Trends in Neurosciences

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Review

# Unravelling consciousness and brain function through the lens of time, space, and information

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**Disentangling how cognitive functions emerge from the interplay of brain dynamics and network architecture is among the major challenges that neuroscientists face. Pharmacological and pathological perturbations of consciousness provide a lens to investigate these complex challenges. Here, we review how recent advances about consciousness and the brain's functional organisation have been driven by a common denominator: decomposing brain function into fundamental constituents of time, space, and information. Whereas unconsciousness increases structure–function coupling across scales, psychedelics may decouple brain function from structure. Convergent effects also emerge: anaesthetics, psychedelics, and disorders of consciousness can exhibit similar reconfigurations of the brain's unimodal–transmodal functional axis. Decomposition approaches reveal the potential to translate discoveries across species, with computational modelling providing a path towards mechanistic integration.**

## Highlights

Perturbations of consciousness arise from the interplay of brain network architecture, dynamics, and neuromodulation, providing the opportunity to interrogate the effects of these elements on behaviour and cognition.

Fundamental building blocks of brain function can be identified through the lenses of space, time, and information.

Each lens reveals similarities and differences across pathological and pharmacological perturbations of consciousness, in humans and across different species.

Anaesthesia and brain injury can induce unconsciousness via different mechanisms, but exhibit shared neural signatures across space, time, and information.

During loss of consciousness, the brain's ability to explore functional patterns beyond the dictates of anatomy may become constrained.

The effects of psychedelics may involve decoupling of brain structure and function across spatial and temporal scales.

## Resolving brain complexity

Neuroscientists face the challenge of disentangling how cognitive function emerges from the complex interplay of brain dynamics and network architecture. From development and evolution to mental illness and even consciousness, many of the grand challenges of neuroscience are system-wide phenomena: they encompass multiple intertwined spatial and temporal scales. The brain itself is a paradigmatic example of a complex system, comprised of intricately nested networks and multi-scale dynamics [1]. Embracing this complexity presents notable challenges, but also offers an opportunity to redefine current understanding of brain function.

This opportunity is now within reach because two trends are converging. First, the increasing richness of empirical neuroimaging data allows capturing the complexity of brain function with ever-greater resolution, while also making this complexity harder to ignore. Second, theoretical advances make it possible to tame the complexity of brain data, by discerning its fundamental constituents.

Disentangling the fundamental constituents of a complex system allows neuroscientists to 'zoom in' on neural interactions in terms of: (i) a time-resolved perspective, which recognises that brain activity comprises the ebb and flow of distinct dynamical states; (ii) a multi-scale perspective, viewing the brain in terms of distributed patterns of structure–function relationships across spatial scales; and (iii) an **information** (see Glossary)-resolved perspective [2], disentangling different forms of information storage, transfer, and integration. These apparently distinct approaches are complementary facets of the same common denominator: obtaining greater resolution into specific aspects of the data.

In this article, we review how recent breakthroughs in understanding the brain's functional architecture through neuroimaging have been driven by the common principle of decomposition into fundamental constituents. To illustrate this notion, we focus on the investigation of consciousness

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through neuroimaging. Perturbations of consciousness arise from the complex interplay of brain network structure, dynamics, and **neuromodulation**, providing fertile ground to interrogate their effects on behaviour and cognition. This is made possible by the ability to acquire non-invasive neuroimaging of the entire brain *in vivo* across species, particularly via functional MRI (fMRI). We outline convergent elements across humans, non-human primates, and rodents. The identification of this convergence was made possible by the use of shared neuroimaging tools, shared experimental manipulations, and, crucially, shared ways of decomposing brain function. We conclude by outlining a path forward to integrate multiple decompositions through computational modelling, which also enables shedding light on the neurobiological origins and causal roles of the phenomena that are being decomposed.

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## Progress through contextualisation and decomposition

The traditional approach in neuroimaging has been to map circumscribed cognitive operations onto discrete, spatially localised patches of neural tissue, leading to foundational early successes [3,4]. However, the abundant evidence for regional specialisation from neuropsychology and brain mapping should not be interpreted as precluding the coexistence of distributed function in the brain [5,6]. Formalisms from graph theory were recruited to simultaneously consider the network of interactions between all brain regions, both locally and globally: the functional and structural **connectomes**. Thus, a region's specialisation must be understood in the 'neural context' provided by its interactions with the rest of the brain [7].

We argue that recent experimental and theoretical advances in neuroscience can be understood as manifestations of the next step in this process: establishing context for the functional interactions themselves. This is made possible by an array of decomposition techniques, which yield different lenses to resolve functional interactions: in terms of their temporal dynamics, their distributed spatial scales, and the types of information they convey (Figure 1).

In this article, we use 'decomposition' to encompass both: (i) summarising the data in terms of a small number of principal/independent components, extracted from the data themselves (i.e., dimensionality reduction); and (ii) re-representing the data in terms of a prespecified set of constituent elements, acting as 'building blocks'. What is common across both cases is that each decomposition provides a lens to bring into focus specific aspects of the data.

Throughout the history of science, the principle of decomposition has been a catalyst of scientific discovery. Decomposition (as dimensionality reduction) has been instrumental in facilitating data compression, with popular approaches in neuroimaging being unsupervised clustering and principal/independent components analysis (PCA/ICA): their purpose is to provide insight about a dataset by identifying its most important dimensions [8–10] (note that a variety of alternative criteria may be adopted for determining the number of dimensions, as reviewed in [10]). Crucially, although a sparser re-representation of the data is often insightful, not all insightful re-representations of the data must be sparser. Another important usage of decomposition approaches is to 'translate' data into a common alphabet of fundamental building blocks that enables taxonomisation, systematic comparison, and prediction. A celebrated example is the decomposition of chemical elements into their atomic constituents: the resulting periodic table of elements catalysed the shift from alchemy to modern chemistry. Here, we use 'decomposition' to encompass both meanings: data compression/dimensionality reduction, and translation into a common alphabet.

### A case study: decomposing consciousness

The inquiry into the neural bases of consciousness and its perturbations is a particularly fruitful test-case to illustrate the trend of decomposing neural interactions as the common principle

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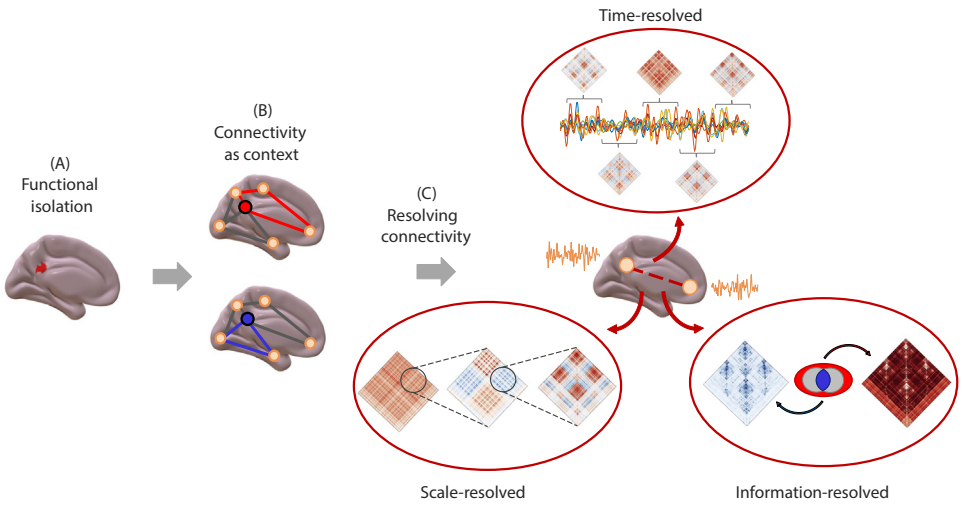



