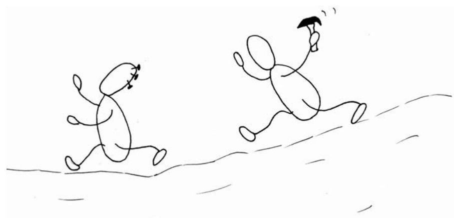
Contents

CHAPTER 1 Engage your brain

We all have a brain, and most of us use it to great effect. In fact, it no longer comes as any surprise to people that it is their brain which governs all that we do throughout our lives. Not only does it determine everything that we consciously want and think but it also keeps our insides ticking over through many mechanisms we are not even aware of. There are two main ways to examine our behaviour, one being through psychological enquiry which doesn't even need to acknowledge the workings of the brain, e.g. "if this happens, how do we react?" The other direction of attack is through neuroscience, e.g. "how does the brain generate our behaviours?" Nowadays these fields interchange at will; however, every behaviour will have an underlying basis in the brain. It is the most enigmatic organ of the body as, to look at it, there is no indication about how it works and so for long periods in history, it was not given the praise it deserves for being the most important part of our existence.

In times long past, neuroscience and psychology were preceded by philosophy, which in literal terms translates from its original Greek into "the love of knowledge". This is why the highest qualification in the land is a Ph.D (or Doctor of Philosophy) regardless of the field of study. The ancient Greek philosophers were in disagreement over the role of the 1.5 kg gelatinous bag of mostly water. Hippocrates (460–379 BCE) purported that the brain was the seat of intelligence and that it was involved in sensation. The father of modern medicine's view did not come out of the blue; he was one of the first proponents of reasoning and observation in medical practice. Hippocrates had a more "humoral" (related to the body fluids) theory of health by which he meant the recognized body fluids of the time, i.e. the blood, phlegm, yellow bile and black bile, needed to be kept in balance for good health. Illness was thought to be caused when these fluids were out of balance and treatment of this would include bloodletting or purging of the body fluids. Three millennia previous to this, the ancient Egyptians also used a form of purging for diseases of the head. Called trepanation, it involved boring holes in the skull while the patient was still alive. We know this because in the skulls found in archaeological digs in whom trepanation has been carried out, there is evidence of healing.



This procedure may have been carried out to relieve headaches or mental illness, often attributed at that time to the presence of trapped spirits in the head. A hole would be the obvious way to let them out. On the other hand, the ancient Egyptians didn't rate the brain highly enough to bury it with the body, instead sucking it out through the nostrils prior to burial. They believed the seat of the soul (or the very essence of our existence) was in the heart and this view prevailed until the time of Hippocrates who, as we know, believed in the opposite.

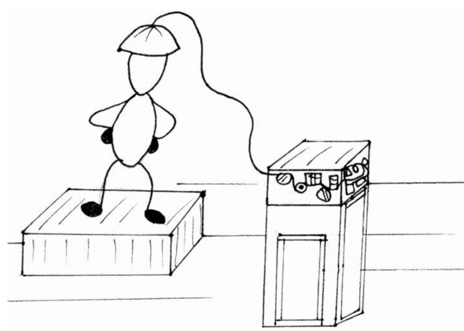
So it would seem that we have all been agreed about the brain's role in our behaviour since around 400 BCE, right? Wrong. Not everybody agreed with Hippocrates, the most influential of which was Aristotle, born around five years before Hippocrates died. Aristotle (384–322 BCE) favoured the heart as being the place where our mind "lives" and like any good philosopher, he had arguments he thought proved it. Among these was the view that the brain was on the periphery, sitting as it does on a stalk on the top of the body, and so its function must be to cool the blood whereas the heart was placed at the centre of bodily function thereby heating up the blood. Aristotle also thought that the heart was essential to life, the brain not so much. Of course, now we know this is completely untrue as you can live for a finite period of time (albeit short) with a stopped heart but once your brain stops, you are legally dead. He also thought that the heart is affected by emotion and the brain is emotionless, unlike the current view that the brain is central to emotional processing and production. Further to this he thought that the heart is connected to the sense organs via the blood vessels but that the brain is not connected to the sense organs. Well, we now know we can't sense anything without our brain and that the sensory connections are neural, not vascular. There is no doubt that Aristotle, student of Plato, teacher of Alexander the Great, was a fine thinker and indeed was the founder of one of the pillars of logic that still stands today, but the scientific grounding of these influential thoughts still left a bit to be desired. Sometimes knowledge is led down the garden path by supposition or personal belief; this was one such time.

