Title: The legacies of A.O. Dennis Willows and Peter A. Getting: Neuroscience research using *Tritonia*

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Abstract

This review was inspired by a January 2024 conference held at Friday Harbor Laboratories, WA, honoring the pioneering work of A.O. Dennis Willows, who initiated research on the sea slug *Tritonia diomedea* (now *T. exsulans*). A chance discovery while he was a student at a summer course there has, over the years, led to many insights into the roles of identified neurons in neural circuits and their influence on behavior. Among Dennis's trainees was Peter Getting, whose later groundbreaking work on central pattern generators profoundly influenced the field and included one of the earliest uses of realistic modeling for understanding neural circuits. Research on *Tritonia* has led to key conceptual advances in polymorphic or multifunctional neural networks, intrinsic neuromodulation, and the evolution of neural circuits. It also has enhanced our understanding of geomagnetic sensing, learning and memory mechanisms, prepulse inhibition, and even drug-induced hallucinations. Although the community of researchers studying *Tritonia* has never been large, its contributions to neuroscience have been substantial, underscoring the importance of examining a diverse array of animal species rather than focusing on a small number of standard model organisms.

Introduction

In the summer of 1966, an Eastsound bottom trawl at Friday Harbor Laboratories, WA, returned with a large, unfamiliar pink mollusc. It was soon identified as the nudibranch *Tritonia diomedea*, given the name "Nathan," and placed in the Marine Invertebrate Zoology class tanks. Little did anyone realize at the time that Nathan would launch many careers and lead to a series of fundamental discoveries in neuroscience.

Among the class attendees was A.O. Dennis Willows (Fig. 1A), a graduate student of Graham Hoyle, who at that point was studying neuromuscular transmission in a wide variety of invertebrates (1) including animals as different as barnacles (2), horseshoe crabs (3), and sea squirts (4), and who had recently started to investigate the nervous system in locusts (5). When Nathan died, Dennis dissected the sea slug and noticed a structure filled with orange spheres, some of which were large enough to be seen without a microscope. He wondered if these could be the giant neurons recently discovered in other gastropods. Utilizing his neurophysiology skills from his PhD training, Dennis penetrated one of these spheres with a glass microelectrode in a second animal. The oscilloscope erupted with a string of action potentials, instantly identifying them as among the largest neuronal somata in the animal kingdom (up to ~1mm in diameter).

Dennis devised an intact animal preparation and was astonished to observe that stimulating different neurons with injected current produced unique body movements, including swimming (Fig. 2). This novel finding resulted in a single-authored Science paper titled "Behavioral acts produced by stimulation of single, identifiable brain cells" (6), and marked the beginning of a neurophysiological preparation that has, over the years, contributed to many fundamental discoveries about neural network function.

Propelled by his talent, curiosity, and ingenuity, Dennis's career progressed rapidly after this unplanned discovery, with additional papers in Nature (9), Science (8), and Scientific American (7) in rapid succession. A year after earning his PhD, he joined the faculty at the University of Washington, and two short years later, after being encouraged to apply by more senior faculty members, he was appointed as Director of their marine biology station, Friday Harbor Laboratories (FHL), a post he then held for 35 years. Dennis has chronicled his experiences in an as-yet unpublished memoir titled, "Sea life and my life at a marine laboratory" (https://tinyurl.com/Dennis-Willows-Memoir-2024). While serving as FHL Director, Dennis mentored a succession of graduate students and postdocs, many of whom went on to secure academic positions and train subsequent generations of scientists. His scientific lineage, including many individuals not named here due to space constraints, can be seen on Neurotree (https://neurotree.org/neurotree/tree.php?pid=4796).

In January 2024, a one-day conference was held at FHL, with Dennis in attendance, to honor his remarkable scientific legacy. This gathering of the majority of scientists to have worked on *Tritonia* prompted us to contribute this review of the science that has emerged from nearly six decades of work on this remarkable organism. In attendance at the conference were also people whose lives and careers were affected by the culture of support and openness that Dennis cultivated at FHL. When he wrote in his memoir, "…exceptional things happened

because exceptional people were attracted to exceptional biological resources, housed, and supported by relevant modern facilities not available at other research universities", Dennis modestly left out his own exceptional role. Through his advocacy and leadership, Dennis touched many lives and facilitated a great number of scientific discoveries.

Many threads lead back to Dennis when looking at his direct scientific descendants. For example, Ken Lohmann, a PhD student in Dennis's lab, demonstrated that *Tritonia* responds to geomagnetic stimuli (10, 11). This discovery inspired Ken to extend his research to other animals, including sea turtles (12). Today, the cellular and molecular basis for magnetoreception is studied in a wide variety of animals (13). Patsy Dickinson, one of Dennis's first students, studied neurons controlling gill retraction in a number of species (14). She did her postdoctoral work in France, where she transferred her understanding of identified neurons to the crustacean stomatogastric system, identifying neuromodulatory neurons for the first time (15, 16). Another student, Stuart Thompson, obtained his first recordings of potassium channel currents in *Tritonia* neurons (17) and went on to study many other ionic currents in molluscs (18) and vertebrates (19). A postdoc in Dennis's lab, Ronald Chase (1940 - 2022), studied optic responses in *Tritonia* (20, 21). He devoted his career to studying the neural basis of behavior in snails and wrote the book, "Behavior and its Neural Control in Gastropod Molluscs" (22). Several of Dennis's former students, including Russell Wyeth and James Murray, have returned to FHL for numerous summers to work and teach. They have published on the natural behavior of *Tritonia* in the field, as well as the neural bases of turning and orienting responses to water movements (23-28).

