CHAPTER 2

HARDWARE

Introduction

Medical practitioners helping those with mental disorders need some understanding of structures at three levels: the brain (macroscopic), neuron and synapse (microscopic), and released chemicals and medications (sub-microscopic).

This chapter begins with a brief overview. It ends with detailed information on particular structures, which is beyond the needs of the medical students.

One does not need an extensive knowledge of this this hardware to have a fair understanding of mental disorders.

Overview

Brain

The brain is a 1.4 kilo white/grey structure which from the outside looks like two scooped handfuls of cocktail sausages, with the consistency of cold boiled egg.
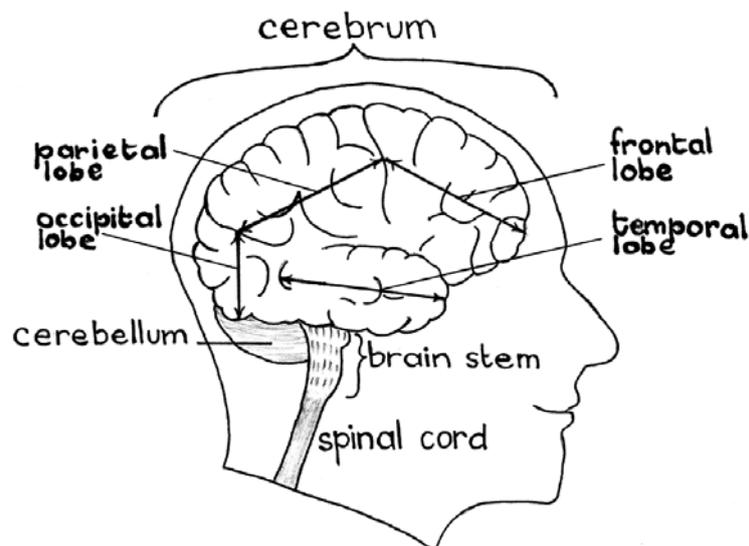

Illustration. The right side of the human brain. The most prominent feature is the cerebrum, which is divided into right and left cerebral hemispheres, and these are divided into different lobes.

The brain is miraculous and important. It receives unprecedented protection; it is enclosed in the hard bone case (the skull) and wrapped in three layers of specialized soft tissue. Also, it floats in a fluid, called the cerebrospinal fluid (CSF), which is contained between two layers of soft tissue. These structures and the CSF preserve the brain from piercing instruments or blunt blows.

In addition, the brain cells are not in immediate contact with the blood. It is shielded by a special arrangement of cells in the walls of the blood vessels which enter the brain. This arrangement, called the blood brain barrier (BBB), protects the brain cells from infection by organisms and from some chemicals and drugs.

These protective mechanisms are among the reasons why the brain activities which underpin the mental disorders have remained a mystery. They make it very difficult to "get a handle" on the chemical and electrical processes of normal and pathological brains.

The brain is composed of 25 billion nerve cells (neurons) and each is connected to around 1000 others. Thus, at any time, there is an incomprehensible number of electrical impulses (or messages) flashing around a vast array of brain circuits.

The brain receives a continuous stream of information from outside and inside the body and controls life preserving responses, from the automatic, unnoticed modulation to the blood pressure, to the sudden stamping on a footbrake. It receives information in the form of words and derives both literal and abstract meaning. It is the organ of emotional experience and intellectual activity. In dealing with stress, it co-ordinates the responses of the nervous, the endocrine and the immune systems. It is an awe-inspiring structure.

Soon after conception, the brain and spinal cord begin to develop from a hollow tube of cells (called the neural tube). The part which becomes the brain grows in length and thickness. With the increase in length this structure becomes sharply bent (forwards and backward) in various places. The variations means that some parts become much bulkier than others. This bending and thickening obscures the amazing complexity of the hidden structures. The central cavity of the neural tube expands at particular sites to form hollow volumes (ventricles). These contain CSF. Through small openings, the CSF in the ventricles is continuous with the CSF in which the brain floats.

The largest and most obvious brain structure is the cerebrum. The part of the neural tube which becomes the cerebrum expands and as bread dough with too much self-raising flour flows over the sides of the baking tin, so the cerebrum droops down and hides other brain structures. The cerebrum is the only part you would see if you rode past a brain on a galloping horse.

On closer examination we see a deep division (fissure) passing from the front to the back. Thus the cerebrum looks like two separate half kilo piles of small sausages, and these are referred to as the left and right cerebral hemispheres. These are joined by a thick bridge of white matter (the corpus callosum) which can only be seen when the hemispheres are pulled apart. Other deep fissures pass across the cerebral hemispheres, dividing them into

a series of lobes: frontal, parietal, occipital and temporal lobes (which can be seen from the outside) and the insula and limbic lobes (which are mainly internal structures).

The outer 2-5 mm of the cerebral hemispheres is called the cerebral cortex. This is the famous "grey matter", as in, "Why don't you use your grey matter?" Nerve cells (neurons) are like knitting needles or "aldente" spaghetti with a knot at one end. This knot is the "body" of the cell and the long thin part is called the axon. The axon conducts electrical impulses and is wrapped in white fatty insulation (myelin sheath). The cell bodies do not have insulation. The grey matter is composed predominantly of cell bodies, and they sit on top of scarves of white insulated wiring (as in the white corpus callosum mentioned in the last paragraph). The neurons are held in place by specialized (glial) cells, which can be likened to scaffolding.

Details are sketchy, but mental disorders may be associated with defects in the cell bodies and in the axons, as well as with the connections between cells (synapses). Recent evidence indicates that the glial supporting cells, which were formerly considered to be passive, may play a neuron-nurturing role (Huerta et al, 2006), and accordingly, dysfunction of these cells may also underpin mental disorders (Bernstein et al, 2014).

Some axons take information away to distant sites, such as impulses to muscles when evasive action is required. Others axons bring information back to the cortex from distant parts, such as news of a stubbed toe. Short axons (of the association neurons) convey information from one area of the cortex to an adjacent area.

Within each cerebral hemisphere there are hosts of important structures. The ventricles, which were mentioned above, are large in the upper part of the brain. Along with other structures, and between the scarves of descending and ascending white matter, there are three sub-systems composed of clumps of grey matter (cell bodies, as in the cortex) and related connecting white matter. These are the limbic system, the basal ganglia and the thalamus.

The limbic system is composed of two sets of structures, one on each side of the brain. They are toward, but not in, the midline. They form continuous circles of tissue, like large donuts hanging on the bridge-like corpus callosum and other midline structures. Major parts include the longitudinal striae, the hippocampus and the amygdala, parts of the cortex which overlay these three structures (sometimes called the limbic lobe), the fornix and the mammillary bodies. The hippocampus and amygdala are located in the temporal lobes of the cerebrum, which are deep to the temple and behind the eye. The limbic system plays a central role in emotion, appetite and memory, and deficits in these structures are believed to underpin a number of mental disorders.
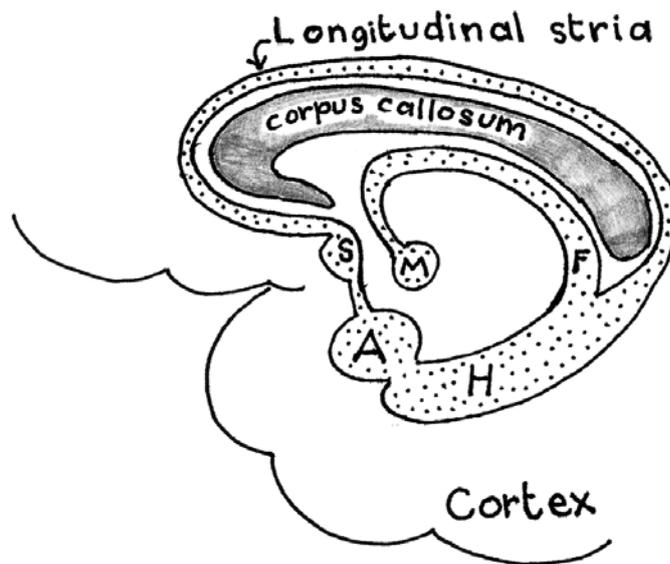
Illustration. The limbic system is a circuit of neurons located close to the midline on both sides of the brain. A, amygdala. H, hippocampus. F, fornix. M, mammillary body. S septal nucleus.

