ANNUAL REVIEWS

Annual Review of Biophysics

Toward Principles of Brain Network Organization and Function

Suman Kulkarni[1] and Dani S. Bassett[1,2,3,4]

[1]Department of Physics & Astronomy, University of Pennsylvania, Philadelphia, Pennsylvania, USA; email: sumank@sas.upenn.edu

[2]Department of Bioengineering, Department of Electrical & Systems Engineering, Department of Neurology, and Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA; email: dsb@seas.upenn.edu

[3]Santa Fe Institute, Santa Fe, New Mexico, USA

[4]Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

Annu. Rev. Biophys. 2025. 54:353–78

First published as a Review in Advance on February 14, 2025

The *Annual Review of Biophysics* is online at biophys.annualreviews.org

https://doi.org/10.1146/annurev-biophys-030722-110624

Keywords

neuroscience, connectomics, graph theory, statistical physics

Abstract

The brain is immensely complex, with diverse components and dynamic interactions building upon one another to orchestrate a wide range of behaviors. Understanding patterns of these complex interactions and how they are coordinated to support collective neural function is critical for parsing human and animal behavior, treating mental illness, and developing artificial intelligence. Rapid experimental advances in imaging, recording, and perturbing neural systems across various species now provide opportunities to distill underlying principles of brain organization and function. Here, we take stock of recent progress and review methods used in the statistical analysis of brain networks, drawing from fields of statistical physics, network theory, and information theory. Our discussion is organized by scale, starting with models of individual neurons and extending to large-scale networks mapped across brain regions. We then examine organizing principles and constraints that shape the biological structure and function of neural circuits. We conclude with an overview of several critical frontiers, including expanding current models, fostering tighter feedback between theory and experiment, and leveraging perturbative approaches to understand neural systems. Alongside these efforts, we highlight the importance of contextualizing their contributions by linking them to formal accounts of explanation and causation.

Contents

1. INTRODUCTION

Recent years have witnessed remarkable experimental strides in producing detailed, large-scale maps of neural systems and in developing methods to probe and perturb neural activity. Advances in electron microscopy and volumetric reconstruction techniques now allow researchers to examine increasingly larger organisms at the cellular level by mapping out synaptic connections between neurons. While the synaptic connectivity of the nematode *Caenorhabditis elegans* was first mapped in 1986 (201), we now have maps of an adult fly (*Drosophila melanogaster*) brain (52, 162) and portions of the mouse (*Mus musculus*) (122) and human cerebral cortex (167), among other species (76, 158, 190). These fine-scale maps add to approaches that probe connectivity at coarser scales, such as diffusion tensor imaging (DTI) and magnetic resonance imaging (MRI) (56, 104, 130). In addition to these measures of structure, technological advances in large-scale recordings of neuronal activity—such as optical calcium imaging and electrophysiological probes—now make it possible to measure the activity of thousands of neurons simultaneously (136, 172, 181, 200). In fact, with Neuropixels probes, researchers can track neuronal activity at high spatiotemporal resolution in freely moving animals (90, 136, 172). With this increasing access to large quantities of experimental data comes opportunities to develop quantitative methods that can cope with these large datasets and distill from them underlying principles of brain structure and function.

A central theme in the study of neural systems is to examine how macroscopic functions and behaviors arise from fine-scale interactions between neural elements. This perspective aligns well with the framework of statistical physics, which studies the macroscopic behavior of large ensembles of interacting microscopic entities. However, a major caveat here is that in traditional applications of statistical physics, the elementary components of studied systems are relatively simple and well-understood. That is, collective effects result from the interaction of many simple elements rather than from the complex behaviors of the entities themselves. In contrast, the brain is highly complex, characterized by heterogeneous and dynamic elements and interactions that span multiple scales. For instance, at the cellular level, neurons display astounding diversity in their structure, gene expression, and biophysical properties (106, 137, 169, 210). Within the mammalian retina alone there are at least 60 different cell types (117), and such specialization is a common feature across brain regions. A key challenge then is determining which details are

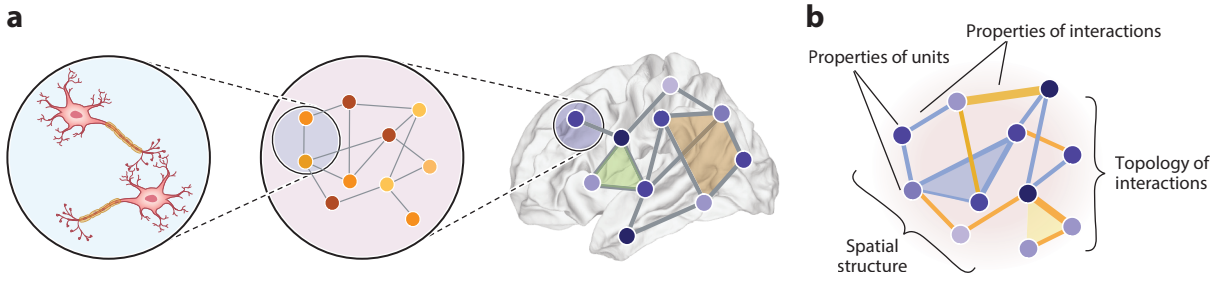

Figure 1

Organization of the brain viewed at different scales. (*a*) At the fine scale, neural systems are composed of interacting neurons (*left*). To study the activity arising from the collective behavior of groups of neurons, researchers build coarse-grained models describing networks of neurons (*center*). To study the large-scale activity of an entire brain, researchers consider even coarser descriptions where nodes correspond to brain regions or neuronal populations (*right*). (*b*) The activity and functioning of neural systems are governed by the individual properties of the units, the properties of their interactions, and the structure of interactions. Together, all these factors shape the dynamics of the network itself and the dynamics of activity that occurs on the network.

important for a specific research question. Despite the complexity and inherent messiness associated with living systems, one hopes to take some inspiration from statistical physics and develop simple, tractable models that capture important properties of the system. Here, we discuss opportunities that recent large-scale experimental efforts provide to glean principles of neural system design and function. Our account is explicitly multiscale, focusing on methods rooted in statistical physics, network theory, and information theory.

We structure our initial discussion in Sections 2–4 on the basis of spatial scales (as depicted in **Figure 1**), focusing on the organization and modeling approaches relevant at each scale. It is important to note, however, that there is no clean separation between these scales and they are interdependent. While information at small scales (such as neuron properties) influences larger-scale phenomena (such as overall network function), large-scale processes can also feed back to smaller scales. For example, neural systems exhibit plasticity, wherein behavior or brain activity at the network level can reshape connections between neurons (111). Another example, operating on shorter timescales, is attention modulation, where large-scale networks involved in attention regulation can modulate the activity of neurons in sensory areas like the visual cortex (147). This top-down influence can enhance the firing rates and selectivity of neurons processing stimuli. Recognizing such feedback loops is important as we build a multiscale picture of the brain.

We begin our discussion at the fine scale in Section 2 with a brief overview of detailed biophysical models of individual neurons. In Section 3, we discuss small populations of neurons, surveying modeling approaches and their associated trade-offs. Section 4 expands to large-scale brain networks, where we first outline methods used to study the structure and activity of large brain regions at both coarse and fine resolutions and then discuss how tools from physics and mathematics are used to analyze these datasets. With this multi-scale picture built in Sections 2–4, Section 5 explores biological design principles and constraints that shape the properties and functioning of brain networks discussed throughout the review. In Section 6, we describe several critical frontiers: expanding theory and modeling to make sense of the latest connectome datasets, enhancing the feedback loop between theory and experiment, and using perturbative approaches to better understand neural systems. We conclude with an overview of formal accounts of explanation and causation in the context of neurophysics, underscoring the importance of contextualizing ongoing efforts.

2. ORGANIZATION AND MODELS AT THE CELLULAR LEVEL

Although this review primarily focuses on large brain networks, it is crucial to discuss the neurons that make up the brain (see **Figure 1**). Neuron biophysical properties can affect both information processing within individual cells and collective behavior of networks of neurons. For example, the biophysical properties of neurons can influence synchronization (71, 75), which is crucial for information processing, and abnormalities in synchronization are linked to brain disorders (31, 89, 180). Morphologically, neurons are specialized structures that allow for communication and computations: Dendrites branch out extensively to collect signals from other neurons, while the axon extends to transmit signals onward. There is enormous diversity in the morphological, physiological, and connectional features of neurons, which influences their functional properties (106, 117, 137, 169, 210). Neurons transmit information in the form of electrical pulses (called spikes or action potentials) characterized by a rapid change in membrane potential over very short timescales, though there are classes of nonspiking neurons that generate graded potentials instead (including many neurons in the *C. elegans* nervous system) (127, 149). Once a spike is generated, neurons relay signals to neighboring neurons through synaptic connections that may be chemical (orchestrated through neurotransmitters) or electrical (through gap junction channels that connect neurons). Ultimately, a combination of all the excitatory or inhibitory influences on a neuron determines whether it generates an action potential.

A cornerstone for computational neuroscience was the Hodgkin–Huxley model (80), developed in the 1950s to describe the generation of action potentials in a space-clamped squid giant axon. This detailed biophysical model describes the generation of action potentials through fast depolarizing and slow hyperpolarizing currents. The original model consists of a system of four coupled, nonlinear differential equations with parameters obtained from neurophysiological recordings (80). This model has been extended in several ways to study different kinds of neurons, for example, incorporating additional ion channels (78) (since most neurons have more ion channels) and stochastic elements (70). At the same time, the relatively high dimensionality of the Hodgkin–Huxley model has motivated simpler lower-dimensional models that can still reproduce many key features of neuronal dynamics. These include the FitzHugh–Nagumo model (59), the Hindmarsh–Rose model (79), and the Morris–Lecar model (125, 148). These simplified models are far more amenable to mathematical analysis and facilitate efficient large-scale simulations of groups of neurons. A distinct approach is to consider phenomenological models that do not directly capture the detailed biophysics of spike generation. Examples of this include the integrate-and-fire model.[1] At its heart, this model uses a differential equation to describe membrane potential dynamics. Spikes are said to occur when the potential crosses a threshold, following which the potential is algorithmically reset to a certain value below the threshold. Several modifications of this model exist with varying levels of biophysical realism, including nonlinear (63) and adaptive (27) integrate-and-fire models. Another popular model is the Izhikevich model, which combines some of the biologically realistic aspects of Hodgkin–Huxley–type models with the computational efficiency of integrate-and-fire–type models (84). At the extreme end of abstraction are artificial neuron models. One of the earliest examples is the McCulloch–Pitts neuron (118), a binary model whose output is based on a weighted sum of its inputs. Subsequent extensions, including the perceptron (151) and Hopfield networks (82), laid the groundwork for future developments in machine learning.

As noted above, neurons have an intricate spatial structure and are not point-like objects. Much of the total membrane area of neurons is occupied by the dendritic tree, whose structure and extent

[1]This model was originally introduced long before the mechanisms of spike generation were even known (99).

influence the neuron's properties and firing rate (108). Dendrites are typically modeled using a cable equation describing the potential as a function of time and space, and the numerous branches can be accounted for using compartmental models. While ion channels can also be added to these compartments for more biological realism, a more tractable approach is to lump all processes responsible for spike generation in the soma and treat the dendrites as passive cables. In addition to dendrites, the length and the level of myelination of axons can affect signal conduction (69). Evidently, there is astounding diversity in neuronal properties and morphology that can influence activity. Consequently, it is useful to classify action potentials into excitability classes according to the type of bifurcation that occurs close to the threshold (57, 148). For more detailed descriptions of the models discussed in this section, we refer the reader to References 57, 69, and 143.

