



# Rethinking brain-wide interactions through multi-region ‘network of networks’ models

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The neural control of behavior is distributed across many functionally and anatomically distinct brain regions even in small nervous systems. While classical neuroscience models treated these regions as a set of hierarchically isolated nodes, the brain comprises a recurrently interconnected network in which each region is intimately modulated by many others. Uncovering these interactions is now possible through experimental techniques that access large neural populations from many brain regions simultaneously. Harnessing these large-scale datasets, however, requires new theoretical approaches. Here, we review recent work to understand brain-wide interactions using multi-region ‘network of networks’ models and discuss how they can guide future experiments. We also emphasize the importance of multi-region recordings, and posit that studying individual components in isolation will be insufficient to understand the neural basis of behavior.

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## Introduction

Animal behavior — whether hunting, running, sleeping, or building a nest — arises from precisely coordinated activity spanning the entire brain. Rather than operate as a uniform network of neurons, the brain organizes throughout development into a large number of distinct, but interconnected, brain regions. Most animals demonstrate such anatomical modularity within the brain [1], and neuroscience researchers seeking to understand fundamental computational principles of the brain have thus adopted a similarly compartmentalized perspective (Figure 1a). In this view, ‘low level’ sensory regions relay information about the external world to ‘high level’

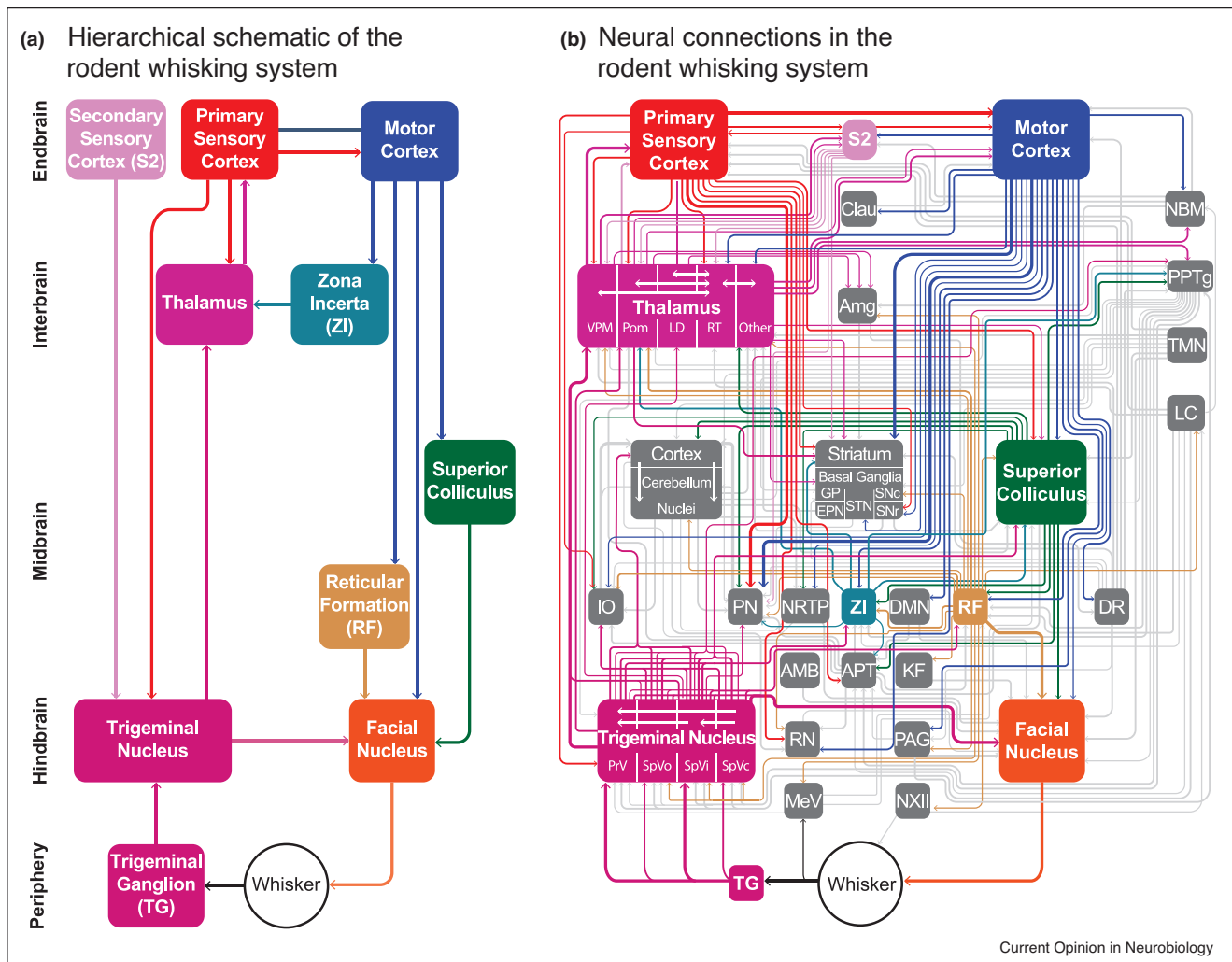
regions coordinating behavior, that in turn instruct low-level output or motor regions. However, such a simplified hierarchical view of the brain cannot account for the myriad, complex ways in which different regions are connected (Figure 1b), with a large amount of recurrent connections between many low level and high level brain regions. Because of this architecture, brain regions should not be considered as a discrete set of independent nodes. Instead, they form a complex and heterogeneous ‘network of networks’ to turn sensory information from the world into thought and action. In the following sections, we consider the challenges this organization poses for studying and understanding brain function, and highlight modeling approaches that can enable researchers to untangle the complex web of multi-region interactions. We conclude that a multi-region view of the brain is critical to understand neural computation, and that future experimental work should aim to record from numerous regions and diverse cell types, rather than denser sampling of a spatially localized population.