Figure 1. Progressive refinement in the characterisation of brain function. From considering the function of brain regions in isolation (A), connectomics and 'neural context' (B) shift the focus to connectivity between regions. (C) With this perspective, one can 'zoom in' on connections themselves, through the lens of time, space, and information: a connection between the same regions can be expressed differently at different points in time (time-resolved functional connectivity), or different spatial scales, or for different types of information ('information-resolved' view from information decomposition). Venn diagram of the information held by two sources (grey circles) shows the redundancy between them as the blue overlap, indicating that this information is present in each source; synergy is indicated by the encompassing red oval, indicating that neither source can provide this information on its own.

underlying recent progress. Loss of consciousness (LOC; typically identified as loss of behavioural responsiveness) can arise from different perturbations of the brain's delicate functioning, ranging from transient anaesthetic interventions, to brain injury and chronic **disorders of consciousness (DoC)** [11–19]. However, **psychedelic** drugs can also profoundly alter consciousness, but without suppressing it [19–21]. Therefore, in recent years, prominent advances have arisen from using neuroimaging to compare different ways of losing responsiveness (anaesthesia, DoC, sleep), or different kinds of pharmacological alterations (anaesthetics, psychedelics, and other psychoactive substances), both within and across species (including humans, macaque and marmoset monkeys, rats, and mice) [11–14,16,17,19,20,22–30]. Here, we highlight how different decompositions applied to fMRI recordings have advanced the neuroscientific understanding of consciousness and its perturbations, as a running example of how this approach may benefit neuroscience more broadly.

## Decomposing time: from static connectivity to dynamics

Even at rest, the brain is never idle, and both consciousness and cognition are best understood as processes that unfold over time. One way to investigate the brain's dynamism is to characterise them in terms of various 'brain states', understood as distinct, recurrent patterns of brain activity or functional coupling that emerge from, and have consequences for, physiology and/or behaviour [31]. In contrast to calculating time-averaged activity or connectivity patterns over an entire scanning session, 'time-resolved' analyses based on dynamic brain states provide a window into the distinct configurations that take place at different points in time, providing a time-resolved perspective on brain function [32–38]. Arguably, two main approaches of disentangling the temporal dimension of brain function have emerged in the literature: (i) by studying the number of available brain states and the transitions between them, and (ii) by analysing the characteristics of the time-resolved states themselves. In what follows we highlight some of the more prominent applications to the study of consciousness and its perturbations and what insights they have enabled.

## Glossary

**Co-activation patterns (CAPs):** recurrent patterns of brain regions that tend to be active at the same time as each other, typically in terms of relative BOLD signal.
**Connectome:** the network of connections between brain regions, whether physical white-matter tracts (structural connectome), or statistical relationship between functional time-series (functional connectome).
**Disorders of consciousness (DoC):** syndromes including coma, vegetative state/unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS), typically due to traumatic or anoxic brain injury, characterised by behavioural unresponsiveness to environmental stimuli and believed to involve reduced/absent consciousness.
**Dynamic functional connectivity (FC):** also termed time-varying functional connectivity; the identification of a number of functional connectivity patterns that recur over time, often through data-driven clustering of connectivity over short subsets of the full scan.
**Electroencephalographic (EEG) microstates:** transient, temporally recurrent patterns of EEG activity.
**Embedding:** re-representation of an object (here, brain connectivity) in a low-dimensional space that preserves the relationships between the object's constituent elements.
**Fourier transform:** mathematical re-representation of a signal from the temporal domain to the domain of temporal frequencies.
**Gradient:** in the context of the current article, 'gradient' refers to a spatial pattern of variation reflecting the position of each brain region in a low-dimensional space.
**Information:** in the Shannon formalism, information reflects reduction in entropy (uncertainty about the value of a variable) upon observing the value of other variables.
**Integrated information:** proposed measure of consciousness from integrated information theory, intended to quantify the extent to which 'the whole of a system is greater than the sum of the parts'.
**Macroscale computational model:** simulation of regional brain activity, often encompassing the entire brain or cortex. Such models typically comprise: (i) a

### State transitions and functional repertoire

Regardless of the specific method used to detect brain states (see [33,39] for reviews of different approaches and methodological avenues), it is well established that their resulting dynamics vary according to anatomy, cognitive demands, individual differences, and pathology [33,35,38–41]. Hence, it is reasonable to hypothesise that the patterns of occurrence of different brain states can shed light on the brain's capacity to support different cognitive operations.

This approach has revealed similarities across ways of losing consciousness, across modalities, and across species. Although dynamic reconfigurations of functional connectivity (FC) can be observed even in the unconscious (unresponsive) brain, the brain tends to visit a more limited repertoire of states across pathological and pharmacological LOC [14]. A restricted dynamical repertoire is observed in humans anaesthetised with several anaesthetics, in terms of fewer time-varying patterns of brain activity or connectivity being visited: **co-activation patterns (CAPs)** [12] and **dynamic FC** [14,42,43] from fMRI, but also **electroencephalographic (EEG) micro-states** [41,44]. These results generalise across species. A single state tended to dominate the fMRI dynamics of macaques anaesthetised with propofol or sevoflurane [22,45,46]; anaesthetised mice stop 'visiting' unique CAPs that are characteristic of wakefulness [47]; and a single principal component dominates the dynamics of ultra-fast fMRI in anaesthetised rats [48].

Beyond anaesthesia, DoC patients also exhibit a restricted repertoire of CAPs [12,13] and preferentially dwell in low-complexity, structurally coupled states of dynamic FC [14,49]. Similar results were obtained for deep sleep during simultaneous EEG-fMRI: different methods indicate that wakefulness-specific states are rarely visited during deep sleep, when instead a single sleep-specific state predominates [43,50,51] and fewer state transitions are observed [50,52]. Changes in repertoire characteristics have also been reported under psychedelics: both psilocybin and the non-classic psychedelic nitrous oxide increase the prevalence of a state of global coherence/co-activation, whether assessed by CAPs or dynamic FC [20,53,54]. LSD and psilocybin also reshape the transitions between CAPs, corresponding to increased ease and diversity of transitions [55].

