The physics of brain network structure, function and control

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Abstract | The brain is characterized by heterogeneous patterns of structural connections supporting unparalleled feats of cognition and a wide range of behaviours. New non-invasive imaging techniques now allow comprehensive mapping of these patterns. However, a fundamental challenge remains to understand how the brain's structural wiring supports cognitive processes, with major implications for personalized mental health treatments. Here, we review recent efforts to meet this challenge, drawing on physics intuitions, models and theories, spanning the domains of statistical mechanics, information theory, dynamical systems and control. We first describe the organizing principles of brain network architecture instantiated in structural wiring under constraints of spatial embedding and energy minimization. We then survey models of brain network function that stipulate how neural activity propagates along structural connections. Finally, we discuss perturbative experiments and models for brain network control; these use the physics of signal transmission along structural connections to infer intrinsic control processes that support goal-directed behaviour and to inform stimulation-based therapies for neurological and psychiatric disease. Throughout, we highlight open questions that invite the creative efforts of pioneering physicists.

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https://doi.org/10.1038/s42254-019-0040-8

The term neurophysics, coined in the 1970s[1], reflects the fact that in the contemporary study of the brain, nearly all domains of physics are not only relevant but also essential. The fundamentals of electricity and magnetism are critical for building theoretical models of neurons and the transmission of action potentials[2]. These theories are increasingly informed by mechanics to understand how force-generating and load-bearing proteins bend, curl, kink, buckle, constrict and stretch to mediate neuronal signalling and plasticity[3]. Thermodynamic principles come into play when predicting how the brain samples the environment (action) or shifts the distribution of information that it encodes (perception)[4]. Collectively, theories of brain function are either buttressed or dismantled by imaging. Common tools include magnetic resonance imaging (MRI)[5] and magnetoencephalography (MEG)[6]. The latter uses superconducting quantum interference devices (SQUIDs) and next-generation quantum sensors that can be embedded into wearable systems to measure brain function while allowing free and natural movement[7]. Meanwhile, the recent development of tools for nanoscale analysis and the corresponding design and synthesis of nanomaterials have generated optical, electrical and chemical methods that enable the simultaneous measurement and manipulation of the activity of thousands or even millions of neurons[8]. Additionally, beyond its relevance for continued imaging advancements[9], optics has come to the fore of neuroscience over the past decade with the development of optogenetics, which uses light to alter neural processing at the level of single spikes and synaptic events, offering reliable millisecond-timescale control of excitatory and inhibitory synaptic transmission[10].

By applying these tools at the intersection of physics and neuroscience, physicists have generated important insights concerning the inner workings of the brain and its component parts (for more on the history of neurophysics, see Supplementary Information section 1). At the same time, it has become clear that it is not only the behaviour of the brain's individual components but also the interactions between tens of brain regions or between hundreds or thousands of neurons in concert that generate the mind's functional states[8]. Indeed, from neural interactions emerge computation[11], communication[12] and information propagation[13]. The overarching goal of mapping these interactions in neural systems has motivated multibillion-dollar investments across the United States (the Brain Initiative generally and the Human Connectome Project specifically[14]), the European Union (the Blue Brain Project[15]), China (the China Brain Project[16]) and Japan (Japan's Brain/MINDS project[17]).

Although it is clear that interactions are paramount, exactly how the functions of the mind arise from them

Key points

- From the first measurement of the nerve impulse by Hermann von Helmholtz in 1849 to the cutting-edge superconducting devices used in magnetoencephalography, physics and neuroscience have always been inextricably linked.
- Today, network neuroscience — the study of the brain as a complex web of interacting components — draws intuitions and techniques from nearly every branch of physics.
- The architecture of structural connections between neurons or brain regions is constrained by requirements of energy minimization and efficient information transfer.
- The materialization of long-range correlations and synchronization from the collective firing of individual neurons conjures notions of emergence and criticality from statistical mechanics.
- Together, these investigations of brain network structure and function guide targeted treatments for cognitive disorders using theories of network control.
- Now more than ever, understanding the complexities of the mind lies at the feet of curious and pioneering physicists.

remains one of the fundamental open questions of neuroscience[18]. To physicists, such a notion of function arising from many interacting elements exists naturally within the purview of statistical mechanics[19] with one major caveat: the interaction patterns observed in the brain are far from regular, unlike those of crystalline structures, and are also far from random, unlike those of fully disordered systems[20]. Indeed, the heterogeneity of interaction patterns in neural systems — across a range of spatial and temporal scales — limits the utility of continuum models or mean-field theories, which would otherwise comprise natural first approaches. Fortunately, similarly heterogeneous interactions have been observed in other technological, social and biological systems, leading to the development of the statistical mechanics of complex networks[21]. The resultant area of inquiry includes criteria for building network models of complex systems[22], statistics to quantify the architecture of those networks[23], models to stipulate the dynamics that can occur both in and on networks[24–26] and theories of network function and control[27,28].

Here, we provide a brief survey for curious physicists. Our Review spans the network-based approaches, statistics, models and theories that are used to understand the brain. The interpretations that can be rationally drawn from such efforts depend upon the nature of the network representation[22], including its descriptive, explanatory and predictive validity — topics that are treated with some philosophical rigour elsewhere[29]. We discuss the physics of brain network structure, beginning with an exposition on measurement before turning to modelling. We then discuss the physics of brain network function, followed by a description of perturbation experiments and brain network control. Our goal is to provide an accessible introduction to the field and to inspire physicists to courageously tackle some of the most pressing questions surrounding the inner workings of the mind.

The physics of brain network structure

We begin with a discussion of the architecture, or structural wiring, of networks in the brain, focusing on the measurement and modelling of their key organizational features (see Supplementary Information section 2 for a primer on networks). Edges in structural brain networks represent physical connections between two elements. For example, synapses support the propagation of information between neurons[30], and white matter tracts define physical pathways of communication between brain regions[31]. In physics, it has long been recognized that the organization of such structural connections can determine the qualitative large-scale features of a system[21]. For example, the Ising model on a 1D lattice remains paramagnetic across all temperatures[32], whereas in two dimensions or more, the system spontaneously breaks symmetry, yielding the type of bulk magnetization exhibited by magnets on a refrigerator door[33,34]. Similarly, the organization of structural wiring in the brain largely determines the types of mental processes and cognitive functions that can be supported[35–39], including memory[40–42], learning[43,44], vision[45] and motor control[46]. Importantly, the wiring of the brain is highly heterogeneous, which presents a unique set of challenges. Below, we review some powerful experimental and theoretical tools that allow us to distil the brain's structural complexity to a number of fundamental organizing principles.

