QUANTUM THEORY
John Polkinghorne
RENAISSANCE ART
Geraldine A. Johnson
ROMAN BRITAIN Peter Salway
ROUSSEAU Robert Wokler
RUSSELL A. C. Grayling
RUSSIAN LITERATURE
Catriona Kelly
THE RUSSIAN REVOLUTION
S. A. Smith
SCHIZOPHRENIA
Chris Frith and Eve Johnstone
SCHOPENHAUER
Christopher Janaway
SHAKESPEARE Germaine Greer
SIKHISM Eleanor Nesbitt
SOCIAL AND CULTURAL ANTHROPOLOGY
John Monaghan and Peter Just
SOCIALISM Michael Newman
SOCIOLOGY Steve Bruce
SOCRATES C. C. W. Taylor
THE SPANISH CIVIL WAR
Helen Graham
SPINOZA Roger Scruton
STUART BRITAIN John Morrill
TERRORISM Charles Townshend
THEOLOGY David F. Ford
THE HISTORY OF TIME
Leofranc Holford-Strevens
TRAGEDY Adrian Poole
THE TUDORS John Guy
TWENTIETH-CENTURY BRITAIN Kenneth O. Morgan
THE VIKINGS Julian D. Richards
WITTGENSTEIN A. C. Grayling
WORLD MUSIC Philip Bohlman
THE WORLD TRADE ORGANIZATION
Amrita Narlikar

Available soon:

AFRICAN HISTORY
John Parker and Richard Rathbone
ANGLICANISM Mark Chapman
CHAOS Leonard Smith
CITIZENSHIP Richard Bellamy
CONTEMPORARY ART
Julian Stallabrass
DERRIDA Simon Glendinning
ECONOMICS Partha Dasgupta
GLOBAL CATASTROPHES
Bill McGuire
EXISTENTIALISM Thomas Flynn
THE FIRST WORLD WAR
Michael Howard
FUNDAMENTALISM
Malise Ruthven
HIV/AIDS Alan Whiteside
INTERNATIONAL RELATIONS
Paul Wilkinson
JAZZ Brian Morton
MANDELA Tom Lodge
PERCEPTION Richard Gregory
PHILOSOPHY OF LAW
Raymond Wacks
PHILOSOPHY OF RELIGION
Jack Copeland and Diane Proudfoot
PHOTOGRAPHY Steve Edwards
PSYCHIATRY Tom Burns
RACISM Ali Rattansi
THE RAJ Denis Judd
THE RENAISSANCE Jerry Brotton
ROMAN EMPIRE
Christopher Kelly
ROMANTICISM Duncan Wu

For more information visit our web site
www.oup.co.uk/general/vsi/

Michael O'Shea

THE BRAIN

A Very Short Introduction

© 2005

OXFORD
UNIVERSITY PRESS

Chapter 3

Signalling in the brain: getting connected

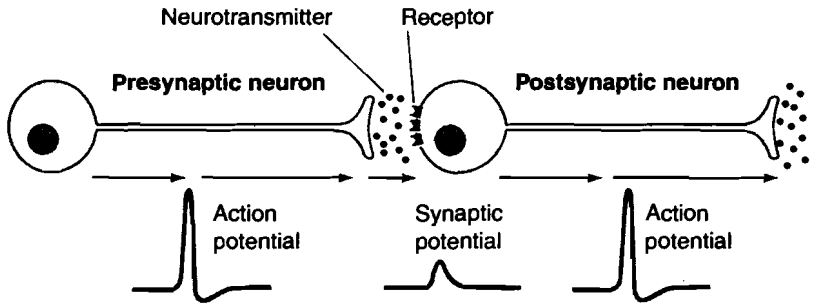
The problem of connection, the sending of information effectively around the nervous system, arises because signals must be communicated undistorted over the length of the body, which might be a very large distance indeed, in the case of the blue whale for example. Coupled to this is the fact that, in an unforgiving world, animals must react quickly to be an effective predator or so as to avoid being eaten. So the basic requirements of signalling coded information in the nervous system are that the signals have to be routed correctly and sent reliably over long distances *as rapidly as possible.*

In order to achieve this neurons convey and encode information electrically. Brief electrical pulses (lasting a few thousandths of a second), known as action potentials or nerve impulses, travel along biological cables (axons) that extend from the cell bodies of neurons to connect their input to their outputs with other neurons. Compared to the speed of electrical information traffic along the wires in a computer (close to the speed of light), conduction velocities of impulses in the brain are slow, about 120 metres per second in the fastest conducting axons. When they reach the terminals of axons, impulses trigger the release of chemical signals that are able to initiate or suppress electrical signals in other neurons. In this way neurons transmit information from one to another by an alternating chain of electrical and chemical signals.