### Time-resolved structure–function coupling and anti-coordinated patterns

Complementary to the investigation of state transitions, another fruitful line of research focuses on the properties of the states themselves. If a state is visited more often or for longer than others, the properties that set it apart from other states can provide insights into its role for brain function. By lumping the different dynamical states together, traditional 'static' FC is unable to illuminate the unique characteristics of each state, providing a time-averaged description that may obscure crucial aspects of brain function and its alterations.

As a prominent example, dynamic functional states of high similarity to the underlying structural connectivity (structurally coupled) and predominantly short-range connectivity are disproportionately frequent during unresponsiveness (Figure 2). This phenomenon has been observed with different methods and for different anaesthetics, as well as during sleep [43,56] and in DoC patients [14,49]; and even in different species: human [14,43,49], macaque [22,45], rat [57], and mouse [47]. Deep-brain stimulation of the centro-median thalamus, which can restore behavioural responsiveness despite continuous anaesthetic infusion in macaques [58–60], and rats [61], also restores the ability of anaesthetised macaques' brains to visit wakefulness-specific states characterised by lower structure–function coupling (similarity between time-resolved FC and structural connectivity) [46]. Even when a link is not explicitly drawn, the states that are visited more often during consciousness than LOC tend to be dominated by **transmodal** cortical networks [12,49], which are known to be relatively decoupled from the underlying structure [62,63].

mathematical account of each brain region's local dynamics (e.g., Kuramoto oscillator, or excitatory and inhibitory neuronal populations); and (ii) a wiring diagram of how regions are connected (e.g., from diffusion MRI tractography, tract-tracing, or simple geometric rules).

**Modules:** groups of nodes that are more interconnected with each other than with the rest of the network.

**Neuromodulation:** physiological process whereby chemicals regulate the activity of neurons (exogenous neuromodulation via electric stimulation is also possible).

**Psychedelics:** chemicals that induce an altered state of consciousness, which can involve diverse subjective manifestations, including sense of meaning and connection, hallucinations, and depersonalisation/'ego dissolution'.

**Redundancy:** information that can be obtained from each individual one among several sources, so that it would remain available even if one source were removed.

**Synergy:** information that can only be obtained by combining multiple sources of information together, so that it would become unavailable if any one source were removed.

**Transmodal cortex:** regions of the cortex that perform associative functions.

**Unimodal cortex:** visual, auditory, somatosensory, and motor regions of the cortex, which process information pertaining to a single modality.

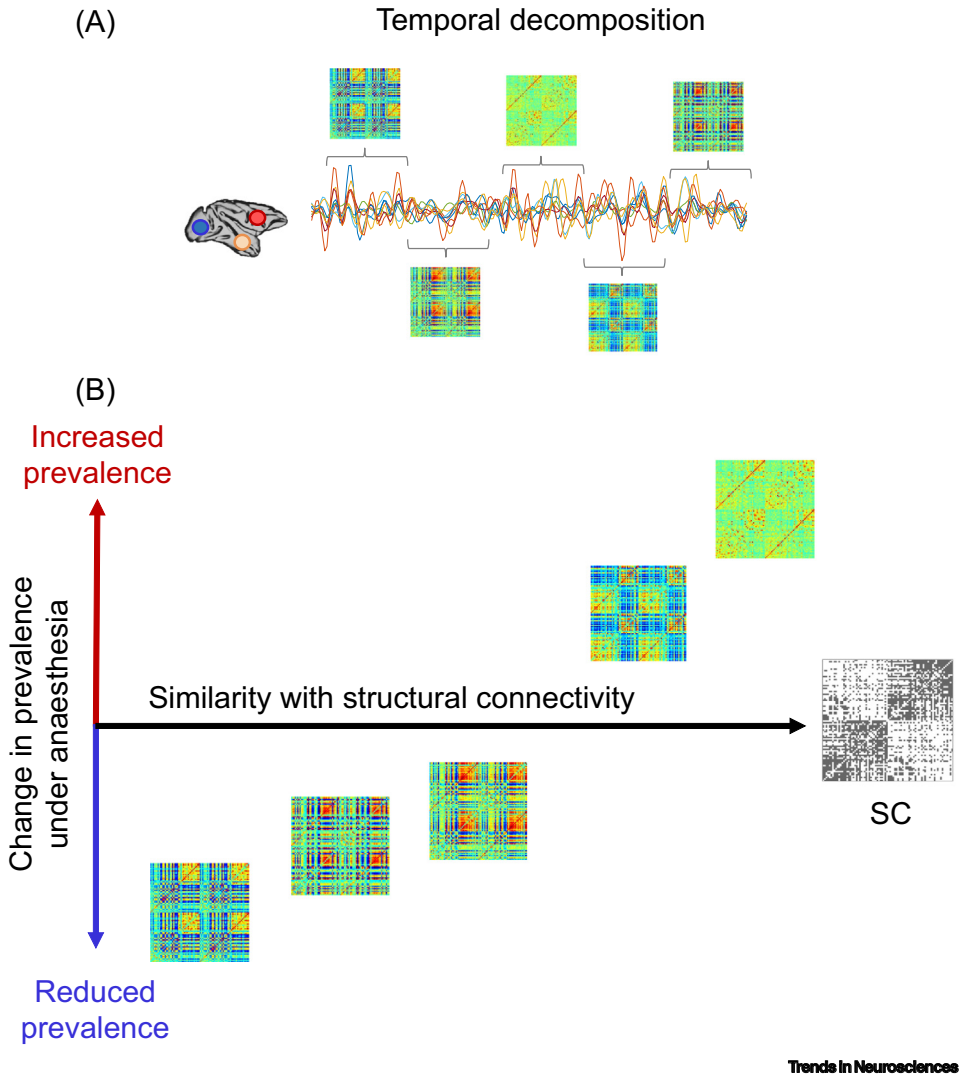



Figure 2. Temporal decomposition reveals consciousness-related changes in structure–function coupling. (A) States of dynamic functional connectivity can be obtained (among several methods) by clustering the correlation patterns between regional fMRI time-series obtained during short portions of the full scan period. (B) Both anaesthesia (shown here for the macaque) [45] and disorders of consciousness [14] increase the prevalence of the more structurally coupled states in fMRI brain dynamics, at the expense of the structurally decoupled ones that are less similar to the underlying structural connectome. Adapted from [45]. Abbreviation: SC, structural connectivity.

Conversely, temporal decomposition has revealed that function becomes decoupled from structure under the effects of psychedelics. LSD reduces coupling between the structural connectome and a state of dynamic FC characterised by high network segregation (low prevalence of connectivity between **modules**) [64]. This effect of LSD was not apparent when only considering static FC [64]. The time-resolved approach also dissolved an apparent paradox, whereby both psychedelics and LOC were found to reduce the prevalence of anti-coordinated functional patterns in the brain (i.e., negative temporal correlation, or anti-phase) [12,13,21,45–47,64–70]. Time-resolved analysis showed that this apparent similarity is due to traditional static FC 'blurring' temporally distinct effects: the reduced occurrence of anti-coordinated patterns induced by LSD [64] and

anaesthesia/DoC [15] pertains to different dynamical states, demonstrating the value of temporal decomposition for understanding shared and distinct features of different perturbations of consciousness.