Measuring brain network structure

Network neuroscience — an approach to understand the brain by recording, analysing and modelling the interactions between its component parts — is founded upon the idea that the brain comprises a complex web of distinct neural elements[47]. At the neuronal level, this notion, known as the neuron doctrine, arose in the 19th century and was bolstered in the 1930s by the development of electron microscopy, which provided detailed measurements of the physical connections between neurons. Perhaps the most impressive application of electron microscopy remains the complete mapping of connections between the 302 neurons in the nematode *Caenorhabditis elegans*[48]. Since this achievement, scientists have generated even more intricate reconstructions of synaptic connectivity in other animals, from a mapping of the optic medulla in the visual system of the fruitfly *Drosophila* to the enumeration of connections between 950 distinct neurons in the mouse retina[45,49]. These efforts push towards the ultimate goal of reconstructing the neuronal wiring diagram of an entire human brain[50].

Concurrently with these achievements using electron microscopy, complementary advances in non-invasive imaging have allowed unprecedented views of mesoscale brain structure in vivo. Introduced in the 1970s, computerized axial tomography (CAT) provided among the most detailed anatomic images of the human brain to date, with resolution down to the 0.1 mm scale[51]. MRI, which concedes a coarser spatial resolution of 1 mm but delivers a superior temporal resolution of approximately 20 ms, was developed soon after CAT. MRI sparked an explosion of refinements, a notable example being diffusion tensor imaging (DTI)[52]. Whereas standard CAT and MRI techniques capture cross-sectional images of the brain, DTI traces the diffusion of water molecules through white matter tracts to reconstruct the large-scale neural pathways connecting distinct brain

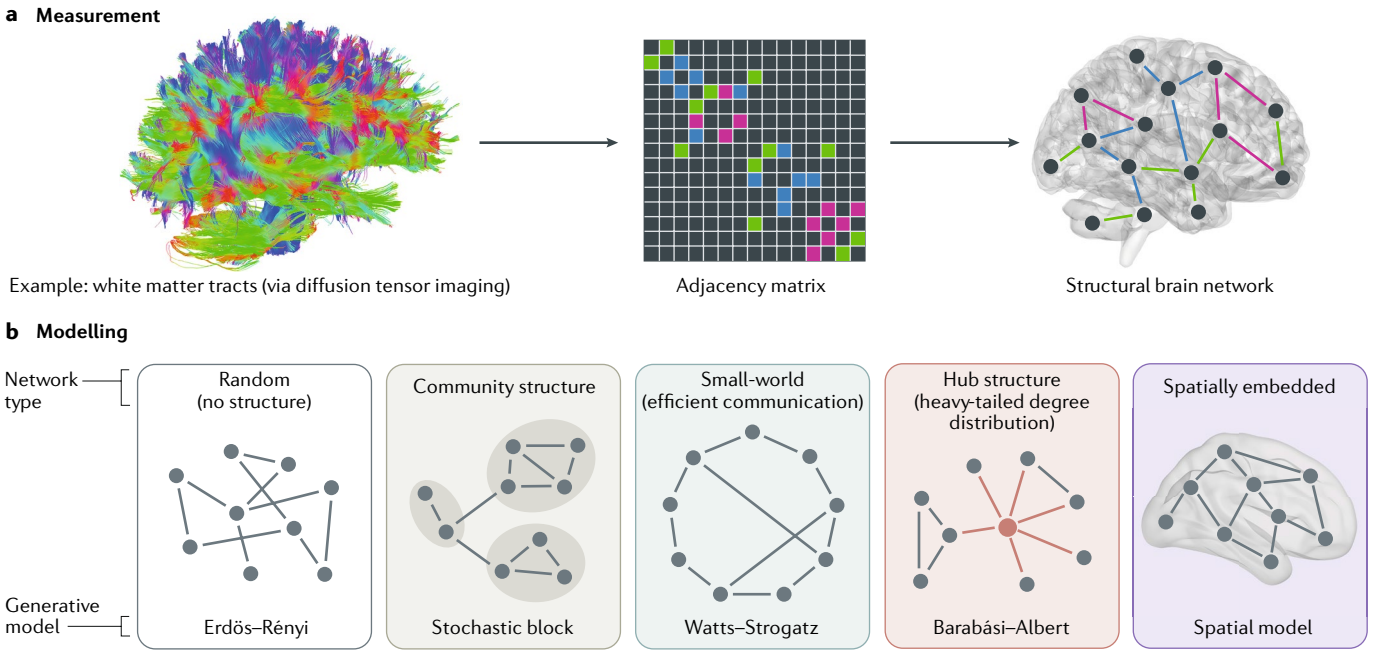


Fig. 1 | **Measuring and modelling brain network structure. a** | The measurement of brain network structure begins with data specifying the physical connections between neurons or brain regions, such as white matter tracts measured via diffusion tensor imaging (left panel). The data are discretized into non-overlapping grey matter volumes representing distinct nodes. From this discretization, an adjacency matrix A is constructed, where A_{ij} encodes the connection strength between nodes i and j (centre panel; colours represent connection strengths). This adjacency matrix, in turn, defines a structural brain network (right panel) constructed from the original measurements of physical connectivity. **b** | Architectural features of structural brain networks can be captured using generative network models. The simplest such model is the Erdös–Rényi model, which has entirely random structure. Networks with modular structure, divided into communities with dense connectivity, are constructed using the stochastic block model. Small-world networks, which balance efficient communication and high clustering, are generated using the Watts–Strogatz model. Networks with hub structure, characterized by a heavy-tailed degree distribution, are typically constructed using a preferential attachment model such as the Barabási–Albert model. Spatially embedded networks, with connectivity constrained to exist within a physical volume, are generated through the use of spatial network models.

regions[53,54]. Such tract tracing techniques have been used to uncover the interregional connectivity within human[54], macaque[55,56], cat[57], mouse[58] and fly[59] brains. Given measurements of the anatomical wires connecting a set of neural elements, be they synapses linking neurons or white matter tracts connecting brain regions, one can construct a structural brain network by placing edges between elements that share a physical connection (FIG. 1a). Ongoing experimental efforts to acquire these measurements provide rich network data sets detailing the brain's structural organization.

Modelling brain network structure

A first glance at the brain's wiring reveals that it is far from homogeneous — this is not surprising considering the array of physical, energetic and cognitive constraints that the brain is required to balance[60]. To handle this heterogeneity, researchers have increasingly turned to network science for mathematical tools and intuitions[61,62] and to distil the explosion of experimental data down to a number of cogent organizing principles. Here, we review some important properties that are thought to characterize structural brain networks, and introduce several generative network models that help explain how these properties arise from biological mechanisms (FIG. 1b).

Random structure. Although healthy members of a species exhibit anatomical similarities in brain structure, the instantiation of physical connections in each individual is far from deterministic. Indeed, in humans, in vivo imaging techniques such as DTI have revealed stark differences in brain structure not only between individuals[63] but also within the same individual over time[64,65]. Importantly, these structural differences have been linked to variability in a wide range of traits[66], including empathy[67], introspection[68], fear acquisition[69] and even political orientation[70].

To study the mathematical properties of random networks and to understand the types of biological mechanisms that give rise to qualitative structural properties, it is useful to consider generative network models[61]. The simplest and most common model for generating random networks is the Erdös–Rényi model[71], in which each pair of nodes is connected independently with fixed probability P. Although the Erdös–Rényi model has interesting mathematical properties, such as a binomial degree distribution, it has no discernible structure and does not reflect the mechanisms by which networks grow in the brain. Accordingly, to understand some of the principles underlying naturally occurring brain networks, it is necessary to consider generative models that yield networks with realistic properties.

