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Conclusions

The fact that the CNSs of diverse members of the arthropod phyla are essentially similar and show clear differences from vertebrate CNSs has never been disputed. Nevertheless, it is interesting to see how many features are shared between the nervous systems of arthropods and vertebrates. Their development is driven by genes and transcription factors that are similar, indeed homologous. Neurons build a nervous system and have similar ionic channel compositions in arthropods and vertebrates. In both cases, neurons communicate with each other through synapses, chemical or electrical, and these are even built by the products of homologous genes. They use the same transmitters. And even the segmentation of the CNS (brain and nerve cord) has a similar overall organization.

The differences are in the details, particularly in features that are important for nervous system specializations. In vertebrates, the need for fast propagation of action potentials is supported by the myelination of axons. The vertebrate brain is generally larger and more complex (with exceptions such as the very large brains of some cephalopods), and responsible for higher cognitive functions. Motor neurons and sensory neurons can put a similar set of neurotransmitters to different uses. And gastrulation generates a different position for the nerve cord, ventral *versus* dorsal, though this may not be a fundamental difference.

The overwhelming similarities between the nervous system, and especially the neuronal network structure, argue that work on invertebrates will continue to provide general insights, and the case for research on invertebrate species is strengthened by their experimental tractability and the powerful tools for genetic analysis available, particularly for the fruit fly *Drosophila*. And of course, invertebrates are fascinating in their own right.

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Primer

Evolution of highly diverse forms of behavior in molluscs

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Members of the phylum Mollusca demonstrate the animal kingdom's tremendous diversity of body morphology, size and complexity of the nervous system, as well as diversity of behavioral repertoires, ranging from very simple to highly flexible. Molluscs include Solenogastres, with their worm-like bodies and behavior (see phylogenetic tree; Figure 1); Bivalvia (mussels and clams), protected by shells and practically immobile; and the cephalopods, such as the octopus, cuttlefish and squid. The latter are strange-looking animals with nervous systems comprising up to half a billion neurons, which mediate the complex behaviors that characterize these freely moving, highly visual predators. Molluscs are undoubtedly special — their extraordinary evolutionary advance somehow managed to sidestep the acquisition of the rigid skeleton that appears essential to the evolution of other 'successful' phyla: the exoskeleton in ecdysozoan invertebrates and the internal skeleton in Deuterostomia, including *vertebrates*.

A skeletal body provides stability and enables, through lever action, efficient exploitation of muscle forces for the generation of rapid movements. By contrast, molluscs must use their muscles for both body support and movement. Having a skeleton also simplifies motor control, because motor commands are limited to a rather restricted number of control variables (degrees of freedom) dictated by the number of joints. Indeed, except for cephalopods, molluscs are not renowned for their motor capabilities. The flexibility and speed of cephalopod motor behaviors have been achieved through radical changes in morphology, and the

