The physics of brain network structure, function, and control

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The brain is a complex organ characterized by heterogeneous patterns of structural connections supporting unparalleled feats of cognition and a wide range of behaviors. New noninvasive imaging techniques now allow these patterns to be carefully and comprehensively mapped in individual humans and animals. Yet, it remains a fundamental challenge to understand how the brain’s structural wiring supports cognitive processes, with major implications for the personalized treatment of mental health disorders. Here, we review recent efforts to meet this challenge that draw on intuitions, models, and theories from physics, spanning the domains of statistical mechanics, information theory, and dynamical systems and control. We begin by considering the organizing principles of brain network architecture instantiated in structural wiring under constraints of symmetry, spatial embedding, and energy minimization. We next consider models of brain network function that stipulate how neural activity propagates along these structural connections, producing the long-range interactions and collective dynamics that support a rich repertoire of system functions. Finally, we consider perturbative experiments and models for brain network control, which leverage the physics of signal transmission along structural wires to infer intrinsic control processes that support goal-directed behavior and to inform stimulation-based therapies for neurological disease and psychiatric disorders. Throughout, we highlight several open questions in the physics of brain network structure, function, and control that will require creative efforts from physicists willing to brave the complexities of living matter.
It is our good fortune as physicists to seek to understand the nature of the observable world around us. In this inquiry, we need not reach to contemporary science to appreciate the fact that our perception of the world around us is inextricably linked to the world within us: the mind. Indeed, even Aristotle c. 350 B.C. noted that it is by mapping the structure of the world that the human comes to understand their own mind [1]. “Mind thinks itself because it shares the nature of the object of thought; for it becomes an object of thought in coming into contact with and thinking its objects, so that mind and object of thought are the same” [2]. Over the ensuing 2000-plus years, it has not completely escaped notice that the mappers of the world have unique contributions to offer the mapping of the mind (from Thales of Miletus, c. 624–546 B.C., to Leonardo Da Vinci, 1452–1519). More recently, it is notable that nearly all famous physicists of the early 20th century—Albert Einstein, Niels Bohr, Erwin Schroedinger, Werner Heisenberg, Max Born—considered the philosophical implications of their observations and theories [3]. In the post-war era, philosophical musings turned to particularly conspicuous empirical contributions at the intersection of neuroscience and artificial intelligence, spanning polymath John von Neumann’s work enhancing our understanding of computational architectures [4] and physicist John Hopfield’s invention of the associative neural network, which revolutionized our understanding of collective computation [5].

In the contemporary study of the mind and its fundamental organ—the brain—nearly all of the domains of physics, perhaps with the exception of relativity, are not only relevant but truly essential, motivating the early coinage of the term *neurophysics* some four decades ago [6]. The fundamentals of electricity and magnetism prove critical for building theoretical models of neu-
rons and the transmission of action potentials\textsuperscript{7}. These theories are being increasingly informed by mechanics to understand how force-generating and load-bearing proteins bend, curl, kink, buckle, constrict, and stretch to mediate neuronal signaling and plasticity\textsuperscript{8}. Principles from thermodynamics come into play when predicting how the brain samples the environment (action) or shifts the distribution of information that it encodes (perception)\textsuperscript{9}. Collectively, theories of brain function are either buttressed or dismantled by imaging, with common tools including magnetic resonance imaging\textsuperscript{10} and magnetoencephalography\textsuperscript{11}, the latter being built on superconducting quantum interference devices and next-generation quantum sensors that can be embedded into a system that can be worn like a helmet, revolutionizing our ability to measure brain function while allowing free and natural movement\textsuperscript{12}. Moreover, recent developments in nanoscale analysis tools and in the design and synthesis of nanomaterials have generated optical, electrical, and chemical methods to explore brain function by enabling simultaneous measurement and manipulation of the activity of thousands or even millions of neurons\textsuperscript{13}. Beyond its relevance for continued imaging advancements\textsuperscript{14}, optics has come to the fore of neuroscience over the last decade with the development of optogenetics, an approach that 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\textsuperscript{15}.

Such astounding advances, enabled by the intersection of physics and neuroscience, have motivated the construction of a National Brain Observatory at the Argonne National Laboratory (Director: Peter Littlewood, previously of Cavendish Laboratories) funded by the National Science Foundation, as well as frequent media coverage including titles in the APS News such as...
“Physicists, the Brain is Calling You.” And as physicists answer the call, our understanding of the brain deepens and our ability to mark and measure its component parts expands. Yet alongside this growing systematization and archivation, we have begun to face an increasing realization that it is the interactions between hundreds or thousands of neurons that generate the mind’s functional states. Indeed, from interactions among neural components emerge computation, communication, and information propagation. We can confidently state of neuroscience what Henri Poincare, the French mathematician, theoretical physicist, and philosopher of science, states of science generally: “The aim of science is not things themselves, as the dogmatists in their simplicity imagine, but the relations among things; outside these relations there is no reality knowable.”

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), the European Union (the Blue Brain Project), China (the China Brain Project), and Japan (Japan’s Brain/MINDS project).

While it is clear that interactions are paramount, exactly how the functions of the mind arise from these interactions remains one of the fundamental open questions of brain science. To the physicist, such a question appears to exist naturally within the purview of statistical mechanics, with one major caveat: the interaction patterns observed in the brain are far from regular, such as those observed in crystalline structures, and are also far from random, such as those observed in fully disordered systems. Indeed, the observed heterogeneity of interaction patterns in neural systems—across a range of spatial and temporal scales—generally limits the utility of basic continuum models or mean-field theories, which would otherwise comprise our natural first ap-
proaches. Fortunately, similar observations of interaction heterogeneity have been made in other technological, social, and biological systems, leading to concerted efforts to develop a statistical mechanics of complex networks. The resultant area of inquiry includes criteria for building a network model of a complex system, statistics to quantify the architecture of that network, models to stipulate the dynamics that can occur both in and on a network, and theories of network function and control.

Here, we provide a brief review for the curious physicist, spanning the network-based approaches, statistics, models, and theories that have recently been used to understand the brain. Importantly, the interpretations that can be rationally drawn from all such efforts depend upon the nature of the network representation, including its descriptive, explanatory, and predictive validity—topics that are treated with some philosophical rigor elsewhere. Following a simple primer on the nature of network models, we discuss the physics of brain network structure, beginning with an exposition regarding measurement before turning to an exposition regarding modeling. In a parallel line of discourse, we then discuss the physics of brain network function, followed by a description of perturbation experiments and brain network control. In each section we separate our remarks into the known and the unknown, the past and the future, the fact and the speculation. Our goal is to provide an accessible introduction to the field, and to inspire the younger generation of physicists to courageously tackle some of the most pressing open questions surrounding the inner workings of the mind.