## Decomposing space: distributed function across spatial scales

In addition to all-or-none mapping of circumscribed cognitive operations onto spatially discrete regions, some brain processes may instead depend on graded contributions from multiple overlapping and spatially discontiguous patterns, working in concert across scales [71–74]. Whereas traditional neuroimaging views functional brain activity in terms of signals corresponding to discrete spatial locations, distributed approaches propose to view brain function as composed of overlapping contributions from distinct spatial scales. Thus, the traditional spatially-resolved approach and the scale-resolved approach provide complementary perspectives: one isolates each region and has revealed that key cortical and subcortical regions are involved in supporting consciousness [15,21,25,46,58–60,75–77]. The other instead disentangles different spatial scales (Figure 3, Key figure). Two approaches have become prominent in recent years to investigate distributed function in the brain: re-representing brain function in terms of overlapping functional **gradients** (Figure 3A) and re-representing it in terms of distributed structure–function relationships: across scales, rather than across time (Figure 3B).

### Functional gradients: low-dimensional distributed patterns

The brain's intrinsic functional organisation can be re-represented in terms of a small set of continuous, spatially overlapping whole-brain patterns, termed 'functional gradients' (Figure 3A and Box 1) [78]. Gradients map FC to a low-dimensional space where proximity indicates functional similarity. Each gradient represents a dimension in this space and the regions whose FC is most different along that dimension, known as 'anchoring points', establish opposite extremes (Figure 3B). For example, the principal gradient of human FC is anchored in the **unimodal cortex** at one end and in the transmodal association cortex at the other end [78] (Figure 3A).

This framework has contributed to recent progress in the study of pathological and pharmacological perturbations of consciousness. Both propofol anaesthesia and DoC (which induce both unresponsiveness and unconsciousness) are characterised by reduced differentiation between the unimodal and transmodal ends of the principal FC gradient (Figure 3C) [13]. This effect on the principal gradient is not shared by ketamine anaesthesia, which induces unresponsiveness, but preserves conscious experience in the form of vivid dreams [13]. Therefore, the authors proposed that principal gradient integrity may help to dissociate LOC from mere loss of behavioural responsiveness, a thorny issue with deep clinical implications [79]. During both sleep and dexmedetomidine sedation, the spatial organisation of human blood oxygen level-dependent (BOLD) dynamics loses its association with the principal unimodal-transmodal gradient [23]. The same was observed in macaque electrocorticography across sleep and anaesthesia [23]. Further demonstrating generalisability across species, in the macaque brain the range of the principal gradient is diminished by anaesthesia with propofol, sevoflurane, and ketamine and restored upon recovery of behavioural arousal induced by centromedian thalamic stimulation [80].

However, the interpretation of the principal gradient specifically reflecting consciousness (as recently argued [79]) may be challenged by recent reports that serotonergic psychedelics LSD, psilocybin [81], and DMT [82], all consistently induce an analogous degradation of the principal gradient. Crucially, none of these drugs render individuals unconscious: rather, they distort consciousness. Therefore, degradation of the unimodal–transmodal gradient may be a more general feature of altered consciousness, rather than a marker of its loss.

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## Key figure

### Multi-scale decompositions of brain function and consciousness

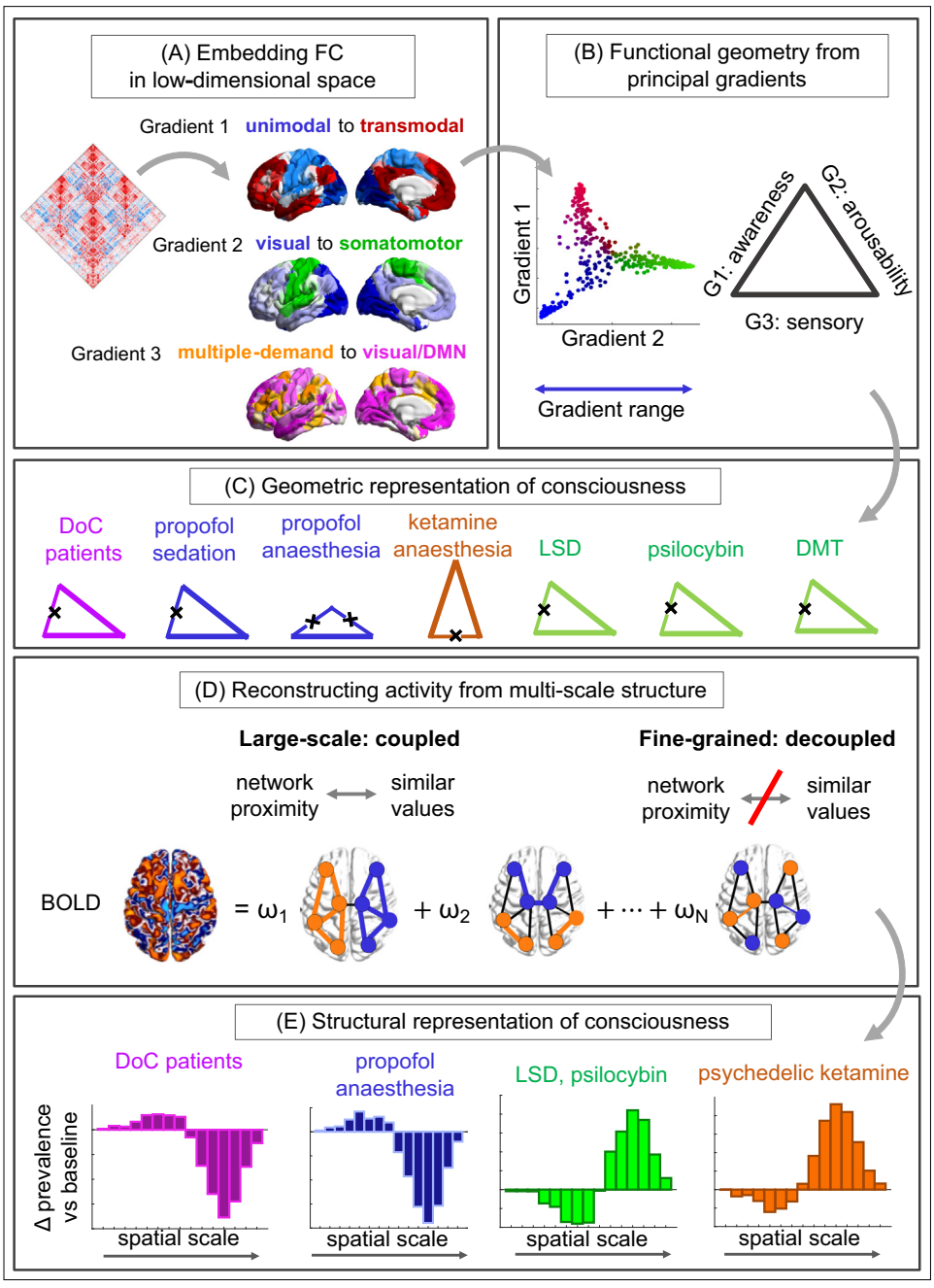



Figure 3. (A) Functional gradients provide a low-dimensional embedding of functional data [here, functional connectivity from blood oxygen level-dependent (BOLD) signals]. The first three gradients are shown and the anchoring points of each gradient are identified by different colours. (B) Representation of the first two gradients as a 2D scatterplot shows that anchoring points

