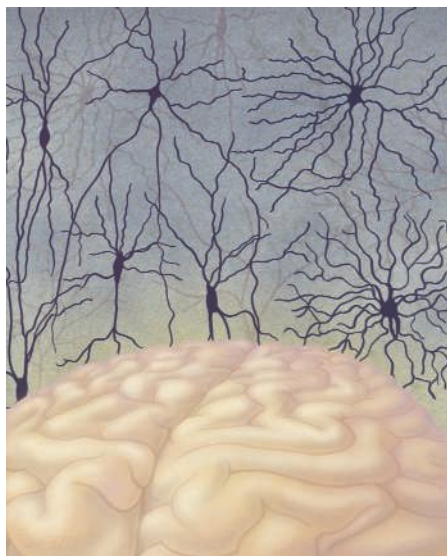




But how did they all get started? What did the first neurons and nervous systems look like, and what advantages did they confer on the animals that possessed them? These were questions the father of evolution, Charles Darwin, was ill-equipped to address. Although comparative neuroanatomy dates back to ancient Greece, the tools of the trade had not been refined much by the mid-19th century. In Darwin's day, anatomists were limited to gross observations of brains; they knew relatively little about the workings of nerves themselves. Only around the time Darwin died in 1882 were scientists beginning to develop stains to label individual cells for more detailed postmortem neuroanatomical studies. Methods for investigating the electrical properties of individual neurons in living brain tissue were still decades away, to say nothing of techniques for investigating genes and genomes.

In addition, there is some intellectual inertia that may need to be overcome, some researchers say. "If you look at any other organ or structure, people easily assume it could evolve multiple times, ... but for some reason, people are stuck on [a single origin] of neurons," says Leonid Moroz, an evolutionary neurobiologist at the Whitney Laboratory in St. Augustine, Florida.

Like nervous systems, nerve cells come in many varieties. Neurons are easy to recognize but somewhat slippery to define. They all share directionality—i.e., the ability to receive information at one end and transmit information at the other. Electrical excitability is another defining feature; a neuron can regulate the flow of ions across its outer

possibilities, and they're not mutually exclusive, Arendt says. Moroz agrees: "Neurons may have appeared in multiple lineages in a relatively short time."

Consistent with this idea, some crucial components of neurons exist in many cell types that predate the first neurons. Voltage-gated ion channels, tiny pores that control the flow of ions across a neuron's outer membrane to create electrical signals, can be found in bacteria and archaeobacteria, notes Robert Meech, a neurophysiologist at the University of Bristol in the United Kingdom. And in the 1960s, researchers found that when the single-celled *Paramecium caudatum* bumps

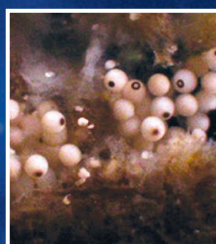
THE YEAR OF
DARWIN



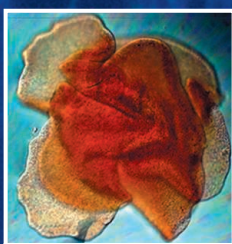
This essay is the seventh in a monthly series. For more on evolutionary topics online, see the Origins blog at blogs.sciencemag.org/origins. For more on the nervous system, listen to a podcast by author Greg Miller at www.sciencemag.org/multimedia/podcast.

EARLY ANIMAL EVOLUTION

○ Possible origin of neurons ○ Possible origin of centralized nervous system



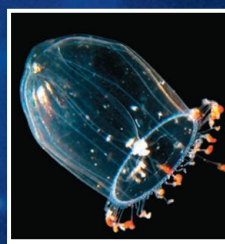
Porifera (Sponges)



Placozoa



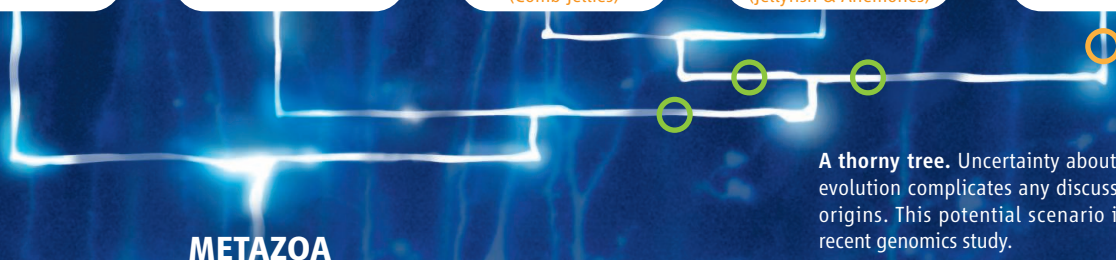
Ctenophora
(Comb Jellies)



Cnidaria
(Jellyfish & Anemones)



Bilateria (all animals
with bilateral symmetry)



METAZOA

A thorny tree. Uncertainty about early animal evolution complicates any discussion of neural origins. This potential scenario is based on a recent genomics study.

into an obstacle, a voltage change sweeps from one end to the other, much like the “action potentials” that convey a signal down the length of a neuron. In *Paramecium*, this electrical blip reverses the beat of its cilia, temporarily altering its course. Electrical excitability, it seems, evolved long before neurons made it their specialty.