## Understanding behavior generated by interacting brain regions

What are the implications of this highly recurrent organization for neuroscientists studying the neural basis of behavior? To understand the computations performed by a given set of neurons, we must be able to observe not only the outputs of these neurons, but also the inputs driving them. Many researchers historically aimed to characterize a brain region by recording outputs (e.g. action potentials in V1) in response to known external inputs (e.g. gratings of light presented to the retina). However, the complex connections between brain regions pose a problem; there are few, if any, cells in the brain that respond solely to external, measurable stimuli. Most of the nervous system, even retinal cells [4], are modulated by descending inputs related to brain states such as arousal [5]. Given the recurrent organization of the brain, each cell should be viewed not just through the lens of external or environmental stimuli, but from the perspective of the other cells in the brain that provide input.

Fully characterizing a neuron of interest requires knowledge of both its spiking output as well as the current state of the surrounding cells. Studying individual regions of the brain in isolation will thus inevitably reach a limit. Fortunately, modern experimental techniques enable unprecedented access to the brain through the ability to observe and manipulate thousands of neurons simultaneously, often

Figure 1



**(a)** A hierarchical model of the various sensory and motor brain regions underlying whisking in rodents. Adapted from Ref. [2]. **(b)** A detailed map of the known neural connections linking the brain regions underlying whisking in rodents. S2, secondary somatosensory cortex; Clau, claustrum; NBM, nucleus basalis magnocellularis; VPM, medial ventroposterior nucleus; Pom, medial posterior nucleus; LD, laterodorsal nucleus; RT, reticular nucleus; Amg, amygdala; PPTg, pedunculopontine tegmental nucleus and the laterodorsal tegmental nucleus; TMN, tuberomammillary nucleus; LC, locus coeruleus; GP, globus pallidus; EPN, entopeduncular nucleus; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; IO, inferior olive; PN, pontine nucleus; NRTPT, nucleus reticularis tegmenti pontis; DMN, deep mesencephalic nucleus; DR, dorsal raphe nucleus; AMB, ambiguus nucleus; APT, anterior pretectal nucleus; KF, Kölliker-Fuse nucleus and parabrachial complex; RN, red nucleus; PAG, periaqueductal gray; PrV, principal trigeminal nucleus; SpVo, spinal trigeminal nucleus pars oralis; SpVi, spinal trigeminal nucleus pars interpolaris; SpVc, spinal trigeminal nucleus pars caudalis; MeV, mesencephalic trigeminal nucleus; NXII, hypoglossal nucleus. Adapted from Ref. [3].