3. MODELING SMALL GROUPS OF NEURONS

In principle, one could keep adding detail to neuron models to account for various biological nuances. However, there is a trade-off here between building models that are extremely detailed and building models that are tractable. This is particularly important for research questions aimed at understanding how large populations of neurons orchestrate activity, function, and behavior. The challenge with detailed models is not solely a matter of the computational power required. These models rely on numerous biophysical parameters that can be difficult to measure reliably in experiments. Ideally, parameters for each neuron could be estimated from in vivo experiments (93, 187, 202). However, this requires experiments to collect data for each type of ion channel, many of whose details may still be unknown. When such experiments are infeasible, parameters are often tuned in an ad hoc manner. Even when measured, these parameters are often obtained under specific conditions, making them less generalizable. Models with hundreds of parameters can also become difficult to reliably estimate, interpret, and analyze. Even for a small and relatively well-studied organism like *C. elegans*, which has 302 neurons, including the dozens of (known) ion channels can result in a large number of parameters. Further, many parameter combinations can produce similar neural activity and network behavior (115, 142). While this degeneracy may be a feature rather than a drawback (possibly underpinning resilience) (55, 142), it makes detailed bottom-up approaches challenging.

Detailed biophysical models are valuable for understanding cellular processes, yet how these processes combine to produce the complex macroscopic behaviors observed even in relatively simple organisms remains unclear. Not all details at the cellular level may be relevant to higher-level processes in organisms. Moreover, experiments in humans and other large animals typically track the activity of regions rather than individual neurons. These considerations align well with principles from statistical physics, which provides a framework for studying macroscopic phenomena emerging from large ensembles of interacting microscopic entities. To examine collective behavior, it often suffices to use coarse-grained descriptions that capture essential features without accounting for every detail. Across fields of science, from physics to systems biology, several multiparameter models display behaviors that largely depend only on a few key parameters, with other parameters being relatively unimportant for model behavior and prediction (110, 179). For instance, understanding the propagation of sound waves requires knowledge of coarse-grained properties such as the density and compressibility of matter rather than the precise shape of each molecule. Such an approach of building minimal models is not to diminish the value of detailed explanations but to underscore that the choice of model depends on the phenomena under study and the research questions of interest. Inspired by statistical physics, a natural question arises: Can similar principles guide the study of nervous systems? How do fine-scale, microscopic descriptions of brain organization connect to the functioning of entire nervous systems and the behaviors they support?

To model larger populations of neurons, researchers typically track the average activity of groups of neurons rather than modeling individual spikes of every neuron. Indeed, there is evidence that the brain tends to be organized into assemblies of neurons that display strongly correlated activity, operating as a functionally homogeneous unit (26, 46). Broadly speaking, there are two different approaches to construct such lower-dimensional average-rate models. The first is to build phenomenological neural mass models that capture observations at the scale of neuron groups. The second, more bottom-up approach involves developing approximations of spiking neuron models. In general, population-level models are better suited to study data recordings that reflect coarse-grained neural activity, such as electroencephalography (EEG) or magnetoencephalography (MEG), which are commonly used in humans and large animals where invasive fine-scale single-neuron-resolution studies are not always possible (44, 45, 176).

A popular phenomenological model is the Wilson–Cowan model, which (in its original form) describes the average firing rates of two homogeneous populations of excitatory and inhibitory neurons (48, 204). Another example is the Jansen–Rit model (85), which was developed as a model for EEG recordings. Coarse-grained neural mass models like these have been used to describe various phenomena, such as seizure activity observed in epilepsy (119, 168), traveling waves in the visual cortex (150, 203), visual hallucination patterns (58), working memory (48), and the impact of Alzheimer disease proteins (144). While such phenomenological models are insightful, it can be difficult to directly connect them to microscale properties of neurons as they lack sufficient detail (22, 40). Instead, bottom-up approaches, wherein neuron models are reduced either exactly or through approximation schemes, provide an opportunity to bridge dynamics on microscopic and macroscopic scales (22, 25, 35, 40). A common approach is to start with spiking neuron models that incorporate basic microscopic properties of a neuron (typically a variant of the integrate-and-fire model), and develop a mean-field approximation (40, 49, 124, 146).

Such neural mass models are also key ingredients for modeling approaches used in the Virtual Brain (157, 160, 161), which aims to simulate collective whole-brain dynamics. A key goal of this initiative is to build digital twins capturing most relevant features, enabling researchers to test specific hypotheses and intervention strategies for health care and personalized medicine (194). Ongoing efforts focus on applying these models to health care applications, including multiple sclerosis (192), epilepsy (88), aging (100), and Parkinson disease (3). A key challenge in building such biophysically principled models is inferring the microscopic parameters that underlie macroscale recordings. Efforts such as the Human Neocortical Neurosolver (129) are underway to study the circuit-level and cellular level mechanisms and origins of measured EEG/MEG signals. A better understanding of these origins could be useful for predictions of neural function and disease and in probing the effects of stimulation on neural systems (33, 135). As our discussion has already reached the regime of large datasets, in the next section we discuss larger brain networks in more detail.

4. ANALYZING LARGE NETWORKS

With experimental advances, we are now obtaining increasingly high-quality and large-scale data on both the structure and the activity of neural systems. Tools from complex systems provide a means to represent and analyze these data. Although we primarily discussed networks of interconnected neurons in the previous sections, these tools can be applied to various types of brain network models representing connections or interactions at scales that are either coarser or finer. These also include models that do not solely reflect anatomical connections, such as maps of signal propagation. Before surveying these methods, we first discuss the kinds of brain networks that researchers typically study. Our goal is to build a high-level understanding of the information these

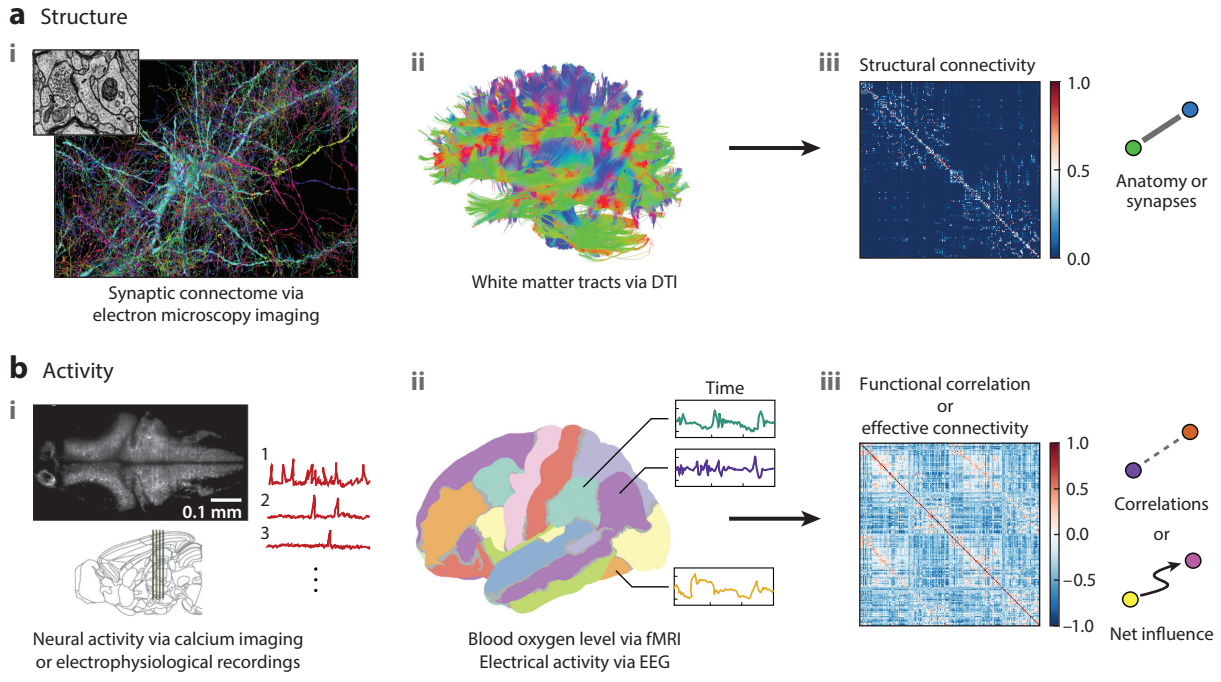

Figure 2

Measuring brain network structure and activity. Various experimental techniques are used to probe the structure and activity of neural systems at different resolutions. (*a*, *i*) For the fine-scale structure of the brain, electron microscopy imaging can be used to map out neurons and their synaptic connections. Subpanel inset adapted with permission from Reference 167. Subpanel main image adapted from data in Reference 167 (CC BY 4.0). (*ii*) To measure the brain's macroscale axonal or white matter organization, DTI is used. Subpanel adapted from Reference 135 (CC BY 4.0). (*iii*) From these structural data, whether mapping connections at the microscale or at the macroscale, an adjacency matrix can be constructed, with entries weighted appropriately. Colors represent connection strength. In DTI, nodes represent nonoverlapping gray matter volumes, while in synaptic connectomes, nodes represent individual neurons. (*b*, *i*) At the microscale, activity of neurons can be measured using fluorescence calcium imaging (*top*) or electrophysiological methods (*bottom*). Top image in subpanel *i* adapted from Reference 186 (CC BY 4.0). Bottom image in subpanel *i* adapted with permission from Reference 172. (*ii*) Large-scale brain activity is typically monitored by measuring blood oxygen level variations in different parts of the brain using fMRI or by measuring the overall electrical activity using EEG. Subpanel adapted from Reference 135 (CC BY 4.0). (*iii*) Similarities between pairs of activity time series can be calculated and represented in a functional correlation matrix. Alternatively, direct or indirect causal measures of the net influence of one region (or neuron) on another can be calculated as effective connectivity. Abbreviations: DTI, diffusion tensor imaging; EEG, electroencephalography; fMRI, functional magnetic resonance imaging.

brain networks capture; for more detailed discussion, we refer the reader to recent review articles and books (60, 96, 211). Very broadly speaking, most brain networks fall into two categories: those that capture relationships of structure and those that capture relationships of activity, as depicted in **Figure 2**.

Advances in electron microscopy and automated image analysis have enabled detailed 3D reconstructions of brain networks at single-neuron resolutions (28). These connectomes map out neurons and the chemical synapses between them (see **Figure 2*a***). We now have connectomes for a range for species, including *C. elegans* (201), larval zebrafish (76), larval and adult *Drosophila* (41, 52, 162), and parts of the mouse (122) and human (167) cortex. Simultaneously, noninvasive methods have made it possible to study neural circuits in humans and larger animals. Techniques like diffusion MRI tractography and DTI track the diffusion of water molecules to reconstruct

white matter tracts connecting distinct brain regions (60, 211) (see **Figure 2*a***). Whether mapping synapses linking neurons or white matter tracts connecting brain regions, one can construct structural brain networks that capture how neural elements are wired together. The nodes and edges in these networks are defined according to the method used to quantify them. For networks built from methods that probe the microscale structure, such as electron microscopy, nodes represent individual neurons and edges are generally weighted on the basis of the number of synapses between neuron pairs. For networks built from methods that probe the macroscale structure, such as DTI, nodes represent brain regions and edges are weighted on the basis of the strength and density of the white matter tracts connecting them (60). Building appropriate representations of structural data is an ongoing challenge, and the best approach depends upon researchers' goals and the data available. It is important to recognize the assumptions and limitations of current methods. For instance, synaptic networks are typically weighted by synapse count, but not all synapses may have the same strength or neurotransmitter type. Similarly, current tractography algorithms used in macroscale studies are unable to resolve the directionality of connections (163). In Section 6, we elaborate on how more detail can be incorporated in models when available.