The basal ganglia is predominantly composed of cell bodies (grey matter), and again, there is one set of structures on each side of the brain. The basal ganglia looks somewhat like a tadpole curled into an open ring. It stands on its tail, the opening facing forwards. A scarf of white matter (the internal capsule) slants downwards, between the head and tail of this structure. It is a smooth, apparently single structure, but it can be dissected into sub-structures. The head of the tadpole is composed of the caudate and the lentiform nucleus (putamen and globus pallidus). The tail is composed of the tail of the caudate, and at the end is a knob called the amygdala.

It may have been noticed that the amygdala was earlier named as part of the limbic system. These are integrated systems and a structure can be a component of more than one system. The basal ganglia has long been known for a prominent role in movement, but more recently it has been recognised as having a role in emotional regulation. Abnormalities in the basal ganglia have been described in schizophrenia (Tamagaki et al, 2005; Chua et al, 2007). Recent work has found that major depressive disorder (but not bipolar depression) is associated with smaller basal ganglia (Kempton, et al, 2011).
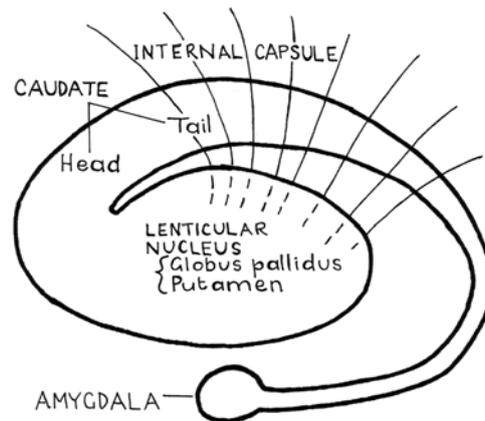
Illustration. The basal ganglia is a paired continuous grey matter structure; one is located in each hemisphere.

The thalamus is two oval masses of grey matter (like two hen eggs), one either side of a narrow envelope-like (third) ventricle, which is situated in the midline. The thalamus sits on top of the brain stem which continues below as the spinal cord. The thalamus is the major relay centre for all sensations, except smell. It has a role in language and memory. A role in mental disorder is probable (Andreasen et al, 1999; see later).
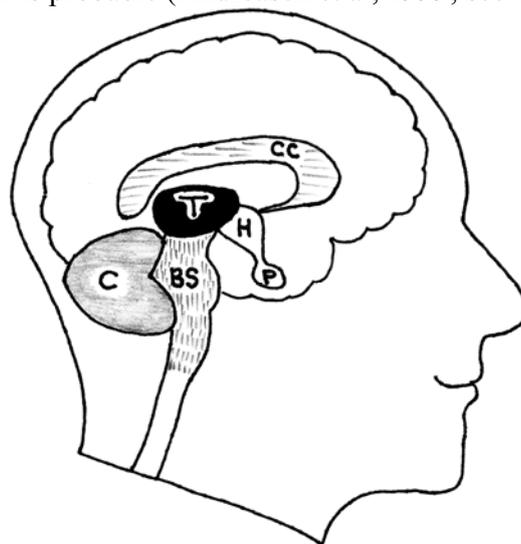

Illustration. The left side of the brain, showing some deep structures. This view would be seen by cutting down between the left and right cerebral hemispheres (between the eyes) and lifting the right side away. CC, the corpus callosum, the bridge which connects the two hemispheres. T, thalamus. The thalamus is surrounded by other brain tissue, and only a small part of the base can be seen without cutting more of the brain away. C, cerebellum. BS, brain stem. H, hypothalamus. P, pituitary.

As mentioned, the cerebrum is like bread with too much yeast, which has expanded and flowed down around the structures beneath. Parts of the brain stem and hypothalamus can only be seen if the edges of the cerebral cortex are lifted away, or the brain is turned upside down.

The brain stem is a thumb-like structure sitting in the mid-line, immediately below the thalamus. It extends down to the foramen magnum (hole in the base of the skull) where it becomes continuous with the upper end of the spinal cord. The spaghetti-like axons of the neurons pass through the brain stem carrying messages in both directions. There are also clumps of grey matter (called nuclei) in the brain stem. These provide activation to keep the brain alert, and regulate the heartbeat, breathing and blood pressure, and enable reflexes such as swallowing, sneezing, coughing and blinking. Defects in the brain stem are involved in a number of mental disorders, including panic disorder in which rapid heart rate and fear are important features.

The hypothalamus is finger-tip-like structure which projects down and forward from the thalamus. It is composed of clumps of grey matter. In the midline, a stalk of nerve cells extends down from the front of the hypothalamus to form the pituitary gland. The hypothalamus controls much of the endocrine system by releasing various hormones. It also controls the autonomic nervous system, which is the nerve supply to the organs of the body. Together, the endocrine system and the autonomic nervous system assist the body to respond to stress, maintain fluid balance, body temperature, appetite, sexual behaviour, blood pressure and other functions. The hypothalamus is believed to be important in many mental disorders, as most have features of disturbance of appetite, sexual function and sleep.

The cerebellum is scallop shaped structure which projects backwards from the thalamus and brain stem, to which it is connected by thick bands of axons. It sits in the midline at the base of the skull. It is important in the co-ordination of movement. Some research suggests the cerebellum is also important in the co-ordination of thinking and that defects in cerebellar function are involved in schizophrenia (Andreasen et al, 1999; Shevelkin et al, 2014).

Neuron

Every organ in the body is composed of cells designed for particular tasks. One unique cell of the brain (and the rest of the nervous system) is the neuron, which is designed to receive and transmit impulses (signals/messages). Neurons connect and communicate with each other.
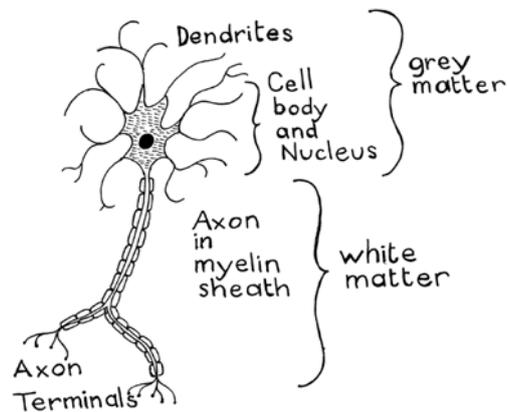
Illustration. The nerve cell or neuron. An astounding structure.

Neurons are so fine that they can only be seen with a microscope. They vary greatly in length. Some are very short and communicate only with nearby cells, while others such as those which pass from the spinal cord down to the big toe, may be a meter long (well, nearly).

The most common type of neuron is composed of three parts: 1) the cell body, 2) numerous short projections from the cell body called dendrites, and 3) the long thin spaghetti-like projection from the cell body called the axon.

The cell body contains the nucleus (which contains the genes) and other essential structures. Most of the materials needed by the neuron are synthesized in the cell body, and transported to distant parts, including the far distant end of the axon.

The dendrites receive nerve impulses and conduct them to the cell body. The axon conducts impulses away from the cell body, toward connections (usually on dendrites) with other neurons. The axon divides into thousands of tiny branches, called synaptic terminals, which form junctions, called synapses, with the dendrites or cell bodies of other neurons. If a cell body was the size of a marble (rather than microscopic), the axon would be in the order of 3 mm wide and could be up to 400 meters long.

Transmission of impulses is possible because of the wonderful properties of the membrane enclosing the neuron. In the resting (not actively transmitting) neuron, the material inside the membrane (the cytoplasm) is negatively charged in relation to the material outside the membrane (extracellular fluid). This is the result of the special positioning of charged chemicals (ions). There is a slight excess of negative ions inside the membrane and a slight excess of positive ions outside the membrane.

The imbalance of ions is maintained by several factors which work together. Most important are tiny sodium pumps in the cell membrane, which pump sodium ions (positively charged) out of the cell.

When a stimulus applied to the cell membrane is sufficiently strong, the potential difference between the inside and outside of the cell is reduced below a threshold level.

This causes local ion channels to open, sodium ions flow into the cell, and there is complete, temporary, loss of charge imbalance across the membrane. These changes cause similar changes in adjacent areas (chain reaction), and by this mechanism, an electrical impulse progresses along the axon.

Various processes restore the charge imbalance across the membrane. The entire process of depolarization and repolarization takes less than one thousandth of a second. The discovery of the details of this electrical impulse, which take place in microscopic cells during less than one thousandth of a second, speaks to the enormous capacity of the human brain.

Synapse

As mentioned, each human brain is composed of about 25 billion neurons. Each forms about 1000 connections (synapses) with other neurons. The number of synapses in the brain is in the order of 1 followed by fifteen zeros. And thus, in every human brain there are about as many synapses as there were leaves in the Amazon jungle.

