Review

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The molecular mechanisms that underlie neural network assembly

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Abstract: Neural networks are groups of interconnected neurons, which collectively give rise to emergent neural activities and functions that cannot be explained by the activity of single neurons. How neural networks are assembled is poorly understood. While all aspects of neuronal development are essential for the assembly of a functional neural network, we know little about high-level principles that govern neural network assembly beyond the basic steps of neuronal development. In this review, I use vertebrate spinal motor columns, *Drosophila* larval motor circuit, and the lamination in the vertebrate inner retina to highlight the spatial codes, temporal codes, and cell adhesion codes for neural network assembly. Nevertheless, these examples only show preliminary connections between neural network development and their functions. Much needs to be done to understand the molecular mechanisms that underlie the assembly of functional neural networks.

Keywords: assembly; development; molecular mechanism; neural network.

Neural networks are groups of neurons interconnected to each other for certain functions [1, 2]. They give rise to emergent neural activities and functions that cannot be explained by the activity of single neurons. Many behaviors can only be represented by the activity of a neural network, rather than by single neurons. Besides being instrumental to understanding the nervous system, the concept of neural network has inspired computational scientist to model them and to use them for computation. For example, deep-learning networks in computer science simulate neurons as nodes and arrange them into computational layers, and then link them by connections with adjustable strength based on learning rules.

How neural networks are assembled is poorly understood. It is conceivable that the vast majority of neural networks are formed during the development of the nervous system. However, mature nervous system may also form new networks as a result of sensory experience. We know very little about how neural networks are assembled in either case. Compared with sensory experience-dependent network assembly, more is known about the assembly during development, typically as a byproduct of studies that are focused on other neurodevelopmental topics.

In theory, every developmental step contributes to neural network assembly. Traditionally, studies of these developmental steps are separated and form different research fields. For example, studies on neurogenesis and neuronal differentiation focus on how neural precursors and progenitors give rise to different types of neurons in certain amounts. Axon guidance is another example of a research field in neural development. While these focuses are necessary and have been successful, they typically do not connect the specific aspects of neuronal development with the functions of mature neurons, particularly those from the perspective of neural networks. There is thus an important knowledge gap between what we know about different aspects of neural development and what we know about neuronal functions.

An important question in this regard is whether there are high-level molecular logics that govern neural network assembly beyond basic neurodevelopmental steps such as the specification of neuronal types and post-mitotic development of neurons. In this review, I summarize—from the perspective of developmental biology—several key challenges in understanding the assembly of neural networks, and highlight three examples in which some molecular mechanisms are known.

A brief overview of the basic steps of neural network assembly

Neural network assembly is an orchestrated developmental process that involve multiple aspects including

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neuronal fate specificity, neuronal migration, axon and dendrite development, and synaptogenesis [3–6]. While all these aspects are essential for the assembly of a functional neural network, are they coordinated by a higher-level mechanism?

The specification of neuronal types is likely the first step in the assembly of a neural network. Morphogens, such as Wnts, form gradients along body or regional axes and thus provide positional information to guide the specification of neural precursors and progenitors. Typically, morphogens do so by inducing signaling that lead to the expression of specific transcription factors in the neural precursors or progenitors [7]. Besides the spatial guidance by morphogens, sequential expression of different transcription factors (i.e., temporal code) during neural progenitor differentiation also plays important roles in neuron type specification (see the section "*Drosophila* larval motor circuit: temporal codes" below). As we discuss later, in some systems the early step of neuron fate specification is linked to the later incorporation of the neurons into a neural network for behavior.

After neuronal types in a neural network are specified, neurons develop their axons, dendrites and synapses. Different neuron types have distinct morphologies of axons and dendrites and synaptic connectivity. After the neuronal types in a network are established, neurons develop their dendrites and axons to connect with each other. This process is guided to achieve specific connectivity in the network. Long range and short-range guidance cues instruct axonal growth cones during their growth. These attractive or repulsive cues, which are secreted by target cells or cells that are at close proximity of the growing axons, act on the guidance receptors on the surface of axonal growth cones [8, 9].

