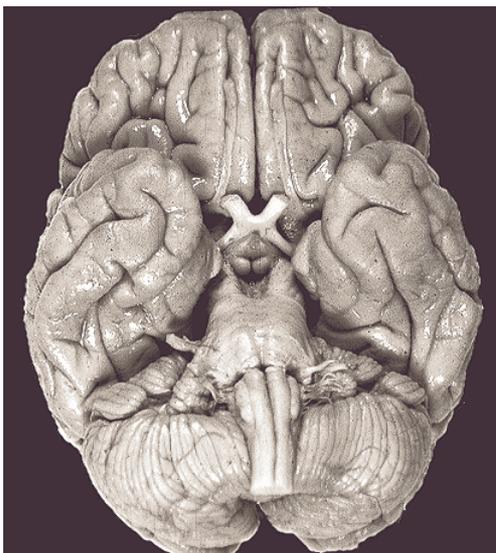


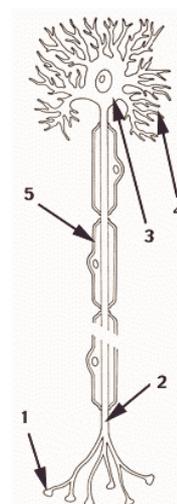
Introduction. Psychology is the study of the mind; whether directly or indirectly, this involves the study of the brain, for the brain is responsible for our sensory perceptions, our thoughts, our memories, our emotions, and our actions. The brain is one of the most complex systems ever studied; the way in which the concerted action of 10^{11} neurons gives rise to thinking, behaving humans remains in large part a mystery. The progress that has been made in our understanding of this system depends upon both ‘top-down’ and ‘bottom-up’ approaches to neuroscience and psychology.

Welcome to the practical course. The purpose of this practical is to provide an introduction to neurobiology for those with no previous experience of this subject. We will cover the gross anatomical structure of the nervous system, examine how neurons work and how they connect to each other, and review some of the techniques used to study the functioning brain. We will cover some principles of sensory and motor systems and touch on the many information processing systems that lie between sensation and action. Of necessity, the tour will in places be cursory, but I hope it will serve to give you an overview of what various major parts of the brain do.

Macroscopic structure of the brain. The main structures of the central nervous system (CNS) will be demonstrated. The *spinal cord* ascends into the *hindbrain*, comprising the *medulla* and *pons* and behind that the *cerebellum*. Above the pons lies the *midbrain*. (The medulla, pons and midbrain are collectively known as the *brain stem*.) Moving further up, we reach the *diencephalon* (including the *thalamus* and *hypothalamus*). Atop this sits the *telencephalon*, which in humans is by far the largest part of the brain; it comprises the left and right *cerebral hemispheres*. It includes the *cerebral cortex*, which is massive and convoluted in humans and divided into frontal, parietal, occipital, and temporal lobes. The two cortical hemispheres are connected by the *corpus callosum*. The telencephalon also includes a number of subcortical structures, particularly the *basal ganglia*, *hippocampus*, and *amygdala*.



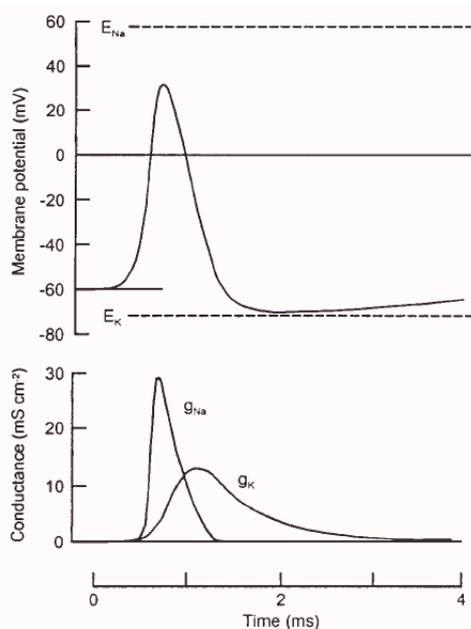
Brains. Top left: lateral view. Top right: midline view.
Bottom left: ventral view.