On the brink

To hunt for additional clues about neuron evolution, researchers have turned to some of the most primitive animals alive on Earth today: sponges. Many scientists think these marine and freshwater filter feeders are the living creatures most similar to the common ancestor of all animals. And to many researchers, sponges look like animals on the verge of a nervous breakthrough. Sponges don’t have a nervous system, or even neurons, but they do have a surprising number of the building blocks that would be needed to put a nervous system together.

Researchers working to unravel the genome of the marine sponge *Amphimedon queenslandica* reported in *PLoS ONE* in 2007 that these animals contain the genetic blueprints for a set of proteins typically found on the receiving side of a synapse. In neurons, these proteins provide a scaffold that anchors neurotransmitter receptors to the cells’ outer membrane. Yet electron microscope studies have failed to find synapses in sponges. And although their genomes contain genes for some neurotransmitter receptors, sponges appear to lack the type of receptors used for most excitatory neural communication in other animals. Thus, the function of these synaptic scaffold

folding proteins in a sponge is a mystery, says Kenneth Kosik, a neuroscientist at the University of California, Santa Barbara, who led the study.

Last year, the *Amphimedon* genome yielded another surprising find. A team led by Bernard Degnan of the University of Queensland in Brisbane, Australia, reported in *Current Biology* that cells in the sponge’s larvae express a handful of genes that spur neural precursor cells to develop into full-fledged neurons in more complex animals.

“I think everybody agrees that nervous systems were at first diffuse and then evolved to be centralized. ... But there’s no consensus yet on exactly when this happened.”

—Detlev Arendt,

European Molecular Biology Laboratory

Inserting the sponge version of one of these genes into frog embryos and fruit fly larvae led to the birth of extra neurons. Degnan suspects that the cells that express them might be a type of protoneuron. These cells sit on the outer surface of the sponge larvae, and Degnan speculates that they may somehow help the free-floating larvae sense their environment and find a suitable place to settle down and metamorphose into their adult form.

Physiological experiments with sponges have also turned up signs of neural foreshadowing. Some sponges, for example, generate action potentials. In a 1997 *Nature* paper, Leys and Mackie reported that when the glass sponge *Rhabdocalyptus dawsoni* gets bumped or detects sediment in the water it filters for food, a voltage change sweeps across its body, and the cilia that pump water through the sponge’s body shut down. (The glass sponge is essentially one giant cell with a continuous, weblike intracellular space.) This electrical blip lasts about 5 seconds, compared with a millisecond or so for most action potentials in neurons, but it seems to accomplish the same basic goal as a reflex mediated by neurons: generating a coordinated response to an external stimulus.

All in all, says Leys, sponges provide a tantalizing picture of what an animal on the brink of evolving a nervous system might look like. Their cells have many of the

right components, but some assembly is still required. And although they have a wider behavioral repertoire than most people realize, Leys says, their “reflexes” are far slower than those of animals with a nervous system.

But some researchers argue that sponges aren’t the most primitive living animals. In one controversial study, published in the 10 April 2008 issue of *Nature*, a team of European and North American researchers

CREDITS (FROM LEFT TO RIGHT): (BACKGROUND) DR. JONATHAN CLARKE; WELLCOMER IMAGES; BRYONY FAHEY; ANA SIGNOROVITCH/VALE; STEVEN G. JOHNSON/WIKIPEDIA; KEVIN RASKOFF, 2005; JENNY HUANG/WIKIPEDIA

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reported that their analysis of 150 gene fragments from each of 77 animal taxa suggested that ctenophores, not sponges, are the lowest branch on the animal tree of life. Ctenophores, or comb jellies, are translucent, bloblike marine organisms that bear a passing resemblance to some jellyfish. Like true jellies, ctenophores have bona fide neurons and a simple netlike nervous system. Their position at the base of the animal family tree—if it stands up—would shake up many researchers' views on nervous system evolution.

Among the unpalatable implications, in the eyes of some researchers, is that if ctenophores came before sponges, the

neurobiologist at the University of Montreal in Canada: "The potential is there. How much they use it is what we have to figure out."