In addition to structural mappings, various experimental techniques are used to probe brain activity at different scales (see **Figure 2*b***). At the neuronal scale, calcium imaging and electrophysiological recordings are used to monitor the activity of individual neurons. These methods have enabled simultaneous whole-brain measurements of single-neuron activity in small transparent animals like *C. elegans*, hydra, and zebrafish (145, 181, 209). Efforts are now underway to expand the number of neurons that can be simultaneously tracked in *Drosophila* and in mammals (47, 90, 136). Further, Neuropixels probes now enable single-spike-resolution recordings in large populations of neurons distributed across brain regions in freely moving animals, with the ability to track this activity over the scale of weeks and even months (90, 136, 172). The ability to perform such recordings stably over longer timescales opens up exciting opportunities to understand processes such as learning, memory, and behavior (172). In humans, researchers use noninvasive methods like EEG, which records electrical activity through sensors placed on the scalp, and functional MRI (fMRI), which uses blood oxygen levels in 3D brain images as a proxy for neural activity (60). When building networks from fMRI or EEG data, researchers measure correlations, coherence, or other statistical dependences between the activity of different regions to quantify functional similarity (60, 96). We note that correlative approaches, though insightful, do not provide direct measures of causality. Such activity maps capture both the intrinsic properties of neural systems and the influence of external stimuli. For instance, neural activity can change depending on the type of sound or visual stimulus an individual encounters. Understanding how the brain encodes and reflects external information is central to the study of neural coding and representation and can reveal how both intrinsic structure and external factors shape neural activity.

From these datasets, tools developed in physics and mathematics enable researchers to uncover patterns of organization that may not otherwise be immediately apparent. Across different organisms and spatial scales, such efforts have identified properties common in brain networks across organisms. These include small-world properties (9), heavy-tailed edge weight and degree distributions (109), modularity (77, 171), and the existence of hubs (178, 185), among others. The presence of these features across vastly different species suggests that there might be general organizing principles at play and that these features might support specific functions, which we explore in detail in Section 5. We also remark that while network science provides an array of metrics to quantify organization, the goal has never been to be merely descriptive. Instead, the goal is to seek insight into how these properties arise and their implications for neural function (13).

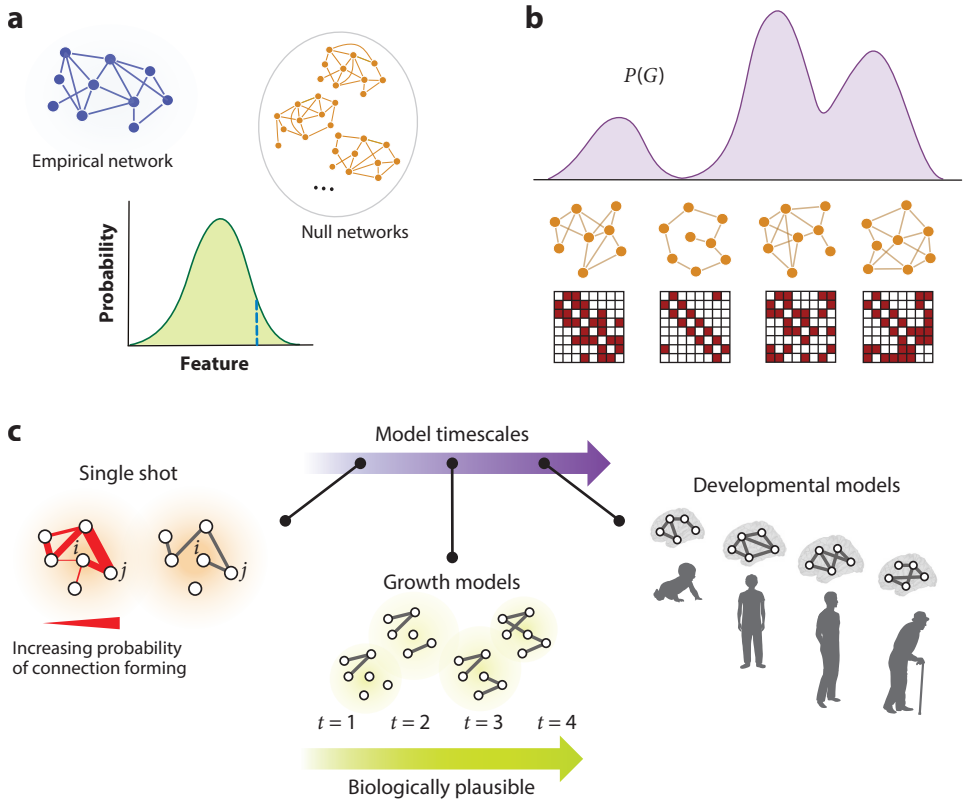

Figure 3

Statistical analysis of brain networks. (*a*) Comparisons with null networks facilitate a principled assessment of how significant an empirically observed property is. To determine whether a feature of the empirical network is statistically unlikely, one can generate an ensemble of null networks. These null networks preserve specific desired properties of the empirical network, forming the null hypothesis, but are otherwise random. The feature of interest can then be calculated for each null network to obtain a probability distribution of the feature under the null hypothesis. (*b*) The exponential random graph model enables the generation of ensembles from the ground up that constrain certain properties, producing a probability distribution in the space of all possible graphs. Such an ensemble can then be used to test whether the constrained properties are explanatory of an observed network's structure. These ensembles can also function as null networks. (*c*) More broadly, generative modeling is a framework for constructing synthetic networks based on a set of rules. The space of generative models can span different timescales. In single shot models, connection probabilities are defined early on, and the network is generated in a single step. More biologically realistic models operate on timescales closer to that of development and can be used to model network growth and development. Intermediate models lie between these two extremes, where the network grows over arbitrary timescales that do not have biological interpretation. Panel *c* adapted from Reference 21 (CC BY 4.0).

When a new network and its features are examined, comparisons with null models enable researchers to benchmark the significance of these features (189) (**Figure 3*a***). Null models are ensembles of networks that preserve certain selected features of a network but are otherwise random. In the best scenario, null models can disentangle a given network feature from other network properties, though this may not always be possible. The selection of graphs for sampling null models requires careful consideration. For example, the Erdős–Rényi graph model, which places edges between nodes with equal probability, often does not reflect processes or constraints relevant to

the brain. Conversely, null models that constrain the space of graphs too much can potentially limit how generalizable the results are. Constraints inherent to the empirical network, such as the presence of self-loops or multi-edges, can be usefully reflected in the null graph space, as these can directly affect conclusions (61). In practice, null networks are typically obtained by either rewiring the original network according to specific rules or building them from the ground up using generative models (189). An example of a rewiring model is the degree-preserving configuration model, which involves rewiring the graph using double-edge swaps among edges (61). This model retains the exact degree sequence, preserving features like hubs and heavy-tailed degree distributions that are typical of brain networks, allowing researchers to assess how the network's degree sequence influences features of interest. Rewired null models can also be constructed to make the edge swaps based on other constraints, such as edge weight or path lengths.

In contrast to rewiring models, generative models build networks from scratch using specific rules, such as homophilic attachment or minimization of the total edge length (21, 189). Generative modeling is also insightful for examining design principles that shape network features. Since brain networks are an outcome of biological processes that are inherently noisy, it is often useful to view neural systems probabilistically, that is, not as a fixed network but as a distribution over a space of networks informed by biologically motivated design principles. Exponential random graph models provide a means to obtain such a probability distribution and to systematically explore local design principles behind real networks (50, 170). A part of the family of maximum entropy models (86), the exponential random graph probability distribution reproduces certain selected features but is otherwise maximally random (**Figure 3*b***). Although our discussion thus far has focused on static networks, brain networks—both structural and functional—are dynamic. Exponential random graphs can be appended with this information by creating a time series and estimating parameters for this sequence. These are termed temporal exponential random graph models (50).

As discussed above, neuroscience experiments can now record the activity of thousands of neurons simultaneously. Although this number is rapidly increasing, it still represents only a fraction of the total number of neurons involved in complex behaviors, such as movement, in larger organisms. However, controlled experiments across different brain regions suggest that neural activity is highly structured and tends to be confined to lower-dimensional manifolds (38, 42, 65, 67)—in other words, the number of latent variables required to explain observed variance is far fewer than the number of recorded neurons. These lower-dimensional manifolds are spanned by patterns of activity termed neural modes, which provide building blocks of neural dynamics and function. Many statistical dimensionality reduction techniques have been developed to obtain lower-dimensional representations from high-dimensional datasets of neural activity (42, 87). Building empirical models of the nonlinear dynamics underlying population activity and inferring meaningful latent representations are ongoing endeavors, increasingly aided by deep learning techniques (134, 175). Such models can illuminate the relationship between neural activity and behavior and even inform therapeutic intervention strategies such as deep brain stimulation. Future work aimed at relating neural population geometry to circuit mechanisms and biological properties could enhance the impact of these approaches (38).

Another framework to examine the structure of neural activity, rooted in statistical physics, is based on the maximum entropy principle. This approach involves constructing probability distributions over the space of network states that match selected observed properties of the system while otherwise remaining as random as possible (86, 164). Initially, pairwise maximum entropy models were developed by constraining over the average activity and correlations between pairs of elements (4, 164). Although this method effectively captured correlations among tens of neurons, it struggled to capture correlations among hundreds of neurons sampled across more distant

subgroups (66, 120), hinting at the role of higher-order correlations for such samples. While higher-order correlations can be incorporated manually to improve these models (66), a more scalable approach for larger datasets is based on random projections (114). The philosophy behind random projections is also rooted in statistical mechanics: Higher-order interactions are captured in the form of random projections, and the structure of this randomness is constrained using data. Maximum caliber models, which generalize the maximum entropy principle to account for dynamic correlations, are a less explored class of models (140). Incorporating such time dependence into maximum entropy models to model temporal dynamics of neural activity is an important direction that could complement methods used to infer latent dynamics described previously, thereby potentially aiding interpretability.

With these experimental and theoretical tools, understanding how the brain's structure constrains neural dynamics and how these dynamics in turn support function is a central pursuit in neuroscience. For instance, how do animals process information from a vast array of sensory cues to reliably navigate their environment? How is the brain's circuitry organized to support decision-making based on sensory input and learning? The ability to measure circuit activity and structure within increasingly larger neuronal populations is enabling researchers to explore these questions in greater depth. The visual system, in particular, has been pivotal in investigating brain function and the neural mechanisms underlying sensory processing. For example, research has shown that certain retinal neurons fire specifically in response to stimuli moving in one direction while showing minimal response to movement in the opposite direction due to asymmetric responses by upstream neurons (5, 6, 24). Connectomes have also helped clarify circuit motifs and dynamics in central brain regions, which link to important functions like self-location and goal-directed navigation (7, 83, 94, 165). Additionally, experiments in primates and rodents indicate that the neocortex exhibits choice-selective activity during perceptual decision-making tasks. The ability to record populations of activity during behavioral tasks, along with access to ensemble wiring diagrams, now enables researchers to study how the brain circuitry supports decision-making (98, 126) and learning (11, 126). Investigating the statistical dependence of function on structure—or the structure–function coupling in brain networks—is an active area of research and ongoing work aims to understand how this relationship varies across brain regions, over time, and between individuals (62). We note, however, that the relationship between structure and function in neural circuits is not straightforward. While neural activity is certainly constrained by its structural backbone, structure alone may not be sufficient to explain circuit operation. Integrating insights from structural measurements with additional information about the system will help better our understanding of the operation of neural circuits, which we expand upon in Section 6.

We also emphasize that neural systems are not closed entities; their structure and functioning are shaped by the external world. Neural circuits evolve over evolutionary timescales, adapt during development, and adjust through learning to the structure of the world around them. These adaptations may enable the brain to operate efficiently despite various physical and biological constraints. In Section 5, we explore factors that shape neural systems and discuss potential functional affordances that their organization and working provide.