In this review, we focus on the legacy of research on *Tritonia* by Dennis Willows and Peter Getting (Fig. 1B), who joined Dennis's lab as a postdoc in the early 1970's. Tragically, Peter suffered a brain hemorrhage in 1988 that left him incapacitated until his death in 2006. However, in the decade and a half that he worked on *Tritonia*, Peter's findings and ideas revolutionized research on central pattern generators (CPGs). Responding to the field's frustration that as CPG circuits across species were described, they were turning out to be quite different from one another (29), Peter articulated that we might find common ground at a lower level, in the "building blocks" of pattern generators. He asserted that the categories of synaptic interactions and excitability properties would themselves be found to be common across examples (30, 31). Peter's contributions have had a lasting impact on our understanding of neural circuits and their role in generating rhythmic behaviors. With a background in electrical engineering, Peter designed his own line of widely-used amplifiers and stimulators, and was also exploring ways for 1980's personal computers to aid in automated 3D microscopy (32). His brilliance and versatility would undoubtedly have led to many more fundamental discoveries had his career not been tragically cut short in his forties.

The historical context leading to Dennis's findings

As the prestige of the journals publishing Dennis's early papers demonstrate, his mid-1960s studies were truly groundbreaking. At the time, the understanding of the role of individual neurons in behavior was still in its infancy. It was known that direct stimulation of individual giant axons in squid (33) and crayfish (34, 35) could elicit reasonably complex behavioral

components or even entire behavioral sequences, showing that certain individual neurons could have significant, coordinating roles. However, studying subsurface axons posed considerable technical challenges. Fortunately, histological research had established that many gastropod molluscs have large neuronal somata conveniently located on the external surfaces of their ganglia.

A pivotal 1958 study described several neurons in the Mediterranean sea slug *Aplysia depilans* that, based on their location, appearance, and firing patterns, were identifiable as unique individuals in every animal (36). Building on this, Ladislav Tauc published a series of studies in the early 1960s on the largest of these neurons, which would later be formally named R2 (37, 38). Eric Kandel, having become aware of these findings, traveled to France for a postdoctoral fellowship with Tauc. Together, they produced several electrophysiological studies on R2 (e.g (39)), as well as on the uniquely identifiable giant metacerebral cells of the terrestrial snail *Helix* (40).

Identified neurons and cell atlases

At the heart of Dennis's and Peter's work was the finding that many neurons in *Tritonia* are individually identifiable, prompting them to create naming schemes for their identification (41, 42) (Fig. 3A,B). Concurrent research on other gastropod molluscs (43, 44) as well as annelids, insects and crustaceans also focused on cataloging identified neurons (45). This research employed techniques such as intracellular microelectrode recordings, dye injections, and immunohistochemistry.

The first intracellular recordings from *Tritonia* neurons, to our knowledge, appeared in a 1964 Russian paper (46). Dennis published his initial *Tritonia* recordings the following year, discussing the advantages of *Tritonia* and other nudibranchs for studies on the neuronal basis of behavior (47). This was soon followed by his landmark *Science* paper (6), in which he mapped 35 neurons, demonstrating that many, when stimulated to fire, produced unique movements in an intact animal preparation. That same year, Kandel's group published a study identifying 17 unique neurons and 8 neuron clusters in *Aplysia* (48). Also in 1967, a study in lobsters mapped 21 pairs of uniquely identifiable neurons in that animal's ganglia (49). These contemporaneous demonstrations that in some preparations one can map re-identifiable neurons with specific roles in behavior were transformative for the field. The existence of such neurons raised the exciting possibility that entire circuits could be mapped at the level of individual neurons, opening the door to the pursuit of general principles of network function (45, 50).

Dennis initiated studies on the neurons' connectivity, creating matrices of projection patterns. To represent the neurons better, he even commissioned a large plaster model of the *Tritonia* brain to display the three-dimensional arrangement of the cells (Fig 3C). Although identified neurons have played a crucial role in the conceptual advances made in *Tritonia* and other gastropod molluscs (51), finding a consistent rubric for neuronal identification has proven to be notoriously challenging (52). Unlike *Drosophila* and *C. elegans*, where the cellular lineages that lead to the development of neuronal types has been tracked (53-55), the developmental origins of neurons

with individual identities in gastropods remains a mystery. Modern single-cell RNA sequencing techniques hold promise for identifying larger numbers of neurons in gastropods, as has been done with another nudibranch, *Berghia stephanieae* (56).

The difficulty of cataloging neurons is not unique to invertebrates and remains an area of active research across various nervous systems (57-59). It has been a major focus of the Brain Initiative (60), the Allen Brain Cell Atlas, and other initiatives. Neurochemical phenotype, neuronal morphology, and synaptic connectivity are all aspects of neural identity that were used to identify neurons in *Tritonia* and continue to be used in all systems. One lesson that can be applied from gastropods to other systems is that some features of neural identity are less likely to change across species than others (61). For example, electrophysiological properties, synaptic connectivity, and receptor expression are more variable than axon projections or neurotransmitter phenotype (62, 63).

Central Pattern Generators

Peter Getting was one of the first researchers to articulate the criteria needed for a neuron to be considered a member of a CPG (64). In the 1970s and 80s Peter and his colleagues identified the neurons in the central pattern generator for *Tritonia's* escape swim. Their work, detailed in a series of papers describing the neurons and their synaptic connections to one another, culminated in a comprehensive 1983 review article (64). The confirmed CPG members consisted of just 5 neurons on each side of the brain: cerebral neuron 2 (C2), three dorsal swim interneurons (DSIs), which fired with C2 in the dorsal phase of the swim, and ventral swim interneuron VSI-B, which fired in the ventral phase (65). All of these interneurons met the criteria that Peter established for CPG membership: they fired rhythmic bursts of action potentials during the swim motor pattern, they made monosynaptic connections onto one another and onto pedal ganglion efferent neurons, and each could shift the phase of the entire swim rhythm when their firing was forcibly changed with intracellular current injection. Another CPG candidate, VSI-A, met the first two criteria but failed to shift the swim rhythm phase when its firing was manipulated.