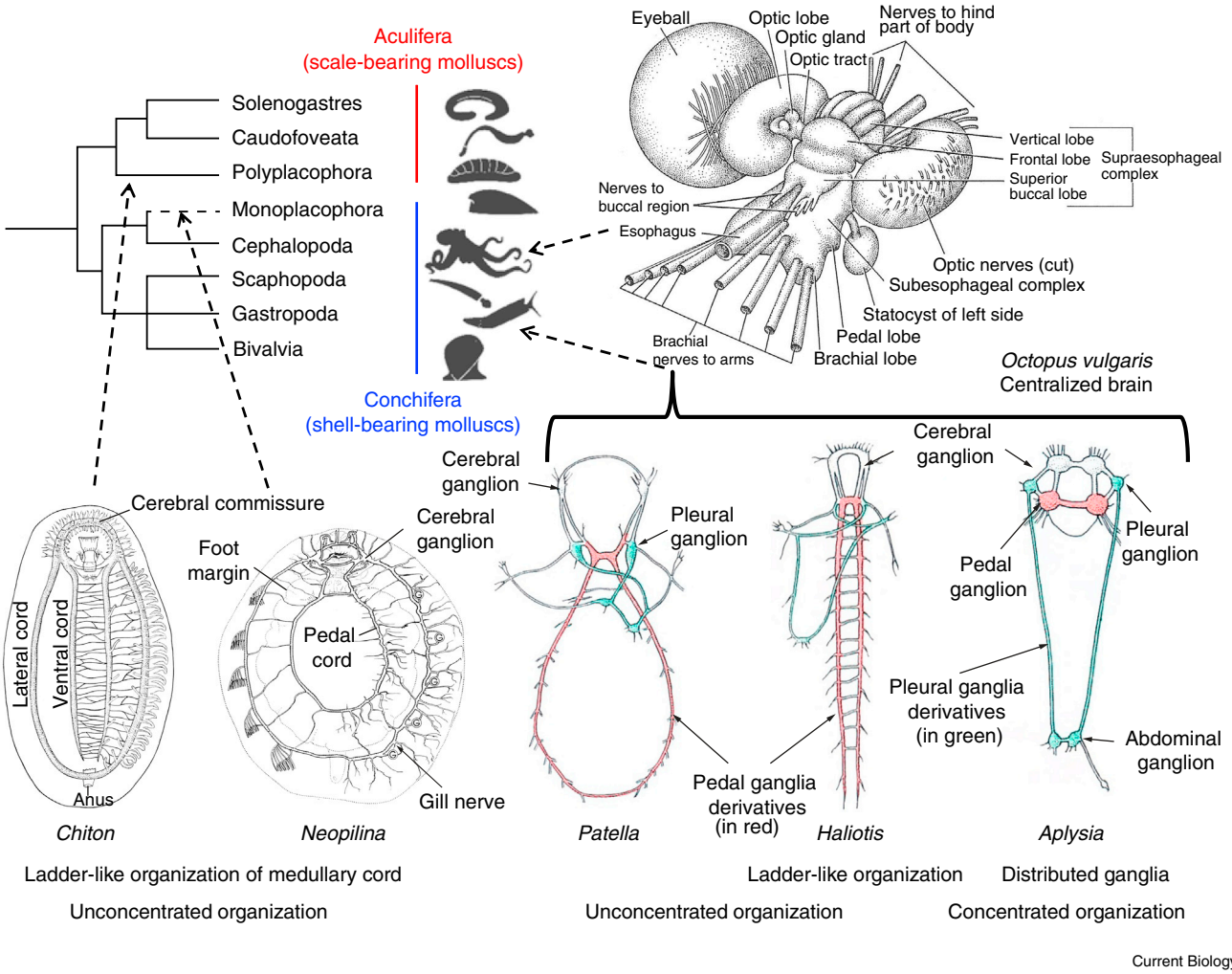

Figure 1. Diversity among molluscan nervous systems.
The extreme diversity of molluscan nervous systems shown in relation to their position in the phylogenetic tree (taken from Stögere *et al.*, 2013). The examples illustrate similarities among different groups, as well as the differences within the same group (see text). The derivatives of the pedal ganglia are shown in red, the components of the pleural-parietal ganglia are shown in green, and the cerebral ganglia are uncolored (Figures adapted from Bullock & Horridge 1965, except *Octopus* brain, which is taken from Brusca and Brusca (1990) with permission of Sinauer Associates.)

expansion of neuronal number by 4–5 orders of magnitude relative to other molluscs.

An intriguing hypothesis is that the vast diversity of molluscan morphology and behavior has resulted from the lack of skeletal constraints. This idea is supported by the discovery that gene families important in setting body morphology (like the Hox family) have 'lost' their collinear patterns of expression in the two behaviorally most advanced molluscan classes — gastropods and cephalopods. Furthermore, the recent sequencing of the genome and multiple transcriptomes of the California two-spot octopus by Albertin *et al.* revealed that cephalopods may have achieved their supremacy among invertebrates in motor and cognitive abilities through the expansion of two developmentally important gene families (C2H2s and protocadherins), extensive transposable element activity, and genome rearrangements, rather than through gains in the platforms of core genes. These findings suggest that the diversity of molluscs arose from their more 'modular' developmental frameworks, which allow greater variability and independence in selecting evolutionarily successful solutions.

In this Primer we first discuss how the diversity among molluscs illustrates the co-evolution of body morphology and the nervous system in order to accommodate, in an embodied way, the different levels of behavioral complexity. We then use the examples of simple and complex forms of learning and memory in *Aplysia californica* and *Octopus vulgaris* to demonstrate the diversity of the learning-related molecular and cellular mechanisms in molluscs.

