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Perspective

How heterogeneity shapes dynamics and computation in the brain

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SUMMARY

Much effort has been spent clustering neurons into transcriptomic or functional cell types and characterizing the differences between them. Beyond subdividing neurons into categories, we must recognize that no two neurons are identical and that graded physiological or transcriptomic properties exist within cells of a given type. This often overlooked "within-type" heterogeneity is a specific neuronal implementation of what statistical physics refers to as "disorder" and exhibits rich computational properties, the identification of which may shed crucial insights into theories of brain function. In this perspective article, we address this gap by highlighting theoretical frameworks for the study of neural tissue heterogeneity and discussing the benefits and implications of within-type heterogeneity for neural network dynamics, computation, and self-organization.

INTRODUCTION: THE HETEROGENEOUS BRAIN

The growth of technologies for high-throughput transcriptomic profiling, projection tracing, and multi-neuron recordings has yielded massive new datasets that characterize neuron and circuit physiology with unprecedented detail.[1–5] One strategy to deal with these data is to cluster neurons into discrete cell types based on morphological, physiological, and molecular grounds, facilitating the comparison of cell populations between regions and brains. But even within the most narrowly defined cell type, we find substantial neuron-to-neuron differences in cell properties, as reviewed in Cembrowski and Menon.[6] Cortical and hippocampal cell types express large, continuous within-type variation in function-defining properties such as their membrane time constant or spike thresholds.[2,7–10] In mouse motor cortex, for example, membrane time constants of parvalbumin-expressing interneurons were found to vary between 2 and 18 ms, and membrane time constants of vasoactive intestinal polypeptide (VIP)-expressing interneurons were found to vary between 3 and 30 ms.[1] In a study of the human cortex, layer 2 and 3 pyramidal cells were found to express resting membrane potentials that broadly varied between −90 and −60 mV.[4] Synapses also show variation that is independent of the cell types they connect, as synaptic connections between pairs of cells of a given type can vary in their strength and kinetics by orders of magnitude.[5,11,12] In the human cortex, the excitatory postsynaptic potential (EPSP) amplitudes of connections between layer 2 and 3 pyramidal cells vary by over an order of magnitude, between <0.1 and ≈2 mV, with substantial differences between individual synapses.[4] Similarly broad distributions of EPSP amplitudes, coefficients of variation, and failure rates have also been reported in layer 5B pyramidal cells of rat barrel cortex.[13] Often, the variations of electrophysiological and synaptic properties within a cell type are substantially larger than the differences in the averages of those properties across cell types.[1,4,12]

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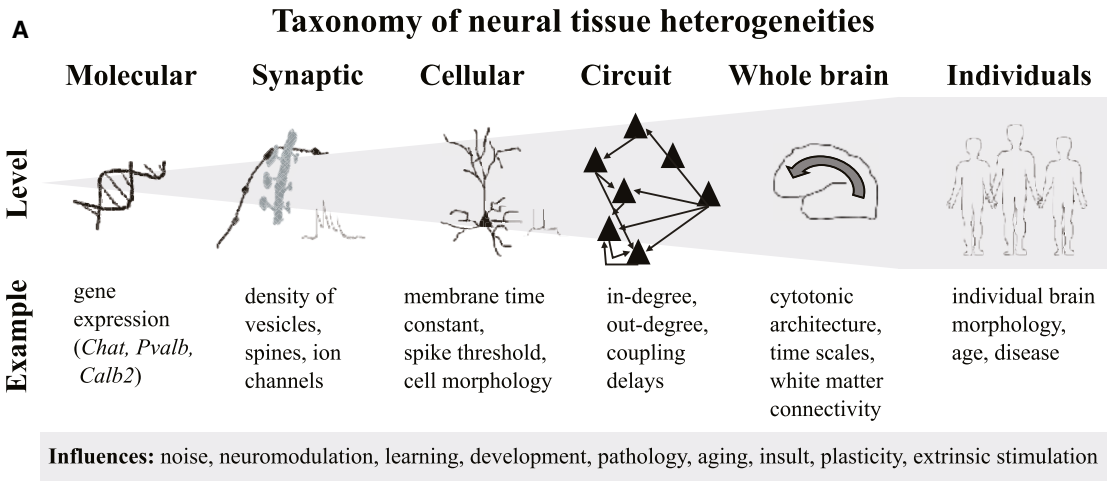

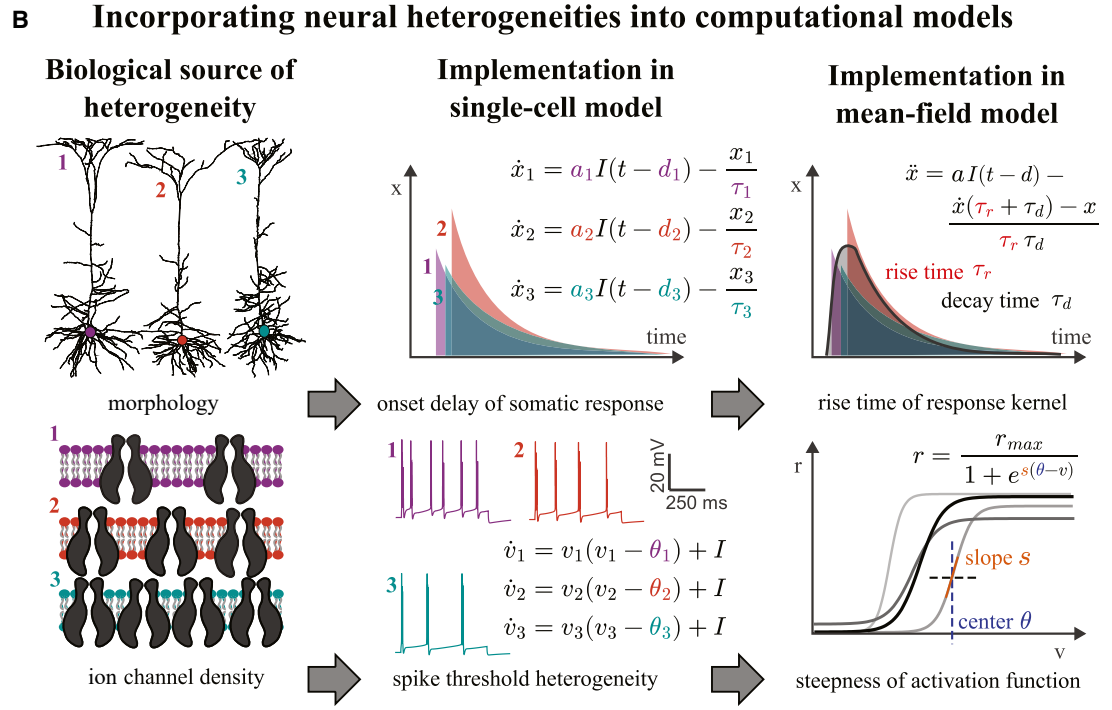

Figure 1. Different forms of heterogeneities and incorporating them into computational models

