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Neuronal Circuit Evolution: From Development to Structure and Adaptive Significance

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Neuronal circuits represent the functional units of the brain. Understanding how the circuits are generated to perform computations will help us understand how the brain functions. Nevertheless, neuronal circuits are not engineered, but have formed through millions of years of animal evolution. We posit that it is necessary to study neuronal circuit evolution to comprehensively understand circuit function. Here, we review our current knowledge regarding the mechanisms that underlie circuit evolution. First, we describe the possible genetic and developmental mechanisms that have contributed to circuit evolution. Then, we discuss the structural changes of circuits during evolution and how these changes affected circuit function. Finally, we try to put circuit evolution in an ecological context and assess the adaptive significance of specific examples. We argue that, thanks to the advent of new tools and technologies, evolutionary neurobiology now allows us to address questions regarding the evolution of circuitry and behavior that were unimaginable until very recently.

A neuronal circuit is formed when a group of neurons are connected to each other by synapses and participate in the same function. Historically, the term was first used to explain the amplification through feedback of neuronal circuit activity that could lead to neurological problems by the psychiatrist Lawrence Kubie in 1930 (Kubie 1930). It was then appropriated and immortalized by Walter Pitts who, in the beginning of the 1940s, studied patterns of excitation and inhibition in neuronal circuits (Pitts 1942). Since then, the notion of neuronal circuits has been used as a functional unit of larger brain networks, as it can perform basic logical and/or arithmetic functions, which is why it has inspired the design of artificial neural networks in computing. While neuronal circuits can become extremely complex, our basic understanding of them comes from studies of relatively simple circuits.

The sea slug *Aplysia californica* has been used historically as a neuroscience research model because of the relative simplicity of its neuronal circuitry involved in learning, as well as the large size of its neurons. The simple underlying circuitry of the *Aplysia* gill and siphon withdrawal reflex allowed Eric Kandel and others to study nonassociative learning (habituation, dishabituation, and sensitization) and start uncovering the cellular and circuit basis of a complex behavior. Similarly, the relatively small crustacean stomatogastric nervous system (composed of about 30 neurons) that controls the motion of the gut has

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been used as a model circuit to understand motor pattern generation (Marder and Calabrese 1996) and how central pattern generators (CPGs) can be activated and modified by neuromodulators. Despite being relatively simple, these models are still very difficult to completely understand, and the question arises as to how did the first (and presumably simpler) neural circuits evolve?

Before studying how neuronal circuits evolved, it is necessary to understand the origins and evolution of neurons. The evolutionary origin of neurons is still unresolved; in fact, recent phylogenetic studies that place ctenophores as sister to all other animals (Schultz et al. 2023) suggest that nervous systems evolved twice independently in the Metazoa, once in Ctenophora, and once in the common ancestor of Bilateria and Cnidaria. This is also supported by fundamental differences in the architecture of their respective neuronal systems (Burkhardt et al. 2023) and the molecular components of their synapses (Arendt 2020). In any case, it is likely that neurons evolved in an early metazoan from existing epithelial cells (neurosecretory or mechanosensory cells) either to coordinate a bodily response to environmental challenges or to control cilia beating (discussed in more detail later). These early cells would probably qualify as sensory neurons that transmitted information to motor cells, via electrical or chemical protosynapses. These protoneurons then acquired their current sophisticated synaptic machinery in a stepwise manner (Arendt 2020).

While these protoneurons were probably sufficient in small animals for sensory-to-motor transformation, the evolution of neuronal circuits allowed animals to integrate information from multiple sensory cells in an efficient manner (Jékely 2011). This generated an intermediate cell (a motor neuron) that could integrate neuronal input in a sensory modality-specific manner and allow for a reduction of wiring length, which decreases the required energy to build axons and signal through them.

Building and maintaining a nervous system is a very costly investment. Indeed, whether one looks at a whole brain, circuits, or cells, their physical location is decided by the effort to minimize unnecessary wiring (Cherniak 1994, 1995). Therefore, the selective advantages of an increasingly complex circuit should outweigh the metabolic, wiring, and signaling costs. By reducing axonal length to minimize these costs, neuronal cells were concentrated in specific locations, which probably led to the centralization of the nervous system soon after the evolution of the first circuits, as elements of centralization can be found in Cnidaria. This centralization is more prominent in Bilateria, which led to the gradual formation of a central processing unit, the brain, which allowed also for an increase in cognitive capacity (Martinez and Sprecher 2020), which in turn let bilaterians expand, differentiate, invade different environments, and generate an impressive organismal diversity.

It comes as no surprise that our understanding of the evolution of neurons, neuronal circuits, and central nervous systems comes from comparative approaches.

- Comparisons at the level of gene expression have been instrumental in the identification of homologous neuronal structures and circuits across different taxa.
- Comparisons at the level of neuronal type composition have allowed us to discover instances and mechanisms of neuronal type evolution.
- Comparisons at the level of circuitry (i.e., the evolution of new connections, changes in synaptic strength, or sign—excitatory or inhibitory—revealed the evolution of circuit structure).
- Comparisons at the level of brain regions uncovered cases of circuit or region duplications and eliminations.