Community structure. A well-studied structural property of the brain is its division into distinct anatomical regions, which are widely thought to be responsible for specialized cognitive functions[72]. Interestingly, the large-scale structures of brain networks in several mammalian species have connections organized such that they naturally partition into densely connected communities separated by sparse inter-community connectivity[73–76]. Moreover, these clusters of high connectivity closely resemble postulated anatomical subdivisions[74]. It has therefore been argued that the so-called community structure of brain networks segregates the brain into subnetworks with specific cognitive functions[77–81]. Practically speaking, extracting the community structure of a real-world network requires algorithms for community detection — techniques that are now applied throughout network neuroscience[82,83]. From a complementary perspective, networks with a predefined community structure can be generated using the stochastic block model, in which nodes are assigned to distinct communities and an edge is placed between each pair of nodes with a probability that depends on the nodes' community assignments[84,85]. Such stochastic block networks are often used as null models to distinguish between properties of brain networks that are implied simply by their community structure and those that require additional biological mechanisms[61,85].

Small-world structure. Seemingly in contradiction to their striking community structure, large-scale brain networks exhibit average path lengths between all pairs of nodes that are much shorter than those of a typical random network[60,86,87]. This competition between high clustering and short average path length is thought to facilitate the simultaneous segregation and integration of information in the brain[88], possibly minimizing the total number of computational steps needed to process external stimuli[89,90]. 'Small-world' topology, in which clustering is high and average path length is low, is exhibited by other real-world systems, most notably social networks[91]. The Watts–Strogatz model[92] captures this behaviour by supposing that small-world networks are an interpolation between two extreme configurations: a ring lattice, in which nodes are arranged along a circle and connected to their k nearest neighbours on either side, and an Erdös–Rényi random network. Consequently, the presence of small-world structure in the brain suggests that efficient communication emerges from a finely tuned balance of lattice-like organization and structural disorder.

Hub structure. In addition to their modular and small-world structure, many large-scale brain networks also feature high-degree 'hubs', which form a densely interconnected structural core[93]. Acting as bridges between distinct communities, these specialized hub regions are thought to help minimize overall path lengths across the network[75] and facilitate the integration of information[88]. Supporting the notion of a centralized core, many studies have identified hubs within the parietal and prefrontal regions, areas that are often active during a wide range of cognitive functions[93,94]. Such core–periphery architecture is characterized by a heavy-tailed degree distribution, such as that observed in scale-free networks, in some cases arising through preferential attachment mechanisms[95]. In the Barabási–Albert model[96], for instance, nodes are added to a network sequentially, and each new node i forms an edge with each existing node j with a probability proportional to the degree of j. Thus, new nodes preferentially attach to existing nodes of high degree, creating a 'rich club' of centralized hubs that bridge otherwise distant regions of the network.

Spatial structure. Thus far, we have focused on the topological properties of brain networks. However, brain networks are also physically constrained to exist within a tight 3D volume, and their structural connections are metabolically driven to minimize total wiring distance[60,77,90]. Such physical and metabolic constraints are captured by spatial (or geometric) network models that embed networks into 3D Euclidean space and penalize the formation of long-distance connections[61]. The simplest such model assumes that the probability of two nodes i and j forming an edge is proportional to $d_{ij}^{-\alpha}$, where d_{ij} is the physical distance between node i and node j and $\alpha \geq 0$ tunes the metabolic cost associated with constructing connections of a given length[97]. If the number of nodes and edges is fixed, then, much like the Watts–Strogatz model, this spatial model interpolates between a lattice-like structure, in which nodes connect only to their nearest neighbours ($\alpha \to \infty$), and an Erdös–Rényi random network ($\alpha = 0$).

Competition between structural properties. Although the modular, small-world, heavy-tailed and inherently physical properties of brain networks provide simple organizing principles, the overall structure of the brain is determined by a continuous and dynamical weighting of these principles against one another. Accordingly, an accurate generative model should explain multiple real-world properties simultaneously[61]. With this goal in mind, recent work has shown that an impressive range of brain network properties can be understood as arising from competition between two competing factors: a metabolic penalty for the formation of long-distance connections and a topological incentive to connect regions with similar inputs[98]. Indeed, in human, *C. elegans* and mouse brains, the total wiring distance is consistently greater than minimal, supporting the notion that brain networks weigh the costs of long-distance connections against the functional benefits of an integrated network topology[77,99]. Together, these efforts towards a comprehensive generative model are vital for both understanding healthy brain network structure and informing the diagnosis, prognosis, prevention and treatment of mental health disorders[100,101].

The future of brain network structure

As experimental measurements of structural connections in the brain become increasingly detailed, an important research direction is the bridging of brain network structures at different spatiotemporal scales[102–104]. Such cross-scale approaches could link protein interaction networks within neurons to the wiring of synaptic connectivity between neurons, to mesoscale networks

connecting brain regions, all the way to social networks linking distinct organisms (Supplementary Information section 3). The goal of such cross-scale integration is to understand how the architecture of connectivity at each of these scales emerges from the scale below. Practically, researchers have begun to address this goal by employing hierarchical network models[105], which treat each node at a given scale as an entire subnetwork at the scale below[106].

Perhaps the most ambitious goal is the reconstruction of the entire human connectome — a comprehensive map of connections in the brain — at the scale of individual neurons, a goal that pushes the current boundaries of 3D electron microscopy and statistical image reconstruction[50]. Extensive mapping efforts in other species have revealed notable and quantifiable neuronal diversity[107,108], suggesting the importance of extending network models to include non-identical units. At the mesoscale, advances in non-invasive imaging now make it possible to track changes in structural connectivity over time[109–112]. Analysis of these temporally ordered measurements requires the extension of graph theoretic tools to study networks with evolving connections[83]. Notably, these so-called temporal networks[113] were recently shown to be easier to control, requiring less energy to attain a desired pattern of neural activity, than their static counterparts[114].

In addition, properly modelling the dynamics of brain networks requires understanding the dynamics of the neurons and brain regions that exist on brain networks. For example, Donald Hebb posited in 1949 that the strength of a synaptic connection increases with the persistent synchronized firing of its presynaptic and postsynaptic neurons[115]. Such Hebbian plasticity has been observed in vitro[116] and is thought to explain many aspects of brain network structure[117,118]. More generally, Hebb's postulate highlights the fact that a complete understanding of the brain cannot simply include a description of its structural wiring; it must also stipulate the types of dynamics supported by this physical circuitry.

