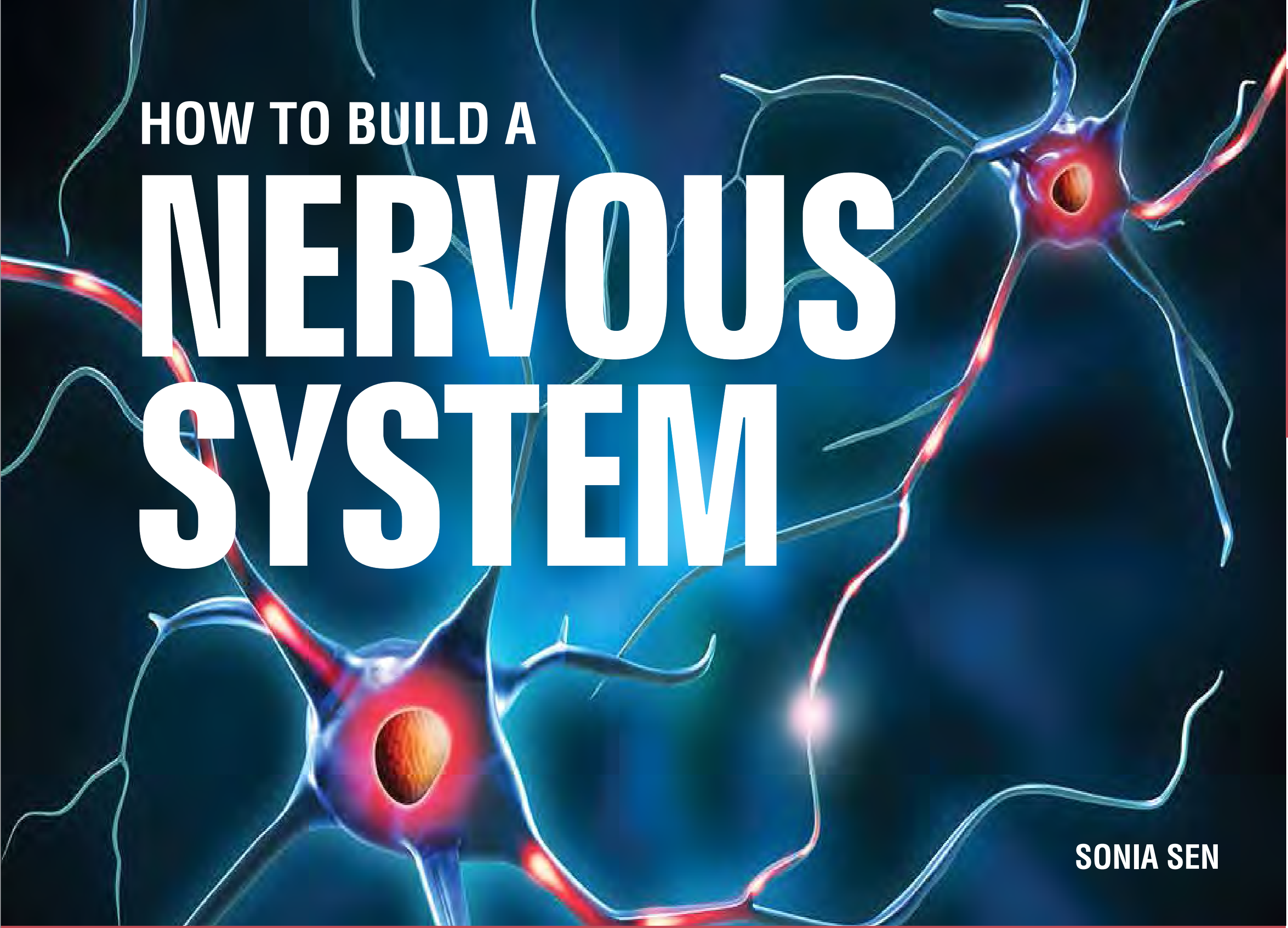
HOW TO BUILD A NERVOUS SYSTEM



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Animals constantly interact with their environment for the most vital of functions - finding food, avoiding predators or courting a prospective mate. What role does our nervous system play in these interactions? What do we know about this vital organ system and how it is made?