Altogether, comparative studies have painted a picture of the mechanisms that allowed circuits to evolve, how this affects neuronal circuit structure, and the selective pressure that led to these changes. In this review, we first focus on the genetic and developmental mechanisms that underlie the generation of neuronal circuitry. Then, we delve into the structural and functional changes that have occurred in these neuronal circuits throughout evolution. We further examine the adaptive significance of evolutionary changes

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in neuronal circuitry in their ecological context. Finally, we conclude by touching upon emerging research areas and future directions.

GENETIC AND DEVELOPMENTAL MECHANISMS

How can a neuronal circuit evolve? To answer this question (reviewed by Tosches 2017), we need to consider the position circuits acquire in the evolutionary process. Obviously, natural selection acts upon animal behavior: Evolutionary pressure and natural selection will allow individuals with certain behaviors to survive. For these behaviors to be transmitted to the next generation, they must result from genetic differences that occurred through random mutation in certain genes. As multiple genes are involved in a given behavior at different levels of neurogenesis and/or neuronal function, they might affect neuronal identity or circuit structure. These genes can be divided into four broad categories (Fig. 1) that are discussed below.

1. Genes that affect the effective size of the neuronal progenitor pool, such as members of signaling pathways (Hh, Notch, insulin, and oth-

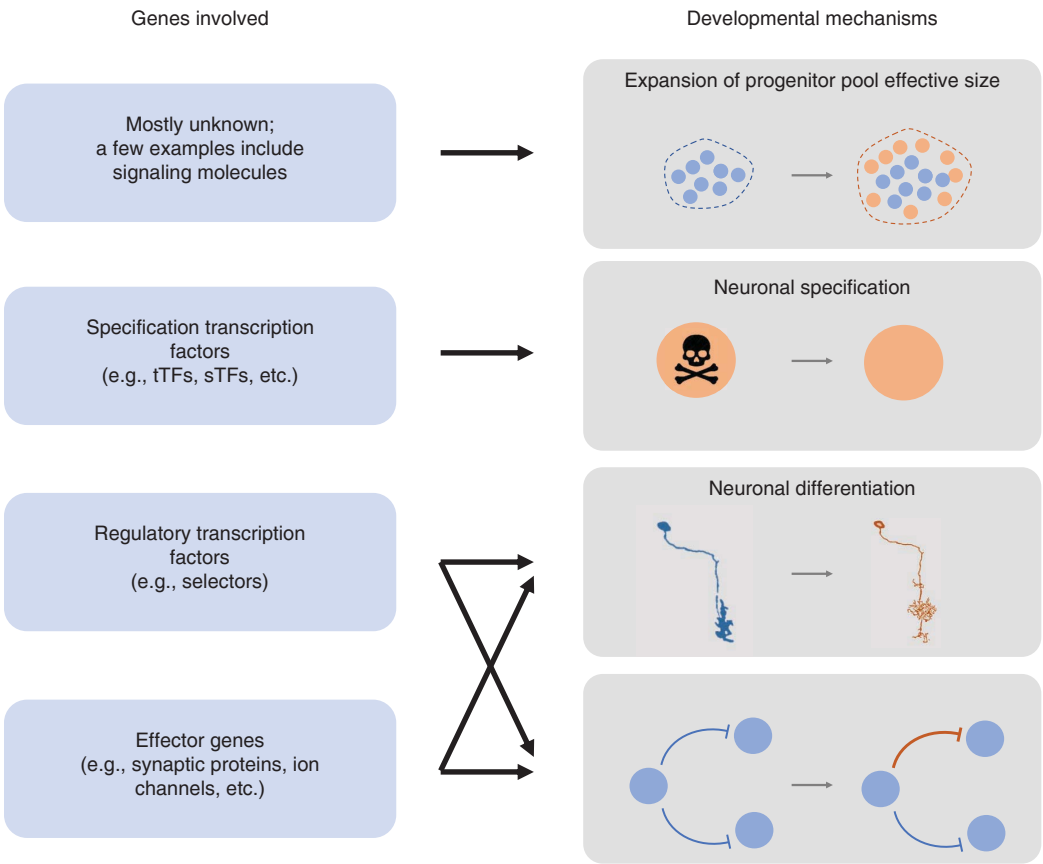

Figure 1. Genetic and developmental mechanisms of circuit evolution. We can distinguish genes that are involved in neuronal circuit evolution into four categories. Alterations in the expression pattern of these genes can differentially affect neuronal developmental mechanisms and lead to the evolution of different neuronal circuits. Genes involved in the expansion of the progenitor pool effective size, as well as specification factors, act at the level of the progenitors and can lead to the evolution and development of new neuronal types. On the other hand, regulatory transcription factors and their downstream effectors act at the level of the postmitotic neurons and can affect specific neuronal characters (such as arborization locations or synaptic strength).