The chemical signals are released at specialized sites called synapses, at which the chemical signals (neurotransmitters) pass across a very narrow gap separating two neurons. Released neurotransmitter molecules work by binding to and thereby activating specialized receptor molecules located on the surface of the receiving neuron on the other side of the synapse.

An activated receptor causes a brief electrical response, called a synaptic potential, in the receiving neuron. These potentials may be either inhibitory or excitatory depending on whether the voltage in the receiving neuron becomes more negative (inhibitory or hyperpolarizing) or less negative (excitatory or depolarizing). Inhibitory potentials make the receiving neuron less likely to fire a nerve impulse. Excitatory potentials increase that probability. A 'decision' to produce nerve impulses is therefore made through the summation of all of the inhibitory and excitatory potentials impinging on a neuron. Once a critical threshold voltage is reached by this summation, nerve impulses will be generated. The more the excitation, the higher will be the frequency of the impulse train. An important way that information is coded in the brain is by the impulse frequency (number of impulses or action potentials per second) and by the pattern of impulses. Nerve impulses travel rapidly along the axon, feeding information to many other neurons where the process of neurotransmitter release and chemical communication is repeated.

Neurons may receive chemical signals from hundreds of other neurons through a thousand or more synapses on their surfaces, each having some influence on the 'decision' to fire a nerve impulse and on the firing rate. The complexity of the resulting signalling network in the brain is almost unimaginable: one hundred billion neurons each with one thousand synapses, producing a machine with one hundred trillion interconnections! If you started to count them at one per second you would still be counting 30 million years from now!



3. Neuron-to-neuron communication. An electrical action potential or nerve impulse travels at speeds up to 120 metres per second along the axon of the presynaptic neuron. When it reaches the synapse the impulse causes neurotransmitter molecules to be released. Receptor molecules react to the neurotransmitter molecules causing the postsynaptic neuron to be either excited (illustrated) or inhibited. An inhibitory synaptic potential would dip below the resting potential, making the postsynaptic neuron less likely to fire an action potential

Physics and the problem of electrical signalling

When a neuron is inactive or at rest there exists a stable negative voltage across the membrane of about –70mv, known as the resting potential. When excited by another neuron, or in the case of a sensory receptor cell by a sensory stimulus, the neuron may generate a train of action potentials. Nerve impulses attain a positive voltage of about +50mv before returning to the resting potential. So the total voltage excursion of a nerve impulse is about 120mv or 0.12 volts.

We need now to understand something about how these electrical impulses are generated and propagated along axons in the wet, salty, and gelatinous medium that is the brain: a very unsuitable environment for an electrical signalling system. The problem is made even more difficult by the dreadful electrical properties of axons. Axons are very poor conductors of electricity, so bad in fact that over relatively short distances, far less than a typical axon's length, most of the original signal will leak away into the salty surroundings. This inescapable problem is a consequence of the

way the laws of physics apply to the flow of electricity in electrical cables immersed in salty water.

These laws were first formulated by the British scientist Lord Kelvin (1824–1907) who figured out how to send telegraphic information across the Atlantic Ocean through a submarine cable. Lord Kelvin defined a parameter called the 'length constant', which allows us to compare how good different types of cable are at transmitting electrical signals over a distance. A length constant is the distance over which about two-thirds of the electrical signal's amplitude will be lost and its value can vary enormously. For example, the length constant of a submarine cable is a few tens of miles. This means it is not possible simply to lay a cable across the Atlantic and expect an electrical signal injected at one end to appear at the other end undiminished, several thousands of kilometres away.

For a submarine cable, the length constant is a small fraction of the distance over which information must be sent and the same is true for biological cables, axons. So in a similarly salty environment both submarine cables and axons must detect a failing electrical signal and boost it back to its original strength before sending it on its way again. In submarine cables booster amplifiers placed at regular intervals achieve this, and axons solve the problem in a rather similar way. But how, using the unlikely ingredients of a few proteins, fats, some smaller organic molecules, and plenty of salty water, can nerve cells make a battery-powered amplifier?