(A) Top: hierarchical taxonomy of neural tissue heterogeneities. From left to right: molecular to whole-brain and inter-individual heterogeneities. Below the schemes, examples are given for each of the levels (middle). Bottom: at each of the different levels, neural tissue heterogeneity is influenced by a variety of factors. (B) Two examples of how neural tissue heterogeneity can be incorporated into computational models. Subcellular heterogeneities in morphology and ion channel distributions can be directly implemented in detailed multi-compartment models of a single cell. In simpler point neuron models, morphological heterogeneity can lead to differences in the amplitude a, onset delay d, and decay time constant τ of the postsynaptic response x to pre-synaptic firing. Cell-to-cell variability in ion channel distributions may translate to heterogeneity in the spike thresholds θ that control at which value of the membrane potential v a spike is generated. At the population level, the level of heterogeneity in onset delay d can lead to different rise times τ_r of the population response, whereas the level of heterogeneity in spike threshold θ determines the slope s of the population activation function.

In reckoning with large-scale functional and physiological data, then, we need a strategy for understanding that goes beyond the dividing of neurons into categories. What are the functional consequences of heterogeneity in the brain, be it at the level of molecules, synapses, cells, or circuits (see Figure 1)? Does heterogeneity of computational elements (neurons, synapses, and microcircuits) within a given type play a role in and of itself that is distinct from the function of differences between cell types? Or is heterogeneity within cell types biological noise, an epiphenomenon that stable brain function should be invariant to?

A few years ago, Cembrowski and Spruston called for studies to address the functional role of within-type heterogeneity, concluding that "heterogeneity is likely to be a general and

crucial feature of the mammalian brain."[14] An increasing number of studies support this conclusion.[15–19] Here, we attempt to integrate insight from various fields—computational neuroscience, statistical physics, network science, neuromorphic computing, and artificial intelligence—into a coherent perspective on heterogeneous brain networks. We discuss the implications of neural heterogeneity for the dynamics and function of brain networks at different scales and highlight recent theoretical developments that promise new mechanistic insights into the role of heterogeneity. Moreover, we argue for analog computing systems as a physical model to study the effects of structural heterogeneity on neural network function. Finally, we propose a key role of heterogeneity for adapting neural systems and outline novel research directions for understanding the self-organization properties of heterogeneous neural systems.

EFFECTS OF HETEROGENEITY ON NEURAL DYNAMICS

Brain function emerges from coordinated activity across multiple levels of organization, including individual neurons, local circuits, and entire brain regions. Each of these levels can be viewed from a network perspective as a set of nodes that are connected by edges, where both nodes and edges can express heterogeneity in their intrinsic properties (Figure 1). For example, in a network of neurons, the existence of neurons of different cell types is a form of nodal heterogeneity, while the variation of synaptic weights between them is a form of edge heterogeneity.

The dynamic consequences of edge heterogeneity have been long studied, beginning with early work on disordered systems in statistical physics, such as spin glasses.[20] Mathematical methods and mechanistic results from this field have been adapted to neuroscience, where they inform our intuitions of computation in biological and artificial neural networks (see Box 1).

But in traditional statistical physics systems, all nodes in a network are identical particles, and only their connecting edges vary. Brain networks differ from nonliving physical systems: they are comprised of regions and cell types that are physiologically, morphologically, and functionally diverse, granting them both edge and nodal heterogeneity. Figure 1B presents examples that illustrate how such heterogeneity can be incorporated into mathematical models at both single-cell and population levels. The computational consequences of nodal heterogeneity have only recently received closer attention. In this section, we explore how heterogeneity among network nodes affects coordinated brain activity, integrating findings from both neural network models and other complex systems.

Heterogeneity can both promote and suppress neural synchrony

A first area of impact of nodal heterogeneity is in the capacity of networks of spiking neurons to synchronize their firing. Synchronization of spiking is one of two phenomena that can promote spatiotemporal pattern formation in brain activity (see Figure 2A), the other being correlations in firing rates driven by recurrence or common input.[50] Transient synchronization of local spiking activity has been connected to various brain functions (e.g., movement control, memory formation, and language[51]). Prolonged or spatially extended synchronization, on the other hand, is indicative of neurological disorders (e.g., epilepsy, Parkinson's disease, and Alzheimer's disease[52]), with some notable exceptions such as the sustained synchrony in the suprachiasmatic nucleus (which controls circadian rhythms) and during slow-wave sleep. As synchronization is generally a nonlinear phenomenon, mathematical models are required to gain a mechanistic understanding of the system properties that cause transitions between synchronous and asynchronous states of neural networks. Below, we discuss the role of neural heterogeneity for spike synchronization.

Insights from models of coupled intrinsic oscillators

Nodal heterogeneity has traditionally been viewed as a barrier to synchronization in complex systems. This view is based on studies of phase oscillator networks, where each node is an oscillator characterized by a phase, and oscillator pairs interact with a coupling strength proportional to their phase difference (e.g., Kuramoto oscillator networks). In such networks, greater variability in intrinsic oscillator frequency requires stronger coupling to achieve global synchrony.[53] However, over the past two decades, a more complex picture has emerged. For a range of conditions, intermediate levels of nodal heterogeneity can actually *stabilize* synchrony in higher-dimensional oscillator models, such as the Stuart-Landau model describing the phase-amplitude behavior close to a Hopf bifurcation.[54,55] Synchronization induced by nodal heterogeneity has now been predicted or observed in a broad class of systems. Examples include persistent oscillations induced by reactivity heterogeneity in active particles[56] and enhanced robustness in cardiac pacemakers induced by heterogeneity in electrophysiological and calcium cycling parameters.[57]

Importantly, the effects of nodal heterogeneity extend beyond global transitions between asynchronous and synchronous states. It also influences the formation of complex spatiotemporal patterns. For example, heterogeneity in intrinsic frequencies can either promote or inhibit chimera states,[58] where synchronous and asynchronous subpopulations coexist within the same network. These mixed states are particularly relevant to brain dynamics, where transient synchronization typically occurs within subpopulations of neurons.[59]

Translation to neural systems

How do the insights from coupled oscillator models translate to biological neural networks? Unlike phase oscillator systems, neural networks have multiple forms of coupling, including electrical gap-junction coupling, excitatory and inhibitory ionotropic coupling, and slow metabotropic coupling. A recurrently connected population of a single cell type can be approximated as a coupled oscillator system only when most neurons in the population are in a regular spiking regime or are electrically coupled. In such cases, consistent with phase oscillator models, intrinsic neural heterogeneity tends to desynchronize population dynamics.[15,60,61] It does so by counteracting synchrony that would otherwise be induced by shared external input or recurrent excitation.[62]

In the more common case where neurons are mostly coupled via chemical synapses and are not in a regular spiking regime, it is not immediately clear whether predictions from more general coupled oscillator models apply. Interestingly, intermediate