Philosophy and early medicine, including investigations of the function of the brain, was a truly international affair. The Roman Empire had Aelius Galenous (130–200 CE), known as Galen, a Greek physician, writer and philosopher, who clearly followed the clinical observation tradition founded by Hippocrates. Galen was employed to treat gladiators after arena battles and as such witnessed some horrific injuries including those to the brain and spine. His impression of the effects of the damage he saw was no doubt influenced by his "hobby" of dissections of sheep, pig and monkey brains (Roman law prohibited dissection of human bodies.). Galen could have produced some "garden path" science of his own as his deductions were reportedly based on poking a freshly dissected brain with his finger; however, he came to the right conclusions, amazingly. The two main visible parts of the brain are the soft cerebrum, and the hard cerebellum, which is at the back of the brain and underneath the cerebrum. Galen deduced that the cerebral cortex is involved in sensation and perception as well as memory whilst the cerebellum is primarily involved in movement control. These views are restricted, but not essentially wrong, but I think they must have been based on Galen's experience with gladiator injury and not just poking brains with his finger. If only he had stopped there, but he went on to establish a different garden path entirely. In his dissected brains, he found hollow areas called ventricles, which to him, fitted the humoral theory of Hippocrates to a T and so he purported that the fluid of the four humours flows from ventricle to ventricle via the nerves which he thought were hollow tubes, initiating movement and registering sensation.

This view was to last for nearly a millennium and a half. René Descartes (1596–1650) in fact was a great proponent of the ventricular view as he tried to explain the brain in terms of machines.

This was around the time that inventors were coming up with ideas for hydraulically controlled machines. If fluid is forced out of the ventricles through the nerves then this could bring about movement as the muscles are "pumped up" so to speak. Think about that next time you are on a fairground ride. However, Descartes was more specific than Galen in that he placed the seat of the mind in the brain and linked the mind to the body. The interaction between the non-material mind and the physical body was still unclear at this time though with Descartes believing that the mind controls the brain through the pineal body, the structure of the brain through which the mind flows (although now we know that pineal damage doesn't lead to a "loss of mind" but a rather more minor disturbance to your biological rhythms like your body not knowing the difference between night and day). And so, the mind–body problem was born leading quite naturally to the field of dualism, the philosophical position that behaviour is controlled by two entities. The test for the presence of a mind was twofold: the presence of language and reasoned action. Unfortunately, this pretty much discounted animals as being in possession of a mind (although Descartes himself by all accounts was devoted to his dog, Monsieur Grat) and also led to the gross mistreatment of patients in mental institutions, as if they were "out of their mind", they could feel no pain etc. Nowadays it is accepted that our mind, or consciousness as it is now called, is brought about by the activity of our brain and is not a separate entity, a movement termed materialism, but its ethereal nature still causes neuroscientists problems in trying to define how it comes about.

Within 200 years, scientists were less concerned by the ventricular humoral view of Hippocrates, Galen and Descartes and had dissected the brain to observe bumps or gyri on the brain's surface as well as sulci or fissures, grey matter and white matter as well as the definition of lobes within which certain functions must lie (now called the frontal, parietal, temporal and occipital lobes). However, there was one more garden path yet to walk and discount. Just at the time scientists were beginning to attribute different functions to different areas of the brain, Franz Joseph Gall (1758–1828) started his pioneering work into the localization of function in the brain. Gall had a stepwise argument that went something like this. The brain is the organ of the mind. The mind is composed of multiple distinct, innate faculties. Because they are distinct, each faculty must have a separate seat or "organ" in the brain. The size of an organ, other things being equal, is a measure of its power. The shape of the brain is determined by the development of the various organs. And now, the pièce de résistance – are you ready? Here it comes, brace yourself. As the skull takes its shape from the brain, the surface of the skull can be read as an accurate index of psychological aptitudes and tendencies. Well, Gall was doing fine purporting the view that is the cornerstone of materialism, that all behaviour can be fully accounted for by brain function, the view that guides contemporary research, even without recourse to philosophy of the mind. But in his last point, Gall was proposing that we could tell what somebody was good at based on the lumps and bumps on their head. Originally called cranioscopy, it was later renamed as phrenology. Due to the lack of scientific proof, phenology was marginalized by the scientific community although it was popular amongst the talking classes with the presence of one of Lavery's Electric Phrenonmeter in the country shows of the early 1900s being a real draw at least 75 years after the theory was put forward. You had to stand on a box and have a helmet type apparatus "read" your skull features and then it would tell you your strengths and weaknesses. A map was devised, through correlating numerous people's skills with their skullscapes, showing what the different regions were for. Some of these skulls are still on show in the Rolletmuseam in Baden, Austria, Gall's birthplace. According to this, I should be good at the accordion, duelling and imitation, all at the same time I should imagine. Suffice it to say, I am not good at any of these things, even in isolation. My skull is shaped the way it is simply because I was always bumping into things as a kid and it has no bearing on the function of the brain housed inside. Thankfully, in my case.