Some of the most exciting things about animals are their intriguing behaviours. Ants trailing behind each other, kingfishers diving to catch fish, lizards dropping their tails, cuckoos chasing crows, octopuses changing their colour and shape, spiders building webs, even people on the train holding their nose as it goes past a sugar factory… all these are examples of the fascinating things animals do to find food, avoid anything that is noxious, escape predators, attract mates, or rear their young.

Despite their apparent complexity, each of these behaviours involves three steps:

1. Sense the environment: Animals survey their environment through various 'sensory stimuli' such as light (through vision), sound (through hearing), volatile and non-volatile chemicals (through smelling and tasting) and pressure (through touch).
2. Process the sensory information: Once animals receive sensory information, they need to process it to make a decision about it – does the environment pose a threat, an opportunity for food, or a possible mate?
3. Produce a response: Once a decision is made, animals need to produce an appropriate behavioural response to the stimulus – avoid it, eat it, or mate with it!

These interactions between animals and their environment are mediated by the nervous system.

What is the nervous system?

Most multicellular animals, from jellyfish to human beings, possess some sort of a nervous system. While some of these are relatively simple, others are infinitely more complex. Despite these differences in complexity, their nervous systems are made up of essentially the same kinds of cells, and operate in similar manner.

Nervous systems act as communication networks within organisms. This ‘network’ is made up of special cells called neurons that are intricately connected to each other. Neurons have the unique ability to receive chemical information from one end, convert it into an electrical signal so that it passes very quickly through to its other end, and then convert it back to a chemical signal that the next neuron can pick up. This form of chemical communication between two neurons happens at junctions called ‘synapses’. This ability of neurons to transmit information rapidly is what allows you to quickly withdraw your arm when you touch a tumbler of hot coffee: the sensory neurons in your hand sense the heat, quickly relay this information to interneurons, which tell the muscles in your arm to contract (outlined in Fig. 1).

Have you noticed that this is like a simple electrical circuit? And while this is the simplest possible circuit, for a very simple behaviour, involving just three neurons, other circuits can involve many, many more neurons. Such circuits are often also intricately interconnected, giving circuit diagrams of even the simplest nervous systems a gargantuan complexity. Something else you might have noticed even in this very simple circuit is that all three neurons look very different from each other. This is another striking feature of nervous systems – neurons can be of the most diverse and beautiful shapes and types!