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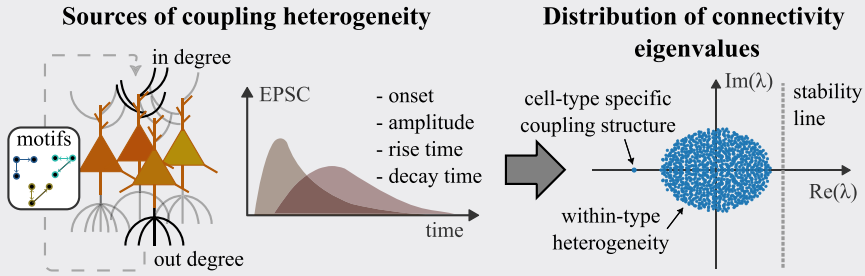
Box 1. Edge heterogeneity



While our perspective focuses on neural heterogeneity, it is worth noting that synaptic properties are also highly heterogeneous: whether due to homeostatic scaling, past plasticity events, or biological noise, pre- and postsynaptic elements vary across synapses of a given neuron or cell type.[12] This variation in synaptic properties affects the dimensionality,[5,21–24] synchronization and coordination properties,[25–27] stability and resilience to perturbations,[28–30] and intrinsic timescales of neural networks.[25,31–33] The effect of synaptic coupling properties on emergent circuit function has seen extensive prior discussion; therefore, we do not cover it in depth in this article. However, given the strong similarities between neural and synaptic heterogeneity in terms of their effect on certain aspects of network dynamics and function, we here briefly summarize some key findings to provide context for the remainder of the article.

DELAY HETEROGENEITY

One form of temporal disorder in neural systems is introduced through the delay between a presynaptic somatic action potential and the onset of the initial response in the soma of its postsynaptic target.[4] Delay coupling can induce highly complex spatiotemporal dynamics in neural networks that would express simple steady-state dynamics in the case of zero-delay coupling.[34] As a consequence, distributed delays change the signal processing properties of a neural network[35,36] and serve as a form of distributed network memory that has been shown to significantly boost the performance of artificial neural networks on temporal feature detection tasks.[37]

TIMESCALE HETEROGENEITY

Another form of temporal disorder is the heterogeneity in temporal response profiles of electrochemical synapses, which can span an order of magnitude, even within a synapse type.[12] In artificial neural networks, synaptic timescale heterogeneity allows for temporal feature integration at distinct timescales, thus improving performance on temporal feature detection tasks such as auditory perception.[38]

COUPLING STRENGTH HETEROGENEITY

A ubiquitous form of structural disorder in neural networks is the sparseness and variable strength of synaptic connectivity. While the mean coupling and excitation-inhibition ratio between neurons or populations determines the average coordination between network elements,[39,40] heterogeneity in network connectivity determines the complexity of cross-neuronal coordination.[23–27,41] The connectivity eigenvalue spectrum induced by the various forms of coupling heterogeneity quantifies the effective interactions between network units and determines both the spatial and temporal organization of neural activities.[25,33,42] Through statistical field theory,[43] it has been revealed that synaptic heterogeneity acts as a control parameter that shapes the stability of network states.[25,44] Close to a critical point, neurons transition to chaotic dynamics in certain models,[28] improving network performance in functions such as classification,[30] signal propagation,[45] and memory.[29,46] The critical regime supports these functions by diverse neural correlations,[25,27] dynamic modes with rich response properties,[25] coordination across large spatial distances, and distributed neural representations.[26,41] Changes in connectivity fine structure, such as reciprocal, convergent, divergent, and chain motifs, have a particularly strong impact on global dynamical features in this regime.[5,22–24,47–49]

levels of neural heterogeneity have still been found to promote synchronization in some cases,[63,64] consistent with predictions from coupled oscillator models.[54,55] This is caused by the dependency of the network firing rate on the level of neural heterogeneity (see Figure 2B). While heterogeneity typically impedes phase alignment, it can be the case that, below a critical level of neural heterogeneity, the average firing rate of a network is too low to support persistent oscillations.[65] By raising the average firing rate of the network, increased heterogeneity can enable synchronized states to occur in these scenarios.[63]

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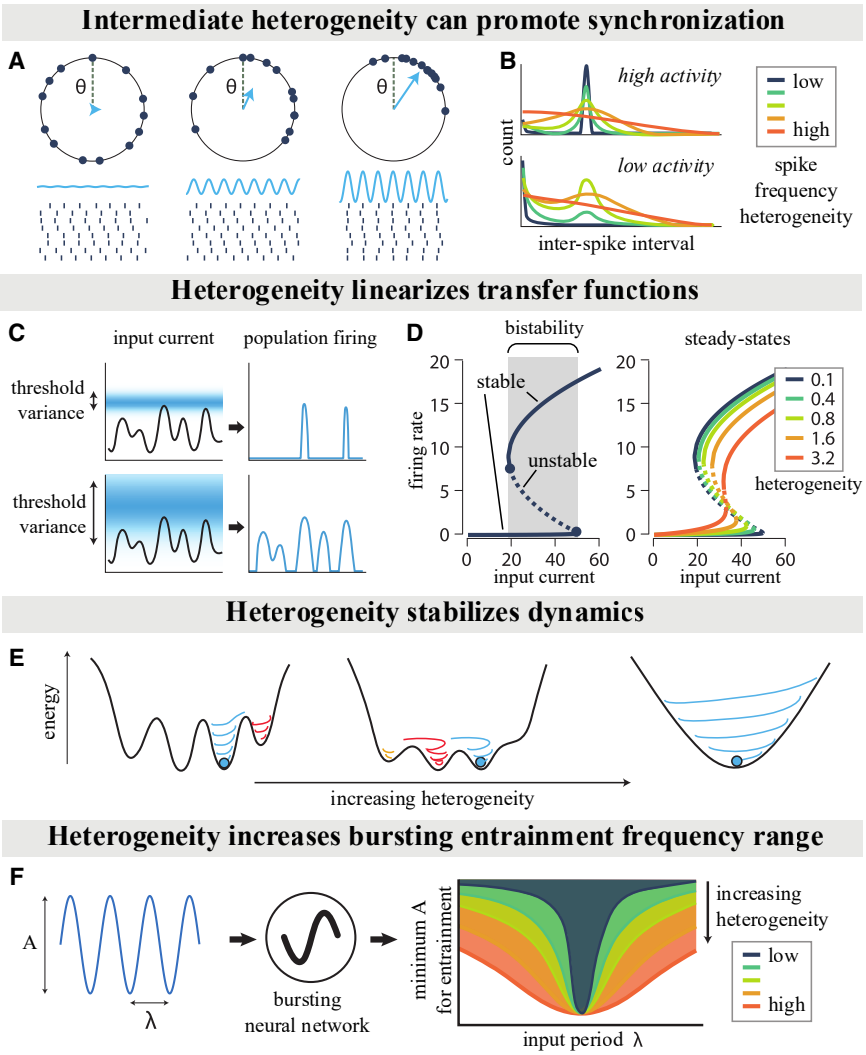

Figure 2. Effects of nodal heterogeneity on neural network computation through dynamics

(A) Synchronization of spiking neurons, each described by a phase θ, leads to the emergence of a macroscopic oscillation.

