In celebration of cerebration

Colin Blakemore

The weight of past scholarship presses heavily on the shoulders of anyone who is invited to accept William Harvey's challenge to his eponymous Orators to 'Exhort the Fellows and Members of the College to search and study out the secrets of Nature by way of Experiment'. Since the first Harveian Oration, given on St Luke's Day, 1665, exactly 340 years ago, the scientific and clinical stories told by previous distinguished Orators provide an oral history of knowledge, from Harvey's extraordinary era to the present day. Harvey himself extends the lineage of scholarship back further. To Galileo, who was a Professor at Padua when Harvey studied medicine there. To William Shakespeare, who lodged at Puddle Dock, a few streets away from Harvey's residence near St Martin's Church in London. To his friends, John Donne and Thomas Hobbes. And to Francis Bacon, proponent of inductive reasoning, father of the scientific method, and an inspiration to those who later founded the Royal Society.

Bacon was a close colleague of Harvey, who was his private physician. In 1618, three years after his election as Lumleian Lecturer at the Royal College of Physicians, Harvey was appointed Physician Extraordinary to James 1, and in the same year Francis Bacon was made Lord Chancellor. Bacon published his seminal work on inductive reasoning, *Novum Organon*, in 1620, when Harvey was consolidating his evidence for the circulation of the blood.

It is tempting to imagine Harvey and Bacon deep in discussion about the acquisition of knowledge, about the victory of evidence over dogma. Bacon certainly observed Harvey at work:

> *I have oft seene Dr. William Harvey, the new doctor from Padua, at Bartholomew Hospital, in the presence of the learned doctors, force a purple, distilling liquor through the veines of a dead body, and, after it had descended to the heart, liver, and lungs, the blood-coloured liquor returneth againe to the face which blacke and full of blood, or pale, meagre, and bloodless before, doth blush and beautifie, as if with life; you would think the body breathed; the very lippe is warme to look upon; but we are mock'd with art as there is no pulse gainst the finger and though the arteries seem full, yet no life is present. The legs, waist, arms, hands, brow, and limbs seem alive, but we can never ransome nature.*

Harvey published *De Motu Cordis* in 1628, two years after Francis Bacon had died from bronchitis, which he contracted after standing outside in bitter weather, stuffing a chicken with snow in an effort to discover the principles of refrigeration.

Harvey is often credited with the invention of medical research – the search for factual evidence about bodily function and disease. As Sir William Osler put it, *De Motu Cordis* marked 'the break of the modern spirit with the old traditions'. In his dedication of *De Motu Cordis* to the President and Physicians of the Royal College, Harvey wrote:

> *I profess both to learn and to teach anatomy not from books but from dissections; not from the positions of philosophers but from the fabric of nature.*
>
> (Harvey, 1628)

From the Circle of Blood to the Circle of Willis

My subject is the brain – the cerebral cortex in particular. I shall discuss the present state of knowledge of the function of this, the most remarkable and mysterious of organs. But my perspective is a personal one and I apologise for the necessarily selective bibliography, which cannot do justice to the vast literature of this field.

Marcello Malpighi (1628–1694), whose discovery of capillaries provided the final piece of evidence for Harvey's hypothesis of the circulation of blood, wrote: 'I recognize and believe that the structure of the brain is … wholly incapable of explaining the phenomena of the senses and of such noble operations' (cited by Critchley, 1966). In the speculations at the end of James Collier's (1934) Harveian Oration, he wrote:

> *In the progress of neurology the all-essential labours of the Physiologist and of the Anatomist have almost reached finality. Much addition to the wealth of their discoveries is not to be expected in the future.*

Collier was wrong. The flood of knowledge about the nervous system in the past 50 years has been astonishing, even to those of us who have been swept along by its current. Nevertheless, we all labour under a cloud of practical and philosophical uncertainty. The capacity for human understanding has given insight into the nature of matter, the origin of the universe, the basis of life and its evolution. But it is reasonable to ask whether the human brain is capable of understanding itself. The fact is that,

The Harveian Oration is given annually at the Royal College of Physicians of London under an indenture of William Harvey in 1656. This article is based on the 2005 Oration given on 18 October 2005 by **Colin Blakemore** FMedSci Hon FIBiol Hon FRCP FRS, Waynflete Professor of Physiology, University of Oxford; Chief Executive, Medical Research Council, London

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despite the remarkable advances in techniques for studying the living human brain, especially through the various methods for functional imaging, there are fundamental limits to their spatial and temporal resolutions, which limit their capacity to reveal underlying neural mechanisms. Most of what we know of the processing of information in the brain has come from the study of animals. However, we should not be pessimistic about the challenge of understanding the human brain, unless human brains embody some principle of operation that is fundamentally different from those of the brains of other animals.

William Harvey is, of course, remembered principally for his work on the circulation, but his role as Lumleian Lecturer, from 1615 to 1656, and as a teacher in Oxford, from 1642 to 1646, demanded a much wider knowledge of, and contribution to anatomy and physiology. His views on the nervous system are documented in *De Generatione* (1651), the *Prelectiones* (translated, 1886) and *De Motu Locali Animalium* (Whitteridge, 1958), and were reviewed brilliantly by Sir Russell Brain in his Harveian Oration (1959).

Harvey was influenced by Fabricius, his anatomy teacher in Padua. Following Galen and Vesalius, Fabricius believed that muscle contraction results from some sort of force or impulse ('power without a substance' as Galen had called it) passing down the nerves from the brain. Harvey was particularly interested in the distinction between involuntary motor functions, 'natural' as he called them, and those that are under voluntary control. He described the movements of a cockerel after decapitation:

> *they are as the movements of men in delirium and useless and convulsive and irregular as those of drunkards … all confused and without a purpose, because the controlling power of the brain has been taken away.* (Whitteridge, 1958)

He clearly saw the brain as the vehicle of awareness. He proposed that it is responsible not only for voluntary movement, but also for the sensations that underpin the control of such movement. However, not all sensations are made conscious:

> *there is a certain sense or form of touch which is not referred to the common sensorium, nor in any way communicated to the brain, so that we do not perceive by this sense that we feel.* (Whitteridge, 1958)

Harvey accepted the Galenic view that the flow of signals is centripetal, from the brain, to both muscles and sense organs. However, he made the profound proposal that sense organs are not in themselves responsible for conscious feelings:

> *Seeing with our eyes, we still do not know by them what we see, but by another sense or sensitive organ, namely the internal common sensation or common sensorium, by which we examine those things that reach us through each of the external sensoria, and distinguish that which is white from that which is sweet or hard. Now this sensorium commune to which the species or impressions of all the external instruments of sensation are referred, is obviously the brain, which … is held and esteemed to be the adequate instrument of a sensation.* (Whitteridge, 1958)

If the brain is the origin of perceptions, messages from the sense organs must be relayed to the brain. Hence, Harvey conceived of a to-and-fro movement of activity along nerves: 'Does it return along with sensation to the brain?' (Whitteridge, 1958).

Harvey contributed crucial evidence to the debate about whether different kinds of nerves mediate motor control and sensation. He described that: 'if a nerve is compressed in the hip the whole leg becomes numb, and is deprived of sensation but not of movement' (Whitteridge, 1958). And he observed:

> *a servant in the colledg of Physitians in London …*[who] *was exceeding strong to labour, and very able to carry any necessary burthen, and to remove things dextrously, according to the occasion; and yet he was so voyd of feeling that he used to grind his handes against the walles, and against course lumber, when he was employed to rummage any; in so much, that they would runne with bloud, through grating of the skinne, without his feeling of what occasioned it.* (Digby, 1644)

This case, presumably of syringomyelia, provided Harvey with compelling evidence for the separation of motor and sensory pathways.

Although Harvey himself made only modest contributions to the understanding of the nervous system, he played a major role in the birth of modern neuroscience – through his influence on the remarkable group of natural philosophers in Oxford who played such a central role in the establishment of the Royal Society. In 1642, after the start of the Civil War, Harvey, then Physician to Charles I, left London to join the King. Shortly afterwards his apartment in Whitehall Palace was ransacked by Parliamentarian soldiers and most of his documents were destroyed. He tended the King during the Battle of Edgehill and fled with him to Oxford, which became the Royalist capital. Harvey was appointed Warden of Merton College by Royal mandate in 1645.

The community of scholars in Oxford, mostly loyal to the King, welcomed Harvey, who was incorporated MD on 7 December 1642. Harvey not only continued his dissections, but also taught and demonstrated to students and interested Fellows. Among these was Thomas Willis (1621–1675).

In 1636, at the age of 15, Willis matriculated at Christ Church with the intention of entering the church. He was awarded the BA in 1639, and the MA in 1642, the start of the Civil War. Against this turbulent background, Willis, a devout supporter of the Crown, decided to change his studies to medicine. The normal medical course at Oxford lasted 14 years – 14 years of committing Galen, Hippocrates and Aristotle to memory. But Willis enjoyed fast-track training, aided by the unusual circumstances and by his loyalty to the Royal cause. In 1645, Willis enlisted in Dover's regiment in the service of the King. Just a year later he was rewarded with the Bachelor of Medicine degree and he immediately began to practise. That same year, Charles, whose army had been defeated at Naseby and Langport in 1645, fled north and Oxford was surrendered to the Parliamentarians.

On 24 July 1646, Harvey returned to London where he lived with his brother Eliab, a rich merchant. But he left his influence on Thomas Willis, which shows in the rigorous Baconian approach that Willis followed throughout his fruitful career. He continued to refine the skills in dissection that he had presumably first learned from Harvey, as well as from his mentor, William Petty, Tomlins Reader in Anatomy. Willis worked with

several skilled collaborators, including Petty, Richard Lower, Thomas Millington and young Christopher Wren. Wren was only 28 in 1661, when he was appointed Savilian Professor of Astronomy at Oxford, where he spent much of his time in research on physiology and anatomy.

Willis dissected the brains of a wide variety of animals, including humans, whose fresh bodies Petty received from the local hangman under the terms of the Tomlins Readership. Willis made several leaps of understanding about the structure and function of the brain, not least his description of the arterial circle at the base of the brain that still bears his name. He dismissed Galenic and Aristotelian concepts that had held sway for more than 1,500 years (Meyer and Hierons, 1965a,b; Isler, 1968; Hughes, 1989; Molnár, 2004).

Willis was elected to the Royal Society in 1663 and to the Royal College of Physicians in 1664, the year of publication of his most important work, *Cerebri Anatome*, with its remarkable illustrations by Wren (Fig 1). This book recorded his expert dissections of the human brain, his conclusions from observing patients with neurological disorders, and his insightful comparisons with the brains of other animals. Willis anticipated Darwin in his comparison of morphology and function across species, and he developed a correlative approach, linking function to form. This he extended in *De Anima Brutorum* of 1672.

His assiduous notes of clinical signs and symptoms, combined with dissection of the bodies of his patients after their death, provided him with clues to the basis of a variety of disorders. He noted unilateral degeneration of the cerebral peduncle in a case of longstanding unilateral paralysis, and hence explained a phenomenon that had puzzled William Harvey – the fact that lesions of the right side of the forebrain affect movements on the opposite side of the body, because of decussation of the motor outflow through the cerebral peduncles.

His neuropathological observations were published in a number of books, especially the *Pathologiae Cerebri* of 1667, with its novel theories about epilepsy. He gave the first clear descriptions of myasthenia gravis, restless leg syndrome and schizophrenia, as well as malaria, whooping cough, typhoid fever, puerperal fever, and diabetes mellitus.

To neuroscience, Willis will be remembered best for his rejection of the medieval doctrine that ascribed mental functions to the cerebrospinal fluid ('animal spirit') in the ventricles. Vesalius had already questioned this 'Cell Doctrine' on the grounds that animals have ventricles, yet were assumed not to have souls of human quality. Willis turned instead to clinical evidence and to the comparison of brain structure in various species to fuel his hypotheses. Following classical views, he presumed that the all-important animal spirits are produced through distillation of blood in the brain, but that this process took place in the tissue of the cerebral cortex and the cerebellum. Willis followed Pierre Gassendi in proposing that the ventricles, rather than being the repository of mental processes, are merely 'receptacles for the excretions of the brain'.

Willis noted the enormous size of the cerebral hemispheres in humans, compared with animals, and argued that the substance of the cerebrum must be the seat of those mental functions in

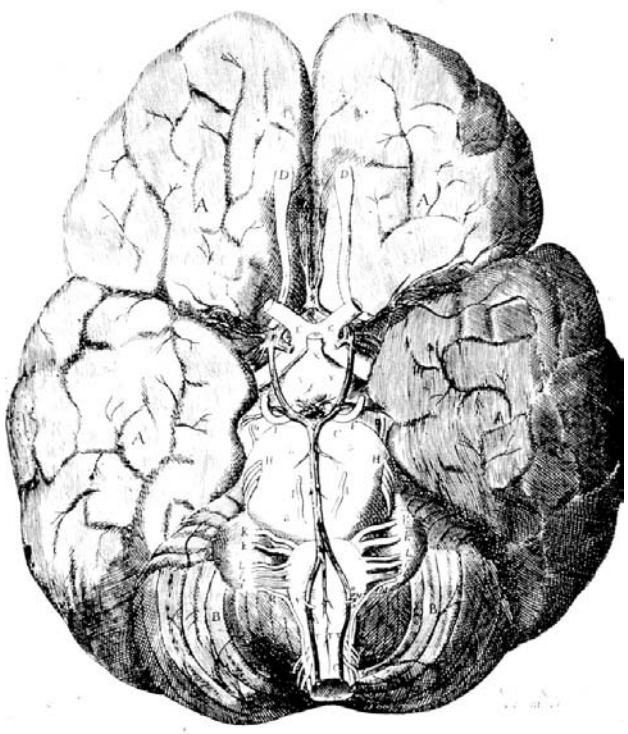


Fig 1. The base of the human brain, drawn by Christopher Wren, from *Cerebri Anatome* (1664) by Thomas Willis. This shows clearly the Circle of Willis (the arterial circle in the centre of the image) and the enormous size of the cerebral hemispheres (A).

which humans excel. Like Gassendi, he imagined that animal spirit flowing out along sensory nerves is somehow reflected back to the cerebral cortex, whence it mediates perception and all its consequences. 'The cerebrum is the primary seat of the rational soul in man, and of the sensitive soul in animals. It is the source of movements and ideas' (Willis, 1664). He assigned perceptual analysis (the sensus communis) to the corpus striatum (a major part of the basal ganglia, to which the cerebral cortex projects), imagination to the corpus callosum, and memory to the cerebral cortex itself. The corpus striatum is, he correctly adduced, involved in the control of voluntary movement, while the cerebellum is responsible for involuntary movement (Meyer and Hierons, 1965a,b).

Pordage's (1681) translation of *Cerebri Anatome* includes the first use of the word neurology and the first in English of 'psychology'. Willis has variously been called 'the founder of clinical neuroscience', 'one of the greatest neuroanatomists of all time' (Molnár, 2004), 'the founder of neurology' (Feindel, 1962) and 'the first Oxford neuropathologist' (Hughes, 1989).