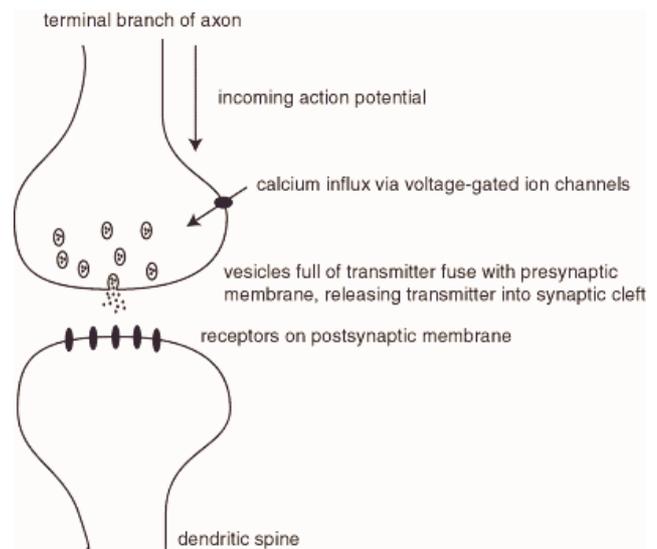
Stylized neuron. (1) Axon terminals; (2) axon; (3) cell body with nucleus; (4) dendrites; (5) surrounding glial cell providing myelin sheath.

Neurons. The nervous system is made up of discrete cells called *neurons*, and ‘support’ cells of various types, collectively known as *glia*. The neuron is encased by a fatty cell membrane that isolates the interior of the cell from the surrounding environment. Neurons vary greatly in size and shape, depending on their location (and function) in the brain. A ‘typical’ neuron has a *cell body*, or *soma*, from which sprout numerous small *dendrites*. Dendrites collect information from many (perhaps 10,000) other neurons via connections called *synapses*. This information is integrated in the region of the dendrites and the cell body, and propagated down the neuron’s single *axon*. Axons vary greatly in length; the longest in a human is about a metre long (and in a whale, many times this). At the very end of the axon it may divide into *collaterals*, which typically make *synapses* on the dendrites of other neurons. Macroscopically, the brain is composed of *grey matter* (collections of neuronal cell bodies) and *white matter* (fibre tracts, i.e. bundles of axons).

The action potential. A basic function common to most neurons is their ability to produce nerve impulses or *action potentials* that travel down the cell membrane. All cells, including neurons, pump sodium ions (Na^+) out of themselves in exchange for potassium (K^+) in the ratio 3:2; this results in a potential difference across the membrane known as the *membrane potential*. In neurons at rest, this is approximately -65 mV (with respect to the outside); this is termed the *resting potential*. If the membrane potential is raised (*depolarization*) sufficiently to reach the neuron’s *threshold*, *voltage-gated sodium channels* open up and allow Na^+ to flow into the cell, depolarizing the membrane further in an explosive fashion via positive feedback. This is an action potential (AP); it is an *all-or-nothing* event (AP size does not vary, so neurons must convey information through the frequency and timing of their firing). The rapid depolarization is soon opposed by the opening of K^+ channels and a consequent efflux of K^+ ; eventually both sets of channels close and the membrane potential returns to its resting potential after $\sim 1 \text{ ms}$ in total. However, by this time the depolarization has already spread passively along the membrane and excited adjacent areas of membrane to do the same thing. The result is that the AP spreads down the surface of the cell like a lit trail of gunpowder. For many neurons, the speed of conduction is increased from $\sim 0.5\text{--}2.0 \text{ m}\cdot\text{s}^{-1}$ to up to $120 \text{ m}\cdot\text{s}^{-1}$ (depending on axon diameter) because glial cells insulate the axon with the fatty substance *myelin*, leaving gaps in the myelin sheath (*nodes of Ranvier*) between which the AP jumps (*saltatory conduction*). The symptoms of multiple sclerosis are caused by patchy demyelination in the CNS.