While axon guidance is an essential step in the assembly of neural networks, how the guidance of axons of different neurons coordinate to form a functional neural network is poorly known. One exception is the topographic projections of neurons in sensory systems. In the vertebrate visual systems, the Eph family of receptors and their ephrin ligands form gradients in growing retinal ganglion cells (RGCs) and their target cells in the midbrain [10]. These gradients guide RGC axons to their targets based on spatial locations of the RGCs. Such topographic arrangement of axon projections may be considered as one of the simplest mechanisms for encoding the spatial information in sensory systems.

The development of dendrites also contribute to the assembly of neural networks. An important role of dendrites development in network assembly is to form specific target areas (e.g., layers in a neuropil) to guide the synapse formation of other neurons. This will be discussed further in the section "The lamination in the vertebrate inner retina: cell adhesion codes".

After axonal growth cones reach the target region, the axon forms synapses with specific targets. The specificity of synaptic connections is a crucial step in network assembly. While synapse formation and specificity are clearly critical for establishing functional neural networks, how these processes are orchestrated during network assembly is not well known. It is interesting to note that several morphogens, which regulate early tissue and organ development, are reused to regulate synapse development. For example, Wnts promote synapse formation in mammalian neurons [11]. In *Drosophila*, Wnt signaling regulates the development of the neuromuscular junction [12]. In *Caenorhabditis elegans* (*C. elegans*), Wnt secreted by hypodermal cells in the tail suppresses synapse formation in the DA9 motoneuron [13]. It is possible that different Wnt ligands leads to promotion or suppression of synapse formation [14]. Because morphogen signaling is spatially arranged in developing nervous system, it might orchestrate neural network assembly by regulating synapse formation in a spatially organized fashion.

Beyond these basic steps of neuronal development, are there higher-level principles that govern the neural network assembly? In the following, I use three examples to highlight spatial codes, temporal codes, and cell adhesion codes in neural network assembly.

Vertebrate spinal motor columns: the spatial codes formed by *Hox* genes

In vertebrates, spinal motor neurons are arranged into longitudinal columns and pools [15], and innervate specific muscles according to their rostrocaudal (i.e., anterior-posterior, or A-P) positions in the spinal cord [16]. In the developing spinal cord, morphogens retinoic acid and fibroblast growth factor (FGF) regulate the expression of the transcription factors encoded by *Hox* genes in neural progenitors along the rostrocaudal axis. *Hox* genes are critical for A-P body patterning in both vertebrates and invertebrates [17]. The protein products of *Hox* genes contain a "homeodomain", which is a DNA-binding domain that is comprised of 60 amino acids. In most vertebrates, over 30 *Hox* genes form four clusters on chromosomes, namely the *HoxA*, *HoxB*, *HoxC*, and *HoxD* clusters. The *Hox* genes are expressed in different segments of the spinal cord along the rostrocaudal axis, and determine the fates of motor neurons along this body axis (Figure 1). The columnar identities of

motor neuron are specified by *Hox* genes. For example, loss of the *Hoxc9* gene, which is specifically expressed in the thoracic segments, causes thoracic motor columns to adopt a brachial identity [18, 19]. Combinations of *Hox* genes further diversify motor neurons into motor pools that innervate specific muscles in the limb [19].

Besides determining the molecular identity of spinal motor neurons, Hox proteins regulate the expression of specific effector genes in postmitotic neurons, thus linking neuron fate specification to the later incorporation of the neurons into neural networks. Hox transcription factors regulate the expression of the key ligand-receptor systems in neuronal migration and axon guidance, including Eph/Ephrin and Robo/Slit, as well as cell adhesion molecules. In spinal motor neurons, Eph/Ephrin signaling guides axons in the lateral motor column (LMC) to choose between a ventral and dorsal trajectory at the base of the limb bud [20] (Figure 1). Hox proteins also regulate the expression of the Robo-Slit guidance molecules. For example, *Hox2* is essential for Robo2 expression in migrating pontine neurons [21], and *Hoxa2* regulates expression of Robo3 to guide the axons of cochlear neurons in the hindbrain [22].