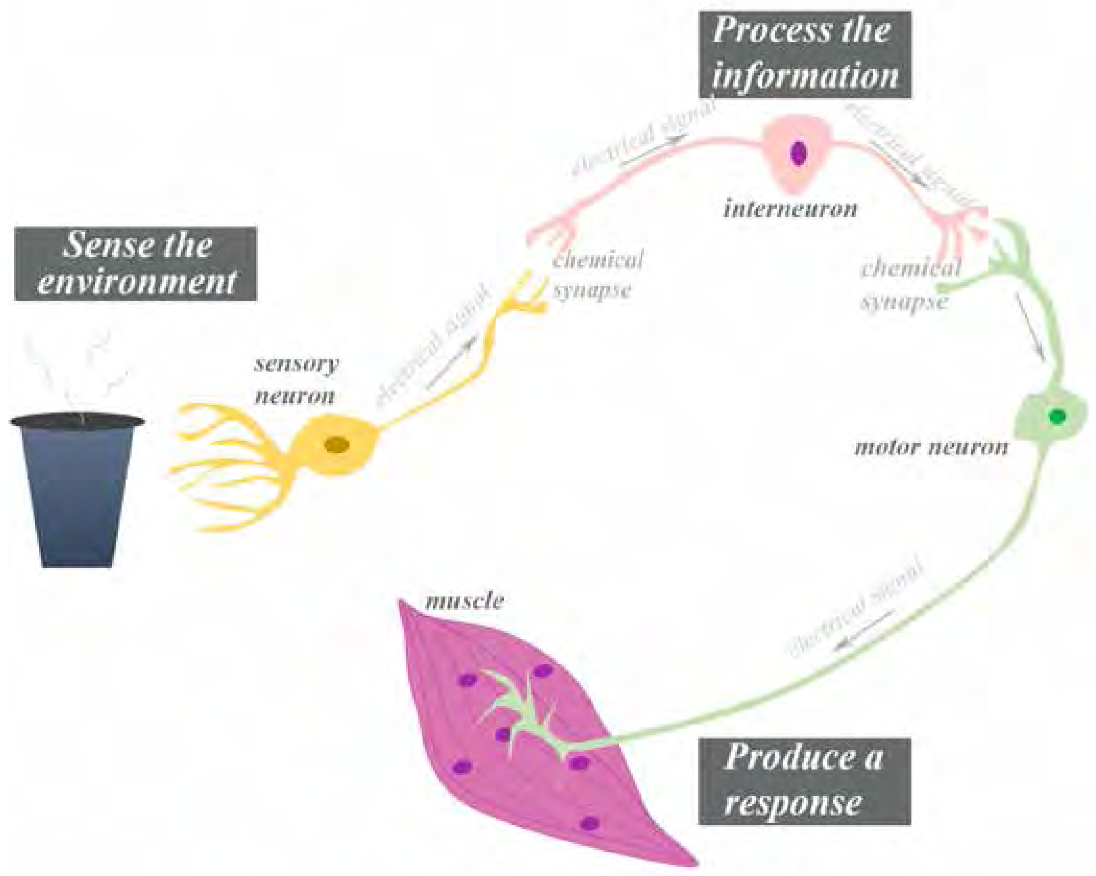

Figure 1. Animals interact with their environment through the nervous system. Sensory neurons in your fingers sense the heat of the coffee tumbler. They quickly relay this information to your spinal cord, where it is processed, and onto an interneuron, which in turn activates a motor neuron in the muscles of your arms, telling them to contract. Notice that all the communication between neurons happens at the synapses, through chemicals called ‘neurotransmitters’. These chemicals can either activate or shut down other neurons. The chemical information a neuron receives is converted into an electrical signal so that information from one end of the neuron is transmitted rapidly to the other end. In this way, through a three-neuron circuit, you are able to retract your hand very quickly from a hot coffee tumbler.

It's easy to see why over the centuries, scientists have been fascinated by nervous systems. How do neurons talk to each other? What are the circuits for different behaviours? How are these circuits built? How are memories stored in them? …The questions are innumerable! Countless people have worked on them and we have learned some extremely fascinating things!

Many ways of studying nervous systems

Scientists have used many approaches to study the nervous system. Studying the 'giant' neuron of squids, we have learnt how proteins control ion exchange across the cell membranes of neurons and how this allows neurons to generate the electrical pulses with which they transmit information rapidly[1]. Scientists have also tried to build circuit diagrams of entire nervous systems by tracing how individual neurons are connected to each other. As a result, we know the circuit diagram for the entire nervous system of the worm, *Caenorhabditis elegans*[2] and of the maggot[3] (the larval stage of the fruit fly, *Drosophila melanogaster*), each of which has 302 and 10,000 neurons respectively. Extensive studies are now underway to do this for parts of the mouse and human brains as well[4]. These studies will undoubtedly be more challenging to reconstruct given that mice have about 70 million neurons and humans have about 80 billion!

Within such complete circuit diagrams, scientists have also tried to trace 'sub-circuits' that are actually functionally important – for example, the three neuron circuits involving the hot coffee tumbler is a functional circuit. More complicated behaviours have more complicated circuits, and scientists use electrical probes inside individual neurons to painstakingly trace out entire functional circuits. One of the first few such studies led to a beautiful illustration of the entire circuit that controls the swimming behaviour of leeches[5]. This may appear mundane, but in reality, it represents a huge leap in our ability to work out the neural wiring circuits that underlie complex behaviours. With new technologies, we can now not only watch neurons when they are active, but also shut down or activate them individually merely by shining light on them or by a small change in the temperature[6,7]! This allows us to trace out more complicated functional circuits in complex nervous systems and, therefore, to understand and compare how animals recognise odours, process visual information, taste, fly, walk and even integrate these complex behaviours!

