscale hierarchy of information flow, ascending from concrete sensory processing in unimodal sensorimotor areas to abstract integrative processing in transmodal association areas [49]. Girn *et al.* assessed the presence of this hierarchical gradient in the above-mentioned LSD and psilocybin data sets and found that both LSD and psilocybin effectively 'flatten' this hierarchical axis relative to placebo by increasing crosstalk between hierarchical extremes [19]. This result has since been replicated with DMT [127]. These findings suggest that the increases in global integration observed in the psychedelic state are specifically marked by reduced differentiation along the principal hierarchical axis of the brain.

The self-organizing activity of the brain during wakefulness has also been found to exhibit dynamical properties consistent with being near a critical threshold between stability and chaos [50], a notion referred to as 'criticality' [51]. The theoretical appeal of criticality in characterizing brain

function has been highlighted and investigated for over two decades [52]. Complex systems that are tuned close to criticality exhibit a variety of computationally desirable properties, including an increased ability to adaptively and flexibly respond to inputs [53], an increased dynamic range of states [54], and an increased ability to encode, store, and propagate information [55]. Signatures of criticality include scale invariance (i.e., power law statistics), fractal/self-similar structure, the presence of long-range correlations, and strong sensitivity to external perturbations, also known as 'critical slowing' [56]. Several investigations have found evidence of these signatures in the human brain, including: (i) scale-invariant power law distributions in neural avalanches observed in neuronal cultures [57], clusters of activation during resting-state fMRI [58], and the duration of interregional phase-locking as measured by fMRI and MEG ([59], although see [60]); (ii) fractal structure in brain structure and function (e.g., [61]); and (iii) small-world organization consistent with the presence of long-range correlations [62].

With respect to psychedelics, several indices of criticality have been found to be increased in the psychedelic state relative to placebo, consistent with previous theoretical proposals [63,64]. Atasoy *et al.* found increases in the goodness of fit of harmonic brain-state dynamics to power laws after LSD, as well as an increase in the 'critical exponent', which indexes closeness to a critical point [65]. An additional analysis of this data set, as well as the above-mentioned psilocybin data set, found that the spatial and temporal 'fractal dimension' of cortical FC was increased with LSD and the spatial dimension was increased with psilocybin [66]. In a more direct assessment of criticality, a recent study analyzed this LSD data set and found that LSD tuned low-frequency cortical dynamics closer to a mathematically well-defined edge-of-chaos critical point relative to normal wakefulness [50]. Finally, findings with these and additional data sets also suggest that psychedelics increase the prevalence of long-range correlations and increase small-worldness [12,13,67,68].

Another important feature of brain activity that is relevant to criticality is 'metastability', which corresponds to a regime in which a system easefully and continuously traverses a sequence of states without falling into a given stable attractor [69] (Figure 1B). Computational and/or empirical studies have found that the resting conscious brain exhibits metastability [64,70,71], and individual differences in the degree of metastability have been linked to psychopathology (e.g., [72]) and cognition (e.g., [71]). The concept of metastability is closely linked to the entropy of the dynamics of a system. Used in this sense, entropy is an information-theoretic quantity that indexes two fundamental dynamical properties: the temporal complexity or diversity of the trajectories of the dynamics of a system, and their unpredictability.

Notably, increased entropy of neural dynamics has been a consistent finding with psychedelics across multiple data sets, spanning psilocybin [fMRI and magnetoencephalography (MEG)], LSD (fMRI and MEG), and DMT (fMRI and electroencephalography; EEG), and with an ayahuasca data set (fMRI) [63,64,73–79,127]. These investigations have consistently revealed global increases in entropy in the psychedelic state, underpinned by changes that are greatest and most consistent in parietal and occipital cortices [73–76]. This consistency is likely a result of the fact that measures of entropy abstract from analyzing specific spatially specific patterns, and instead assess the diversity or unpredictability of the signal over time. We also highlight increases in brain entropy with comparable altered states to the psychedelic state, namely ketamine-induced dissociation [76], REM sleep [80,81], meditative states [82], and the pre-ictal aura of temporal lobe epilepsy [83]; although see [84] for a potentially discrepant finding. Moreover, just as increases in brain entropy may track increases in subjective intensity under psychedelics [127], brain entropy reliably decreases during states of reduced consciousness, such as anesthesia [85], non-REM sleep [81], and disorders of consciousness [86]. In addition to regional

changes in entropy, several studies have provided evidence for increases in the diversity of brain states that are also suggestive of increased metastability. These include: increased variance in network synchrony with psilocybin [47,64]; a greater diversity of FC motifs with psilocybin [87]; a larger repertoire of harmonic brain states with LSD [65]; and a reduction in the energy required for brain state transitions combined with a more diverse sequence of brain states with LSD [88]. These studies collectively suggest an increase in metastable neural dynamics in the psychedelic state, reflective of a more easeful and diverse traversal of brain states.