The species of sensible things

Willis realised that the rich convolutions of the cerebral cortex serve to increase even further the surface area of man's enormous brain:

the anfractuous or crankling brain, like a plot of ground, planted every where with nooks and corners, and dauks and mole-hills, hath a far

more ample extension, than if its superficies were plain and even.
(Willis, 1664)

And he suggested that the various faculties that he ascribed to the cerebrum – perception, rationality, will, the control of movement, and especially the memories that underpin these functions – might depend on different parts of its convoluted surface:

the animal Spirits, for the various acts of Imagination and Memory, ought to be moved within certain and distinct limited or bounded places, and those motions to be often iterated or repeated though the same tracts or paths: for that reason, these manifold convolutions and infoldings of the brain are required for these divers manners of ordinations of the animal Spirits, to wit, that in the Cells or Store-houses severally placed, might be kept the species of sensible things. (Willis, 1664)

The cerebral cortex is indeed a patchwork of specialised modules, and the definition of this functional diversity has been a major theme of neurology, neuroanatomy and neuroscience for the past 200 years. The prologue to this story was something of a false start. At the end of the eighteenth century, the Viennese physician and anatomist, Franz-Joseph Gall, proposed that a wide variety of mental functions are localised in 'organs' distributed across the surface of the brain, the competence of which could be judged by palpation of bumps on the surface of the skull. This was, of course, the hypothesis of phrenology. To a modern neuroscientist, the kinds of functions that Gall imagined populate the brain look quaint, even bizarre – such faculties as ideality, hope and benevolence. Nevertheless, phrenology enjoyed a brief period of scientific respectability. But soon it came under criticism, not only because of absence of clear correlation between bumps on many parts of the head and underlying neuroanatomical structures, but also because of the lack of statistical rigour in the derivation of evidence. Indeed, the hostile reaction of the scientific and medical community against phrenology in the first half of the nineteenth century held back the march of genuine evidence for localisation of function in the cerebral hemispheres.

The French physiologist, Pierre Jean Marie Flourens, led the opposition to phrenology with experimental work showing that animals, mainly birds, in which the forebrain had been damaged, generally recovered without residual highly specific deficits of function. In 1824, he wrote: 'All sensations, all perceptions, and all volitions occupy the same seat in these organs. The faculty of sensation, percept and volition is then essentially one faculty.'

The famous observations of Pierre Paul Broca, reported to the Anthropological Society of Paris in 1861, were a turning point in the history of neuroscience. He described patients, whom he followed to autopsy, who had suffered a defect of language – an aphasia – as a result of brain damage, usually caused by stroke. The particular form of aphasia – now called Broca's aphasia – involved a deficit in the formulation and expression of language, while comprehension was generally quite normal. In each of his patients Broca found that part of the frontal lobe of the cerebral hemispheres had been damaged – on the left side in all of them. This discovery of Broca's area, and the striking evidence for localisation of language function, was followed by a flood of evidence, from neurologists, then physiologists and anatomists, testifying to the segregation of sensory and motor functions in particular parts of the hemisphere (Young, 1970).

To a large extent, the early evidence for localised function came from documenting the specific behavioural consequences of injury, whether in human patients or in experimental animals. The fact that damage to the cortex often leads to a rather clean excision of some perceptual or motor function, while leaving the rest of cognition reasonably intact, tells us something profound about the organisation of the cortex. While it does consist of modules devoted to the different senses, language, motor control etc, and while there is generally a flow of information through these processing modules, proceeding from sensory input to motor output, most of the individual parts are not essential for the function of the whole. Unlike, say, the electronic circuitry of a hi-fi system or television, where damage to a single component usually compromises the function of the entire device, the cortex is more like a piano. Loss of a single key, or hammer, or string leaves the instrument imperfect and melodically handicapped, but does not cripple it completely.

The function of any region of the brain depends on three things: where its input comes from; where its output goes; and what kind of processing is performed on the information in the circuitry of the particular area. One would expect, then, that differences in function would be reflected in differences in structural appearance. To an untutored eye, the 3 mm thick grey matter of the human neocortex, which covers the visible parts of the cerebral hemispheres, is everywhere similar. Indeed, there is a common plan to its organisation, with six layers of nerve cells and fibres. Layer 1 is relatively free of cell bodies. Nerve fibres bringing information in terminate mainly in the middle – layer 4. The lower layers contain many large nerve cell bodies, whose axons mainly descend to subcortical structures and the spinal cord. And cells of layers 2 and 3 have rich local lateral interconnectivity, as well as sending long-range axons mainly to other regions of the cortex, including the other hemisphere.

But there are indeed variations on this general theme in different regions of the cerebral cortex. In 1776, the Italian anatomist, Francesco Gennari, noticed that the region of cortex at the posterior pole of the occipital lobe, and extending forwards on the medial surface of the hemisphere, around and lining the calcarine fissure, has a distinct stripe of white matter – a fibre layer – in the middle of the grey. This became known as the 'stria of Gennari', and led to this region of cortex being called striate cortex. Gennari saw that his white stripe stopped abruptly at the boundaries of this region. This striate cortex turned out to be one of the most distinctive functionally specialised areas of the cerebral hemisphere. It is the primary visual cortex, which receives signals from the eyes. The observations of Gordon Holmes on infantry soldiers in the First World War who had survived after penetrating shrapnel injury, showed that discrete damage of the striate cortex leads to a corresponding patch of blindness in the visual field.

The German anatomist, Korbinian Brodmann (1909),

employing only simple stains for nerve cells and fibres, scrutinised sections of the neocortex of many species under his microscope, and detected regional differences in cortical architecture, most of them far more subtle than Gennari's stripe, but still distinctive enough for him to map out the subdivisions of the cortex and to compare them across species. Just as for the striate cortex, which Brodmann called area 17, he described sharp transitions in architecture between neighbouring regions. In humans, he distinguished 52 such anatomical areas, covering the entire hemisphere (Fig 2). Significantly, although he was able to recognise many comparable regions in other animals, the total numbers were smaller than in man. Indeed, the number of distinct areas was related to the overall size of the cerebral cortex, and this, in turn, to the richness of behavioural repertoire across species.

Several of Brodmann's areas corresponded to sensory and motor subdivisions in animals, which were then being described by physiologists, supplementing the impressions gained from clinical observations on the effects of brain damage. And, in turn, new techniques for tracing the connections of tracts of nerve fibres in the brain enabled anatomists to start to determine the patterns of inputs to and outputs from Brodmann's areas. It turns out that the entire sheet of the neocortex receives incoming fibres from the thalamus – a huge cluster of nuclei (groups of nerve cells) – lying in the diencephalon below the forebrain. Indeed, the nuclei of the thalamus correspond to the major divisions of the cortex: each nucleus connects principally to one region of the cortex. In turn, each thalamic nucleus receives its input from a particular sense organ or from a subcortical motor nucleus. Hence, the thalamus is the gateway to the architecture of the cortex, serving as its major source of incoming information and distributing that information across the array of specialised areas. The next step was to define the functions being carried out in these regions.

The pioneering work of Edgar Adrian at Cambridge, using the capillary electrometer to record impulses from individual axons in teased peripheral nerves, established a number of crucial characteristics of sensory nerve fibres (Adrian, 1947):

- Such fibres are generally silent in the absence of an appropriate sensory stimulus.
- Each fibre is selectively responsive to a particular type of sensory stimulation.
- The fibre responds with a discharge of impulses, the frequency of which depends on how close the stimulus is to the optimal for that fibre and how intense it is.
- Many fibres exhibit adaptation; the discharge frequency falls rapidly, even with a constant stimulus.

The principles by which sensory nerves, especially those of the optic nerve, encode information, were most comprehensively described by Horace Barlow, who worked in Adrian's department at Cambridge in the 1950s. Barlow argued that sensory nerves perform a kind of compression of the overwhelming flood of information that is received at the level of individual sensory receptors (see Barlow, 1972). In the eye, signals from some 150 million photoreceptors are conveyed to the brain in

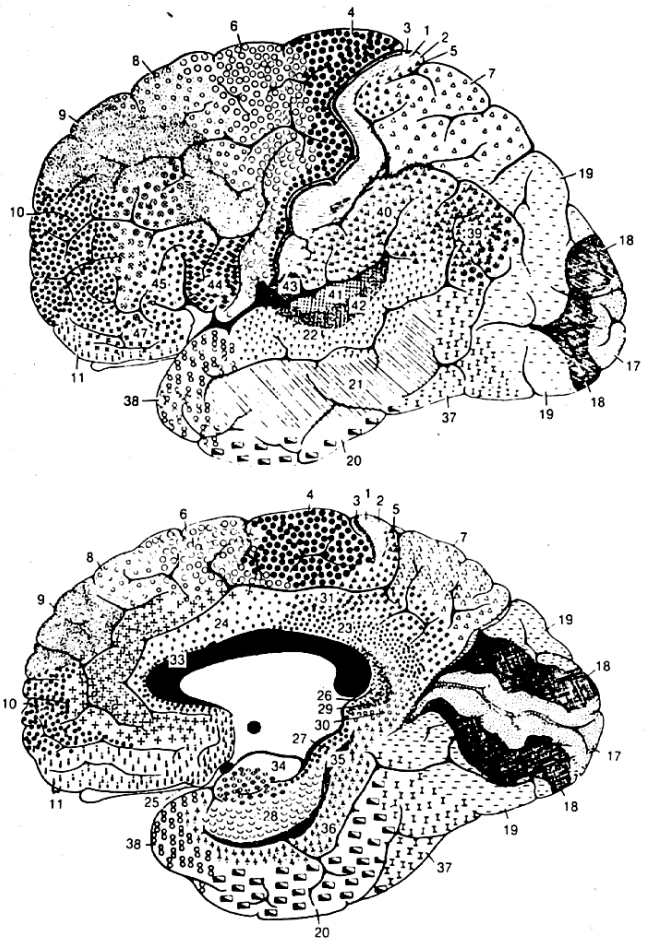


Fig 2. Brodmann's (1909) illustrations of the left cerebral hemisphere of the human brain, viewed from the side (*top*) and the right hemisphere from the medial aspect. Brodmann's areas, defined by simple observation of stained sections of the cortex, are shown with different stippling and shading. They bear Brodmann's numbers, which are still widely employed to describe cortical areas.

about 1.5 million optic nerve fibres. Moreover, the dynamic range of sensory nerves is startlingly poor. They usually fire at no more than about 200 impulses per second at best, compared with, say, the 15 log units of variation of intensity of light that the eye can deal with. Temporal adaptation serves to differentiate the signal and hence to increase the dynamic range. And the selectivity of sensory nerves divides amongst them the task of encoding the nature of the stimulus.

Barlow himself, recording from the optic nerve of the frog, described a process known as lateral inhibition (independently discovered by Keffer Hartline in the eye of the horseshoe crab). Each optic nerve fibre receives signals from a limited region of the retinal surface – its 'receptive field'. Barlow found that light falling on surrounding regions of the retina can inhibit responses caused by light on the centre of the receptive field. He realised that lateral inhibition, which is mediated by networks of lateral connections within the retina, performs a spatial analogue of adaptation. It spatially differentiates the image,

reducing signals related to the average intensity of the image and heightening information about contrast and borders in the image (see Barlow, 1982).

These tricks of information compression enable sensory systems to perform with remarkable efficiency, despite the limited channel capacity of the sensory nerves to the brain.

Steve Kuffler, himself a highly influential cellular neuroscientist, told me about a conversation he had had with Edgar Adrian, while walking along King's Parade in Cambridge in the mid-fifties. They were discussing the work of Barlow and Hartline, when Adrian said that the real excitement had yet to come, if the techniques for recording from individual nerve cells and fibres in anaesthetised animals could be used to study the processing of information in the visual area of the cortex – the striate cortex. Perhaps Kuffler remembered that conversation when a young Canadian, David Hubel, joined his department at Johns Hopkins in 1958. Kuffler suggested that he should work with Torsten Wiesel, a Swede, who was already recording from neurons in the cat retina. Together, Hubel and Wiesel began a series of elegant studies on the visual cortex of cats and monkeys, which have enormously advanced our understanding of the function of the cerebral cortex (see Hubel, 1988).

Nerves from the sense organs, as Barlow and others had shown, generally provide a compressed description of the pattern of stimulation striking the sensory surface. In higher mammals, some optic nerve fibres respond to a sudden local brightening of a particular spot on the retina, while others respond to local darkening. So, they 'pixellate' the image, rather like a digital camera, and describe it to the brain as the distribution of local brightnesses in the image. Those fibres enter the visual part of the thalamus, the lateral geniculate nucleus, where there are roughly the same number of cell bodies as there are incoming fibres, and hence there is, on average, simply one-to-one transmission of signals and the basic form of the representation of information is unchanged. Indeed, the function of sensory nuclei of the thalamus remains something of a mystery. One interesting idea is that descending signals from the corresponding region of cortex modulate the transmission of information in the thalamus.

Significantly, remarkable transformations of representation occur in sensory areas of the cortex, to which the main sensory thalamic nuclei project. Hubel and Wiesel famously showed that individual cells in the visual cortex of anaesthetised cats and monkeys respond selectively to lines and edges in the visual image, each cell responding best to a contour at a particular orientation. Different cells prefer different orientations, and hence the population of cells encodes all the possible orientations of lines and edges in the visual image, presumably playing a role in representing the shapes of objects.

Most remarkable was the discovery of an invisible microarchitecture of the visual cortex – a systematic local mapping of sensory properties across the primary visual area. Vernon Mountcastle, who had pioneered the use of microelectrodes to record from individual neurons in the somatic sensory cortex, had shown that neurons in that sensory area are also selectively responsive to different types of stimulation – touch, hair movement, vibration, joint movement, etc – and that cells with the same kind of preference are arranged in 'columns', all sharing the same basic property, extending from the surface down to the white matter below. Hubel and Wiesel showed that this is also true for two properties of neurons in the visual cortex – their orientation preference and the eye that dominates them (the majority of cells respond to a similar visual stimulus through either eye, but tend to be dominated by one or the other). Hence, the cortex is organised into 'ocular dominance columns' and 'orientation columns' and these two columnar patterns overlap each other (Fig 3).

Ocular dominance columns have a relatively simple anatomical basis. Cells of the lateral geniculate nucleus are monocularly driven – they each receive input from only one eye. Their axons terminate in layer 4 of the striate cortex in a distinctive pattern – alternating regions of left-eye and right-eye inputs, forming narrow bands or stripes of terminal territories in layer 4. Consequently, nerve cells in layer 4 are also usually monocular, reflecting the dominant synaptic input to them. The columnar structure is imposed on the cortex by the simple anatomical pattern of termination in layer 4. Axons from cells of layer 4 project, mainly upwards, to cells in other layers. Although there is considerable overlap of axons from neighbouring left-eye and right-eye regions, hence providing binocular input to cells outside layer 4, the pattern of dominance by the two eyes is maintained through the whole depth of the grey matter, leading to the alternating ocular dominance regions described by Hubel and Wiesel.

The existence of the fine mosaic of orientation columns, and the beautiful regularity of its pattern, is much harder to explain, because the incoming fibres from the thalamus are not themselves selective for lines and edges. This property is generated by nerve circuitry within the visual cortex itself. Although the anatomical basis of orientation selectivity remains unclear, it seems likely that it is initially created as a result of the combination of excitatory inputs to cells early in the cortical circuitry. The selectivity for a contour at one orientation results from the spatial arrangement of the receptive fields of incoming fibres that converge on to the particular cortical cell. This is almost certainly not the whole story because there is evidence that inhibition between cortical cells, mediated by the vast array of small, local inhibitory neurons in the cortex, plays a part in refining the selectivity of many cortical cells (Sillito *et al*, 1980).