The synapse is a critical component of the nervous system, and is the focus of most current drug treatments of mental disorders. The connection is usually between a projection from the end of an axon to the body or dendrites of another cell.

Illustration. The synapse in action. Above is a presynaptic neuron and below, a postsynaptic neuron. 1, A local neurotransmitter factory. 2, A neurotransmitter storage vesicle. 3, At the arrival of an electrical impulse, a vesicle fuses with the terminal membrane and neurotransmitters are released. 4, Neurotransmitters in the synaptic gap. 5, A neurotransmitter approaches a postsynaptic receptor. 6, Neurotransmitters fitting into receptors and initiating an electrical impulse in the postsynaptic neuron. 7, A neurotransmitter moves toward an auto-receptor on the presynaptic neuron. 8, A neurotransmitter fits into an auto-transmitter and slows the further release of neurotransmitters from the presynaptic neuron. 9, Oxidases (chemicals located in the synaptic gap) destroy neurotransmitters in the gap. 10, A neurotransmitter is taken back into the presynaptic neuron through a reuptake (transporter) mechanism, to be stored in a vesicle, ready for future reuse.

At the synapse there is a tiny gap (called the synaptic gap or cleft) between the end of the transmitting (presynaptic) axon and the dendrite or body of the receiving (postsynaptic) neuron. The electrical pulse stops when it reaches the synaptic gap. For the message to pass across the gap a special chemical (neurotransmitter) is released by the pre-synaptic neuron (triggered by the arrival of the electrical impulse), which passes across the gap and fits into a special receptor (like a docking space ship) on the post-synaptic neuron. This docking process triggers an electrical impulse, which then travels along the axon of the postsynaptic neuron.

There are at least 200 different neurotransmitters in the brain. Those believed to be most important in mental disorders are listed in the following box. Neurons predominantly release a single type neurotransmitters, but recent research indicates that a neuron can release more than one type.

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Monoamines
        Dopamine
        Serotonin
        Norepinephrine
        Histamine
Amino Acids
        Gamma amino butyric acid (GABA)
        Glutamate
Others
        Acetylcholine
        Nitric oxide
        Adenosine
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Neurotransmitters believed to be important in mental disorders.

Neurotransmitters may be synthesised in the cell bodies of neurons and transported down the axon to the nerve (axon) terminal, or they may be synthesised locally at the terminal. In either case, they are stored at the terminals in special containers (vesicles).

Current pharmacological treatment of mental disorders rests on our understanding of the events which follow the arrival of an electrical impulse at the axon terminal. At the arrival of the electrical impulse a vesicle fuses with the presynaptic membrane, opens and empties neurotransmitter into the synaptic gap. Various events may then transpire. First, the neurotransmitter may pass across the gap and fit into a receptor on the postsynaptic membrane and initiate an electrical impulse. Second, the neurotransmitter my move through the gap and fit into a receptor on the presynaptic membrane, that is, fit into a receptor on the neuron from which it was released. [These receptors are called auto-receptors. When an auto-receptor is activated, it turns off the release of further neurotransmitters. Thus, auto-receptors may act as a break or regulator. This can only happen, of course, when sufficient neurotransmitter is available for some to reach the auto-receptors to press the brake.] Third, the neurotransmitter may be destroyed by naturally occurring chemicals (oxidases) which are located in the gap. This is another mode of regulation, which prevents excessive stimulation of the second neuron. Fourth, the neurotransmitter may return back into the presynaptic neuron by special reuptake mechanisms and be restored in a vesicle. There is no order to these events. On release, a particular neurotransmitter molecule may be immediately destroyed in the gap, while another may fit into a postsynaptic receptor, release, move to and fit into an auto-receptor and finally return into the neuron of origin via a reuptake mechanism, to be reused later.

In a general sense, current thinking is that most mental disorders have to do with insufficient or excessive release of one or more specific neurotransmitters. Accordingly, medications are developed to perform particular actions. They act on one specific, or sometimes more than one neurotransmitter or receptors. The actions of medications include increasing the release of neurotransmitters, activating postsynaptic or auto-receptors (that is, to act like neurotransmitters), blocking postsynaptic or auto-receptors (that is, preventing natural neurotransmitters doing their job), and inactivating the reuptake mechanism or inactivating the destructive oxidases (so that more neurotransmitter remains available in the synaptic gap). The currently available drugs function like bath plugs or bailing buckets. A new wave of drugs for the treatment of mental disorders is being developed. These include hormones and other agents which will encourage neurons to refresh or repair themselves, but these may not be available in clinical practice for some years.

The GABAergic system

Gamma aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the brain. It is widely distributed and has a role in modulating dopaminergic, serotonergic and noradrenergic neurons. Dysfunction of the GABAergic system has been proposed as a cause of mood disorder (Brambilla et al, 2003) and schizophrenia (Richetto et al, 2013).
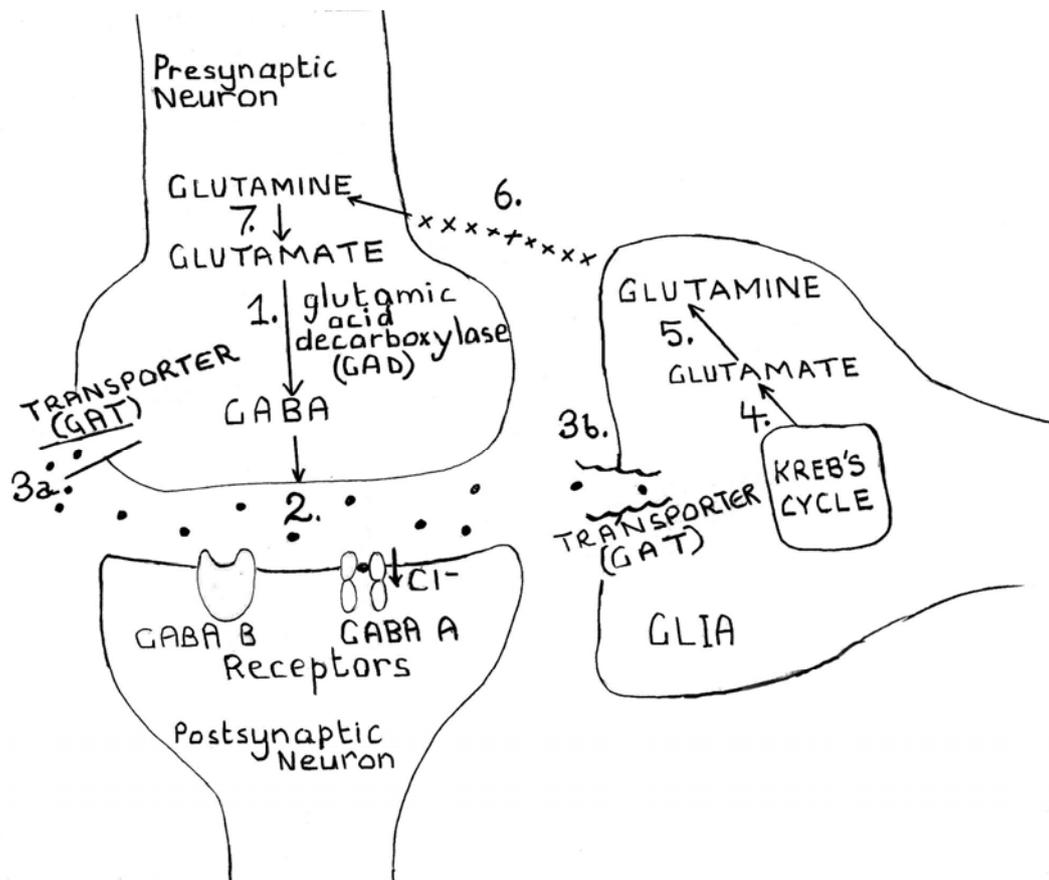
Illustration.
1) GABA is generated in the presynaptic neuron – from glutamate – through the action of glutamic acid decarboxylase (GAD).
2) It is released into the synaptic cleft, and passes across to activate the GABA A or B receptors. Activation of the GABA A receptor (ionotropic) results in chloride ions (Cl⁻) entering the cell, which causes hyperpolarization and reduced excitability.
3) a. GABA may be taken back into the presynaptic neuron by a GABA transporter (GAT)
   b. GABA may be taken into glial cells by a GAT.
4) In the glial cell GABA is converted, via Kreb's cycle, to glutamate
5) This glutamate is converted to glutamine
6) This glutamine then passes into the presynaptic neuron
7) Where it is converted back into glutamate

Benzodiazepines modify the GABA A receptor, such that inhibition by GABA is more effective. Because the GABAergic system modulates the actions of other neurotransmitters, it will probably become more important in mental disorder management, as our understanding grows and new pharmacological agents become available.