The physics of brain network function

Structural brain networks represent the physical wiring between neural elements, but knowledge of this circuitry alone is not sufficient to understand how the brain works. For this reason, we turn our attention to models of brain network function that stipulate how neural activity propagates along structural connections. Just as the brain's structure is a network of distinct nerve cells, the brain's cognitive functions arise from the collective activity of individual neurons[8,12,18,119,120]. To understand how neural elements combine to generate the brain's rich repertoire of cognitive functions[121], analogies are often drawn with notions of emergence in statistical mechanics[18,119,122]. Indeed, growing evidence suggests that the dynamics of individual neurons and brain regions, when embedded in networks of structural connections, can produce the types of long-range correlations and collective patterns of activity that are observed in the brain[119,123–128]. Here, we traverse what is known about brain network function in relatively broad strokes, from the firing of distinct neurons to the networked activity of the entire brain.

Measuring brain network function

A rich menu of experimental techniques exists for measuring brain dynamics across length scales. At the neuronal level, invasive methods in animals — such as electrophysiological recordings of brain slice preparations in vitro[129,130] and calcium imaging of neuronal activity in vivo[131,132] — have provided a detailed understanding of synaptic communication. At the regional level, complementary minimally invasive imaging techniques have identified fundamental properties of information processing in humans[133]. These advances in mesoscale functional imaging can largely be traced to the efforts of physicists. MEG methods, for example, use SQUIDs to directly measure the magnetic fields generated by electrical currents in the brain[7,134]; positron emission tomography (PET) measures the positron emission of radioisotopes, produced in cyclotrons, to reconstruct the metabolic activity of neural tissue[135]. Over the past 20 years, measurements of brain dynamics have been increasingly dominated by functional MRI (fMRI)[136], which estimates neural activity by calculating contrasts in blood oxygen levels without relying on the invasive injections and radiation that limit the applicability of other imaging techniques[137]. This progress in functional brain imaging has galvanized the field of network neuroscience by making detailed data sets of large-scale neural activity widely accessible.

One particularly important application of functional brain imaging has been the study of so-called functional brain networks[138], which have allowed researchers to investigate the organization of neural activity using tools from network science. In functional brain networks, as in their structural counterparts, nodes represent physical neural elements, ranging in size from individual neurons to distinct brain regions[139]. However, whereas structural brain networks define the connectivity between elements on the basis of physical measures of neural wiring, functional brain networks define connectivity on the basis of the similarity between two elements' dynamics[139].

Consider the common example of a large-scale functional brain network calculated from fMRI measurements of regional activity[138] (FIG. 2a). First, blood oxygen levels indirectly reflecting neural activity are measured within 3D non-overlapping voxels. Spatially contiguous collections of voxels each represent a distinct brain region. After preprocessing the signal to correct for sources of systematic noise such as fluctuations in heart rate, the activity of each brain region is discretized in time, yielding a time series of neural activity that can be encoded as a vector. Finally, functional connectivity is quantified by the similarity between each pair of brain regions, for example, using the Pearson correlation between the two regions' activity time series[123,140]. The end result, even for different types of functional data and different choices for the preprocessing steps and similarity metric, is a functional brain network representing the organization of neural activity.

The organizing principles of functional brain networks can be elucidated using techniques from network science. Such efforts have demonstrated that large-scale functional brain networks, much like structural networks, exhibit signs of modular, small-world,

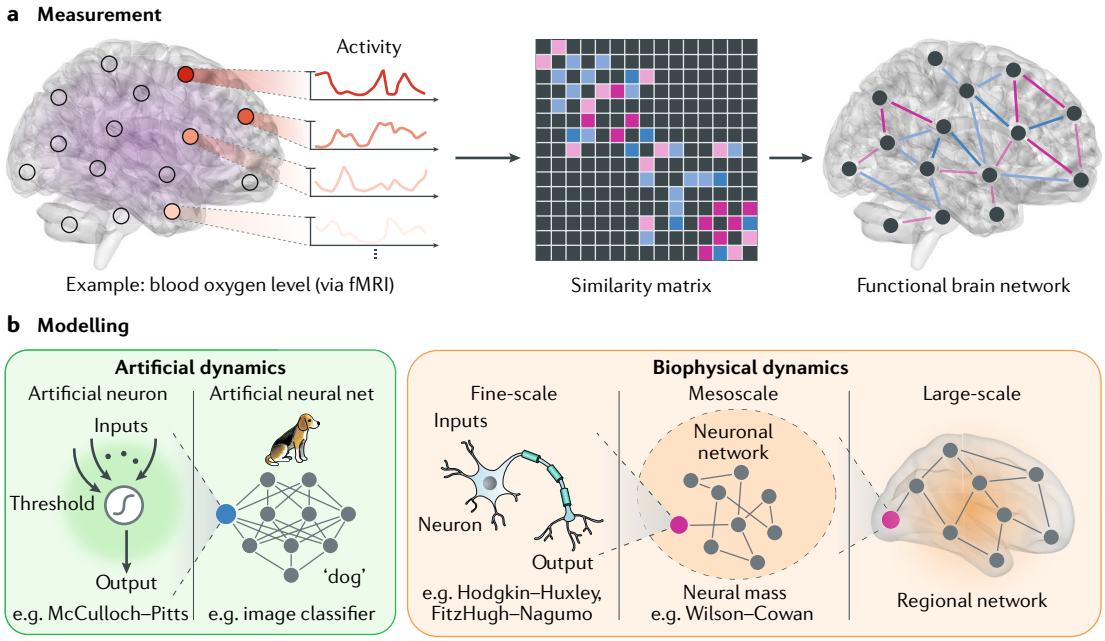


Fig. 2 | **Measuring and modelling brain network function. a** | The measurement of brain network function begins with experimental data specifying the activity of neurons or brain regions, such as variations in blood oxygen level in different parts of the brain measured using functional magnetic resonance imaging (fMRI) (left panel). The similarities between pairs of activity time series (described by measures such as correlation or synchronization) are encoded in a similarity matrix (centre panel; colours represent similarity values). This matrix, in turn, defines a functional brain network constructed from our original measurements of neural activity (right panel). **b** | Models of artificial neurons (left panel) take in a weighted combination of inputs, which they pass through a nonlinear threshold function to generate an output. Networks of artificial neurons, from deep neural networks to Hopfield networks, can reproduce key aspects of human information processing, such as learning from examples and storing memories. By contrast, biophysical models (right panel) of individual neurons capture realistic functional features such as the propagation of the nerve impulse. When interconnected with artificial synapses, these models can simulate entire neuronal networks. Complementary mesoscale approaches, including neural mass models, average over a population of neurons to derive a mean firing rate. To simulate the large-scale activity of an entire brain, neural mass models representing brain regions are embedded into a network with connectivity derived from measurements of neural tracts, such as those calculated using diffusion tensor imaging (FIG. 1a).

heavy-tailed and metabolically constrained organization[138,141–144]. The existence of strong functional community structure, for example, further supports the hypothesis that brain networks segregate into subnetworks with specialized cognitive functions[145,146]. Moreover, the presence of high clustering and short average path length, combined with the existence of high-degree hub regions, highlights the competing functional pressures of information segregation and integration in the brain[143,147]. Metabolic constraints on the brain's structural wiring are also evident in its functional connectivity[148], with spatially localized brain regions generally supporting more strongly correlated activity than distant regions[60].