Getting a head

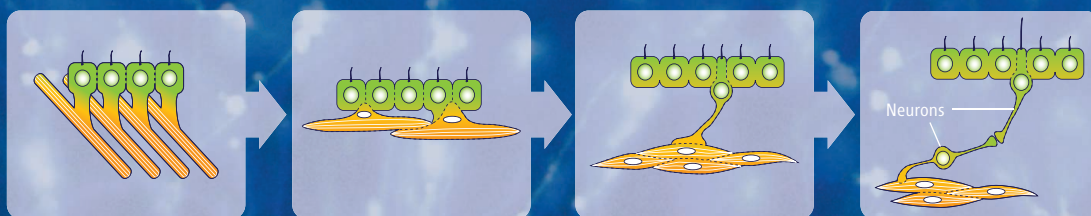
Just as sponges, comb jellies, and sea anemones may hold clues to how the first nerves and nerve nets arose, other creatures may shed light on the evolution of more complex neural circuitry. "I think everybody agrees that nervous systems were at first diffuse and then evolved to be centralized," with a concentration of neurons in the front end of the animal—that is, a brain—and a nerve cord connecting it to the rest of the body, says Arendt. "But

possibilities," he says. Because most but not all modern bilaterians have a centralized nervous system, there will be awkward implications no matter what. If the bilaterian ancestor had a diffuse nervous system, centralized nervous systems must have originated multiple times in multiple bilaterian lineages—a far less parsimonious scenario than a single origin. On the other hand, if the ancestor had a centralized nervous system, several lineages, including that of *Saccoglossus*, must have later reverted to a diffuse nervous system—an apparent downgrade that's hard to explain.

The puzzles don't end there. Fast-forwarding a bit in evolutionary time raises a

ORIGINS OF NEURONS

One way to build a neuron. Neurons may have arisen from multifunctional cells—like those in a jellyfish's bell (far left)—that gradually became more specialized.



assorted nervous system components that have turned up in sponges may not be foreshadowing after all but rather the remnants of a nervous system that was lost after the sponge lineage split off from that of ctenophores.

What's new, jellyfish?

Another contender for most primitive animals with a proper nervous system are cnidarians, a group that includes the true jellyfish, corals, and sea anemones. As in ctenophores, the nervous system of cnidarians is often described as a "nerve net." This description is apt for anemones, which have a diffuse web of neurons with no discernible concentration of neurons in any one place. But some jellyfish, such as the bell-shaped *Aequorea victoria*, are more organized, with clearly defined bundles of nerves running around the base of the bell.

Cnidarian neurons generate action potentials and release neurotransmitters to communicate across synapses. The genome of the starlet sea anemone, *Nematostella vectensis*, reveals a surprisingly large array of genes encoding enzymes that synthesize or break down neurotransmitters, as well as receptors for these signaling molecules (*Science*, 6 July 2007, p. 86). The genome hints at a complexity of neural signaling similar to that seen in more complex animals, says Michel Anctil, a comparative

there's no consensus yet on exactly when this happened." Arendt and others have argued that a centralized nervous system existed in the ancestor of all bilaterally symmetrical animals, or bilaterians.

Studies dating back to the early 1990s have found that several genes involved in shaping the central nervous system as it develops in fruit flies are expressed in a similar pattern and play a similar role in nervous system development in vertebrates and in distantly related invertebrates such as annelid worms. That implies that these genes were already present in the last common ancestor of all these creatures—the ancestor of all bilaterians—and suggests to Arendt and others that this ancestor had a centralized nervous system.

But not everyone is so sure. Christopher Lowe of the University of Chicago in Illinois and colleagues have found that *Saccoglossus kowalevskii*, a wormlike creature that belongs to the group of invertebrates most closely related to vertebrates, the hemichordates, has many of the same neural development genes expressed in a similar pattern. Yet *Saccoglossus* has a mostly diffuse nervous system. If having the genes and expressing them in a given pattern isn't sufficient to establish a centralized nervous system, that leaves open the possibility that the bilaterian ancestor had a diffuse nervous system, Lowe says. "I would argue that we have a range of

new set of questions. What is the origin of the myelin insulation that speeds conduction down axons and ensures the fidelity of neural signals? Or of the glial cells that are proving to have important roles in brain function and appear to be more numerous in complex nervous systems?

For that matter, how many ways are there to build a complex brain? Aristotle's notion of a *scala naturae*, or natural ladder, influenced the thinking of researchers well into the 20th century, says R. Glenn Northcutt, an expert on vertebrate brain evolution at the University of California, San Diego. "It was assumed that all vertebrates and invertebrates could be arranged in a linear series, with man and the angels at the top," Northcutt says, but "we now know that's just nonsense." Most researchers now agree that equally complex—but anatomically different—brains have evolved in birds, mammals, and other animal lineages, Northcutt says: "At least four or five times independently, ... major radiations of vertebrates have evolved complex brain structure." But whether brains that are put together differently operate on similar principles is still an open question. And then there is the enduring question of what, if anything, is special about the human brain. Perhaps the emerging clues about the long evolutionary path we've taken will one day help us decide where we are.

—GREG MILLER