We note that, despite the promise of the above-described findings with psychedelic data sets, such findings are highly preliminary and require replication across a wider range of research groups. Our theoretical proposal, described in the following section, only partially rests upon such evidence, and draws more generally on concepts from complexity science, which have found empirical support in the characterization of general brain function. Ultimately, a primary motivation of the present paper is to provide theoretical justification for additional empirical investigations that apply complexity science approaches to psychedelic datasets.

Psychedelics as catalysts for a distinct mode of whole-brain functioning

Psychedelics are known for their ability to induce potent subjective effects that vary widely across individuals and across experiences for a given individual [89–91]. Assuming the existence of a direct mapping between the dynamics of subjective experience and the dynamics of brain function, it is reasonable to expect that this subjective variability is mirrored by neural variability. This reasoning does not lead one to expect a canonical spatial pattern of neural (de)activation or network FC changes that defines the psychedelic experience. Rather, it is more likely that subjects idiosyncratically traverse a range of neural states, in direct correspondence with an idiosyncratic traversal of mental states. Therefore, properties most relevant to psychedelic brain action may be more likely found by examining how neural activity dynamically evolves, as opposed to searching for a representative neural pattern.

Accordingly, we propose that psychedelics can be more accurately seen as shifting the brain into a distinct mode of functioning, which features an altered set of systems-level dynamical properties, summarized by the concepts of increased entropy, metastability, and criticality. These properties have implications for the spontaneous activity of the brain and its response to perturbation. In particular, they represent a flexible and diverse dynamical regime that is tuned for information propagation and strong sensitivity to perturbations (i.e., exteroceptive and interoceptive inputs). Critically, this characterization aligns with core characteristics of the subjective effects elicited by psychedelics, as well as their underlying neurobiological mechanisms.

Notably, this perspective provides an intuitive lens to understand the significant inter- and intra-individual variability of psychedelic subjective effects [98] and their strong sensitivity to nonpharmacological factors (i.e., ‘set and setting’ as described in psychedelic-assisted psychotherapy [27]). A pertinent concept here is the complexity science concept of ‘nonergodicity’, which refers to a dynamical regime in which different initial conditions of a system lead to distinct temporal trajectories following a perturbation. In the context of psychedelics, ‘initial conditions’ refers to the personal and environmental factors present at the time of psychedelic administration [i.e., one’s current cognitive-emotional state, beliefs, and expectations (set), and one’s physical, social, and cultural environment (setting)], while ‘perturbation’ refers to psychedelic effects. In this view, psychedelic administration represents a pharmacological perturbation that elicits a spatiotemporal trajectory of neural dynamics (and accompanying subjective dynamics) that varies based on a given individual’s brain structural and functional architecture, as well as their acute neuro–cognitive–affective–perceptual state during drug effects (Figure 2).