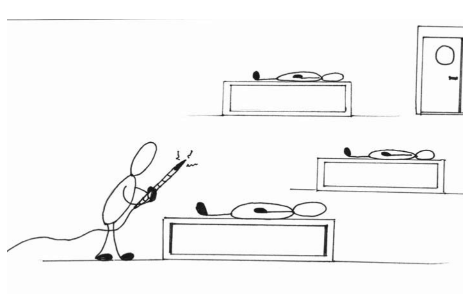


It was around this time of the late 1800s that Camillo Golgi (1843–1926) and Santiago Ramon y Cajal (1852–1934) used similar staining techniques to discover what the brain was made of. Neurons are translucent under the microscope and so the application of a stain shows up the different components of neurons and shows their structure. Golgi used a silver stain to show that it was composed of a large network of interconnected "tubes" but Cajal showed that in addition to this, nerve cells were in fact discrete entities and also that they became more complex in their structure with age. Golgi and Cajal were awarded a joint Nobel Prize for Medicine in 1906. But the two had fallen out over their differing views, Golgi believing that the nerve cells that he could see through the microscope acted like the blood vessels of the body whereas Cajal correctly saw them as separate entities with their own functions and not just "transit stations" in a network. The argument even bubbled over into their acceptance speeches for the Nobel Prize with one attacking the other's views in their respective speeches. Well, it wasn't the Peace Prize they won.... In truth however, there would be no Cajal without Golgi's methods and Cajal knew and acknowledged this saying that Golgi's theories of the nervous system were based on his education and the prevailing views at the time whereas Cajal looked beyond this to see what was possible and not just what should be based on what was thought to be the present case.

The grouping together of these nerve cells or neurons as they are now known was shown by Korbinian Brodmann (1868–1918) in 1908 to be a clue to the localization of different functions. In fact, this classification of regions still survives use to this day. Simultaneous to these cellular discoveries, physicians and scientists were documenting patients with different forms of brain damage more rigorously. In this field called neuropsychology, inferences could be made about the function of the damaged regions based on what function was lost. If a patient was impaired in some way, say he couldn't see, and he had damage to the back of his brain, then a neuropsychologist puts two and two together to determine that information from the eyes must be processed at the back of the brain. In 1861, Pierre Paul Broca (1824–1880) had a patient called Tan, so called because the only thing he could say was "TAN". When Tan died, a post-mortem revealed that syphilis had damaged a specific part of his frontal lobe, forever to be attributed to speech production and indeed named Broca's area. Later, Karl

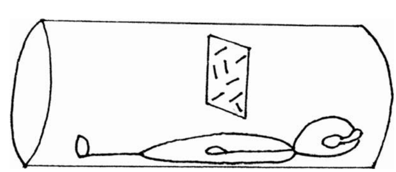
Kleist (1879–1960) compiled a comprehensive functional mapping of the cerebral cortex from the case notes of some 1600 head-wound casualties from the First World War which advanced our knowledge about the brain regions involved in certain functions. However, the problem with neuropsychology is twofold; you usually had to wait for a patient to die before you could attribute their behavioural change to a particular brain region and the brain regions damaged were often very large so it was hard to define small regions as having particular functions.