A simple primer on networks. To make the ensuing discussion more concrete, here we take a
brief moment to define what we mean by a network and to describe a few ways in which we can summarize its architecture. Importantly, the points that we make in this subsection are agnostic to the system that the network represents, whether it be a brain, a granular material, or a quantum system. By far the simplest network representation of a system is a binary undirected graph in which identical nodes represent system components and identical edges indicate relations or connections between pairs of nodes (Fig. 1, center). While we will of course build on this simple description in later sections as appropriate to the content under scrutiny, here we note that such a network can be encoded in an adjacency matrix $A$. Each matrix element $A_{ij}$ indicates the strength of connectivity between node $i$ and node $j$. When all edge strengths are of identical weight unity, the network represented by the adjacency matrix is said to be binary. When edges have a range of weights, the network represented by the adjacency matrix is said to be weighted. When $A = A^\top$, the network represented by the matrix is said to be undirected, and when $A \neq A^\top$, the network represented by the matrix is said to be directed.

One can extend this simple encoding to study increasingly complex network models including multilayer, multislice, and multiplex networks, dynamic or temporal networks, annotated networks, hypergraphs, and simplicial complexes. One can also calculate various statistics to quantify the architecture of the network and to infer the function thereof (Fig. 1, circumjacent). Intuitively, these statistics range from measures of the local structure in the network, which depend solely on the architecture of links directly emanating from a given node (e.g., degree and clustering), to measures of the global structure in the network, which depend on the complex pattern of connections between all nodes in the network (e.g., path lengths and centrality).
Figure 1 | **A network primer.** Here we provide an accessible illustration of the mathematical form of a network and a few important characteristics of a network’s topology. *(Center)* Perhaps the simplest type of network contains identical nodes, illustrated by grey circles, each of which represents a system component. A pair of nodes can be connected by an edge, illustrated by a charcoal line, which represents a relation or connection between the two nodes. In the accepted terminology of the field, the pattern of edges among nodes is referred to as the network’s *topology*. *(Circumjacent)* A network’s topology can be probed by statistics that characterize local, mesoscale, or global architecture. For example, the simplest local statistics include (i) the degree, or number of edges emanating from a node, and (ii) the clustering coefficient, or ratio of connected triangles to connected triples. Two simple notions of mesoscale structure include (i) community structure, where internally dense and externally sparse groups of nodes exist, and (ii) cavity structure, where edges between nodes are conspicuously absent, creating holes in the network. Finally, the simplest global statistics include (i) path-length, or the smallest number of edges needed to be traversed to move from one node to another within the network, and (ii) notions of centrality such as betweenness centrality, which quantifies the number of shortest paths between nodes $i$ and $j$ that must pass through node $v$. Collectively, the network representation and associated statistics can provide critical insights into the function of the system under study.
Intermediate statistics exist to study structure at the mesoscale, such as community structure, where nodes in a community are more densely interconnected with one another than expected under an appropriate random network null model \cite{45-47}. As we will see, the encoding of a system as a network and the quantitative assessment of its architecture can provide important insights into its function \cite{34,48}.

**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 modeling of their key organizational features. Each edge in a structural brain network represents a physical connection between two elements. For example, synapses support the propagation of information between neurons \cite{49} and white matter tracts define physical pathways of communication between brain regions \cite{50}. In physics, it has long been recognized that the organization of such structural connections can determine the qualitative large-scale features of a system \cite{28}. In the Ising model, for instance, a one-dimensional lattice remains paramagnetic across all temperatures \cite{51}, while in two dimensions or more, the system spontaneously breaks symmetry, yielding the type of bulk magnetization exhibited by magnets on a refrigerator \cite{52,53}. Similarly, the organization of structural wiring in the brain largely determines the types of mental processes and cognitive functions that can be supported \cite{54,58}, from memory \cite{59,61} to learning \cite{62,63} and from vision \cite{64} to motion \cite{65}. However, unlike many physics applications, which assume simple lattice or random network architectures, the wiring of the brain is highly heterogeneous, often making symmetry arguments and mean-field descriptions far from applicable \cite{27}. While this
heterogeneity presents a unique set of challenges, in what follows we review some powerful experimental and theoretical tools that allow us to distill the brain’s structural complexity to a number of fundamental organizing principles.

**Measuring brain network structure.** Some of the earliest empirical measurements of the brain’s structural connectivity can be traced to Camillo Golgi, who in 1873 soaked blocks of brain tissue in silver-nitrate solution to provide among the first glimpses of the intricate branching of nerve cells. Soon after, Santiago Ramón y Cajal combined Golgi’s method with light microscopy to achieve stunning pictures establishing that neurons do not exist in solitude; they instead combine to form intricate networks of physical connections. This notion that the brain comprises a complex web of distinct components, known as the neuron doctrine, established the foundation upon which modern network neuroscience has flourished. The introduction of the electron microscope in the 1930s provided even more detailed measurements of the physical connections between neurons. Perhaps the most impressive application remains the complete mapping of interconnections between the 302 neurons in the nematode *C. elegans*. Since this achievement, reconstructions of the synaptic connectivity in other animals have evolved rapidly, from a mapping of the optic medulla in the visual system of the fruit fly *Drosophila* to the enumeration of connections between 950 distinct neurons in the mouse retina. Recently, efforts have even extended toward the ultimate goal of reconstructing the neuronal wiring diagram of an entire human brain.

Concurrently with these achievements using electron microscopy, complimentary efforts in tract tracing have revealed the mesoscale structure of the macaque, cat, mouse, and
**Drosophila** Particularly important for our understanding of human cognition are recent advances in noninvasive imaging that have allowed unprecedented views of the mesoscale structure of the brain *in vivo*. Introduced in the 1970s, computerized axial tomography (CAT) provided among the most detailed anatomic images of the human brain to date. Soon after, the development of magnetic resonance imagining (MRI) sparked an explosion of refinements, a notable example being diffusion tensor imaging (DTI). While standard CAT and MRI techniques capture cross-sectional images of the brain, DTI traces the diffusion of water through white matter tracts to reconstruct the large-scale neural pathways connecting brain regions (Fig. 2a). These ongoing efforts, from the mapping of fine-scale synaptic wiring at the neuronal level to the reconstruction of large-scale neural pathways between brain regions, continue to provide rich network datasets detailing the brain’s structural organization.