The brain's batteries and impulses

The brain is a major consumer of bodily energy. While it is only 2 per cent of our body weight, it consumes 20 per cent of our energy and moreover 80 per cent of the brain's energy consumption is devoted to a single task: producing biological batteries, the power source of the amplifiers of electrical signals in axons.

Neurons in fact create two batteries. One has a value of about 50mv

and faces inwards (positive pole inside) and the other has a value of about 70mv and faces outwards (positive pole outside). If the 70mv battery is turned ON and the 50mv battery OFF, the inside of the neuron will have a potential of –70mv. On the other hand if we now turn OFF the 70mv battery and turn ON the 50mv battery, then the inside will be positive by the value of the inward facing battery: i.e. +50mv. At the peak of an action potential the membrane voltage reaches about +50 mv before returning within a thousandth of a second to its resting value of about –70 mv. It is as if the action potential results from the rapid switching ON and OFF of the batteries in a well-defined sequence. This sequence of switching is initiated by a positive shift of the voltage across the membrane. If the positive change in voltage reaches a critical threshold value, the +50mv battery is turned on and a nerve impulse is initiated.

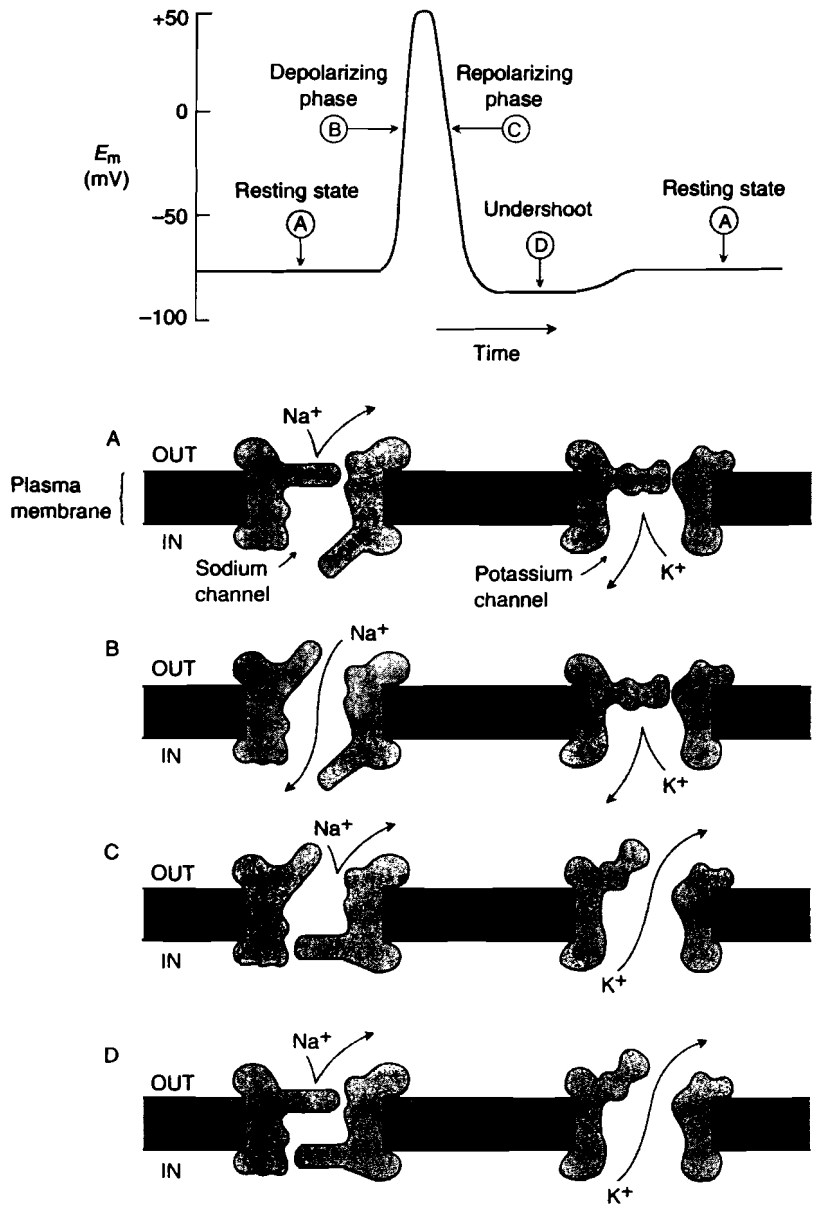
These batteries are 'charged up' by proteins that literally pump two positively charged ions in opposite directions across the membrane of the neuron. The process requires energy to be expended and this is achieved by the ability of molecular-scale pumps to couple the expenditure of metabolic energy to the movement of ions. Sodium ions are pumped out of the neuron whilst potassium ions are pumped in. These ions are derived from sodium chloride (table salt) and potassium chloride that are dissolved in the fluid surrounding all of our cells, providing a salt-water environment for them that is similar to the composition of the sea water in which cellular life had its origins. The pumping creates an imbalance between the inside and outside concentrations of the two ions. Sodium ions are maintained at about tenfold higher concentration outside than inside the neuron and approximately the reverse situation exists for potassium. These concentration gradients, in the absence of barriers, would result in sodium entering and potassium leaving the neuron.