The Glutamatergic system

Glutamate is the most abundant excitatory neurotransmitter in the brain. The glutamatergic system may play a role in mental disorder, and recently, drugs acting on glutamate receptors have produced rapid and dramatic beneficial effects for individuals with treatment resistant mood disorder (Diazgranados et al, 2010 a&b).

A recent study suggests schizophrenia may be the result of glutamate abnormalities in the thalamic projections to the cortex (Sodhi et al, 2011). Confirmation is required.
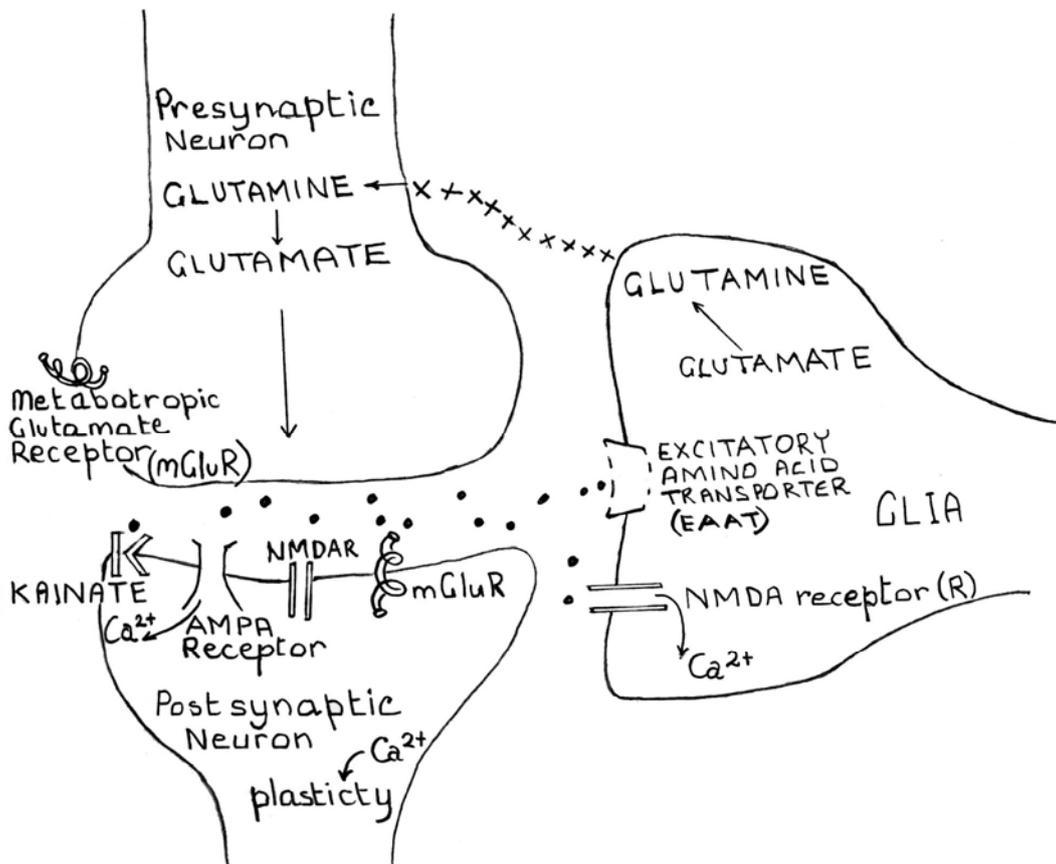

Illustration. Glutamate is released into the synaptic cleft and may activate various receptors on the postsynaptic membrane:
1. N-methyl-D-aspartate (NMDA; ionotropic)
2. AMPA (the chemical name is too long to remember; ionotropic)
3. Kainate (ionotropic)
4. Metabotropic glutamate receptor (mGluR)

Glutamate reaching glia may:
1. activate NMDA receptors
2. be taken into the cell by excitatory amino acid transporter (EAAT).
3. is converted to glutamine and passed back to presynaptic neurons, where it is transformed back into glutamate.

This system and the actions of pharmacological agents are incompletely understood. Ketamine, which appears to have beneficial antidepressant effects (Diazgranados et al, 2010 a&b), is thought to provide NMDA receptor antagonism and AMPA receptor activation.

Excitingly, a recent Nature report suggests that NMDA receptor antagonists cause increased production of brain-derived Neurotrophic factor (BDNF; Autry et al, 2011).

Additional details of structures of particular interest

Additional details are presented of some structures which are believed to play a role in mental life and certain psychiatric disorders.

It is not necessary to have a complete knowledge of the structure and function of the brain to comprehend mental disorders, as they are currently conceptualized.

However, the biological underpinning mechanisms are being slowly revealed, and a detailed knowledge will become essential as newer pharmacological agents become available.

Hippocampus

A better title is, 'the hippocampal formation'. The hippocampal formation is composed of three parts: 1) the dentate gyrus, 2) the hippocampus (better referred to as the hippocampus proper), and 3) the subiculum.

These have a cylindrical form. Think of a rolled up newspaper with a loose advertising pamphlet inside. The subiculum and the hippocampus proper are continuous and are like the newspaper, the dentate gyrus is like the pamphlet, that is, a separate piece (although, further back in evolution, it was continuous with the other two parts).
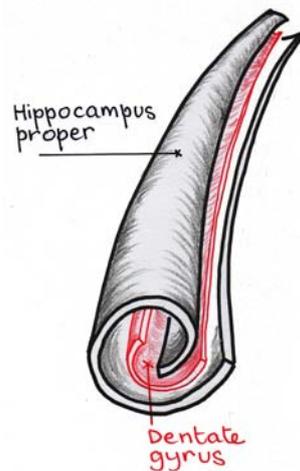
Illustration. Hippocampal formation: the newspaper and the advertising pamphlet.
The name hippocampus comes from the similarity in cross section to a sea horse. Greek:
hippos = horse (the hippocampus is not to be confused with the hippopotamus, the "horse
of the river"). The sea horse is commonly depicted as "S" shaped.

The hippocampal formation lies in the temporal lobe, immediately below (indenting the
floor of) the inferior horn of the lateral ventricle.

Therefore, looking at the medial aspect of the temporal lobe, not much of the
hippocampal formation can be seen. On this aspect, the parahippocampal gyrus is the
dominant feature (that is, the cortex overlying the hippocampus). The part of the
parahippocampal gyrus closest to the hippocampal formation is called the entorhinal
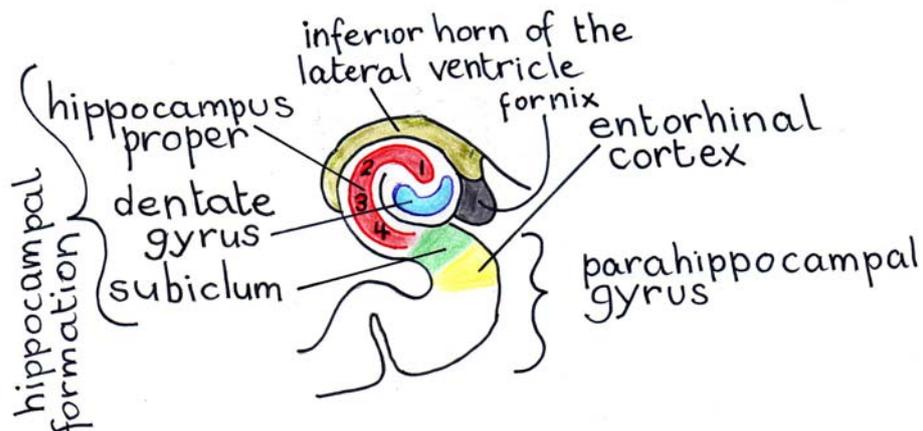cortex.

Illustration. The hippocampal formation (composed of the dentate gyrus, hippocampus
proper and subiculum) in cross-section (coronal) pushing up into the floor of the inferior
horn of the lateral ventricle (in the temporal lobe). The hippocampus proper is also called
Ammon's horn (or cornus ammonis) after an Egyptian god who had ram's horns. On an
histological basis this structure has been divided into 4 regions: (cornus ammonis) CA1
to CA4 (see numbers 1 to 4 in the illustration). Then comes the subclinium, which is
continuous with the entorhinal cortex.