Although neuropsychology is still a valuable tool in our quest to understand the brain, we now have other methods at our disposal to understand how the normal, healthy human brain works. We can eavesdrop on brain waves using electroencephalography (EEG). Since Luigi Galvini (1737–1798) and his experiments on frog muscles, we have known that electricity is very important to muscle contraction whether or not the muscle is attached to a living body. In fact, this point got Galvini's nephew, Giovanni Aldini, into trouble. He travelled all over Europe reanimating dead bodies with electricity and is reported to have inspired Mary Shelley to write Frankenstein two decades later. The most famous of his "performances" involved a rectal probe and the attempt to bring the recently hanged body of murderer (although the evidence was allegedly thin) George Forster back to life shocking the Royal College of Surgeons in London in 1802 with the spasmodic movements like kicking out and punching the air that the dead body produced. The *London Times* was worried and wrote, "It appeared to the uniformed part of the bystanders as if the wretched man was on the eve of being restored to life". Unsurprisingly, such public displays were soon after outlawed. Undeterred, Aldini continued his experiments with live animals and found that he could excite the brains of oxen and went further to report electrical cures for a number of mental illnesses, his methods being a direct precursor to electroconvulsive therapy used as a last resort in mental illnesses which do not respond to other treatments today.



His work was also the forbearer of cardiac shock treatment. Of course, we now know that the nervous system including the brain and all the peripheral nerves and the transfer of signals between neurons and between neurons and muscles for example, works by the transference of an electrical signal via chemicals (more of that later). The electrical activity in a particular part of the brain tells us that that bit is active and even better, we can listen out to see how different bits talk to each other. This is very useful when investigating epilepsy – when the neural activity is very erratic, but it is also very handy when exploring what happens in our brain when we are asleep or doing tasks requiring attention for example. It is one of the gooier techniques as it involves placing a cap, with varying numbers of listening posts, or electrodes, generally from 64 to 128 embedded into it, on the head and injecting electrode gel into each electrode so that there is good contact between the electrode and the scalp through which the brain waves can pass so that the computer software can represent them as squiggles on a screen. Therefore, one of the most important components in an EEG lab is a nice big sink in which to wash your participants' hair!

Imaging techniques, on the other hand, are not messy at all and let us see structural components within the head. These range from X-ray through to its more advanced counterpart CT (computerized tomography) scanning which differs from X-ray in that it produces cross-sectional pictures of the brain without having to put the patient into awkward positions. The scanning technique most commonly used in neuroscience today however is MRI or magnetic resonance imaging, which uses a strong magnetic field to align all the water molecules in your brain in one direction and then applies a radio wave to see how the water molecules respond. The response is different across areas and depends on damage etc. and it produces very detailed (and beautiful) pictures of the brain by taking images at 1mm intervals called slices. The computer software then reconstitutes these into the entire brain so that we can look at structures from any angle. We can also track the blood flow in the brain using functional MRI (fMRI) which is particularly useful when trying to work out what part of the brain is involved if the person lying in



the scanner is doing a visual task, or thinking about the Queen, as blood will flow to the area involved. The software translates this blood flow into areas of activity with different colours denoting how much the area is involved in the processing of the task. These are then located on the picture of that person's brain, my so-called splodges of activation (see Figure 1.1).

However, one disadvantage of fMRI is that areas not really necessary for the processing of the task can "light-up"; also you can only correlate activations with behaviour; you don't know that that area caused the behaviour. So, we need a way of examining the absolute involvement of a brain region in the production of a function in the non-damaged brain.

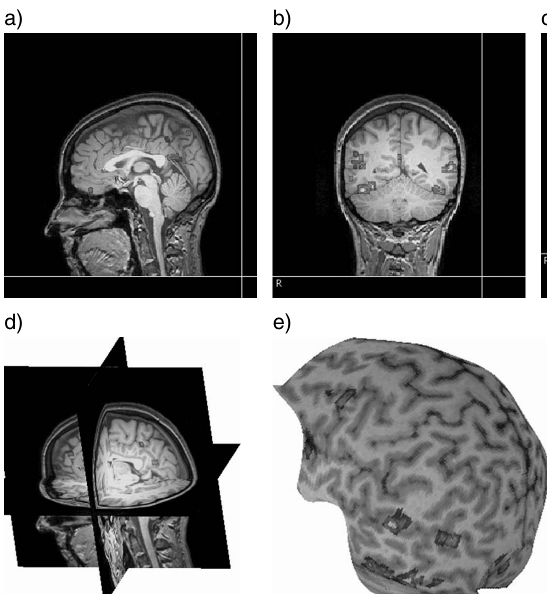


Figure 1.1 fMRI activations in my brain when I am looking at faces. In the upper pictures (sagittal, coronal and transverse views respectively) the scans are flipped so that the right of my brain is on the left and the left is on the right according to radiological convention. This is my excuse for not knowing my left from my right. The bottom pictures represent a multiplanar reconstruction and a curvilinear representation. Images acquired using BrainSight™ software (Rough Research, Canada).