The action potential



Schematic of synaptic transmission

Synapses and neurotransmission. Although neurons occasionally interface with each other electrically, most synapses are chemical. The *presynaptic terminal* contains *synaptic vesicles* — packets containing a chemical *neurotransmitter*. The type of neurotransmitter varies depending on the neuron (it is true enough for our purposes today to say that one neuron produces only one transmitter). When an AP arrives at a *presynaptic terminal*, it triggers voltage-gated calcium (Ca^{2+}) channels which let Ca^{2+} into the cell. Ca^{2+} is a signalling ion that triggers the vesicles to fuse with the presynaptic membrane, releasing their contents into the *synaptic cleft*. The neurotransmitter molecules diffuse across the cleft (20–40 nm wide) and reach the *postsynaptic membrane*, where they bind to specific *receptor* proteins. This whole process takes of the order of 1 ms.

What happens next depends on the receptor. Often, the receptor is a *ligand-gated ion channel*; when the neurotransmitter binds to the receptor, an ion channel in the receptor opens. If the channel is permeable to Na^+ , this will depolarize the postsynaptic membrane and cause an *excitatory postsynaptic potential (EPSP)*. If it is permeable to chloride (Cl^-) instead, the membrane will hyperpolarize — an *inhibitory postsynaptic potential (IPSP)*. (Incidentally, excitatory and inhibitory synapses can be distinguished morphologically.) The size of the postsynaptic potential is small — EPSPs are

typically 0.4 mV, and even at the postsynaptic neuron's most sensitive site near the cell body, 10 mV of depolarization is required to bring the neuron to threshold and fire an AP. However, if enough EPSPs arrive at the neuron and are close enough to each other in space and time (and overcome any inhibition from IPSPs) they may sum and trigger an AP. In this way the postsynaptic neuron can *integrate* information from many incoming presynaptic synapses in a complex fashion, making a decision as to whether or not to fire.

'Classical' neurotransmitters that possess ligand-gated ion channel receptors and operate in this manner include acetylcholine (ACh, an excitatory transmitter used at the neuromuscular junction and in the cerebral cortex), glutamate (the main excitatory transmitter in the brain) and GABA (γ -aminobutyric acid, the brain's predominant inhibitory transmitter). In addition, however, ACh, glutamate, and many other neurotransmitters (dopamine, noradrenaline, serotonin, histamine...) possess receptors that are not ligand-gated ion channels; instead they are *G-protein-coupled receptors*, which are enzymes that catalyse a cascade of chemical activity within the cell. Though these operate on a much slower timescale, they can lead to a huge range of different effects (such as alterations in gene expression and protein synthesis in the neuron and changes in the sensitivities of ligand-gated ion channel receptors). Thus, they can modify the manner in which neurons respond to 'classical' neurotransmitters, often termed *neuromodulation*.

Synaptic plasticity and learning. At its simplest, learning occurs when the nervous system alters the manner in which it responds to a given stimulus. Learning can occur at the level of the individual synapse; one mechanism is that of *long-term potentiation (LTP)* of glutamatergic synapses. Glutamate binds to 'AMPA'-type glutamate receptors, which are conventional ligand-gated Na^+ channels. It also binds to 'NMDA'-type receptors; these are special and allow Ca^{2+} through, but only when glutamate is present *and* the neuron is already depolarized (they are ligand- *and* voltage-gated ion channels). To sketch the key mechanism, let's imagine two glutamatergic neurons (A and B) making synapses onto the same neuron (C). Suppose A is strong enough to activate neuron C, but B is too weak. When B fires on its own, it releases glutamate which binds to AMPA and to NMDA receptors. Because the depolarization caused by the AMPA receptors at this synapse is not great, the NMDA receptors do not open. If A fires at the same time as B, however, neuron C is fully depolarized *and* there is glutamate in B's synaptic cleft; therefore the NMDA receptors at synapse B open. Ca^{2+} flows in through them, and this triggers a long-lasting and specific strengthening of synapse B, such that B may subsequently be capable of activating C on its own. Whereas previously only A activated C, now B can do so; B has become *associated* with A/C. LTP is certainly a mechanism by which simple associative learning occurs in invertebrates, and it occurs in the mammalian nervous system; to what degree LTP represents a model of human memory formation is debated.