Coevolution of nervous system, body morphology and behavior in molluscs

A review of the main molluscan groups demonstrates how the anatomy of the nervous system

has adapted to body morphology and lifestyle. The nervous system of the chitons — large flatworm-like molluscs protected by eight overlapping shell plates— is organized in a ladder-like fashion of medullary cords, with the neurons distributed along the cords (Figure1). Such an arrangement permits finer control of locomotion in these animals. This local organization is not true segmentation, suggesting that it is due to convergent evolution rather than to shared ancestry. This same principle seems to be general to all Mollusca groups, as demonstrated in Figure 1.

In scaphopods, gastropods, and bivalves of the Conchifera (shell-bearing) class (Figure 1), the nervous system consists of distributed ganglia (clusters of nerve cells) that are interconnected by axonal fibers that run between the ganglia in connectives and commissures (Figure 1). In these animals, each ganglion is located close to the affector (sensory) or effector (motor) organs. In cephalopods, the central brain is organized into a set of closely interconnected ganglia (lobes), which retains the typical invertebrate organization of a circumesophageal ring (Figure 1), and comprises about 40 interconnected lobes, each with a more or less specific function. The lobes show the common structure of invertebrate ganglia: an outer layer of neuronal cell bodies, from each of which projects a single neurite that passes into a central neuropil, where it ramifies into dendritic and/or axonal terminal trees.

However, a recent study of cephalopod brain neurogenesis reported that this brain is not embryologically derived from a ganglionic organization. Moreover, the peripheral nervous system of the *Octopus* arm, which contains two-thirds of the half billion neurons of the *Octopus* nervous system, is organized similarly to other molluscs. Specifically, the axial nerve cord of the arm, which controls the intrinsic muscular system, resembles the medullary cord organization in Chitons (Figure 1), probably to better regulate the wave-like arm movements characteristic of the *Octopus*. On the other hand, each

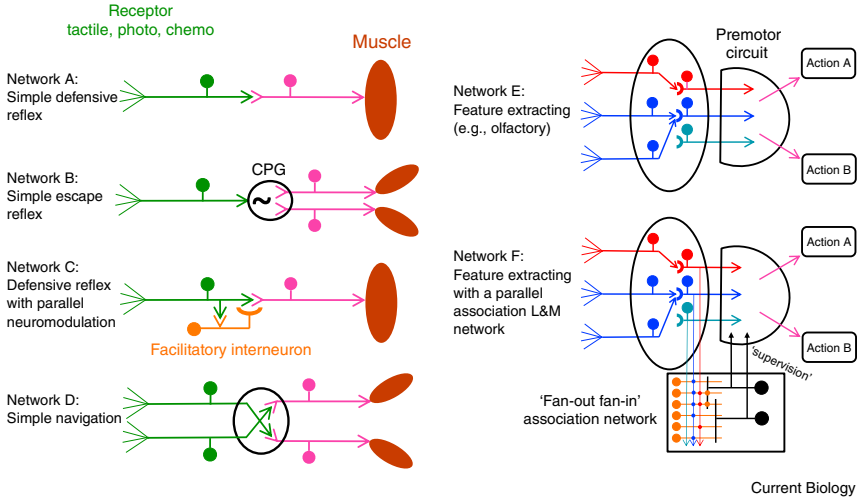

Figure 2. The neural bases of molluscan behavioral diversity.
Network schemes showing the correlation between the level of complexity of molluscan behaviors and the number of sensory modalities involved in the behaviors (see text). The examples range from a simple defensive reflex (Network A) to the associative learning and memory network of the octopus (Network F). The neurons are schematized as a typical invertebrate monopolar neuron.

of the 200–300 arm suckers has its own ganglion that mediates autonomous sensory-motor functions. Finally, a specific organization is not restricted by phylogenetic class. In the monoplacophorans, like *Neopilina* (Figure 1), which also belong to Conchifera, the adult nervous system resembles the medullary cords typical of chitons in the Aculiferan (scale-bearing) group (Figure 1).