Highly specialized protein molecules called ion channels restrict this passage of sodium and potassium into and out of the neuron by

acting as molecular gatekeepers. Mobile parts of the molecule, 'gates', open and close in an orderly sequence. This molecular machinery enables the membrane to control the switching on and off of the sodium and potassium batteries. Each potassium channel has a single gate, known as the activation gate because when opened the flow of potassium is activated. The sodium channel is more complicated and has two gates, the activation gate and an inactivation gate. When the sodium activation gates are open sodium floods into the neuron due to the concentration gradient. This is equivalent to turning ON the 50mv sodium battery, making the inside of the neuron reach its maximum positive potential of +50mv at the peak of the nerve impulse. When the potassium gates open, equivalent to turning ON the –70mv battery, potassium flows out.

Now let's consider how nerve cells generate an electrical impulse from about –70mv to about +50mv and back in a few milliseconds. At the resting potential of about –70mv the sodium battery is switched off, so sodium flow is virtually entirely blocked because, although the inactivation gates are open, the activation gates are closed. The potassium battery is partly on because a small proportion of the potassium channel gates are open and some potassium is therefore free to flow out of the neuron, leaving the inside negative. To move the voltage to +50mv the activation gates for the inward flow of sodium must be opened. Then, to return to the resting potential the sodium gates must be closed and the potassium battery fully switched on, so that potassium flows out. The sequence of opening and closing during a nerve impulse is shown in Figure 4.

In order to understand these crucial parts of the signalling story we need know what causes the molecular-scale gates to open and close. The answer is that they are sensitive to the voltage across the membrane, allowing the detection of small changes in voltage and their amplification into discrete pulses of much greater amplitude. But how can these channel proteins sense and respond to the



4. Action potential and ion channels. This illustrates how the molecular ion gates and channels in the nerve cell membrane (plasma membrane) behave at different stages (A to D) of the action potential

voltage across the membrane? It would seem that the proteins would have to be very sensitive indeed to changes in voltage – after all, a change of just a few thousandths of a volt across the membrane can be sufficient to trigger the opening of a channel gate.

Take a channel's eye view of the fluctuating membrane voltage however and we get a more realistic impression of the strength of the electrical forces acting on them. The membrane is exceedingly thin (about one millionth of a centimetre) and the total voltage change across this membrane during an action potential is 0.12 volts. If we take the thinness of the membrane into account, the fluctuation experienced by the protein is an enormous 120,000 volts per centimetre. As the gates of the ion channels are themselves electrically charged, they will be moved by the change in the electrical forces across the membrane. It is this movement of the ion gates that is the key to understanding how a small electrical excitation is amplified into a full-blown nerve impulse. The first gates to respond to an excitation are the ones preventing the entry of sodium. A very small excitation will open a few of these gates, allowing the inflow of sodium. This will cause the voltage to become even more positive, thus opening more sodium gates. If enough sodium gates are opened we quickly enter a positive feedback loop, leading inexorably to the turning on of the +50mv sodium battery at the peak of the nerve impulse. The voltage returns to its resting voltage by the delayed closure of the sodium inactivation gates and by the delayed opening of the potassium gates.

Speed is important

Biological cables are inherently slow conductors of signals because the nerve impulse depends on the movement of ions across a membrane rather than the displacement of electrons along a wire. Higher transmission speed can be achieved by improving the insulation of the axon membrane and by increasing the electrical conductivity of the axon's core. The latter can be achieved simply by increasing the axon's diameter. The fatter the axon the faster the

transmission; for speed you need giant axons. Unfortunately this solution has significant practical drawbacks. The relationship between axon diameter and conduction speed is unfavourable – to double the speed you must quadruple the diameter (conduction velocity is proportional to the square root of the axon diameter). So to obtain significant gains in speed we would have to produce axons of gigantic girth. A related drawback is that a brain would contain fast components, but inevitably there would be fewer of them. Evolving high performance brains depended in part on the miniaturization of the brain's components and on getting as many fast neurons as possible packed into a small volume. For this, evolutionary selection pressure did not favour giant neurons.

