Mind like a sponge: evolutionary paths to the brain

The human brain is one of the most complex arrangements of matter of which we know. This reflects the fact that despite current advances in neuroscience we still do not have a comprehensive understanding of the structure or function of the human brain. It is perhaps understandable that there is still much about the evolution of the brain, and how it came to be so complex, that remains a mystery. This complexity did not arise all at once. The lineage of the human brain can be traced back to the origin and subsequent assemblage of the key neural properties necessary for core functions of generating, sharing and propagating electrical signals.

One valuable way to study the evolution of the brain is the fossil record, as it provides insight into the shape and existence of macrostructures, including organs. However, studying the fossil record is a bit like looking at a series of snapshots that were taken many years apart. Some of these snapshots are blurry, and some have begun to show their age, making it difficult to stitch them together into a complete story. We also know that even modern brains come in many shapes and sizes, from the pea-sized brains of hummingbirds to the enormous brains of sperm whales, yet all are perfectly serviceable brains for their respective environments. We may also find an occasional fossilized brain, but there is a limit to the degree of detail that can be obtained from any fossilized tissue. Molecules such as proteins and neurotransmitters, for example, are well beyond this limit. To see more, one needs a different set of tools.

Modern techniques of molecular biology, including cladistics, have begun to reveal these hidden treasures of the brain’s history by allowing investigators to infer homology and relatedness among genes and gene clusters. A DNA sequence accumulates mutations at a gradual rate. By tracking the relative number and types of mutations from the DNA of various species, scientists can put together an evolutionary ‘tree’ that allows us to use the rates of specific mutations to infer relatedness among species. Thus, if we observe a group containing several species that all contain a particular mutation, we can infer that these species share a common ancestor that also carried that genetic mutation. This process identifies similar genes to those we possess and allows geneticists to estimate how much a gene may have changed over millions of years.

These sorts of techniques allow us to investigate the molecular evolution of the brain by framing the essential features that would eventually be incorporated into brains, and to ask when they arose. As a start, essential building blocks to build a brain would be those key features that provide a neuron with the ability to generate electrical signals and to transmit them to other neurons. For this brief article, we focus on three such features: ion channels, synaptic transmission and supporting myelination.

**Ion channels**

The functions of a brain are based on electrical signals, and the electrogenic capacity of the brain depends on ion channels. Early on, single-celled organisms such as bacteria and paramecia may have needed ion channels for maintaining osmotic balance, with the generation of electrical signals by some of these being a side benefit. Early variants of voltage-gated channels possessed characteristics consistent with modern channels, including a channel pore, domains that confer voltage sensitivity and an ion-selectivity filter. The mammalian brain contains ion channels to specifically transport (for example) calcium, sodium and potassium. The transport of these charged particles across the cell membrane is the driving force behind neuronal activation. As a more complex brain evolved, rates and types of ion flux began to regulate more advanced states.

Calcium channels play an essential role in transducing changes in membrane depolarization into intracellular calcium transients to drive internal signalling pathways and generate electrical responses. The evolution of calcium channels is well documented in bilaterian (animals with bilateral symmetry and a head region) species, yet little is known about calcium channels in non-bilaterian species. In order to fill this gap in evolutionary history, Moran and Zakon investigated

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**Abbreviations**: MBP, myelin basic protein; MYA, million years ago.
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the origins of calcium channel subunits by comparing the gene sequences for various subunits of *Nematostella vectensis* (sea anemones) with those of other species. Sea anemones, included in the phylum Cnidaria, have radially symmetric non-centralized nervous systems. According to this phylogenetic comparison among species of sea anemones, the first α1 subunit of calcium channels appeared very early in eukaryote evolution, at least as early as the common ancestor of Viridiplantae (plants and green algae), Apusozoa (flagellate protozoa) and Opisthokonta (a broad group containing both metazoans and fungi)\(^5\). Calcium channels can be classified as L, N/P/Q/R or T, depending on their voltage-sensitivity. It is believed that this separation occurred early in evolutionary history, before the common ancestor of choanoflagellates and metazoans. Choanoflagellates possess a single calcium channel gene that is ancestral to L and N/P/Q/R subtypes, but the evolution of T-type calcium channels is not known\(^5\).