I was a medical student in Cambridge in the early sixties, when the early papers of Hubel and Wiesel were being published. The impact of their discoveries on both physiologists and psychologists was immense. Suddenly, the previously imponderable question of how the cerebral cortex works began to look tractable. Microelectrode recording in anaesthetised animals offered a way of listening in to the conversation within the brain, the conversation by which the internal understanding of the outside world is constructed.

During my undergraduate studies, I was inspired by such leading vision researchers as Richard Gregory, Larry Weiskrantz, Fergus Campbell and Alan Cowey. I then had the great good fortune, in 1965, to go to work with Horace Barlow, who had recently moved to the University of California in Berkeley. I was keen to follow up Hubel and Wiesel's discovery that most cells in

the visual cortex of the cat receive matched signals from the two eyes, and we quickly set up a simple laboratory to record from single neurons in the cortex. I was fascinated by the perceptual phenomenon of binocular rivalry – the fact that when the two eyes view completely different images, say vertical stripes in one eye and horizontal in the other, conscious awareness alternates between them every few seconds. I was keen to see how cells in the cat's cortex would react to unmatched images. Horace Barlow immediately saw that the more important question was how these neurons combine information from matched images, as in normal binocular vision, and, in particular, whether they might be able to interpret the tiny differences between the retinal images to provide information about the third dimension of visual space. (The experiments on binocular rivalry had to wait for nearly 30 years, when Frank Sengpiel in my laboratory in Oxford discovered that when binocular cells are confronted with conflicting images in the two eyes they can indeed suppress one input or the other (Sengpiel and Blakemore, 1994).)

Barlow and I were only a few weeks into our work when news came that Peter Bishop in Australia was also working on binocular interaction in the visual cortex. Bishop was principally interested in the precise way in which cells combine incoming signals from the two eyes, so Horace invited Jack Pettigrew, a young medical student from Bishop's laboratory, to visit Berkeley to pursue the question of stereoscopic vision. In a wonderfully productive collaboration in the summer of 1966, we showed that binocular cells are selective for the stereoscopic distances of lines and edges in the visual field (Barlow *et al*, 1967), and Bishop's group came to the same conclusion (Nikara *et al*, 1968).

It was clear that the activity of sensory neurons in the cortex is inherently ambiguous. A change in the firing of impulses could be due to alteration in any one of a number of different features of the visual image (Blakemore, 1975). The nature of the visual image must be encoded among the entire population of neurons. The language of the cortex is more like an oratorio than an aria: the voices of many neurons are involved in conveying the message.

The past four decades have been the era of cortical cartography. The cortex is indeed composed of a patchwork of functional regions. Some correspond precisely to Brodmann's anatomical areas; in other cases, several functional modules fill a single Brodmann area. Surprisingly, the majority of these regions are devoted to the senses, with more than half of the entire cerebral cortex in monkeys consisting of visual areas. Almost all the incoming optic radiation fibres from the lateral geniculate nucleus terminate in the primary visual cortex (striate cortex, area 17, V1), but the output fibres from that area then distribute the information over the entire array of some 30 extrastriate areas. Semir Zeki was probably the first to propose explicitly that the multiplicity of visual areas provides a division of analytical labour, with the neurons in each area devoted to processing a particular aspect of the information sent forward from V1 (see Zeki, 1993). For many areas, the functional specialisation, if there is one, has yet to be defined. But the evidence for dedication of function is very strong for certain visual areas. In particular, a region known as MT or V5 is centrally involved in the analysis of motion in the visual field (see Parker and Newsome, 1998). Cells in this area respond selectively to moving images and they are arranged in a columnar micromap, each column of cells responding to movement in a particular direction, with a progressive shift in preferred direction from column to column. In a series of remarkable experiments in awake, trained monkeys, Bill Newsome and others have shown that some individual neurons in area MT can detect patterns of coherently moving dots, masked with randomly moving dots, just as efficiently as the monkey itself can (see Parker and Newsome, 1998). The detections and discriminations that underpin our perception of the world might each depend on signals from tiny communities of

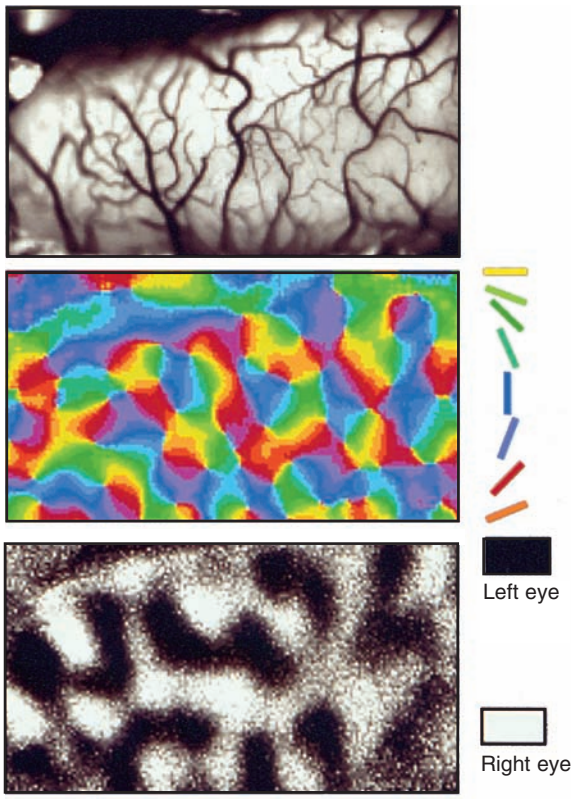


Fig 3. The columnar organisation of the cat's primary visual cortex, revealed by optical imaging. The three panels show a small region (about 5.5 mm wide) of the surface of the primary visual cortex of an anaesthetised cat, viewed with a video camera. The top panel is a normal image, showing the vascular pattern on the surface of the cortex. The bottom image shows as dark patches the regions in which there was a local change in oxygenation of haemoglobin, as judged by the reflectance of red light from the cortex, during visual stimulation of the left eye alone. The white areas responded to stimulation of the right eye. The worm-like pattern is typical of ocular dominance columns in cat V1. The middle panel shows the activity in the same region of cortex produced by stimulating both eyes with moving stripes of various orientations. The colours represent regions of cortex that were most strongly activated by the orientations indicated by the coloured line segments on the right. These results from the work of Hübener *et al* (1997) are reproduced by kind permission of Tobias Bonhoeffer.

neurons, exquisitely adapted for the analysis of a particular sensory feature.

Recent advances in medical imaging have given us new ways of indirectly observing activity in the living human brain. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) reveal changes in blood flow, which are presumed to reflect changes in local neuronal activity. The pseudo-coloured images of glowing slices of brain have already become familiar icons of science. Their immediacy is compelling, but it is important not to overinterpret them. They are nothing more than statistical maps of the probability of a change in local blood flow correlated with some task being carried out by the subject. The spatial resolution of these techniques is millimetres, while nerve cells and axons are three orders of magnitude smaller. And the temporal resolution of the haemodynamic response is several seconds, while the events relevant to information processing (nerve impulses and synaptic events) are again at least three orders of magnitude faster. Functional neuroimaging can tell us *where* things happen in the human brain; clever interpretation of them can even reveal something about the likely pattern of connections between activated regions (see Friston *et al*, 1993; Bartels and Zeki, 2005). But they say very little about the neural 'computations' that determine brain function.

Despite these reservations, functional neuroimaging, set against the backdrop of work on animals, especially primates, has enormously advanced our knowledge of the partitioning of the human cerebral cortex. Some general conclusions emerge from this work. First, there are compelling homologies between the properties of sensory and motor areas of the cortex in monkeys and humans. But, second, the number of such areas is larger in the human cortex, especially in the distant reaches of sensory networks, which seem to be involved in the recognition and memory of sensory input.

The cerebral cortex computes a representation of the reality of the outside world

The analogy between brains and computers is hotly contested. However, if we define computing liberally enough (as the implementation of instructions to generate conclusions from data), the nervous system certainly computes. The cerebral cortex, with 85% of all the neurons in the brain, is surely the primary site of neural computation.

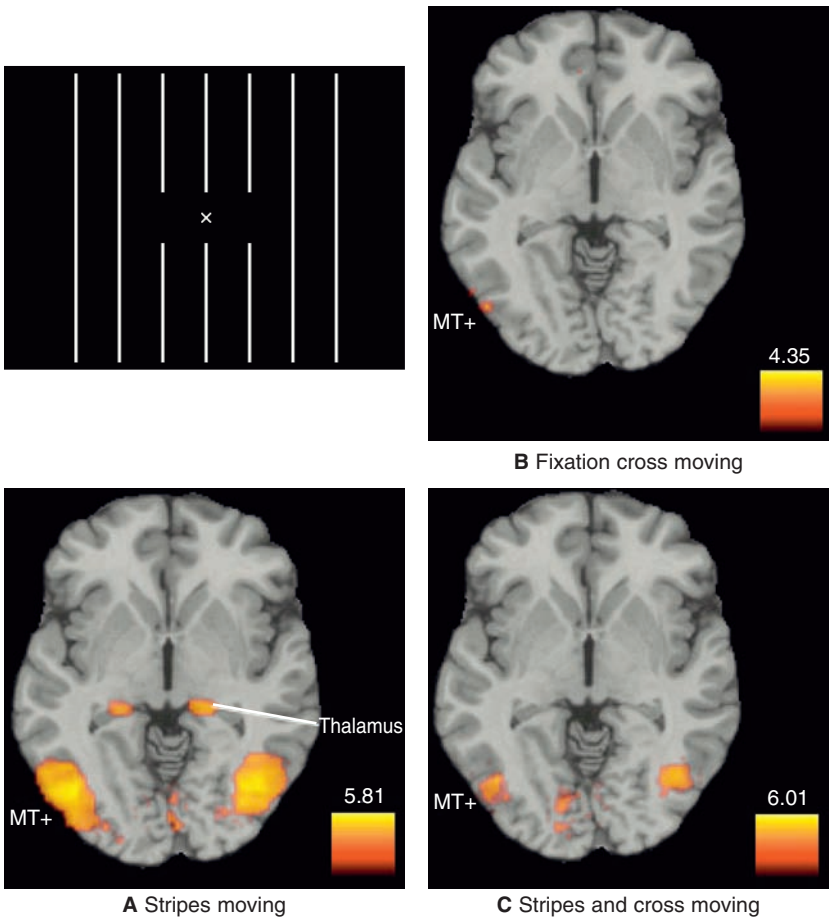
The nature of the computations or processes performed by cortical circuitry is not understood or generally agreed. But the results of recording experiments in animals, combined with data from neuroimaging in humans, support the idea that a primary role for the cortex is the computation of a representation of the outside world and of plans of action appropriate to that world.

The proliferation of sensory cortical areas through mammalian evolution provides evidence for the selection of representational ability as a primary driver for the evolution of the cortex. The type of information leaving the retina (namely a pixellated version of the retinal image) is not fundamentally different for a fish and a monkey. But the monkey can more completely interpret the temporal and spatial patterns of information, in terms of the objects and events in the outside world. This is presumably dependent on the additional stages of analysis of that information in the multitude of visual areas of the cortex.

The processing of visual motion in the area MT or V5 provides excellent examples of the way in which re-analysis of visual information – in ways that are impossible for the retina or even for V1 – can provide more veridical information about the true nature of the external world (see Parker and Newsome, 1998). Cells in MT respond selectively to one direction of movement. Some neurons of V1, in anaesthetised monkeys, are also direction selective, as well as being selective to the orientation of line stimuli. But their 'blindness' to contours of other orientations makes them unable to signal correctly the true direction of motion of textured surfaces made up of features of various orientation. Now, to a human (or monkey) observer, two patterns of moving stripes, of different orientation, appear to lock together and to move in a single direction, the shared vector of movement of the two sets of stripes. Some neurons of MT appear to be able to perform the necessary computation to signal the perceived direction of motion of such grating mixtures (Movshon *et al*, 1985): they have the same preference for the shared direction of such fused gratings as they have for lines of one orientation. Interestingly, a significant fraction of direction-selective neurons in V1 has this property in awake monkeys, probably as a result of feedback of signals from MT to V1 (Guo *et al*, 2004).

Another simple but vital computation that appears to be performed by the human homologue of MT (usually called MT+, to include flanking regions also involved in motion analysis) concerns the discrimination between motion in the retinal image genuinely caused by movement of objects in external space (passive motion) and that generated by tracking movements of the eyes (active motion). We do not see the external world moving when we move our eyes, and it is clear that this depends on a comparison of information from the retina with an internal record of intended eye movements – a 'corollary discharge'. The underlying algebra is very simple, but where is it performed? That is the question behind some recent work from my laboratory by Loredana Santoro, using fMRI (see Santoro *et al*, 2003). Figure 4 summarises the results.

In these experiments, the subject, lying in the scanner, viewed a screen in an otherwise darkened room. On the black screen was a small central white cross, which the subject was instructed to fixate with their eyes continuously, surrounded by white stripes. The cross, or the stripes, or both together, could oscillate back and forth on the screen. When the stripes alone moved, and fixation was stationary on the cross (causing passive retinal image motion), there was strong activation of human MT+ (Fig 4A), as previously described. But when the cross underwent identical oscillation and the stripes were stationary (producing almost exactly the same pattern of motion in the retinal image, but active rather than passive), there was virtually no significant activation of MT+ resulting from the stripes (Fig 4B). This suggests that human MT+ receives corollary discharge about eye movement and is able to perform the



B Fixation cross moving

A Stripes moving

C Stripes and cross moving

Fig 4. Results from Santoro *et al* (2003), illustrating the way in which human area MT+ appears to compute a representation of true motion in the external world. In a 3T MRI scanner (at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) the subject viewed the image shown in the top left panel. **A:** A high-resolution structural MRI view of a horizontal section at the level of the area MT+ (and also the primary visual cortex, V1, at the occipital pole). The colour scale indicates the Z statistic for increased blood flow in the coloured voxels on the image, and the number is the maximum Z value in the image. Data for 21 subjects are pooled. MT+ is strongly activated by passive motion (stripes moving back and forth, with fixation held on the stationary cross). **B:** Area MT+ is not clearly activated by active motion of the retinal image of the stripes, produced by back-and-forth movement of the fixation cross without movement of the stripes. **C:** When both cross and stripes move together, and both are perceived as moving, MT+ is quite strongly activated, despite the fact that the retinal image of the stripes is virtually stationary.

basic computation to distinguish between passive and active motion. The hypothesis that human MT is signalling true motion in the external world, as perceived, is strongly supported by the results in Fig 4C. In this case, both cross and stripes moved exactly together and the subject tracked the cross. Hence there was very little movement of the image of the stripes on the retina, although they were, of course, perceived to move (with the eyes). Under these circumstances MT+ is active, implying that it signals perceived motion, not merely retinal image displacement.

A paradox of consciousness

Consciousness is the skeleton in the cupboard of modern neuroscience. Most of the progress of this science has been achieved on the back of a studied disregard for subjectivity – what it feels like to have a brain. That messy issue was left to psychologists and philosophers, while biologists got on with the job of trying to explain how the physics and chemistry of nerve cells account for the behaviour of organisms.

Always in the background was Descartes' dictum – *cogito ergo sum* – the notion that one's certainty of one's own existence as a thinking being is the only experience that one cannot doubt. With the emergence of cognitive neuroscience in the past ten years or so, neuroscientists have increasingly, if reluctantly, started to embrace the issue of consciousness.