Fruit flies show us how to build a brain

Another approach has been to understand how these complicated circuits are built so that no wiring mistakes are made. In a previous example, the fact that everyone on a train smelled the volatiles from the sugar factory, recognised it as malodourous, and brought their hands up to hold their noses at roughly the same time means that all of them possess the same functional circuit for this sequence of events. That the neurons in one person are connected up in exactly the same way as they are in another means that there must be rules that allow such a complex circuitry to be built repeatedly in every person. What are the rules that instruct the formation of the nervous system and its complicated circuitry?

Over the last couple of decades, we have gained considerable knowledge about this process. This understanding comes not from studies in human beings, but from studying other animals such as mice, fish, fruit flies and worms. Though there are large differences in the nervous systems of these animals and the way they develop, there are many common principles that have emerged. In contrast to its insignificant size and less than flattering reputation in kitchens across the world, the contribution of the humble fruit fly to this understanding has been extraordinary!

With about 100,000 neurons, the nervous system of adult flies is rather complex. At first glance, its structure and the complicated connectivity seem devoid of any rules that could govern its construction. But research has shown that there **are** rules and some very simple ones too! So how does its egg, which is a single cell, go on to generate 100,000 neurons of different shapes and types, and how are they connected up correctly?

Making neural stem cells

To deal with this problem, the fly embryo first makes stem cells. Stem cells are a neat trick used in almost all tissues of nearly all developing embryos to increase the number and types of cells that can be produced. This is because when a stem cell divides into two, one of the cells becomes a specialised cell and the other is a copy of itself. This allows the stem cell to generate many specialised cells, while continuously replenishing its own numbers. The stem cells that make the nervous system in the fly embryo are called

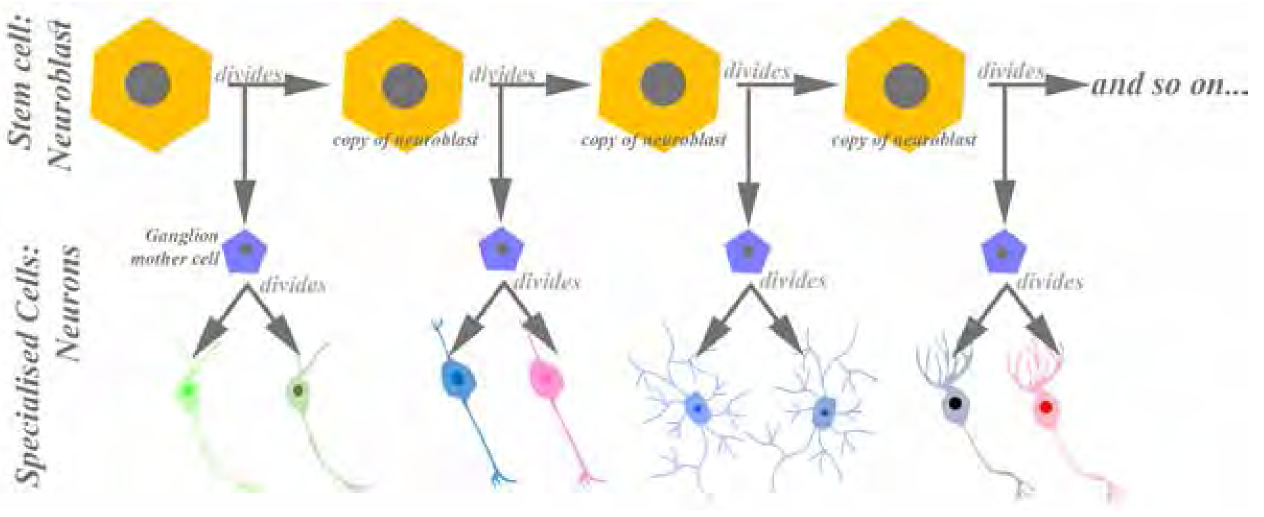

Figure 2. Stem cells in development. Stem cells are used in the development of many tissues to generate large numbers and types of cells. A stem cell divides asymmetrically: one of the cells is usually a specialised cell type, while the other is a stem cell. In the fly's nervous system, the stem cell is the neuroblast; and the specialised cell it produces with each division (the ganglion mother cell), divides once more to give rise to two neurons. Notice in this example that a single neuroblast has given rise to eight neurons with just four divisions.