*(Figure legend continued at the bottom of the next page.)*

### Structural eigenmodes: re-representing function in terms of structure

In addition to obtaining a low-dimensional representation of the functional data (i.e., decomposition as data compression), it is also possible to derive multi-scale distributed patterns from brain anatomy, using them to re-represent brain activity altogether: whether in terms of structural connectivity [49,62,83], spatial proximity [84], or cortical curvature and geometry [72,85–88], among others (Box 1). We refer to the bases of the re-representation as 'structural eigenmodes'. Decomposition of brain activity in terms of structural eigenmodes enables interrogating the contribution of global structural patterns at different spatial scales. Like functional gradients, structural eigenmodes are spatially overlapping whole-brain patterns, each providing resolution into a specific spatial scale (granularity): from entire hemispheres, to just a few millimetres [83].

Whereas the time-resolved approach reflects structure–function similarity at different points in time, structural eigenmodes allows investigating how structure constrains function across spatial scales, providing complementary insights: time-resolved and scale-resolved. Predominance of large-scale structural eigenmodes in the functional signal indicates that function is constrained by the underlying structure: elements that are similar to one another in terms of large-scale structure (highly interconnected on the connectome, or geometrically proximal) will tend to exhibit similar functional signals to one another (Figure 3D). Predominance of fine-grained patterns instead indicates that the spatial organisation of the functional signal is relatively unconstrained by the underlying structure [62] (Figure 3D).

Decomposing brain activity into the eigenmodes of a high-resolution structural connectome, 'connectome harmonic decomposition' (CHD), revealed that the psychedelics LSD, psilocybin, and sub-anaesthetic ketamine induce decoupling of function from network structure: they increase the contribution of fine-grained (high-frequency) eigenmodes, at the expense of large-scale (low-frequency) ones [16,89] (Figure 3E). The same CHD approach revealed that propofol- and brain injury-induced unconsciousness (distinct from mere unresponsiveness) manifest as the opposite pattern: increased contribution of large-scale structural eigenmodes, at the expense of high-frequency ones [16] (Figure 3E). Increased contribution of large-scale structural eigenmodes was also observed in DoC patients using individualised connectomes [49] and using EEG alpha-band and the eigenmodes of electrodes' Euclidean distances [84]. These results were recently extended to the macaque brain, with a shift towards greater contribution of large-scale structural eigenmodes being observed under anaesthesia with propofol, sevoflurane, and ketamine and reversed by centro-median thalamic stimulation that also induces recovery of behavioural arousal [80].

## Decomposing information: synergistic interactions

Another way of decomposing brain function is by considering the brain as an information processing system [2,90] and identifying the different types of information it relies on. In particular,

correspond to the two extremes of each gradient. Interpretation of gradients is adapted from [13]. (C) Perturbations of human consciousness can be mapped into this low-dimensional space, in terms of which gradients exhibit a restricted range (distance between its anchoring points) compared with baseline [13,81,82]. (D) Structural eigenmodes re-represent the signal from the space domain, to the domain of spatial scales. This is analogous to how the Fourier transform re-represents a signal from the temporal domain to the domain of temporal frequencies (Box 1). Large-scale structural eigenmodes indicate that the spatial organisation of the signal is closely aligned with the underlying organisation of the structural connectome. Nodes that are highly interconnected to one another exhibit similar functional signals to one another (indicated by colour). Fine-grained patterns indicate a divergence between the spatial organisation of the functional signal and underlying network structure: nodes may exhibit different functional signals even if they are closely connected. The relative prevalence of different structural eigenmodes indicates whether the signal is more or less structurally coupled. (E) Connectome harmonics (structural eigenmodes from the high-resolution human connectome) show that loss of consciousness and psychedelics have opposite mappings on the spectrum of eigenmode frequencies (adapted from [16,89]). Abbreviations: DMN, default mode network; DoC, disorders of consciousness; FC, functional connectivity.

recent accounts have revealed that (Shannon) information is not a monolithic entity: rather, several fundamentally distinct 'kinds' of information exist [2]. Two sources can possess information about a given target that is either unique (each source provides independent information), **redundant** (the same information is provided by both sources, such that all uncertainty is resolved upon observing any one of them) or **synergistic** (complementary information, which is available only when both sources are considered together) [91,92]. As an example, 3D vision emerges from combining inputs from the two eyes, such that closing either eye abolishes it: it requires cooperation between them [2].

Partial information decomposition and its extensions provide a formal framework that allows to distinguish these qualitatively different phenomena [91,92]. This general mathematical framework is not restricted to neuroscience and has found applications as diverse as genetic networks [93,94], sociocultural data [95], music [96], and financial markets [97]. In neuroscience, applications of information decomposition range from entire brains [92,98–100] to neuronal cultures [101,102]. Information decomposition complements approaches to conceptualise and quantify neural information in terms of encoding and decoding [103]. It can be used to track 'extrinsic' information: how external stimuli predict neural activity and how neural activity in turn predicts behaviour [90,104–109]. However, information decomposition can also be applied to task-free neural time-series (e.g., from fMRI, electrophysiology). In the brain, spontaneous activity is not random: the brain's future state is partly determined by its past state(s). This means that regions'/neurons' past state holds 'intrinsic' information about their future state: how much uncertainty about the regions' future activity is resolved by knowing the past of both (synergy) and how much is resolved equally by either of them (redundancy) [92,98–100]. This application is entirely

## Box 1. Eigenmodes in the brain

Functional gradients and structural eigenmodes rely on the mathematics of eigenmode decomposition [146]. Eigenmode decomposition is a mathematical approach underpinning multiple widely used techniques in neuroscience, including principal components analysis (PCA) and the **Fourier transform** (Figure I).

PCA provides an illustrative example. PCA re-represents high-dimensional data in terms of few principal components explaining most of the variance, identified by rotating the axes on which the data is represented. Functional gradients [78] and 'functional harmonics' [147] are analogous to PCA's principal components, but obtained via nonlinear eigendecomposition (such as diffusion map **embedding**) [148] whereas PCA is linear. Re-representing functional data in terms of patterns extracted from the same data also underlies the 'connectivity domain' approach [74], based on independent components analysis.

Structural eigenmodes are also obtained through nonlinear eigendecomposition (specific algorithms differ: see [148] for a review) but with one key difference: how their bases are built. In PCA and functional gradients, the new 'basis functions' (in the mathematical sense) to re-represent the data are extracted from the functional data themselves (e.g., BOLD signals) and the goal is data compression by highlighting the most relevant patterns. Conversely, structural eigenmodes re-represent brain function in terms of an independent basis function: the eigenmodes are obtained from structural connectivity [49,62,83], geometry [84,86,87], or cortical folding [72,85]. Similar eigenmodes can be extracted from different bases, even across species (Figure I).