(B) Inter-spike interval distributions for neural networks with different levels of heterogeneity (color-coded). For high network activity, heterogeneity has a purely desynchronizing effect. For low network activity, intermediate levels of heterogeneity can promote synchronization.

(C) Dynamic response of a neural population to input fluctuations for two different levels of spike threshold variance (blue-shaded regions). Increased threshold variance makes the population more sensitive to input fluctuations.

(D) Left: bifurcation diagram of a homogeneous, recurrently coupled neural population, where solid (dotted) lines depict stable (unstable) steady-state firing rates of the population. The gray region indicates an input regime in which the system is bistable, meaning that stable low and high firing rate states coexist. Right: neural heterogeneity (color-coded) linearizes the relationship between the steady-state firing rate and input current.

(E) Effect of heterogeneity on the energy landscape and corresponding phase transitions of a dynamical system. As heterogeneity increases, the energy barriers between coexisting equilibria become smaller and eventually disappear.

(F) Entrainment of an intrinsically oscillating neural network, driven by a periodic driver, as a function of the driving frequency and amplitude. Colored regions in parameter space mark where entrainment occurs.

In contrast to single-cell-type models, most biological neural networks consist of multiple functionally, morphologically, or molecularly defined cell types, such as pyramidal cells and inhibitory interneuron types in the cortex. At the scale of multiple neural populations, synchronized oscillations can emerge between coupled pools of excitatory and inhibitory neurons. In this case, the interacting pools function as a single, mesoscopic dynamical unit.[66,67] There are three types of heterogeneity to consider in such systems: heterogeneity within the excitatory pool, within the inhibitory pool, and between interacting mesoscopic units.

Just as at the single-neuron level, heterogeneity within excitatory and inhibitory pools tends to prevent the emergence of synchrony in regular spiking regimes,[17,62] and again, intermediate levels of heterogeneity can promote synchrony in cases of low network activity.[64] This suggests that the effect of heterogeneity on synchrony is invariant to the particular mechanism that is driving that synchrony (recurrent coupling within a pool of neurons vs. interactions between excitatory and inhibitory pools of neurons). Further studies are needed to test whether this principle extends to other mechanisms of synchronization, such as spike-triggered adaptation in neurons and synapses.[68,69]

Networks of mesoscopic neural circuits are a popular model for studying interactions between brain areas via white matter connections.[70] Connections between brain areas are organized hierarchically and often correlate with local features like the timescale of neural activity.[16] Little is known about how nodal heterogeneity affects such hierarchically structured, highly non-random networks. Most research at this level has focused on how heterogeneity can improve predictions of functional connectivity in whole-brain models of fMRI data.[71,72] We propose that future studies should move beyond functional connectivity prediction and examine how nodal heterogeneity affects macroscopic phenomena such as wave propagation across brain areas, large-scale synchronization (e.g., in epilepsy), and transitions between functional states like the default-mode network. Early work suggests that nodal heterogeneity reduces multistability in small-scale models, from a single neural population[62] to a few coupled populations.[73,74] But it remains unclear whether this effect holds at the macroscopic level, where coupling and nodal heterogeneity are correlated and hierarchically organized.[16]

Stabilizing effects of nodal heterogeneity

How do the effects of heterogeneity on neural synchrony contribute to stable brain function? This becomes clearer when

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viewed through the lens of a disease. Recent studies have shown that pyramidal neurons exhibit reduced biophysical diversity in tissue resected from human participants with epilepsy.[17] This loss of heterogeneity, particularly in cell-intrinsic excitability, appears to compromise the brain's functional resilience, making it more prone to pathological dynamics.[65] Similar patterns of declining heterogeneity promoting pathological activity have been reported in other neurological conditions as well.[75,76] These findings reflect a long-standing idea in mathematical biology: heterogeneity promotes stability of function in complex systems.[77]

Heterogeneity promotes linearization

In the context of neural dynamics, stability can be understood as the system's ability to maintain healthy function in the face of disturbances such as environmental perturbations,[78] external stimuli,[65] pathological disruptions,[78] and/or plasticity during development and learning.[79] Heterogeneity allows neural circuits to maintain stable function across a wider range of disturbances,[80] compensating for perturbations by distributing them across the population and thereby avoiding abrupt shifts in activity (see Figure 2C). This results in the linearization of the population transfer function, which describes the relationship between the input to the population and the resulting neuron-averaged firing rate (see Figure 2D). The linearizing effect of heterogeneity is supported by theoretical results, which show that nodal heterogeneity makes the system's stability (specifically, its Jacobian eigenvalue spectrum) less sensitive to changes in parameters such as connectivity, network size, and response gain, and also stabilizes specific dynamical states like synchrony.[65]

Heterogeneity promotes trivialization

In statistical mechanics, trivialization refers to a reduction in the number of equilibria in a system, making it less prone to express sudden, qualitative shifts in dynamics.[81] Heterogeneity can induce this kind of trivialization in the energy landscape of neural systems (see Figure 2E), constraining their dynamics around fewer but more stable states.[82,83] This restructuring has direct functional consequences for the system, as reflected in its response to extrinsic stimulation. In bistable and excitable systems, intermediate levels of heterogeneity can induce resonance, enhancing entrainment by a periodic driving input.[84] In stochastically driven coupled oscillator systems, there are scenarios for which spatial heterogeneity in the input can facilitate synchronization.[85,86] Again, heterogeneity appears to have similar functional consequences in networks of recurrently coupled neurons. Heterogeneity lowers the activation threshold for some neurons, enabling them to drive others into collective entrainment to a periodic driver.[87] If such recurrent networks are in an oscillatory regime, heterogeneity makes them more easily entrained by a wider range of frequencies (see Figure 2F), with richer phase relationships to the periodic driver.[62,88]

Thus, heterogeneity-induced stabilization of neural dynamics does not necessarily render the system less flexible. On the contrary, intermediate levels of heterogeneity typically make neural populations respond more flexibly to a broader range of inputs, striking a balance between order and responsiveness that may be essential for healthy brain function.

HETEROGENEITY CONTROLS COMPUTATION IN NEURAL NETWORKS

While the previous section examined how neural heterogeneity affects network dynamics, we now ask how it impacts neural computation. To this end, we consider several conceptual frameworks of computation in neural networks and explore how heterogeneity affects a network's computational capacity in each. We continue to focus on nodal heterogeneity (but see Box 1 for the functional impact of edge heterogeneity).