**Modeling brain network structure.** A first glance at the structural wiring of the brain reveals that it is far from homogeneous—a fact that is not surprising considering the array of physical, energetic, and functional constraints imposed on the brain. To deal with this heterogeneity, researchers have increasingly turned to the field of network science for mathematical tools and intuition. The primary goal of this interdisciplinary effort has been to distill the explosion of experimental data down to a number of cogent organizing principles. Notably, generative modeling efforts span the structural brain networks in *C. elegans*, the mouse, cat, macaque, and human. Here we review some important properties that are thought to characterize such brain networks, while also introducing canonical network models that explain how these properties can arise in networked systems (Fig. 2b).
Figure 2 | **Measuring and modeling brain network structure.**

**a** | The measurement of brain network structure begins with experimental data specifying the physical interconnections between neurons or brain regions. As an example, we consider a dataset of white matter tracts measured via DTI. First, the data is discretized into non-overlapping gray matter volumes representing distinct nodes. Then, one constructs an adjacency matrix $A$, where $A_{ij}$ represents the connection strength between nodes $i$ and $j$. This adjacency matrix, in turn, defines a structural brain network constructed from our original measurements of physical connectivity.

**b** | To capture an architectural feature of structural brain networks, we utilize generative network models. The simplest type of random network has no discernible structure and is generated by the Erdős–Rényi model. Small-world networks, which balance efficient communication and high clustering under reasonable assumptions of dynamics, are generated using the Watts–Strogatz model. Scale-free networks, with power-law degree distributions characterized by a small number of high-degree hub nodes, are constructed via the preferential attachment or so-called Barabási–Albert model. Networks with modular structure, divided into communities with dense connectivity, are built using the stochastic block model. Spatially embedded networks, whose connectivity is constrained to exist within a physical volume, are generated through the use of geometric network models.
The simplest and most common model for generating random networks is the Erdős–Rényi (ER) model. In the ER model, the probability that a given pair of nodes $i$ and $j$ is connected by an edge (i.e., the probability $A_{ij} = 1$) is a constant $P$, such that

$$\Pr(A_{ij} = 1) = P. \quad (1)$$

While networks generated by the ER model have no discernible structure, networks in the brain are required to support efficient communication. This requirement for efficient communication constrains brain networks to have short average path lengths between their elements while simultaneously maintaining high average clustering. Remarkably, Duncan Watts and Steven Strogatz showed that this “small-world” phenomenon arises organically in networks that interpolate between the randomized structure of an ER network and the lattice structure of a ring graph.

In addition to their high clustering and short average path lengths, many brain networks display heavy-tailed degree distributions characterized by a small number of hub nodes with unusually high degree. Such architecture is reminiscent of that observed in scale-free networks, which are widely thought to arise from preferential attachment mechanisms. In the Barabási–Albert (BA) model, for instance, nodes are added to the network in sequential order, and at the time node $i$ is added, the probability that it forms an edge with a preexisting node $j$ is proportional the degree of node $j$ (denoted $k_j$), such that

$$\Pr(A_{ij} = 1) \propto k_j. \quad (2)$$

In this way, new nodes preferentially form edges with existing nodes of high degree, giving rise to
a small number of high-degree hub nodes. Notably, hubs in the brain tend to connect to other hubs, forming a “rich-club” thought to support information integration and robustness to injury.

While the Watts-Strogatz (WS) and BA models capture the small-worldness and heavy-tailed degree distributions exhibited by many networks found in nature, brain networks are also known to organize into densely-connected communities of elements. This community (or modular) structure is thought to divide brain networks into building blocks or subnetworks of high connectivity that often correspond to specialized functional components. To generate networks with defined modular structure, researchers predominantly use the stochastic block model, wherein nodes are assigned to distinct communities and edges are placed between nodes depending on their community assignments. For example, if node $i$ belongs to community $C_u$ and node $j$ belongs to community $C_v$, then the probability of $i$ and $j$ forming an edge is given by

$$\Pr(A_{ij} = 1) = P_{uv},$$

where the matrix $P$ defines the network’s community structure. In addition to generating networks with modular structure, a vibrant branch of research also focuses on developing methods for detecting communities in real-world networks, many of which are now applied throughout network neuroscience.

Finally, beyond the topological network properties described above, brain networks are also physically constrained to exist inside a tight three-dimensional volume and their structural connections are energetically driven to minimize total wiring distance. These physical and
energetic constraints are captured by geometric network models, which embed networks into three-dimensional Euclidean space. The simplest such model assumes that the probability of two nodes forming an edge is inversely related to the physical distance between the two nodes (denoted $d_{ij}$), such that

$$\Pr(A_{ij} = 1) \propto d_{ij}^{-\alpha},$$

where the exponent $\alpha \geq 0$ defines the energetic cost associated with constructing connections of a given length. All together, the small-world, rich-club, modular, and inherently physical nature of brain networks provides simple organizing principles for handling the heterogeneity of the brain’s structural wiring and reveals important clues about the functional and energetic constraints that guide the development of healthy cognitive systems.

**The future of brain network structure.** Current advances in neuroimaging techniques and graph theory continue to expand our ability to measure and model the architecture of structural connections in the brain. Perhaps the most ambitious endeavor is the reconstruction of the entire human connectome at the scale of individual neurons, an effort which continues to push the boundaries of 3D electron microscopy and statistical image reconstruction. Similar mapping efforts in other species have revealed extensive and quantifiable neuronal diversity, suggesting the importance of extending network models to include non-identical units. At the mesoscale, advances in noninvasive imaging have allowed researchers to begin tracking changes in structural connectivity over time. To analyze these temporally ordered measurements, network scientists have extended standard static graph theoretic tools to study networks with dynamically evolving connections. Notably, these so-called temporal networks were recently shown to be easier to
control, requiring less energy to attain a desired state, than their static counterparts [117].

As measurements of brain networks become increasingly detailed, another important direction is the bridging of structure at different spatiotemporal scales [118–120]. 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 and all the way to social networks linking distinct organisms (Box 1). 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 [121], which treat each node at the macroscale as an entire subnetwork at the microscale [122].