The widely used Fourier transform is another application of eigenmode decomposition: the signal is re-represented from the time domain to the domain of temporal frequencies (Figure I). In this case the modes in question (termed harmonic modes) are sinusoids of different temporal frequency. High-frequency temporal harmonics correspond to fast-changing signals, such that data-points may have very different values even if they are close in time. Low-frequency temporal harmonics correspond to signals that vary slowly over time, such that temporally contiguous data-points have similar values.

Decomposition into temporal frequencies has a long history in the neuroscience of consciousness. Gamma-band oscillations were among the first proposed neural correlates of consciousness [149,150]. EEG oscillations are the gold-standard for sleep staging, and slow waves (1–4 Hz) increase in anaesthesia and disorders of consciousness [59,76,129–131], possibly providing a neural marker of brain dissociation from the environment, distinct from behavioural unresponsiveness [76,131]. However, the association is imperfect: conscious states can co-occur with slow waves (as in Angelman syndrome) and unconscious states [non-rapid eye movement (NREM) sleep] can occur without slow waves (as in dup15q syndrome) [151].

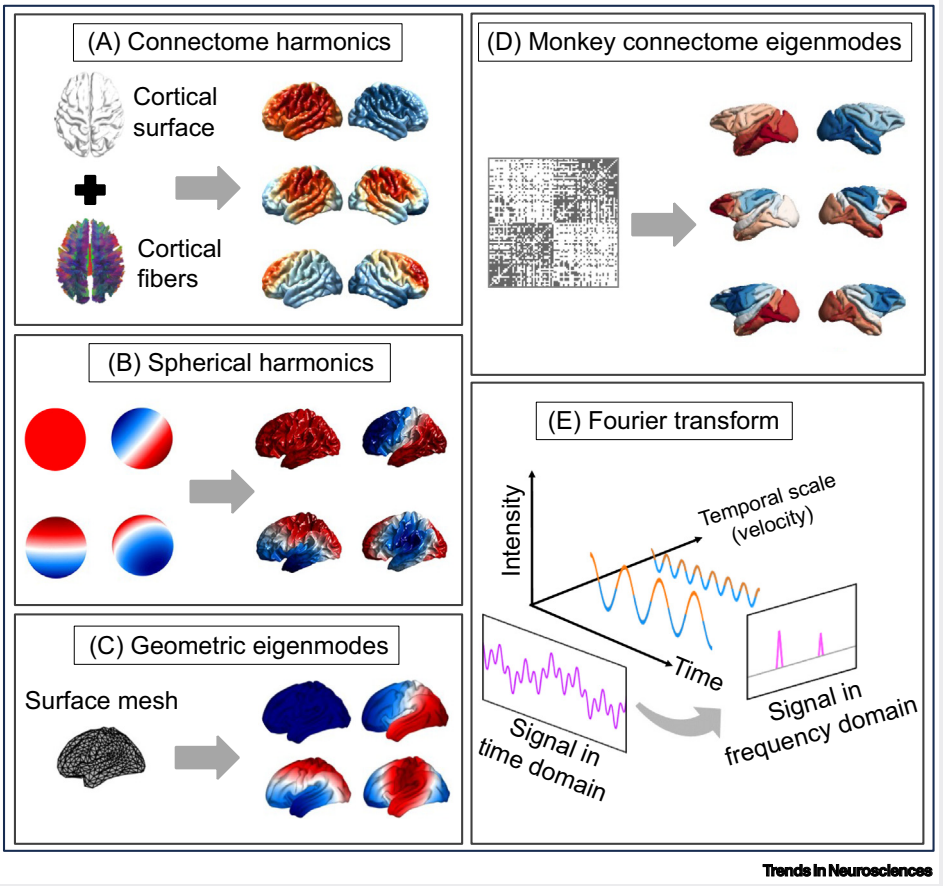



Figure I. Eigenmodes in the brain. (A) Connectome harmonics are obtained from high-resolution diffusion MRI tractography (adapted from [83]). (B) Spherical harmonics are obtained from the geometry of a sphere (adapted from [87]). (C) Geometric eigenmodes are obtained from the geometry of a high-resolution mesh of cortical folding (adapted from [72]). (D) A macaque analogue of connectome harmonics can be obtained at lower resolution from a macaque structural connectome that combines tract-tracing with diffusion MRI tractography (adapted from [80]), showing similarity with many human patterns. (E) Illustration of the Fourier transform as re-representation of the signal from the time domain to the domain of temporal frequencies (adapted from [16]).

analogous to the widely-used resting-state FC (temporal correlation between time-series), but with additional insight obtained by distinguishing different information dynamics. Specifically, one can distinguish between integration as 'combining information' (synergy) versus integration as 'having the same information' (redundancy) [2]. Although appealing for its conceptual simplicity, traditional FC can only reflect the similarity between different regions' temporal fluctuations and therefore it is unsuitable to distinguish between these fundamentally different phenomena, instead simply reflecting redundancy between regions [99,100,110]. Indeed, correlation is maximal when one element simply copies the other, corresponding to maximum redundancy, and no synergy. It is worth highlighting that Shannon's well-known definition is not the only way to operationalise information. Alternatives include extended definitions of entropy [111] and non-Shannon quantities developed in recent versions of the **integrated information** theory of consciousness (IIT) [112–116], which posit that 'information is a shape in concept space' [112] and propose an alternative, stronger formalisation of 'intrinsic' information [117,118]. Future work should explore the

empirical potential of these alternative operationalisations of information for neuroimaging analysis (see Outstanding questions).

### Insights about neural function from information decomposition

Information decomposition can be applied both to extrinsic and intrinsic (Shannon) information, as well as different species and imaging modalities. This key strength has led to several fruitful applications. fMRI studies of intrinsic dynamics have shown that although all brain regions engage in both synergistic and redundant interactions, their relative prevalence across regions is neither uniform nor random. Sensorimotor functions are supported by a modular backbone of structurally coupled redundant interactions, which dominate in primary cortices [99,100,110]. Redundancy provides robustness against single points of failure: information that is redundantly provided will not be lost, if any one source is disrupted. This may be especially warranted for the brain's input–output systems, given their pivotal role for enabling behaviour [2].

By contrast, synergistic interactions are structurally decoupled and predominate in higher-order association cortices, bridging across different brain modules to support higher cognitive functions [99,100,110]. Corroborating the role of synergy for integrative function, the prevalence of synergy correlates with both post-mortem and *in vivo* markers of synaptic density [100]. Synergistic (as opposed to redundant) interactions also appear to be specifically enhanced in humans over other primates [100], especially in evolutionarily expanded regions [100]. This is noteworthy because synergy enables the exploitation of additional information, beyond the sum of individual sources' contributions. Its increased prevalence in humans may therefore hint at a fundamental computational difference between species.