Two main tracts join the hippocampal formation: 1) the perforant pathway, and 2) the fornix. Both of these tracts have ingoing and outgoing pathways (afferent and efferent), but the perforant pathway is predominantly afferent, and the fornix is predominantly efferent. The perforant pathway is largely within the parahippocampal gyrus and cannot be seen from the outside. The fornix is a more prominent structure, which will be described in greater detail shortly. It is mentioned here because it can be seen on the medial surface of the temporal lobe, and appears in cross section illustrations.
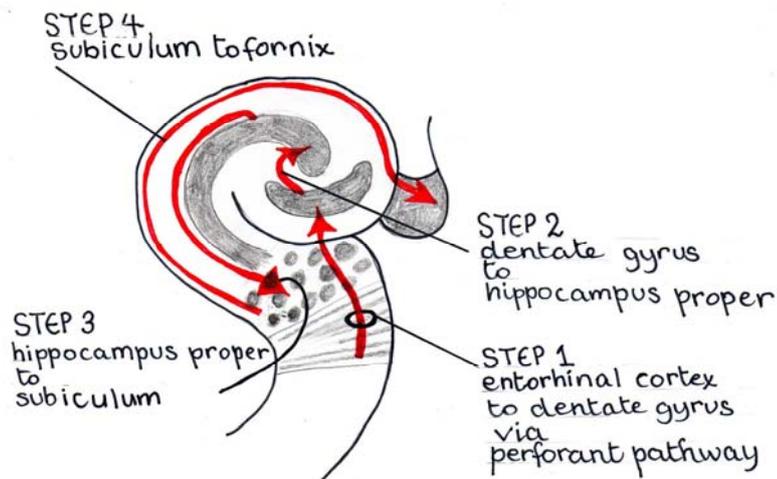

Illustration. The major route of information flow through the hippocampal formation. This illustration is greatly simplified. Information passes in both directions, but the predominant direction is as shown, and can be considered as four steps: Step 1, fibres in the perforant pathway enter via the entorhinal cortex and end in the dentate gyrus; Step 2, fibres passing from the dentate gyrus to the hippocampus proper; Step 3, fibres passing from the hippocampus proper to the subiculum (the illustration is oversimplified at this point, as there is usually at least some connection between different parts of the hippocampus proper before fibres pass to the entorhinal cortex); Step 4, fibres passing from the subiculum through the hippocampal formation to reach the fornix.

The circuitry of the hippocampal formation makes it well suited to memory function, but also makes it vulnerable to damage. One neuron from the dentate gyrus connects with about 12 neurons in the hippocampus proper, each of which then communicates (via axon collaterals) with about 50 excitatory and about 25 inhibitory hippocampus proper cells. Thus, there is potentially a 60 000 % amplification of excitation, and 30 000 % amplification of inhibition.

The hippocampal formation is a highly plastic. This also makes it well suited to memory function, and may offer the potential for repair. Two main mechanisms are reported: dendritic remodelling and neurogenesis.

Dendritic remodelling includes dendritic retraction and simplification during stressful experiences (Sousa et al, 2000). Interestingly, in hibernating animals, dendritic

remodelling occurs within hours of the onset of hibernation and is reversed within hours of awakening from wakening hibernation (Popov et al, 1992).

Neurogenesis, until recently, has been thought to be limited to intrauterine life. However, evidence now indicates that new neurons are born in the dentate nucleus throughout life.

In animal studies, stress has been shown to stimulate dendritic remodelling (Popov et al, 1992) and suppress neurogenesis (Gould et al, 1997).

(An aside: many other types of plastic change have been described in the CNS more generally. Three are of particular interest: the "strengthening" of synapses (Shashoua, 1985), synaptogenesis (the formation of new synapses), and dendritic pruning. In strengthening of synapses, the microscopic structures becomes darker and thicker, and function more efficiently (transmit signals more readily). Synaptogenesis is usually accompanied by some sprouting of dendrites. These changes are associated with learning, and presumably, psychotherapy. Dendritic pruning (which continues during early adulthood) is the removal of dendrites which are superfluous and may actually be making the organism less efficient. This form of pruning is a normal process, and is probably distinct from the dendritic remodelling arising from stress. One theory of the aetiology of schizophrenia proposes excessive pruning leading to that disorder.)

Psychiatric disorders and the hippocampus

The hippocampus is important in the laying down of new memories (that is, facts, declarative memory). Damage to both hippocampi results in failure to lay down new memories (anterograde amnesia), but old memories are retained (presumably old memories are stored elsewhere, probably the cortical association areas).

Difficulty with laying down new memories is observed with bilateral damage: chronic temporal lobe epilepsy, surgical resection and trauma. It is seen as a temporary phenomenon with bilateral electroconvulsive therapy (ECT; an electrical treatment of severe depression). While temporary, post-ECT amnesia can be distressing, unilateral ECT (applying energy to one side of the head only) is not associated with the same degree of memory disturbance, and is the preferred method (depending on various clinical factors).

Korsakoff's psychosis (amnestic syndrome, most commonly resulting from thiamine deficiency) is associated with bilateral damage to the mammillary bodies and other periaqueductal grey matter. (The mammillary bodies being a major focus of output from the hippocampus, via the fornix.)

Individuals with bilateral hippocampal damage can continue to learn motor skills (which is more a basal ganglia function).

Reduced hippocampal volume has been described in posttraumatic stress disorder (PTSD; Bremner et al, 1995), depression (Bremner et al, 2000), and early life abuse (Schmahl et al, 2003). Studies have demonstrated reduced declarative memory in PTSD (Brewin, 2001); this is consistent with hippocampal damage.

Recent work has found that major depressive disorder (but not bipolar depression) is associated with smaller hippocampi (Kempton, et al, 2011).

Fornix

The fornix is a white matter structure with carries information from and to (predominantly from) the hippocampal formation. A crus (leg) of fornix emerges from each hippocampal formation posteriorly and arches forward and toward the midline. These legs join to form a single midline structure (body of the fornix) which is attached to the septum pellucidum (a thin vertical membrane which separates the lateral ventricles) on the roof of the third ventricle. The body continues forward and divides into left and right columns, which pass through the hypothalamus to enter the mamillary bodies. The fornix sends fibres to the septal area, thalamus and hypothalamus.

Psychiatric disorders do not appear to be associated with isolated fornix pathology, however, one diffusion tensor imaging (DTI) study suggests fornix pathology is associated with anorexia nervosa (Kazlouski et al, 2011), and increasingly, schizophrenia is being associated with widespread white matter abnormalities, including the fornix (Lee et al, 2013). A post-mortem study suggests the mammillary bodies are compromised in depression (Bernstein et al, 2012). Abnormalities of the fornix have been demonstrated in 'amnestic mild cognitive impairment' (a prodromal stage of Alzheimer's Disease; Zhuang et al, 2013).
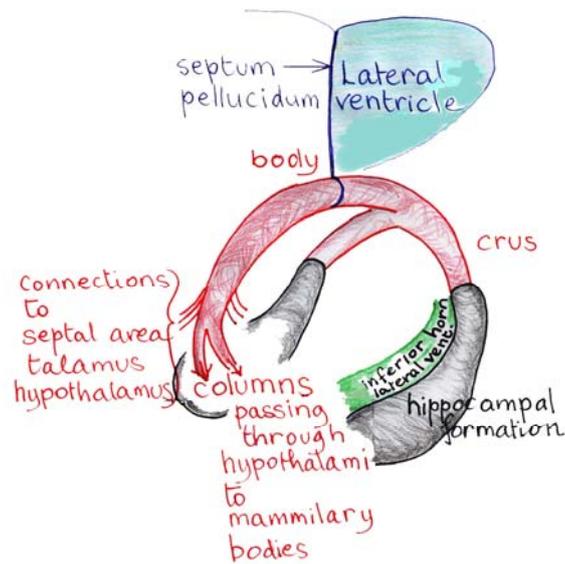
Illustration. The crura, body and columns of the fornix. The hippocampal formation is immediately beneath the floor of the inferior horn of the lateral ventricle, and the body of the fornix is shown at the bottom of the septum pellucidum, which separates the lateral ventricles.

Papez Circuit

In 1937, James Papez described a neural loop which could theoretically allow the coordination of the neocortex, limbic structures and the hypothalamus, and form the anatomical substrate of emotion. While an oversimplification (given current knowledge), Papez Circuit stimulated much research, and remains a fair summary of some aspects of this complicated topic.