In light of the similarities between the brain's functional and structural organization, it is tempting to suspect that functional brain networks closely resemble the physical wiring upon which they exist[149,150]. However, understanding how a functional brain network arises from its underlying structural connectivity remains a subject of intense academic focus[151], with two approaches providing complementary insights. The first approach takes as inputs a measurement of structural connectivity and a model of neural dynamics and seeks to predict the resulting functional connectivity between units, which can be compared with observations[29,62,104,152–154]. Conversely, a second approach requires measurements of neural dynamics and seeks to infer the underlying structural connectivity, as is common, for example, in the inference of maximum entropy models[126,155]. In what follows, it will become clear that the mapping from brain structure to brain function is highly nonlinear[156], requiring intuitions and techniques from disparate branches of physics.

Modelling brain network function

To understand how the physical connections in the brain give rise to its functional properties, statistical mechanical intuition dictates that the starting point should be a study of the dynamics of individual elements. Given accurate models of the interactions between individual neurons or the communication between brain regions, these neural elements can be linked together in a network to predict macroscopic features of the brain's function from its underlying structure[29,62]. Interestingly, the history of modelling in neuroscience has followed precisely this path, beginning with models of neuronal dynamics[11,157,158], then increasing in scale to mean-field

neural mass models of brain regions[159,160] and eventually achieving models of entire networks of neurons or brain regions[126,161,162]. We review important developments in the modelling of neural dynamics, dividing the modelling techniques into two distinct classes (FIG. 2b): those with artificial dynamics and those with biophysically realistic dynamics. Models from each of these two classes are able to reproduce important aspects of neural activity and system function that have been observed in physiological and behavioural experiments.

Artificial models. One of the earliest mathematical models of neural activity is the McCulloch–Pitts neuron, proposed in the mid-1940s to describe the logical functioning of an individual nerve cell[11]. The model accepts binary inputs, combines them using linear weights and produces a binary output reflecting whether or not the weighted sum of inputs exceeds a given threshold (FIG. 2b). Albeit a simple caricature of neuronal dynamics, this model has been shown to reproduce important qualitative features of neuronal activity, including the linear summation of excitatory inputs[163] and the binary 'all-or-none' response indicating whether the integrated signal exceeds the neuron's threshold potential[164]. Moreover, models that connect the inputs and outputs of multiple McCulloch–Pitts neurons have provided deep insights about how brain networks perform basic cognitive functions. For example, soon after the introduction of the McCulloch–Pitts model, it was demonstrated that networks of artificial neurons could be used to represent any Boolean function (that is, any function mapping a list of binary variables to a binary output), thereby establishing the capability of neural networks to perform logical computations[1].

Whereas their ability to perform basic computations was quickly realized, it was not clear at the outset whether artificial neural networks could reproduce other cognitive functions, such as learning or storing memories. The ability to learn was first demonstrated in the 1950s when it was recognized that the weights on the inputs to a McCulloch–Pitts neuron could be tuned such that the output defines a binary classifier. Known as the perceptron, this algorithm enabled a single McCulloch–Pitts neuron to segregate incoming data into one of two classes by learning from past examples. This remarkable result directly inspired more advanced learning algorithms, including support vector machines[165] and artificial neural networks[166], effectively setting in motion the study of machine learning. Today, deep neural networks, consisting of multiple layers of artificial neurons feeding in one direction from the input layer to the output layer (FIG. 2b), are able to mimic a range of impressive cognitive functions performed by the brain[167]. The expanding list of applications includes processing and identifying images of objects, scenes and people[168]; recognizing, interpreting and responding to spoken language[169]; and formulating strategies and making decisions in adversarial settings[170].

Neural networks can also store and recall memories. It was shown in the 1980s that the synaptic weights connecting a set of McCulloch–Pitts neurons can be adjusted in a Hebbian fashion such that the resulting 'Hopfield network' is able to 'memorize' a number of desired activity states[161] (that is, configurations of the network in which each neuron is either active or inactive). The number of memorized states grows linearly with the number of neurons in the network[171], and errors in recall often yield states that are semantically similar to — or differ only by one or two neurons from — the target state, a phenomenon commonly observed in humans[172].

The memorized activity states can be interpreted as local minima of an associated energy function, making each Hopfield network equivalent to an Ising model at zero temperature[34]. More recently, Ising-like models have been used to explain the critical or avalanche-like behaviour of activity in neural ensembles[173], which is thought to support adaptation to environmental changes[174], information storage[175], optimal information transmission[176], maximal dynamic range[177,178] and computational power[179]. The connection to statistical mechanics is also evident in the use of maximum entropy techniques to construct data-based models of neuronal dynamics. These maximum entropy models, which are equivalent to networks of Ising spins with specially chosen external fields and interaction strengths, have been shown to predict the observed long-range correlations within networks of neurons and brain regions[126,155]. Together, artificial models of neural dynamics, from simple McCulloch–Pitts neurons to artificial neural networks and data-driven maximum entropy models, continue to inform our understanding of brain networks as information processing systems.

Biophysical models. Although artificial models continue to generate insights about the nature of neural computation, they only vaguely resemble the complex biophysical mechanisms that guide observable neural activity. One of the first biophysically realistic models of the electrical behaviour of an individual neuron, the Hodgkin–Huxley model, was achieved nearly a decade after the introduction of the McCulloch–Pitts neuron[157]. Beginning from a principled description of the initiation and propagation of action potentials in living neurons, the Hodgkin–Huxley model explains important qualitative aspects of neuronal behaviour[1], including the spontaneous emergence of limit cycles or oscillations in activity[180] and the presence of a Hopf bifurcation in the neuronal firing rate, which is thought to underlie the all-or-none principle[157] (FIG. 2b). Subsequent extensions of the Hodgkin–Huxley model extend biophysical realism by incorporating multiple ion channel populations[181], the complex geometries of dendrites and axons[182] and more realistic stochastic dynamics yielding thermodynamic and hybrid Hodgkin–Huxley models[183,184]. Concurrent with these descriptive improvements, several simplified neuronal models were developed to facilitate efficient large-scale simulations of groups of neurons, including the FitzHugh–Nagumo model[158,185].

Simplifications in neuronal modelling, paired with fine-scale measurements of the synaptic wiring in several animals, have spurred large-scale simulations of real neuronal circuits (FIG. 2b). For example, on the heels of mapping the entire *C. elegans* connectome[48], researchers

began simulating the 302-neuron network at the cellular level[186], eventually even including the nematode's entire muscular system and representations of its physical environment[187]. Despite these and other efforts to simulate the *Drosophila* brain[188] and the rat neocortical column[189], it remains unclear how networks of neurons combine to generate the complex range of behaviours observed in even these relatively simple organisms.