Neurostimulation, the most common of which is Transcranial Magnetic Stimulation (TMS for short), allows us a window on this issue. A brief magnetic pulse is sent through the skull (see Figure 1.2), and via Michael Faraday's groundbreaking principles of

Figure 1.2 My colleague Dr Alison Lane applying magnetic pulses to Dave Knight. We get our subjects to wear a swimming cap as it means we can mark the place we want to send our magnetic pulse into easily. We used to mark the scalp but this saves us fishing about in people's hair.

electromagnetic induction (a magnetic field outside a tissue can induce an electrical field inside the tissue) first put forth in 1831, and given that the brain works by electricity, a very small bit of the brain (about 1 cm) is turned on for a very short period of time (0.001 of a second). The subject is usually given a task to do, and if the bit of brain being safely switched on by TMS is involved in the processing of that task, then subjects will be a little bit slower doing the task.

This is because if the brain is active with respect to the magnetic pulse, it will not be able to respond to the processing of the task so this gives us an indication of how necessary that area is for the task. TMS has been used to ask questions about normal human brains that were previously asked using neuropsychological patients or animal experimentation. It has big advantages over these methods however in that in patients for example, the lesion tends to be large and so localizing a function to a particular area is difficult, and the effects of TMS are completely reversed within seconds.

The techniques mentioned so far have not just been used to discover what individual neurons look like, and how they are grouped but also how they work together to bring about functions such as reading, writing, talking, seeing and all of the other things you will find out about in later pages. The structure of the brain has been examined such that we have names for all the different parts. Sometimes these names relate to what the area does so we'll talk about that later but most of the time our names are based on where the area is in the brain. So, here's a brief overview of all the different parts you will come across later when we are talking about how the brain does what it does. The cerebrum (Latin for "brain") comprises the outer layer, which is called the cerebral cortex, and also the sub-cortical (under the cortex) structures. The cerebral cortex has a right hemisphere and a left hemisphere and the subcortical structures are also paired including the basal ganglia (ganglion means a biological tissue mass, in this case a bunch of neurons) which are important in the control of movement amongst other things, and the hippocampus (Latin for "sea horse" which is what the structure looks like) and entorhinal cortex and fornix (Latin for "arch", which is what it looks like), the cingulate cortex and amygdala (Greek for "almond", which is what each amygdala resembles) which are all important in memory formation and emotion.

The two hemispheres of the cerebrum are connected by a tract of nerve fibres that allow the two sides of the brain to communicate with each other and is called the corpus callosum. Each hemisphere can also be divided up into lobes, so called because of the bones of the skull they lie underneath; frontal, important in movement, thinking and planning; parietal (parietal bone relates to the Latin for wall), important in touch, balance and spatial awareness; temporal (the temporal bone supports the part of the face known as the temple), important in hearing, speech comprehension, memory and visual recognition; and the occipital (occipital bone relates to the Latin for back of the head), which is devoted to visual processing. The frontal lobe is separated from the parietal by the central sulcus and the bottom of the parietal lobe is separated from the top of the temporal lobe by the lateral fissure and the two hemispheres are separated by the longitudinal fissure (see Figure 1.3).

The sub cortical structures fall under this lobe system too; for example, the hippocampus is in the medial (or middle of) temporal lobe. Underneath the cerebrum we have the brainstem made up of the cerebellum (Latin for little brain because that's what it