Learning input-output transformations with heterogeneous neural networks

Broadly speaking, neural networks compute by learning transformations of input patterns into output responses. How does heterogeneity of nodes in a network affect the capacity of that network to learn a family of such transformations? One fundamental type of transformation networks must learn is signal detection, where the network must determine the presence or absence of some target signal within an input stream. In feedforward networks, heterogeneity has been found to improve signal detection by linearizing the network's overall response function (see Figure 2D) and by decorrelating responses across the population.[89–91] In this context, heterogeneity acts as quenched disorder, similarly to noise: both can enhance signal processing at intermediate levels by means of stochastic resonance (see Figure 2C).[92,93] Indeed, when noise and heterogeneity follow the same probability distribution, their effects on the population dynamics have been found to be indistinguishable at the macroscopic level.[73,94] Thus, for computations that rely on the macroscopic state of a network, like signal detection via the average population firing rate, neural heterogeneity and noise may be considered functionally equivalent.

However, this equivalence breaks down for computations that rely on the identity of individual neurons. Unlike noise, which introduces trial-to-trial variability and undermines consistent neuron-level encoding, neural heterogeneity preserves a stable mapping between input features and neural responses and can reduce trial-to-trial variability in the presence of metastable neural dynamics.[83] This stability allows downstream circuits or readout layers to exploit neuron-specific tuning for reliable signal readout, something not possible for added noise.[32,62,95,96] Indeed, it has been shown that neural heterogeneity contributes to stable odor representations in the olfactory bulb[15,97] as well as to stimulus orientation encoding in the visual cortex.[98]

Further insight into the computational impact of neural heterogeneity comes from studies of sequence learning in networks with heterogeneous intrinsic timescales. Timescale heterogeneity enables spatial demixing of broadband input streams: small clusters of neurons respond preferentially to fast-changing inputs, while larger clusters track slower input components.[32] This provides a theoretical basis for the empirical finding in primates that the presence of multiple timescales in a neural population improves performance on complex tasks.[99] It also explains the computational finding that not only does neural heterogeneity improve classification accuracy,[73,83,100] but it also naturally emerges when neuron-intrinsic parameters are optimized on complex machine learning tasks.[101,102]

Computation via phase transitions in neural networks

Neural computation may also be studied through the lens of dynamical systems theory, where neural networks compute by evolving along low-dimensional manifolds, with the geometry of attractors and repellers governing the computational properties of the system.[103] In this view, stable fixed points can provide memory states, the separatrix of unstable fixed points can define decision boundaries, and limit cycles can serve as central pattern generators. This framework has gained popularity with the growing adoption of large-scale neural recordings in behaving vertebrates, which often show that the trajectory of neural activity along low-dimensional manifolds can encode behaviorally relevant variables.[50,104] The topological properties of those manifolds share key features with the variables they encode, features that are reminiscent of dynamical systems governed by stable and unstable equilibria.[105]

Recent theoretical work identifies neural heterogeneity as a key control variable for shaping the type, number, and stability of equilibria in neural systems.[106] In recurrent neural networks, tuning neural heterogeneity can trigger phase transitions from asynchronous to synchronous regimes, often associated with changes in the number and stability of limit cycles in the system.[82,107] In multistable network regimes, heterogeneity controls the width of basins of attraction around fixed points, changing the threshold for which transient inputs to a neural network cause transitions between different stable equilibria, as well as the dynamics of spontaneous switching between metastable states caused by network-intrinsic noise.[62,73,100] Specifically, increasing heterogeneity accelerates the switching dynamics between states by lowering energy barriers between them (see Figure 2E), until heterogeneity becomes large enough that a phase transition occurs and the metastable fixed points collapse to a single stable attractor.[83]

This phase transition was proposed as a neural mechanism for the inverted-U relationship between task performance and arousal level, whereby optimal behavioral performance occurs at an intermediate level of arousal near a critical point.[108] Phase transitions driven by nodal heterogeneity have also been explored in randomly coupled neural networks, where a large repertoire of network phases was discovered, including several ergodicity-breaking phases in which the network performs multi-tasking without any parameter optimization.[96] Going beyond heterogeneity as quenched disorder, by tuning the heterogeneity via optimization, one can strongly enhance the expressivity of neural networks with random couplings.[109] Neural networks with random weights and learned biases can achieve performance comparable to fully trained networks at the price of large width. In this context, tunable heterogeneity acts as a contextual control signal that toggles the network's internal state to implement different input/output relationships.

Computing with heterogeneous neuromorphic devices

Neuromorphic circuits aim to implement the principles of spike-based neural computation by leveraging the physics of electronic circuits and emerging memory devices.[110] Both the spatial and temporal variability of neuromorphic spiking networks have characteristics that are similar to those measured in biological neural substrates.[110–112] In contrast to artificial neural networks implemented on standard computers, neuromorphic systems can emulate biological neural network dynamics in continuous time. Exhibiting structural heterogeneity in computing parameters such as neuronal time constants, firing rates, synaptic weights, or dendritic delays (see Figures 3A and 3B), neuromorphic systems have a constraint in common with biological neural systems—both must enable reliable and robust computation amid such heterogeneity. Below, we describe insight gained from the neuromorphic field on how parameter heterogeneity impacts the computational capacity of neuromorphic devices. As a comprehensive review of the work on neuromorphic heterogeneity is beyond the scope of this article, we instead focus on two particular neuromorphic architectures that directly connect to the topics of this section: (1) computing via phase transitions between multiple stable states and (2) learning input-output transformations with heterogeneous computing substrates.

Computing with multi-stabilities

Reliable signal processing requires stable, precise representations. Nervous systems are able to represent signals in a reliable and robust way by using a population code,[116,117] which includes inhibition balancing for temporal precision[118] and winner-takes-all (WTA) mechanisms for spatial precision.[119–121] By implementing recurrent excitatory-inhibitory networks configured as soft-WTA networks with mixed-signal neuromorphic processors, it is possible to represent sensory signals reliably and robustly. Neuromorphic hardware setups that couple multiple instances of these networks together have the capacity to process real-world sensory signals and leverage them for solving tasks in real time.[113,122] An important computational primitive that allows one to relate neural computation with mathematical models of computation is the finite state machine (FSM),[123,124] which can be implemented using spiking neural networks on mixed-signal neuromorphic chips.[125] These networks are called neural state machines (NSMs), because they comprise state-holding soft-WTA networks of spiking neurons that can transition to different states when the appropriate external input is provided (see Figures 3C and 3D). As we discussed in the previous section, neural heterogeneity controls the number and stability of different states in neural networks, and multi-stability typically ceases to exist for high levels of heterogeneity.[62,82,83] Networks of NSMs provide an excellent physical model to analyze precisely how device heterogeneity impacts reliable computation with multi-stable devices and how problems that might arise from heterogeneity can be mitigated (see Liang and Indiveri,[114] Liang and Indiveri,[126] and Cotteret et al.[127] for examples).