Relationships among nervous systems, bodies and levels of behavioral complexity

The behavior of all molluscs, albeit to a lesser degree in cephalopods, involves simple reflexes that are mediated by Network A, schematized in Figure 2. Perhaps the best-known example is the defensive withdrawal response to a tactile stimulus. When touched, the animal retracts its body into its shell or, in the case of the gastropods, which have lost their shells, contracts its extended organs (tentacle, gill, siphon, etc.). This defensive withdrawal reflex (DWR) has been studied extensively in the marine snail *Aplysia californica* by Eric Kandel and others. (Kandel was awarded the Nobel Prize for Medicine in 2000 for his research in *Aplysia*.) This simple behavior, which is mediated by a single sensory modality, touch, shows non-associative and associative short- and long-term modulation, and is expressed in the same neurons that directly produce the reflex (Figure 2, Network C).

Two molluscan classes, Bivalvia and Polyplacophora (chitons), are protected by shells and scales, respectively. These have evolved a unique defensive reflex that is mediated by simple, light-detecting eyes distributed along the mantle or within the shell. Instead of evolving complex computation, the optical properties of these eyes have been selected to detect specific visual parameters or features (light intensity or direction and velocity of passing shadows). The physical properties of the eye in these animals allow it to act as an optical alarm system that triggers, for example, a reflexive closure of the two valves of the ark clam (Figure 2, Network A).

A somewhat more sophisticated level of defensive behavior is escape behavior, in which a tactile, light or odor stimulus evokes whole animal behavior (Figure 2, Network B). In this defensive behavior, particularly prominent in gastropods that have lost their protective shells (e.g. nudibranchs), the stimulus may activate a central pattern generator (CPG) that drives escape swimming.

Two of the molluscan classes, the gastropods and cephalopods, possess

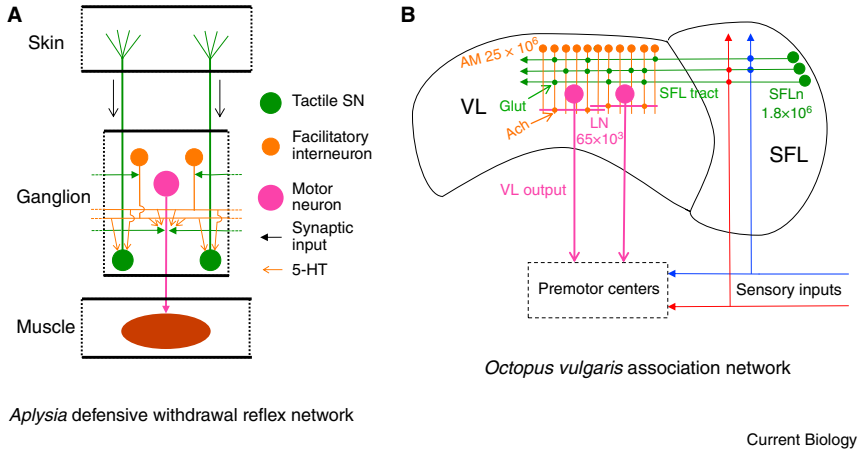

Figure 3. Wiring diagrams for a simple and a complex learning and memory network.
The network organization of the defensive withdrawal reflex of *Aplysia* (A) and the associative learning and memory network of the *Octopus* vertical lobe (B). The vertical lobe comprises a 'fan-out fan-in' pattern of neural connectivity, which is also characteristic of the insect mushroom body and of an artificial machine learning classifier. VL, vertical lobe; SFL, superior frontal lobe; SFLn, superior frontal lobe neuron; AM, amacrine interneurons; LN, large efferent neuron; Ach, acetylcholine; Glut, glutamate.

true eyes and a well-developed head (cephalic) region. The development of the head is associated with the goal-directed locomotion shown in these groups. The directional information about the external world can be extracted through the visual and/or olfactory system (Figure 2, Network D). To direct the animal's locomotion, the sensory receptors are concentrated in a pair of organs at the front of the animal's head. The stereoscopic sensory information is processed in the cerebral ganglion or 'brain', whose size and associated structures correlate with the total potential amount of sensory input from the visual and the olfactory systems. A simple computational algorithm, which compares the chemical or light intensities between each of the two cephalic receptors and then computes the weighted motor outputs (Network D), may suffice for a simple goal-directed movement.