5. DESIGN PRINCIPLES AND FUNCTIONAL AFFORDANCES

We have discussed so far how advances in experimental research and mathematical tools have enabled systematic analysis of neural systems. Despite the inherent stochastic and noisy nature of biological processes, neural systems display remarkable structure and organization across various spatial and temporal scales. Many of these features are observed across vastly different organisms, suggesting general design principles at play (183). Alongside these common features, though,

distinctions across organisms and sensory modalities within an organism could reflect specific adaptations and different constraints. Indeed, the brain must perform extremely complex and diverse processes under stringent resource constraints—be it space, material, energy, or time—in a manner that is fast and adaptable. This prompts key questions: What biological design principles shape the organization of neural systems across spatial scales and in different functional domains? How does the observed organization enhance information processing given various constraints? Recent experimental and modeling advances can be used to infer potential design principles and test out hypotheses across various organisms and developmental stages. These principles can illuminate how neural systems achieve high levels of performance and how their structure supports function. Additionally, such principles could offer insights into how perturbations might affect neural circuit organization and function, with implications for behavior and dysfunction. While determining whether these principles are indeed causal may require further experimental characterization, they nevertheless provide valuable general insights.

Several factors influence the architecture and functioning of brain networks, including the need to manage metabolic and material costs (32), to ensure efficient information transmission (32, 184), to maintain robustness to noise or injury, and to adapt to process new information (**Figure 4**). However, prior to discussing these factors, we first emphasize that brain networks are inherently spatial. Circuits in the brain are physically embedded in 3D space within a fixed enclosure and the neurons themselves have intricate spatial structure. This spatial nature constrains brain growth, development, and function (159, 174). It is important to consider this fact when applying tools from network science, as certain models do not account for spatial information.

One of the earliest observations in larger neural systems is that various sensory, cognitive, and motor functions are localized to specialized brain regions or modules that interact with one another. Within brain regions, further specialization occurs: For instance, the visual cortex contains

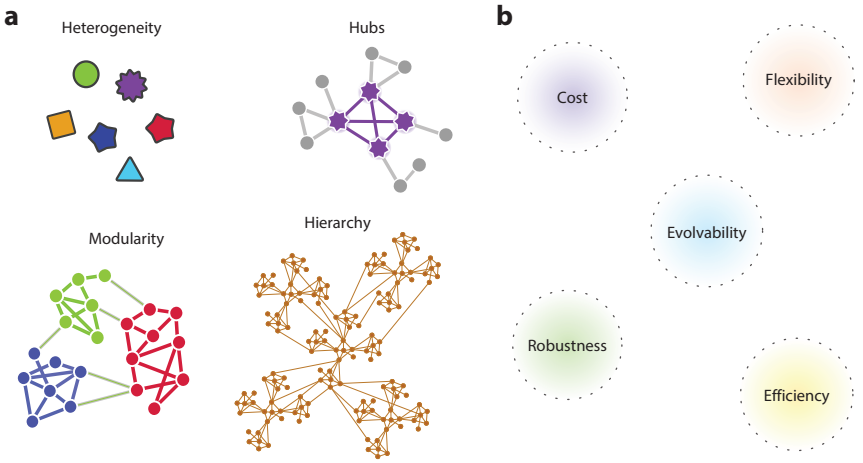

Figure 4

Organizing principles that shape the structure and workings of neural circuits at various scales. (*a*) Network motifs commonly observed in neural systems show immense heterogeneity in both their components and interaction patterns. Many large-scale brain networks possess community structure, displaying modularity at several scales organized hierarchically. Large-scale brain networks also feature high-degree hubs that form a densely connected core. (*b*) These observed patterns could be shaped by various biologically motivated design principles. Neural systems balance managing energetic and material costs, being robust to noise and external perturbations, and remaining flexible enough to adapt to new environments. While optimizing for these constraints, their functioning must also be efficient.

regions that process different image features, while the motor cortex has regions that control different parts of the body. Even within brain regions, neurons exhibit diverse shapes, sizes, gene expressions, and biophysical properties (74, 106, 117, 210). Researchers often classify neurons into distinct cell types to manage this diversity (210). However, the boundaries between cell types are not always clear-cut, and significant variation exists even within these populations (137, 210). Evidence suggests that this heterogeneity may not merely be a by-product of noisy processes but instead could play a role in controlling the computational properties of neural circuits (68) and enhancing learning (138).

Several studies have examined the modular and hierarchical structure in both structural and functional networks across organisms (8, 77, 121). Modularity is thought to reflect segregation and functional specialization, which can also make the network robust to perturbations, either internal (in the form of noise or genetic variation) or external (in the form of injury) (92). Another feature of large-scale brain networks is their small-world architecture (9, 105, 198). That is, in addition to high clustering in tightly connected modules, the brain has short characteristic path lengths. This architecture supports the idea that the brain balances segregation and integration, with modules for local information processing and efficient routes for long-range communication (166). The brain has to process and communicate immense amounts of information under strict time, material, and energetic costs. Physical connections in the brain come with a cost of building and maintenance, a factor that becomes important particularly for larger brains. However, the presence of long-distance connections between regions that are anatomically distant suggests that the brain does not strictly minimize wiring costs. Rather, the pressure for minimizing wiring competes with pressures for efficient communication (10, 30, 91), and the brain negotiates a trade-off between these factors. In addition to the modular and small-world structure, large-scale brain networks are heterogeneous, featuring nodes that form a rich core of densely connected hubs (185). These hubs are thought to play important roles in various functions, serving as broadcasters of information. Further, these hubs also reduce the overall average path length across the network, supporting integration of information.

From a metabolic standpoint, the brain is one of the most energy-expensive systems within an organism: The human brain is 2% of the body weight but 20% of its metabolic load (73, 173). Yet the brain manages to carry out impressive feats of computation, communication, and cognition while operating on an energy budget far lower than that of modern computers. Understanding how brains represent, process, and communicate information efficiently while minimizing energy costs is a classical problem in neuroscience (73, 102). Several strategies have been proposed to explain how the brain optimizes its energy usage. Studies suggest that the brain employs sparse coding strategies, where sensory stimuli are encoded by the activity of a small subset of neurons, helping reduce the overall energy consumption (131). A significant portion of the brain's energy budget is consumed to maintain communication between neurons (103), and synaptic signaling in the brain is thought to have evolved to maximize the amount of information transmitted per molecule of ATP (132). At the network level, the brain's modular and hierarchical architecture likely helps conserve energy costs by localizing information processing and reducing the metabolic burden of long-range communication. Additionally, studies have also suggested that neural circuits are adapted to the structure of the world, efficiently predicting incoming sensory input (133, 141, 196). Such predictive coding may further contribute to energy efficiency by reducing the computational load involved in processing sensory information.

6. CURRENT FRONTIERS

We now discuss exciting opportunities for research aimed at improving our understanding of neural systems in light of recent advances (**Figure 5**). Broadly speaking, we classify these directions

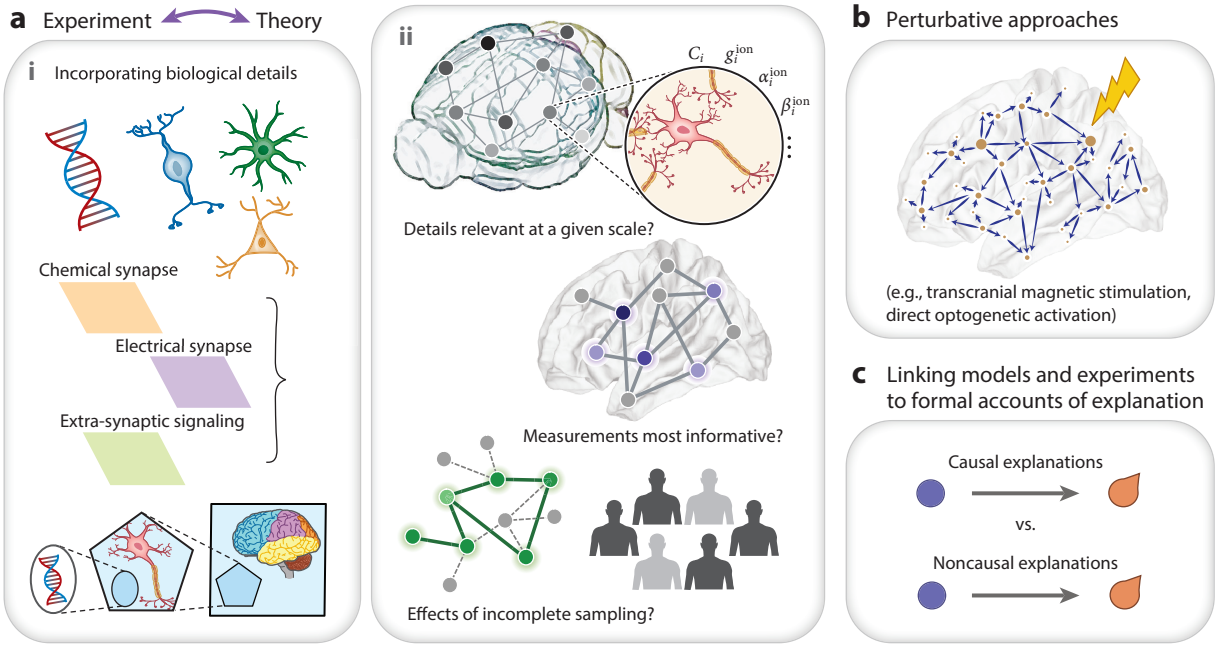

Figure 5

Ongoing and emerging future directions. (*a*) Effectively bridging experimental data and models is an important area of ongoing research. (*i*) Expanding theoretical tools and models to account for biological details now accessible through experiments. These expanded models also inspire efforts to bridge between scales of description. (*ii*) Leveraging theoretical tools to guide experimental efforts and measurements. This could involve identifying the key measurements that are most informative for behaviors of interest at a given scale and examining the effects of incomplete measurements. (*b*) Perturbative techniques provide new opportunities to improve our understanding of neural systems. (*c*) Linking the contributions of modeling and experiments to distinct kinds of explanations can inform the design of effective experimental and theoretical approaches.

into four key themes. The first theme involves expanding theory and modeling to keep up with data coming from large-scale experiments. The second theme relates to how theory can feed back into experiments and guide measurements. Together, these two themes contribute to strengthening the loop between theory and experiment. The third theme explores how methods for perturbing neural systems open new ways of understanding the brain. Finally, the fourth theme emphasizes linking modeling and experiments to formal accounts of explanation and causation to contextualize their contributions.

6.1. Expanding Models to Make Sense of Connectomes

As discussed in Sections 3 and 4, tools from mathematics and physics have been applied to brain data across various scales—from macroscale connectivity between brain regions (56, 104, 185) to microscale synaptic connectivity between neurons (107, 109, 188)—to uncover patterns of organization. Of these, the microscale cellular structure of neural systems is now becoming increasingly accessible across different organisms (1, 52, 167). Using tools from network theory, researchers have recently identified circuit motifs of biological interest across the whole-brain connectome of the *Drosophila* brain (107). Such quantitative tools have helped identify highly connected neurons that could serve as broadcasters and integrators, circuit motifs that could be key for local computations, and differences in connectivity across brain regions. The availability of such data across species has also enabled researchers to identify potential rules that could underlie observed

properties of connectomes (109). Ongoing efforts aim to map connectomes of larger animals and track changes across developmental stages. These studies are expected to offer deeper insights into how neural systems are organized and function throughout development (205), as well as reveal comparative patterns across different species (29, 183). Examining how connectomes vary across individuals of a given species is another important direction of ongoing efforts. Such variability could stem from individual experiences and inherent noisy biological processes. Characterizing differences across brain regions, identifying underlying causes for observed differences, and investigating how these differences affect computational processes and behavior are exciting avenues for future research. These efforts hold potential for advancing our understanding of both typical and atypical brain development (191).