with cellular-level resolution [6]. These tools allow neuroscientists to extend beyond the reference points of behavioral output or sensory input and study the activity of a particular brain region with respect to its interactions with other brain regions. However, these large-scale datasets carry their own challenges. Most existing approaches to study interactions between brain regions have addressed simple scenarios of two interacting regions [7–11]. As the number of recorded brain regions increases, the number of possible pairwise interactions between these regions increases quadratically, even without considering the

possibility of long-range or indirect interactions. To fully leverage the power of modern experimental datasets, we require new theoretical and computational tools to quantitatively model the interactions within the complex circuitry in the brain.

### Recurrent neural network models of neural activity

The field of artificial neural networks emerged from neuroscience, attempting to mimic the computational power of the brain. The units in these models are analogous to

neurons, integrating information from many sources through weighted connections, and output rules governed by nonlinearities. By studying a population of these units, an observer or readout unit can extract information and make decisions about the nature of the inputs driving the network. Recurrent neural networks (RNNs) are a special class of artificial neural network models where each unit both outputs to and receives input from all other units in the network (Figure 2a). This connectivity is described by a weight matrix (which we refer to as the ‘directed interaction’ matrix) relating all presynaptic units to their postsynaptic targets.

RNN models of a single brain region have emerged as a powerful tool to study neural computation, elucidating potential means by which neural circuits can generate the desired dynamics. Typically, chaotic RNNs are trained to produce desired activity patterns based on a specific pattern of external input [12,13]. Single-region RNN models have been applied to understand neural population dynamics underlying flexible timing of behavior [14–16], sequence generation [17], or the movement of the arm for reaching [18]. Since the precise connectivity and dynamics of the model are known, researchers can peek inside the ‘black box’ that transforms the known inputs to the behavioral output to reverse-engineer the properties of the network [19]. For example, analysis of the single-region RNNs can unveil latent dynamical structure such as attractors [20] and fixed points [21]. This view provides a means to generate or test potential hypotheses to feedback into experimental studies.

Recent work introduced a new class of data-driven RNN models [22]. Rather than treat the RNN as a black box to generate some output, these models are directly constrained by experimentally recorded neural data. During training, an initially random connectivity matrix ( $J$ ) is modified such that the time-varying activity of each RNN unit tracks a target experimental neuron [22,23]. Like the single-region RNN models described above, these data-driven RNNs also provide access to a critical component that is difficult or impossible to obtain experimentally: a ‘directed interaction’ matrix (Figure 2a) describing the functional weights linking pairs of neurons. Since the models are fit directly to observed time-series recordings, they provide a unique means to analyze the dynamics underlying the experimental data. Data-driven RNN models have been used to study cellular and synaptic mechanisms enabling short-term memory [24], as well as circuit mechanisms of sequence propagation [22].