In addition to understanding the dynamic evolution and hierarchical nature of brain network architecture, it has also long been hypothesized that the structure of brain networks depends critically on the dynamics (or function) that they support [31,123]. For instance, in his 1949 book *The Organization of Behavior*, Donald Hebb postulated that the strength of a synaptic connection increases with the persistent synchronized firing of its pre- and postsynaptic neurons [124]. 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

While structural brain networks represent the physical wiring between neural elements (e.g., between individual neurons or brain regions), 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 neuron doctrine postulates that the brain’s structure is divided into a network of distinct nerve cells, it is also widely expected that the brain’s cognitive functions arise from the collective activity of individual neurons. To understand how the firing of simple nerve cells can give rise to the brain’s rich repertoire of cognitive functions, analogies are often drawn with notions of emergence in statistical mechanics. Developed concurrently with the neuron doctrine in the late 19th century, statistical mechanics established (among other achievements) that the thermodynamic laws governing the macroscopic behavior of gas molecules can be derived from the microscopic dynamics of the molecules themselves. Similarly, 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 we observe in the brain. Here we traverse what is known about brain network function in relatively broad strokes, from the dynamics of distinct neurons to the networked activity of the entire brain.

Measuring brain network function. The first measurements of the brain’s functional organization date to 1815, when Marie-Jean-Pierre Flourens pioneered the use of localized lesions in the
brains of living animals to observe their effects on behavior. Through his experiments, Flourens discovered that the cerebellum regulates motor control, the cerebral cortex supports higher cognition, and the brain stem controls vital functions. The remainder of the 19th century brought increasingly detailed measurements of the brain’s functional organization, from the demonstration that the occipital lobe regulates vision to the discovery that the left frontal lobe is essential for speech. These discoveries, combined with the early images of neural circuits captured by Ramón y Cajal, culminated in Thomas Scott Sherrington’s book *The Integrative Action of the Nervous System*, which proposed the notion that neurons behave in functional groups.

Meanwhile, in 1849 the physicist Hermann von Helmholtz achieved the first electrical measurements of a nerve impulse, sparking a wave of experiments investigating the electrical properties of the nervous system. Through invasive measurements in animals using newly-developed electroencephalography (EEG) techniques, it quickly became clear that individual neurons communicate with one another via electrical signals, thus providing a clear mechanism explaining how information is propagated and manipulated in the brain. Today, scientists possess a rich menu of experimental techniques for measuring brain dynamics across a range of scales. At the neuronal level, the development of invasive methods in animals, such as electrophysiological recordings of brain slice preparations *in vitro* and calcium imaging of neuronal activity *in vivo* have vastly expanded our understanding of synaptic communication. At the mesoscale, complimentary minimally-invasive imaging techniques have identified fundamental properties of information processing in humans. Interestingly, these advances in mesoscale functional (as opposed to structural) imaging can largely be traced to the efforts of physicists. MEG methods,
for instance, use superconducting quantum interference devices (SQUIDS) to directly measure the magnetic fields generated by electrical currents in the brain \textsuperscript{12,139}, and PET techniques measure the positron emission of radioisotopes produced in cyclotrons to reconstruct the metabolic activity of neural tissue \textsuperscript{150}. Over the last twenty years, measurements of brain dynamics have been increasingly dominated by functional MRI (fMRI) \textsuperscript{151}, 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 \textsuperscript{152}. This modern progress in functional brain imaging has galvanized the field of network neuroscience by making detailed datasets of networked neural activity widely accessible.

One particularly important use of these measurement techniques has been the study of so-called functional brain networks \textsuperscript{153}, which have allowed researchers to adopt tools from network science to investigate the organization of neural activity. In functional brain networks, as in their structural counterparts, nodes represent physical neural elements, ranging in size from individual neurons to distinct brain regions \textsuperscript{154}. However, whereas structural brain networks define the connectivity between elements based on physical measures of neural wiring (e.g., synapses between neurons or white matter tracts between brain regions), functional brain networks define connectivity based on the similarity between two elements’ dynamics \textsuperscript{153,154}. For example, the strength of a functional edge between two brain regions is often defined by the Pearson correlation between the regions’ activity time series (Fig. 3a) \textsuperscript{130,155}. Once a researcher settles on an appropriate measure of statistical similarity (e.g., Pearson correlation, synchronization, etc.), they can utilize techniques from network science to study the key organizing features of the induced network.
Such efforts have demonstrated that functional brain networks, much like structural ones, exhibit signs of small-world, modular, and physically constrained organization. Given these organizational similarities, it is tempting to suspect that functional brain networks closely reflect the physical wiring upon which they exist. However, the relationship between brain function and structure is highly nonlinear, and understanding how a functional brain network arises from its underlying structural connectivity remains a subject of intense academic focus.

Modeling brain network function. To understand how the web of physical connections in the brain gives rise to macroscopic functional properties, statistical mechanical intuition dictates that we should begin by studying the dynamics of individual elements. Once we have settled on accurate biophysical models of individual neurons and brain regions, we can link these elements together in a network to predict macroscopic features of the brain’s function from its underlying structure. Interestingly, the history of modeling in neuroscience has followed precisely this path, beginning with models of neuronal dynamics, eventually increasing in scale to mean-field neural mass models, and finally reaching models of entire networks of neurons and neural masses. Here we review important developments in the modeling of neural dynamics, dividing the modeling techniques into two complimentary classes: those with discrete artificial dynamics and those with continuous biophysical dynamics (Fig. 3b). As we will see, models from these two generic classes are able to reproduce qualitatively different aspects of observed neural behavior.

Discrete artificial models. The first discrete model of neural activity—indeed, one of the earliest
Figure 3 | Measuring and modeling brain network function. 

a | The measurement of brain network function begins with experimental data specifying the activity of neurons or brain regions. As an example, we consider changes in blood oxygen level in different parts of the brain measured via fMRI. Calculating the similarity (e.g., correlation or synchronization) between each pair of activity time series, one arrives at a similarity matrix. This matrix, in turn, defines a functional brain network constructed from our original measurements of neural activity.