'neuroblasts'. The specialised cells (called 'ganglion mother cells'), divide once more to give rise to two neurons that never divide again. This means that each time a neuroblast divides, it generates two neurons (as seen in Fig. 2).

Neuroblasts are formed very early in the development of the embryo. The fruit fly takes about ten days to metamorphose from an egg, through larval and pupal stages, into the adult fly. On the first day, the egg is shaped like a hollow rugby ball surrounded by a single layer of similar cells. Interactions between neighbouring cells cause some of them to enlarge and pop into the inside of the embryo. These enlarged cells are the neuroblasts. About 500 of them are formed along the entire length of the embryo, and go on to produce all of the 100,000 diverse neurons of the fly's nervous system!

How do such few cells produce all these different types of neurons?

Making diverse neuron types

Neuroblasts do two things to achieve this. First, each time a given neuroblast divides, it produces different neurons (instead of the same one over and over again). Second, each of the 500 neuroblasts generates a different set of neurons[8] (as seen in Fig. 3).

But what makes one neuroblast different from another? And what makes each of them act differently over time? Neuroblasts use a system that is akin to using phone numbers. Each person has a different phone number, dialling which connects you specifically to them – a person's phone number is thus their unique identity code. Similarly, each neuroblast can be identified by a unique code of genes that are switched on in it, and in no other neuroblast.

Changes over time are accomplished by a very interesting strategy. If each neuroblast makes different neurons as it ages, it must have a way of 'keeping time'. In fact, neuroblasts do exactly this by using a 'molecular clock'! A molecular clock is set up by genes being turned on and off, in a tightly regulated sequence, over time. For example, gene 1 turns gene 2 on and is itself switched off; gene 2 then turns gene 3 on and is itself switched off… and so on. This will result in a sequence of genes that are turned on – first gene 1, then gene 2, then gene 3… and so on. So, if a neuroblast was in the 'time window' of gene 1, it would generate a certain kind of neuron; whereas if it was in the 'time window' of gene 4, it would generate a different kind of neuron, and so on.

In this way, a handful of initially similar neuroblasts acquire unique molecular identity codes (**combination** of genes that are switched on in it) that make them different from each other. In addition, a molecular clock (**sequence** of genes that are turned on) makes them change over time[8]. As a result of these