Voltage-gated sodium channels are a foundation of mammalian brain function due to their abundance in the axonal processes of mammalian neurons. Sodium-permeable channels pre-dated the evolution of nervous systems and can even be seen in bacteria that evolved 3 billion years ago\(^7\) (Figure 1). However, the relationship between bacterial sodium-permeable channels and eukaryotic sodium channels is unclear\(^6\). Sodium channels appear to have developed in three different lineages: in bacteria, cnidarians and bilaterians\(^2\). Of these, the Na\(_1\) family of channels is the likely common ancestor of human sodium channels. Interestingly, sodium channels share a similar transmembrane structure with many calcium channels, and it is believed that sodium channels may have evolved from calcium channels (reviewed by Zakon\(^6\)).

Recent analysis of the gene clusters that code for potassium channels\(^1\) showed that several of these are more highly conserved than originally thought. Eight major classes of voltage-gated potassium channels are conserved between cnidarians and bilaterians, and at least six of these classes evolved before the cnidarian–bilaterian split, at least 570 million years ago (MYA)\(^1\). At least four of these genes can be found in the basal invertebrate *Trichoplax adhaerens*, of the Placozoa phylum, an early ancestor of Cnidaria, Porifera and Bilateria\(^1,8\).

Our early ancestors dating at least to the Ediacaran period, ~570 MYA\(^8\), contained some of the most rudimentary yet crucial building blocks for generating neural signals. The studies cited, and others, have demonstrated that ion channels evolved very early for regulatory activities such as maintaining osmotic balance. As organisms grew more complex, so did these ion channels. Thus the building blocks for regulating neural transmission were in place early in evolution, providing a solid foundation for building a brain.

Figure 1. A comparison between the eukaryotic (NaV) and bacterial (BacNaV) pore-forming units. The two sodium channels share many important features including voltage-dependent activation and ion selectivity. This implies that there was significant structural conservation during evolution. Biochemists now study the much simpler bacterial channels to better understand the human form and to aid in drug discovery.

Figure 2. An artistic reconstruction of the Ediacaran biota, which existed about 570 MYA. These species showed a wide range of morphological features and are considered the first bilaterians. They averaged 10 cm in length, but were mostly flat; the world was probably 2D at the time! 1, Eoporopita; 2, Charniodiscus; 3, Dickinsonia; 4, Arkarua; 5, Spriggina; 6, Praecambridium; 7, soft-bodied ‘trilobite’; 8, Kimberella. (Figure 1 A from R. Glenn Northcutt, Evolution of centralized nervous systems: Two schools of evolutionary thought. PNAS 2012 109: 10626-10633)
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Figure 3. Schematic diagram illustrating the convergence of several key features that characterize the evolution of nervous systems. Ion channels have been around for billions of years, but the emergence of cohesive multicellular life required a molecular organization that may have been conferred by proteins found in modern synapses. More recently, myelinated axons enabled rapid electrical signalling and occurred at about the time brains joined simpler nerve nets in the tree of life.

**Synaptic proteins**

Generating electrical signals, although useful, is of limited use for would-be brains without a means of sharing the state of this activity with neighbours. This was a basic requirement before true neural networks could evolve. Chooanoflagellates, which are considered to be the closest relative to metazoans (choanoflagellates and metazoans diverged at least 540 MYA), are unicellular colony-forming eukaryotes that contain many of the same genes that are found in neurons. These genes allow metazoans and choanoflagellates to coordinate activity with members of their colony, and appear to be highly conserved throughout evolutionary history and may have been most useful as multicellularity was selected for during evolution.

Sponges are considered to be the oldest living metazoan. Amazingly, the genome of the poriferan demosponge *Amphimedon queenslandica* contains almost a complete set of genes homologous with those that help form the mammalian synapse. The cells of sponges can co-ordinate activity through generating action potentials and by releasing chemicals in a way that is strikingly similar to the release of neurotransmitters from neurons. It seems that at this early evolutionary stage, nature had already produced many of the component parts needed to build a brain.