b | We divide models of neural activity into two classes: discrete models with artificial dynamics (left) and continuous models with biophysically realistic dynamics (right). Across both discrete and continuous models, the state of a neural system at time $t$ is represented by a vector $\mathbf{x}(t)$, where each entry $x_i(t)$ defines the state of element $i$. In discrete models, the evolution of a single element is defined by a dynamical equation of the form $x_i(t+1) = f_i(\mathbf{x}(t))$, where $f_i(\cdot)$ defines the dynamics of element $i$. Discrete models of this form, from the MP neuron to various artificial neural networks, have been shown to reproduce key aspects of information processing and pattern recognition in the brain. By contrast, continuous models typically define the evolution of an individual element using a differential equation of the form $\dot{x}_i = g_i(\mathbf{x})$, where $g_i(\cdot)$ defines the dynamics of element $i$. Such continuous models are able to capture realistic features of individual neurons and neural masses (e.g., using the Hodgkin–Huxley or Wilson–Cowan models) and predict large-scale properties of neuronal circuits and entire brain networks (e.g., by simulating networks of FitzHugh–Nagumo neurons or Kuramoto oscillators, respectively).
mathematical models of neural activity whatsoever—was proposed in the mid-1940s by Warren McCulloch and Walter Pitts to describe the logical functioning of an individual neuron\(^\text{17}\). Known as the MP neuron, their model accepted binary inputs, combined these inputs using linear weights, and produced a binary output reflecting whether or not the weighted sum of inputs exceeded a given threshold. Albeit a simple caricature of neuronal dynamics, this model has been shown to reproduce behaviors exhibited by real neurons\(^\text{168,169}\) and has provided deep insights about the computational capabilities of neural networks. Researchers quickly realized, for instance, that any Boolean function could be represented as a network of MP neurons\(^\text{6}\). Another notable application was the perceptron\(^\text{170}\), wherein the input weights for a single MP neuron are chosen such that the output defines a linear classifier, which is able to categorize incoming data into linearly-separable groups. By linking the inputs and outputs of perceptron-like neurons via artificial synapses, researchers began developing artificial neural networks that could classify increasingly complex streams of data\(^\text{171,172}\).

Today, these networks of artificial neurons are able to reproduce a wide range of impressive functions that we have come to expect from the brain\(^\text{173}\), from pattern identification\(^\text{174}\) and speech recognition\(^\text{175}\) to decision making\(^\text{176}\) and game-playing\(^\text{177}\). One particularly important example of an artificial neural network was introduced by John Hopfield in 1982 as a model for understanding human memory\(^\text{5}\). Hopfield showed that the synaptic weights connecting a set of MP neurons can be tuned in such a way that the network is able to “memorize” a number of desired states. These memorized states, it turns out, are local minima of an associated energy function, making each Hopfield network equivalent to an Ising model\(^\text{53}\). More recently, Ising-
like dynamics have also been used to model the cascade or avalanche-like behavior of activity in neural ensembles, which is thought to support adaptation, optimal information storage, optimal information transmission, optimal dynamic range, and computational power. Further building upon this connection to statistical mechanics, scientists have recently used maximum entropy techniques to construct data-based models of neuronal dynamics. These maximum entropy models, which are equivalent to networks of MP neurons with specially-chosen thresholds and synaptic weights, have been shown to predict the long-range correlations observed in real networks of neurons and brain regions. Together, discrete models of neural dynamics, from simple MP neurons to artificial neural networks and data-driven maximum entropy models, continue to expand our understanding of neural networks as information processing systems.

*Continuous biophysical models.* Nearly a decade after the introduction of the MP neuron, Alan Lloyd Hodgkin and Andrew Fielding Huxley achieved a pioneering biophysical model of the neuron’s electrical behavior. While much more computationally expensive than the MP neuron, the Hodgkin–Huxley (HH) model captures key aspects of the initiation and propagation of action potentials measured in living neurons. Subsequent extensions of the HH model introduced further biophysical realism by including ion channel behavior and the complex geometries of dendrites and axons based on experimental data. A number of simplified models of neuronal dynamics were also developed, such as the FitzHugh–Nagumo model, which, in conjunction with the advancement of computing power in the 1960s, opened the door for efficient simulations of large networks of neurons.
Concurrently with these improvements in neuronal modeling, researchers began developing complimentary mean-field descriptions of the coarse-grained activity of entire neuronal populations. Known as neural mass models, these efforts culminated in the foundational Wilson–Cowan (WC) model of population dynamics. By including both inhibitory and excitatory interactions between neurons, the WC model predicts stable oscillations as well as hysteresis in the activity of neuronal populations, both of which are key features observed in functional measurements. This progress was extended to include spatial fluctuations in activity, yielding neural field models that exhibit other behaviors typically observed in the brain, including regions of localized activity and traveling waves.

While neural mass and neural field methods have been shown to replicate many salient features of individual neuronal populations, to facilitate the simulation of large networks of interacting populations neuroscientists have frequently turned to simplified models of coupled oscillators. One model in particular, the Kuramoto model, has provided critical insights about the emergence of synchronization in brain networks, which is thought to play a role in information processing, neuronal communication, and motor coordination. For example, by connecting oscillators into a realistic structural network linking cortical regions, the Kuramoto model has been shown to reproduce the types of patterned fluctuations in activity that are observed in fMRI data. Thus, whereas discrete models of artificial neurons have generated insights about the computational capabilities of neural networks, continuous biophysical models of neural dynamics continue to provide increasingly realistic descriptions of the synchronization and long-range correlations that characterize experimental observations of brain function.
**The future of brain network function.** Over the last two centuries, our understanding of the brain’s functional organization and information processing capabilities has progressed immensely. Despite this progress, the modern neuroscientist remains fundamentally limited by the experimental and theoretical tools at their disposal. Invasive techniques such as intracranial electrocorticography, and even minimally invasive techniques such as stereotactic electroencephalography (sEEG), provide immense precision in mapping human brain dynamics, but remain constrained to patients with medically refractory epilepsy. Other noninvasive imaging techniques all suffer from trade-offs between spatial and temporal resolution; methods that directly measure electromagnetic signals (e.g., EEG and MEG) have high temporal resolution but low spatial resolution, while measurements of blood flow and metabolic activity (e.g., via fMRI or PET) have relatively high spatial accuracy but poor resolution in time. Even fMRI—widely considered the standard for high spatial resolution—integrates signals over hundreds of thousands of neurons and several seconds. Consequently, any changes in neural activity that occur over tens of thousands of neurons or even over the span of a second are imperceivable on a standard fMRI scan.

To improve the precision of functional neuroimaging (fMRI in particular), recent efforts have leveraged modern 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. Additionally, in order to draw general conclusions from the neuroimaging results of distinct individuals, impressive strides have been made to correct for anatomical heterogeneities between people’s brains. Together, advances in image process-
ing have begun to push neuroimaging from a tool exclusively used for academic research to one that can aide in the diagnosis and treatment of psychiatric disorders such as schizophrenia and Alzheimer’s disease.

In addition to the limitations of current imaging techniques, data analysis and models in network neuroscience have historically been limited to dyadic relationships between neural elements, such as synapses connecting pairs of neurons or Pearson correlations between pairs of brain regions. While these dyadic notions of connectivity have provided important insights about the brain’s circuitry, mounting evidence suggests that higher-order interactions between three or more elements are also crucial for understanding the large-scale behavior of entire brain networks. In order 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. For example, one notable method known as persistent homology has been utilized to extrapolate conclusions about neural activity across scales, escape the problem of selecting appropriate thresholds for functional edge strengths, and extract principled mesoscale features of network organization.