While Hox proteins link cell fate specification with postmitotic development of neurons along the A-P body axis, it remains unclear how they contribute to neural network assembly at a level higher than these two aspects of neuronal development. The expression of the same *Hox* gene in a group of neurons might facilitate the connection among them and ensure synaptic specificity, leading to the assembly of a neural network among the motor neurons and interneurons in the same rostrocaudal segment that share similar *Hox* gene expression profiles [19]. However, this interesting model is yet to be tested.

Hox genes were first discovered in *Drosophila*, but much less is understood about *Drosophila Hox* genes's role in neural network assembly. *Hox* genes are essential for the innervation of fly legs. The muscles that the motor neurons innervate relate to the birth order of the neurons. The early-born LinA lineage of motor neurons innervate the proximal part of the leg, while later-born neurons innervate the distal part. The levels of the Hox protein Antennapedia (Antp) forms a gradient in the LinA lineage of neurons, with high levels in late-born motor neurons and decreasing levels in early-born neurons [23]. Loss of Antp decreases axons innervating distal muscles, while enhancing Antp expression result in excessive distal axons and fewer proximal axons. While these findings show that the graded expression of Hox proteins can instruct the axon growth for proper target selection at the neuromuscular junction, whether and how *Hox* genes organize neural network assembly remain to be determined.

Drosophila larval motor circuit: temporal codes

The correlation between the birth-time of neurons within a neuronal lineage and their integration into a neural circuit

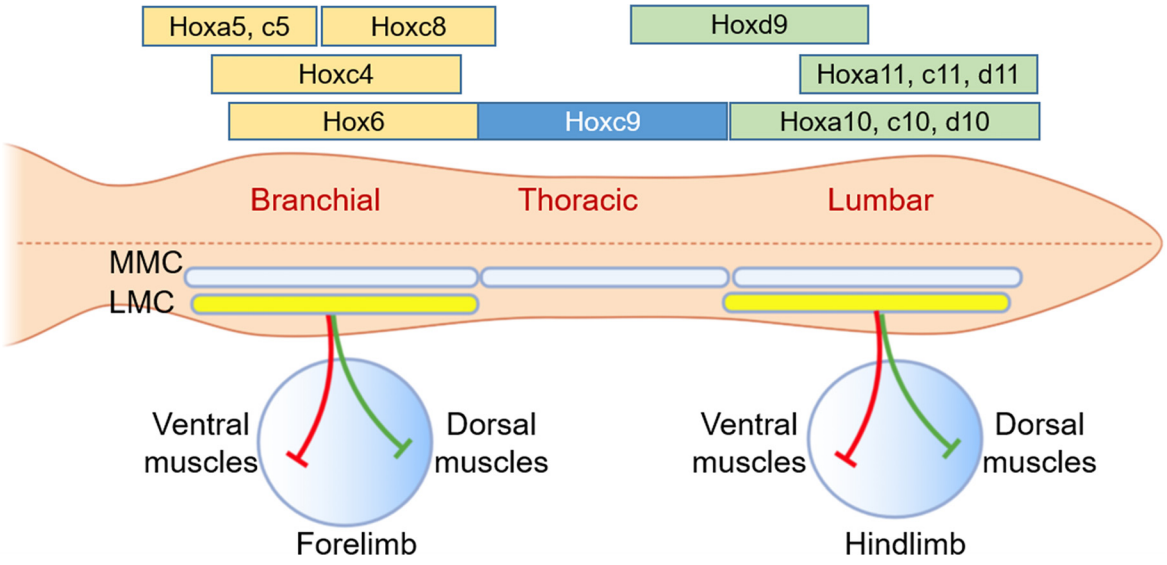

Figure 1: *Hox* genes expressed in different segments of the spinal cord determine the fates of motor neurons along the rostrocaudal axis. The lateral motor column (LMC) and medial motor column (MMC) are shown in the schematic spinal cord. Axons in LMC choose between a ventral and dorsal trajectory to innervate the limbs. The colored rectangles above the schematic spinal cord show the expression of some of the *Hox* genes.

has been observed in *Drosophila*. Different neural progenitor cells divide at different developmental times to produce "a temporal cohort" of neurons [24]. Powerful genetic approaches and resources available in *Drosophila* have led to the discovery that temporal cohorts are an organizational unit of motor circuits.