This contrast between the simplicity of neuronal dynamics and the apparent complexity of large-scale neural behaviour hints at the crucial role of emergence. To understand how macroscopic behaviours emerge within groups of neurons, researchers began developing mean-field descriptions of large neuronal populations. Known as neural mass models, these efforts culminated in the Wilson–Cowan model of population dynamics[160]. Whereas previous neural mass models considered only excitatory interactions between neurons, the Wilson–Cowan model also includes inhibitory interactions, thereby enabling the collective neural oscillations observed in experiments as well as the emergence of other key properties of neural behaviour, including the existence of multiple stable states and hysteresis in the neural response to stimuli[160]. This progress was further extended to include spatial fluctuations in activity, yielding neural field models that exhibit other behaviours typically observed in the brain, including regions of localized activity[190] and travelling waves[191].

Along similar lines, networks of neural mass models with connections based on non-invasive measures of regional connectivity in humans can be used to simulate whole sections of the human brain[192] (FIG. 2b), opening the door for comparisons with experimental measurements of regional activity. This approach has driven a deeper understanding of the relationship between brain structure and function. For example, it has been demonstrated that the whole spectrum of MEG and electroencephalography (EEG) recordings of electrical activity can be reproduced by networked models of neural masses[152] and that the functional connectivity within such recordings depends critically on the coupling strength between neural masses[153].

Large-scale simulations of the entire human brain are further facilitated by simplified neural mass models, such as the Kuramoto model of oscillatory dynamics[162,193]. These efforts have provided insights about the spontaneous synchronization of neural oscillations[194], a phenomenon that is thought to play a critical role in neural communication[195], information processing[196] and motor coordination[197]. Moreover, simulations of simple Kuramoto oscillators embedded into realistic maps of the human connectome are able to reproduce the patterned fluctuations in activity and long-range correlations observed in fMRI data[154].

The future of brain network function

Neuroscientists remain fundamentally limited by the experimental and theoretical tools at their disposal[198,199]. Invasive techniques such as intracranial and stereotactic electrocorticography[200–202] provide immense precision in mapping human brain dynamics, but they remain constrained to patients with medically refractory epilepsy that require invasive mapping of seizure onset zones prior to surgical resection of diseased tissue. All other non-invasive imaging techniques suffer from trade-offs between spatial and temporal resolution[203]; methods that directly measure electromagnetic signals (such as EEG and MEG) have high temporal resolution but low spatial resolution, whereas measurements of blood flow and metabolic activity (such as those obtained via fMRI or PET) have relatively high spatial accuracy but poor resolution in time. Even fMRI — widely considered the standard for high spatial resolution in humans — integrates signals over hundreds of thousands of neurons and several seconds[204]. Consequently, any changes in neural activity that occur over tens of thousands of neurons or even over the span of a second are imperceptible on a standard fMRI scan.

To improve the precision of functional neuroimaging (fMRI in particular), recent efforts have leveraged advances in image processing to strengthen the signal and reduce background noise. For example, to minimize the inevitable effects of head movements and fluctuations in blood flow during scanning, fMRI signals are increasingly corrected using techniques similar to image stabilization in video cameras[205]. Additionally, to draw general conclusions from neuroimaging results across a group of subjects, impressive strides have been made to correct for inter-subject heterogeneities in brain structure[206]. Together, advances in image processing have begun to push neuroimaging from a tool exclusively used for academic research to one that can aid in the diagnosis and treatment of psychiatric disorders such as schizophrenia and Alzheimer disease[207–209].

Beyond data collection, data analysis and models in network neuroscience have historically been limited to pairwise relationships between neural elements, such as synapses connecting pairs of neurons or Pearson correlations between pairs of brain regions[29,62]. These dyadic notions of connectivity have provided important insights about the brain's circuitry, but mounting evidence suggests that higher-order interactions between three or more elements are also crucial for understanding the large-scale behaviour of entire brain networks[155,210,211]. To study these higher-order connections, recent efforts have focused on generalizing traditional definitions and intuitions from network science, primarily by adopting methods from algebraic topology[212]. One notable approach, known as persistent homology, makes it possible to extrapolate conclusions about neural activity across scales, escape the problem of selecting appropriate thresholds for edge strengths[213] and extract mesoscale features of network organization without relying on arbitrary thresholds[211,214].

Efforts have also been made to expand traditional metrics of functional connectivity, which are typically based on correlation, to include more sophisticated notions of causality[144]. Because causality reflects the flow of information in a network from one element to another, efforts to uncover causal relationships between neurons and brain regions have naturally drawn inspiration from information theory (Supplementary Information section 4)[215]. From mutual information to

transfer entropy, information theoretic notions of functional connectivity are increasingly used to quantify the flow of information in the brain[196,216,217]. These measures of causality, in turn, have real-world implications for controlling brain networks and intervening to treat neurological disease and psychiatric disorders.

The physics of brain network control

A complete understanding of the structure and function of the brain should enable interventions to shift the brain's dynamics and facilitate desirable behaviours. An important implication of the brain's networked structure is that localized perturbations (such as targeted lesions or stimulation) not only yield localized effects but also induce indirect effects that propagate along neural pathways[218,219]. Thus, the task of controlling brain dynamics requires knowledge of how signals transmit along the brain's structural wires, making the problem inherently one of network control[220]. Building upon targeted lesioning experiments in animals and clinical interventions in humans, efforts towards a theory of network control in the brain have taken shape in recent years. These efforts have inspired fundamental questions[221], such as whether brain networks are structured to facilitate control[222], what the principles are that allow brain networks to control themselves towards desired activity states[223,224] and whether it is possible to leverage these principles to inform stimulation-based therapies for neurological diseases and psychiatric disorders[225–228]. To address these questions, here we review the frontiers in the physics of brain network control.

Targeted and clinical perturbations

In humans, evidence for functional localization has typically relied on patients with localized brain damage (for example, due to a stroke or head trauma). Historical studies of this kind have revealed, for instance, that damage to one-half of the occipital lobe often induces blindness in the opposite field of vision[229] and that lesions in the frontal lobe can result in memory loss and an increase in impulsivity and risk taking[230]. More recently, advances in non-invasive stimulation techniques such as transcranial magnetic stimulation (TMS)[231], which induces 'transient' lesions by disrupting the brain's normal electrical activity, have opened the door for the control of localized brain functions, including perception[232], learning[233], language processing[234] and attention[235]. These non-invasive techniques have been supplemented by more invasive deep brain stimulation (DBS) methods, which use electrodes implanted in the brain to provide targeted therapies for a number of psychiatric and neurological disorders[231,236]. By focusing electromagnetic stimulation on the brain regions associated with specific disorders, both TMS and DBS have been used to treat Parkinson disease, epilepsy, depression and schizophrenia, among other disorders that are resistant to traditional therapies[237,238]. Despite these therapeutic benefits, it remains unclear exactly how and why TMS and DBS are so effective[218,236]; however, recent evidence suggests that the answers rely on a deeper understanding of the indirect effects of stimulation that are mediated by the brain's physical circuitry[239,240].