The first part of the loop has been described under the headings of Hippocampus and Fornix.
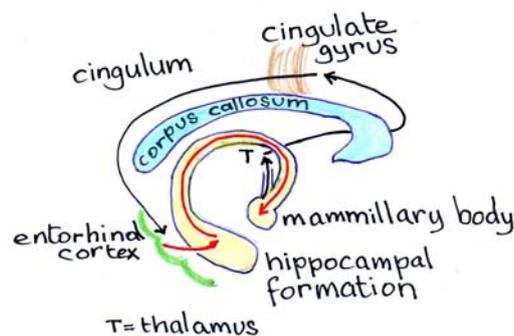

Illustration. Papez Circuit. Information passes 1) from the entorhinal cortex to the hippocampal formation, 2) forward in the fornix to the mamillary bodies. Papez described information passing, 3) from the mamillary bodies to the thalamus, and 4) from the thalamus via the cingulum (within the cingulate gyrus) back to the entorhinal cortex.

Amygdala

The amygdala is three nuclei, in front of the tip of the hippocampal formation. It causes a bulge on the parahippocampal gyrus which is known as the uncus. It also abuts the putamen and the tail of the cordate within the temporal lobe (which led to it being considered part of the basal ganglia, rather than the limbic system, by early authors).

The amygdala receives a vast amount of highly processed sensory information. Visceral inputs (particularly olfactory) are prominent.

Fibers leave the amygdala through two main pathways: stria terminalis and the ventral amygdalofugal pathway. The stria terminalis passes forward in the lateral ventricle in the groove between the caudate nucleus and the thalamus, and distributes fibres to the caudate, putamen, septal nuclei, ventral striatum (nucleus accumbens) and hypothalamus.

The letters "fug" in amygdalofugal have the same root as those letters in the word "fugitive", where they indicate running away, usually in an indiscriminate manner. The ventral amygdalofugal pathway passes beneath the basal ganglia structures and relays information to a wide array of structures at the base of the brain and beyond: thalamus, hypothalamus, septal nuclei, ventral striatum and brainstem structures.

In addition to the two large outflows, locally, fibres extend from the amygdala to the entorhinal cortex and other temporal lobe structures.
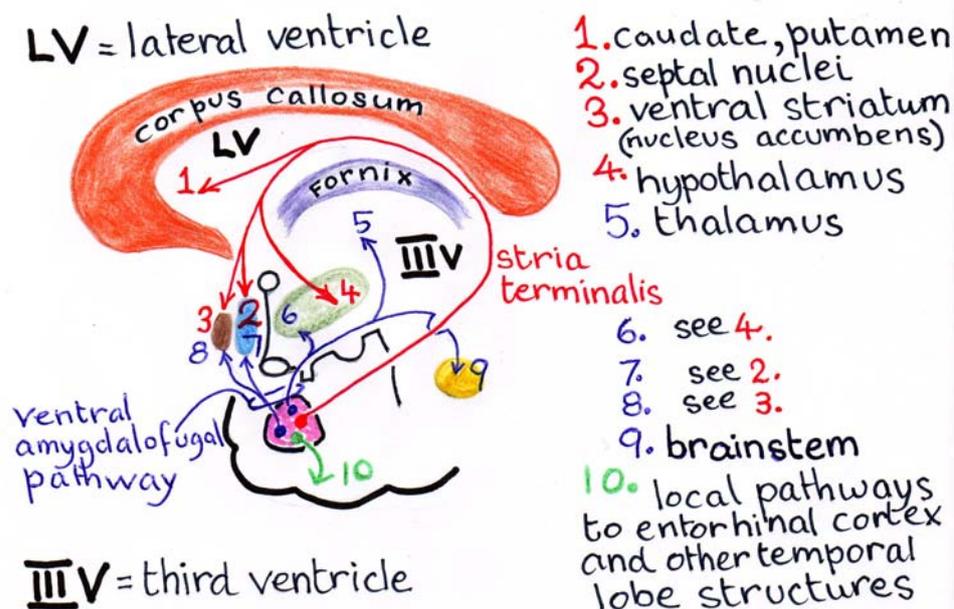

Illustration. Diagrammatic representation of the outputs of the amygdala. Two main pathways: stria terminalis and ventral amygdalofugal (arriving at some common destinations). Also, there are also outputs to local temporal lobe structures including the entorhinal cortex.

The ventral striatum is a ventral fusion of the putamen and caudate. (This structure, also known as the nucleus accumbens, is mentioned in Chapter 12, which deals with substance use disorders.) It serves as a link between the limbic system and the basal ganglia, and has a role in addictive behaviour.

The connections of the amygdala with the septal nuclei, hypothalamus and prefrontal cortex suggest it has a role in drive-related behaviours and the subjective feelings which accompany them. While the hippocampus is involved in learning that an event has happened (the fact), the amygdala is involved with learning whether to consider something is "good" or "bad".

Stimulation of the amygdala (man and other animals) causes fear, with the full autonomic accompaniments.

Disorders and the amygdala

Bilateral damage to the amygdalae produces the Kluver-Bucy (1939) syndrome: 1) placidity and failure to respond to threats (predators), 2) males become hypersexual and are indiscriminate regarding gender and species, 3) inordinate attention to all sensory stimuli, examining objects orally, and eating them (if at all possible) resulting in weight gain, and 4) incessantly examining the same objects. The animal has the behaviour patterns for satisfying the basic drives, but cannot determine the appropriate context in which to do so.

PTSD may involve amygdala pathology. Imaging studies demonstrate exaggerated amygdala activity when the PTSD patient is exposed to fear stimuli. This may be due to a primary increase in the activity in the amygdala, or secondary to a loss of inhibition of the amygdala by the medial prefrontal cortex (Brown et al, 2013).

Exaggerated amygdala activity has also been observed in other anxiety (Charney, 2003) and depressive disorders (Drevets et al, 2002).

Amygdala (but not hippocampal) volume is increased in cases of severely disturbed care in infancy (Lupien et al, 2011). Amygdala (but not hippocampal) volume is decreased in somatic symptom disorder (Atmaca et al, 2011a).

Thalamus
(Greek: "inner cucumber")

"All the input from all our senses flows into it. It takes selective note of what should be given high priority and lets you throw the rest away. Zap. Gone."

                                                                    Nancy Andreasen, 2001

The thalamus is a cucumber shaped grey matter structure (earlier described by another author as 2 hens eggs side by side), about 4 cm in length. It is composed of left and right thalami are separated by the 3rd ventricle. Laterally, the internal capsule separates the thalamus from the globus pallidus and putamen. Anteriorly the thalamus extends to the interventricular foramen superiorly, and the mamillary bodies inferiorly. The posterior pole, or pulvinar, is free (not attached to other structures) and external. The pulvinar are located on either side of the pineal gland and overhang the colliculi. The superior surface of the thalamus is free and covered by a thin layer of white matter, with the subarachnoid space extending from the posterior pole, anteriorly, up to the interventricular foramen. Inferiorly the thalamus is continuous posteriorly with the brain stem, and anteriorly with the hypothalamus.

The thalamus is applied to the superior-posterior 2/3 of the 3rd ventricle (the hypothalamus is applied to the inferior-anterior 1/3).
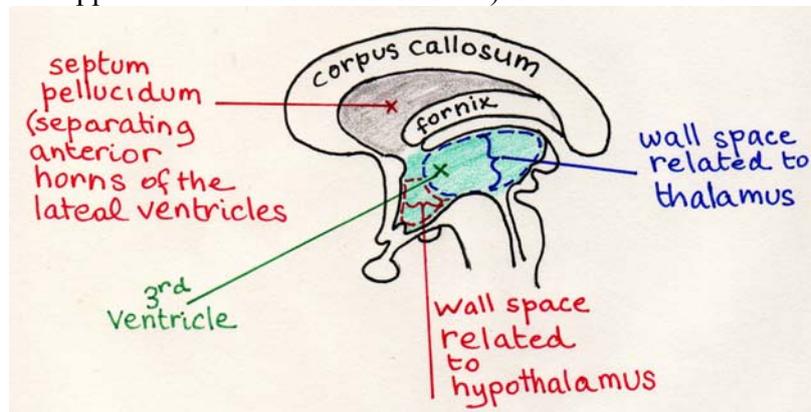

Illustration. The relationship of the thalamus and hypothalamus to the 3rd ventricle.