The role of temporal codes in neural network assembly has been demonstrated in the NB3-3 neuroblast lineage in the larval nerve cord. The NB3-3 lineage produces a motor neuron and several Eve^+ lateral (EL) interneurons that express the transcription factor Even-skipped (Eve). Some ELs are born earlier than others, forming an early-born and a late-born cohorts [25] (Figure 2). Optogenetic activation of early-born ELs induces nociceptive escape behavior, whereas that of late-born ELs induces an abnormal crawling. The two cohorts of ELs receive inputs—directly or indirectly—from two different types of sensory neurons: early-born ELs receives inputs from mechanosensors, whereas late-born ELs receive inputs from proprioceptors [25–27]. Thus, the NB3-3 lineage generates two cohorts of neurons whose functions and connectivity depend on their birth-time.

Temporal cohorts of motor neurons also exist in adult *Drosophila*. The LinA lineage produces an early cohort of motor neurons that innervate muscles in the proximal tibia or proximal femur portion of the leg, and a late cohort that produces motor neurons innervating muscles in the distal tibia or distal femur portion of the leg [28]. Whether or not the connectivity of these cohorts are similar or distinct remains to be determined.

Interestingly, in zebrafish early-born neurons contribute to fast escape, whereas later-born neurons contribute to refined movements [29, 30]. These suggest that the sequential addition of neurons into motor networks for distinct behaviors might be an evolutionarily conserved mechanism.

The molecular mechanisms that determine the temporal cohorts are unclear. Many mechanisms can potentially cause the difference between early-born and late-born neurons. These include the sequential expression of intrinsic temporal transcription factors and the changing cellular environment that influence cell fate determination or the availability of synaptic partners. During the differentiation of neuroblasts in *Drosophila* embryos, a series of transcription factors are sequentially expressed in neuroblasts—from Hunchback, Kruppel, Nubbin/POU-domain-protein-2 (Pdm2), Castor, to Grainy head [31, 32]. The expression of these transcription factors at specific developmental times leads to the production of distinct type of motor neurons. Consequently, temporal transcription factors play a role in specifying—in some cases even determines—the muscle target that a motor neuron innervates [33]. It is noteworthy that the intrinsic transcription factors do not explain all aspects of the temporal codes of motor circuit assembly. The changing cellular environment likely plays a critical role in the assembly of motor circuits too.

The lamination in the vertebrate inner retina: cell adhesion codes

The vertebrate retina is organized into layers of neuronal cell bodies and synaptic regions [34]. Upon detection of photons, photoreceptors in the outmost part of the retina activate bipolar cells (BCs), which in turn activate the output neurons RGCs. The BC axons and RGC dendrites form a thick layer of neuropil, called inner plexiform layer (IPL) (Figure 3). Amacrine cells, which are interneurons, modulate the BC-RGC synapses. There are a variety of BCs, RGCs, and amacrine cells, each of which has unique physiological properties and is responsible for specific aspects of visual processing. Some BCs and RGCs are activated by light, exhibiting "ON" responses to light; some are activated by the disappearance of light, exhibiting