Peter concluded that the *Tritonia* swim CPG is an example of a network oscillator because none of these neurons has endogenous bursting properties; the rhythm emerges from the synaptic interactions of the members (66). Peter Getting's work was seminal in demonstrating that some CPGs operate as network oscillators. Subsequent studies showed that swim CPGs in other sea slugs, such as *Melibe* (67), *Dendronotus* (68), and *Pleurobranchaea* (69) are also network oscillators. This stands in contrast with other well-studied CPGs, such as the pyloric CPG in the crustacean stomatogastric ganglion, whose rhythmic activity is dependent upon endogenous bursting properties of individual neurons (70, 71). In CPGs consisting of large ensembles of neurons, it is difficult to fully test the network oscillator hypothesis. However, in *Tritonia* and other sea slugs, with their small number of individually identifiable neurons, the hypothesis can be unambiguously tested by recording from and perturbing the activity of all of the participating neurons and by modeling the circuit to demonstrate that is sufficient to produce rhythmic activity.

In parallel with his work on *Tritonia*, Peter spent his final working years also researching neural circuits in mammals, aiming to identify general principles of motor pattern generation applicable across phyla. A series papers published by Peter's lab after his stroke examined the neural basis of respiratory rhythm generation in guinea pigs (72-77). This work foreshadowed the later research on the Pre-Bötzinger nucleus as the site of rhythmogenesis for breathing (78). Ironically, there is still controversy in the field as to whether the respiratory CPG is a network oscillator or dependent upon intrinsic bursting properties of neurons (79, 80).

Computer simulations of CPG networks

Peter applied one of the earliest examples of realistic network modeling to evaluate whether the known CPG neurons were sufficient to generate the swim rhythm (81, 82). He modeled each neuron's excitability, the waveforms of their monosynaptic connections, and set the strengths of those connections based on how the neurons influenced each other when driven by intracellular current injection. Once all parameters were set, he tested the response of the network simulation to synaptic input. His first simulation failed to oscillate until he significantly strengthened a particular inhibitory synapse, which led him to search for and discover a missing CPG neuron, which he named VSI-B. When this neuron was incorporated into a subsequent simulation, the network oscillated similarly to the biological network, reinforcing the conclusion that the essential members of the CPG had been identified (83). Although neural network modeling is commonplace now, Getting's use of realistic network simulations to evaluate the completeness of our understanding of a CPG circuit was groundbreaking in the mid-1980s. Unfortunately, these were among his last publications on *Tritonia* before he suffered his debilitating stroke.

Intrinsic neuromodulation

Paul Katz met Peter Getting a month before Peter's brain hemorrhage and heard him speak about a recent discovery that the DSI neurons are serotonergic and have a neuromodulatory role in addition to their synaptic role in the CPG. Paul later joined the lab of Peter's former postdoc, Bill Frost, and together they showed that the DSIs modulate the synaptic strength and excitability of the other CPG members during the production of swim motor program (84-86). The discovery of "intrinsic neuromodulation" in *Tritonia* was distinct from the predominant view of neuromodulation at the time, which was that it arose from sources extrinsic to the modulated circuits and thus was optional to operation of the neural circuit. In contrast, intrinsic modulation meant the that neuromodulatory actions were as much a part of the operation of the circuit as the classic synaptic actions (87).

The characterization of intrinsic neuromodulation in *Tritonia* was possible because the circuit and the neurons were delineated already, allowing measurements of synaptic strength to be compared in the same neurons under the same conditions over hours and across individuals. The concept that some circuits self-modulate is now widely accepted not just in invertebrates (87-89), but in vertebrate neural circuits as well (90-93). It changes how we think of neural circuits, from being static entities that always process information the same way to systems that change over time in response to their own activity.

Although Peter's simulation did not explicitly include the modulation that reconfigures the network, it might have been unintentionally included because of the way that he made measurements for the model, which did not control for background firing. Following their bursting during the swim motor program, the DSIs remain tonically active at an elevated rate for nearly an hour, keeping the network in a modulated state (94). Suspecting that Peter's baseline measurements for his models may have thus inadvertently incorporated the effects of intrinsic neuromodulation, Bill Frost and his colleagues reconstructed the CPG model from scratch, using newly collected data from rested, unmodulated, preparations. The new, unmodulated simulation failed to generate the swim motor program. The model was then used in an exploratory manner to identify potential missing components of the swim CPG (95, 96). The missing element to configure the swim CPG into a functional circuit seems to be the serotonergic neuromodulation.

Polymorphic networks

Another fundamental concept, that of polymorphic or multifunctional neural circuits (Fig. 4), arose out of a chance conversation that Peter had with Eve Marder at a party, as recounted by Eve, who is now recognized as a leader in the field of neuromodulation of neural circuits for her work in the crustacean stomatogastric ganglion (p. 108 in ref. 97). Both Peter and Eve came away from that conversation with the idea that an anatomically-defined network of neurons can be reconfigured into different functional circuits (31). This notion of polymorphic networks was critical for understanding the stomatogastric system (98) and continues to resonate in the study of more complex networks (99) and neural ensembles in the brain (100).

Tritonia rarely exhibits an escape swim behavior (25). The neurons that comprise the *Tritonia* swim CPG only perform that function for about a minute. The rest of the time, the same neurons participate in the generation of other behaviors such as reflexive withdrawals (101) and crawling (94, 102). As mentioned in the previous section, the reconfiguration of the anatomically-defined network into a functional swim CPG appears to require the intrinsic serotonergic modulation the DSIs make onto other members of the swim network (65).

Thus, an important conclusion from this work is that *Tritonia*'s swim circuit does not simply exist in the brain waiting to be activated; the circuit is modulated into existence. This mechanism allows neurons to participate in other behaviors when there is no functional CPG circuit (94, 102). It also provides a safety feature to raise the threshold for producing the escape swim because the motor pattern cannot be triggered without the input that aligns the firing of the DSIs, allowing them to modulate the properties of the other neurons that participate in the CPG (86, 103).