The next level of behavioral complexity arises when behavior is based on the quality of the sensory signals rather than on their intensity. Here the 'physical' solution lies in having receptors for each modality (for example, an odor-specific sensory neuron) and a neural network that can process this multi-channel information. Certain gastropods, like the terrestrial *Helix pomatia*, possess a specific lobe-like structure, the protocerebrum, that can analyze the quality of incoming olfactory information. The protocerebrum has the glomerular organization that characterizes the neural structures dedicated to olfactory processing in nematodes, arthropods and vertebrates (Figure 2, Network E). This emphasizes the importance of specialized anatomical features within the nervous system for a specific computational function.

Molluscan 'image-forming' eyes have evolved only in cephalopods. Seeing the external world with a camera-like eye requires projecting the image of the external world onto a two-dimensional array of photoreceptors (such as in the retina) whose density determines the level of optical resolution. Such camera-like eyes have been achieved by convergent and independent evolution in cephalopods and vertebrates. (In *Nautilus* the optical mechanism for projecting the image onto the retina circumvents the need for a lens by using pinhole optics.) Analysis of the genetic basis of the independent evolution of these camera-like eyes indicates that about 70% of the octopus genes are conserved in the human eye. This suggests that the evolution of camera-like eyes used a limited number of protein-coding genes that were already present in our last common bilaterian ancestor, which lived 660–680 million years ago.

The cephalopods' camera-like eyes marvelously illustrate convergent evolution. Yet, the electrical responses of photoreceptors to light in the retinas of cephalopods and vertebrates differ, suggesting that there was no corresponding evolutionary pressure for invertebrates and vertebrates to converge on the same mechanism of light transduction. Thus, neuronal network evolution and development are highly adaptive; the mechanisms necessary to achieve the same level of information processing can evolve in a variety of ways. As we show below, the synaptic mechanisms of learning and memory in two cephalopods, the *Octopus* and cuttlefish (*Sepia officinalis*), provide further support for this idea.

Evolution of learning and memory in molluscs — extreme diversity in molecular solutions

In this section, we address the variability in the neuronal mechanisms that mediate simple and complex behavioral flexibility in two well studied molluscs, *Aplysia californica* and *Octopus vulgaris.* In particular, we compare forms of synaptic plasticity underlying simple forms of learning and memory exhibited by the defensive withdrawal reflex (DWR) of the gastropod *Aplysia* with those expressed by the vertical lobe (VL) system of the *Octopus*.

Network organization and learning-related plasticity of the DWR

The core neuronal circuit regulating the DWR comprises only two types of neurons (Figure 2, Network A) — sensory and motor neurons. The network gains greater behavioral flexibility from a comparatively restricted population of interneurons and modulatory interneurons that are also activated by the sensory neurons (Figure 2, Network C; Figure 3A). Significantly, learning-related neurobiological changes in the DWR system are predominately restricted to the relatively small number of neurons that comprise the reflex circuit itself.

The *Aplysia* DWR is evoked by activation of primary sensory neurons — the receptors of which reside in the animal's skin — that respond to mechanical pressure. The most basic component of behavioral plasticity in the simple DWR network results from intrinsic synaptic alterations, including homosynaptic depression and homosynaptic facilitation, of the monosynaptic connection between the sensory neurons and the motor neurons.

Homosynaptic plasticity in the DWR circuit

Homosynaptic plasticity is induced at a synapse through its autonomous activity. In the DWR network this form of plasticity is best demonstrated by activity-dependent *synaptic depression*. Homosynaptic depression occurs upon repeated low frequency (at rates greater than ~1 per 3 min) activation of the sensory neuron, and is due to a progressive decrease in release of glutamate, the sensory neuron transmitter. This mechanism ensures that only the sensory neurons that are repeatedly activated by a weak, invariant tactile stimulus 'learn' to ignore the stimulus. Homosynaptic depression mediates short-term (<1 h) habituation of the DWR.