Nonetheless, giant axons certainly do exist in brains. There are many examples in the nervous systems of invertebrate and lower vertebrates, where they tend to be involved in initiating very rapid responses such as escape reactions. An example of particular note is the giant axon of the squid, which can be up to 1 mm in diameter and transmits nerve impulses from the brain to the body musculature at several metres per second. This axon activates the animal's emergency escape behaviour, which requires the rapid contraction of the mantel cavity causing an explosive expulsion of water and a 'jet propelled' escape. In the 1940s the enormous dimensions of this particular axon attracted the attention of two British physiologists, Alan Lloyd Hodgkin and Andrew Fielding Huxley. They conducted a series of elegant experiments on the nerve impulse, using the size of the squid's giant axon to their advantage. Their experiments led to the discovery of voltage-sensitive sodium and potassium flow and to the ionic theory of the action potential described above. The Hodgkin and Huxley account of the action potential in the squid axon was to earn them a share of the Nobel Prize for Physiology and Medicine in 1963, not least because the principles and mechanisms uncovered in the squid were universal – explaining even how our axons transmit electrical signals. It seems a little unfair on the squid that there is no formal

acknowledgement of its contribution to one of the most outstanding achievements of 20th-century science.

Transmission speeds in excess of 100 metres per second are possible by improving the axon's insulation with a multilayered Swiss-roll-like wrapping called myelin. At approximately 1 mm intervals the myelin wrapping is interrupted by gaps known as nodes of Ranvier where the axonal membrane is exposed. Voltage sensitive sodium channels are concentrated at the nodes and the nerve impulse seems to jump from node to node with negligible delay. The autoimmune disease known as multiple sclerosis (MS) cruelly highlights the importance of myelin in normal brain and bodily function. In MS the body's immune system damages the myelin and the ability of axons to conduct action potentials is disrupted. This produces various symptoms including unsteady movements of the limbs, blurred vision, abnormal eye movements, loss of coordination, slow word recall, and forgetfulness.

Myelin is produced by glia, cells in the nervous system that outnumber neurons at least tenfold. There are many other functions of glial cells; for example, the microglia are able to move around the brain, consuming dead cellular debris as they go. Other glial cells can alter the way neurons interact with one another, suggesting that the idea that glia merely provide supportive roles for neurons is wrong. Indeed recent experiments have shown that glial cells can detect changes in the voltage across their membranes and are responsive to chemical signals from neurons. Others are able physically to cover or uncover regions of communication between neurons, suggesting they can direct information traffic between different parts of the brain. If, as now seems probable, the neurons and glial cells are together essential for information processing, then by considering only the neurons we have vastly underestimated the complexity of the brain machine.

From neuron to neuron

Neuron to neuron communication occurs at specialized points of contact between nerve cells called synapses and there is perhaps in excess of 100 trillion of them in the human brain. Synaptic communications are essentially private, in the sense that a single synapse allows one neuron to speak to just one other. The cell bodies of communicating neurons need not be close to one another because neurons can reach out with long connecting processes. Synapses however are not the sole means of between-neuron communication and an important distinction can be drawn between point-to-point information transmission mediated by them (the brain's wiring diagram) and a more global form of non-synaptic information transmission (for which wireless broadcasting is a better analogy).

The point-to-point nature of synaptic communication between the wire-like fibrous extensions of neurons is reminiscent of an electronic circuit. Indeed the synaptic 'wiring diagram' of connections required for a particular brain function may be referred to as the neural 'circuit' for that function. Synapses require two neurons to cooperate in the formation of a small region of either direct contact (an electrical synapse) or very close apposition (a chemical synapse). Where there is direct contact, electrical signals pass with almost no delay from one neuron to another through protein pores that perforate the membranes of both neurons at the point of contact. Usually electrical synapses are bi-directional, electricity being able to pass equally well in both directions. Electrical synapses can be thought of as soldered joints in an electronic circuit; they are highly reliable connections and invariant in their operation, neither adding to nor subtracting from the signal passing between components. The speed and reliability of electrical synapses is exploited in neural circuits required for the activation of a flight response. In an escape behaviour there is no time for complicated information processing; escape must be executed as quickly and reliably as possible and this is a job ideally

suited to the simple, slavish, and fast properties of electrical synapses. The next time you unsuccessfully try to swat a fly your failure will be due to the speed of transmission of visual information (about you) passing through electrical synapses in the escaping fly's brain.