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ers) (Homem et al. 2015). The number, as well as the timing of divisions of the progenitors, could have profound effects on the evolution of new circuitry. An increase in the effective size of neuronal progenitors relieves the newly evolved neurons from selective pressure (as their ancestral counterparts continue to play their ancestral roles) and allows them to diversify freely (Oakley 2003; Chakraborty and Jarvis 2015; Grillner and Robertson 2016). The modular organization of animal brains from insects to vertebrates suggests that duplication or multiplication of existing pools of progenitors is at the basis of neuronal circuit evolution. One such example is the evolution of cerebellar nuclei; while the cerebellum itself is conserved in vertebrates, the numbers of its nuclei vary from none (jawless vertebrates) to three in mammals. The cellular composition and architecture of each nucleus in mice (three nuclei) and chickens (two nuclei) suggest that there exists an archetypal nucleus that has repeatedly duplicated during vertebrate evolution (Kebschul et al. 2020). Similarly, the vertebrate cerebral cortex has been suggested to evolve through the expansion of radial glial progenitors and/or transit amplifying progenitors that has allowed the expansion of the three-layered cerebral cortex in turtles to the six-layered one in mammals (Briscoe and Ragsdale 2018; Tosches et al. 2018; Lin et al. 2021). Importantly, all radial glial progenitors undergo a fairly fixed set of divisions to output a specific number of neurons that occupy progressively the more superficial layers of the cortex, which supports their common evolutionary origin. Interestingly, sister neurons (neurons that originate from the same division of a radial glial progenitor) preferentially form synapses with each other (Lin et al. 2023). This raises an appealing model where whole circuits can evolve through the expansion of the radial glial progenitor pool. This modular organization is not restricted to vertebrates. The insect brain is also clonally organized (i.e., distinct neuronal lineages of stem cells—called neuroblasts in insects—occupy specific parts of the insect brain and are involved in the same function) (Ito et al. 2013). Because of this lineage-based architecture, it has been proposed that neural networks can evolve and diversify in a modular manner in different species (Kandimalla et al. 2023).

Similarly, the timing and duration of neuronal progenitor proliferation also play an important role (reviewed in Fenlon 2022). For example, differences in the timing (heterochronies) in the switch from proliferative to neurogenic divisions of radial glial progenitors and in the duration of the neurogenesis period can explain, to a large extent, the variation in the number of cortical neurons (Picco et al. 2018) and the expansion of the upper cortical layer (Caviness et al. 1995; Rakic 1995; Kriegstein et al. 2006). Genes involved in signaling pathways, such as Notch (NOTCH2NL; Fiddes et al. 2018; Suzuki et al. 2018) and Wnt pathways (FZD8; Boyd et al. 2015), are also implicated in the dynamics of progenitor proliferation (Suzuki 2020; Pinson and Huttner 2021).

2. Neuronal specification genes are regulators of gene expression and secreted molecules that act usually in neuronal progenitors and are responsible for specifying the identity of their neuronal progeny. Temporal and spatial transcription factors, for example, pattern neuronal progenitors based on their age and location in the tissue and allow them to generate diverse neurons. Altering the expression of any of these genes during development has an immediate impact on neuronal identity. Nevertheless, it is still unknown how the expression of these genes has changed during evolution.

One of the potential neuronal fates that is specified by these genes is cell death; neurons are preprogrammed to undergo programmed cell death, which occurs immediately after their specification. Preventing cell death in different neuronal lineages in *Drosophila* allows neurons to acquire a different fate when mature, and incorporate into circuits. Interestingly, this new circuitry can often be found to be present in other insects (Pop et al. 2020; Prieto-Godino et al. 2020), suggesting that there is a reserve of regulatory networks that can be recruited in different species.

3. Regulatory effector genes control gene expression and act cell autonomously downstream from neuronal specification genes to implement the specified identity of the neuron. They regulate

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(directly or indirectly) effector gene expression. Altering the expression of these genes can change some or all aspects of neuronal identity. For example, *Fezf2* is expressed in mouse corticospinal neurons and is able to regulate both neurotransmitter identity by activating glutamatergic genes (such as *VGlut1*) and inhibiting GABAergic ones (such as *Gad1*), and connectivity by regulating the expression of *EphB1* that controls the ipsilateral extension to the corticospinal tract (Lodato et al. 2014).

Regulatory effector genes that are expressed throughout development and persist into adulthood have been termed terminal selectors. The concept of terminal selector genes that define neuronal identity has been defined in worms where they act in a concerted manner to regulate all neuronal type-specific effector genes. Misexpression or down-regulation of terminal selectors leads to a complete change of neuronal identity; they have, therefore, been hypothesized to operate as a main evolutionary driver to generate diverse cell types (Arlotta and Hobert 2015; Cros and Hobert 2022). Such terminal selectors have been found in many species, including *Drosophila*, where targeted modifications of terminal selector expression in the visual brain allow the transdetermination of a neuron into another type (Özel et al. 2022).