Francis Crick played an important part in moving the question of consciousness into the mainstream of neuroscience with his book, *The astonishing hypothesis* (Crick, 1994). That hypothesis is that

> *'You', your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behavior of a vast assembly of nerve cells and their associated molecules. As Lewis Carroll's Alice might have phrased it: 'You're nothing but a pack of neurons'.*

Actually this hypothesis would not have been astonishing to the Hippocratic school, who, in the fifth century BC wrote:

> *Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant.*

Nor to the eighteenth century physician, Pierre Jean Georges Cabanis (1757–1808), who declared: 'The brain secretes thought as the liver secretes bile'.

What was astonishing was not the conjecture that awareness, in all its manifestations, depends on the physical function of the brain. It was the fact that the call to neuroscientists to tackle this

issue came from one of the most influential reductionists of the twentieth century.

Crick focused on what he called the Neural Correlate of Consciousness (NCC) – the necessary state of neurons to generate conscious experiences. It is clear that most of what the brain is doing at any time is not within the domain of awareness. Some crucial decision-making, such as the control of the heart and the gut, never bothers the conscious mind. Other functions rarely do – such as the control of breathing. More significant, we also are never aware of much of the detail of sensory analysis and motor control: we have no idea of the pre-processing in sense organs or the intricate choice of motor units for any particular movement. Our awareness is a constantly shifting Executive Summary of the vast computational task of running the body.

Even among those parts of neural processing that can enter conscious experience, most are excluded most of the time. The process of attention sweeps across the landscape of candidates for consciousness, selecting at any one time only a tiny amount of information to display on the screen of awareness.

Few philosophers accept that defining the NCC would solve the problem entirely. To many, the *nature* of conscious states is still the metaphysically challenging issue (see McGinn, 1994) – the 'hard problem', as David Chalmers (1996) has dubbed it.

Nevertheless, it would be significant to discover what properties of the brain – presumably involving the cerebral cortex – lead to the generation of personal experience. One route towards the NCC has come through research on ambiguous visual stimuli, which can be perceived in more than one way. The significance of such illusions to the issue of private experience is obvious. A fixed physical stimulus gives rise to a constant retinal image, but the subjective interpretation changes suddenly and dramatically. If the underlying changes of neural activity could be defined, it would surely give some clue to the fundamental process of generating subjective experience.

Binocular rivalry and figure-ground reversal (Rubin, 1915) are well known examples of such perceptual ambiguity. Electrophysiologists have detected changes in neuronal activity, at various stages in the visual pathway, which might account for the alternations in eye dominance that occur when different images are seen by the two eyes (Sengpiel and Blakemore, 1994; see Andrews *et al*, 2004). And functional neuroimaging in humans has at least revealed changes in activity in the extrastriate visual cortex correlated directly with perceptual shifts in the famous 'vase–face' illusion, a simple array of dark and light shapes whose contours can be seen either as a pair of profile faces or as the outline of a vase (Fig 5C). Activity in the fusiform face area of the right hemisphere increases specifically as the perceptual interpretation switches from vase to face, compared with a switch from face to vase, despite the fact that the physical stimulus remains the same (Fig 5D). This implies that the neural events leading to a particular state of visual awareness involve an overall increase in activity in early visual cortical areas that represent that particular form of visual stimulus.

While visual awareness has remained the principal target of the seekers of the NCC, the more challenging aspect of subjectivity is surely the sense of self, the overwhelming feeling that one is the internal helmsman of one's actions, and that one plans one's own future. The impression of freedom of choice and of action through intention is fundamental to being a person. This is clearly of enormous relevance to clinicians because the irretrievable loss of personhood, in these terms, is tantamount to mortality.

However, there is growing scepticism about the extent to which the subjective representation of intention correlates with the actual brain mechanisms that produce action (see Wegner, 2002). One tantalising piece of evidence comes from work showing that neural activity in the frontal lobes (the readiness potential), which precedes actions, starts some time before the moment at which a person believes that he or she has chosen to carry out some simple task, such as pointing a finger (Libet, 1996).

Ian McEwen puts the dilemma into the mind of Briony Tallis, the thoughtful 13-year-old in his novel *Atonement* (McEwan, 2002). Briony was sitting, looking at her hands:

> *She bent her finger and straightened it. The mystery was in the instance before it moved, the dividing moment between not moving and moving, when her intention took effect. It was like a wave breaking. If she could only find herself at the crest, she thought, she might find the secret of herself, that part of her that was really in charge … When did it know to move, when did she know to move it?*

Briony went on to ask whether everyone mattered to themselves as much as she did to herself. If not, she concluded, she was 'surrounded by machines, intelligent and pleasant enough on the outside, but lacking the bright and private *inside* feeling she had'.

As Daniel Dennett points out, Libet's experiment does not rule out the existence of intentional mechanisms in the human brain (Dennett, 2003). It means that the 'Cartesian ego' – the subjective impression of a self – is not the actual initiator of action, but not necessarily that the neural mechanism responsible for generating action is not free. That begs the question of what kind of freedom needs to be explained. Human beings are not crude automatons, slaves to immediate sensory stimulation or simple motivations. The literature of brain imaging is full of evidence of 'top-down' involvement in the direction of attention and in decision-making. Moreover, our capacity to interpret the intentions of other human beings (and other animals) plays an important role in social behaviour, and abnormalities of socialisation, especially autism, are associated with abnormal development of this 'Theory of Mind' (Frith, 1991).

There is evidence for a specific neural system for the recognition of planned action. In the premotor, frontal cortical region of monkey, some neurons (so-called 'mirror neurons') that respond before the execution of specific motor acts by the monkey also respond when the monkey sees other monkeys or humans carrying out the same acts (see Rizzolatti and Craighero, 2004; Gallese *et al*, 2004). The amygdala in humans, which is active during experiences of disgust, appears to have similar 'third-person' properties: it is also activated when one views other people in a state of disgust.

Very recently, Iacoboni *et al* (2005) reported that the mirror

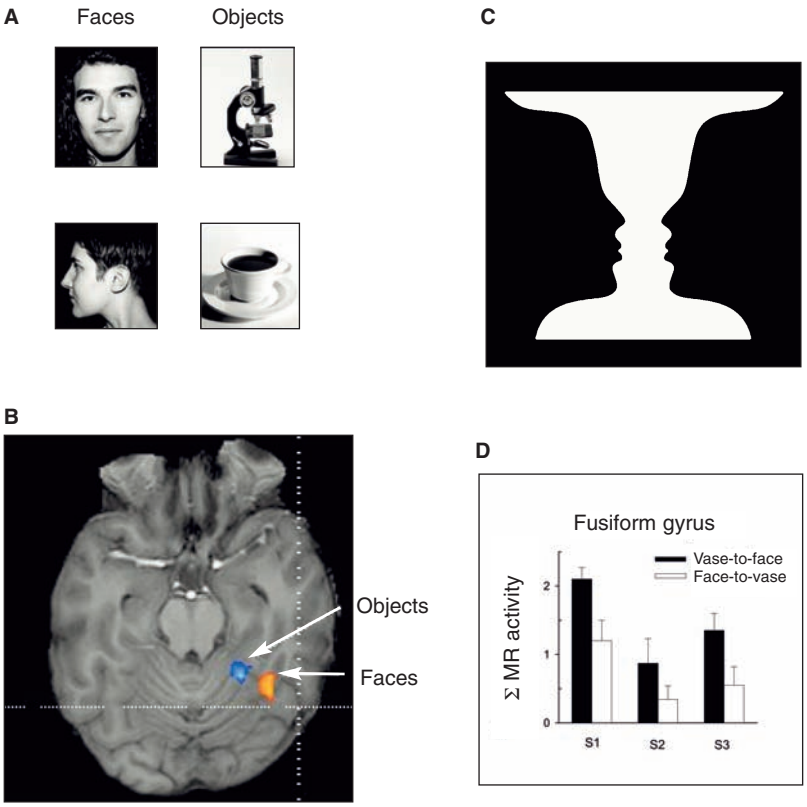


Fig 5. Neuroimaging of cortical activity while viewing an ambiguous image. A: Initially, subjects lying in the MRI scanner were presented with a randomised sequence of photographs of faces and man-made objects, examples of which are shown. **B:** A horizontal section at the level of the fusiform gyrus, at the entry to the temporal lobe, shows the principal areas that were more activated by face images (orange: the fusiform face area) and objects (a region in the parahippocampal gyrus). **C:** The subject was then shown the ambiguous Rubin vase–face illusion and indicated by pushing buttons when their perception switched from face to vase and vice versa. The MR activation was monitored in an event-related procedure. **D:** For the three subjects, S1, S2 and S3, these histograms show the activity produced in the fusiform face area associated with a perceptual switch from vase to face (filled column) and from face to vase (unfilled). Clearly, the fusiform face area is more strongly activated by the former than by the latter, although the physical stimulus was always the same. This implies that the conscious interpretation of faces was correlated with the strength of activity in this area. Interestingly, activity in the parahippocampal area did not distinguish significantly between face–vase and vase–face transitions. Data from Andrews *et al* (2002), reprinted with permission from Elsevier.

system in humans appears to be influenced by the *intentional* context of viewed movements. When a person watches a movie of someone else picking up a mug, the activity of the right prefrontal cortex is considerably stronger if the mug is set in a context that reinforces the intentional nature of the movement (together with a sugar bowl, milk jug, and a plate of biscuits) than when it is alone.

Both the personal feeling of intention and the existence of specific mechanisms for recognising intention in others might be taken to support the view that conscious, willed actions are an essential part of the machinery of human behaviour. But there are deep epistemological problems here. The simultaneous belief that conscious states are caused by neural events and that consciousness is important, in the sense that it has been selected for during evolution, raises a substantial paradox.

Let us assume, as I think that most people, certainly most neuroscientists, do, that the entire content of conscious experience is caused by corresponding and antecedent neural events. This implies that every separate component of conscious experience – every colour, shape, sound, smell, thought, memory, intention, etc – results from a unique and precisely equivalent neural event. It follows that, unless some magic happens within conscious states to process or add information, being conscious adds precisely nothing to the information that is present in the neuronal activity that leads to consciousness.

Moreover, all actions depend on neuronal signals. As Charles Sherrington (1906) put it: 'to move things is all mankind can do ... whether in whispering a syllable, or in felling a forest'. Muscles are moved by the impulses of motor neurons. So, neuronal activity is the antecedent both of conscious experience and of action, and the entire content of conscious experience has its informational equivalent in the activity of the neurons that generate it.

It follows that being conscious plays no direct role in the generation of action. Although it is often assumed that the mechanisms of consciousness must have evolved, because of some adaptive value in being conscious, it cannot be the case that consciousness adds value (unless one postulates that something is added to the informational content of awareness that is not in the neurons that make it; and that conscious states can somehow act downwards on neurons and convey that new information to them, so as to influence action).

The paradox leads to the conclusion that consciousness itself cannot have evolved by Darwinian selection. The underlying neural mechanism, which happens to produce consciousness, is the phenotype that has been selected by evolution. Being conscious is an epiphenomenon.

My hunch is that the special neural system that creates consciousness, especially self-consciousness, has evolved to support the structure of language. The syntactical form of language is essentially intentional: subjects choose to do things, expressed by verbs. Just think how difficult it would be to describe one's own actions or those of others without the intentional structure of language. Our awareness of ourselves is not the medium of decision-making. It is not even a reflection of the actual processes of decision-making in our brains. It is the product of a 'meta-representation' – an illusory description of the outside world and the inside workings.

How does the cortex develop: how did it evolve?

The central nervous system is the most highly differentiated organ in the body. It is divided into a large number of distinct parts, from the individual segments of the spinal cord to the subdivisions of the brain, within which there is distinctive differentiation of neurons and the formation of characteristic fibre pathways. At levels below the cerebral cortex, there is good evidence that the partitioning of the nervous system is controlled by a temporal pattern of expression of particular genes, which trigger further, local changes in gene expression, resulting in the specialised regional architecture (Brown *et al*, 2001). A major issue concerns regional differentiation in the cerebral cortex. How are the 100 or more specialised areas of the human cortex generated?

The neurons and glia that make up the adult cortex are generated as daughters of progenitor cells in the proliferative epithelium that lines the expanding front end of the neural tube. Until quite recently it was thought that all the cells of the cortex are born locally, in the neuroepithelium of the telencephalon, and that they simply migrate radially out to the surface of the forebrain, where they accumulate, in an inside-out sequence, to form the layers of the cortex. If this were the case, any early pattern of discrete gene expression within the neuroepithelium might become reflected in the particular pattern of mature cells in the region of cortex directly above each part of the epithelium. This is the 'protomap' hypothesis of Rakic (1988, 1995).

Several regulatory factors and transcription factors are indeed expressed locally within the developing forebrain, or in gradients across it (see Donoghue and Rakic, 1999; López-Bendito and Molnár, 2003). And the concentration of growth factors, including Fibroblast Growth Factor 8, which is secreted from a source in the anterior telencephalon, can influence the ultimate position of specialised regions within the cortical sheet. However, there is no evidence that each of the huge number of cytoarchitectonic and functional subdivisions of the cortex corresponds to a precise domain of gene expression in the epithelium. Indeed, neural stem cells in the epithelium migrate tangentially over large distances, contributing daughter cells to many different parts of the cortex (Walsh and Cepko, 1998); and the interneurons of the cortex are not generated locally but migrate tangentially into the cortex from the basal telencephalic region (Parnavelas, 2000). It is difficult to imagine how all of this diverse input could be orchestrated so as to generate the final specialised local structure and the sharp boundaries between areas, without some refining, epigenetic influence.