With the recent development of whole-brain neuroimaging methods such as fMRI, evidence is mounting that brain regions are heavily interdependent on one another, often working in unison to process information and formulate responses[88,138]. For example, after being trained to associate an auditory stimulus with a visual event, human subjects who were presented with the auditory stimulus alone exhibited increased activity in the occipital lobe, which is traditionally thought of as reserved for visual processing[241]. Experiments such as these reveal how activity or stimulation in one part of the brain can propagate along neural pathways to induce activity in disparate parts. Network models of brain dynamics are increasingly used to understand the system-wide impacts of targeted stimulation[239,240]. These efforts have resulted in the identification of neural circuits, rather than isolated regions, that are critical for reducing the symptoms of Parkinson disease[240,242]. Similar network-based approaches are also used to suppress epileptic seizures using DBS[243], to non-invasively treat depression using TMS[244] and to modulate consciousness during surgery using anaesthesia[245]. Moreover, stimulating and recording neural activity in several brain regions simultaneously enables closed-loop strategies for dynamically updating targeted treatments[246,247]. Meanwhile, clinical applications are increasingly informed by detailed computational simulations of perturbations to specific brain regions, typically employing networked biophysical models such as those discussed above[248,249]. Together, these experimental and computational studies of targeted stimulation have opened the door for sophisticated strategies for shifting neural activity with the ultimate goal of guiding the brain towards healthy cognitive patterns.

Network control in the brain

Increasingly, strategies for targeted stimulation and brain network control are being informed by tools from control theory in mathematics and intuitions from cognitive control in psychology. Control theory seeks to elucidate how a system, described by a mathematical model, can be influenced to move towards a desired state[220,250] (see BOX 1). Cognitive control, in contrast, encompasses a broad class of processes by which the brain enacts control over itself, typically to achieve an abstract goal or desired response[251]. For example, dating to the early 1970s, neurophysiological studies revealed that the act of holding an object in working memory induces a sustained neural response in the prefrontal cortex[252,253]. In fact, the prefrontal cortex is believed to play a key role in many cognitive control processes, from the representation of complex goal-directed behaviours[254] to the support of flexible responses to changes in the environment[255]. However, it remains unclear how these notions of cognitive control (as defined by psychologists and cognitive neuroscientists) compare with theories of network control (as defined by physicists and engineers) and how knowledge of the brain's intrinsic control processes can inform targeted therapies for mental illness.

To address these questions, we begin by comparing cognitive notions of intrinsic control with theoretical measures of control and controllability in brain

networks (see BOX 1). For example, it is interesting to ask which brain regions are most capable of inducing desired neural responses in other brain regions that are responsible for common functions such as vision, audition and motor coordination. Methods from control theory have provided a partial answer to this question: the strongest driver nodes corresponded to brain regions with high communicability — or many topological paths through the structural brain network — to the target brain regions[256]. In a related study, commonly observed activity states were simulated on a structural brain network, and it was discovered that optimal control nodes tend to have high degree, or many direct neighbors, in the network[257]. Moreover, when this rich club of hub regions is destroyed by simulated lesioning, the ability of the brain to make common transitions is significantly reduced.

In addition to studying the roles of specific control trajectories, complementary approaches have considered trajectory-independent metrics[258]. If the control input is limited to a single node, it is possible to quantify the ability of that node to steer the dynamics of the entire system. For example, the average controllability of a node represents the extent to which controlling that node can drive the network to many nearby states[223], whereas a node's modal controllability quantifies its ability to push the network towards states that are distant in state space or that can only be reached by surmounting large barriers in control energy[258] (FIG. 3a). Averaging these metrics over all nodes in a system gives an estimate of the inherent controllability of an entire network itself. Control-theoretic efforts such as these have only recently been applied to understand the locomotion of the nematode[259] and the networked behaviour of the brain more broadly[219,221,260], promising new strategies for stimulation-based therapies and fresh insights about the brain's capacity for intrinsic control.

Comparing control-theoretic measures of node controllability with the cognitive functions associated with each brain region demonstrates that different types of controllers are located in distinct areas of the brain (FIG. 3b)[223]. For example, brain regions that behave as average controllers are disproportionately located in the default-mode system, which is associated with baseline neural activity; modal controllers are primarily located in cognitive control systems. These observations are particularly interesting because they suggest that regions associated with the default mode are optimally positioned to push the system into many easily reachable states, whereas regions associated with cognitive control are optimally positioned to steer the system towards distant states.

As a final layer of abstraction, by averaging over all regions to quantify the mean controllability of an entire brain network — rather than studying the controllabilities of specific brain regions — it is seen that brain networks as a whole are finely tuned to maximize both average and modal controllability, thereby supporting a variety of possible control strategies[261]. Furthermore, comparing subjects in different stages of adolescence reveals that brain network controllability increases with age, suggesting that neural circuitry evolves over time to support increasingly complex dynamics. In related studies, metrics of network controllability were found to differ by sex[262] and to be altered in individuals with high genetic risk of bipolar disorder[224]. Together, these results suggest that network control theory, by taking into account the complex wiring of the brain, promises to enrich our understanding of the brain's control principles[260].

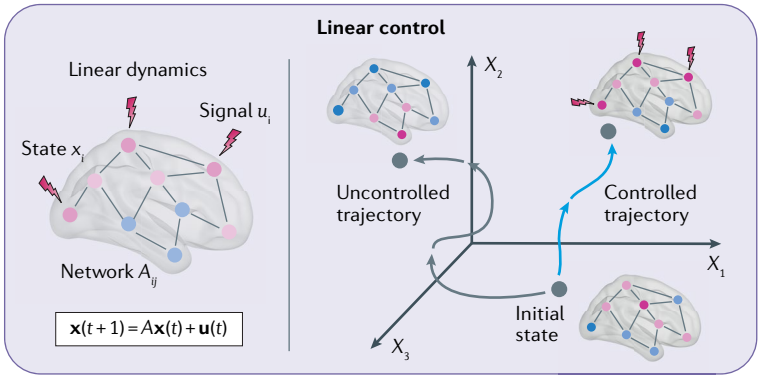
The future of brain network control

Emerging efforts at the intersection of neuroscience and control theory are informing clinical therapies that move beyond stimulation of entire brain regions and control strategies that assume linear dynamics. These efforts include techniques for fine-scale control of neural activity[263–266], even down to the level of individual neurons[267,268]; systems-identification approaches that allow the incorporation of effective connectivity measurements to inform control, superseding solely structural explanations[269]; and generalizations of linear control theory that include realistic nonlinear dynamics[270,271]. Among recent advances in the manipulation of fine-scale neural activity, the most promising tool is arguably optogenetics, which offers millisecond-scale optical control of specific cell types within the brains of conscious animals[263,264]. Its striking precision[265], in some cases even down to single-cell resolution[267,268], has enabled investigations of the nature of causal signals between neurons and how these signals give rise to qualitative changes in animal behaviour[266].