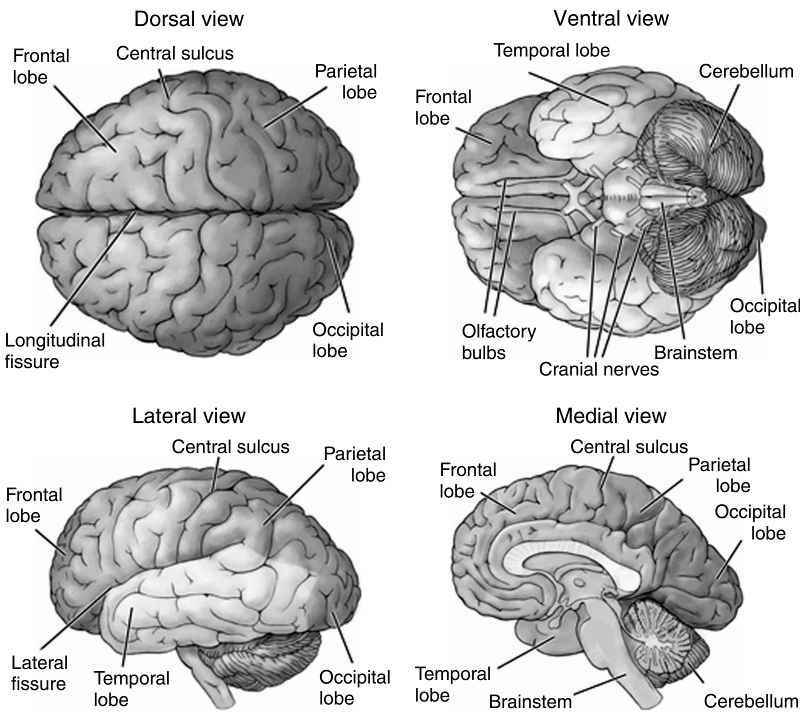


Figure 1.3 The divisions of lobes in the human brain.

Source: From *An Introduction to Brain and Behavior*, 3rd edn, by Bryan Kolb and Ian Q. Whishaw © 2011 by Worth Publishers. Used with permission.

looks like, the hard part Galen liked to poke at) at the back of the brain, a region very important in the timing and accuracy of movements; the midbrain and diencephalon (Latin for inter-brain), which includes the thalamus, hypothalamus and pituitary. This is my favourite part of the brain. It controls all of the mechanisms that keep us ticking over without our knowledge (known as homeostatic or control mechanisms) that are mind blowing in their sheer vastness of effect and the simplicity of their control. Various clumps of cells in the midbrain and diencephalon control the brain's general level of alertness and regulate processes such as breathing, heartbeat and blood pressure. Utterly marvellous system. I'll convince you later. The brainstem evolved more than 500 million years ago and is rather like the entire brain of a present day reptile. As you move down from the midbrain through the brainstem to exit the cranium or skull you pass through the pons (bridge) and medulla, and beyond the cranium this tract of nerve fibres becomes the spinal cord. The cerebrum is what gives us voluntary behaviour and thinking skills, better visual and movement abilities whilst the brainstem takes care of the unconscious part of our existence.

There are also a few ways to think about the nervous system as a whole (see Figure 1.4). The central nervous system (CNS) refers to the brain and spinal cord whilst the peripheral nervous system (PNS) consists of all of the nerves outside of the brain and spinal cord. Within the PNS we have the somatic nervous system, all the nerves involved in voluntary control of our skeletons, as well as the autonomic nervous system (ANS), which helps to carry out all of our homeostatic mechanisms by sending neurons to the heart, kidneys and all the other visceral organs. The ANS has two aspects, the sympathetic nervous system, which is the excitatory one, and the parasympathethic system, which calms us down. It is the ANS that is involved in the "fight or flight response" you will no doubt have heard of.

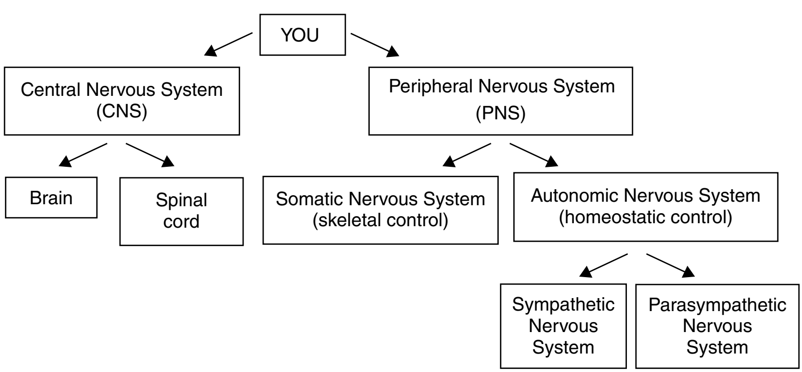


Figure 1.4 How your nervous system is split up according to whether your neurons live in the central (CNS) or peripheral nervous system (PNS). The PNS has responsibility for all of your internal processes that you are not aware of.