A rival theory, the 'protocortex' hypothesis, was proposed originally by O'Leary (1989), on the basis of experiments in which explants of rat embryonic cortex, removed before innervation by

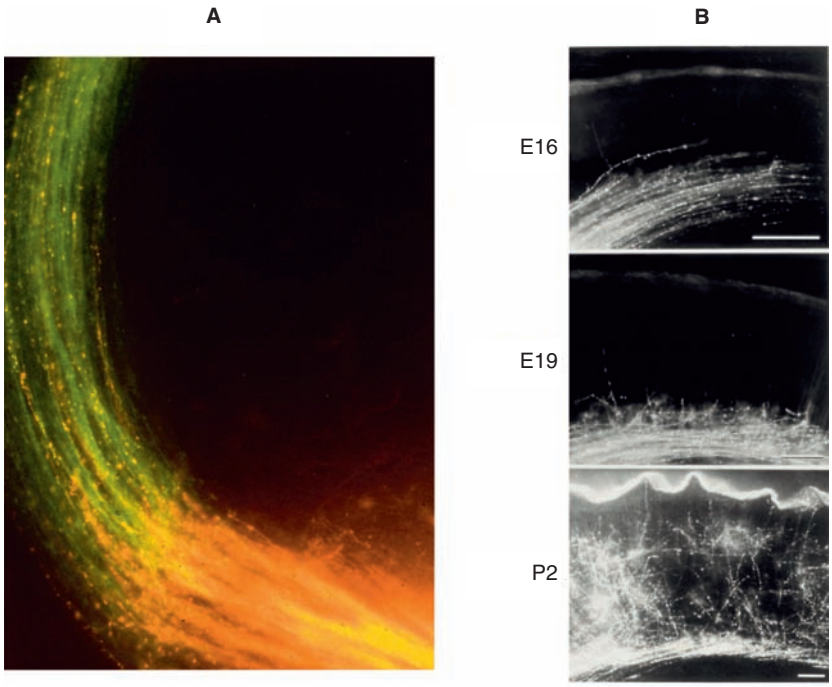


Fig 6. Results, modified from Molnár *et al* (1998), who used lipid-soluble carbocyanine dyes to stain axons in fixed tissue from the rat brain. A: A fluorescence micrograph of a coronal section through the left hemisphere of a rat embryo on the 15th post-conceptual day (gestation is about 21 days in the rat). Tiny crystals of different dyes were placed in the posterior dorsal thalamus (orange) and the dorsal surface of the developing cortex (green). The green axons are from transient neurons in the pre-plate, which migrated from the neuroepithelium into position below the pial surface only about 24 hours earlier. The orange axons are thalamic fibres, which have passed through the primitive internal capsule (*bottom right corner)* and confronted the cortifugal axons in the 'handshake' region, at the entrance to the intermediate zone. They are growing over the surface of the cortical fibres, towards their target cortical area. **B:** Fluorescence micrographs of coronal sections of the dorsal part of the cortex. The pial surface is visible near the top of each panel. The thalamic fibres alone have been labelled by placement of a crystal of carbocyanine dye in the dorsal thalamus. At embryonic day 16 (E16: *top panel*), the fibres form a highly ordered array, approaching the subplate layer below the immature cortex. The axons rest in the subplate layer, where they form temporary synapses on subplate cell bodies. At E19, two days before birth, thalamic fibres start to advance into the cortical plate. By postnatal day 2 (P2), just after the neurons of layer 4 have migrated into position, thalamic fibres reach that layer, and start to branch and form synaptic connections on cortical neurons. Scale bars: 100 μm.

thalamic fibres and transplanted into a different region of the hemisphere in a neonatal recipient animal, had taken on the cytoarchitectonic appearance of the host region. The hypothesis suggests that the neocortex is generated as a uniform, uncommitted sheet, and that the particular pattern of thalamic axons innervating it somehow influences the final organisation of each area. That influence could come through the direct contribution to cortical architecture of thalamic axons, but more likely through influence on the selective survival, morphological growth and connectivity of neurons in the cortex.

Crucial to this hypothesis is evidence that the initial axonal projections from the thalamus to the cortex are topographically organised and that they arrive before the onset of regional cytoarchitectonic specialisation. Each sense organ provides input to a particular thalamic nucleus, or set of adjacent nuclei, which in turn project to particular regions of the cortex (visual at the posterior pole, auditory to the temporal cortex, and somatic sensory to the more dorsal parietal region; see Fig 8A). But even before arrival of sensory axons at the thalamus, the nuclei have sent their axons with unerring precision towards the correct region of the cortex.

A great deal is now known about the guidance of thalamic axons to the cortex (see Molnár and Blakemore, 1995; López-Bendito and Molnár, 2003). Axons grow out from the primordial thalamus as an ordered array at an early stage, when the first neurons of the cortex have only just started to arrive under the pial surface, to form the so-called pre-plate. It turns out that these pre-plate cells (most of which die at around the time of birth) send an equally ordered array of pioneering fibres down through the intermediate zone of the developing cerebral wall (McConnell *et al*, 1989). The wave of thalamic axons advances through the primitive internal capsule and under the ganglionic eminence, the junction of diencephalon and telencephalon, where there are important molecular signals that help to keep the axons on track. As they enter the intermediate zone, they confront the descending cortical axons and proceed to grow over that sheaf of fibres (Fig 6A). This 'handshake' between the two sets of fibres probably plays an important role in the subsequent guidance of thalamic fibres towards the appropriate region of cortex (see Molnár and Blakemore, 1995).

In all mammalian species examined, thalamic axons arrive at their corresponding region of cortex some time before the layers of the cortex are fully formed and the fibres accumulate on the layer of subplate cells (part of the original pre-plate population) underneath the thickening cortex. This 'waiting period' lasts from a couple of days or so in rodents to several weeks in primates. *In vitro* co-culturing of explants of embryonic rat thalamus and slices of neonatal rat cortex has revealed a cascade of interactions between the two tissues, determined by molecular signals produced by the cortex (Molnár and Blakemore, 1991). In particular, the sudden invasion of the cortex by thalamic axons and their subsequent termination on cells of layer 4 (Fig 6B) appear to depend on the sequential expression of membrane-bound, growth-permissive factors and then 'stop' signals in the cortex (see Molnár and Blakemore, 1995).

Co-culture has established that there is no absolute, chemospecific matching of regions of thalamus to areas of cortex (Fig 7C). However, it is likely that the particular distribution of axons across the cortical plate is influenced *in vivo* by the expression of affinity factors, locally and in gradients within the cortex (see López-Bendito and Molnár, 2003).

Although gradients of molecular signals in the cortex, perhaps

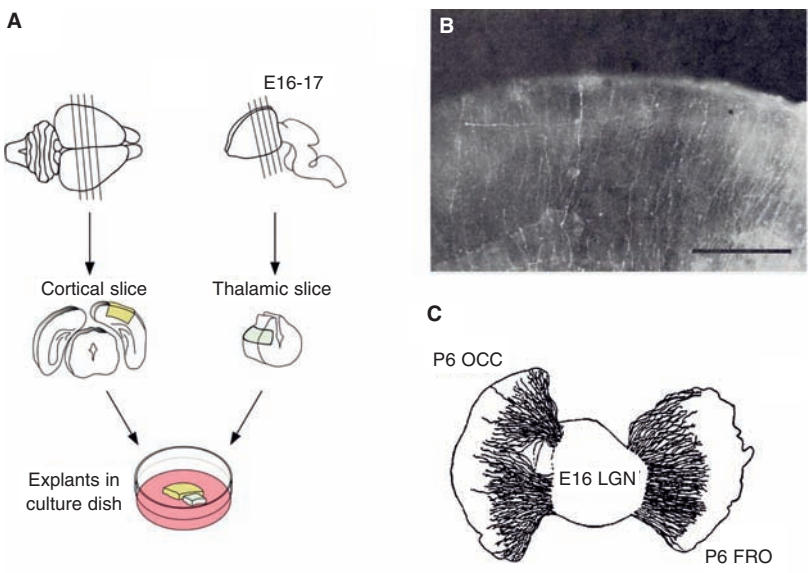


Fig 7. A: The procedure for co-culturing slices of cortex, taken from neonatal rats (killed by overdose of anaesthetic) and tiny explants of the dorsal thalamus from E16-17 rat embryos (see Molnár and Blakemore, 1991). The thalamic explant was incubated with carbocyanine dye, to stain any outgrowing axons, and the two fragments were then placed close to each other in a culture dish. **B:** A fluorescence micrograph of a slice of cortex, taken on the day of birth, after 24 hours of culture with an explant of the visual nucleus of the thalamus (LGN) from an embryo on the 16th post-conceptual day (E16). Fluorescently labelled thalamic axons are seen streaming radially through the cortex, but, with a slice taken before P2, the axons do not terminate in the middle of the cortex: they continue to grow up to and through the pial surface. Scale bar: 100 µm. **C:** Camera lucida tracing of axons from an explant of E16 posterior dorsal thalamus, in a triple co-culture, involving a slice of P6 occipital cortex (OCC, on the left) and a slice of frontal cortex (FRO) from the same animal on the right. This region of thalamus would normally have innervated only the occipital cortex *in vivo*, but axon ingrowth into the frontal cortex was indistinguishable from that into the correct target. (Note that the axons branch and terminate in layer 4 of the cortex in a slice older than P2.)

expressed in the axons of the early descending corticofugal fibres, play a part in determining the topographic distribution of thalamic projection to the cortex, the pattern might relate simply to the ordered pattern of outgrowth of thalamic axons, as a parallel array, which is maintained throughout the pathway. Figure 8B,C illustrates an experiment to demonstrate this ordering in the pathway. Three tiny crystals of carbocyanine dye were placed into the dorsal surface of the fixed brain of an E16 rat embryo (just after the arrival of the array of thalamic fibres under the corresponding cortical areas). The dyes diffused along all the thalamic axons reaching each cortical area (as well as the early cortical fibres running downwards). The horizontal section in Fig 8C shows the three distinctly labelled bundles of axons, indicated by coloured arrows. The ventral diencephalon is in the bottom left part of the panel, and the basal telencephalon in the upper right. The thalamic fibres undergo a 90° twist as they leave the diencephalon, but their order is maintained throughout the pathway.

During mammalian evolution, there appears to have been correlated enlargement of the thalamus and of the cerebral cortex (see Rakic, 1995). Indeed, the proliferation in the number of cortical areas is matched by an increase in the number and complexity of thalamic relay nuclei. The way in which the array of thalamic axons maintains topographic order and fits itself to the cortical sheet provides some hints about the otherwise mysterious co-evolution of thalamus and cortex. Any mutational change in the size of the thalamus or of the cortex might have led to autoregulated changes in the mapping from thalamus to cortex.

A simple test of the idea of autoregulation could be provided by removing part of the developing cortical sheet before arrival of thalamic fibres: autoregulation might match the thalamic input to the reduced area of the target. Such an experiment is all but impossible in eutherian mammals, in which thalamic axons reach the cortex during embryonic stages. Damage to the cortex after birth simply leads to retrograde degeneration of the corresponding thalamic nuclei. Huffman *et al* (1999) took advantage of the very immature state of the brain in newborn marsupials, and performed this experiment on the opossum, in which thalamic axons do not reach the dorsal cortex until more than a week after birth (Fig 9A; Molnár *et al*, 1998). The result was clear. Although the resulting maps of sensory areas were distorted compared with normal, the entire array was compressed on to the much diminished cortical surface. Equally important, the thalamus was uniformly reduced in size on the operated size. The thalamus had regulated its projection to fill the space available and, in turn, was itself regulated by the size of the target.

The human brain is about four times larger than that of a gorilla or chimpanzee, and twice as large as that of *Homo erectus*. Much of the difference is due to the extraordinary expansion of the cerebral cortex. The sudden explosion of the cortex, perhaps some 100,000–200,000 years ago, remains a puzzle for evolutionary biology. The remarkable size of the cortex has given humans their capacity for discovery and invention, for exploration, for culture. But what drove the enlargement of the cerebral cortex at a much earlier stage, when there seems to have been rather little for it to do? Evolutionary biologists have speculated that the enlargement was driven by selection for the special skills that the bigger brain allowed. But most of the cultural advances that presumably depended on the creative properties of the cortex – agriculture, art, writing and reading, science – occurred long after the increase in brain size, and after the genetic variation underlying speciation.

Let us look at this in a different way. A quadrupling of brain size requires only two additional cycles of cell division among the stem cells that make the brain. A single mutation in mice, recently described, leads to a large increase in the size of the brain (Rakic, 2004), because it prolongs cell proliferation. Perhaps a more pertinent question is why other animals' brains are so small? What

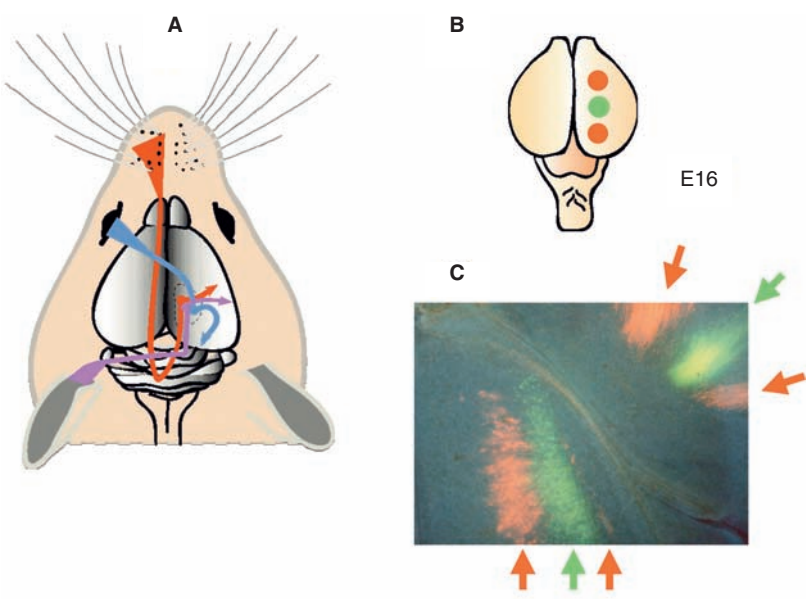


Fig 8. A: The general mammalian pattern of projection from sense organs to thalamic nuclei, to regions of the cortex is shown schematically for a rodent. The optic nerve (blue) connects to the lateral geniculate nucleus in the posterior thalamus, which in turn projects to the posterior pole of the cortex. The auditory projection (purple) passes to the medial geniculate nucleus, which projects to the temporal cortex. And the somatic sensory pathways (shown here from the whisker pad – red) project to the ventral part of the dorsal thalamus and thence to the somatic sensory area of the parietal cortex. (Illustration kindly provided by Zoltán Molnár.) **B:** Dorsal view of an E16 rat brain. Three crystals of carbocyanine dye were placed into the dorsal surface of the cortex, at the positions indicated by the coloured spots. **C:** Fluorescence micrograph of a horizontal section through the ventral part of the diencephalon (*lower left*) and telencephalon (*upper right*). The three bundles of thalamic axons, indicated by the coloured arrows, are clearly distinguishable. Note that there is a 90° twist in the pathway below this plane of section, as the axon array turns to enter the primitive internal capsule.

normally constrains the size of the brain? The usual response is that the brain is a very expensive organ. It is metabolically hungry. The human brain consumes about one-fifth of all the oxygen and all the glucose in the circulation. Then, perhaps the environment of early *Homo sapiens* in the savannah of East Africa was so clement, so bountiful, that this was not a serious constraint for early man. Could it be that the huge expansion of the human brain was essentially an empty mutation – a genetic anomaly whose costs were not large enough for it to be selected against. And when environmental challenges arose (for instance, the drying up of lakes in East Africa), the versatility and intelligence of that big brain might have provided the adaptability needed to preserve it.

The special role of individual experience

Axon terminals are secretory structures. They produce transmitter substances, in response to the arrival of impulses conducted along the fibre from the cell body, and they can also secrete growth factors and modulators of synaptic transmission. The role of impulses in triggering the release of molecules from the nerve terminal gives activity a special role in the development and maintenance of the central nervous system.

There is a wealth of evidence, from clinical observation and experimentation, that individual sensory and motor experience early in postnatal life has a profound influence on the maturation of cortical function. Indeed, spontaneously generated impulse activity appears to play a part in nervous development at even earlier stages. For instance, there is evidence that waves of activity, which sweep slowly across the cells of the developing retina, regulate the distribution of optic nerve axons over the lateral geniculate nucleus of the thalamus and the formation of eye-specific layers in that structure (Stellwagen and Shatz, 2002; see Sengpiel and Kind, 2002). Interestingly, however, the prenatal outgrowth and guidance of thalamic fibres, and their targeted invasion of the cortex, are not obviously disturbed in mice with a null mutation of the *SNAP-25* gene, in which there is no impulse-mediated synaptic transmission (Molnár *et al*, 2002).

The role of early sensory stimulation in the development of sensory areas of the cortex has been the subject of intense interest since Wiesel and Hubel (1963) first discovered that deprivation of vision (by closure of one eye) leads to a dramatic failure of development in the primary visual cortex of cats. The majority of cortical neurons, at least those outside layer 4, where thalamic axons terminate, lose their effective input from the deprived eye and can be driven only by stimulation through the non-deprived eye. This physiological change is at least partly correlated with a modification in the pattern of right-eye and left-eye thalamic axons in layer 4 of the cortex. The fact that the influence of activity is competitive and instructional, rather than merely being due to the loss of synaptic connections that are not used, is dramatically illustrated by the reversal of these changes, if deprivation of the eyes is reversed (Blakemore and Van Sluyters, 1974).