Another important form of activity-dependent homosynaptic plasticity of the sensory-motor synapse is long-term potentiation (LTP). This form of synaptic enhancement, induced by synchronous pre- and postsynaptic activity, was first proposed in 1949 as a mechanism for associative learning by the Canadian psychologist Donald Hebb. Hebbian LTP — initially discovered in the hippocampus, a brain structure known to be critically important for many forms of associative learning and memory — is mediated by *N*-methyl-D-aspartate-(NMDA)-type glutamate receptors (NMDARs). Hebbian/NMDAR-dependent LTP is not unique to the hippocampus; it has been described at synapses in other regions of the vertebrate nervous system, and is prominent at the *Aplysia* sensory–motor synapse. As its name suggests, LTP is a persistent form of synaptic plasticity and is thought to mediate types of learning and memory that last for hours. In *Aplysia,* NMDAR-dependent LTP mediates classical conditioning of the DWR. It is induced, for example, by siphon stimulation, the conditioned stimulus (CS), which activates the sensory neuron, paired with electrical shock of the tail, the unconditioned stimulus (US), which depolarizes the motor neuron through an excitatory interneuronal pathway. The simultaneous presynaptic activity and postsynaptic depolarization causes the opening of postsynaptic NMDAR channels, thereby producing LTP of the sensory–motor synapse.

Heterosynaptic plasticity in the DWR circuit

In the DWR network, the sensory neurons activate the motor neurons and, in parallel, also activate interneurons, some of which release various neuromodulatory transmitters. Some of these modulatory interneurons re-innervate the sensory neurons (Figure 2, Network C; Figure 3A). The best studied modulatory interneurons in *Aplysia* are the serotonergic facilitatory interneurons; these synapse onto the presynaptic terminals of the sensory neurons, as well as the cell bodies of both sensory and motor neurons. The neuromodulatory transmitters mediate various forms of short- and long-term heterosynaptic modulation of the sensory-motor synaptic connection and of the excitability of the sensory and motor neurons.

Serotonin (5-HT) is released from the terminals of the facilitatory interneurons onto both the sensory and motor neurons in response to noxious or arousing stimulation. Because the sensory neurons mediate the perception of a tactile stimulus that triggers the DWR and of a noxious stimulus (in the laboratory this is commonly a shock applied to the animal's tail), what differentiates a noxious stimulus from a harmless stimulus is the amount of released 5-HT (Figure 2, Network C; Figure 3A). This is a function of the number and intensity of the sensory cells activated. The forms of synaptic plasticity mediated by 5-HT are referred to as 'heterosynaptic' because they depend critically on mechanisms extrinsic to the sensory-motor synapse. Heterosynaptic, 5-HT-dependent facilitation of the sensory-motor synapses mediates behavioral enhancement of the DWR, most prominently *sensitization* and *dishabituation*. Dishabituation, the enhancement of a habituated response, is distinct from sensitization because it requires a preceding form of learning (habituation); in contrast, sensitization is the enhancement of a nonhabituated response.

Serotonin appears to mediate both forms of learning through the parallel activation of somewhat distinct biochemical and molecular pathways. Thus, sensitization involves 5-HT-dependent activation of cAMP-dependent kinase A (PKA), which phosphorylates and blocks specific types of K^+ channels in the sensory neuron; the blockage of the K^+ channels, in turn, causes prolongation of the presynaptic action potential. The broader action potential increases Ca^{2+} entry into the presynaptic terminal, thereby enhancing transmitter release.

Dishabituation, by contrast, involves activation of presynaptic protein kinase C (PKC). Interestingly, the mechanism of presynaptic facilitation during dishabituation is independent of the broadening of the presynaptic action potential. Rather, 5-HT appears to facilitate synapses depressed during habituation through a different mechanism, possibly involving PKC-stimulated enhancement of presynaptic vesicle mobilization, which serves to counteract the vesicle depletion that occurs during habituation.

In addition to the nonassociative forms of heterosynaptic facilitation that underlie behavioral sensitization and dishabituation, the DWR circuit exhibits an associative form of heterosynaptic facilitation, activity-dependent facilitation, which mediates classical conditioning together with NMDAR-dependent LTP. Activity-dependent facilitation (ADF) is produced by activation of the sensory-motor synapse in the presence of 5-HT. During classical conditioning, the CS-induced firing of the sensory neuron occurs in conjunction with release of 5-HT

from facilitatory interneurons due to the US (tail shock), resulting in the enhancement of the biochemical cascade that mediates 5-HT's effect on transmitter release.