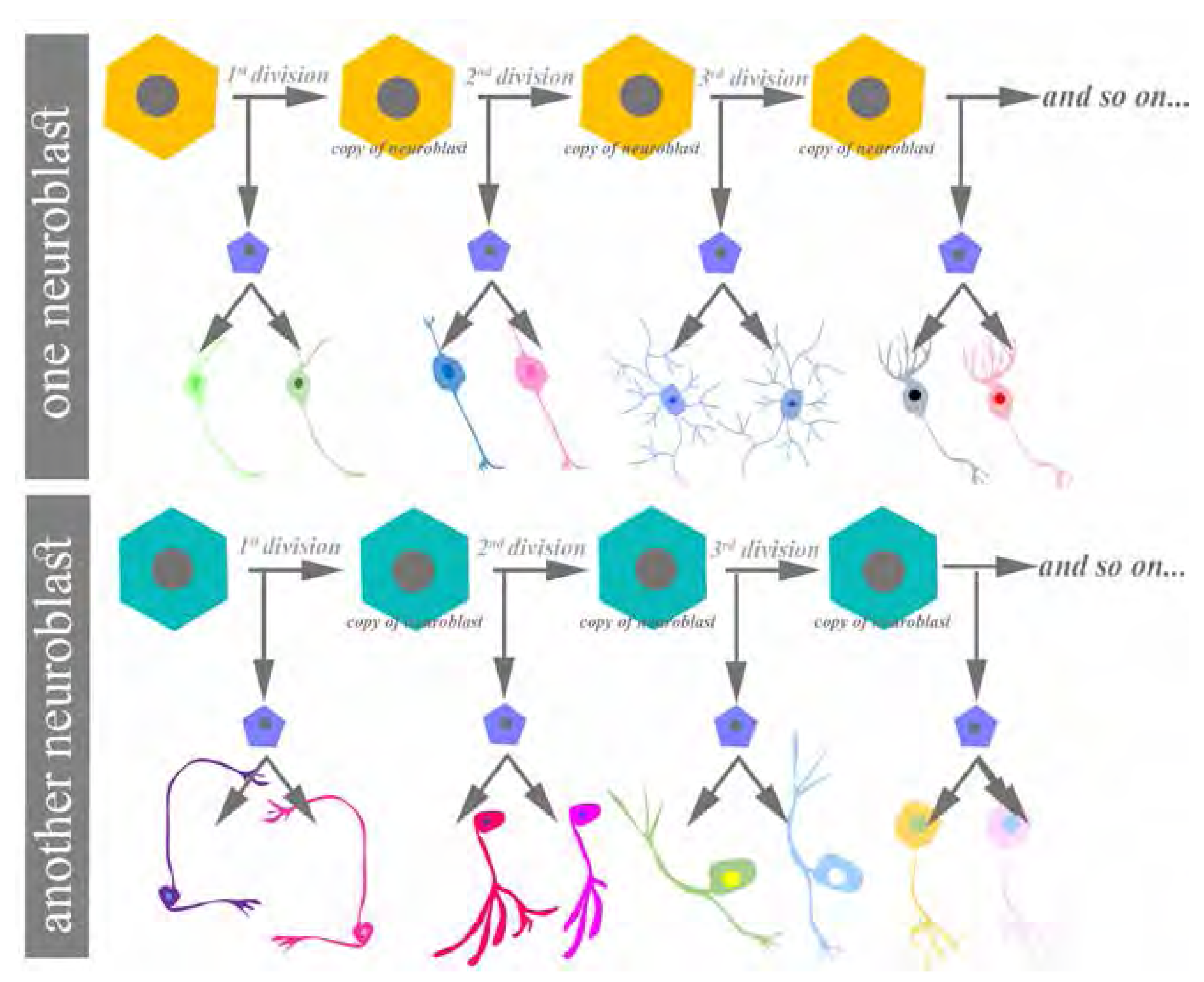

Figure 3. Many different kinds of neurons are produced from a small pool of stem cells. Each of the stem cells in the brain has a unique combination of genes switched on, and this makes each of them unique – like an identity code. This is represented as different coloured neuroblasts in the diagram above. Because each neuroblast is different, they can each generate a unique set of neurons. Over and above this identity code, another set of genes is switched on in a very precise sequence in the life of a neuroblast. This sequence allows a neuroblast to 'keep time', which it uses to generate different neurons at different times. In this image, you can see that with each division, different kinds of neurons are made. The interaction of these 'identity genes' with 'time genes', allows a few hundred neuroblasts to generate many thousands of different kinds of neurons!

interactions between genes over space and time, a few neuroblasts generate an amazing diversity of neurons in the brain!

Modules in the brain

Undoubtedly the most beautiful of principles that emerged from these studies has been that the brain does not have to be built piecemeal, but in modules. This is because neurons produced by a particular neuroblast tend to stay together and wire into the same functional sub-circuits in the brain. For example, a particular neuroblast called 'ALad1' in the fly brain makes about 120 neurons, all of which participate in the sub-circuit that allows a fly to smell. Similarly, another neuroblast called 'LALv1' produces another set of about 150 neurons that participate in the sub-circuit that allows the fly to process visual information while it flies[9]. This means that the fly brain does not have to have a strategy to control the wiring of 100,000 neurons, but only of about 500 modules of neurons. This reduces the wiring problem by many orders of magnitude (see Fig. 4)!