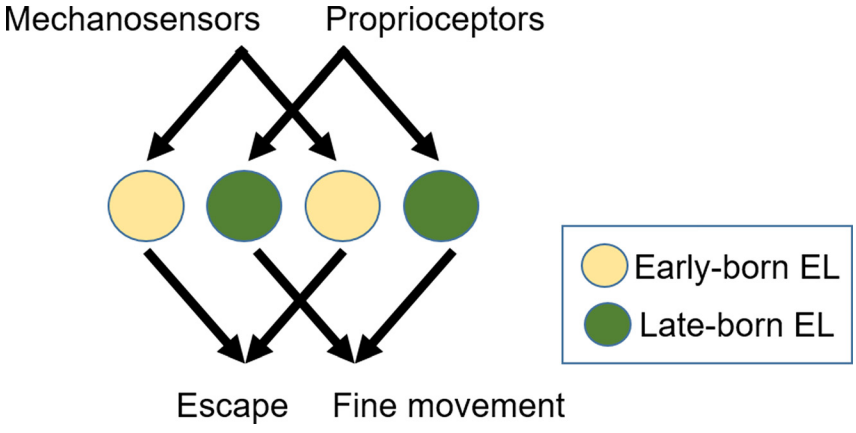

Figure 2: The birth-time of EL neurons determines their connectivity and functions. The NB3-3 lineage produces several Eve + lateral (EL) interneurons in the nerve cord of the *Drosophila* larva. Early-born ELs receive inputs from mechanosensors, whereas late-born ELs receive inputs from proprioceptors. Activation of early-born ELs induces nociceptive escape behavior, whereas that of late-born ELs induces abnormal crawling.

"OFF" responses [35, 36]. There are also RGCs that respond to both the appearance and disappearance of light, and are called "ON–OFF" RGCs. The IPL consists of several sublayers called sublaminae. One important functional arrangement of the IPL sublaminae is that synapses formed by ON-type BCs and RGCs are located in the inner half of the IPL, while those formed by OFF-type BCs and RGCs are in the outer half (Figure 3). As such, the ON/OFF physiological responses of the retinal network are encoded spatially in the IPL.

Cell adhesion molecules play a critical role in the IPL lamination. Live imaging of fluorescently labeled neurons in zebrafish revealed the steps that lead to the formation of IPL laminae [37]. Amacrine cells first extend processes to form a primitive IPL. These processes further laminate, forming a scaffold for RGC dendrites to grow on [38]. RGC dendrites recognize the cell adhesion molecules on the amacrine scaffold; they extend dendrites from inner to outer laminae, and then selectively elaborate their dendrites in a specific sublamina.

In mature mouse retina, starburst amacrine cells form synapses with ON–OFF direction-selective ganglion cells (ooDSGCs) (Figure 3). Once starburst cells migrate to the IPL, they start to expressed a transmembrane protein called Multiple EGF-like domains 10 (MEGF10) [39]. This protein mediates the homophilic cell adhesion between the processes of starburst cells, leading to the formation of two sublaminae in the IPL [40]. Loss of MEGF10 eliminates the lamination, causing ooDSGCs to extend dendrites to other locations of IPL. The growth of ooDSGC dendrites requires the cell adhesion mediated by the cadherin family of cell adhesion molecules that are produced by starburst cells [41]. Different types of cadherins are located in different sublaminae of IPL, forming a cell adhesion code of each sublamina that guides the development of dendrites, axons, and synapses. Besides starburst amacrine cells, other types of amacrine cells also participate in the formation of IPL sublaminae and guide the dendritic growth of specific types of RGCs.

The transcription factor Satb1 determines that ooDSGC dendrites growth in two sublaminae and thus plays a role in lamination [42]. Loss of Satb1 causes ooDSGCs to lose the dendrites in the ON sublamina. Satb1's function is in part mediated by the immunoglobulin superfamily adhesion molecule Contactin-5 (Cntn5). Cntn5 is expressed in both ooDSGCs and their synaptic partner starburst amacrine cells, and mediate homophilic adhesion to stabilize dendritic branches.