Posterior-inferiorly, posteriorly and superiorly, the thalamus is cupped by the lateral ventricles and the tail of the caudate. Superiorly, between the thalami, lies the body of the fornix. Anterior to the thalamus, the columns of the fornix project downward and then posteriorly, passing through the hypothalamus, to reach the mamillary bodies. The stria terminalis (passing from the amygdala to the septal nuclei and other anterior structures) lies on the thalamus, lateral to the body of the fornix.
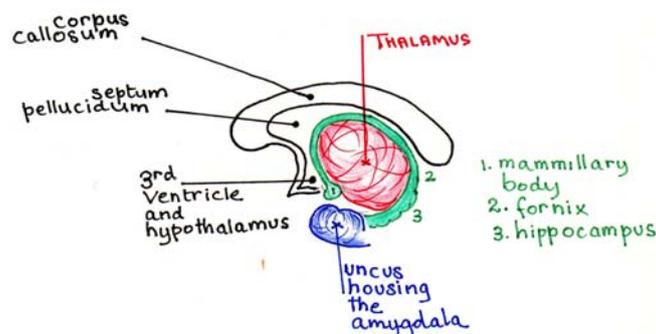

Illustration. The relationship of the thalamus to hippocampus, fornix and mamillary bodies.

The thalamus is the largest component (80%) of the diencephalon (the others being the hypothalamus, subthalamus, and the epithalamus).

The thalamus is divided into three divisions (medal, lateral and anterior) by a thin sheet of fibres (internal medullary lamina). Each division contains a number of nuclei, and there are also nuclei within the lamina. Examples include the protuberances of the pulvinar known as the medial and lateral geniculate bodies (associated with hearing and sight respectively).

The **thalamic reticular nucleus**, a thin sheet of cells which partially covers the lateral aspect of the thalamus, deserves special mention. It is developmentally and anatomically distinct from the rest of the thalamus, and has a somewhat different mode of function (see below).

All sensory information passed on to the cerebral cortex is relayed via the thalamus. The nuclei perform two functions: 1) as part of the passage by which information reaches the cortex, and 2) as sites at which decisions are made about which information will be passed on cortex for further processing.

The thalamic nuclei (with the exception of the reticular nucleus) have two main components: 1) the cell bodies of neurons which project out of the thalamus, and 2) small inhibitory neurons that use GABA as a neurotransmitter.
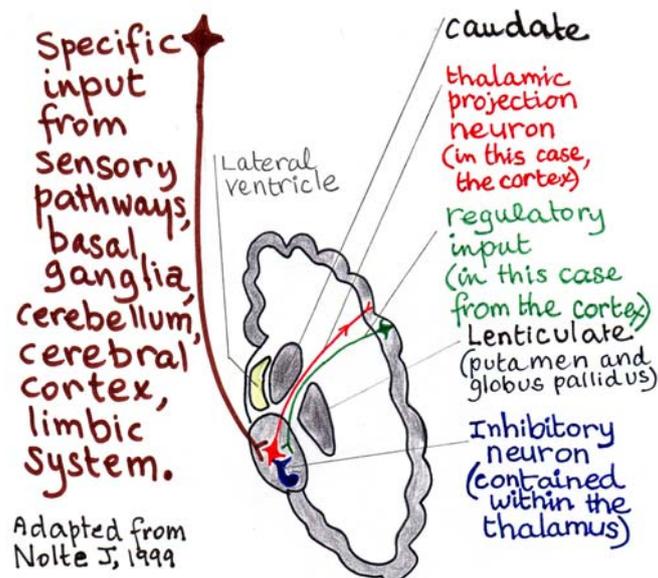

Illustration. Here, the thalamus is depicted as a single large nucleus. The nuclei are composed of cell bodies which project to the cortex and small internal inhibitory neurons. The nuclei receive input from a range of sensory pathways. They project information to the cortex, and also receive regulatory input from the cortex (usually from the same region to which they project). The input and output of the thalamus contributes to the internal capsule (which separates the thalamus from the globus pallidus and putamen).

Unlike all other nuclei, the thalamic reticular nucleus projects to other thalamic nuclei, rather than the cortex. Axons travelling between the thalamus and the cortex (in both directions) transverse the reticular nucleus. As they do, they give off collaterals to the reticular nucleus. The reticular nucleus is an important source of regulatory inputs to the thalamus. Thus, it is a second mechanism of thalamic information modification.

In addition to involvement in circuits incorporating the cerebral cortex, the thalamus is involved in circuits which incorporate the cerebellum, basal ganglia and limbic structures.

All connections between the thalamus and the cerebral cortex and most of the connections between the thalamus and other subcortical structures travel through the internal capsule. This is a sheet of white matter with two limbs. The anterior limb separates the head of the caudate from the lentiform nucleus (putamen and globus pallidus); the posterior limb separates the thalamus from the lentiform nucleus.

Thalamus and mental disorders

Localised infarcts, particularly bilateral, may cause cognitive deficits, poor verbal fluency and apathy.

Over many years, authors have suggested that thalamic pathology contributes to the aetiology of schizophrenia. Imaging studies reveal significantly reduced thalamus size in groups with schizophrenia (Chua et al, 2007). Volumetric abnormalities reported in twin studies suggest genetic factors influence the thalamic structure in schizophrenia (Ettinger et al, 2007). Schizophrenia may be the result of glutamate abnormalities in the projections of the thalamus to the cortex (Sodhi et al, 2011), and a higher overall thalamocortical connectivity has been demonstrated (Klingner et al, 2013).

Recent suggestions have suggested a role for the thalamus in obsessive compulsive disorder (Atmaca, 2011b) and late-life depression (Sexton et al, 2013).

Frontal-subcortical circuits

Five circuits link frontal cortex, basal ganglia and the thalamus (Alexander et al, 1986). Disruption of three of these produce cognitive and neuropsychiatric symptoms. (Disruptions of the other two, those originating in the supplementary motor area and the frontal eye fields, are not associated with known neuropsychiatric symptoms.)

Cortical site of origin	Function	Neuropsychiatric symptom
Dorsolateral prefrontal	Executive functions	Executive dysfunction (segmented drawings, poor recall, word list generation, serial hand sequencing, etc)
Lateral orbitofrontal	Personality (socially appropriate behaviour, empathy)	Disinhibition, irritability, lability, tracklessness, euphoria
Anterior cingulate	Motivation	Apathy, rarely moving, incontinent, monosyllabic responses, indifference to surroundings

These circuits have the same basic anatomic organization, and each have a "direct" and an "indirect route".

Direct route
1. Frontal cortex to striatum (caudate/putamen)
2. Striatum to globus pallidus interna
3. Globus pallidus interna to thalamus
4. Thalamus to frontal cortex site of origin

Indirect route
1. Frontal cortex to striatum (caudate/putamen)
2. Striatum to globus pallidus externa
3. Globus pallidus externa to subthalamic nucleus
4. Subthalamic nucleus to globus pallidus interna
5. Globus pallidus interna to thalamus
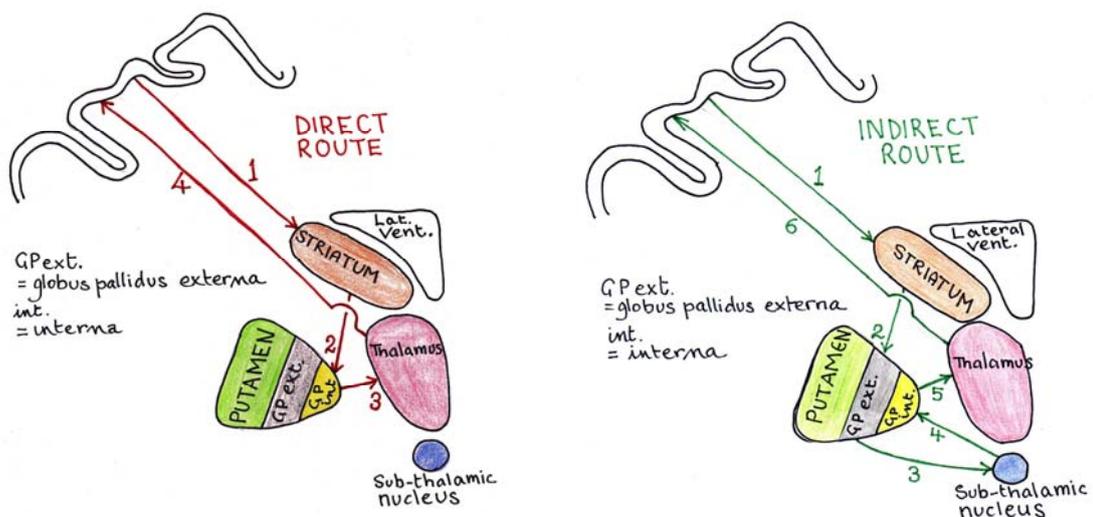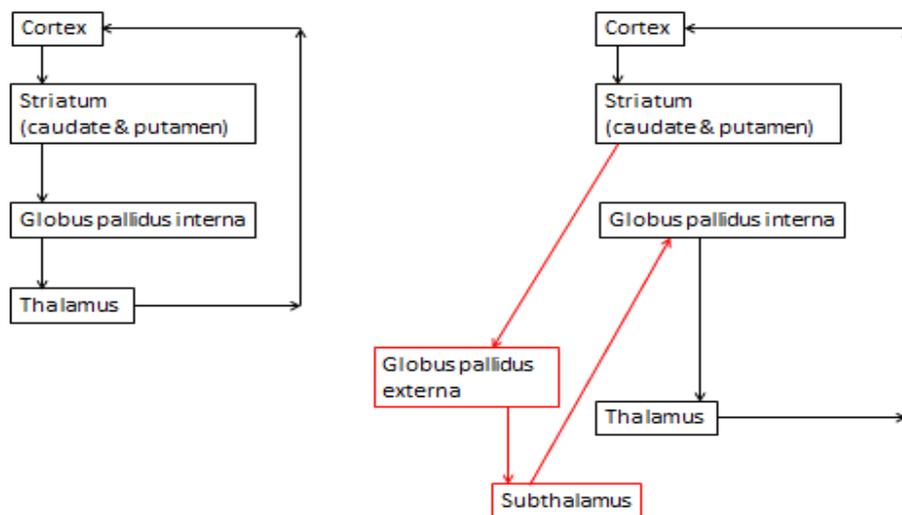6. Thalamus to frontal cortex site of origin.