4. Finally, effector genes actually implement identity. These are ion channels, genes involved in the synthesis of neurotransmitters and their receptors, synaptic genes, etc. While changes in these genes do not impact neuronal circuitry per se, they can have immediate effects on animal behavior. Changes in effector genes have been found in closely related species. A very prominent example is the genetic cause of the behavioral differences between the prairie vole (*Microtus ochrogaster*) and the montane vole (*Microtus montanus*): The former forms monogamous pairs while the latter is solitary and does not associate with former mates. This behavioral distinction is caused by a difference in the expression distribution of the receptors for the neuromodulatory neuropeptides oxytocin and vasopressin, which are responsible for the pair-bonding behavior in prairie voles (Insel et al. 1995; Young et al. 1997, 1999; Katz and Harris-Warrick 1999). Notably, this has been challenged recently, as it was shown that prairie voles can form long-term pairs in the absence of an oxytocin receptor (Berendzen et al. 2023). Similarly, the cosmopolitan drosophilids, *Drosophila melanogaster* and *Drosophila simulans*, are reproductively isolated from each other partly by a difference in their response to a pheromone that is produced by the *D. melanogaster* females, 7,11-heptacosadiene, which attracts *D. melanogaster* males but repulses *D. simulans* males. This differential response is due to a change in the balance between excitation and repression in response to the pheromone from the presynaptic neurons (vAB3 and mAL neurons, respectively) onto the courtship-promoting P1 neurons (Seeholzer et al. 2018).

It is clear that genetic changes can affect neuronal development and, thus, neuronal identity and circuitry at different levels and to different extents. Neurodevelopmental genes and their regulatory networks that are active at the progenitor state (i.e., the first two categories) (Fig. 1) are largely more conserved and, hence, less often involved, probably due to their limited number (progenitor pool size is regulated by a handful of signaling pathways and neuronal specification genes tend to be members of very conserved transcription factor families). Moreover, most of these genes are pleiotropic and involved in many different processes; therefore, changes in these genes are rarer. On the other hand, neuronal type-specific genes, such as regulatory effectors and effector genes are likely evolutionary tinkerers (Jacob 1977) that can change neuronal type identity or parts of it between closely related species (Fig. 1).

STRUCTURAL AND FUNCTIONAL EVOLUTION OF NEURONAL CIRCUITS

The evolutionary origin of neurons is still unresolved (Jékely 2011; Arendt 2021), although it has been proposed that neurons evolved at least twice in Metazoa. Recent single-cell mRNA sequencing data from Placozoa that lack clearly identifiable neuronal cells identified key neuronal components (such as presynaptic scaffold) in peptidergic secretory cells that come from progenitors with neurogenic ontogenetic modules

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(Najle et al. 2023). These data support the idea that neuronal cells evolved from neurosecretory cells and acted as "sensorimotor neurons" to coordinate potentially ciliary beating (Fig. 2A).

How did the first circuits evolve? It is likely that the first circuits originated from these sensorimotor neurons through a "division of labor" (Mackie 1970; Arendt 2008) where the sensorimotor neuron duplicated and generated two neurons (a sensory neuron and a motor neuron) that were synaptically connected and formed the first basal neuronal circuit (Fig. 2B). An alternative scenario for the evolution of the first circuit also relies on the "division of labor" of an ancestral myoepithelial sensory cell, whose duplication led to a sensory neuron in the surface and a motor neuron. Finally, it has also been proposed that the first neuronal circuits evolved to coordinate body parts of an increasingly complex system (Jékely et al. 2015).

While less likely, we cannot dismiss the possibility that neuronal circuits evolved more than once: they may have evolved (1) from secretory cells, as supported by molecular evidence from Placozoa (Najle et al. 2023) and vertebrates that show a close relationship between neuronal and secretory cells, and (2) from myocytes, as suggested by the close relation of ectodermal neurons and myocytes in cnidarians (Arendt 2021).

After basal connectivity was acquired, circuits slowly became more complex. It is possible that the first interneurons arose to integrate and process information from multiple sensory protoneurons (Fig. 2C; Jékely 2011). Moreover, sensory information might have had to be differently processed before forwarding it to the motor cells. For example, an interneuron might serve to send both excitatory signals to one motor cell as well as inhibitory information to a different motor cell to achieve more elaborate motor output (Fig. 2C). This interneuron may have duplicated during evolution and divided its labor to increase the complexity of the circuit. Similarly, during eye evolution, it has been hypothesized that with the increase in the number of photoreceptors, some of them assumed a "processing role" and became interneurons. With increased processing needs, the interneurons likely divided their labor and generated first- and second-order interneurons that were likely organized into what we recognize today as optic ganglia (neuropils) (Arendt et al. 2009).

As animals became more complex with diverse cell types, the neuronal circuits had to adapt. Several mechanisms can collectively account for the generation of more complex circuitry (Fig. 2D):

- As mentioned in the previous section, neural circuits may evolve by the duplication of progenitor regions that generate entire circuit modules and their subsequent divergence. This mode of evolution is very prevalent and efficient as it relies on functioning preexisting modules being co-opted for a different function. Besides the evolution of cerebellar nuclei mentioned earlier (Kebschul et al. 2020), the evolution of vertebrate basal ganglia has been proposed to rely on modular evolution, where each module controls a specific behavior, such as locomotion, eye movements, posture, and chewing. Each of these modular circuits contains a pathway of striatal projection neurons that disinhibit the brainstem motor centers and control a motor program, and a pathway of a different type of striatal projection neurons and intrinsic basal ganglia nuclei that inhibit competing motor programs (Grillner and Robertson 2016). These modules could be theoretically gained or lost independently during evolution. A similar mode of evolution can also be found in the hypothalamus (Xie and Dorsky 2017).
- A subcategory of the above mechanism is the exaptation (co-option of a trait for a function that is different from the one for which it originally evolved) in different contexts of self-organizing neuronal mini-circuits, such as CPGs. In the vertebrate spinal cord, CPG circuits that are responsible for limb locomotion originated in vertebrates lacking limbs (Grillner 2006; Grillner and Jessell 2009; Dasen 2017). In particular, the limb flexor CPGs may have been co-opted from the CPGs that were used to activate axial muscles during undulatory locomotion, while the extensor CPG might have evolved from premotor circuits