Command neurons

For many years, a much-debated topic was the legitimacy of the command neuron concept – the notion that some behaviors may be hierarchically controlled by single neurons playing such outsized roles that they are both necessary and sufficient for the behavior to occur (104). In 1996, while penetrating axons crossing the central commissure with a dye-filled electrode, Bill

Frost encountered an axon that, when driven to fire action potentials, triggered the swim motor program. Thirty minutes later the dye had spread to the cell body, allowing the soma to be targeted in subsequent preparations with intracellular electrodes. This neuron was named the dorsal ramp interneuron (DRI), for the neuron that Peter Getting had inferred from voltage clamp studies must exist to provide the excitatory input in the DSI neurons that drives the motor program. By simultaneously exciting the three bilateral pairs of DSIs, DRI activates the intrinsic neuromodulation that configures the resting network into a functional swim CPG circuit (103).

DRI has the hallmark features of a command neuron, being both necessary and sufficient for sensory input to activate the swim motor program (105). At that time, a few command neuron examples had been identified in other preparations, but these generally drove single-phase reflex actions, such as the C-start escape response produced by the fish Mauthner cell (106). *Tritonia's* DRI neuron, with its massive monosynaptic excitatory connections onto the DSI population, remains a premier example of a complex behavior under the control of a single command neuron.

Evolution of neural circuits

One of the strengths of research on *Tritonia* is the presence of individually identifiable neurons, which can be recognized not only across animals within this species but also across different species (Fig 5). Dennis Willows examined the function of homologous neurons in other species of the genus *Tritonia* (107). Homologs of *Tritonia* neurons were also identified in many other heterobranch molluscs (108), enabling comparisons of circuits composed of these homologous neurons (61). James Newcomb had studied the swim CPG in the nudibranch, *Melibe leonina* for his MS thesis (109). He joined Paul Katz's lab for his PhD and showed that neurons homologous to the DSIs are present in *Melibe*, but are not part of the swim CPG and instead provide extrinsic modulation to the *Melibe* swim CPG (110).

Work in Paul Katz's lab later showed that the same (homologous) neurons could have different functions in different species, even when the swimming behaviors were homologous (shared by a most recent common ancestor) (111-113). This means that while the neurons and behaviors are homologous, the synaptic connectivity has diverged, demonstrating that neural circuitry represents a different level of biological hierarchy from behavior and can have its own evolutionary history (114).

Studies on the evolution of neural circuits underlying behavior are increasing in number (115). For example, research has explored the evolution of neural circuits underlying calling songs, mate preference, and food preference in several drosophilid species (116, 117). This growing body of comparative work is fueled in part by the application of molecular tools originally developed in traditional model organisms to closely related species.

Network storage of overlapping memories

In the 1960's and 70's several laboratories started using a variety of gastropods, such as *Aplysia* (118), *Hermissenda* (119), *Pleurobranchaea* (120), and *Lymnaea* (121), for

neurophysiological studies of the neural mechanisms underlying learning and memory (Fig 5B). Given Getting's pioneering work building a computational model of the *Tritonia* CPG (82), this preparation appeared to be fertile ground for advancing synaptic studies of learning mechanisms to the network level. After completing his PhD training with Eric Kandel, Bill Frost joined Peter Getting's lab to explore this topic in *Tritonia*. A 1971 behavioral study by Dennis Willows had demonstrated sensitization and habituation of the escape swim behavior (122). Over the following years, a series of studies expanded our knowledge of *Tritonia's* non-associative learning abilities, including habituation (123-125), dishabituation (126), and sensitization (127). When swim-evoking stimuli are delivered successively at 2-minute intervals, the first stimulus produces sensitization, evident as a quickening of swim onset, quickening of gill and rhinophore withdrawal latencies, lower swim threshold, more swim cycles, and increased jump height off the substrate as the swim begins (127, 128). As trials continue, the number of cycles per swim steadily decreases due to habituation, along with an increase in swim threshold and a lengthening of cycle period (129, 130). In many cases latency sensitization persists even as cycle number habituation becomes fully developed, indicating that these two forms of learning are mediated by separate network mechanisms (130, 131). Attempts have also been made in *Tritonia*, though with limited success, to test for classical conditioning (122, 132, 133).

Electrophysiological studies have identified two circuit modifications associated with *Tritonia's* swim sensitization. First, an initial swim stimulus induces long-lasting elevated tonic firing (up to 1 hour) in the serotonergic DSI neurons of the swim CPG (94). Directly driving one or two DSIs at a similarly elevated tonic rate produces a shortening of onset latency for the swim motor program, indicating a key role for these modulatory neurons in this feature of sensitization. More recently, large-scale optical recording with voltage sensitive dyes revealed that sensitization also involves a serotonin-mediated expansion of the number of pedal ganglion neurons that burst during the swim rhythm (134, 135).

Less is known about the cellular mechanisms mediating habituation of the *Tritonia* escape swim. Like in many other systems, the synapses made from the afferent neurons to network interneurons decrement in strength with repeated intracellular stimulation (136). Additionally, the fact that cycle number habituation produced by stimulation of tail afferent neurons generalizes to swims evoked by stimulation of head afferent neurons suggests that the network plasticity mediating habituation is located, in part, in interneuronal pathways (123). There are many excellent reviews of the contributions of invertebrate systems to the neurobiology of learning and memory (50, 137).

Prepulse inhibition.

In mammals, an innocuous stimulus can potently inhibit awareness of and responses to a closely following startle stimulus. The mechanism of this phenomenon, termed prepulse inhibition (PPI), is of particular interest because a loss of PPI has been shown to occur early in the development of schizophrenia (138). An initial study established *Tritonia* as the first invertebrate demonstrated to display prepulse inhibition: a brief tactile prepulse powerfully inhibits the ability of a closely following aversive tail stimulus to trigger the escape swim (139).

Further work identified the first cellular mechanism for prepulse inhibition in any species: prepulse-elicited presynaptic inhibition of transmitter release from the afferent neurons that initiate the startle response. This process is mediated by a newly identified inhibitory interneuron, Pl9 (140). Subsequent studies in vertebrates have identified similar mechanisms, indicating its universality across phylogeny (141, 142). Additionally, a later study in *Tritonia* identified a second contributing cellular mechanism: prepulse-elicited conduction block of incoming afferent neuron action potentials conveying the startle stimulus to the brain, also mediated by Pl9 (143).