In the late 1960s, when it seemed possible that the effects of monocular deprivation were due to selective degenerative changes in ocular dominance columns initially dominated by the deprived eye, it occurred to me that early deprivation of experience of contours of a particular orientation might cause selective degenerative changes in the cortex, which might provide a way of directly visualising the orientation columnar structure of the cortex. I reared kittens whose visual experience was limited to periods in large cylindrical chambers, the interior walls of which were painted with stripes, either horizontal or vertical (Fig 10). In one way the experiment was a failure: there were no obvious degenerative changes in the cortex that might have corresponded to the columnar structure. However, when

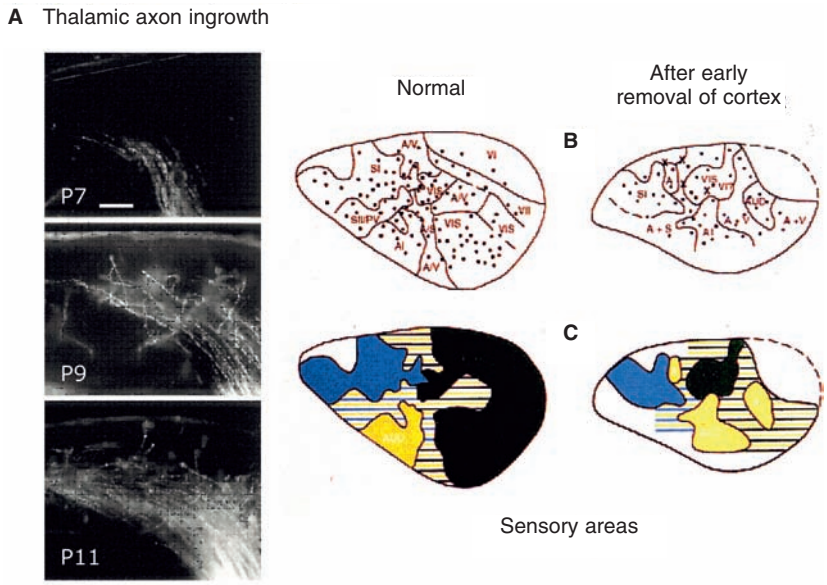


Fig 9. Autoregulation of the mapping from thalamus to cortex, demonstrated by cortical removal in a marsupial, the south American grey short-tailed opossum (*Monodelphis domestica*). **A:** Fluorescence micrographs, showing labelled thalamic axons approaching the immature cortex a week after birth (P7) and growing into the cortical plate over the following four days. Modified from Molnár *et al* (1998). Scale bar 100 μm. (Compare this with stages occurring before birth in the rat, Fig 6). **B:** Maps of sensory areas in the cortex of the left hemisphere of anaesthetised opossums: a normal adult (*left*) and an adult in which approximately the posterior half of the hemisphere had been removed, under anaesthetic on P4, before the arrival of thalamic axons. Dots mark microelectrode penetrations and boundaries are drawn around areas of response to visual (V), auditory (A) or somatic (S) stimulation. **C:** The same results are shown with colours indicating the modality of each area: black = visual; yellow = auditory; blue = somatic. Areas of mixed response are indicated by coloured lines. Note that, although the visual area is smaller, it is still present, even though the region of the hemisphere that it should have occupied had been ablated. Data from Huffman *et al* (1999).

Grahame Cooper and I recorded from the primary visual cortex of such cats, we found a dramatic influence of the early selective exposure – a marked reduction in the proportion of neurons preferring orientations that the animal had not experienced when young (Blakemore and Cooper, 1970).

For many years, this observation remained controversial. Although it was eventually replicated, in one way or another, in at least 10 other laboratories around the world, there was still intense debate about its significance and interpretation (see Sengpiel *et al*, 1999). In particular, there was the question of whether the result could be explained merely by selective deprivation of columns of cells innately 'tuned' to the deprived orientation, causing them eventually to become unresponsive.

I remember well a seminar that I gave about this research in the early 1970s, in the Physiological Laboratory in Cambridge, where I worked. I was puzzled about the apparent incompatibility of my results with Cooper and the prevailing view at that time, that orientation selectivity, and hence the orientation columnar structure of the cortex, were hard-wired. So, I skirted around this problem in my talk. Francis Crick came down from the MRC Laboratory of Molecular Biology to attend the seminar. To my amazement and admiration, even though he had not yet publicly switched the focus of his interests from molecular biology to neuroscience, he asked the most penetrating question: how could these results be reconciled with what was known of the orientation columnar structure?

Subsequently, Van Sluyters and I showed that the orientation columnar structure of the cat visual cortex is not fully established without visual experience (Blakemore and Van Sluyters, 1975). There is a population of cells (probably receiving direct input from thalamic axons) that are pre-specified for particular orientations, as soon as the kitten's eyes first open, and subsequent work, using the metabolic marker tritiated 2-deoxyglucose, showed that these clusters of pre-specified neurons form a pattern across the middle layers of the cortex, around which the columnar structure 'crystallises' (Thompson *et al*, 1983). But a large fraction of cortical neurons in kittens is non-selective or very poorly selective for orientation, and Van Sluyters and I (Blakemore and Van Sluyters, 1975) suggested that the population might become biased as a result of selective exposure, through a simple associative learning mechanism, which would normally impose the usual columnar architecture on the cortex.

Singer *et al* (1981) applied the 2-deoxyglucose method to this question. They saw expansion of the areas of activity representing the experienced orientation, and the survival of only small areas, mainly restricted to the middle layers of the cortex, after early experience restricted to one orientation. Recently, Sengpiel *et al* (1999) have used optical recording to provide definitive evidence

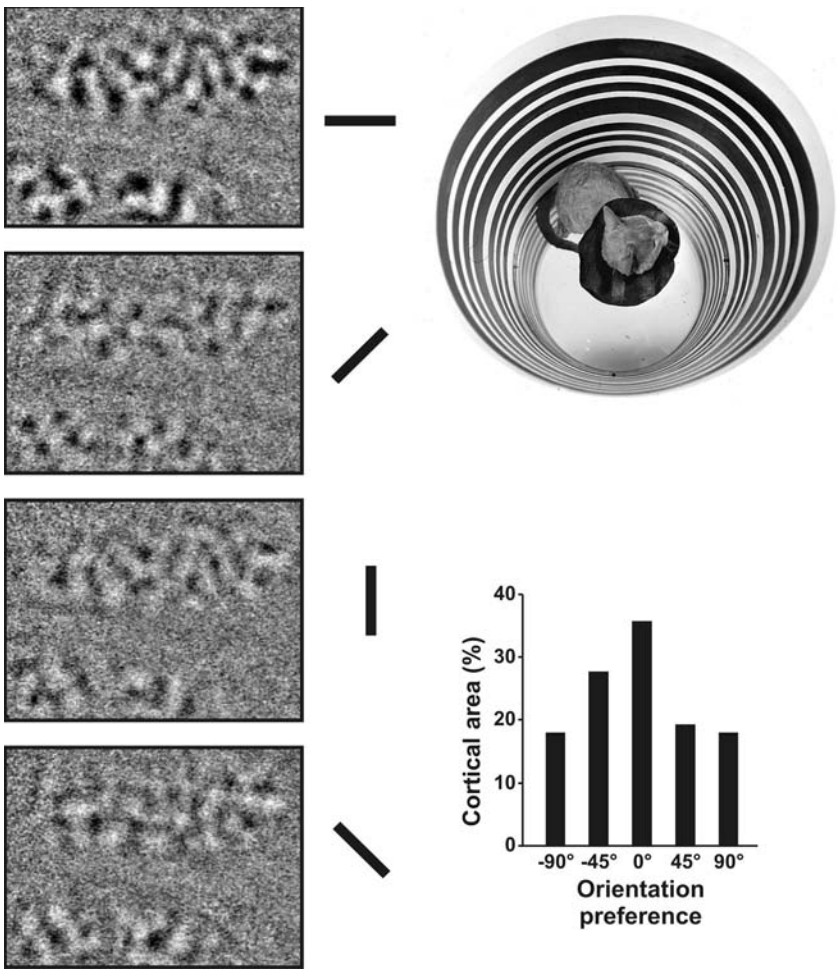


Fig 10. Results from the study of Sengpiel *et al* (1999), who used optical imaging (see Fig 3) to reveal the reorganisation of orientation columns in the cat visual cortex (V1) resulting from early selective exposure to contours of one orientation. The inset photograph shows a cat, wearing a ruff to restrict vision of its own body, standing on a glass platform in a large cylindrical chamber, the internal walls of which were painted with high-contrast horizontal stripes. The cats in this study were exposed to the striped environment for a total of 75–120 hours between $2\frac{1}{2}$ and 6 weeks of age. Each image on the left shows a view, about 8 mm across, of V1 of the right hemisphere (*at the top*) and part of the left V1 (*bottom*), in an anaesthetised cat. During the collection of each optical recording, moving stripes were projected on to a screen in front of the cat's eyes, the orientation of the stripes indicated by the line segment next to each frame. Areas of neuronal activation appear dark. Clearly, the regions of cortex responding to the horizontal stripes (the orientation experienced earlier in life) were much larger than those responding to other orientations. The histogram (*bottom right*) plots the cortical area devoted to the different orientations, zero being horizontal. Early exposure produces a substantial expansion in the size of columns devoted to the experienced orientation. Data kindly provided by the authors.

for an instructive role of visual experience in establishing the orientation columnar structure of the cortex (Fig 10).

When I first became interested in the influence of the environment on the development of the visual cortex, it was conventional to consider genetic and environmental influences as quite distinct – almost in conflict with each other. I suppose that one can see that tension as a modern expression of the battle between nativism and empiricism in philosophy. However, since the function of cells is ultimately determined by the production of proteins, environmental influences must surely act as epigenetic modulators of gene function. In other words, the capacity for the environment to have a beneficial influence on the development of the brain must itself depend on genetic mechanisms. The emergence, during evolution, of genes that enable neural activity to have an organising effect on neurons, was a transcendent step in evolution – a genetic mechanism that empowered the brain to acquire new information from the environment, and hence to break out of the information straitjacket of the genetic code.

There has been much work on the molecular basis of neuronal plasticity in the past few years, trying to track down the genes that underlie the ability of synapses to change as a result of activity passing through them. Much effort has concentrated on the hippocampus, a phylogenetically ancient area of archicortex, which is thought to be involved in the laying down of episodic memory of personal experience and spatial memories. But there has also been progress in defining the molecular bases of synaptic plasticity in developing areas of the neocortex (see Berardi *et al*, 2003).

The area of the rodent somatic sensory cortex that receives input from the whiskers has provided a model system for such work. In this region there is a remarkably explicit correlation between cortical architecture and the nature of the sensory input. As Hendrick Van der Loos and Tom Woolsey discovered (Woolsey and Van der Loos, 1970), there is a structural pattern of fibres and cells in layer 4 of this region that directly reflects its input (Fig 11). The afferent fibres carrying signals from each individual whisker congregate in a dense plexus in layer 4 during the first few days after birth, and these plexuses are segregated from each other to form a pattern across layer 4 that corresponds precisely to the arrangement of the whiskers. The neurons in layer 4, which are initially randomly distributed, become displaced to form 'walls' of neurons, with their dendrites directed in towards the plexus of axons that they surround. Each wall-plus-plexus is called a 'barrel'.

Van der Loos and Woolsey (1973) provided strong evidence that the formation of barrels is influenced by activity from the whiskers, arriving along the incoming fibres. They reared mice with one row of whiskers clipped (or with the follicles cauterised) so as to provide partial deprivation of sensory input, comparable to monocular deprivation. This procedure, occurring in the first week of life, leads to a striking anomaly: barrels fail to form normally for the row of unstimulated whiskers (Fig 11C).

In the search for the molecular basis of the activity-dependent process, attention has focused on the various classes of receptor in the post-synaptic membranes of cortical neurons to which glutamate binds, since this is the transmitter substance released by thalamic axons, and on the intracellular pathways through which those receptors signal (see Hannan *et al*, 2001; Erzurumlu

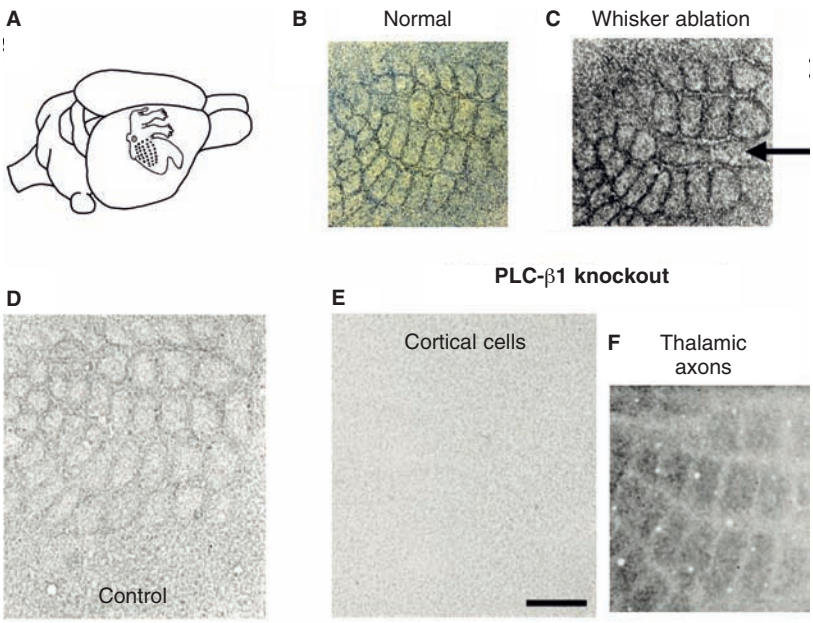


Fig 11. Studies of the 'barrel field', the region of the somatic sensory cortex of rodents that receives input from the facial whiskers, has provided important evidence about the genetic basis of activity-dependent plasticity of sensory areas during early sensitive periods. A: The somatic sensory cortex in the mouse contains an expanded region representing the massive sensory innervation of the whiskers. **B:** A tangential section through layer 4 (where thalamic axons terminate) of the region of cortex of an adult mouse receiving input from the whiskers, stained to show the cortical cell bodies, reveals the cells densely packed to form the walls of the 'barrels', which form a pattern corresponding to the array of whiskers on the opposite side of the face. In the middle of each barrel is a plexus of thalamic fibres carrying signals from one whisker. **C:** A similar section from a mouse that had one row of whiskers trimmed for the first weeks of life, to produce selective deprivation. The corresponding set of barrels has failed to develop normally (arrow). **D:** A similar section showing the barrel field of a 1-week-old mouse, with the cortical cell bodies stained. The barrels have clearly formed by this age. **E:** Sections from a 1-week-old mouse with a null mutation of the gene for phospholipase C-β1, an enzyme that is activated via the metabotropic glutamate receptor (mGluR5), which is stimulated by glutamate released by thalamic axons. This gene knockout prevents the normal migration of cortical cells to form the walls of the barrels. Knockout of mGluR5 produces a very similar phenotype. Scale bar = 100 μm. **F:** In a section from the same knockout mouse, a stain for thalamic axons reveals that they have still segregated normally to form the whisker pattern of plexuses. The mGluR5-phospholipase C-β1 pathway appears to be involved specifically in the activity-dependent process by which cortical cells are redistributed to form barrel walls.

and Kind, 2001; Barnett *et al*, 2005). Genetic modification has proved a valuable tool for the analysis of these molecular mechanisms (Fig 11). Knockout of two different classes of glutamate receptor, as well as a number of internal messenger molecules that signal from the glutamate receptors, has been shown to disrupt the normal formation of barrels. It is clear that the genome encodes substantial molecular machinery that provides neurons with the capacity to modify their structure and the efficiency of their synapses, on the basis of their impulse activity.