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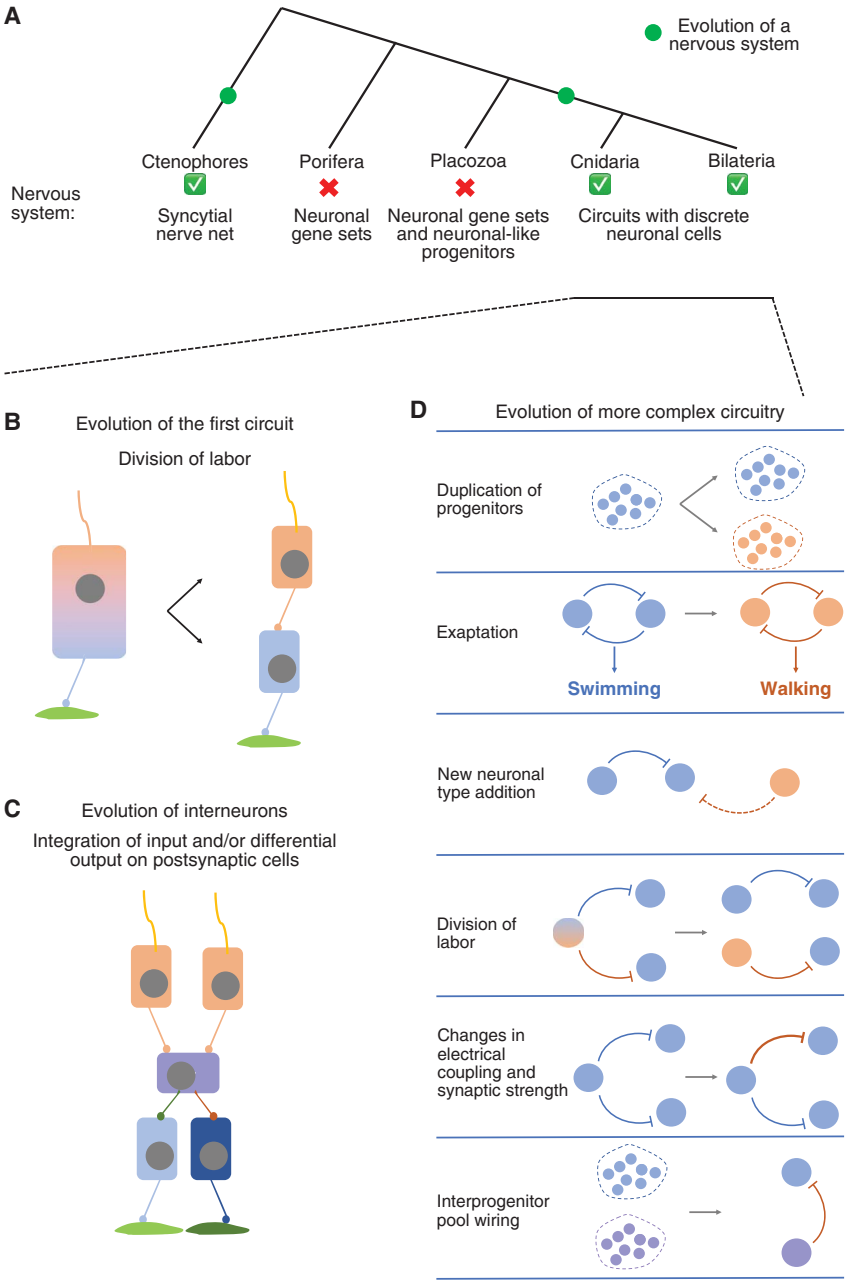

Figure 2. Structural evolution of neuronal circuits. (*A*) Based on current knowledge, the most parsimonious scenario for the evolution of neurons includes their independent emergence in ctenophores and the common ancestor of cnidarian and bilaterian animals. On the other hand, while Porifera and Placozoa lack bona fide neurons, they have neuronal gene sets and neuronal-like progenitors, respectively, which argues for a stepwise evolution of neurons. (*B*) Focusing on the common ancestor of cnidarians and bilaterians, the evolution of the first neuronal circuit involved probably the division of labor of an ancestral sensorimotor cell (orange–blue cell) and the evolution of synaptically connected sensory (orange) and motor (blue) cells. (*C*) Further elaboration of neuronal circuits and the evolution of interneurons (purple) was probably triggered by the need for integration of presynaptic input (orange cells) and/or the need for differential output onto postsynaptic partners (blue cells) (e.g., inhibitory [red] and excitatory [green]). (*D*) Subsequently, a number of different mechanisms were involved in the further complexification of neuronal circuitry, including duplication of progenitors, exaptation of neuronal circuits from one function (e.g., swimming) to another (e.g., walking), the addition of new neuronal types in existing circuitry, division of labor of one cell type into two cell types, changes in electrical coupling or synaptic strength, and interprogenitor pool wiring.