As neuroscientists, we have many technical terms to make us sound very clever indeed but really, there's no need to be freaked out. We could use simpler terms like forward, back, to the side, but instead we like to use anterior, posterior and lateral (see Figure 1.5). Medial means to the middle, inferior means below

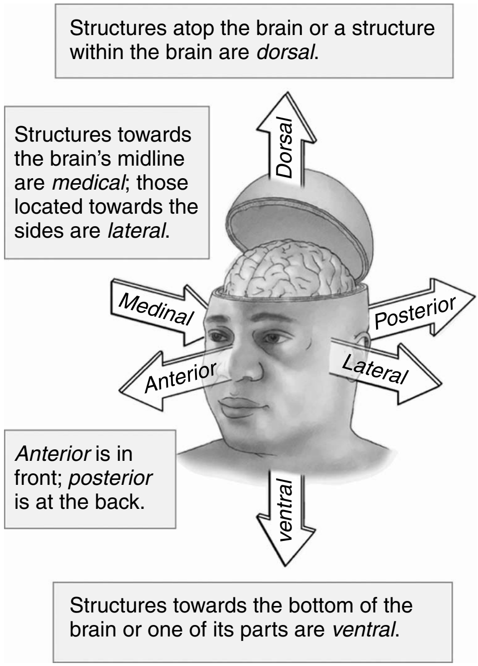


Figure 1.5 The main directional jargon that we use to talk about places in the brain. In addition to which lobe you are in, you can signpost to any part of the brain using these words.

Source: From *An Introduction to Brain and Behavior*, 3rd edn by Bryan Kolb and Ian Q. Whishaw © 2011 by Worth Publishers. Used with permission.

and superior means above. Dorsal means towards the top of the brain, ventral means towards the bottom. Rostral, rhymes with nostril, and means to the front, where your nostrils live funnily enough. Caudal comes from the Latin "Caudum" meaning tail and indeed means towards the tail. In animal, caudal can be interchanged with posterior but in non-tailed humans it is more accurately interchanged with inferior. Pre- means before, and so the prefrontal cortex is the part of the frontal cortex that lies before the frontal pole, the bit at the very front of the brain which is called the orbitofrontal cortex as it is near the eye socket (orbit) region.

And so if I ask you where the dorsolateral prefrontal cortex is, you will be able to confidently tell me that this is a region that lies towards the top and to the side of the prefrontal cerebral cortex.

You can really work out where any region is using these short cuts. Easy right? Ok, maybe not. But once you start finding out what these different regions do, it gets much easier. But first of all, we must find out what the brain is made of and how these bits make it work.

Feeling curious?

Brain, Vision, Memory: Tales in the History of Neuroscience by Charles C. Gross. 2009; MIT Press and *A Hole in the Head: More Tales in the History of Neuroscience* by Charles G. Gross. 2012; MIT Press. *Entertaining stories from the history of neuroscience. A great way in to the topic.*

Philosophical Foundations of Neuroscience by M. R. Bennett, P. M. S. Hacker. 2003; Wiley-Blackwell. *A provoking read that challenges assumptions.*

Milestones in Neuroscience Research compiled by Eric Chudler, a director of education and outreach at the University of Washington. http://faculty.washington.edu/chudler/hist.html *A handy timeline of important events in the history of neuroscience.*

Kenneth S. Kosik (2003) Opinion: "Beyond Phrenology, at Last". *Nature Reviews Neuroscience* 4, 234–239 (March) | doi:10.1038/nrn1053. *An account of the history of the integrated nature of neuroscience research.*

Vincent Walsh and Alan Cowey "Transcranial Magnetic Stimulation and Cognitive Neuroscience" *Nature Reviews Neuroscience* 1, 73–80, doi:10.1038/35036239 *A great introduction to the technique even if we all now agree that the term virtual lesion is very misleading! If you liked this, Vincent Walsh (with Alvaro Pascual-Leone) also wrote a book on the subject called Transcranial Magnetic Stimulation: A Neurochronometrics of mind published by MIT press in 2005.*

Neuroanatomy: An Illustrated Colour Text by Alan R. Crossman & David Neary. 2010; Churchill Livingstone. *A good guide to the anatomy of the brain.*

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