Exploiting heterogeneity during learning

One of the most effective strategies that biology uses to mitigate noise and carry out reliable computation is to use adaptation and plasticity at different temporal and spatial scales.[128,129] A wide range of spike-based learning models have been proposed that are compatible with neuromorphic implementations.[130] For example, the neuromorphic architecture MEMSORN incorporates Hebbian plasticity at synapses and intrinsic plasticity of neurons.[131] The model utilizes the inherent device heterogeneity of the spiking network to enhance local learning of neuronal and synaptic parameters, leading to considerably better performance in a sequence prediction task compared with a more

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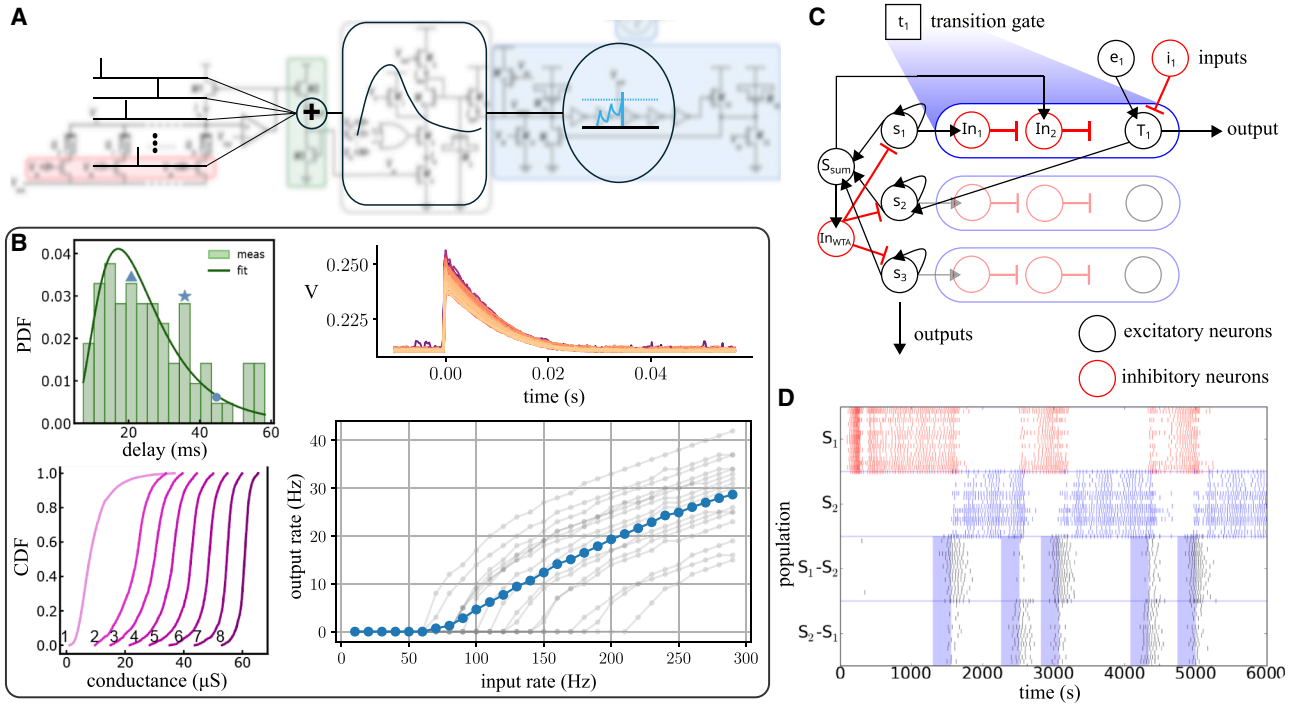

Figure 3. Stable computation in heterogeneous neuromorphic devices

(A) Block diagram of signal processing on a neuromorphic chip (spikes arrive at dendrites with length-dependent delays *d* and weights *w*, are summed on the dendritic branch, and produce an excitatory postsynaptic current [EPSC], which drives a leaky integrate-and-fire process).

(B) Distributions of synaptic, dendritic, EPSC, and firing rate responses in (A). Reprinted from D'Agostino et al.[113]

(C) Network diagram of an NSM, adapted from Liang and Indiveri.[114] Populations of neurons representing internal states "S_i" compete in a WTA network. All state-transition populations "T_i" are inhibited by the "S_{SUM}" population, except for the (disinhibited) one providing input to the winner state.

(D) Spiking activity observed in a neuromorphic chip physically implementing an NSM. Inputs were provided at arbitrary intervals to the transition neurons (blue shadings). Consistent with the diagram in (C), the neural system reliably flips its state at each presentation of the input. Reprinted from Neftci et al.[115]

homogeneous model.[131] Similar effects have been reported in other neuromorphic architectures, where intrinsic heterogeneity of the spiking neurons enhanced the stimulus representation of the network.[132,133]

DenRAM[113] is another neuromorphic architecture that incorporates dendrites, which leverage resistive memories to account for both the strength and the temporal delay of connections between pairs of neurons. The variability of resistive memories can be used to generate a distribution of delays in this architecture, thus enriching the dynamics that the network can generate. Optimizing the weight parameters associated with each resistive memory amounts to selecting samples of the delay distribution that benefit temporal feature detection, which led to an increased classification performance in a sequence learning task.[113] Moreover, DenRAM showed that using this learning scheme, one can reduce the number of required parameters for the same task by an order of magnitude.

Neuromorphic devices as benchmarks for theories of neural computation

Much of our theoretical understanding of neural dynamics and computation is based on mathematical equations that model the single neuron as an electric circuit. While neuromorphic devices do not function by ion flows across semi-permeable membranes, they are also electric circuits that share the same fundamental physics of carrier transport (i.e., diffusion, Boltzmann distributions, etc.) and can therefore well approximate the electrical features of biological neurons and synapses. As demonstrated by the examples described in this section, the way neural heterogeneity affects neuromorphic circuits is in many ways similar to how it affects biological neural networks. A crucial advantage of neuromorphic systems is that we know their composition and can measure most system parameters. Therefore, we can build an accurate mathematical model for any given neuromorphic circuit that can be used to predict its dynamics in real-world applications. Furthermore, neuromorphic systems can be trained on a wide range of tasks, allowing researchers to create benchmarks, compare different architectures on identical tasks, run parameter studies, and identify technical applications that go beyond fundamental neuroscience questions. Finally, neuromorphic architectures run and compute in real time, permitting the study of long-term plasticity and other biological phenomena that evolve on multiple timescales in parallel, in closed-loop interactions with the environment, allowing explorations and research studies that are difficult to do with conventional computers. Since device heterogeneity in neuromorphic systems is not just fabrication noise but, to a certain extent, can be controlled experimentally,[134] we argue that neuromorphic systems serve as an excellent physical model for theory-driven research on the role of heterogeneity for computing in complex systems such as the brain.