Despite its more recent inception, information decomposition has already begun to contribute to progress about consciousness and its neural substrate. On the theoretical front, information decomposition has illuminated similarities and differences between numerous proposed measures of IIT's 'integrated information' ($\Phi$), showing that despite all intending to capture 'the extent to which the whole is greater than the sum of its parts', in practice they each reflect different combinations of information dynamics. Decomposing different $\Phi$ measures represents major progress because it allows understanding and predicting their respective behaviours under different scenarios. For example, the original measure $\Phi^{WMS}$ from [119] can sometimes be negative and the alternative measure of integrated information termed 'causal density' [120] can exceed the mutual information between system's past and future [121]. These observations were initially used to dismiss $\Phi^{WMS}$ and causal density as suitable measures of integrated information [121]. Information decomposition explains why such 'counterintuitive' behaviours occur: causal density is inflated by double-counting synergistic dynamics, whereas $\Phi^{WMS}$ will be negative whenever a system is redundancy-dominated, because $\Phi^{WMS}$ involves subtracting the system's redundancy [92]. Once individual information dynamics have been disentangled, it becomes straightforward to propose 'revised' measures that exactly capture one's desired information dynamics [92].

The theoretical progress afforded by information decomposition translates directly into empirical progress. A revised measure of integrated information, $\Phi_R$ (which does not subtract the redundancy) revealed that synergy-based integration in human fMRI signals is consistently reduced between high-synergy brain regions when responsiveness is lost: both in DoC patients and in anaesthetised volunteers compared with both wakefulness and post-anaesthetic recovery [122]. Crucially, the similarity between anaesthesia and DoC was obscured when the original $\Phi^{WMS}$ was used, demonstrating how the conceptual clarity brought by information decomposition enables practical discovery [122]. Notably, the shared reductions of $\Phi_R$ all occurred in regions that satisfied an information-theoretic definition of the 'global workspace' from global neuronal workspace theory

of consciousness [122–124]. Thus, the authors proposed that pharmacological and pathological LOC could both be understood as a breakdown of the brain's 'synergistic global workspace' [100], pointing towards a potential convergence of two prominent theories of consciousness, when viewed through the lens of information decomposition [125–128]. More broadly, this work revealed that acute pharmacological intervention and lesion-induced connectome perturbations can have convergent effects on information dynamics in the human brain. Being a relatively recent development, the perspective of information decomposition is yet to be applied more widely to further states of altered consciousness, such as sleep or psychedelics: its extension could provide ample opportunities for further discovery.

## Catalysing integrative discovery by combining decompositions

Overall, the case study of consciousness shows that the different lenses offered by decomposition approaches can lead to tangible progress on complex neuroscientific questions. Information decomposition has revealed that 'integrated information' can arise from diverse information dynamics and, even without committing to specific theoretical accounts, the shared reduction in integrated information across DoC and anaesthesia validates the longstanding intuition that consciousness requires the coexistence of integration and differentiation [125–128]. Functional geometry has further proven capable of reflecting different aspects of subjective experience beyond mere responsiveness, not only across perturbations of consciousness but also in psychiatric conditions. Perhaps the most well-established discovery, provided by both temporal and eigenmode decompositions, is that increased structure–function coupling is a consistent neural marker of LOC, across species and across diverse pathological and pharmacological perturbations of consciousness. Conversely, reduced structure–function coupling seems to characterise the psychedelic experience in humans' brains, even when elicited by drugs with widely different molecular mechanisms. Taken together, these lines of research have revealed that brain structure–function coupling can track the presence (vs. absence) and diversity of subjective experience and is under bi-directional control by neuromodulation and thalamic activity.

Crucially, it is only when integrating multiple decompositions and multiple perturbations (different anaesthetics, DoC, different psychedelics) that the full picture emerges. Diverse ways of becoming unconscious appear to share common neural signatures; likewise, the psychedelic state can manifest similarly across different drugs. However, some of these signatures (functional geometry) may be shared across LOC and the psychedelic state, whereas others (structure–function coupling) are diametrically opposite between the two. Thus, decompositions along different dimensions provide a way to illuminate both similarities and differences between phenomena of interest. Rather than seeking to explain each phenomenon in isolation, different phenomena can be compared and contextualised against each other, adopting various decompositions to disentangle the dimensions along which they are alike and those that set them apart.

The different decompositions reviewed here are neither redundant nor antithetical with each other, nor with the more common approaches focusing on temporal frequencies [59,76,129–131] (Box 1). They also complement extensive evidence from spatial localisation approaches, implicating specific cortical and subcortical regions in supporting consciousness [15,21,25,46,58–60,75–77]. Recent developments are already combining information decomposition with time- and frequency-resolved approaches [99,132,133] (e.g., revealing that the effects of anaesthesia on synergy and redundancy in macaque electrocorticography are driven by δ and γ temporal frequency bands) [132]. Extending these efforts, by further combining, for example, temporal and eigenmode decompositions in the same dataset [134], or by applying them to further alterations of consciousness, such as dreaming [135], will provide a path towards a more comprehensive understanding of the different facets of brain function.

However, there is a need to understand the neurobiological origins and mechanistic roles of the phenomena that are being decomposed. The fact that decompositions can be applied across imaging modalities and across species with greater experimental accessibility than humans, offers a fruitful avenue of progress in this direction. A prominent example is the discovery, in macaques, that anaesthetic-induced structure–function coupling and collapse of the principal gradient are both reversed when consciousness is restored by centro-median thalamus stimulation [46,80]. Computational models may represent another promising avenue to develop a mechanistic account of how multiple aspects of neurobiology shape functional properties, dissociating them from each other in ways that are still beyond the capabilities of experimental research *in vivo* [136] (Figure 4). The ability to bridge scales and modalities is one of the key advantages of computational modelling [136] (Box 2).