At the same time, existing mathematical tools can be expanded to incorporate biologically relevant information as well as dynamics that are more relevant to neuroscience (43) (**Figure 5*a***, **subpanel *i***). While measurements of structure do provide useful insight into neural systems, understanding circuit function likely requires information about cell type, synapse type, and firing dynamics. One approach to improve the biological descriptiveness of existing models is to overlay these attributes onto nodes and edges as metadata, creating annotated networks (15, 128). This method can bridge abstract models with important microscale features, opening up new opportunities for discovery. It enables researchers to explore sophisticated questions, such as how observed patterns of structural connectivity relate to microscale biological attributes (15, 16). Other useful extensions of network representations include multilayer (95, 182) and higher-order (14, 23) networks. Multilayer networks provide a framework to study different kinds of interactions within neural systems and to integrate multiscale data (139, 182). For instance, neural systems can be modeled as a multilayer network to capture different modes of communication, including synapses, gap junctions, monoamines, and neuropeptides (17). Multilayer networks can also be used to capture temporal information, allowing researchers to examine how networks evolve over time (12, 81, 177). Capturing temporal aspects of brain activity and structure, including modeling the relationship between dynamics on networks and dynamics of networks (18), is a crucial area for current and future efforts. In general, machine learning approaches to extract relevant features from graphs are also growing increasingly popular (208). Graph neural networks—a class of deep learning models to perform inference on graph-structured data (20, 207)—could be particularly useful for connectomics. These approaches have been used to build predictive models of large-scale neural activity (195, 199). Such models might be helpful in generating experimentally testable hypotheses for the computational role of individual neurons or circuit elements and for linking network structure to task performance.

6.2. Bridging Theory and Experiments: Insights from Theoretical Analysis

This review highlights the potential of theory and modeling to provide valuable insights into the functioning of neural systems by leveraging large-scale experimental recordings. Equally important is the question of whether these models can actively inform future experimental efforts. Below, we explore several ways in which tighter feedback between theory and experiment could be achieved. In biological modeling, researchers are often confronted with a vast amount of detail, making it challenging to identify which aspects are essential for a specific research goal. For example, the biophysical models of large-scale brain activity discussed in Section 3 can often involve on the order of hundreds of parameters. Previous research has shown that many multiparameter models across physics and biology exhibit sloppiness, where a few key parameter combinations predominantly influence model behavior, while the rest are relatively unimportant for prediction (72, 110, 179). Applying this approach to models of large-scale neural activity could illustrate how

sensitive these models are to different parameters (**Figure 5*a*, subpanel *ii***). By identifying which parameters are critical at a given scale, researchers can guide experimental efforts to measure these parameters more accurately or select the most appropriate model.

One of the current priorities in the field is to expand the number of neurons and brain regions recorded simultaneously during behavioral tasks. Although current techniques allow for the recording of up to tens of thousands of neurons, this number still represents only a fraction of neurons involved in a given task, particularly in larger animals like mice and primates. As discussed in Section 4, experiments that tightly control behavior have shown that neural activity patterns are constrained and occupy low-dimensional manifolds (38, 42, 65, 67). This suggests that despite undersampling, it may still be possible to build reasonable models of neural activity. Efforts to increase the scope of recordings will certainly be useful for understanding neural function in complex tasks. However, theoretical insights can also help identify which neuron populations or brain regions provide the most informative data about overall circuit activity and function (**Figure 5*a*, subpanel *ii***). This strategy could be especially valuable in human neuroscience, where it can guide more effective probe placement. By optimizing probe placement, researchers may be able to reduce the number of required electrodes, thereby decreasing health risks.

Given that most studies of larger organisms are based on incomplete sampling—either by recording only a subset of regions (39) or by examining only a small population (116)—it is still important to carefully study biases introduced by such partial measurement (**Figure 5*a*, subpanel *ii***). A deeper understanding of the effects of partial measurements could in turn guide experimental efforts and the allocation of resources, potentially identifying regions that could benefit from more sampling and regions that do not require as much. Additionally, systematically examining noise in experimental measurements that could bias measurements is key to maximizing the impact of experimental methods (181).

6.3. Perturbative Approaches to Understanding Neural Systems

In recent years, significant progress has been made in perturbative techniques that allow direct manipulation of neural elements—be it brain regions in humans or even single neurons in smaller animals (**Figure 5*b***). Combining these perturbative methods with recording techniques enables researchers to directly measure how activity propagates through neural circuits. Such approaches are particularly valuable for studying network-level phenomena and establishing causal relationships within neural systems. By using simultaneous stimulation and recording, the interactions or network can be inferred in a principled manner (101). For instance, transcranial magnetic stimulation has become an increasingly prominent tool in human neuroscience for inducing localized neural activity and observing its effects (193). For smaller model organisms, it is possible to stimulate even single neurons with light or to ablate groups of neurons (145). These simpler organisms can thus serve as a test bed for simulating the behavior of an entire nervous system. These perturbative approaches have the potential to open new avenues for neural system modeling and understanding, offering exciting opportunities to test hypotheses derived from models.

6.4. Linking Theory and Modeling to Different Kinds of Explanations

As efforts progress on the experimental and theoretical fronts, it is also worth discussing the kinds of explanations that can be sought and gained (**Figure 5*c***). Explanations come in a variety of kinds, and can be distinguished in multiple ways. Perhaps the most commonly raised distinction is between causal and noncausal explanations (206). Causal explanations are often sought to explain why or how a phenomenon occurs, while noncausal explanations are often sought to explain what a phenomenon is. However, it is also possible to identify noncausal explanations to answer why

and how questions. A prime example is a mathematical explanation, wherein an equation is used to explain a phenomenon such as a process, behavior, or dynamics (113).

In this review we have focused on approaches from statistical physics, information theory, and network science that can be used to explain principles of brain network architecture and function. Do these approaches provide causal explanations, noncausal explanations, both, or neither? When our methods focus on mathematical descriptions (such as, for example, the maximum entropy model), we may be excavating noncausal mathematical explanations. When our methods focus on network topology, we may be excavating structural explanations. In some cases, structural explanations can be causal, as has been investigated in regard to social phenomena (155) and topological factors (154), whereas in other cases, structural explanations can be noncausal (97). In addition to causal structural explanations, the approaches canvassed in this review also have potential to provide other causal factors, including pathways (152), mechanisms (156), and cascades, triggering causes (53) and causal constraints.

The accessibility of this causal diversity motivates a renewed examination of how we as scholars approach scientific problem solving (153). Detecting a cause is less satisfying than determining what type of cause is involved and why. How might we design experiments, models, and theory to distinguish types of causation in brain network function? How might distinctions between causal relationships influence how we engage in causal reasoning or use causal knowledge to control the functional outcomes of neural systems? Engaging these and related questions is important as we aim to shape future research and the training of young scholars interested in understanding the brain.

7. OUTLOOK

The brain is an astounding feat of natural engineering whose structure and function are becoming increasingly accessible to the tools of modern science. As experimental techniques continue to mature, physicists generally and biophysicists specifically have contributed markedly to the development and application of models and theory. In this review we have canvassed those contributions and associated recent advances in the use of statistical mechanics, information theory, and network science with the goal of identifying principles of brain network architecture and function. Spanning from models of single neurons and small groups to large-scale ensembles and networks, the efforts examined here have proven useful in isolating design principles of neural systems and the functional affordances thereof. As these efforts continue to produce insights in the coming years, we envision several critical frontiers. These include expanding models to make sense of connectomes, using theoretical analysis to guide experiments and measurements, and using perturbative approaches to provide new kinds of understanding. Throughout these (and other) expansions, we think it will be critical to link the contributions of modeling and theory to distinct kinds of explanations. By pursuing both causal and noncausal explanations, and by detecting specific types of causes, the field of neurophysics will be poised to better design effective and specific experimental, computational, and theoretical approaches, better engage in causal reasoning, and better use causal knowledge to control the functional outcomes of neural systems.

8. CITATION DIVERSITY STATEMENT

Recent work in several fields of science has identified a bias in citation practices, such that papers from women and other minority scholars are undercited relative to the number of such papers in the field (19, 34, 36, 51, 54, 64, 112, 123, 197). Here we sought to proactively consider choosing references that reflect the diversity of the field in thought, form of contribution, gender, race, ethnicity, and other factors. First, we obtained the predicted gender of the first and last authors

of each reference by using databases that store the probability of a first name being carried by a woman (54, 212). By this measure (and excluding self-citations to the first and last authors of our current paper), our references contain 11.38% woman(first)/woman(last), 13.94% man/woman, 19.21% woman/man, and 55.47% man/man. This method is limited in that (*a*) names, pronouns, and social media profiles used to construct the databases may not, in every case, be indicative of gender identity and that (*b*) it cannot account for intersex, nonbinary, or transgender people. Second, we obtained the predicted racial/ethnic category of the first and last authors of each reference by databases that store the probability of a first and last name being carried by an author of color (2, 37). By this measure (and excluding self-citations), our references contain 10.38% author of color (first)/author of color(last), 13.44% white author/author of color, 21.31% author of color/white author, and 54.86% white author/white author. This method is limited in that (*a*) names, census entries, and Wikipedia profiles used to make the predictions may not be indicative of racial/ethnic identity and that (*b*) the method cannot account for Indigenous and mixed-race authors, or authors who may face differential biases due to the ambiguous racialization or ethnicization of their names. We look forward to future work that could help us to better understand how to support equitable practices in science.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors thank L. Papadopoulos, C.W. Lynn, A. Winn, C.G. Alexandersen, J.K. Brynildsen, I. Stallworthy, and S. Patankar for helpful comments on earlier drafts of the article. The authors acknowledge support from the Army Research Office MURI program [W911NF2410228]. The content is solely the responsibility of the authors and does not necessarily represent the official views of any of the funding agencies.

LITERATURE CITED

1. Abbott LF, Bock DD, Callaway EM, Denk W, Dulac C, et al. 2020. The mind of a mouse. *Cell* 182(6):1372–76
2. Ambekar A, Ward C, Mohammed J, Male S, Skiena S. 2009. Name-ethnicity classification from open sources. In *Proceedings of the 15th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, ed. JJF Elder IV, F Fogelman-Soulié, P Flach, M Zaki, pp. 49–58. New York: Assoc. Comput. Mach.
3. Angiolelli M, Depannemaecker D, Agouram H, Régis J, Carron R, et al. 2024. The virtual Parkinsonian patient. medRxiv 2024.07.08.24309856. **https://doi.org/10.1101/2024.07.08.24309856**
4. Ashourvan A, Shah P, Pines A, Gu S, Lynn CW, et al. 2021. Pairwise maximum entropy model explains the role of white matter structure in shaping emergent co-activation states. *Commun. Biol.* 4(1):210
5. Barlow HB, Hill RM. 1963. Selective sensitivity to direction of movement in ganglion cells of the rabbit retina. *Science* 139(3553):412–14
6. Barlow HB, Levick WR. 1965. The mechanism of directionally selective units in rabbit's retina. *J. Physiol.* 178(3):477–504
7. Barry C, Burgess N. 2014. Neural mechanisms of self-location. *Curr. Biol.* 24(8):R330–39
8. Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A. 2008. Hierarchical organization of human cortical networks in health and schizophrenia. *J. Neurosci.* 28(37):9239–48
9. Bassett DS, Bullmore ET. 2017. Small-world brain networks revisited. *Neuroscientist* 23(5):499–516