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used for postural correction (Bagnall and McLean 2014; Dasen 2017).

- Another obvious way to complexify circuits is adding new neuronal types into preexisting circuits. For example, based on transcriptomic comparisons of neurons in mammals and reptiles, it appears that the neocortical circuits are evolutionary mosaics of deeply conserved GABAergic interneurons and very divergent glutamatergic pyramidal neurons (Tosches et al. 2018; Tosches 2021; Hain et al. 2022). Similarly, in the spinal cord, although ipsilateral V2a-type excitatory neurons, and commissural V0-type inhibitory neurons can be found in all vertebrates (lamprey, tadpole, zebrafish, and mouse), the V3, V1, V2b, and dorsal dI6 interneurons have only evolved in jawed vertebrates (Wilson and Sweeney 2023).
- The "division of labor" model also accounts for adding complexity to neuronal circuits. In the same example of the spinal cord, the complexity in movement patterns and gaits is correlated with the division of cardinal classes of interneurons into distinct subtypes.
- Circuits can also evolve by changes in electrical coupling and synaptic strength (Katz 2007), as exemplified by the species-specific mate preferences between *D. melanogaster* and *D. simulans* that depend on alterations in the synaptic strength of vAB3 and mAL pathways to P1 neurons (Seeholzer et al. 2018).
- Circuits can also evolve and become more complex by interprogenitor pool wiring (Suzuki and Sato 2017) (i.e., by combining neurons that come from different progenitor pools). An obvious example of this is the mammalian cerebral cortex that is formed by the GABAergic cells that migrate from the eminences and the glutamatergic cells that are born in the cortex.
- Finally, circuits can evolve by the addition (Edwards et al. 1999) and elimination of synapses (Ebbesson 1980; Tosches 2021), which can alter the functional output of the neuronal circuit.

The above mechanisms can account, more or less, for the evolution of the complex neuronal circuits that we observe today. As a rule, as animal bodies became more complex with more cell types, they had to be controlled by more complex nervous systems; therefore, most of the mechanisms did increase the number and synaptic complexity of neuronal cell types. A few exceptions of circuit simplifications serve to prove the rule.

ADAPTIVE SIGNIFICANCE AND ECOLOGICAL CONTEXT

Before delving into behavioral evolution, it is important to note that hotspots of genetic variation that allow neuronal systems to adapt to evolutionary challenges are often found in genes that can alter sensory perception; sensory genes, such as receptors for chemosensation, evolve very rapidly (Cande et al. 2013). They can also affect metabolic processes outside of the nervous system; for example, genetic variation that affects metabolism influences eating and drinking behavior without necessarily affecting circuitry. These types of behavioral evolution have been reviewed elsewhere (Bendesky and Bargmann 2011; Niepoth and Bendesky 2020); we will focus on how neuronal circuit evolution can change behavioral output in response to different environments and lifestyles.

While the evolution of genetic and developmental mechanisms, as well as that of neuronal circuitry, has been explored in the past, this has not been done in a comprehensive manner for the evolution of behaviors. For this reason, we explore different examples of behavioral evolution that are caused or accompanied by circuitry changes in an effort to identify some general rules.

The Case of Nudibranchs

Nudibranch (which are marine gastropod mollusks) swimming has been a fruitful example to compare similar behaviors and their respective circuits. Nudibranchs undulate their bodies either from left to right or dorsally to ventrally. These types of swimming have evolved independently in different species. Interestingly, different circuitries can give rise to the same behaviors.

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Such an example is the circuitry underlying the same left–right body flexion of two nudibranchs, *Melibe leonina* and *Dendronotus iris*: in this circuitry, while the behavioral rhythm and neuronal composition are the same between the two species, the connectivity of homologous neurons differs. Moreover, while neurons that are part of the dorsoventral swim CPG have homologs in species that undulate their bodies from left to right, these homologous neurons are not part of the left–right swim circuitry. These examples indicate that multiple circuits that can serve the exact same (rhythmic) behavior (Fig. 3A; Newcomb et al. 2012; Sakurai and Katz 2015; Katz 2016; Jourjine and Hoekstra 2021). A general rule that arises from these studies is that one cannot homologize behaviors on the basis of how similar or dissimilar their underlying circuits are and, vice versa, the circuitry cannot be predicted by behavior, although it can be a good approximation (Newcomb et al. 2012).

Circuit Modularity as a Means to Evolve New Behaviors

Circuits can evolve by whole duplication of progenitor regions that lead to duplicated circuits. But how does this influence behaviors? In birds, whole circuit duplication has been suggested to contribute to song learning (Feenders et al. 2008; Chakraborty and Jarvis 2015). In particular, it was hypothesized that, in vocal learners, the forebrain motor learning circuit that connects to the brainstem circuits that control vocalization is a product of duplication of other motor learning circuits that receive auditory, somatosensory, or other sensory input (Fig. 3B).