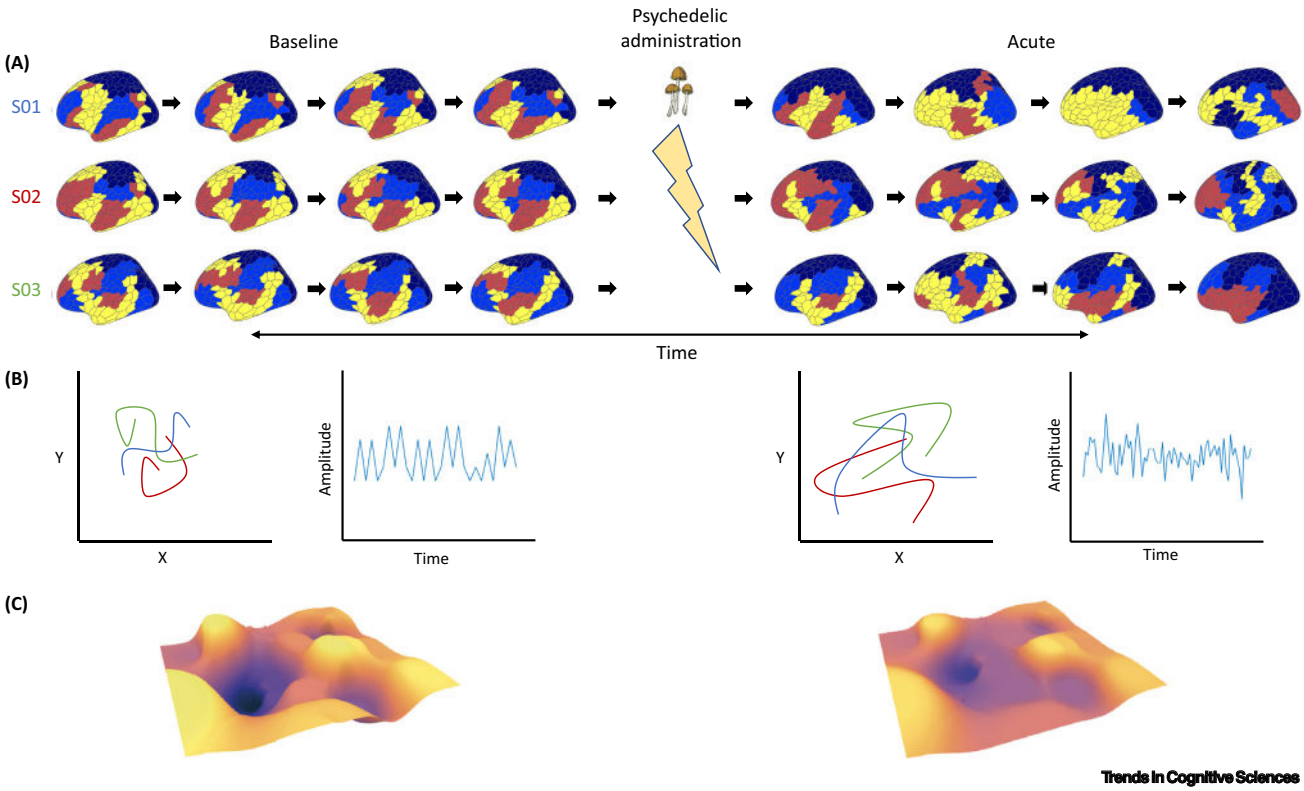

Figure 2. A cartoon of the proposed complex systems conception of psychedelic large-scale brain action. (A) A toy example of large-scale neural dynamics at baseline (pre-psychedelic administration) and during acute psychedelic effects. Acutely, brain states become more diverse, temporally variable, and more likely to inhabit highly integrated states. (B) For each of baseline and acute, toy examples of an exploration of phase space (left left and right left) and a given regional timeseries (left right and right right). Acutely, the brain explores an expanded phase space indicative of relatively unconstrained and freely exploring dynamics, and this also manifests as an increase in neural entropy. (C) Toy surface renderings representing attractor landscapes in each of baseline and acute states. Acutely, the landscape becomes relatively flattened and more meta-stable, such that the brain easefully traverses a variety of states with a reduced likelihood of fixation within a given attractor.

Although speculative at this stage, the flexibility and diversity of brain dynamics in the psychedelic state, as found in several empirical investigations (e.g., [9,76,87,92]), may relate to reports of an ability to escape entrenched patterns of thinking, to view relationships and life situations from a broader, more equanimous perspective, and to have psychological insights [93–95]. It also aligns with reports of relatively unconstrained and dream-like cognition as evidenced by assessments of 'primary process thinking' and 'cognitive bizarreness' [64,96–99]. Furthermore, such changes can be conceptualized as a flattening of the attractor landscape (see Box 2 for a description of attractors). In other words, the brain may have a reduced tendency to get 'stuck' in habitual (and sometimes maladaptive) mental states, and an eased ability to move between them, consistent with increased metastability and the findings of other studies [9,92]. See [26] for a thoughtful discussion of attractor landscape flattening with psychedelics and its potential relationship to therapeutic effects.

An increase in the sensitivity of the system (i.e., the brain) to perturbations can be understood as a plausible mechanistic underpinning the strong context dependency of psychedelic drug effects and is consistent with the role of serotonergic neurotransmission in regulating environmental sensitivity [100,101]. Finally, the notion of 'tuning for information propagation', a signature of systems close to criticality, is supported by findings of increased global integration and reduced hierarchical differentiation, and may relate to experiences of a blurring or dissolving of the subject–object distinction found in ego-dissolution and related experiences, increased semantic activation/associative thinking, and a putative increased sensitivity of high-level beliefs to bottom-up information [6,102–106].

Critically, this view also accords with the underlying neurobiological mechanisms of serotonergic psychedelics. Research has reliably demonstrated that partial agonism at the (excitatory) 5-HT2A receptor accounts for the primary subjective and neural effects of these drugs [2,107]. Evidence from high-resolution *in vivo* positron emission tomography (PET) imaging in humans has indicated that 5-HT2A receptor densities are highest in association cortices (as well as primary visual cortex) [36] and *in vitro* work has additionally found that these receptors are located predominantly on the apical dendrites of layer 5 glutamatergic pyramidal cells [108]. Critically, association cortices are among the most interconnected and functionally flexible regions of the brain, with connections, mediated by layer 5 pyramidal cells, facilitating interactions between spatially distributed and functionally distinct neural systems [109]. Therefore, the cortical localization of 5-HT2A receptors suggests a potent ability to modulate global brain dynamics. Moreover, given these characteristics, excitatory modulation of association cortex is likely to result in a diverse set of possible downstream neural consequences. Supporting this, a recent investigation found that direct electrical stimulation of regions of association cortex elicited subjective effects that were the most rich and diverse of all cortical areas [110]. As such, a shift in the dynamical mode of global brain function, rather than a uniform set of regional or network changes, can be understood as a more theoretically plausible consequence of psychedelic-induced, 5-HT2A-mediated excitatory modulation of layer 5 pyramidal cells in association cortices.