10. Bassett DS, Greenfield DL, Meyer-Lindenberg A, Weinberger DR, Moore SW, Bullmore ET. 2010. Efficient physical embedding of topologically complex information processing networks in brains and computer circuits. *PLOS Comput. Biol.* 6(4):e1000748
11. Bassett DS, Wymbs NF, Porter MA, Mucha PJ, Carlson JM, Grafton ST. 2011. Dynamic reconfiguration of human brain networks during learning. *PNAS* 108(18):7641–46
12. Bassett DS, Wymbs NF, Rombach MP, Porter MA, Mucha PJ, Grafton ST. 2013. Task-based core-periphery organization of human brain dynamics. *PLOS Comput. Biol.* 9(9):e1003171
13. Bassett DS, Zurn P, Gold JI. 2018. On the nature and use of models in network neuroscience. *Nat. Rev. Neurosci.* 19(9):566–78
14. Battiston F, Cencetti G, Iacopini I, Latora V, Lucas M, et al. 2020. Networks beyond pairwise interactions: structure and dynamics. *Phys. Rep.* 874:1–92
15. Bazinet V, Hansen JY, Misic B. 2023. Towards a biologically annotated brain connectome. *Nat. Rev. Neurosci.* 24(12):747–60
16. Bazinet V, Hansen JY, Vos de Wael R, Bernhardt BC, van den Heuvel MP, Misic B. 2023. Assortative mixing in micro-architecturally annotated brain connectomes. *Nat. Commun.* 14(1):2850
17. Bentley B, Branicky R, Barnes CL, Chew YL, Yemini E, et al. 2016. The multilayer connectome of *Caenorhabditis elegans*. *PLOS Comput. Biol.* 12(12):e1005283
18. Berner R, Gross T, Kuehn C, Kurths J, Yanchuk S. 2023. Adaptive dynamical networks. *Phys. Rep.* 1031:1–59
19. Bertolero MA, Dworkin JD, David SU, Lloreda CL, Srivastava P, et al. 2020. Racial and ethnic imbalance in neuroscience reference lists and intersections with gender. bioRxiv 2020.10.12.336230. **https://doi.org/10.1101/2020.10.12.336230**
20. Bessadok A, Mahjoub MA, Rekik I. 2022. Graph neural networks in network neuroscience. *IEEE Trans. Pattern Anal. Mach. Intell.* 45(5):5833–48
21. Betzel RF, Bassett DS. 2017. Generative models for network neuroscience: prospects and promise. *J. R. Soc. Interface* 14(136):20170623
22. Bick C, Goodfellow M, Laing CR, Martens EA. 2020. Understanding the dynamics of biological and neural oscillator networks through exact mean-field reductions: a review. *J. Math. Neurosci.* 10(1):9
23. Bick C, Gross E, Harrington HA, Schaub MT. 2023. What are higher-order networks? *SIAM Rev.* 65(3):686–731
24. Borst A, Helmstaedter M. 2015. Common circuit design in fly and mammalian motion vision. *Nat. Neurosci.* 18(8):1067–76
25. Breakspear M. 2017. Dynamic models of large-scale brain activity. *Nat. Neurosci.* 20(3):340–52
26. Breakspear M, Terry J. 2002. Nonlinear interdependence in neural systems: motivation, theory, and relevance. *Int. J. Neurosci.* 112(10):1263–84
27. Brette R, Gerstner W. 2005. Adaptive exponential integrate-and-fire model as an effective description of neuronal activity. *J. Neurophysiol.* 94(5):3637–42
28. Briggman KL, Bock DD. 2012. Volume electron microscopy for neuronal circuit reconstruction. *Curr. Opin. Neurobiol.* 22(1):154–61
29. Brynildsen JK, Rajan K, Henderson MX, Bassett DS. 2023. Network models to enhance the translational impact of cross-species studies. *Nat. Rev. Neurosci.* 24(9):575–88
30. Budd JML, Kisvárday ZF. 2012. Communication and wiring in the cortical connectome. *Front. Neuroanat.* 6:42
31. Budzinski R, Boaretto B, Prado T, Lopes S. 2019. Phase synchronization and intermittent behavior in healthy and Alzheimer-affected human-brain-based neural network. *Phys. Rev. E* 99(2):022402
32. Bullmore E, Sporns O. 2012. The economy of brain network organization. *Nat. Rev. Neurosci.* 13(5):336–49
33. Cakan C, Obermayer K. 2020. Biophysically grounded mean-field models of neural populations under electrical stimulation. *PLOS Comput. Biol.* 16(4):e1007822
34. Caplar N, Tacchella S, Birrer S. 2017. Quantitative evaluation of gender bias in astronomical publications from citation counts. *Nat. Astron.* 1(6):0141

35. Carlu M, Chehab O, Dalla Porta L, Depannemaecker D, Héricé C, et al. 2020. A mean-field approach to the dynamics of networks of complex neurons, from nonlinear integrate-and-fire to Hodgkin–Huxley models. *J. Neurophysiol.* 123(3):1042–51
36. Chatterjee P, Werner RM. 2021. Gender disparity in citations in high-impact journal articles. *JAMA Netw. Open* 4(7):e2114509
37. Chintalapati R, Laohaprapanon S, Sood G. 2023. Predicting race and ethnicity from the sequence of characters in a name. arXiv:1805.02109v2 [stat.AP]
38. Chung S, Abbott LF. 2021. Neural population geometry: an approach for understanding biological and artificial neural networks. *Curr. Opin. Neurobiol.* 70:137–44
39. Conrad EC, Bernabei JM, Kini LG, Shah P, Mikhail F, et al. 2020. The sensitivity of network statistics to incomplete electrode sampling on intracranial EEG. *Netw. Neurosci.* 4(2):484–506
40. Coombes S, Byrne Á. 2018. Next generation neural mass models. In *Nonlinear Dynamics in Computational Neuroscience*, ed. F Corinto, A Torcini, pp. 1–16. Cham, Switz.: Springer
41. Court R, Costa M, Pilgrim C, Millburn G, Holmes A, et al. 2023. Virtual fly brain—an interactive atlas of the *Drosophila* nervous system. *Front. Physiol.* 14:1076533
42. Cunningham JP, Yu BM. 2014. Dimensionality reduction for large-scale neural recordings. *Nat. Neurosci.* 17(11):1500–9
43. Curto C, Morrison K. 2019. Relating network connectivity to dynamics: opportunities and challenges for theoretical neuroscience. *Curr. Opin. Neurobiol.* 58:11–20
44. David O, Cosmelli D, Friston KJ. 2004. Evaluation of different measures of functional connectivity using a neural mass model. *NeuroImage* 21(2):659–73
45. David O, Friston KJ. 2003. A neural mass model for MEG/EEG: coupling and neuronal dynamics. *NeuroImage* 20(3):1743–55
46. Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston K. 2008. The dynamic brain: from spiking neurons to neural masses and cortical fields. *PLOS Comput. Biol.* 4(8):e1000092
47. Demas J, Manley J, Tejera F, Barber K, Kim H, et al. 2021. High-speed, cortex-wide volumetric recording of neuroactivity at cellular resolution using light beads microscopy. *Nat. Methods* 18(9):1103–11
48. Destexhe A, Sejnowski TJ. 2009. The Wilson–Cowan model, 36 years later. *Biol. Cybernet.* 101(1):1–2
49. Di Volo M, Romagnoni A, Capone C, Destexhe A. 2019. Biologically realistic mean-field models of conductance-based networks of spiking neurons with adaptation. *Neural Comput.* 31(4):653–80
50. Dichio V, Fallani FDV. 2023. Statistical models of complex brain networks: a maximum entropy approach. *Rep. Prog. Phys.* 86:102601
51. Dion ML, Sumner JL, Mitchell SM. 2018. Gendered citation patterns across political science and social science methodology fields. *Polit. Anal.* 26(3):312–27
52. Dorkenwald S, Matsliah A, Sterling AR, Schlegel P, Yu S-c, et al. 2024. Neuronal wiring diagram of an adult brain. *Nature* 634:124–38
53. Dretske F. 2010. Triggering and structuring causes. In *A Companion to the Philosophy of Action*, ed. T O'Connor, C Sandis, pp. 139–44. Chichester, UK: Wiley-Blackwell
54. Dworkin JD, Linn KA, Teich EG, Zurn P, Shinohara RT, Bassett DS. 2020. The extent and drivers of gender imbalance in neuroscience reference lists. *Nat. Neurosci.* 23(8):918–26
55. Edelman GM, Gally JA. 2001. Degeneracy and complexity in biological systems. *PNAS* 98(24):13763–68
56. Elam JS, Glasser MF, Harms MP, Sotiropoulos SN, Andersson JL, et al. 2021. The human connectome project: a retrospective. *NeuroImage* 244:118543
57. Ermentrout B, Terman DH. 2010. *Foundations of Mathematical Neuroscience*. Berlin: Springer
58. Ermentrout GB, Cowan JD. 1979. A mathematical theory of visual hallucination patterns. *Biol. Cybern.* 34(3):137–50
59. FitzHugh R. 1961. Impulses and physiological states in theoretical models of nerve membrane. *Biophys. J.* 1(6):445–66
60. Fornito A, Zalesky A, Bullmore E. 2016. *Fundamentals of Brain Network Analysis*. Cambridge, MA: Academic Press
61. Fosdick BK, Larremore DB, Nishimura J, Ugander J. 2018. Configuring random graph models with fixed degree sequences. *SIAM Rev.* 60(2):315–55

62. Fotiadis P, Parkes L, Davis KA, Satterthwaite TD, Shinohara RT, Bassett DS. 2024. Structure–function coupling in macroscale human brain networks. *Nat. Rev. Neurosci.* 25(10):688–704
63. Fourcaud-Trocmé N, Hansel D, Van Vreeswijk C, Brunel N. 2003. How spike generation mechanisms determine the neuronal response to fluctuating inputs. *J. Neurosci.* 23(37):11628–40
64. Fulvio JM, Akinnola I, Postle BR. 2021. Gender (im)balance in citation practices in cognitive neuroscience. *J. Cogn. Neurosci.* 33(1):3–7
65. Gallego JA, Perich MG, Miller LE, Solla SA. 2017. Neural manifolds for the control of movement. *Neuron* 94(5):978–84
66. Ganmor E, Segev R, Schneidman E. 2011. Sparse low-order interaction network underlies a highly correlated and learnable neural population code. *PNAS* 108(23):9679–84
67. Gao P, Ganguli S. 2015. On simplicity and complexity in the brave new world of large-scale neuroscience. *Curr. Opin. Neurobiol.* 32:148–55
68. Gast R, Solla SA, Kennedy A. 2024. Neural heterogeneity controls computations in spiking neural networks. *PNAS* 121(3):e2311885121
69. Gerstner W, Kistler WM, Naud R, Paninski L. 2014. *Neuronal Dynamics: From Single Neurons to Networks and Models of Cognition*. Cambridge, UK: Cambridge Univ. Press
70. Goldwyn JH, Shea-Brown E. 2011. The what and where of adding channel noise to the Hodgkin-Huxley equations. *PLOS Comput. Biol.* 7(11):e1002247
71. Gowers RP, Schreiber S. 2024. How neuronal morphology impacts the synchronisation state of neuronal networks. *PLOS Comput. Biol.* 20(3):e1011874
72. Gutenkunst RN, Waterfall JJ, Casey FP, Brown KS, Myers CR, Sethna JP. 2007. Universally sloppy parameter sensitivities in systems biology models. *PLOS Comput. Biol.* 3(10):e189
73. Harris JJ, Jolivet R, Attwell D. 2012. Synaptic energy use and supply. *Neuron* 75(5):762–77
74. Harris KD, Shepherd GM. 2015. The neocortical circuit: themes and variations. *Nat. Neurosci.* 18(2):170–81
75. Hesse J, Schleimer JH, Maier N, Schmitz D, Schreiber S. 2022. Temperature elevations can induce switches to homoclinic action potentials that alter neural encoding and synchronization. *Nat. Commun.* 13(1):3934
76. Hildebrand DGC, Cicconet M, Torres RM, Choi W, Quan TM, et al. 2017. Whole-brain serial-section electron microscopy in larval zebrafish. *Nature* 545(7654):345–49
77. Hilgetag CC, Burns GA, O'Neill MA, Scannell JW, Young MP. 2000. Anatomical connectivity defines the organization of clusters of cortical areas in the macaque and the cat. *Philos. Trans. R. Soc. B* 355(1393):91–110
78. Hille B. 2001. *Ion Channels of Excitable Membranes*. Sunderland, MA: Sinauer. 3rd ed.
79. Hindmarsh JL, Rose R. 1984. A model of neuronal bursting using three coupled first order differential equations. *Proc. R. Soc. B* 221(1222):87–102
80. Hodgkin AL, Huxley AF. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117(4):500–44
81. Holme P, Saramäki J. 2012. Temporal networks. *Phys. Rep.* 519(3):97–125
82. Hopfield JJ. 1982. Neural networks and physical systems with emergent collective computational abilities. *PNAS* 79(8):2554–58
83. Hulse BK, Haberkern H, Franconville R, Turner-Evans DB, Takemura S-y, et al. 2021. A connectome of the *Drosophila* central complex reveals network motifs suitable for flexible navigation and context-dependent action selection. *eLife* 10:e66039
84. Izhikevich EM. 2003. Simple model of spiking neurons. *IEEE Trans. Neural Netw.* 14(6):1569–72
85. Jansen BH, Rit VG. 1995. Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. *Biol. Cybern.* 73(4):357–66
86. Jaynes ET. 1957. Information theory and statistical mechanics. *Phys. Rev.* 106(4):620
87. Jazayeri M, Ostojic S. 2021. Interpreting neural computations by examining intrinsic and embedding dimensionality of neural activity. *Curr. Opin. Neurobiol.* 70:113–20
88. Jirsa V, Wang H, Triebkorn P, Hashemi M, Jha J, et al. 2023. Personalised virtual brain models in epilepsy. *Lancet Neurol.* 22(5):443–54