### Scaling to multi-region ‘network of networks’ models

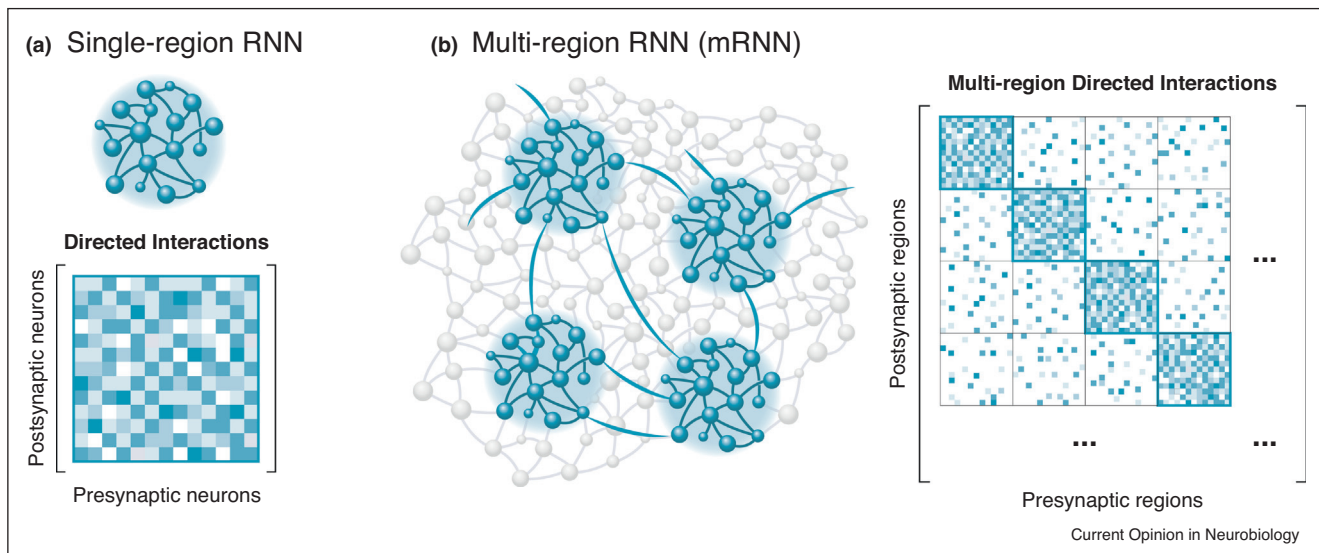
RNNs also provide a platform to study how the structural modularity inherent in brain regions enables behavior. Beyond single-region RNNs, more complex RNNs can be built with distinct submodules representing different brain

regions. This has given rise to a new class of models — multi-region RNNs (mRNNs) — that describes the activity of many brain regions simultaneously. Such models have been applied to show the necessity of different cortical regions to generate perceptual decisions [25,26], select motor plans [27,28] or actions [29] in response to visual cues, generate robust dynamics for motor output [30], and to study interactions between cortical and subcortical regions [31,32]. The data-driven RNN models described previously can also readily scale to model large, multi-region datasets. Rather than consider each region individually, mRNNs fit a single model that describes interactions within the entire dataset simultaneously [23]. This approach gives access to the directed interactions governing the dynamics both within each region and between all pairs of regions. These interactions can be conceptualized as an extension of the directed interaction matrix, where within-region connections are summarized along the diagonal of the matrix, and between-region interactions appear off-diagonal (Figure 2b).

Once trained, the mRNN models provide unique access to study the brain-wide interactions of real neural circuits. By analyzing the mRNN connectivity matrices, researchers can infer the strength and characteristics of directed, functional interactions within the circuit. Importantly, these matrices provide both a magnitude and a direction of interaction — the asymmetry in the weight matrix provides unique weights for outgoing and incoming projections between any pair of brain regions. For example, the model may capture dense, full-rank interactions within a given region due to the many short-range connections, but identify sparser connections between two regions with a small number of highly weighted connections (schematized in Figure 2b). An mRNN was recently applied to whole-brain recordings from larval zebrafish to identify putative pathways between habenula and the raphe nucleus that could enable behavioral state changes in response to inescapable stress [23].

Most regions throughout the brain are engaged when animals perform a task [33], yet the reasons for this widespread activation are not fully understood. The mRNN models can be a powerful tool to understand whole-brain coordination of behavior. For example, mRNN models can be used to identify which brain regions (or combined subcomponents of brain regions) are necessary and sufficient to describe the neural dynamics relevant for a given behavior, that is, the least complex model. The models thus provide insight into which brain regions might be critically mediating a particular behavior and which might be passive observers or responders. This approach is particularly intriguing as a means to explore comparative evolution. For a similar class of behaviors, are the same regions or circuits engaged [34]? What mechanisms or patterns are conserved across species or during development? The mRNN models can also be used to probe the experimental data directly to test predictions

Figure 2



**(a)** Schematic of a recurrent neural network (top) and its associated directed interaction matrix (bottom) relating each presynaptic unit in the columns to each postsynaptic unit in the rows. **(b)** Schematic of a multi-region RNN where four distinct brain regions are sampled out of all of the possible neurons in the brain. This mRNN can be summarized using a multi-region directed interaction matrix summarizing both within-region (shown along the diagonal) and between-region (shown on the off-diagonal) interactions.

for simulated lesion studies or other manipulations to the circuit that may be prohibitively challenging or unethical to perform in behaving animals. Lastly, the views afforded by mRNN models can allow researchers to go beyond anatomical designations into brain regions. By applying clustering algorithms to the directed interaction matrices, for example, researchers may be able to uncover functional multi-region circuits or sub circuits within a single region that underlie the experimental data.