Finally, in addition to generalizing beyond dyadic connections, 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. Since causality reflects the flow of information from one element in a network to another, efforts toward uncovering causal relationships between neurons and brain regions have naturally drawn inspiration from concepts in information theory.
From mutual information to transfer entropy, information theoretic notions of connectivity are increasingly being used to quantify the flow of information in the brain. These measures of causality, in turn, have real-world implications for controlling brain networks and intervening to treat neurological disease and psychiatric disorders.

**Perturbation experiments and the physics of brain network control**

Thus far, we have examined what is known about the structural circuitry connecting neural components in the brain as well as the dynamical laws governing the interactions between these components. An ultimate test of our understanding, however, lies in our ability to control the brain’s behavior. Early attempts to control brain dynamics—dating to Marie-Jean-Pierre Flourens’s lesioning experiments—successfully identified localized brain regions that are important for various cognitive functions. Since these first perturbative experiments, researchers have become increasingly aware of the complex wiring connecting brain regions on the macroscale and neurons on the microscale. An important implication of this networked structure is that localized perturbations (e.g., targeted lesions or stimulation) do not just yield localized effects—they also induce indirect effects that propagate along neural pathways. In this way, 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.

To understand the system-wide impacts of targeted external perturbations, researchers have increasingly drawn comparisons to processes of cognitive control, by which the brain ex-
ecutes intrinsic strategies to control its own behavior. Through analogies with cognitive control, and by leveraging tools from control and dynamical systems theory \cite{15, 224–227}, notions of control and controllability in brain networks have taken a new life, inspiring several fundamental questions \cite{228}. Are brain networks designed to facilitate control \cite{229}? What are the principles that allow brain networks to control themselves toward desired states \cite{224, 230}? Can we leverage these principles to inform stimulation-based therapies for neurological diseases and psychiatric disorders \cite{226, 227, 231, 232}? To address these questions, here we review the current frontiers of brain network control, exploring how the intricate interplay between the brain’s structure and dynamics can support emerging efforts to influence its cognitive functions.

**Linear control and network controllability.** Before investigating the principles of control in the brain, it is useful to review the foundations of network control generally. The primary aim of control theory is to answer the fundamental question: How can a dynamical system be influenced such that it moves toward a desired state? In network control, the system in question typically comprises a complex web of interacting components, and the goal is to drive this networked system toward a desired state by influencing a select number of input nodes (Fig. 4a) \cite{218}. Here we introduce some of the central principles underlying the control of complex networks, with an eye toward applications in network neuroscience.

The starting point for most control theoretic problems is the linear time-invariant control system \cite{233}

\[ x(t+1) = Ax(t) + Bu(t), \]  

(5)
where \( x(t) \in \mathbb{R}^N \) defines the state of the system, \( A \in \mathbb{R}^{N \times N} \) is the interaction matrix, the vector \( u(t) \in \mathbb{R}^M \) defines the input signal, and \( B \in \mathbb{R}^{N \times M} \) identifies the nodes that are directly controlled, where \( B_{ij} \) represents the strength of a signal \( u_j(t) \) on a given node \( i \). In the context of brain networks, \( x(t) \) could represent neural activity (e.g., the BOLD signal measured by fMRI or firing rates measured with single-neuron recordings), \( A \) is typically taken to be a structural connectivity matrix (e.g., white matter tracts estimated using DTI or synapses estimated using electron-microscopy), and \( u(t) \) could define the intensity of electromagnetic simulation to different parts of the brain (e.g., regions or neurons). The reasons for considering linear systems are twofold: (i) they obey the simplest possible dynamics, and therefore represent a natural starting point, and (ii) more complicated nonlinear systems can often be linearized around an equilibrium state.

An important mathematical object in the study of linear control is the controllability Gramian

\[
W = \sum_{t=0}^{T-1} A^t B B^\top (A^\top)^t.
\]

(6)

For example, a linear system is said to be controllable—that is, it can be driven to an arbitrary final state in finite time \( T \)—if and only if the controllability Gramian \( W \) has full rank. In practical applications, many networks that are theoretically controllable cannot be steered to certain states due to limitations on control resources. These practical considerations motivated the introduction of control strategies that minimize the so-called control energy \( E(u) = \sum_{t=0}^{T-1} |u(t)|^2 \). The unique control strategy, for instance, that steers the system from the initial state \( x(0) = 0 \) to a final state \( x(T) = x_f \) with minimum energy is given by

\[
u^*(t) = B^\top (A^\top)^{T-t-1} W^{-1} x_f.
\]

(7)
It can then be seen that the optimal control energy induced by a transition to $x_f$ is simply

$$E(u^*) = x_f^T W^{-1} x_f.$$  \hfill (8)

Thus, by considering strategies for optimal control, we arrive at a natural energy landscape that allows us to ask questions about which states are easier versus harder to achieve. Furthermore, by averaging over many such states, we can begin to build metrics for the controllability of a given network itself. For example, by averaging over all states of unit magnitude, one can see that the average minimum control energy is equal to $\text{Trace}(W^{-1})$. Since for large networks $W$ is often nearly singular, making $\text{Trace}(W^{-1})$ costly to compute, it is common to instead study the average controllability of a system, defined as $\text{Trace}(W)$. Put simply, the average controllability identifies systems that can be driven toward many different states with little effort. If we limit the control input to a single node in the network, then the average controllability quantifies the ability of that individual node to steer the dynamics of the entire system.

In addition to average controllability, linear control theory offers a range of other tools for uncovering the role of network topology in guiding the dynamics of a system. Modal controllability, for instance, quantifies the capacity of a node to push the network toward distant states that are difficult to reach (Fig. 4a). Other approaches attempt to identify the minimum set of driver nodes needed to steer a system toward an arbitrary state, focus on the properties of specific optimal control strategies, or even consider the importance of different edges in propagating control signals. Control theoretic efforts such as these have only recently been applied to understand the locomotion of the nematode specifically and the networked behavior of the brain more broadly. As we will see, these new perspectives have the promise to offer critical
insights about the brain’s dynamics supporting goal-oriented behavior as well as targeted strategies for the diagnosis and treatment of neurological disease and psychiatric disorders.