The *Aplysia* sensory–motor synapse exhibits a greater variety of plasticity than any other synapse known to neurobiology. Why is this so? A likely possibility is that the number of neurons in the DWR circuit is relatively restricted, and the same circuit that mediates the reflex also is used for storing short- and long-term memory traces. Consequently, each synaptic site must carry a greater 'cognitive load' if the animal is to express the full panoply of learning and memory forms that are expressed by *Aplysia*. Another important question is why certain forms of learning require multiple synaptic plasticity mechanisms. An illustrative example is classical conditioning of the DWR, which involves both NMDAR-dependent LTP and ADF. Possibly, NMDAR-dependent LTP is specialized for the mediation of postsynaptic modifications while ADF is better suited for modification of presynaptic properties.

The VL association network: the role of homosynaptic plasticity

The cephalopod VL is organized as a 'fan-out fan-in' matrix of connections among an extremely large number of neurons (~25,000,000). In contrast to the DWR circuit, the VL has evolved to deal efficiently with learned associations among the several sensory modalities that cephalopods use and is organized to work in parallel to the pathway that controls the motor behavior (Figure 2, Network F; Figure 3B).

The sensory information of each sensory modality is first processed in feature-detecting networks (e.g. Figure 2, Network D) or in the optic lobes (see the *Octopus* brain anatomy in Figure 1), after which it undergoes further categorization in the superior frontal lobe (SFL) (see scheme in Figure 3B). The information is then transferred to the VL, where it is represented by sparse synaptic connections between the 1.8 million axons of SFL neurons entering the VL and the 25 million amacrine interneurons (AM) that comprise the input ('fan-out') synaptic layer of the VL. The AMs converge sharply onto the second synaptic layer ('fan-in') of large efferent neurons (LNs), the only output of the VL. The organization of the VL is similar to that of the insect mushroom body — which, like the VL, is involved in associating sensory information of different modalities — as well as the mammalian hippocampus.

The cellular mechanism that evolved for forming associations among sensory stimuli in the *Octopus* VL is LTP. In the *Octopus* VL only those synapses in which the presynaptic terminals are intensely activated undergo LTP. The LTP in the *Octopus* VL occurs at the SFL-to-AM glutamatergic synapses (Figure 3B), whereas in *Sepia* it occurs at the cholinergic connections between the AMs and the large neurons that transmit the output of the VL to other brain regions. This difference represents a good example of versatility in the organization of different learning and memory networks in phylogenetically close animals, and suggests that the cellular and molecular mechanisms in molluscan nervous systems are disposed to significant variations. Mechanistically, LTP in the VL differs from that in the DWR circuit. Whereas LTP of the *Aplysia* sensory-motor synapse is mediated by postsynaptic NMDARs, LTP of the SFL–AM synapses in the *Octopus* VL is not blocked by standard NMDAR antagonists.

On the other hand, LTP in about half of SFL–AM synapses in the VL is mediated by AMPA-type glutamatergic receptors because it is blocked by AMPA/kainate receptor antagonists. In fact, the LTP at the SFL–AM synapses of the *Octopus* appears to resemble the LTP of the glutamatergic synapses between the mossy fibers and CA3 neurons in the mammalian hippocampus, which is also NMDAR-independent and presynaptically expressed.

Neuromodulation in the VL

Similar to its effect on the sensory-motor synapses of *Aplysia*, 5-HT induces short-term presynaptic facilitation of the glutamatergic input to the AMs. Unlike in *Aplysia*, however, prolonged application of 5-HT does not lead to a long-term synaptic facilitation (LTF). But 5-HT indirectly reinforces LTP induction in the VL through its short-term facilitatory effects, suggesting a possible role in transmission of a reward signal into the VL.

Mechanisms of long-term plasticity in Aplysia *and the* Octopus

Perhaps the mechanistically best understood form of long-term synaptic memory, long-term facilitation (LTF) of the sensory-motor synapse, can be induced by repeatedly exposing sensory-motor cocultures to spaced pulses of 5-HT. This *in vitro* 'training' is designed to approximate *in vivo* training, whereby repeated activation of the facilitatory interneurons by strong electrical shocks applied to the animal's skin causes repeated, pulastile release of 5-HT, and thereby persistent sensitization of the DWR. The repeated exposure to 5-HT activates cAMP-dependent early genes within the sensory and motor neurons, which in turn triggers the protein synthesis-dependent long-term structural changes that underlie LTF. The studies of LTF in *Aplysia* were the first to show the involvement of cAMP-inducible genes in long-term synaptic enhancement and long-term memory (LTM). This mechanism is universally found to mediate LTM in invertebrates and mammals.