### Interplay between theorists and experimentalists can improve mRNNs and guide future experiments

Besides describing existing experimental data, mRNN models can be powerful tools to generate testable hypotheses for future experiments. By parsing the multi-region interactions inherent in a dataset, researchers can identify which regions or pathways can best explain the behavioral output. Once identified, the causal relevance of these regions for behavior can be tested with experimental tools such as optogenetic activation or ablation. Furthermore, the mRNN models can make predictions for as-yet-unobserved pathways linking regions, whether direct or indirect. For example, in the larval zebrafish model of behavioral state transitions discussed above, the mRNN model identified a change in interactions from the raphe nucleus to the habenula for which no known anatomical link is known [23\*].

Data-driven mRNN models are directly constrained by experimental data. Thus, the quality and reliability of the models depends on the amount and diversity of data

available. Any experimentally measurable features can be leveraged to improve mRNN models. Connectomics data can be used to build a prior into the mRNN about which pathways are most likely to be directly connected [35–37]. Predetermined cell types could be incorporated into the model to constrain excitatory or inhibitory projections [38,39]. Information about the release of neurotransmitters such as dopamine [40,41] could also be incorporated to help account for long-range or slow-timescale signaling that simultaneously influences the activity of many brain regions. Additionally, non-neuronal data such as glial recordings [42] or behavioral data [43,44] could be incorporated into mRNN models to provide additional constraints and help account for common inputs between neurons [45].

While more data, whether neural or behavioral, is always advantageous, effectively modeling interactions between brain regions requires sampling broadly across as many brain regions as possible. Experimental neuroscientists should thus seek to sample more diverse populations from different regions in the brain, even if it requires more sparse sampling from each region. Behaviorally relevant neural dynamics in many brain regions are typically surprisingly low-dimensional [46,47], and large-scale population dynamics can be accurately reconstructed even with sparse samples of the local population [48,49]. Since behavior arises from coordinated activity of nearly all regions in the brain [33,50,51], we argue that recording from many distinct regions — even with the inevitable tradeoff of smaller numbers of neurons per region — will provide more insight than recording ever larger numbers of neurons from any single region.



## Structural and functional modularity of multi-region circuits

Data-driven mRNNs seek to model the functional interactions between neurons, and thus bears some similarity to the field of functional connectivity [45]. While mRNNs are subject to some of the same limitations, they also offer tangible advantages to traditional approaches such as generalized linear models [7,52,53], Granger causality [54], or dynamical causal modeling [55]. All of these methods provide correlational estimates of interactions and cannot accurately describe causal mechanisms due to confounders like common input or recurrent connectivity [56]. However, recurrence is built into the mRNN models, potentially allowing for more reasonable estimates of directed interactions when the data are appropriately constrained. It is important to emphasize that in all of these methods ‘interactions’ need not correspond to direct synaptic connections. Functional interactions can arise through a multitude of indirect pathways including multi-synapse relays, ephaptic coupling [57], or even through widespread neurotransmitter release [40]. Since data from throughout the brain is fit directly, the mRNN models can meaningfully incorporate these effects during training.

The application of modern analytical tools such as mRNN models to large-scale neuroscientific datasets has the potential to transform how we view neural computation. Brain regions captured by mRNN models reflect the structural modularity of the brain. However, rather than focusing on compartmentalized, hierarchical, and discrete models of cognitive function and behavior, we can leverage these models to develop new, more integrated views of how neural circuits interact to give rise to behavior. Such models can help us to move beyond ‘brain regions’ as the basis of neural function and instead view the brain as a more complex ‘network of networks’ comprising functional building blocks spanning numerous regions. Brain-wide mRNN models can be a first step toward defining these new functional subdivisions.

## Conflicts of interest statement

Nothing declared.

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