An interesting story of convergent evolution still being written concerns ctenophores (comb jellies). The lineage of basal metazoans remains poorly resolved (for example, see Moroz et al.), but it has been hypothesized that ctenophores are a sister taxa to all metazoans, or at least to cnidarians and bilaterians. What makes the evolutionary history of ctenophores particularly interesting is that ctenophores possess many of the same neural markers found in mammals that are usually identifiable only in more evolved metazoan phyla. For example, ctenophores have the ability to induce rapid inward calcium currents and raise calcium concentrations in muscle cells, most likely through the efficacy of L-glutamate as the neuromuscular transmitter. This idea is supported by the unparalleled diversity of glutamergic receptors found in ctenophores, which far exceeds the number of glutamate receptor genes in any other basal metazoan species. Moreover, ctenophores have a slightly different diversification of ion channels from that of other metazoans. Parahoxozoans share many potassium channel gene families with the Porifera, Cnidaria and Bilateria taxa, many of which are absent from ctenophores. A similar case can be made for calcium channels; parahoxozoans share L-type, T-type and N/P/Q/R-type channels, but ctenophores only have N/P/Q/R-type channels.

**Myelination and other specializations**

Some of the earliest identifiable fossils give us information about our early bilaterally symmetrical relatives. There is a debate whether the earliest fossils identified as bilaterians are actually bilaterians; several were later reclassified as protists. These fossils date back to Ediacaran biota, approximately 570 MYA. Some of these early organisms survived into the Early Cambrian era and gave rise to the early bony fish (for a representation of species from the Ediacaran period see Figure 2).

The evolution of bony fish begins an era where fossils can provide even more useful data on the extension of cephalization, the evolutionary trend whereby nervous tissue becomes concentrated at one end of the organism, eventually producing a head region with encapsulated brain. One example is that of *Haikouichthys*, one of the first fish fossils identified from the early Cambrian. Discovery of this genus has given much insight into the evolution of vertebrates, particularly craniates, to which *Haikouichthys* probably belonged. *Haikouichthys* was a jawless fish that possessed complex brain structures, including what appear to be advanced senses and a prototypical vertebral column.

Arguably, one of the most important vertebrate neuronal acquisitions was the evolution of the myelin sheath. The myelin sheath is a fatty layer that surrounds the axons of neurons and enables nerve impulses to travel the length of the organism (in some cases quite a formidable distance) at much higher speeds.

The evolution of myelin was dependent on its protein components, including myelin basic protein (MBP). The earliest evidence of MBP occurs in jawed vertebrates, at about the same time as the hinged jaw in placoderms, and appears to be absent from jawless fish. Acquisition of MBP set the stage for additional modifications, including the development of nodal aggregations of voltage-dependent sodium channels, enabling saltatory conduction. With myelination, fast neural synchronization and greater energy efficiency was suddenly possible in these newly ‘turbo-charged’ neurons, free to operate without the need to maintain...
massive ionic gradients or giant axons. These ‘first fish’ possessing this adaptive set of tools must have been formidable predators and artful dodgers.

Limitations

What we have sketched out in very broad strokes in this speculative article is limited by the fact that many of the comparisons are made against species that are themselves ancestral, and still evolving. The degree to which we can trace the brain’s origins is limited by many factors, including horizontal gene transfer, a process whereby genes may be swapped through asexual means. This means that the ‘tree of life’ metaphor that is often offered may be incomplete, and that some early branches may co-mingle their genetic material[15]. We also cannot say for certain that a gene performed similar functions in ancient creatures as it does in humans. But even with such limitations, a molecular phylogenetic approach is proving to be a useful frame for considering the problem of the early foundation of nervous systems, particularly in establishing the essential set of specialized features that are characteristic of modern brains.

Summary

The brain is a highly adaptive solution to the challenges of living on planet Earth. Although the fossil record indicates the early onset of symmetry and cephalization, the key adaptations of modern brains (ion channels, synaptic proteins, the ability to generate and quickly transmit electrical signals, and the development of an enclosed nervous system) that bloomed around the time of the Cambrian explosion were already well under way before there were nervous ‘systems’, with some features arising over billions of years of evolution (summarized in Figure 3). Some variants of these adaptations may have evolved and died out, perhaps many times, but enough of these features were adaptive that new species carried them forward as part of the brain’s molecular legacy, extending throughout the branches of the tree of life to our brain-bearing cousins, each adapted to their unique environment.

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