**Network control in the brain.** While control theory has only recently gained traction in neuroscience, psychological notions of cognitive control have existed for many years\(^2\)\(^1\). Cognitive control encompasses a broad class of processes by which abstract goals or circumstances influence the brain’s neural activity. 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\(^2\)\(^2\)\(^0\), \(^2\)\(^1\). In fact, the prefrontal cortex is now believed to play a key role in many cognitive control processes, from the representation of complex goal-directed behaviors\(^2\)\(^2\)\(^2\) to the support of flexible responses to changes in the environment\(^2\)\(^3\). But how do these notions of cognitive control (as defined by psychologists and cognitive neuroscientists) compare to theories of network control (as defined by physicists and engineers)? Furthermore, can knowledge of the brain’s intrinsic control processes 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. It is interesting, for example, to ask which trajectories or final states are most accessible in the brain. Toward this end, Gu *et al.* considered the energy landscape of common transitions from a baseline activation state to various final states with heightened activity in areas devoted to vision, audition, and motor function\(^2\)\(^4\). Interestingly, the strongest driver nodes for these common transitions represented brain regions with high communicability—or many topological paths through the brain network—to the target
Controllability metrics

a Linear control

- Targeted control
  - Linear dynamics
  - Signal $u_i$

- Uncontrolled trajectory
- Controlled trajectory
- Initial state
- Final state

$\mathbf{x}(t+1) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}u(t)$

b Internal control

- Average controllability
- Modal controllability

- Auditory
- Ventral attention
- Cingulo-opercular
- Frontoparietal
- Default mode
- Dorsal attention
- Visual
- Somatosensory
- Other

- 1%
- 3%
- 2%
- 11%
- 30%
- 18%
- 4%
- 19%
- 12%
- 15%
- 1%
- 18%
- 12%
- 7%
- 11%
- 1%

- Average controllability
- Modal controllability

- Electrode
- e.g., deep brain stimulation
- e.g., treatment for Parkinson’s disease or epilepsy

Figure 4 | Controlling brain networks in theory and practice. 
a | Techniques for the control of linear systems are simpler and far more developed than techniques for the control of non-linear systems. Recent efforts to apply these techniques to neural systems can be naturally separated into methods for targeted control and for controllability metrics. (Left) Methods for targeted control seek to understand and predict the transition of a system from a specified initial state to a specified final state, with stipulations on the energy required, the distance traversed by the trajectory, and the time horizon over which control is enacted. (Right) Controllability metrics provide summary statistics regarding the ease with which a given node in the network could enact a given control strategy with little energy. Two common metrics are the average controllability, which assesses the ease of moving the system to all nearby states, and the modal controllability, which assesses the ability to move the system to distant states. 
b | Control principles have proven useful in the study of the brain’s internal control processes, such as homeostatic regulation and cognitive control. For example, 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. 
c | Control principles are also useful in the study, design, and optimization of external control processes, such as transcranial magnetic stimulation, grid stimulation, and deep brain stimulation, which are currently being used to treat major depression, epilepsy, and Parkinson’s disease.
brain region. In a related study, Betzel et al. used the structural wiring of the brain to simulate transitions between common activity states. They found that optimal control nodes tended to have high degree in the network, and that when this rich-club of hub regions was destroyed by simulated lesioning—a common model of neurodegenerative disease—the ability of the brain to make common transitions was significantly reduced.

In addition to studying the roles of specific control trajectories, complementary approaches have considered trajectory-independent metrics such as the average and modal controllabilities discussed previously. By comparing control theoretic measures of node controllability with the cognitive functions associated with each brain region, Gu et al. found that different types of controllers were located in distinct areas of the brain (Fig. 4b). For example, brain regions with strong average controllability were disproportionately located in the default mode system, which is associated with baseline dynamics; meanwhile, strong modal controllers were 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, while regions associated with cognitive control are optimally positioned to steer the system toward distant states, far away on the energy landscape. In related studies, metrics of controllability were found to differ by sex and to be correlated with human performance on a range of cognitively demanding tasks, particularly those requiring cognitive control. Notably, these same controllability metrics were found to be altered in bipolar disorder, and in individuals with high genetic risk.
As a final layer of abstraction, rather than studying the controllabilities of specific brain regions, one could envision averaging over all regions to quantify the mean controllability of an entire brain network. Interestingly, by taking precisely this approach, Tang *et al.* established that brain networks as a whole are finely tuned to maximize both average and modal controllability, thereby supporting a diverse range of possible control strategies. Furthermore, by comparing subjects in different stages of adolescence, the researchers found that brain network controllability increases with age, suggesting that neural circuitry evolves over time to support increasingly complex dynamics. Taken together, these studies demonstrate that network measures of optimal control and controllability correspond closely to existing notions of intrinsic and cognitive control in neuroscience. This close correspondence, in turn, suggests that network control theory, by taking into account the complex wiring of the brain, has the promise to enrich our understanding of the brain’s control principles.

**Targeted perturbations and the future of brain network control.** While notions of cognitive control continue to provide insights about how the brain controls itself, researchers are also ultimately interested in developing techniques for controlling the brain through external interventions. These two efforts serve to complement one another, with an improved understanding of the brain’s intrinsic control principles informing targeted therapies for neurological diseases and psychiatric disorders based on external control (Fig. 4c). Perhaps the most successful example of targeted external perturbations is in the treatment of Parkinson’s disease, where deep brain stimulation is frequently used to alleviate clinical symptoms. However, despite its therapeutic benefits, it remains unclear exactly how and why deep brain stimulation is
so effective \textsuperscript{216,248}. Recent attempts to understand the distributed effects of targeted stimulation have naturally employed methods from control and dynamical systems theory \textsuperscript{249,250}. These efforts have resulted in the identification of neural circuits that are critical for reducing the symptoms of Parkinson’s disease \textsuperscript{250,251} as well as the development of closed-loop strategies for dynamically updating brain stimulation based on neural activity \textsuperscript{252,253}. Other notable examples of therapeutic interventions include the use of targeted stimulation for the suppression of epileptic seizures \textsuperscript{227,254–256}, noninvasive transcranial stimulation for the treatment of depression \textsuperscript{257,258}, and dynamically titrated anesthesia for the modulation of consciousness during surgery \textsuperscript{259,260}. Across each of these applications (and a number of others), network control theory is being actively utilized to better understand how the effects of targeted therapies propagate along the brain’s structural wires to induce system-wide changes in behavior \textsuperscript{234}.