TOWARD A THEORY OF COMPUTATION IN HETEROGENEOUS NEURAL SYSTEMS

Heterogeneity is emerging as a central determinant of behavior across a range of complex physical and biological systems. Results from network science suggest that suitably heterogeneous generators promote the stable functioning of power grids,[135] an aspect that has become ever more relevant as power grids incorporate an increasing fraction of energy sources that are more sensitive to environmental fluctuations.[136] Phenotypic heterogeneity in microbial populations makes them more resistant to environmental fluctuations[137] and other forms of stress,[138] with important implications for infection dynamics.[139] In animals, heterogeneity between individuals affects behavior[140] in scenarios as different as the collective motion of an animal group[141,142] and the expression of opinions in social networks.[143]

We here show that brains are no different: neural heterogeneity is inherently connected to brain function. We further argue for a perspective of brain function that goes beyond dividing neurons into increasingly granular sets of cell types. Instead, intrinsic differences between neurons of the same cell type (and the synaptic connections they express; see Box 1) have important consequences for the collective dynamics and functions of neural networks, as reflected in functionally relevant properties such as a network's energy landscape, its stability to perturbation, and its flexibility in multitasking. Our arguments are supported by results in biological neurons, artificial neural networks, and physical neuromorphic computing systems, reflecting the fundamental role of heterogeneity in the organization and function of distributed networks. Finally, due to the tight relationship between neural heterogeneity and neural response variability, the role of neural heterogeneity can be expected to translate to observable behavior,[144] though this relationship requires further experimental investigation. Below, we point out two main directions that we consider promising for developing a theoretical basis for future empirical research on the role of heterogeneity in brain function and organization. We conclude this perspective by discussing specific empirical approaches that would allow testing such a theory of neural heterogeneity.

Self-organized pattern formation in heterogeneous, adaptive neural systems

One exciting area for future exploration is studying the implications of neural heterogeneity for the developmental trajectory of neural networks. Heterogeneity of interacting elements is a central aspect of self-organized pattern formation in adaptive biological systems, including the brain.[145] The strength of synaptic connections between neurons is often plastic and can evolve over time depending on extrinsic modulating factors or the spiking activity of the connected neurons. Theoretical neuroscientists have mathematically formalized this plasticity in a diverse family of activity-dependent rules, such as Hebbian plasticity and spike-timing-dependent plasticity.[146] Since the spiking statistics of a neural population reflect aspects of the electrophysiological heterogeneity in that population, neural heterogeneity might influence structural pattern formation in neural networks through interaction with synaptic plasticity. Initial evidence for such a role of neural heterogeneity comes from two studies, which found that heterogeneous neural network models endowed with spike-timing-dependent plasticity form characteristic coupling structures where highly excitable neurons form stronger synaptic projections than less active neurons.[147,148] Moreover, the same work suggests that neural heterogeneity might bias structural pattern formation toward acyclic, directed synaptic coupling motifs.[148] Interestingly, directed acyclic connectivity appears to be particularly pronounced in human cortical tissue,[5] a result that was obtained in a dataset that also revealed prominent heterogeneity within pyramidal cells related to differences in connectivity and synaptic properties.[4]

It remains an open, pressing question how tissue heterogeneity interacts with various forms of neural and synaptic plasticity to constrain self-organized pattern formation in adaptive neural networks.[149] While theoretical efforts to understand the relationship between neural dynamics and synaptic connectivity have mostly adopted the view that synaptic connectivity determines the spiking statistics in neural networks,[23–26,150,151] we emphasize that heterogeneities in firing-rate controlling properties (e.g., membrane capacitance and spike threshold) may also direct the evolution of synaptic connectivity in a network.

Importantly, many of the elements of a neural network that contribute to its heterogeneity are also themselves plastic.[152] These different forms of plasticity do not act independently but rather accompany each other in a manner that is constrained by molecular signaling. While some forms of plasticity serve learning and adaptation purposes, others serve homeostatic purposes.[153–158] It is therefore likely that heterogeneity and plasticity of neurons and their synaptic connections interact in complex ways to yield neural systems that provide both stability of function and flexibility in learning. Recent developments in mathematical modeling permit the incorporation of different forms of plasticity in neural networks with either neural heterogeneity[68,69] or synaptic heterogeneity.[159,160] Building upon these developments, we expect future work on self-organized pattern formation in heterogeneous, adaptive neural networks to help in understanding how heterogeneity and plasticity interact in the emergence of neural network function.

Dynamic control of heterogeneity

Neural tissue heterogeneity is likely not a static property: rather, physiological properties of neurons are subject to change, albeit on a slower timescale than that of neural dynamics. We propose two mechanisms through which this may be possible.

First, effective heterogeneity of a neural population can arise from variation in the overall synaptic inputs that neurons receive. If heterogeneity exists in the long-range couplings between neural populations in different brain regions, changes in the average firing rate of one region might lead to altered levels of effective neural heterogeneity in the target population through changes in input levels or effective synaptic conductance.[161] Such heterogeneity in synaptic innervation is a form of input heterogeneity, which has been shown to improve stimulus classification accuracy and reaction times in a recurrent neural network model,[73] explaining empirical effects of expectations in the gustatory cortex, locomotion in the visual cortex,[100] and arousal in the auditory cortex.[83] Additionally, changes in the background input heterogeneity have been shown to allow a neural population to

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engage in multiple tasks.[96] Therefore, learned input heterogeneity could serve as a mechanism to produce multiple, context-dependent computations without relearning recurrent weights within a local circuit.

This mechanism for input-related changes in neural heterogeneity requires a separation of timescales among neural activity, in which slow "context" signals between areas create a standing pattern of heterogeneity, while faster firing fluctuations carry out computations. Interestingly, considerable differences in the timescales of neural activity have been reported in studies of macroscopic brain organization.[16,162] Thus, slow changes in input heterogeneity of a neural circuit might be achieved by leveraging the long timescales of activity derived from higher-level contextual inputs.

Neuromodulatory systems are another candidate for the dynamic control of neural population heterogeneity, due to the diverse effects that neuromodulators can have on target neurons. Dopamine, for example, acts through five different postsynaptic receptors, acetylcholine through seven receptor subtypes, and serotonin through at least 14.[163,164] The effects of neuromodulator release depend on the distribution of these receptors at any target neuron or dendritic site. Neuromodulation could thus serve to scale the level of neural or synaptic heterogeneity, inducing phase transitions between different dynamical regimes or setting the optimal level of heterogeneity for a particular neural computation. Further experimental, computational, and theoretical studies will be required to examine whether this is indeed a functional aspect of neuromodulatory signaling. If so, it would underscore the relevance of neural tissue heterogeneity for stable brain function.

Experimental strategies for studying neural heterogeneity

Despite increasing computational evidence for a critical role of neural heterogeneity in brain function, experimental characterization of its impact *in vivo* remains sparse. One reason for this is that it is challenging to manipulate neural heterogeneity in a controlled experiment. Nonetheless, a number of experimental studies exist that relate variation in neural heterogeneity to functional differences. In this final section, starting from these studies, we discuss how neural heterogeneity could be studied experimentally in the future.