It is therefore surprising that the persistent LTP in the association network of the *Octopus* VL appears independent of protein synthesis. Instead, it appears to employ a 'molecular switch', using a covalent state modification of existing molecules to maintain the long-term synaptic change. This molecular switch has evolved through adaptation of the nitric oxide (NO) system that, in invertebrates, mediates various forms of behavioral plasticity, such as feeding-related learning in the gastropod molluscs *Lymnaea* and *Aplysia*. In the *Octopus* VL LTP induction is not mediated by NO because induction is not blocked by nitric oxide synthase (NOS) inhibitors. Nonetheless, such inhibitors transiently block

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the presynaptic expression of LTP. This suggests that the induction of LTP at the SFL–AM synapses involves activity-dependent NOS stimulation, likely in the AM neurons; the postsynaptically synthesized NO then diffuses retrogradely to produce the increase in probability of glutamate release that mediates the expression of LTP at these synapses. Recent results suggest a novel 'self-activation' mechanism, whereby NO can maintain LTP for more than 10 h by NO-mediated reactivation of NOS.

Why does LTF in *Aplysia* use a mechanism that depends on protein synthesis, while LTP in the *Octopus* VL does not? This distinction may be explained by differences in the organization of the two learning and memory systems (Figure 3). As suggested earlier, in the DWR network the memory is stored within the circuit that mediates the behavior; by contrast, the VL in the *Octopus* regulates the acquisition of memory, which is ultimately stored outside the VL. Therefore, in the *Octopus* the molecular memory switch in the VL must persist only long enough to maintain the VL memory until completion of the protein synthesis-dependent memory consolidation, possibly within the circuits that mediate *Octopus* behavior.

In summary, although the simple DWR circuit of *Aplysia* and the dedicated learning and memory system in the VL of the *Octopus* and *Sepia* make use of functionally similar cellular forms of short- and long-term synaptic plasticity, there are significant differences in the specific molecular mechanisms used by these three systems to mediate long-term synaptic plasticity and LTM. This fact points to a high degree of variability in the evolutionary selection within and/or the ontological development of the learning systems of *Aplysia* and the *Octopus*. This variability suggests that the special expansion of developmental and regulatory gene families, together with the unique cephalopod expansion of posttranslational mechanisms, provide the molecular flexibility required to achieve the different forms of neuronal plasticity necessitated by the disparate behavioral repertoires exhibited by molluscs.

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Primer

Myelination

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Myelin is a key evolutionary acquisition that underlay the development of the large, complex nervous systems of all hinged-jaw vertebrates. By promoting rapid, efficient nerve conduction, myelination also made possible the development of the large body size of these vertebrates. In addition to increasing the speed of nerve conduction, myelination has emerged as a source of plasticity in neural circuits that is crucial for proper timing and function. Here, we briefly describe the organization of myelin and of myelinated axons, as well as the functions of myelin in nerve conduction and neural circuits, and consider its potential evolutionary origins.

Formation and organization of myelinated fibers

Myelin is formed by Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS). Each Schwann cell forms a single myelin sheath around an axon. In contrast, each oligodendrocyte forms multiple sheaths (up to 30 or more) around different axons (Figure 1). Along the same axon, sequential myelin sheaths are formed by different oligodendrocytes. Myelin itself forms by the spiral wrapping around an axon of an enormously expanded glial plasma membrane that then compacts. Topological considerations, recently corroborated by live-imaging studies, indicate that the inner turn of this spirally wrapped glial membrane advances around the apposed axon to form the multilamellar, myelin sheath; as it expands radially, it also expands longitudinally.

Electron micrographs of compact myelin demonstrate the familiar appearance of interperiod lines, representing the apposition of the extracellular leaflets of the glial plasma membrane, alternating with major dense lines, resulting from the tight apposition of the cytoplasmic leaflets. The final compact myelin sheath can be composed of as many as 40 or more lamellae. The thickness of the myelin