The continuously dynamic cortex

Perhaps the most striking characteristic of the many examples of the influence of early selective deprivation on sensory systems is that they are effective only during quite well-defined 'sensitive periods'. For instance, in monkeys, monocular deprivation modifies ocular dominance columns in V1 only during the first two months of postnatal life, and whisker deprivation alters anatomical barrel structure only during the first week or so in mice. One interpretation of these limited periods of responsiveness to the sensory environment is that they enable sensory areas to acquire information from the statistical properties of the input, but that neurons must achieve stability of coding if their signals are to be reliably interpretable by areas of cortex to which they send information.

By the 1970s, the concept of early sensory plasticity was generally accepted. But evidence began to gather that the adult cortex is also capable of reorganisation. Initial studies in animals revealed that the mapping of sensory areas of the cortex can shift dramatically, and quite quickly (within days or even faster), in response to the loss of signals from part of the receptor surface (see Buonomano and Merzernich, 1998). Loss of input from some area of the body, caused, for example, by section of a peripheral nerve, results in a rapid change in the body map in the somatic sensory cortex, with areas that formerly represented the 'silent' body part now responding to stimulation of surrounding, still innervated, parts of the body. It appears that the cortex abhors a functional vacuum, and has inherent mechanisms for reallocating responsibility into regions that are silenced through loss of their usual input.

Similar phenomena certainly happen in the human cortex (reviewed by Steven and Blakemore, 2004a). Within a few days after amputation of the forearm, some patients report curious double sensations from intact parts of the same side of the body (Ramachandran *et al*, 1992). Touch on the face or the shoulder elicits a phantom sensation on the missing hand, with a systematic representation of the hand across the surface of the face and the shoulder. Now, those parts of the body project to the regions of somatic sensory cortex immediately adjacent to the area devoted to the missing forearm. The implication is that activity entering the cortex from the face and the shoulder has 'spread' into the vacant hand area, and that the resulting activation of neurons in that area produces sensations that are referred to the hand. Indeed, Yang *et al* (1994), using magnetoencephalography, have shown that amputation leads to such a reorganization of the somatosensory cortical map.

Did Thomas Willis foresee this modifiability of cortical mapping?

> *Hence these folds or rollings about are far more and greater in a man than in any other living Creature, to wit, for the various and manifold actings of the superior Faculties; but they are garnished with an uncertain, and as it were fortuitous series, that the exercises of the animal Function might be free and changeable, and not determined to one.*
>
> (Willis, 1664)

A flood of neuroimaging results has revealed the extraordinary capacity of the cortex to reorganise in response to the pattern of activity, as if to meet ever-changing sensory and motor demands (see Steven and Blakemore, 2004a). For instance, human somatic sensory representations can be modified not just by amputation or anaesthesia, but also by skilled use of a body part (for instance, the fingering hand of players of stringed instruments or the Braille-reading fingers of the blind). The motor cortex also reorganises after even short periods of motor training. In one striking study, Classen *et al* (1998) used transcranial magnetic stimulation (TMS) of the motor cortex to identify a region where stimulation evoked a consistent movement of the thumb in one direction. After the subject had practised moving the thumb in the opposite direction for as little as 10 minutes, TMS of the same area produced a thumb movement in the newly learned direction.

There is still no general agreement about the mechanisms of this local remapping in the adult cortex, but they are presumably different from those operating during classical early sensitive periods. The scale of the shifts in representation can be startlingly large – millimetres, even centimetres, across the surface of the cortex. While there is some evidence for increased axonal distribution in the cortex after long periods of selective sensory deprivation, the range and speed of the changes suggest that modification of the efficacy of existing long-range connections within the cortex is likely to be the principal mechanism. There are indeed sparse, long-range horizontally distributed axons within the cortex, whose remote synaptic contacts might become strengthened as a result of differential patterns of stimulation entering the cortex. Also, synaptic modification within chains of local connections, from neuron to neuron, across the cortex, might play a part. There is evidence that alteration in the pattern of inhibition is involved in the unmasking of weak connections.

Despite all these demonstrations of radical plasticity in the adult cortex, it is less clear whether the capacity for reorganisation is of any value, and, if so, how it conveys an advantage. In early sensory areas, the efficiency of detection and discrimination of individual neurons is often so high that perceptual decisions could be mediated by very small populations of neurons (see Parker and Newsome, 1998). In that case, how can it be useful to have many more neurons committed to a particular sensory function? Also, there is evidence that remapping can produce aberrant sensation (as in the case of the referred sensations of amputees) and dystonic movements (see Steven and Blakemore, 2004a).

Sensory learning does seem to be associated with specific and rapid enlargement of the cortical representation of the receptor input involved in the learning task. Figure 12 illustrates a

graphic example. In this study, Nektarios Mazarakis and colleagues, in my laboratory, used optical imaging to visualise the tiny area of activity in the upper layers of the mouse somatic sensory cortex evoked by stimulation of just one whisker (Mazarakis *et al*, in preparation). Then, for just a few minutes each day, for three days, mice were classically conditioned, by stroking the whisker in combination with a drop of sugar solution delivered to the tongue. This led to distinct expansion of the region activated by that whisker, which did not occur in control mice that had experienced exactly the same whisker stroking but without the sugar.

The capacity of the cortex to reorganise is not limited to changes within circumscribed functional areas. Linkages to distant regions can be facilitated in remarkable ways, in response to major loss of sensory input or gross damage, for instance after stroke. In blind people, the entire posterior one-third of the cerebral cortex loses its normal input, and there has long been speculation about the possibility that it is recruited to support other functions in the brain. Neuroimaging has added weight of evidence to this debate. In the blind, Braille reading and even stimulation of the skin with any textured surface, induces considerable activity in visual areas of the cortex, and the pattern of areas activated (at least in subjects who had vision for some time before becoming blind) relates to the particular tactile stimulus (see Steven and Blakemore, 2004a).

The pathways that enable the cortex to generate such wide-range activation of other regions are still a mystery. It is possible that the entire cortex is linked by a network of sparse cortico-cortical connections that are normally ineffective, but can be selectively strengthened as a result of major changes in sensory input, or conceivably during the normal association of sensory experiences across different modalities. Activation of the auditory cortex by the visual cortex might explain how vision of lip movements during speech substantially assists the interpretation of what is being said (Calvert *et al*, 1997).

Hints about the basis of long-range associative connections in the cortex are coming from the study of the curious condition of synaesthesia – the occurrence of illusory, 'ectopic' sensations in

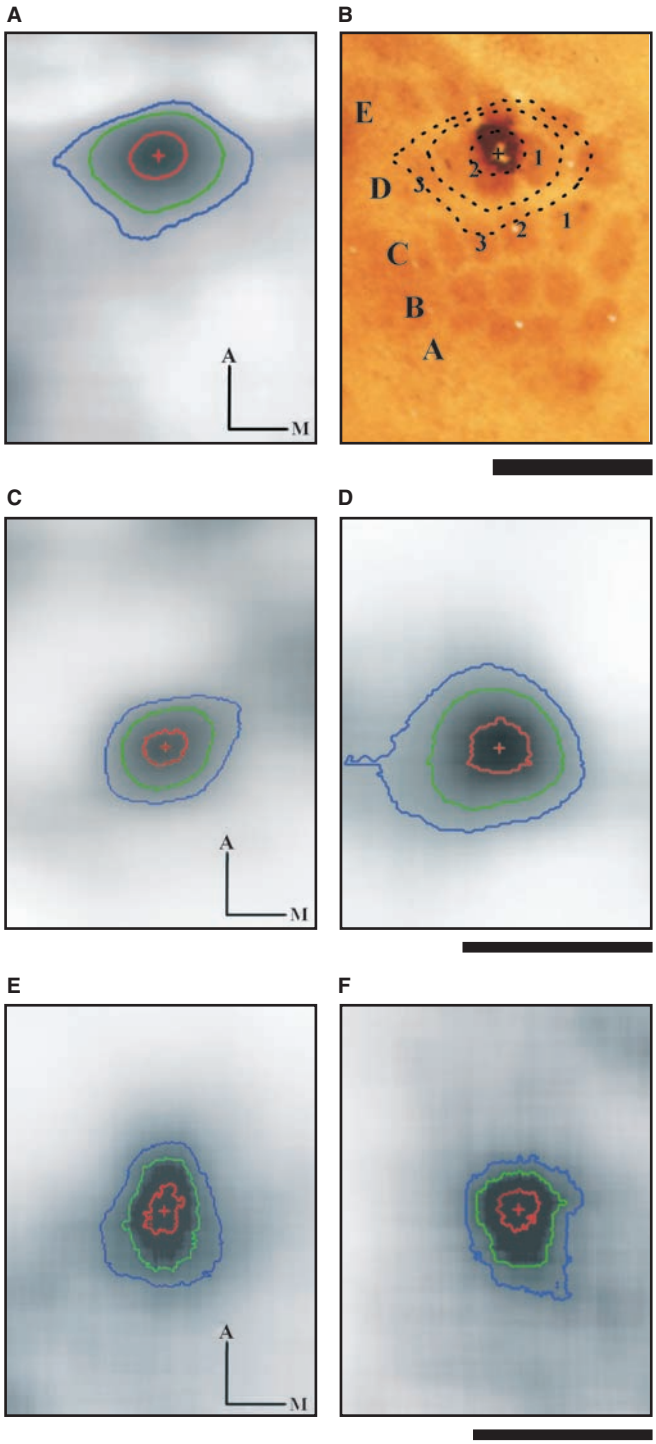


Fig 12. Optical imaging reveals a rapid change in the cortical representation of a single whisker as a result of the simplest form of learning, classical conditioning. The barrel field of the somatic sensory cortex of anaesthetised mice was viewed through the skull with a video camera. Changes in the reflection of red light, dependent on changes in the oxygenation of haemoglobin, are shown as dark areas. **A**: Activation produced by vibration of a single whisker – the D2 whisker. The contours around the dark area enclose 50% (blue), 75% (green) and 95% (red) of the difference in signal between the peak of activity (marked with a red plus) and the background signal (A = anterior; M = medial). **B**: A tangential section of the flattened cortex from the same animal in A, stained to reveal cytochrome oxidase activity, which labels plexuses of thalamic axons in the centres of whisker barrels. A fine needle had been inserted into the cortex at the centre of the optical activity produced by vibration of whisker D2. The resulting lesion is the dark spot, which does indeed lie within the axon plexus corresponding to whisker D2. The 50%, 75% and 95% contours of the optical activity are indicated by the interrupted contours around D2 barrel. The 95% contour corresponds quite well to the anatomical barrel input, but activity spreads over the immediately adjacent barrels. **C,D**: Optical recording of the activation produced by D2 whisker vibration in a single animal, before (C) and after (D) three brief sessions of classical associative conditioning in which stroking this whisker was coupled with the delivery of a drop of sugar solution to the tongue. There was roughly a doubling of the size of the whisker representation. **E,F**: Control images, before and after sessions of whisker stroking, but without delivery of sugar. There was no change in the whisker representation. Hence the expansion seen in D results specifically from the learning paradigm. Scale bars = 1 mm.

association with particular forms of real stimulation. Long treated with scepticism by many clinicians and scientists, synaesthesia has gained credibility and interest, partly through the clear evidence for heritability of this condition, and partly because of the objective evidence for the phantom sensations that has come from neuroimaging.

Interestingly, synaesthesia very commonly involves the attachment of perceptions of colour to non-coloured stimuli, such as letters of the alphabet, or certain spoken words, or music. Colour synaesthetes who become blind sometimes start to attach colour sensations to Braille characters that they touch, and these colours can persist, despite decades of blindness (Steven and Blakemore, 2004b). Figure 13 illustrates results from fMRI on a late-blind synaesthete, who had completely lost light perception ten years earlier (Steven *et al,* 2005). Nevertheless, he had strong persistent colour synaesthesia, in the form of dots or blobs of colour apparently floating in front of his eyes. Braille characters and a variety of categories of spoken words, including 'time words' (days of the week, and months of the year), groups of musical instruments etc, elicited highly reproducible descriptions of colour. The brain response when he listened to 'time words', compared with that for other words that did not generate colours, showed strong activation in area V1 and also in a region of the left inferior extrastriate cortex termed V4/V8, which is activated by genuine coloured stimuli in sighted people (Zeki, 1993). Interestingly, late-blind subjects retain strong visual imagery and this patient was able to imagine colours in his mind's eye. Such imagined colours also caused activation in the extrastriate belt, but in an area somewhat anterior to V4/V8, providing evidence that synaesthetic colours are not simply imagined, in the normal sense.

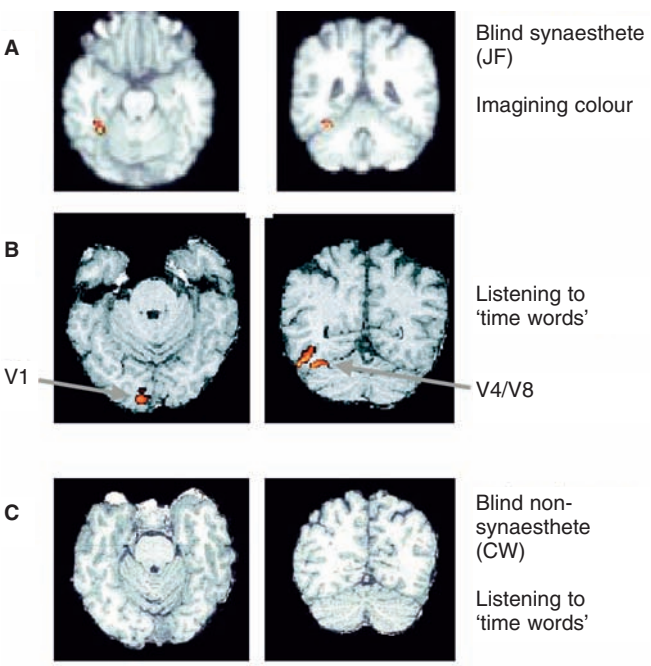


Fig 13. MRI scans show activation of visual cortical areas corresponding to imagined colours and synaesthetic coloured sensations in a late-onset blind individual (JF). **A:** Horizontal scans at different levels through the inferior extrastriate visual cortex. In this case, the orange voxels indicate regions specifically activated as the subject imagined that he was looking at a coloured sweater. **B:** Here the orange areas were activated when the subject listened to 'time words' (days of the week, months of the year), which elicited synaesthetic coloured impressions. Note the activity in the primary visual cortex, V1, and the colour area, V4/V8. **C:** Results of an identical experiment in another late-blind subject who was not synaesthetic. No activation is seen.