Psychoactive drugs. The synapse is the site of action of the vast majority of psychoactive drugs — binding to receptors and altering their activity as agonists or antagonists, triggering neurotransmitter release, or preventing the breakdown or reuptake of transmitter from the synapse. A number of examples will be given, to include psychostimulants, opiates, antipsychotics, and antidepressants. Differences in individual responses to drugs may be attributed in part to natural variation (polymorphism) in receptors.

Methods of studying the functioning brain. As experimentalists, we cannot at present measure or alter the activity of every cell in the brain, and we would be incapable of dealing with this volume of data anyway! We will discuss some commonly-used techniques in neurobiological experimentation. Each has its own advantages and disadvantages. Techniques differ fundamentally as to whether they alter the function of the brain or simply measure it. Measurement techniques vary greatly in spatial and temporal resolution.

Overview of sensory systems. All sensory systems start at the point where a specialized *sensory receptor* detects a stimulus from a particular sensory *modality*. Such modalities include mechanical energy (e.g. hearing, acceleration and balance senses, muscle stretch and tension, somatosensation [touch]), electromagnetic energy (vision), and chemical stimuli (taste, smell, arterial oxygen concentration, pH). Some modalities have *submodalities* (e.g. receptors sensitive to different wavelengths in the case of vision; fine touch and pain in the case of somatosensation). Sensory receptors may be specialized cells or modified neurons. The receptor has a specialized molecular system that transduces the incoming energy into a change in the membrane potential, termed the *receptor potential*. If the receptor is itself a neuron, this may trigger action potentials; alternatively, the graded receptor potential can be transmitted from cell to cell via graded changes in neurotransmitter release until a neuron is reached that fires APs. The frequency of AP firing is directly related to the amplitude of the receptor potential, and thus to the intensity of the stimulus.

For vision, audition, and somatosensation, the sensory information is transmitted, via some intermediary processing stages, to the thalamus ('gateway to the cortex') and then to a primary sensory cortical region (V1 in the occipital lobe, A1 in the temporal lobe, S1 in the parietal lobe), where one can find 'maps' of visual space, frequency, and skin position, respectively. Here, and subsequently in 'secondary' sensory cortical areas, sophisticated processing takes place. Long before the information reaches the thalamus or cortex, however, it has undergone considerable processing as it passes through a series of synapses, to reduce the amount of information transmitted and to make this information more useful. For example, most sensory systems exhibit *lateral inhibition* (by which, for example, excitation at one point on the retina tends to inhibit activity from immediately adjacent areas). This will be illustrated. Lateral inhibition enhances

the brain's ability to detect *contrast* and the edges of objects, which are functionally important. Sensory systems also apply various forms of *temporal* adaptation to the incoming information.

Overview of motor systems. While sensory systems occupy posterior regions of the spinal cord and brain, motor systems are found anteriorly. Most of the muscles in the body are innervated by *primary (alpha) motor neurons* whose cell bodies are located in the anterior horns of the spinal cord; when these cells fire, they stimulate the muscle fibres to contract. Cell groups in the *intermediate zone* of the spinal cord provide surprisingly sophisticated local limb control systems. These cells — and many α -motor neurons themselves, in primates — receive projections (synapses) from neurons in the *primary motor cortex*, in the frontal lobe just anterior to the central sulcus (groove). The primary motor cortex commands aspects of limb velocity (direction and speed) using a distributed code whereby many neurons contribute to the movement of one muscle group, and one neuron contributes to several muscle groups. Overall, however, there is a rough 'body map' in this region of cortex.

In addition to this central system, a number of other regions play their part. The *premotor* and *secondary motor cortices* influence primary motor cortex; they are important in the planning of actions and in tasks involving bimanual coordination. A 'motor' subdivision of the *basal ganglia* is important in the initiation of voluntary movement. The *cerebellum* has many roles but contributes to motor timing; it (and other structures) may store automatic 'motor programs'.

Completing the tour. Perception and action are linked at many levels, from simple and direct reflex arcs in the spinal cord to the most sophisticated systems, incorporating attention, memory, cognition, and motivation. You will cover these as the 1B course progresses; as you do so, think of how the study of structural and functional architecture of the nervous system informs the study of these topics, and vice versa.

References

All much too large to read in full; dip in for detail on any topic we've touched on.

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