While cell adhesion molecules primarily promotes dendritic extensions in specific sublaminae of the IPL, guidance molecules provide repulsion in some sublaminae, which further restricts dendritic lamination in the IPL. The inner laminae of IPL (i.e., the laminae that primarily mediate ON responses) express the guidance molecule semaphoring 6A (Sema6A). The OFF-type amacrine cells express Sema6A's receptor PlexinA2, and as a result, their dendrites are excluded from the inner sublaminae [43, 44]. On the other hand, the inner nuclear layer (INL), which is situated on the outer side of the IPL, express semaphoring 5A and 5B, which prevent neurons expressing their receptors Plexin A1 or A3 to extend dendrites in the INL [45].

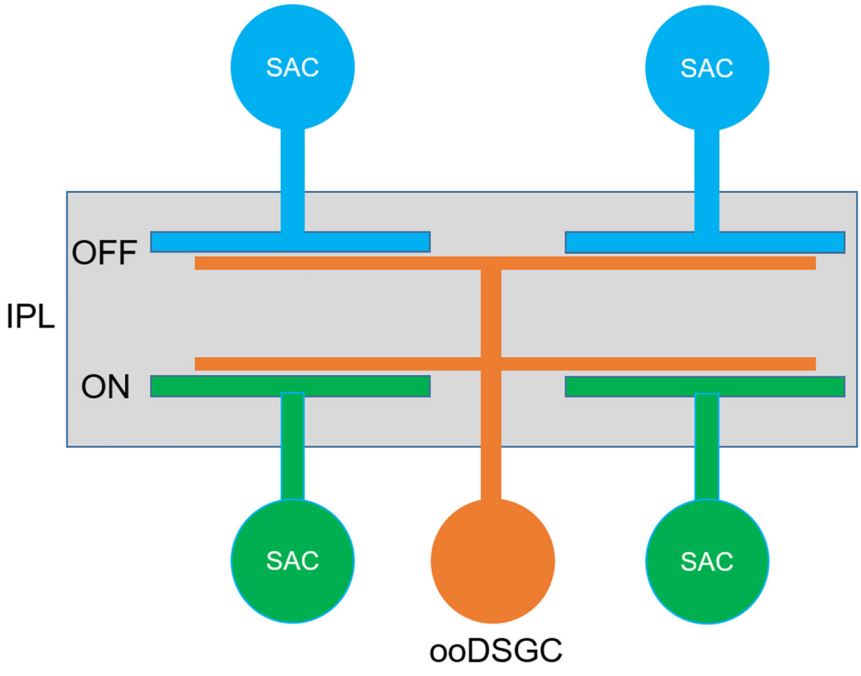

Figure 3: Lamination of the inner plexiform layer the vertebrate retina. During development, ON-type and OFF-type of starburst amacrine cells (SACs) extend processes to form a primitive inner plexiform layer (IPL). These processes form a scaffold for ON–OFF direction-selective ganglion cells (ooDSGCs) dendrites to grow on. ooDSGCs extend dendrites from inner to outer laminae, and then selectively elaborate their dendrites in the ON and OFF sublaminae of the IPL.

Therefore, the establishment of retinal IPL is orchestrated via the promotion of dendritic growth by cell adhesion molecules and the repulsion by guidance molecules.

Summary and future directions

Neural networks can be considered the fundamental unit of brain function [1, 46]. Our understanding about the development of the nervous system has primarily focused on the basic steps of neuronal development, rather than organizational principles of neural network assembly. While every developmental step contributes to neural network assembly, whether and how these steps coordinate or are organized in the network assembly is poorly known. Nevertheless, some studies have shown higher-level molecular logics that govern neural network assembly beyond basic neurodevelopmental steps. It is noteworthy that the examples presented in this review only show preliminary connections between neural network development and their functions. Much needs to be done to understand the molecular mechanisms that underlie the assembly of functional neural networks. Technological advances are key to future studies of functional neural network assembly. For example, technologies that report emergent neural activities of neural networks are needed for evaluating the function of neural networks. Examples of such technologies include large-scale calcium imaging and computational analysis of the activities of neuronal populations. Only after we are able to record neural network activities, can we hope to understand the molecular mechanisms that underlie the assembly of neural networks.

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