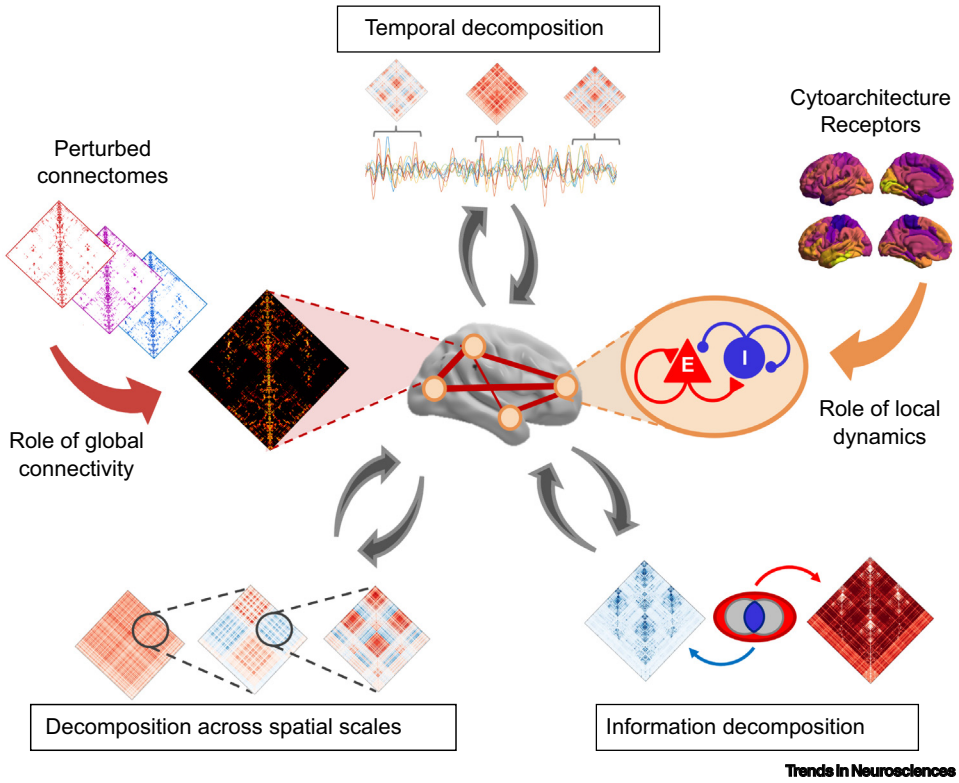



Figure 4. Computational modelling to integrate decompositions and obtain mechanistic insights. Computational models of brain activity come in a variety of forms, from highly detailed to abstract and from cellular-scale to brain regions [136]. Macroscale computational models of brain activity (sometimes also known as 'phenomenological' models) provide a prominent example of how computational modelling can be used to integrate different decompositions and explore the underlying causal mechanisms. Such models typically involve two essential ingredients: a mathematical account of the local dynamics of each region (here illustrated as coupled excitatory and inhibitory neuronal populations), and a wiring diagram of how regions are connected (here illustrated as a structural connectome from diffusion tractography). Each of these ingredients can be perturbed to simulate some intervention or to interrogate their respective contribution to the model's overall dynamics and fit to empirical data. For example, using patients' structural connectomes [139,140], or rewired connectomes [141]; or regional heterogeneity based on microarchitecture or receptor expression (e.g., from PET or transcriptomics) [139,142–144]. The effects on different decompositions can then be assessed to identify the mechanistic role of heterogeneity and connectivity. As an alternative to treating decomposition results as the dependent variable of the simulation, they can also be used as goodness-of-fit functions for the model, to improve models' ability to match the richness of real brain data. These two approaches establish a virtuous cycle between computational modelling and decompositions of brain function, whereby each can shed light and inform the other. Adapted in part from [145].

### Box 2. Computational modelling to integrate decompositions

Computational models ([136]; see Figure 4 in main text) have already provided insights about the potential mechanisms underlying various decompositions in relation to consciousness. At the macroscale, dynamic mean-field models of neuronal populations coupled according to DoC patients' structural connectomes exhibited reduced prevalence of synergistic interactions, recapitulating the reduction observed in empirical fMRI recordings from the same patients and suggesting potential connectomics origins for this information decomposition signature [145]. A Wilson-Cowan model of excitatory and inhibitory populations showed that increasing neuronal excitation induces a shift towards fine-grained eigenmodes [152], reflecting empirical results with psychedelics [16,89]. Shifting the excitation–inhibition balance towards inhibition instead increases the contribution of large-scale structural eigenmodes, consistent with the empirical effects of propofol [16].

Some **macroscale computational models** can be enriched with biological information pertaining to molecular- and cellular-level properties, such as gene [144,153] or receptor expression [139,154], thereby 'linking cellular mechanisms and large-scale dynamics' [136]. Propofol's effects on dynamic FC can be recapitulated by modulating regional inhibition in a mean-field model according to empirical GABA-A receptor distribution [139]; likewise for LSD-induced dynamics and 5-HT2A receptors [154].

Models can also incorporate cellular-scale detail. One such model, comprising dual-compartment layer V pyramidal neurons, recently showed that a measure of integrated information ($\Phi^*$) [113] can be tuned by the thalamic inputs that control coupling between apical and basal cellular compartments [155]. This work provides a potential bridge between the cellular-level empirical observation that anaesthetics decouple apical and basal compartments [156] and the macroscale observation that $\Phi^*$ is diminished by anaesthesia in macaque electrophysiological recordings [60], consistent with dendritic integration theory [157]. Future extensions with information decomposition may explore which specific information dynamics drive the loss of integrated information.

Different decompositions also afford the opportunity to develop computational models that more faithfully capture the richness of brain activity. Enriching models with regional heterogeneity according to functional gradients (from eigenmode decomposition) has provided superior fit to empirical data [144,158]. The measure of goodness-of-fit itself can be refined to account for dynamic connectivity (from temporal decomposition), improving the model's ability to simulate different conditions [159].

Ultimately, modelling necessitates simplifying the true neurobiological complexity, which may be an especially relevant limitation for consciousness [160].

### Outstanding questions

What causal mechanisms control the distinct dimensions of the brain's functional architecture and to what extent are they shared versus distinct across decompositions?

Which of these mechanisms and decompositions are most suitable as targets for therapeutic intervention?

Are some kinds of information preferentially carried by different temporal frequencies, specific temporal states, or at specific spatial scales?

What are the common signatures of altered states (psychedelics, dreaming, psychosis), as revealed by distinct decomposition approaches?

Can information decomposition be extended to the latest developments of integrated information theory?

Which dimensions of the brain's functional architecture are shared across species and which (if any) are uniquely human?

## Concluding remarks

The decomposition approaches that we outlined here are not restricted to a specific scale of investigation, neuroimaging modality, or species. Using the same decomposition and imaging modality across different species provides a 'common currency' to catalyse translational discovery [137], especially in combination with perturbations such as anaesthesia, the effects of which are widely conserved across species [128,138].

Through the running example of consciousness, we illustrated the value of combining the unique perspectives provided by each decomposition. A first key insight is that numerous consistencies exist across pathological and pharmacological ways of losing consciousness. This is observed across each decomposition, with evidence of similar trends across species, offering the promise of translational potential. Secondly, across each decomposition, LOC may preferentially target those aspects of brain function that are most decoupled from brain structure. Synergy, which is structurally decoupled and especially prevalent in structurally decoupled regions, is consistently targeted by pathological and pharmacological LOC, just as structurally decoupled temporal states and structurally decoupled spatial eigenmodes are also consistently suppressed. Thus, different decompositions have provided convergent evidence that consciousness relies on the brain's ability to explore functional patterns beyond the mere dictates of anatomy: across spatial scales, over time, and in terms of how they interact to convey information.

Altogether, the choice of lens through which to view the brain's complexity plays a fundamental role in how neuroscientists understand brain function and its alterations. Although many open questions remain (see Outstanding questions), integrating these different perspectives may provide essential impetus for the next level in the neuroscientific understanding of brain function.

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## Declaration of interests

The authors have no competing interests to declare.

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