Circuit modularity allows also the modular tinkering of neuronal pathways. In insect courtship, *fruitless*-expressing neurons in the central brain are important for the execution of courtship behavior per se in males. Species-specific differences are usually impacting either the sensory pathways that feed into the *fruitless* neurons, or the downstream motor pathways (Ding et al. 2019; Sato et al. 2020). For example, while the structural, electrical, and neurochemical properties of the *fruitless*-expressing pIP10 neurons of *D. melanogaster* and *Drosophila yakuba* are the same, their activation leads to songs that differ in structure and frequency; this difference has to be attributed to the downstream motor pathway.

Finally, circuit modularity allows for the mixing and matching of different circuits. *Drosophila pseudoobscura* males have incorporated a regurgitation behavior in their courtship, whereby they offer a nuptial proboscis-to-proboscis gift to the female before attempting copulation. An evolutionary scenario that could account for this is that the neuronal circuit that was responsible for regurgitation as a feeding behavior became at some point during evolution postsynaptic to the courtship command system.

Collectively, the above examples argue for the importance of circuit modularity for the rapid evolution of new behaviors.

Neuronal Circuits and Social Interactions

Neuronal circuits can also affect and be influenced by the evolution of social interactions. In humans, FOXP2 is the only gene that is currently linked to central aspects of speech and language (Fisher and Scharff 2009), as the haploinsufficiency of FOXP2 impairs both of them. It does so by causing alterations in corticostriatal and corticocerebellar circuits (Vargha-Khadem et al. 2005). Moreover, expression of humanized FOXP2 in mice leads to a decrease in dopamine levels, as well as an increase in total dendrite length and synaptic plasticity of medium spiny neurons (Fig. 3C; Enard et al. 2009). Similarly, in worms, a single gene can affect their "social interaction" in terms of aggregation. The laboratory strain N2 shows low aggregation, as opposed to wild-type strains. This has been attributed to a single mutation in the *npr-1* gene that leads to a single amino acid difference. This mutation causes RMG neurons to reduce the number of electrical synapses they form with sensory neurons that stimulate aggregation.

While the above examples offer a number of basic rules, it is obvious that our knowledge regarding the neuronal circuitry underpinnings of behavioral evolution is very fragmented. With the increasing ability of producing connectomes of differently sized brains, we will soon acquire a more holistic view on this subject.

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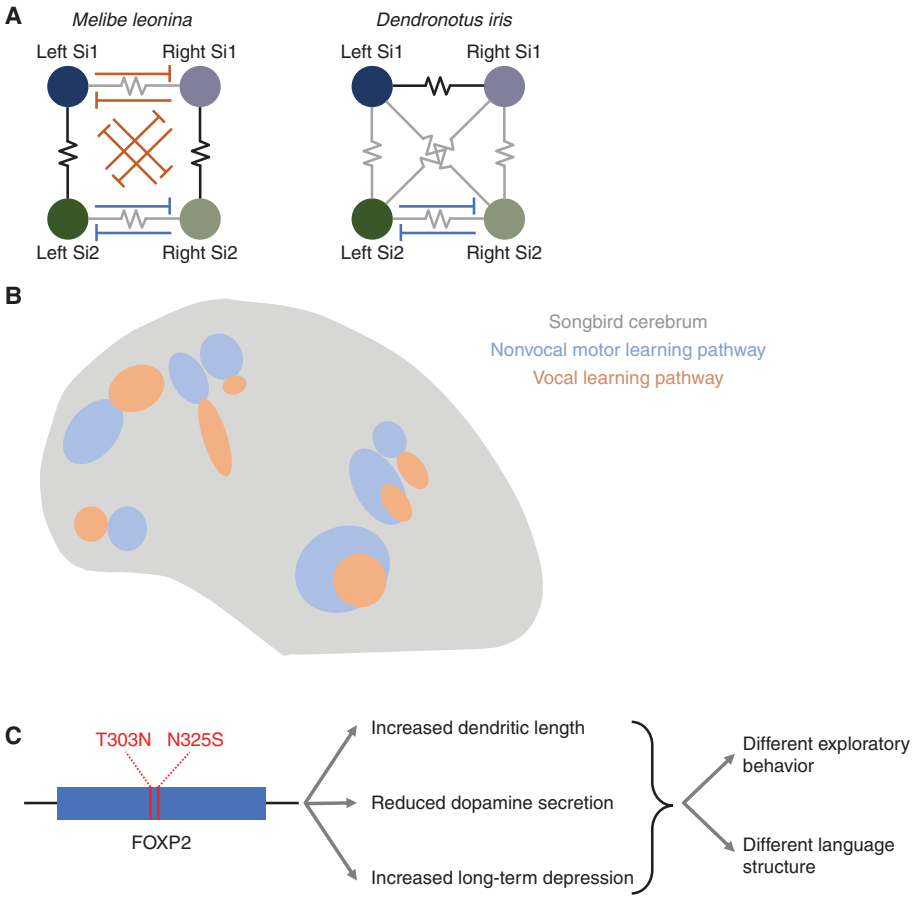