Drug-induced hallucinations.

Sometimes unanticipated results lead to new research directions. Several years ago, Cindy Brandon in Bill Frost's lab injected some *Tritonia* with the psychostimulant amphetamine and observed that, in the minutes to hours following the injection, these animals would occasionally launch spontaneous swims in the absence of an eliciting skin stimulus. Such spontaneous swims were never observed when the same animals were injected with saline. A systematic examination of the swim circuit revealed that these drug-induced swims originated from spontaneous bursts of action potentials in the S-cells, the sensory neurons that typically respond to the animal's seastar predators by firing to trigger the escape swim. In humans, strong or repeated doses of amphetamine and its derivative methamphetamine can elicit hallucinations of aversive skin stimuli. This study speculated that amphetamine might induce similar effects in *Tritonia*, causing the animal to launch escape swim responses to false perceptions, or unconscious hallucinations, of predator contact (144).

This discovery was particularly exciting because the electrophysiological mechanisms underlying hallucinations are poorly understood. A better understanding of these mechanisms could lead to improved therapeutic approaches to manage unwanted hallucinations in humans, such as those associated with schizophrenia. The study further identified a possible triggering mechanism for *Tritonia's* false perceptions. Amphetamine was found to induce plateau potential properties in the sensory neurons mediating the escape swim, rendering them sufficiently unstable that they occasionally underwent spontaneous population bursts. These bursts, interpreted by the nervous system as predator contact, then triggered escape swims. The amphetamine derivative (+/-)-3,4-methylendioxymethamphetamine (MDMA) was recently tested in octopus and found to induce pro-social effects (145), which is similar to the effect it has in humans even though *Octopus bimaculoides* is normally non-social. The work on molluscs demonstrates that probing divergent nervous systems with drugs that affect the same neurotransmitters can help uncover general principles and mechanisms underlying what were thought to be uniquely human experiences.

Conclusions and Perspective

Many foundational discoveries in neuroscience and biology are the result of historical happenstance. For instance, the extensive research on *Tritonia* began from a chance encounter a graduate student had with a pet slug at a marine lab. Similarly, the widespread study of the nematode, *Caenorhabditis elegans*, and the fruit fly, *Drosophila melangaster*, trace back to

pivotal encounters and choices made by Sydney Brenner sixty years ago (146) and Thomas Hunt Morgan more than a century ago (147), respectively. Unlike *C. elegans* and *Drosophila*, which are used as model animals in thousands of labs world-wide, *Tritonia* has been the focus of fewer than a dozen labs over its entire history as a research subject. This is partly because the animals are difficult to culture in the lab (148). Consequently, working with this species typically requires collecting them by diving or trawling, which is logistically challenging and expensive.

Among sea slugs, *Aplysia* comes closest to being a common laboratory animal. Eric Kandel's extensive work with *Aplysia* contributed significantly to his 2000 Nobel Prize in Physiology or Medicine (149). Despite the initial challenges in culturing *Aplysia*, animals of defined ages, raised from eggs, are now available from the federally funded National Resource for *Aplysia* at the University of Miami. In contrast, *Berghia stephanieae*, a nudibranch with a two-month generation time can be raised inexpensively in bulk (150). *Berghia* therefore presents a potential path forward for developing the tools needed to keep gastropod research on par with research on other standard laboratory species. The *Berghia* genome has been sequenced (151) and efforts led by Paul Katz and collaborators are underway to develop molecular tools to make *Berghia* a viable laboratory model.

Although the early advantages of working on neural circuits composed of giant neurons have been superseded by modern genetic, optogenetic, and connectomic techniques available in model invertebrates, there are important reasons to include gastropods in the pantheon of standard neuroscience organisms. First, with about 10,000 neurons, the sea slug brain is of intermediate complexity between *C. elegans* (302 neurons) and *Drosophila* (~100,000 neurons). Second, their large individually identifiable neurons offer a utility not attainable in most other invertebrates. Third, principles of neuroscience need to be tested across a broad range of phyla to determine if they are universal or phylogenetically constrained. For example, research on *C. elegans* and *Drosophila* concluded that the transcription factor unc-4 specifies cholinergic neurons (152, 153). However, in *Berghia*, unc-4 is expressed in serotonergic neurons, not cholinergic neurons, indicating evolutionary shifts in the gene regulatory networks specifying neuronal types (56). Finally, as members of the phylum Mollusca, which includes the highly intelligent octopus, studying sea slugs may provide insights into the principles underlying the function and development of the most complex brains and highest cognitive capacities among the invertebrates (154).

Work on *Tritonia* has demonstrated the outsized effect that studying a unique animal can have on neuroscience. Although the days may have passed when a graduate student can simply impale giant neurons of a sea slug with a microelectrode and make fundamental discoveries, we are now entering a period when techniques developed for a small number of "model organisms" are starting to be applied to a wider variety of species (Fig. 5) (155, 156). The legacy of Dennis Willows and Peter Getting exemplifies the degree to which universal principles can emerge from studying unconventional animals.