Throughout this section, we have focused primarily on simple control strategies that assume idealized linear dynamics and on targeted therapies that rely on the coarse-grained stimulation of entire brain regions. Emerging efforts in neuroscience and control theory, however, are opening the door for a number of significant improvements, including: (i) techniques for fine-scale control of neural activity \textsuperscript{261–264}, even down to the level of individual neurons \textsuperscript{265,266}, (ii) systems identification approaches that allow for the incorporation of effective connectivity measurements to inform control, superseding solely structural explanations \textsuperscript{267}, and (iii) generalizations of linear control theory that include more realistic nonlinear dynamics \textsuperscript{163,164,166}. Among recent advances in the manipulation of fine-scale neural activity, arguably the most promising tool is optogenetics, which offers millisecond-scale optical control of specific cell types within the brains of conscious
animals, It's striking precision, in some cases even down to single-cell resolution, has enabled researchers to investigate the nature of causal signals between neurons and to study how these signals give rise to qualitative changes in animal behavior.

While linear control theory continues to provide critical insights about how signals propagate along the brain’s structural wiring, interactions between neural components, from individual neurons to entire brain regions, are highly nonlinear. Initial efforts to develop a theory of nonlinear control, dating as early as the 1970s, quickly converged to the conclusion that results as strong and general as those derived for linear dynamics could not be obtained for a general nonlinear system. Fortunately, concerted theoretic efforts have led to weaker notions of nonlinear controllability, notable among which are techniques for linearizing nonlinear systems around stable equilibrium states and methods for leveraging the symmetries of a system, such as repeated network motifs, to simplify control strategies. Additional efforts have utilized advances in computing power to simulate the effects of external perturbations across a range of model systems, including networks of FitzHugh–Nagumo neurons, Wilson–Cowan neural masses, and Kuramoto oscillators as well as artificial neural networks such as the Ising model. Together, recent advances in high-precision neural stimulation like optogenetics and our 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 behavior—once considered a topic of science fiction—now has the promise to shape how we think about individualized strategies for guiding healthy brain function.
Conclusions and future directions in the neurophysics of brain networks

The intricate inner workings of the brain remains 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, 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 behavior. Here we reviewed recent advances toward meeting this challenge with an eclectic array of curios from the physicist’s cabinet: statistical mechanics of complex networks, thermodynamics, information theory, dynamical systems theory, and control theory. In the course of our exposition, we considered the principles of small-worldness, interconnected high-degree hubs, modularity, and spatial embedding that provide useful explanations for the architecture of structural brain networks. We then saw these same principles reflected in the organization of long-range synchronization supporting information dissemination, and the computations that can result therefrom. As with any physical system, a natural next step is to probe the validity of our descriptive and explanatory models using perturbative approaches both in theory and experiment. Thus, we next summarized the utility of network control theory in offering insights into internal control processes such as homeostatic regulation and cognitive control, as well as external control processes such as neurostimulation, which are currently being used to treat multiple disorders of mental health.

Throughout the exposition, we described current frontiers in the investigation of brain net-
work structure, function, and control. Although we will not reiterate those points here, we do wish to offer the sentiment that, while the empirical advances laying the foundation of the field have spanned several decades, the network physics of the brain is an incredibly young area, rich with opportunities for discovery. And perhaps—with a bit of courage—we may even begin to provide an empirical constitution to the deeper philosophical questions that humans have wrestled with for millennia: What makes us unique and different from non-human animals? How do we represent abstract concepts such as value to ourselves and others? How are representations transmitted throughout the brain or reconfigured based on new knowledge? What makes a mind from a brain? Physicists, the brain is calling you.
Box 1 | Bridging spatiotemporal scales. In the context of complex systems generally and neural systems specifically, the cutting edge work relates to extending our tools, theories, and intuitions from a single network to so-called multiscale, multilayer, and multiplex networks.39, 283 Perhaps the most obvious context in which to make this extension is from regional networks to cellular-scale neuronal networks.122 Large-scale brain activity provides a coarse-grained encoding of neural processes, and the map from cellular dynamics to regional dynamics reflects rules of system function. By combining these two layers we can address questions like, “How do cellular processes shape circuit behavior?” The next logical extension is to move even further down the natural hierarchy of scales to understand how molecular networks—including gene coexpression networks113, 284–286—shape the behavior of cells.287 Understanding how molecular mechanisms affect large-scale brain network function is critical for the development of effective pharmacological interventions.111, 288, 289 By extending the network model from regions to cells to molecular drivers, we can ask questions like, “How do genetic codes and epigenetic drivers shape circuit behavior across spatial scales?” And in a final extension, it is time to move up in the natural hierarchy of scales to combine information from the connectivity within a single human brain to the connectivity between human brains in large-scale social networks.281, 290, 292 While brain activity and structure offer biological mechanisms for human behaviors, social networks offer external inducers or modulators of those behaviors.293 By extending the network model to this larger scale, we can start to ask—and potentially answer—questions like, “How do brains shape social networks? And how do social ties shape the brain?” This extension will be important in understanding human behavior within the broader contexts of culture and society.
Box 2 | **Information theory and network neuroscience.** At its core the brain is an information processing system, having evolved over millions of years to encode and manipulate a continuous stream of sensory signals. As such, information theory—the science of how signals are encoded and processed—provides a compelling lens through which to study the brain’s function. Information theory began with the 1948 paper “A Mathematical Theory of Communication,” wherein Claude Shannon proposed the entropy of a signal as the natural measure of its information content and derived fundamental limits on the information capacity of a communication channel. Soon after, MacKay and McCulloch adapted the concept of channel capacity to obtain limits on the rate at which one neuron can transmit information to another, sparking the study of information flow in the brain. Subsequent work by Attneave and Barlow proposed the idea that neural activity is optimized for the transmission of sensory information, providing the foundation for future investigations of neural coding.

Despite these initial efforts bridging information theory and neuroscience, progress slowed primarily due to difficulties obtaining unbiased information estimates from neural systems. Improvements in experimental techniques, however, eventually sparked renewed interest, spurring the introduction of robust methods for estimating information theoretic quantities. On the basis of these advancements, information theory has once again become a powerful tool for the net-
work neuroscientist. Recent attempts, for instance, to uncover causal relationships between neural elements have successfully adapted notions of information flow, such as mutual information and transfer entropy\textsuperscript{304,305}. At the same time, efforts to understand large-scale correlations within neuronal populations have utilized the principle of maximum entropy\textsuperscript{306}, resulting in Ising-like models of collective neural behavior\textsuperscript{133,185}. As information theory becomes increasingly integrated into the fabric of neuroscience, physicists are uniquely positioned to pioneer exciting new techniques for investigating the nature of information processing in the brain.
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