Figure 3. Neuronal circuits and behavior. (*A*) The central pattern generator that controls left–right swimming in both the nudibranchs *Melibe leonina* and *Dendronotus iris* consists of two bilaterally paired neurons, Si1 and Si2. Notably, despite the fact that this similar behavior is driven by homologous neurons in the two species, the underlying synaptic and electrical connectivity is substantially different. Differences in synapses are shown in orange. Darker lines show stronger coupling. (Panel *A* based on data in Sakurai and Katz 2015.) (*B*) In the cerebrum of vocal learners (such as songbirds), a duplication of the nonvocal motor learning nuclei (blue) led to the evolution of the adjacent vocal learning pathway (orange), which is necessary for the production of the learned vocalizations. (Panel *B* based on data in Feenders et al. 2008.) (*C*) Two amino acid substitutions that occurred in FOXP2 in the human lineage (after the divergence from that of the chimpanzees) led to a number of neuronal differences in the corticostriatal and corticocerebellar circuits: First, they led to an increased dendritic length and long-term neuronal depression, as well as a decrease in the secretion of dopamine. These neuronal changes caused differences in language structure and exploratory behavior that are believed to be important for the human ability to articulate speech and develop language.

CONCLUDING REMARKS

We presented the current knowledge of the evolution of neuronal circuitry, from genes to circuits to behavior: We described how genetic and developmental mechanisms that underlie circuit differentiation suggest that different genes can affect neuronal circuitry at different developmental levels and, hence, to a different extent. We then reviewed current ideas regarding the evolution of the first circuits and different ways by which that circuits can evolve increasingly complex structures. Finally, we examined the adaptive significance of evolutionary changes in neu-

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ronal circuitry (i.e., how circuits evolved to perform various functions to control different behaviors).

One of the main limitations to understand neuronal evolution has been the difficulty in identifying and comparing homologous circuits between different animals outside the traditional model organisms. Given the fairly recent technological developments that give us access to almost all animals, the future of this field is bright. On the one hand, the advent of single-cell sequencing allows the identification and comparison of orthologous cell types in different species. On the other hand, the increasing feasibility of obtaining new connectomes and the constant development of tools to analyze connectomic data will allow us to compare the circuits in which these orthologous cell types participate. Moreover, not being constrained by model animals will facilitate the investigation of the phylogenetic tree of animals more or less uniformly.

Circuits evolve under an evolutionary pressure to "perform" differently. Small-scale behavioral differences might not be qualitatively detectable. Therefore, it is essential to measure and compare behaviors quantitatively. The development of deep learning methods for pose estimation (i.e., detection of the position and orientation of an animal), such as SLEAP (Pereira et al. 2022) and DeepLabCut (Mathis et al. 2018), allows for the detailed and accurate characterization of different behaviors that could then be quantitatively compared between different species. Importantly, these methods perform multi-animal pose estimation that should enable the quantitation of social behaviors and the concurrent quantitation of behaviors of many animals at once, which can increase statistical power in the analysis of subtle behavioral differences. In combination with connectomics, this will allow us to address how differences in neuronal circuitry are translated into behavioral differences.

This toolkit can also be applied to understand how the human brain evolved (reviewed recently in Sousa et al. 2017; Vanderhaeghen and Polleux 2023). The human brain represents without doubt the most complex tissue in any animal. While the development of the human brain is not exceptionally different from that of nonhuman primates, the differences in cognitive capacities are extreme. A number of human-specific genomic changes have been described that might differentiate human brain development from that of nonhuman primates and cause increased size, neuronal number, as well as a rewired and more complex neuronal circuitry; however, it is likely that we are still missing a very large part of the story. Very recently, transcriptional and epigenetic atlases of the cellular composition of adult and developing humans, as well as nonhuman primates, marmosets, and macaques brains, were made available (Ament et al. 2023; Braun et al. 2023; Chiou et al. 2023; Jorstad et al. 2023a, b; Komiyama 2023; Krienen et al. 2023; Li et al. 2023; Maroso 2023; Micali et al. 2023; Siletti et al. 2023; Tian et al. 2023; Velmeshev et al. 2023; Zhu et al. 2023). These and other efforts will allow us to understand which genetic and developmental mechanisms enabled the human brain to support higher cognitive functions.

While the above techniques can generate unprecedented knowledge regarding the development of the human brain, different experimental tools are needed to probe the function of the identified genes and circuits. Since experimentation on human brains is restricted for ethical and practical reasons, the development of protocols for the generation of human brain organoids ex vivo as well as from different animals (e.g., different vertebrates and primates) (Lázaro et al. 2023) will prove invaluable to test candidates generated from high-throughput sequencing studies, assess their role in the development of human-specific neuronal circuits, and, ultimately, understand the genetic and developmental mechanisms that are responsible for the generation of this complex structure and will also allow for the comparisons of these mechanisms in brain organoids coming from animals that span the phylogenetic tree (Pașca 2018; Tambalo and Lodato 2020; Velasco et al. 2020; Lin et al. 2021; Uzquiano and Arlotta 2022) and might also aid significantly in the understanding of human neurodevelopmental disorders.

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