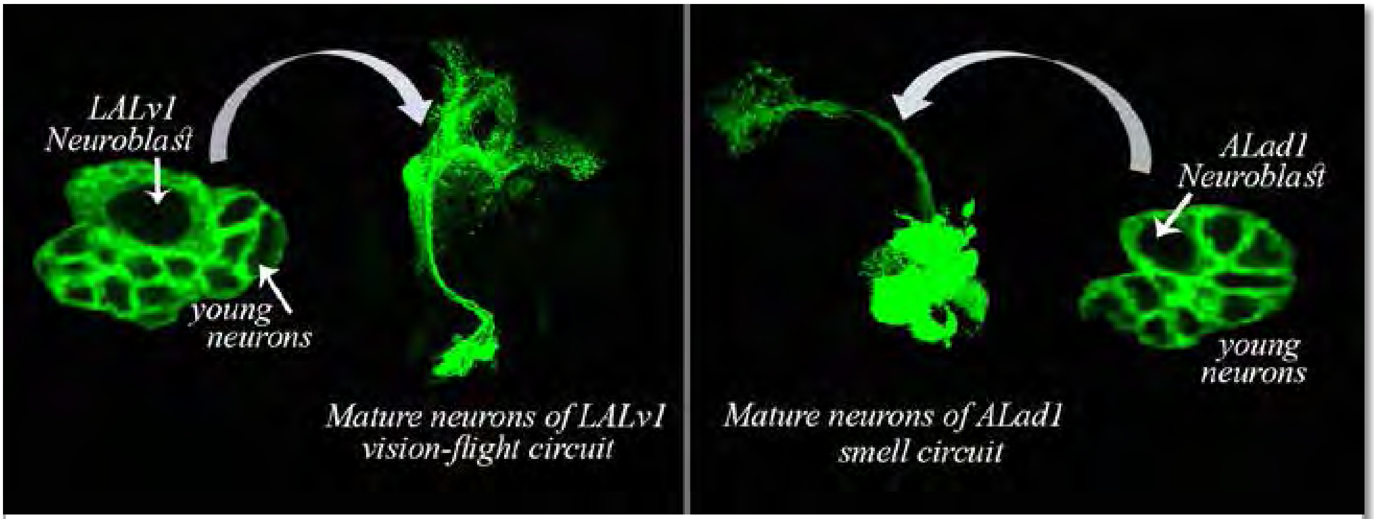

Figure 4. The brain is built in modules. Each neuroblast (the large cells) makes a series of neurons (the smaller cells) that initially stay together. Then, all of them wire into the same functional circuits. For example, all the neurons made by the LALv1 neuroblast wire into the circuit for processing visual information while the fly flies; all the neurons made by the ALad1 neuroblast wire into the circuit for smelling.

Similarities across animals

Is any of this of broader significance or are they peculiar to flies? The kinds of experiments that allowed the numerous scientists across the world to work this out are much harder to do in animals other than in flies. But as information trickles in from ants, bees, fish, mice, and even humans, it's becoming increasingly clear that the general principles are the same, i.e., in the construction of the nervous system, neural stem cells use molecular codes and molecular clocks to generate diverse neuron types; and it is likely that they do this in modules. In fact, in many cases, even the genes used to achieve this are the same! Even more amazingly, the wiring diagrams of many of the sub-circuits they produce are also strikingly similar (refer Fig. 5)! So it is indeed true that insights gained through experiments in unlikely species like the fruit fly are very informative and useful for understanding nervous systems in general.