In vitro *experiments*

Because they offer easy electrophysiological access to neurons, *in vitro* and cell culture preparations are a natural setting to study effects of neural heterogeneity on neural network dynamics and development. For example, two previous studies in cortical slices and developing neural cultures have revealed a dependence of synaptic wiring on neural heterogeneity. Both studies found that highly active neurons form stronger synaptic connections than less active neurons, showing how differences in cell-intrinsic properties can foster differences in cells' functions within a neural population.[165,166] Such connectivity patterns have been found to maximize the number of possible activity patterns that a network can express.[167]

In vitro neural recordings also provide a reduced setting in which to study the effects of pharmacological manipulations on neural heterogeneity and emergent network dynamics. Rather than measuring the effect of a drug on the average firing rate or membrane potential of neurons, the question we would emphasize is the extent to which a manipulation alters the variance of these features across a neural population. This would permit a direct test of the hypothesis that neuromodulatory systems such as dopamine or acetylcholine can dynamically control neural heterogeneity via postsynaptic receptor diversity. Furthermore, the relationship between neural heterogeneity and connectivity may be further examined in developing neural cultures.

Leveraging correlations between brain function and topology

Another natural place to look for neural heterogeneity is in early sensory processing systems, where a common feature detection operation is performed over an often continuously varying input feature space. For example, neurons in the visual system might have receptive fields that tile the visual scene and detect a particular direction of movement. Classically, a neuron's receptive field and response dynamics have been viewed as arising entirely from its connectivity, with topographic projections granting a neuron its spatial (for vision) or spectral (for audition) receptive field, and variations in connectivity determining the cell's feature selectivity.

Study of some sensory systems, however, has revealed an additional role for heterogeneous neuronal physiology in sensory coding. In the mitral cells of the mouse olfactory bulb, electrophysiological heterogeneity has been linked to improved coding accuracy and stability across different experimental settings.[15,168,169] Mitral cells are secondary olfactory neurons that receive convergent input from populations of primary sensory neurons expressing the same odorant receptor. Sensory neuron axons and mitral cell dendrites meet in discrete structures called glomeruli, with each glomerulus dedicated to a single receptor type. Because mitral cells can be uniquely identified by their associated glomerulus, their functional differences can be directly compared with their electrophysiological properties measured with patch-clamp recordings. Using this approach, Angelo et al. showed that while mitral cells as a whole are quite physiologically heterogeneous, the physiological profile of individual cells is tightly linked to their source of input, with mitral cells innervating the same glomerulus showing strikingly similar physiological properties.[168]

A similar strategy, leveraging topological organization to study the relative contributions of node vs. edge heterogeneity to neural responses, has been applied to the fly visual system.[170] The fly compound eye consists of around 800 repeated columnar units, each sampling a small part of visual space. To compute wide-field visual features such as optic flow, flies integrate sensory information across many such columns, meaning columns at many different retinal positions must be capable of extracting a common motion signal. Detailed anatomical study of the fly eye has revealed how structured variation in the dendrites of direction-sensing neurons organizes their preferred directions of motion in a way to support this global calculation.[171]

In a third, non-sensory example, heterogeneity in the membrane time constants of entorhinal cortical stellate cells has been related to grid cell field spacing.[172,173] To achieve this, dorsoventral gradients that exist in the neural encoding of space

in the entorhinal cortex have been leveraged to relate neural heterogeneity to functional heterogeneity.[172]

The common element of these three experimental studies, which suggests a broader approach to studying the functional effects of neural heterogeneity, is that the authors study neural subsystems where neurons can be characterized in terms of both their connectivity and physiology and in terms of their functional tuning over some feature space (odorants, motion direction, or physical space). This allows authors to separately characterize a cell's functional tuning and its topological or physiological properties and to examine the relationship between the two. Similar work had been done relating neuronal populations' functional tuning with their gene expression[174] and projection patterns,[175] suggesting these datasets, when they are performed with single-cell-resolution functional characterization, could be similarly studied in the future.

Changes in neural heterogeneity caused by disease

Yet another opportunity to study effects of heterogeneity is through diseases that disrupt it. The computational studies reviewed here clearly demonstrate that a loss of heterogeneity can substantially alter neural population dynamics. Intriguingly, several neurodegenerative diseases and disorders may have loss of neuronal heterogeneity as a hallmark.

Midbrain dopamine neurons that are implicated in Parkinson's disease vary along a continuum in their intrinsic properties[176] and also exhibit systematic differences in their vulnerability to Parkinson's disease.[177] Selective dopamine neuron degeneration may thus reduce heterogeneity of the overall dopamine neuron population, which may in turn be a driver of pathological neural synchronization in the Parkinsonian striatum and pallidum.[178] As Parkinson's disease causes a number of motor and learning deficits that can be characterized both in humans and in animal models, it might be a well-suited disease model to test the functional implications of a loss in neural heterogeneity. Selective vulnerabilities of neurons related to their morphological, electrophysiological, or biochemical properties have also been reported in a number of other neurodegenerative diseases that cause functional impairments.[179] And across various neurodegenerative disorders, highly excitable neurons and neurons with a low capacity for cell-intrinsic calcium buffering have been identified as particularly vulnerable to disease.[180]

This raises the important question of whether the functional impairments associated with neurodegenerative disease arise due to the loss of a special, privileged-yet-vulnerable class of neurons or whether the real underlying cause of the impairment is the loss of neural heterogeneity that selective neurodegeneration creates. It furthermore suggests restoration of physiological heterogeneity as a potential strategy for rescuing neural circuit function.

CONCLUSIONS

Neural and synaptic heterogeneity is pervasive in vertebrate brains. Rather than treat it as a source of noise, a growing volume of computational and theoretical results predict that this heterogeneity plays a fundamental role in shaping neural network dynamics. The methods we have outlined here connect the neurodynamic effects of neural heterogeneity to the computational properties of neural networks, demonstrating that neural heterogeneity can control input-output transformations and attractor-based computation in neural networks. Experimental approaches *in vitro*, *in vivo*, and in neuromorphic systems now offer direct ways to test these predictions. We believe that accounting for the impact of neural heterogeneity, and particularly its modulation in time, will be essential in understanding the computational role of long-range projections and neuromodulatory systems in the brain. We also highlight the potential significance of loss of neuronal heterogeneity as a hallmark of neurodegenerative disease.

Based on the theoretical findings discussed here, we argue that neuronal cell types should be considered not as averages over morphology, electrophysiology, or biochemistry, but as distributions over those properties. This approach recognizes that variance, skewness, and other statistical moments can be central to the functional role that a particular cell type plays in a neural system. Adopting this shift will not only refine our understanding of structure-function relationships but also set the stage for a new generation of experiments and models that treat heterogeneity as a central principle of brain organization and function.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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