Linear control theory provides critical insights about how signals propagate along the brain's structural

Box 1 | **Linear control and network controllability**

To investigate the principles of control in the brain, it is useful to understand the theory of network control in general. In network control, the system in question typically comprises a complex web of interacting components, and the goal is to drive this networked system towards a desired state by influencing a select number of input nodes[220]. The starting point for most control-theoretic problems is the linear time-invariant control system $\mathbf{x}(t+1) = A\mathbf{x}(t) + \mathbf{u}(t)$, where $\mathbf{x}(t)$ defines the state of the system (for example, the blood-oxygen-level-dependent signal measured by functional magnetic resonance imaging), A is the interaction matrix (for example, representing white matter tracts estimated using diffusion tensor imaging) and $\mathbf{u}(t)$ defines the input signal (such as electromagnetic stimulation using transcranial magnetic simulation or deep brain simulation)[287]. A system is called controllable if it can be driven to any desired state. Often, however, many naturally occurring networks that are theoretically controllable cannot be steered to certain states owing to limitations on control resources[288,289], motivating the introduction of control strategies $\mathbf{u}^*(t)$ that minimize the so-called control energy $E(\mathbf{u}) = \sum_{t=0}^{\infty} |\mathbf{u}(t)|^2$, where the notation $|\cdot|$ denotes the l^2 norm.



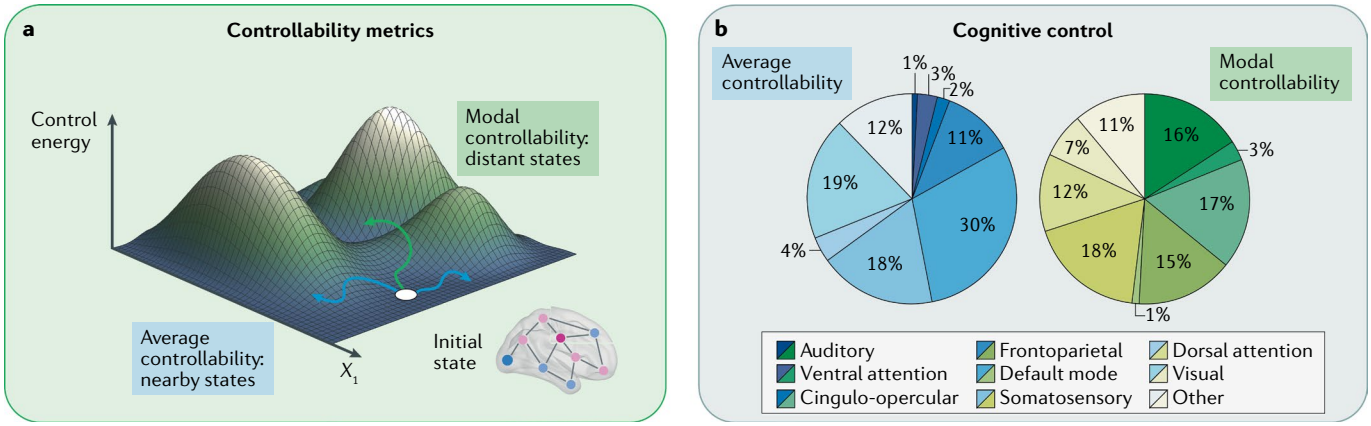


Fig. 3 | **Controllability metrics provide summary statistics regarding the ease with which a given node can enact influence on the network. a** | Average controllability measures the extent to which controlling a single node can drive the network to states that are nearby in the energy landscape of network states. Modal controllability measures the extent to which controlling a single node can drive the network to states that are distant in the energy landscape of network states or that require the network to surmount large energy barriers. **b** | The human brain displays marked levels of both average and modal controllability, and the proportion of average and modal controllers differs across cognitive systems, suggesting the capacity for a diverse repertoire of dynamics. Panel **b** adapted from REF.[223], CC-BY-4.0.

wiring[222,223,256,257]. However, interactions between neural components, from individual neurons to entire brain regions, are highly nonlinear[104]. Initial efforts to develop a theory of nonlinear control, dating to the 1970s[272–274], quickly reached the conclusion that results as strong and general as those derived for linear dynamics could not be obtained for a general nonlinear system[220]. Fortunately, concerted theoretic efforts have led to weaker notions of nonlinear controllability[275], notable among which are techniques for linearizing nonlinear systems around stable equilibrium states[270,271] and methods for leveraging the symmetries of a system[276], such as repeated network motifs, to simplify control strategies[277]. Additional efforts have employed advances in computing power to simulate the effects of external perturbations across a range of model systems, including networks of FitzHugh–Nagumo neurons[276], Wilson–Cowan neural masses[225] and Kuramoto oscillators[278], as well as artificial neural networks including Ising-like models[279,280]. Together, the recent advances in high-precision neural stimulation described above and the emerging understanding of the principles governing nonlinear control are pushing the boundaries of what is considered possible in the investigation of neural activity. Targeted control of the brain's complex behaviour — once a topic of science fiction — now promises to shape targeted therapies for a range of psychiatric and neurological disorders.

Outlook

The intricate inner workings of the brain remain one of the greatest mysteries defying resolution by contemporary scientific inquiry. On the heels of decades of effort investigating the functions of the brain's individual components[281], from neurons to neuronal ensembles and large-scale brain regions, conclusive evidence points to the need for maps and models of the interactions between these components in order to fundamentally understand the brain's ensemble dynamics, circuit function and emergent behaviour[29,282].

We wish to offer the sentiment that, although the empirical advances laying the foundation of the field have spanned several decades, the network physics of the brain is a young area of research, rich with opportunities for discovery. Perhaps, with a bit of courage, neuroscientists and physicists may even begin to provide a scientific embodiment of the deeper philosophical questions that humans have wrestled with for millennia. These questions include what makes humans unique from one another and different from non-human animals[222,283]; how do we represent abstract concepts such as the value of an object or of an idea to ourselves[284] and others[285]; how are representations transmitted throughout the brain or reconfigured on the basis of new knowledge[286]; and what makes a mind from a brain.

Published online 27 March 2019

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Acknowledgements
The authors are grateful to L. Papadopoulos, J. Z. Kim and V. Buch for helpful comments on an earlier version of this manuscript. The authors also thank A. E. Sizemore for artistic inspiration. D.S.B. and C.W.L. acknowledge support from the Penn NSF MRSEC Grant DMR-1720530, the John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation, the ISI Foundation, the Paul Allen Foundation, the Army Research Laboratory (W911NF-10-2-0022), the Army Research Office (Bassett-W911NF-14-1-0679, Grafton-W911NF-16-1-0474 and DCIST- W911NF-17-2-0181), the Office of Naval Research, the US National Institute of Mental Health (2-R01-DC-009209-11, R01-MH112847, R01-MH107235 and R21-M MH-106799), the US National Institute of Child Health and Human Development (1R01HD086888-01), the US National Institute of Neurological Disorders and Stroke (R01 NS099348) and the US National Science Foundation (BCS-1441502, BCS-1430087, NSF PHY-1554488 and BCS-1631550).

Author contributions
All authors contributed to all aspects of manuscript preparation, revision and editing.

Competing interests
The authors declare no competing interests.

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Reviewer information
Nature Reviews Physics thanks Y. He and the other anonymous reviewer(s) for their contribution to the peer review of this work.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s42254-019-0040-8.