Illustration. Direct and indirect routes of frontal-subcortical circuits.

The frontal-subcortical circuits are complex, and only a simplified introduction is attempted. For further details, see Mega and Cummings (1996). These circuits are finely balanced. First, within a particular circuit, different links use different neurotransmitters, including excitatory (glutamate), inhibitory (gamma aminobutyric acid; GABA) and other neurotransmitters (Substance P; endorphins; dopamine, serotonin and acetylcholine). Second, the direct and indirect routes are balanced against each other. Accordingly, lesions at different sites within a particular circuit may lead to similar clinical syndromes.

Frontal-subcortical circuits and disorders

Disturbance of executive function, disinhibition and apathy are well known with macroscopic lesions of the frontal lobes (the frontal lobe syndrome). These are also symptoms of enormous importance in schizophrenia and bipolar where the lesions are less well understood. Aberrant functional connectivity of the frontal-subcortical circuits has been demonstrated in unipolar depression (Marchand et al, 2012).

While the above disorders are associated with decreased neuronal activity in the frontal-subcortical circuits, obsessive compulsive disorder is believed to result from hyperactivity in the orbitofrontal-subcortical circuit. A recent diffusion tensor imaging (DTI) study in OCD found abnormalities in the frontal-subcortical circuit (Chiu et al, 2011).

Circuits involving the cortex and the subcortical structures have been described in the pathophysiology of movement disorders (Albin, 1995). The balance of the direct and indirect routes is important in these disorders. In Huntington's chorea, loss of the indirect route causes increased activity of the thalamus, and consequently, increased stimulation

of the cortex (with resultant chorea). In Parkinson's disease, loss of the nigrostriatal tract (loss of dopamine stimulation of the striatum) results in increased inhibition of the thalamus and decreased stimulation of the cortex (with resultant poverty of movement). Patients with Huntington's disease have an increased frequency of agitation, irritability, anxiety and euphoria (Litvan et al, 1998), while patients with Parkinson's disease an increased frequency of apathy and depression (Aarsland et al, 1999).

Cerebellum
(Latin: "little brain")

The cerebellum occupies only 10% of brain volume, but contains 50% of the brain's neurons (a puzzling fact). It is a fabulously complex structure and its function remains incompletely understood. It is predominantly involved in movement, particularly the coordination of movement. It is known to be involved to some degree in executive functioning, and cerebellar damage may be associated with personality change (blunting of affect and disinhibition have been described). More recently, some evidence suggests a role in certain psychiatric disorders.

With our present knowledge, it is inappropriate to spend much time/space on this topic in a basic text.

The cerebellum is composed of the vermis (a midline structure) and one cerebellar hemisphere on either side. There are 4 subcortical nuclei. The cerebellar cortex is composed of 3 layers: 1) molecular (stellate and basket cells), 2) Purkinje cell layer, 3) granular layer (Golgi type II cells, glomeruli complexes of synapse encased by glial cells). The Purkinje cells are unique, large extensively branching neurons with are confined to the anterio-posterior plane. They project to the deep nuclei and provide the output of the cerebellar cortex. The principal output of the cerebellum is to the thalamus, and thence, to the cerebral cortex. Inputs to the cerebellum are via the climbing fibres and mossy fibres.

An analogy has been drawn between the coordination movement and "the coordination of mental processes", with the proposal that the cerebellum is involved in both activities. The term "cognitive dysmetria" was coined (Andreasen, 1997). One theory states that the disturbance of the mental processes found in schizophrenia may result from dysfunction of a circuit connecting the frontal cortex, thalamus and cerebellum (Rusch et al, 2007; Yeganeh-Doost et al, 2011; Fusar-Poli et al, 2012).

There is some support for smaller volumes of the vermis in people with schizophrenia (Varnas et al, 2007). However, this is by no means the most common neuroimaging finding is this disorder.

There is reduction of cerebellar volume in dementia. There is reduced volume in the pre-dementia stage, and cerebellar volume may be an early marker of the disease (Baldacara et al, 2011).

Fight or flight response

"Stress" (disturbance of homeostasis) triggers the fight or flight response, which protects the organism in danger.

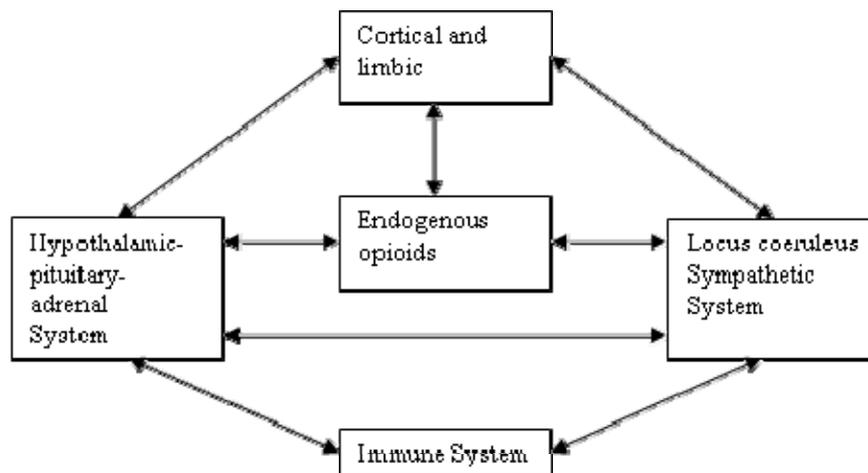Chapter 34, "Psychoneuroimmunology", provides further details and references.

Illustration. The fight or flight response. Arrows indicate extensive interaction between the components.

Hypothalamic-pituitary-adrenal (HPA) axis activation includes the secretion corticotrophin-releasing factor (CRF) by the hypothalamus. This causes the release of adrenocorticotropic hormone (ACTH) by the pituitary, which in turn causes release of cortisol for the adrenal cortex. Cortisol produces and maintains high levels of glucose to support activity.

Simultaneous stimulation of the locus ceruleus (located in the brainstem) leads to noradrenalin pathway activation of the hypothalamus, limbic structures, cortex and sympathetic nervous system. The main limbic structures activated in this process are the hippocampus and amygdala.

Tissue injury liberates cytokines (complex molecules: gamma-interferon, interleukin 1, interleukin 6, tumour necrosis factor), which are carried by the circulation and have an immediate effect on the hypothalamus (Sapolsky, 1992).

In the acute situation, the endogenous opioids are released, presumably to reduce pain (perhaps they also have a role in modulating the release of cortisol; Chrousos, 1992).

Continuous high levels of cortisol breaks down protein (to provide glucose), inhibit replacement of calcium in bones, and damage the hippocampus (Sapolsky, 1996). Evidence also suggests that "dysregulation of the HPA axis" (chronic high cortisol levels) can contribute to depression, anxiety, posttraumatic stress disorder and irritable bowel syndrome.

HPA axis dysfunction appears to involve hyper-stimulation of the CRF-1 (type 1) receptor. CRF-1 receptors are located at multiple anatomical sites. An oral CRF-1 receptor antagonist (which has few side effects) appears to be an effective treatment of stress related disorders, although further studies are required (Kehne, 2007).

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