Figures

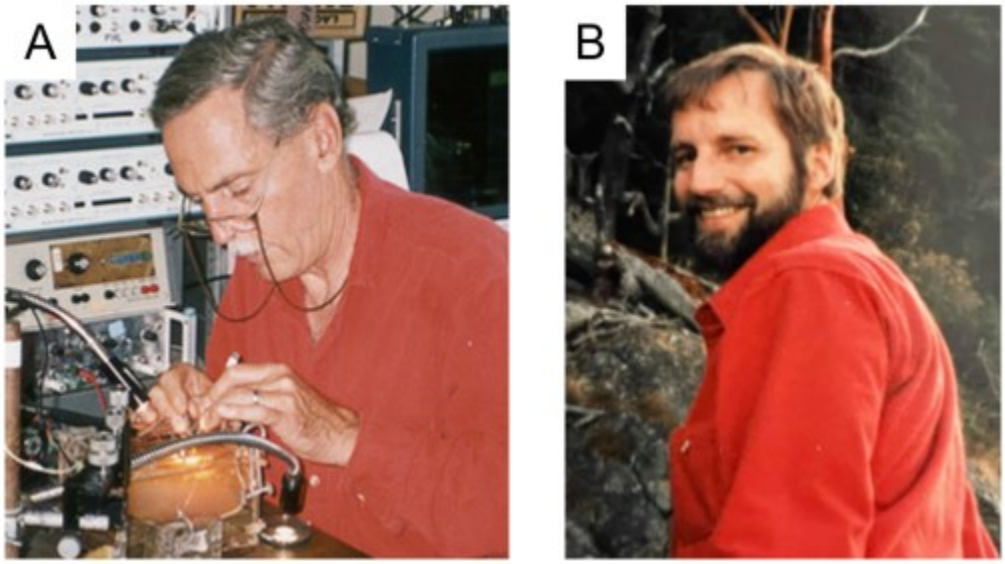


Fig. 1. A. Dennis Willows dissecting a *Tritonia* in 2000. Photo courtesy of Russell Wyeth. **B.** Peter Getting in 1986. Photo courtesy of Ingrid Getting Smith.

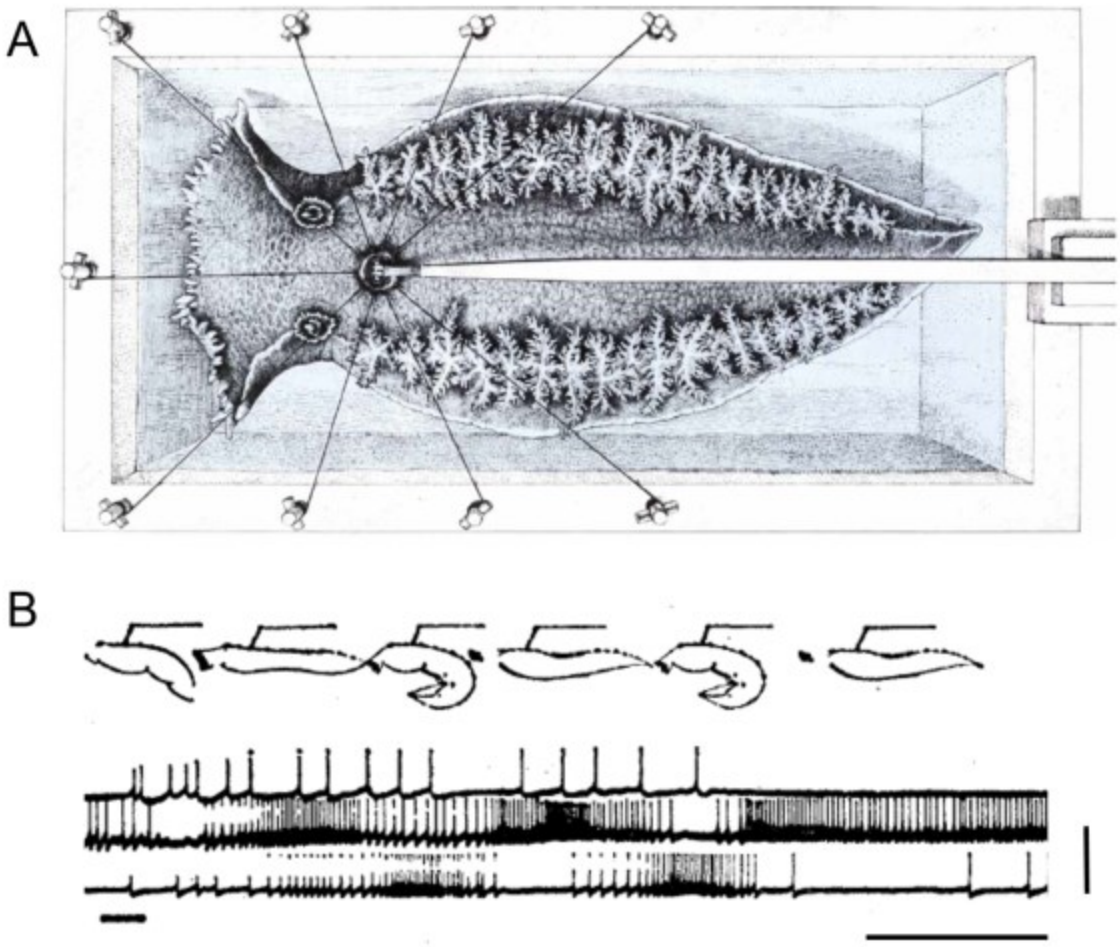


Figure 2. Intact *Tritonia* preparation. A. Dorsal view of the intact *Tritonia* preparation. The animal is suspended in a tank of seawater by threads attached to the edges of a surgical opening made above the brain, which is stabilized on a platform positioned beneath it. Anterior is to the left. Modified with permission from Ref (7) **B.** Sketches of a *Tritonia* viewed from the left side and three simultaneous intracellular microelectrode recordings during a swim episode elicited at the thick horizontal bar near the beginning of the traces. Scale bars 100mV and 5 sec. Modified with permission from Ref (8)