At a typical chemical synapse a narrow gap or cleft between two communicating neurons makes the direct exchange of electrical or chemical signals impossible. For information to be transmitted across the gap the electrical activity of a neuron must cause the release of a chemical message that diffuses across the synaptic cleft to the receiving neuron. The synaptic machinery allowing electrical activity in the signalling neuron to be coupled to the release of neurotransmitter is highly complex and specialized, as are the mechanisms that capture the chemical message and initiate responses in the receiving neuron. This means that the two sides of a chemical synapse are specialized for either sending or for receiving chemical messengers but not both. Signals therefore pass in one direction only, from the pre-synaptic to the post-synaptic neuron. The pre-synaptic side is specialized for the synthesis, storage, and release of a neurotransmitter. On the post-synaptic side the chemical message is recognized and converted into an electrical signal. Usually chemical synapses occur between the axon terminations of the transmitting neuron and the dendrites or cell body of the receiving neuron.

The simplest form of synaptic transmission involves an ion channel receptor (an ionotropic receptor) that is opened by the binding of a neurotransmitter. These mediate a direct and rapid coupling between neurotransmitter binding and the generation of a brief electrical signal in the post-synaptic neuron. There is another important category of 'indirect' neurotransmitter receptors (metabotropic receptors): the signal they generate is biochemical rather than electrical. When a neurotransmitter binds to an indirect receptor it activates a complex cascade of biochemical or metabolic events in the post-synaptic neuron, mediated by special enzymes

that cause the synthesis of signalling molecules called second messengers.

Primary messengers are the neurotransmitters, which transmit information from neuron to neuron. Second messengers are the neuron's internal messenger molecules. It is through their action that the physiological properties of neurons and their synapses can be altered, either briefly or for extended periods of time. Second messengers are even involved in transmitting information from the synapse to the neuron's nucleus where they initiate long-term changes in the pattern of gene expression and protein synthesis that can in turn cause changes in the strength of synapses. It is in the action of second messengers therefore that we must seek a mechanism for the changes in the strength of synapses that accompany the process of memory formation in the brain (see Chapter 6).

The electrical circuit, 'wiring diagram', analogy is a compelling and useful one, but neurons can communicate without synapses. By the release of freely diffusing messenger molecules, such as the gas nitric oxide, some neurons broadcast information through volumes of the brain; communicating with many other neurons within the affected volume, without the need to be directly connected to all of them by synapses. Neurons may participate in both modes of transmission simultaneously. Indeed it may not be possible to understand how a function is performed without knowing both the synaptic wiring diagram of its neural circuit *and* how the circuit is influenced by signals being broadcast into it from elsewhere.

Putting this all together

In this chapter we have examined in some detail the cellular and molecular mechanisms of the most basic of brain functions – the ability of the brain's component cells to communicate with one another. What emerges is a picture of bewildering complexity in which it is not easy to see the wood for the trees. So let us stand back

and imagine our brain with its hundreds of trillions of synaptic connections. Each synapse is potentially a unique computational unit with its own molecular tool kit, history, memory, and function. The neurons and their synapses are in a constant state of flux – the connections are dynamic, changing their strength, size, and location; being formed and unformed. Every second, millions of electrical impulses course along the fine fibrous extensions of the neurons, carrying electrical and chemical messages through a gelatinous interconnected circuitry that is more complex by far than that of any computer. If the interconnecting fibres in just one cubic millimetre of cortical grey matter were unravelled and laid end to end, they would form a strand 5 km (about 3 miles) long! If the connections in the whole brain were unravelled, the strand would be long enough to encircle the earth twice – such is the phenomenal interconnectivity of the brain. And this is only part of the story because the neurons and their connections make up a very small fraction of the brain's cellular machinery. There are as many as 100 glial cells for each nerve cell and we are only beginning to understand just how important they are, not simply carrying out housekeeping jobs but participating in the brain's computations, in among other ways, by regulating synaptic transmission.

This then – the neurons and their connections and their history, their companion glial cells, the multitude of chemical messengers and receptors – is basically all there is to the brain. We are far from understanding how it works as a whole but there is nothing more, no magic, no additional components to account for every thought, each perception and emotion, all of our memories, our personality, fears, loves, and curiosities.