89. Jiruska P, De Curtis M, Jefferys JG, Schevon CA, Schiff SJ, Schindler K. 2013. Synchronization and desynchronization in epilepsy: controversies and hypotheses. *J. Physiol.* 591(4):787–97
90. Jun JJ, Steinmetz NA, Siegle JH, Denman DJ, Bauza M, et al. 2017. Fully integrated silicon probes for high-density recording of neural activity. *Nature* 551(7679):232–36
91. Kaiser M, Hilgetag CC. 2006. Nonoptimal component placement, but short processing paths, due to long-distance projections in neural systems. *PLOS Comput. Biol.* 2(7):e95
92. Kaiser M, Varier S. 2011. Evolution and development of brain networks: from *Caenorhabditis elegans* to *Homo sapiens*. *Network* 22(1–4):143–47
93. Kim J, Leahy W, Shlizerman E. 2019. Neural interactome: interactive simulation of a neuronal system. *Front. Comput. Neurosci.* 13:8
94. Kim SS, Rouault H, Druckmann S, Jayaraman V. 2017. Ring attractor dynamics in the *Drosophila* central brain. *Science* 356(6340):849–53
95. Kivelä M, Arenas A, Barthelemy M, Gleeson JP, Moreno Y, Porter MA. 2014. Multilayer networks. *J. Complex Netw.* 2(3):203–71
96. Korhonen O, Zanin M, Papo D. 2021. Principles and open questions in functional brain network reconstruction. *Hum. Brain Mapp.* 42(11):3680–711
97. Kostić D. 2020. General theory of topological explanations and explanatory asymmetry. *Philos. Trans. R. Soc. B* 375(1796):20190321
98. Kuan AT, Bondanelli G, Driscoll LN, Han J, Kim M, et al. 2024. Synaptic wiring motifs in posterior parietal cortex support decision-making. *Nature* 627(8003):367–73
99. Lapicque L. 1907. Recherches quantitatives sur l'excitation electrique des nerfs. *J. Physiol. Paris* 9:620–35
100. Lavanga M, Stumme J, Yalcinkaya BH, Fousek J, Jockwitz C, et al. 2023. The virtual aging brain: Causal inference supports interhemispheric dedifferentiation in healthy aging. *NeuroImage* 283:120403
101. Lepage KQ, Ching S, Kramer MA. 2013. Inferring evoked brain connectivity through adaptive perturbation. *J. Comput. Neurosci.* 34:303–18
102. Levy WB, Baxter RA. 1996. Energy efficient neural codes. *Neural Comput.* 8(3):531–43
103. Levy WB, Calvert VG. 2021. Communication consumes 35 times more energy than computation in the human cortex, but both costs are needed to predict synapse number. *PNAS* 118(18):e2008173118
104. Li L, Hu X, Preuss TM, Glasser MF, Damen FW, et al. 2013. Mapping putative hubs in human, chimpanzee and rhesus macaque connectomes via diffusion tractography. *NeuroImage* 80:462–74
105. Liao X, Vasilakos AV, He Y. 2017. Small-world human brain networks: perspectives and challenges. *Neurosci. Biobehav. Rev.* 77:286–300
106. Lim L, Mi D, Llorca A, Marn O. 2018. Development and functional diversification of cortical interneurons. *Neuron* 100(2):294–313
107. Lin A, Yang R, Dorkenwald S, Matsliah A, Sterling AR, et al. 2024. Network statistics of the whole-brain connectome of *Drosophila*. *Nature* 634(8032):153-65
108. London M, Häusser M. 2005. Dendritic computation. *Annu. Rev. Neurosci.* 28:503–32
109. Lynn CW, Holmes CM, Palmer SE. 2024. Heavy-tailed neuronal connectivity arises from Hebbian self-organization. *Nat. Phys.* 20(3):484–91
110. Machta BB, Chachra R, Transtrum MK, Sethna JP. 2013. Parameter space compression underlies emergent theories and predictive models. *Science* 342(6158):604–7
111. Magee JC, Grienberger C. 2020. Synaptic plasticity forms and functions. *Annu. Rev. Neurosci.* 43:95–117
112. Maliniak D, Powers R, Walter BF. 2013. The gender citation gap in international relations. *Int. Organ.* 67(4):889–922
113. Mancosu P, Poggiolesi F, Pincock C. 2023. Mathematical explanation. *Stanford Encyclopedia of Philosophy*. **https://plato.stanford.edu/entries/mathematics-explanation/**
114. Maoz O, Tkačik G, Esteki MS, Kiani R, Schneidman E. 2020. Learning probabilistic neural representations with randomly connected circuits. *PNAS* 117(40):25066–73
115. Marder E, Taylor AL. 2011. Multiple models to capture the variability in biological neurons and networks. *Nat. Neurosci.* 14(2):133–38
116. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, et al. 2022. Reproducible brain-wide association studies require thousands of individuals. *Nature* 603(7902):654–60

117. Masland RH. 2012. The neuronal organization of the retina. *Neuron* 76(2):266–80
118. McCulloch WS, Pitts W. 1943. A logical calculus of the ideas immanent in nervous activity. *Bull. Math. Biophys.* 5:115–33
119. Meijer HG, Eissa TL, Kiewiet B, Neuman JF, Schevon CA, et al. 2015. Modeling focal epileptic activity in the Wilson–Cowan model with depolarization block. *J. Math. Neurosci.* 5:7
120. Meshulam L, Gauthier JL, Brody CD, Tank DW, Bialek W. 2023. Successes and failures of simplified models for a network of real neurons. arXiv:2112.14735v2 [physics.bio-ph]
121. Meunier D, Lambiotte R, Bullmore ET. 2010. Modular and hierarchically modular organization of brain networks. *Front. Neurosci.* 4:7572
122. MICrONS Consortium, Bae JA, Baptiste M, Bishop CA, Bodor AL, et al. 2021. Functional connectomics spanning multiple areas of mouse visual cortex. bioRxiv 2021.07.28.454025. **https://doi.org/10.1101/2021.07.28.454025**
123. Mitchell SM, Lange S, Brus H. 2013. Gendered citation patterns in international relations journals. *Int. Stud. Perspect.* 14(4):485–92
124. Montbrió E, Pazó D, Roxin A. 2015. Macroscopic description for networks of spiking neurons. *Phys. Rev. X* 5(2):021028
125. Morris C, Lecar H. 1981. Voltage oscillations in the barnacle giant muscle fiber. *Biophys. J.* 35(1):193–213
126. Najafi F, Elsayed GF, Cao R, Pnevmatikakis E, Latham PE, et al. 2020. Excitatory and inhibitory subnetworks are equally selective during decision-making and emerge simultaneously during learning. *Neuron* 105(1):165–79
127. Naudin L, Laredo JLJ, Corson N. 2022. A simple model of nonspiking neurons. *Neural Comput.* 34(10):2075–101
128. Newman ME, Clauset A. 2016. Structure and inference in annotated networks. *Nat. Commun.* 7(1):11863
129. Neymotin SA, Daniels DS, Caldwell B, McDougal RA, Carnevale NT, et al. 2020. Human Neocortical Neurosolver (HNN), a new software tool for interpreting the cellular and network origin of human MEG/EEG data. *eLife* 9:e51214
130. Oh SW, Harris JA, Ng L, Winslow B, Cain N, et al. 2014. A mesoscale connectome of the mouse brain. *Nature* 508(7495):207–14
131. Olshausen BA, Field DJ. 2004. Sparse coding of sensory inputs. *Curr. Opin. Neurobiol.* 14(4):481–87
132. Padamsey Z, Rochefort NL. 2023. Paying the brain's energy bill. *Curr. Opin. Neurobiol.* 78:102668
133. Palmer SE, Marre O, Berry MJ, Bialek W. 2015. Predictive information in a sensory population. *PNAS* 112(22):6908–13
134. Pandarinath C, O'Shea DJ, Collins J, Jozefowicz R, Stavisky SD, et al. 2018. Inferring single-trial neural population dynamics using sequential auto-encoders. *Nat. Methods* 15(10):805–15
135. Papadopoulos L, Lynn CW, Battaglia D, Bassett DS. 2020. Relations between large-scale brain connectivity and effects of regional stimulation depend on collective dynamical state. *PLOS Comput. Biol.* 16(9):e1008144
136. Paulk AC, Kfir Y, Khanna AR, Mustroph ML, Trautmann EM, et al. 2022. Large-scale neural recordings with single neuron resolution using Neuropixels probes in human cortex. *Nat. Neurosci.* 25(2):252–63
137. Peng H, Xie P, Liu L, Kuang X, Wang Y, et al. 2021. Morphological diversity of single neurons in molecularly defined cell types. *Nature* 598(7879):174–81
138. Perez-Nieves N, Leung VC, Dragotti PL, Goodman DF. 2021. Neural heterogeneity promotes robust learning. *Nat. Commun.* 12(1):5791
139. Presigny C, De Vico Fallani F. 2022. *Colloquium*: multiscale modeling of brain network organization. *Rev. Mod. Phys.* 94(3):031002
140. Pressé S, Ghosh K, Lee J, Dill KA. 2013. Principles of maximum entropy and maximum caliber in statistical physics. *Rev. Mod. Phys.* 85(3):1115
141. Price BH, Gavornik JP. 2022. Efficient temporal coding in the early visual system: existing evidence and future directions. *Front. Comput. Neurosci.* 16:929348
142. Prinz AA, Bucher D, Marder E. 2004. Similar network activity from disparate circuit parameters. *Nat. Neurosci.* 7(12):1345–52
143. Rabinovich MI, Varona P, Selverston AI, Abarbanel HD. 2006. Dynamical principles in neuroscience. *Rev. Mod. Phys.* 78(4):1213