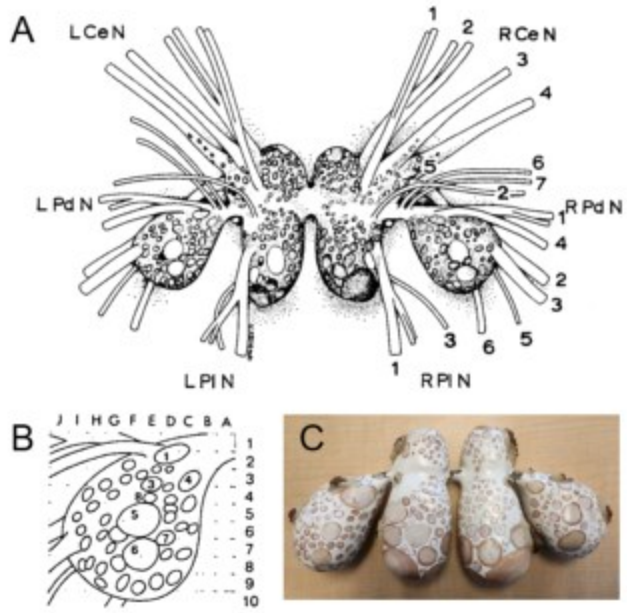


Figure 3. Representations of neurons and nerves of the *Tritonia* brain. A. Drawing of the brain with body wall nerves numbered. **B.** Left pedal ganglion illustrating a rubric for naming neurons and describing their locations. Neurons that were large and identifiable by soma position were given a number in the order that they were studied. The coordinate system of a letter and a number starting at the pedal-cerebral connective was used to describe the locations of other somata. **C.** A plaster model of a *Tritonia* brain commissioned by Dennis to show neurons in 3D. The model originally had flexible tubes that represented the nerves. A and B are modified with permission from Ref (41). C. is a photograph by PSK.

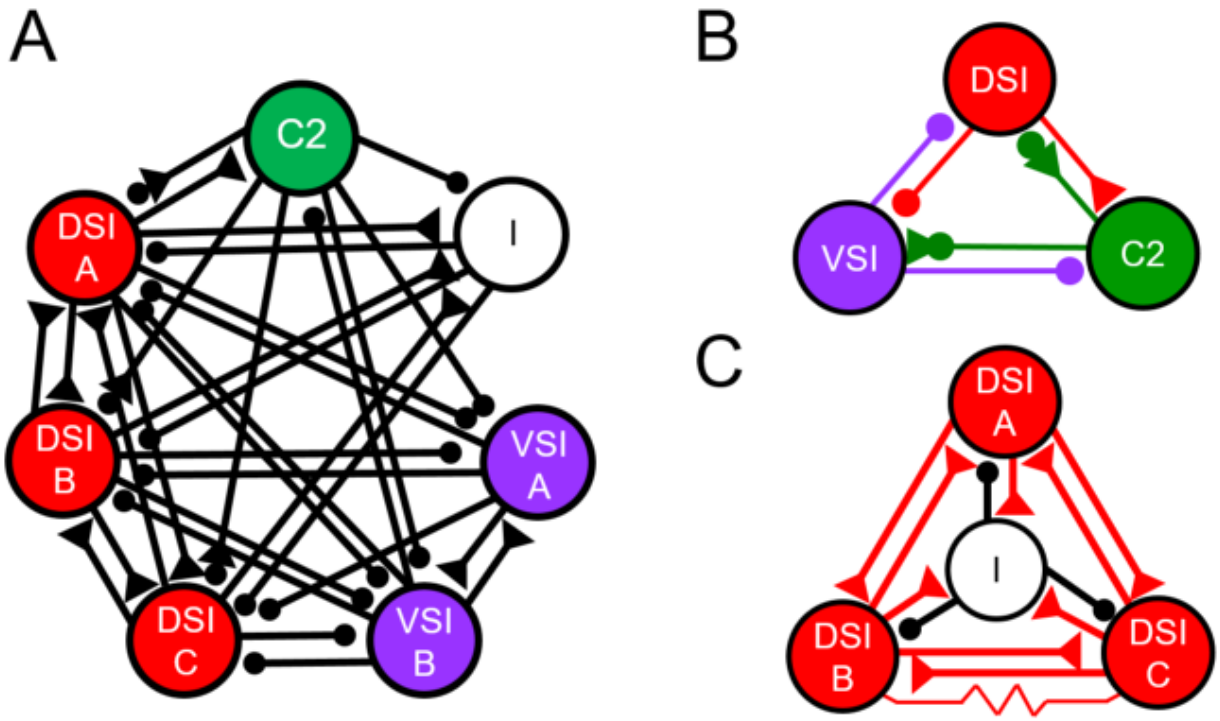


Figure 4. Polymorphic neural network. A. A representation of the anatomically defined network of neurons. **B.** The configuration of neurons that forms a functional swim CPG. **C.** A non-rhythmic configuration of the DSIs inhibiting each other indirectly.