Some aspects of synaesthesia, such as the attachment of colours to letters of the alphabet or Braille characters, must involve individual learning, but the fact that this condition runs in families makes it likely that there is some underlying unusual characteristic of cortical connectivity. One possibility is that there is an overabundance of long-range cortico-cortical connections, which become strengthened through some kind of associative learning process. Diffusion tensor imaging (a variant of MRI that can be used to analyse the regularity of structure of fibre tracts) has shown differences between synaesthetes and non-synaesthetes in the organisation of the white matter beneath the left angular gyrus, a region of the inferior parietal lobe involved in processing of auditory and visual stimuli and in the comprehension of language (Steven, 2004).

Cortical plasticity for clinical good

The plasticity of sensory areas of the cortex early in life instructs cortical organisation on the basis of sensory input. But this carries the risk that sensory deprivation, or imbalance in the function of sense organs, can trigger gross failures of development, such as those seen in animals after monocular deprivation or imbalance of orientation in the early diet. Such errors can lead to functional disorders later in life. *Amblyopia ex anopsia*, the commonest form of visual handicap, affecting perhaps 3% of the population, is a consequence of failure in normal development of the visual cortex. Monocular deprivation (through lid ptosis or corneal opacity, for instance), even for as little as a week, some time in the first year or so of a baby's life, can result in reduced vision through the deprived eye. Differences in refractive state between the two eyes (ansiometropia), such that one retinal image is habitually slightly blurred, can also precipitate amblyopia because of changes in ocular dominance in the visual cortex (Eggers and Blakemore, 1978). And early strabismus (misalignment of the eyes) commonly leads to amblyopia and/or suppression of one image (Sengpiel and Blakemore, 1996; see Barrett *et al*, 2004).

Research on early plasticity of the visual cortex has provided clues to the treatment and prevention of amblyopia. But the window of plasticity of the visual cortex means that attempts at treatment (usually through occlusion of the normal eye) are rarely completely effective after a very early age.

The auditory and language systems of the brain also pass through periods of sensitivity, and disturbances of hearing and language, ranging from otitis media with effusion to lack of early experience of spoken language, can precipitate a variety of subsequent defects in hearing, understanding language and learning (see Moore, 1996). Recent research is concentrating on

the development of remedial treatments for such conditions, based on training in relatively simple auditory discriminations.

A fuller understanding of the molecular basis of normal sensitive periods might eventually bring the capacity to restore plasticity, perhaps pharmacologically, in order to treat such developmental disorders more efficiently.

The possibility that cortical plasticity triggered by organised neural activity might have beneficial effects even in neurodegenerative disorders is the focus of much recent research (see Spires and Hannan, 2005). The chance discovery that enrichment of the sensory environment can delay the onset of motor signs in a

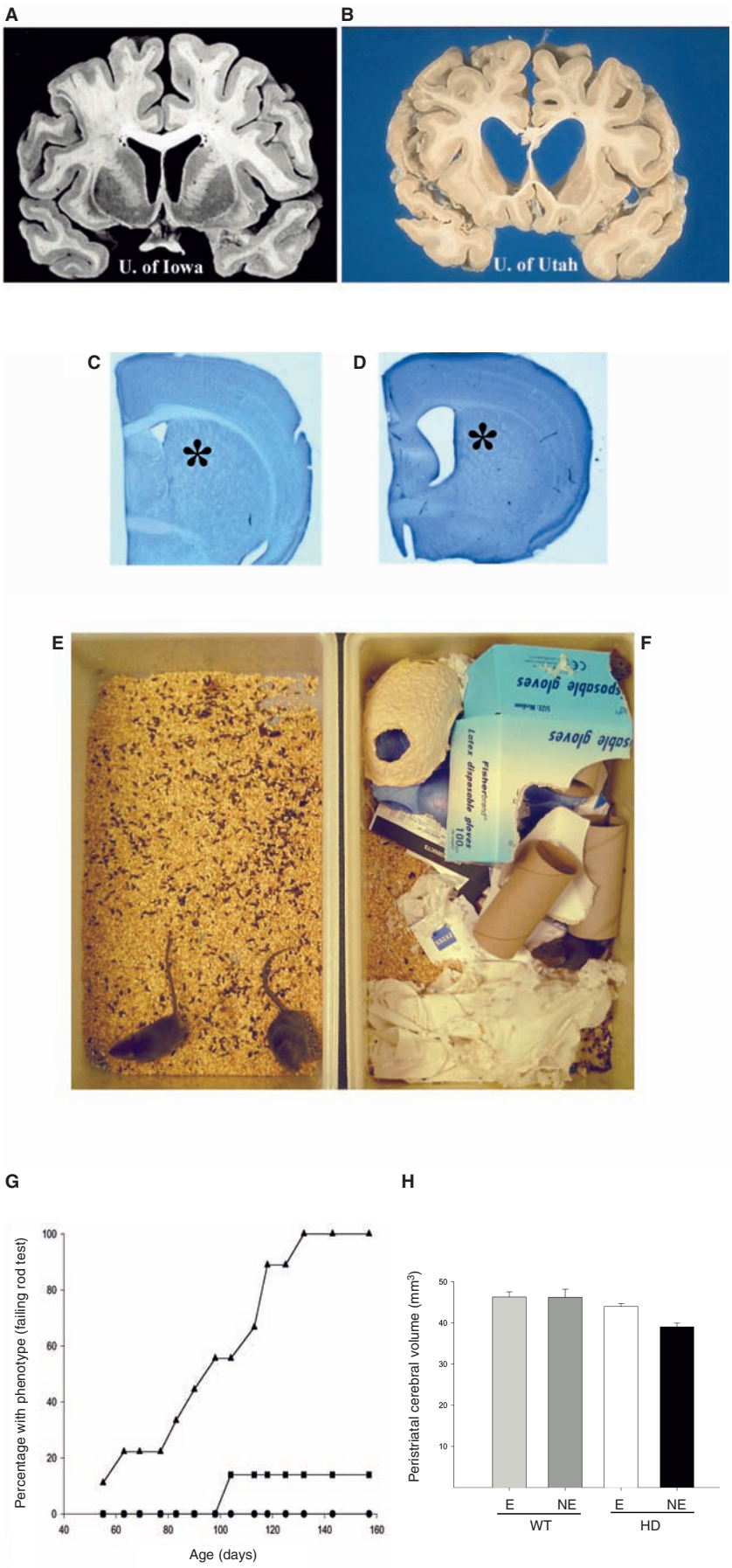


Fig 14. Huntington's disease (HD), an autosomal dominant disorder resulting from a trinucleotide repeat in exon 1 of the *huntingtin* gene, causes severe degeneration of the corpus striatum and the cortex surrounding it, with consequent enlargement of the ventricles. (B is a coronal section through the brain of a Huntington's victim; compare with the normal brain in A.) C and D show comparable sections from a normal mouse (C) and an R6/1 transgenic mouse, with stable expression of the HD gene (D). There is similar neuropathology, and these mice also develop a constellation of cognitive and motor signs that closely matches the syndrome in humans. As part of a programme of environmental enrichment for laboratory mice, Van Dellen *et al* (2000) compared mice housed in normal cages (E) with those reared in cages filled with interesting junk, which was changed every couple of days (F). Surprisingly, the environmental enrichment dramatically delayed the onset of motor signs. **G**: Groups of normal mice (circles), HD mice kept in normal cages (triangles), and HD mice reared in an enriched environment (squares) were tested for motor coordination by placing them on a horizontal wooden rod, suspended above bedding material, to see whether they would turn around and escape without falling off. The ordinate plots the percentage of animals failing this test as a function of time. Normally reared R6/1 HD mice started to fail as early as 50 days of age, and all were failing by 130 days, whereas very few of the environmentally enriched HD mice were failing even at 160 days. **H**: In these mice, degenerative changes were assessed from histological sections, by calculating the volume of the coronal slice of forebrain containing the entire corpus striatum and surrounding cortex. In non-enriched (NE) HD mice, there was a highly significant reduction in peristriatal volume, whereas enrichment (E) prevented this deficit, preserving the volume close to that of normal wild-type (WT) mice, whether environmentally enriched or not. Data of G and H modified from Van Dellen *et al* (2000).

transgenic mouse model of Huntington's disease (Van Dellen *et al*, 2000) revealed an unexpected influence of experience even in this single-gene, dominant disorder (Fig 14).

The mutant *huntingtin* gene results in not only production of aberrant huntingtin protein but also a cascade of molecular disorders, and the specific process of pathogenesis is not fully understood. The fact that enriching the environment delays the disease process provided a means of tackling this issue (Spires *et al*, 2004). Simple proteomic methods showed that a deficit in the level of the important growth factor, brain-derived neurotrophic factor (BDNF), in the corpus striatum of Huntington's disease (HD) mice was prevented by rearing the animals in an enriched environment (Fig 15). Since BDNF levels in the cortex of non-enriched HD mice are normal, the implication is that axonal transport of the protein from cortex to striatum is compromised in HD. Indeed, there is evidence that normal huntingtin is involved in vesicular trafficking. The hypothesis is that exploration of an enriched environment generates more activity in frontal areas of the cortex, and that the increased impulse activity in corticostriatal axons helps to compensate for the protein transport deficit. This result points to reduction of BDNF as an important aetiological factor, which in turn raises the prospect of new therapeutic or preventive approaches to this devastating disease.

Epidemiological studies of large cohorts of ageing people suggest that the incidence of sporadic Alzheimer's disease is reduced in those who have taken part in activities that involve cognitive 'exercise' and in the better educated and those who have higher levels of occupational achievement (see Spires and Hannan, 2005). This has led to interest in the possible value of environmental enrichment in preventing or delaying this common neurodegenerative disease. In a recent study, environmental enrichment was indeed shown to reduce the levels of amyloid β and the deposition of amyloid in a double mutant (APP_{Swe} × PS1ΔE9) mouse model of Alzheimer's (Lazarov *et al*, 2005).

Over the past decade, the dogma that no new neurons can be generated in the adult mammalian brain has been overturned, with the discovery of neural stem cells in parts of the forebrain, especially the subventricular zone, olfactory bulb and dentate gyrus of the hippocampus, and evidence that the production of new neurons is of functional significance (Kempermann *et al*, 2004). There is, of course, great excitement about the prospect of transplantation of stem cell lines into the brain as a therapeutic strategy for stroke and neurodegenerative disorders. But there is also the possibility that stimulation of natural endogenous neurogenesis could be of value in some conditions (Emsley *et al*, 2005).

There is good evidence that changes in cortical organisation in the adult human brain can be induced by repetitive transcranial magnetic stimulation (TMS) (see Siebner and Rothwell 2003). Although this approach is still in its infancy, targeted stimulation can be useful in the treatment of depression (Couturier 2005), anxiety and motor disorders, and it might be of value in schizophrenia and epilepsy (George *et al*, 1999).

Finally, there is considerable interest in the role that natural plasticity of the cerebral cortex might play in recovery from the impact of stroke, and in the design of rehabilitation to optimise this process. The cortex can change its functional organisation radically after either subcortical or cortical stroke. After therapy, new regions can become active in both hemispheres during motor tasks that were initially affected by the stroke, and the extent of this reorganisation is correlated with the improvements in motor contol and strength (see Johansen-Berg *et al*, 2002). TMS has been cleverly used to analyse whether the regions of new activity play a significant role in mediating the recovery. Disruptive TMS over regions of increased activation in the premotor cortex on the side opposite to the stroke did interfere with movements of the stroke-affected hand in patients, and the degree of interference correlated with the magnitude of the new cortical activation that had appeared during recovery. This implies that new activity, even on the opposite side of the brain, is involved in the recovery process.

There is now great interest in the possibility of applying what has been learnt about post-stroke reorganisation to design targeted therapies. Very recently, Hummel *et al* (2005) have shown that transcranial direct current stimulation of the motor cortex on the side on the brain affected by stroke can produce improvements in movement of the paretic hand that last for up to half an hour. This is a start. Combination

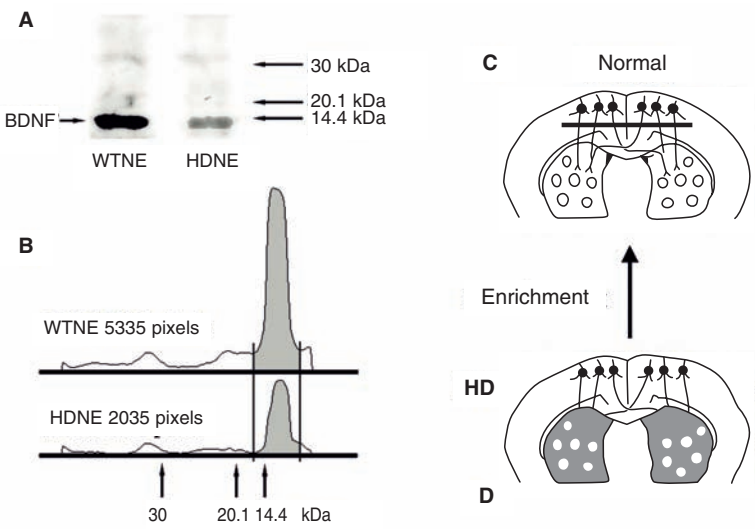


Fig 15. Clues to the pathogenesis of Huntington's disease from studies of protein transport. A: Quantitative Western blotting was employed to measure the levels of brain-derived neurotrophic factor (BDNF) from tissue samples from the corpus striatum of wild-type (WT) and transgenic HD mice. These examples show the much reduced level of BDNF in HD mice reared in a non-enriched (NE) environment. These results are shown as density plots in B. (Data, modified, from Spires *et al* 2004.) Rearing of HD mice in an enriched environment prevents this deficit. BDNF is normally transported to the striatum along corticostriatal axons (C). It seems likely that the abnormal huntingtin protein interferes with normal axonal trafficking and therefore reduces the level of BDNF reaching the striatum (D). The extra neural activity in the frontal cortex elicited by environmental enrichment might compensate for the impaired protein transport and hence 'rescue' the striatum.

of rehabilitation therapy and targeted cortical stimulation might provide a valuable new approach to the treatment of chronic stroke.

On 3 June 1657, at the generous age of 79, William Harvey had a massive stroke.

> *The morning of his death about 10 a clock, he went to speake, and found he had the dead palsey in his tongue; then he sawe what was to become of him, he knew there was then no hopes of his recovery, so presently sends for his young nephewes to come-up to him, to whom he gives one his watch ('twas a minute watch with which he made his experiments); to another, another remembrance, etc.; made signe to ... Sambroke, his apothecary (in Black-Fryars), to lett him blood in the tongue, which did little or no good; and so he ended his dayes.*
>
> (John Aubrey, 1898)

The Fellows of the Royal College of Physicians joined the procession that took Harvey's body to the family vault at Hempstead, Essex. And on St Luke's Day, 18 October 1883, exactly 122 years ago, it was moved to a sarcophagus provided by the College, in the Harvey Chapel at Hempstead Church.

Harvey bequeathed his books and papers to the College, to add to his many other acts of benefaction, not least the construction of a Library, and the endowment of this series of Orations.

Fig 16. Group photograph from a Dahlem Conference on Neurobiology of the Neocortex, held in May 1987. *Back row* (*left to right*): John Allman, Torsten Wiesel, Jon Kaas, Michael Merzenich. *Middle row*: Gunther Stent, Wolf Singer, Hendrik Van der Loos, Pasko Rakic. *Front row*: Joachim Gruel, Michael Stryker, Colin Blakemore.

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The full text of the Harveian Oration is also available in booklet form from the Publications Department of the Royal College of Physicians. The lecture is also published in The Lancet.