144. Ranasinghe KG, Verma P, Cai C, Xie X, Kudo K, et al. 2022. Altered excitatory and inhibitory neuronal subpopulation parameters are distinctly associated with tau and amyloid in Alzheimer's disease. *eLife* 11:e77850
145. Randi F, Sharma AK, Dvali S, Leifer AM. 2023. Neural signal propagation atlas of *Caenorhabditis elegans*. *Nature* 623(7986):406–14
146. Renart A, Brunel N, Wang XJ. 2003. Mean-field theory of recurrent cortical networks: working memory circuits with irregularly spiking neurons. In *Computational Neuroscience: A Comprehensive Approach*, ed. J Feng, pp. 432–90. Boca Raton, FL: CRC Press
147. Reynolds JH, Chelazzi L. 2004. Attentional modulation of visual processing. *Annu. Rev. Neurosci.* 27:611–47
148. Rinzel J, Ermentrout GB. 1998. Analysis of neural excitability and oscillations. *Methods Neuronal Model.* 2:251–92
149. Roberts A, Bush BM. 1981. *Neurones Without Impulses: Their Significance for Vertebrate and Invertebrate Nervous Systems*, Vol. 6. Cambridge, UK: Cambridge Univ. Press
150. Roberts JA, Gollo LL, Abeysuriya RG, Roberts G, Mitchell PB, et al. 2019. Metastable brain waves. *Nat. Commun.* 10(1):1056
151. Rosenblatt F. 1958. The perceptron: a probabilistic model for information storage and organization in the brain. *Psychol. Rev.* 65(6):386–408
152. Ross LN. 2021. Causal concepts in biology: how pathways differ from mechanisms and why it matters. *Br. J. Philos. Sci.* 72(1):131–58
153. Ross LN. 2021. Causes with material continuity. *Biol. Philos.* 36:52
154. Ross LN. 2021. Distinguishing topological and causal explanation. *Synthese* 198:9803–20
155. Ross LN. 2024. What is social structural explanation? A causal account. *Noûs* 58:163–79
156. Ross LN, Bassett DS. 2024. Causation in neuroscience: keeping mechanism meaningful. *Nat. Rev. Neurosci.* 25:81–90
157. Roy D, Sigala R, Breakspear M, McIntosh AR, Jirsa VK, et al. 2014. Using the virtual brain to reveal the role of oscillations and plasticity in shaping brain's dynamical landscape. *Brain Connect.* 4(10):791–811
158. Ryan K, Lu Z, Meinertzhagen IA. 2016. The CNS connectome of a tadpole larva of *Ciona intestinalis* (L.) highlights sidedness in the brain of a chordate sibling. *eLife* 5:e16962
159. Salova A, Kovács IA. 2025. Combined topological and spatial constraints are required to capture the structure of neural connectomes. *Netw. Neurosci.* **https://doi.org/10.1162/netn_a_00428**
160. Sanz-Leon P, Knock SA, Spiegler A, Jirsa VK. 2015. Mathematical framework for large-scale brain network modeling in the virtual brain. *NeuroImage* 111:385–430
161. Sanz Leon P, Knock SA, Woodman MM, Domide L, Mersmann J, et al. 2013. The virtual brain: a simulator of primate brain network dynamics. *Front. Neuroinform.* 7:10
162. Scheffer LK, Xu CS, Januszewski M, Lu Z, Takemura S-y, et al. 2020. A connectome and analysis of the adult *Drosophila* central brain. *eLife* 9:e57443
163. Schilling KG, Nath V, Hansen C, Parvathaneni P, Blaber J, et al. 2019. Limits to anatomical accuracy of diffusion tractography using modern approaches. *NeuroImage* 185:1–11
164. Schneidman E, Berry MJ, Segev R, Bialek W. 2006. Weak pairwise correlations imply strongly correlated network states in a neural population. *Nature* 440(7087):1007–12
165. Seelig JD, Jayaraman V. 2015. Neural dynamics for landmark orientation and angular path integration. *Nature* 521(7551):186–91
166. Seguin C, Sporns O, Zalesky A. 2023. Brain network communication: concepts, models and applications. *Nat. Rev. Neurosci.* 24(9):557–74
167. Shapson-Coe A, Januszewski M, Berger DR, Pope A, Wu Y, et al. 2024. A petavoxel fragment of human cerebral cortex reconstructed at nanoscale resolution. *Science* 384(6696):eadk4858
168. Shusterman V, Troy WC. 2008. From baseline to epileptiform activity: a path to synchronized rhythmicity in large-scale neural networks. *Phys. Rev. E* 77(6):061911
169. Siletti K, Hodge R, Mossi Albiach A, Lee KW, Ding S-L, et al. 2023. Transcriptomic diversity of cell types across the adult human brain. *Science* 382(6667):eadd7046
170. Simpson SL, Hayasaka S, Laurienti PJ. 2011. Exponential random graph modeling for complex brain networks. *PLOS ONE* 6(5):e20039

171. Sporns O, Betzel RF. 2016. Modular brain networks. *Annu. Rev. Psychol.* 67:613–40
172. Steinmetz NA, Aydin C, Lebedeva A, Okun M, Pachitariu M, et al. 2021. Neuropixels 2.0: a miniaturized high-density probe for stable, long-term brain recordings. *Science* 372(6539):eabf4588
173. Sterling P, Laughlin S. 2015. *Principles of Neural Design*. Cambridge, MA: MIT Press
174. Stiso J, Bassett DS. 2018. Spatial embedding imposes constraints on neuronal network architectures. *Trends Cogn. Sci.* 22(12):1127–42
175. Sussillo D, Jozefowicz R, Abbott LF, Pandarinath C. 2016. LFADS - latent factor analysis via dynamical systems. arXiv:1608.06315 [cs.LG]
176. Tesler F, Tort-Colet N, Depannemaecker D, Carlu M, Destexhe A. 2022. Mean-field based framework for forward modeling of LFP and MEG signals. *Front. Comput. Neurosci.* 16:968278
177. Thompson WH, Brantefors P, Fransson P. 2017. From static to temporal network theory: applications to functional brain connectivity. *Netw. Neurosci.* 1(2):69–99
178. Towlson EK, Vértes PE, Ahnert SE, Schafer WR, Bullmore ET. 2013. The rich club of the *C. elegans* neuronal connectome. *J. Neurosci.* 33(15):6380–87
179. Transtrum MK, Machta BB, Brown KS, Daniels BC, Myers CR, Sethna JP. 2015. Perspective: sloppiness and emergent theories in physics, biology, and beyond. *J. Chem. Phys.* 143(1):010901
180. Uhlhaas PJ, Singer W. 2010. Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* 11(2):100–13
181. Urai AE, Doiron B, Leifer AM, Churchland AK. 2022. Large-scale neural recordings call for new insights to link brain and behavior. *Nat. Neurosci.* 25(1):11–19
182. Vaiana M, Muldoon SF. 2020. Multilayer brain networks. *J. Nonlinear Sci.* 30(5):2147–69
183. Van den Heuvel MP, Bullmore ET, Sporns O. 2016. Comparative connectomics. *Trends Cogn. Sci.* 20(5):345–61
184. Van Den Heuvel MP, Kahn RS, Goñi J, Sporns O. 2012. High-cost, high-capacity backbone for global brain communication. *PNAS* 109(28):11372–77
185. Van Den Heuvel MP, Sporns O. 2011. Rich-club organization of the human connectome. *J. Neurosci.* 31(44):15775–86
186. van der Plas TL, Tubiana J, Le Goc G, Migault G, Kunst M, et al. 2023. Neural assemblies uncovered by generative modeling explain whole-brain activity statistics and reflect structural connectivity. *eLife* 12:e83139
187. Van Geit W, Achard P, De Schutter E. 2007. Neurofitter: a parameter tuning package for a wide range of electrophysiological neuron models. *Front. Neuroinform.* 1:89
188. Varshney LR, Chen BL, Paniagua E, Hall DH, Chklovskii DB. 2011. Structural properties of the *Caenorhabditis elegans* neuronal network. *PLOS Comput. Biol.* 7(2):e1001066
189. Váša F, Mišić B. 2022. Null models in network neuroscience. *Nat. Rev. Neurosci.* 23(8):493–504
190. Verasztó C, Jasek S, Gühmann M, Shahidi R, Ueda N, et al. 2020. Whole-animal connectome and cell-type complement of the three-segmented *Platynereis dumerilii* larva. bioRxiv 2020.08.21.260984. **https://doi.org/10.1101/2020.08.21.260984**
191. Vértes PE. 2023. Computational models of typical and atypical brain network development. *Biol. Psychiatry* 93(5):464–70
192. Voigt I, Inojosa H, Dillenseger A, Haase R, Akgün K, Ziemssen T. 2021. Digital twins for multiple sclerosis. *Front. Immunol.* 12:669811
193. Walsh V, Cowey A. 2000. Transcranial magnetic stimulation and cognitive neuroscience. *Nat. Rev. Neurosci.* 1(1):73–80
194. Wang HE, Triebkorn P, Breyton M, Dollomaja B, Lemarechal J-D, et al. 2024. Virtual brain twins: from basic neuroscience to clinical use. *Natl. Sci. Rev.* 11(5):nwae079
195. Wang PY, Sapra S, George VK, Silva GA. 2021. Generalizable machine learning in neuroscience using graph neural networks. *Front. Artif. Intell.* 4:618372
196. Wang S, Segev I, Borst A, Palmer S. 2021. Maximally efficient prediction in the early fly visual system may support evasive flight maneuvers. *PLOS Comput. Biol.* 17(5):e1008965
197. Wang X, Dworkin JD, Zhou D, Stiso J, Falk EB, et al. 2021. Gendered citation practices in the field of communication. *Ann. Int. Commun. Assoc.* 45(2):134–53

198. Watts DJ, Strogatz SH. 1998. Collective dynamics of 'small-world' networks. *Nature* 393(6684):440–42
199. Wein S, Schüller A, Tomé AM, Malloni WM, Greenlee MW, Lang EW. 2022. Forecasting brain activity based on models of spatiotemporal brain dynamics: a comparison of graph neural network architectures. *Netw. Neurosci.* 6(3):665–701
200. Weisenburger S, Vaziri A. 2018. A guide to emerging technologies for large-scale and whole-brain optical imaging of neuronal activity. *Annu. Rev. Neurosci.* 41:431–52
201. White JG, Southgate E, Thomson JN, Brenner S, et al. 1986. The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philos. Trans. R. Soc. B* 314(1165):1–340
202. Willms AR, Baro DJ, Harris-Warrick RM, Guckenheimer J. 1999. An improved parameter estimation method for Hodgkin-Huxley models. *J. Comput. Neurosci.* 6:145–68
203. Wilson HR, Blake R, Lee SH. 2001. Dynamics of travelling waves in visual perception. *Nature* 412(6850):907–10
204. Wilson HR, Cowan JD. 1972. Excitatory and inhibitory interactions in localized populations of model neurons. *Biophys. J.* 12(1):1–24
205. Witvliet D, Mulcahy B, Mitchell JK, Meirovitch Y, Berger DR, et al. 2021. Connectomes across development reveal principles of brain maturation. *Nature* 596(7871):257–61
206. Woodward J, Ross L. 2021. Scientific explanation. *Stanford Encyclopedia of Philosophy*. **https://plato.stanford.edu/entries/scientific-explanation/**
207. Wu Z, Pan S, Chen F, Long G, Zhang C, Philip SY. 2020. A comprehensive survey on graph neural networks. *IEEE Trans. Neural Netw. Learn. Syst.* 32(1):4–24
208. Xia F, Sun K, Yu S, Aziz A, Wan L, et al. 2021. Graph learning: a survey. *IEEE Trans. Artif. Intell.* 2(2):109–27
209. Yamamoto W, Yuste R. 2020. Whole-body imaging of neural and muscle activity during behavior in *Hydra vulgaris*: effect of osmolarity on contraction bursts. *Eneuro* 7(4):ENEURO.0539-19.2020
210. Zeng H, Sanes JR. 2017. Neuronal cell-type classification: challenges, opportunities and the path forward. *Nat. Rev. Neurosci.* 18(9):530–46
211. Zhang F, Daducci A, He Y, Schiavi S, Seguin C, et al. 2022. Quantitative mapping of the brain's structural connectivity using diffusion MRI tractography: a review. *NeuroImage* 249:118870
212. Zhou D, Cornblath EJ, Stiso J, Teich EG, Dworkin JD, et al. 2020. Gender diversity statement and code notebook. Version 1.0. **https://zenodo.org/records/7375250**