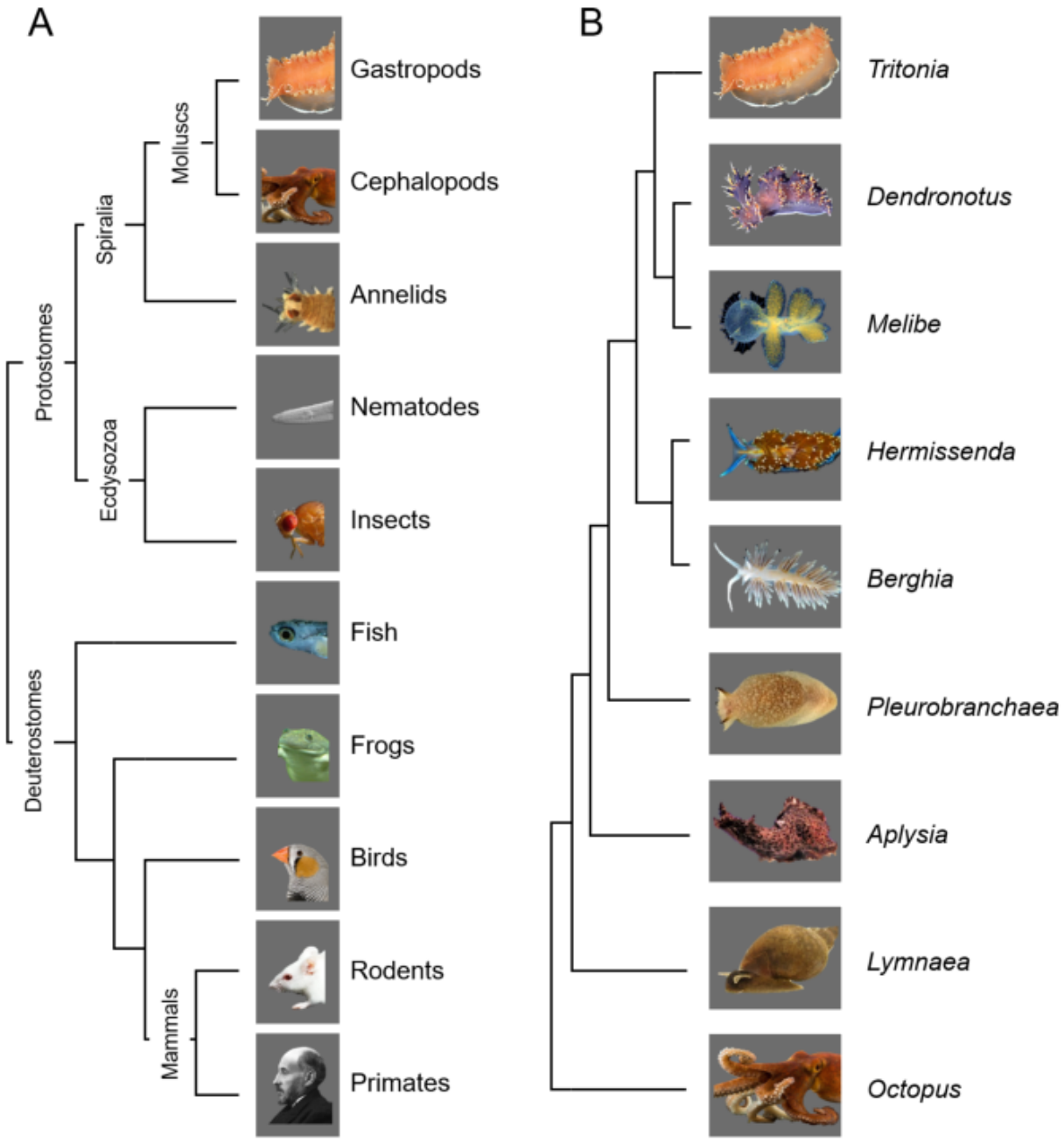
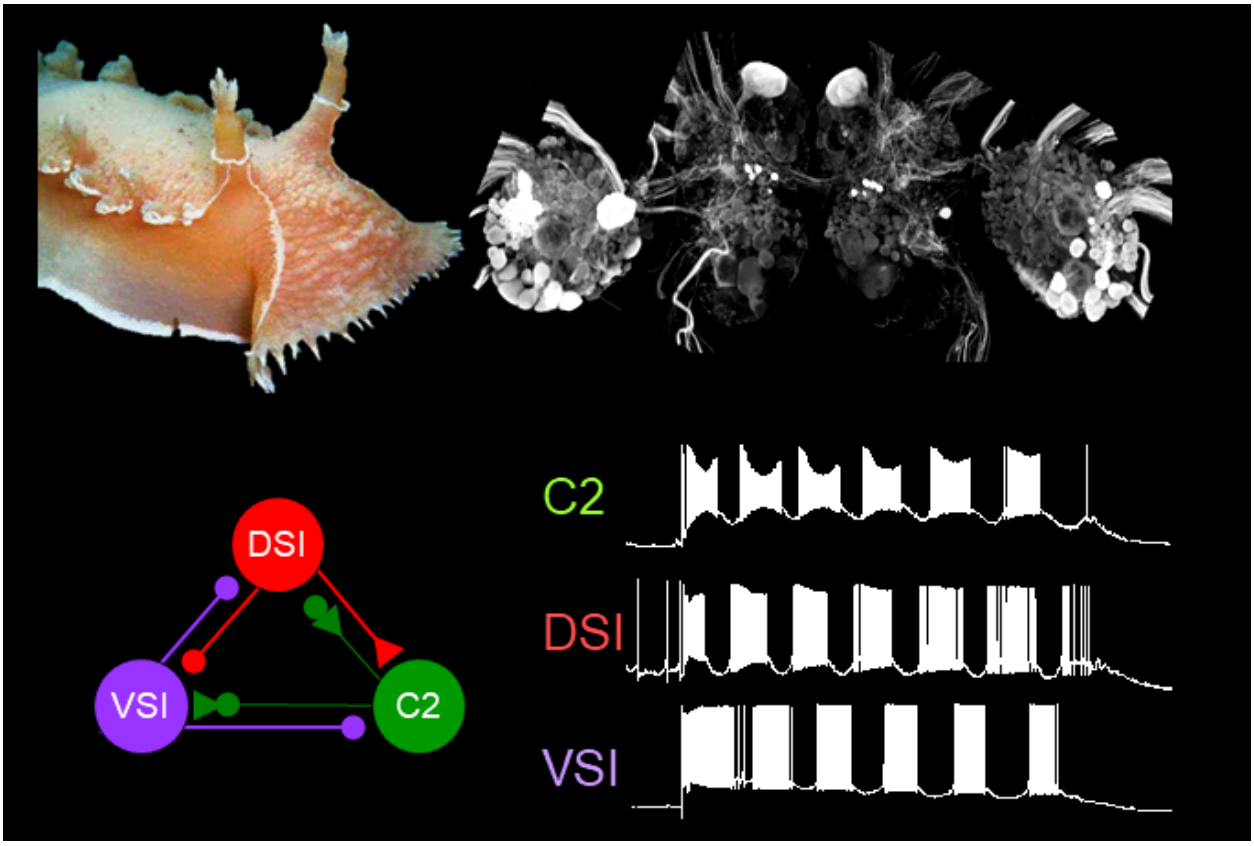


Figure 5. Phylogenies of species used in neuroscience research. A. Phylogenetic tree of all Bilateria. B. Phylogenetic tree of Mollusca showing relationships of species mentioned in this paper. The branch lengths have no meaning.



Graphical Abstract

Dennis Willows and Peter Getting made fundamental discoveries in neuroscience using the mollusc, *Tritonia* (top left), which has large, individually identifiable neurons as can be seen in the image of serotonin immunoreactivity (top left). The central pattern generator for escape swimming consists of just three cell types (bottom left). Intracellular microelectrode recordings from all three neurons shows the motor pattern underlying swimming (bottom right).

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