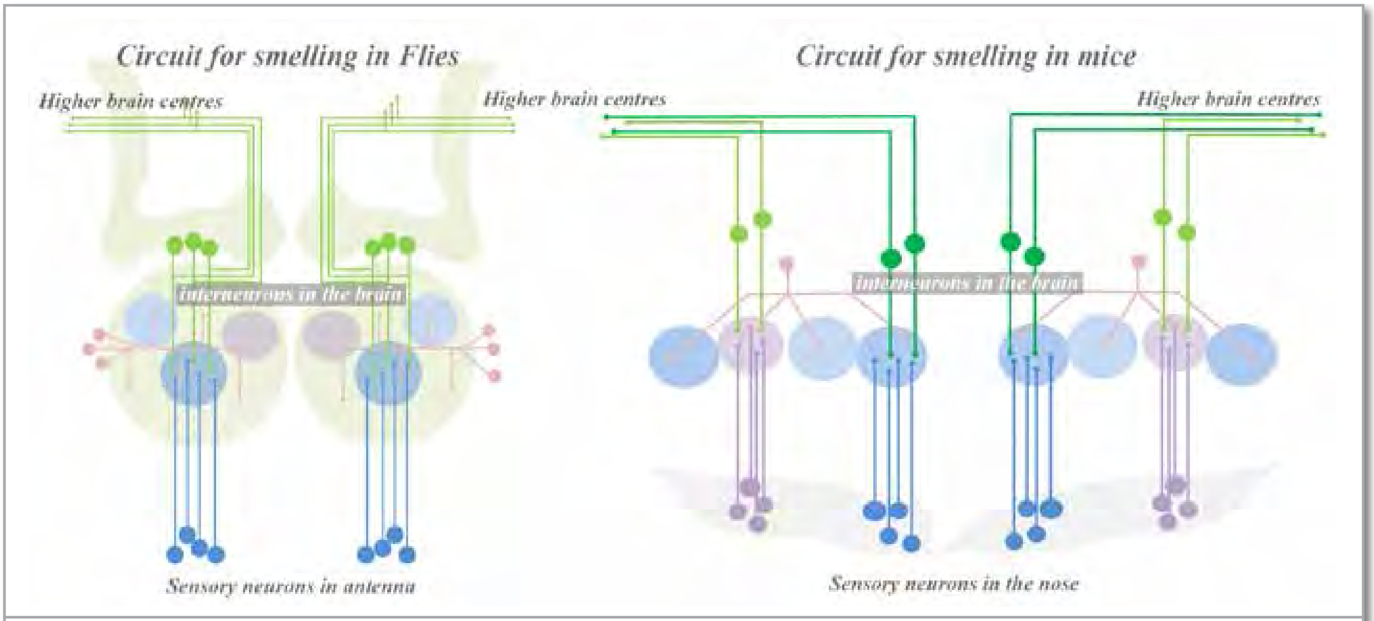

Figure 5. Circuits in different animals have similar wiring diagrams. Many functional circuits have the same kind of connectivity in different animals. For example, compare how sensory neurons in both the fly and the mouse connect to interneurons, transmitting information to higher brain centres. You'll notice that the connectivity is very similar in both cases (adapted from[10])!

Conclusion

Over the years, people have been intrigued by animal behaviour and have applied different techniques to study various creatures and their behaviours. Each one of these techniques, and animals, has helped us understand how animals interact with their environment. The large neurons of squids are perfect to stick electrical probes into; the phenomenal genetic tools available in fruit flies allows us to understand how genes control the process; and mice are excellent models because of their 'closeness' to humans, which is especially important in understanding diseases. Yet, all that we've learned is only a humbling little in comparison to all that we do not know and understand. But along the way we have developed revolutionary new technologies that allow us to push the boundaries of what we know, and make many more exciting new discoveries about the brain and the nervous system!

Resources

1. General overview of the nervous system and neuronal signalling: http://www.nobelprize.org/educational/medicine/nerve_signaling/game/nerve_signaling.html#/plot1
2. How to manipulate neurons with light: https://www.youtube.com/watch?v=I64X7vHSHOE
3. Watch hundreds of neurons fire spontaneously in the brain of a zebrafish[11]: https://www.youtube.com/watch?v=T2H6UdQVEFY
4. Watch thousands of neurons, in the young zebrafish brain, fire in response to different visual stimuli[12]: http://www.wired.com/2014/07/neuron-zebrafish-movie/

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