Finally, while we have emphasized the value of characterizing the spatiotemporal trajectory of neural dynamics elicited by psychedelics, and properties thereof, we note that an alternative complementary approach is to evaluate the presence of subjective-neural substates that recur across subjects. Neurophenomenological approaches, such as those that collect experience-sampling data in conjunction with neuroimaging, may be fruitful in this regard [111].

The concept of 'a shift into a distinct mode of dynamical functioning' proposed here may also apply to a variety of other pharmacological or cognitive interventions. For example, evidence suggests that sedation is associated with a mode of brain function characterized by subcritical brain dynamics and reduced dynamic diversity [85]. In addition, top-down attention and related practices, such as meditation, may be valuably construed as shifts in global functioning, as has also been argued previously [82,112]. Future research may profit from using this lens as a means of understanding various modulations of brain function.

As mentioned above, an important limitation of this framework is that the current supportive empirical evidence with psychedelic data sets, although spanning multiple drugs and imaging modalities, has predominantly been conducted on data collected by a single research group (although note these exceptions [77,78,113]). We hope that the present paper helps galvanize other research groups into conducting similar analyses and evaluating our theoretical claims. One limitation of complexity science analyses is that they are often nontrivial to implement and require particular technical expertise. 'Team Science' collaborations are an effective means of breaking such impasses and are encouraged. Another limitation is that exclusive reliance on a complexity science framework and corresponding systems-level analyses has potential to obscure important spatially specific effects. Ultimately, we contend that complex systems and locationist approaches are complementary, rather than mutually exclusive.

Concluding remarks

We have drawn from empirical findings and theoretical perspectives from complexity science to propose a specific conception of psychedelic brain action; namely, that serotonergic psychedelics shift brain function into a distinct mode that is more flexible, diverse, sensitive, and tuned for information sharing and propagation. This view posits that the effect of psychedelics on the

Outstanding questions

How do distinct measures of dynamical complexity relate to and inform each other? A variety of approaches have been applied in an exploratory manner; now lies the challenge of interrelating these measures and identifying unique applications for each.

How can we best link large-scale neural dynamics to the dynamics of psychedelic subjective effects? Studies so far have related session-level self-report assessments of subjective effects to neural measures. Given the significant variability of psychedelic effects, temporally refined measures of subjective effects, such as afforded by 'experience sampling', are needed in tandem with dynamic neural measures to effectively advance our understanding of mind–brain relationships with psychedelics.

How can we develop principled but practical accounts to bridge large-scale neural dynamics with dynamics at the micro- and mesoscales? Classic psychedelics elicit their primary effects via agonism at the serotonin 2A receptor, which has an excitatory and dysregulating effect on local neural populations. More work is needed explicitly relating these effects to the large-scale dynamics focused on in the present paper.

What role do individual differences in brain and receptor topography have in determining brain responses to psychedelics? A greater understanding of individualized responses to psychedelics is essential for optimizing therapeutic approaches and improving safety and efficacy in clinical settings.

Do the acute neural effects of psychedelic persist in a manner relevant to therapeutic outcomes? How do postacute effects changes over time? Preliminary studies have suggested the presence of postacute carryover effects. However, evidence also exists for differential neural effects depending on the time elapsed (e.g., 24-h post versus 1 week). Further work is needed to evaluate the timecourse of postacute neural and psychological effects and their relationship to therapeutic outcomes.

brain is not to be found in specific spatial locations but rather in the way that the regions of the brain dynamically interact and evolve as a whole. This conception provides an intuitive explanation of several aspects of psychedelic phenomenology, notably including its context dependency and inte-individual variability, and has potential to help unify past neuroimaging findings and guide future investigations.

We believe that future neuroimaging work on the acute psychedelic experience should seek to characterize individual differences in the spatiotemporal neural trajectories elicited by this class of drugs, and their trait- and state-level contributing factors (see Outstanding questions). In addition, we encourage movement away from time-averaged network-based analyses toward more sophisticated, dynamic, and multivariate approaches that examine globally distributed spatiotemporal patterns and trajectories. This can be done via hypothesis-driven applications of the complex systems analyses discussed above, as well as yet-to-be-developed novel methodological approaches. It is our belief that the combination of embracing individual variability and foregrounding spatiotemporal dynamics will serve to generate compelling and unifying mechanistic models of psychedelic brain action, while also informing our understanding of brain function more generally.

Declaration of interests

None declared by authors.

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