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Annual Oration

More Than The Sum Of Its Parts

Royal Victoria Hospital, Thursday 4th October 2007

Stanley A Hawkins

Ladies and gentlemen it is a particular honour to present the Annual Oration. My title is “More than the sum of its parts”. The sub-title is “the Brain”. The Annual Oration has been running regularly since the nineteenth century. By tradition it is held on the first Thursday of October each year. The first recorded oration was in 1827 by Dr James McDonnell, the next recorded oration was in 1852 by Dr Andrew Malcolm[1]. Following his untimely death, to honour his name, his medical colleagues endowed the funds for a competitive prize for junior clinical students. I had the honour of winning this prize in the spring of 1969, so the first oration that I attended was during that year. Following the prize giving Dr Robert Marshall, a retired cardiologist came up to me and said he had won the same prize when he was a young man. He wished me well and said I had a bright future. As I approach my sixtieth birthday, I still like to feel that I have a bright future.

Two neurologists have previously presented the annual oration. The first was Dr Sydney Allison in 1941 while serving in the Royal Naval Volunteer Reserve[2]. His title was “Medicine and the Navy”. The second neurologist was Dr Harold Millar in 1975; his subject was “The Medical Library”[3]. As neither of them talked about the brain, the field is clear for me.

(Frans Hals, Art Archive)

Fig 1. Portrait of René Descartes by Frans Hals from the Louvre, Paris

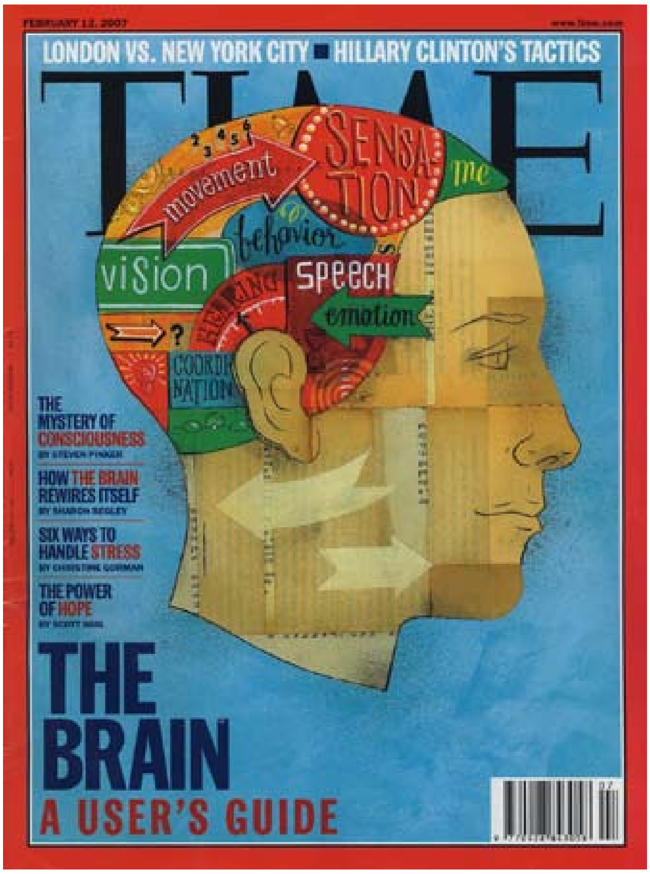

Fig 2. Front cover of Time Magazine Feb12th 2007

Looking at this very distinguished audience, I am filled with a sense of unreality. I am not sure if I am dreaming: if I am going to wake in a few moments with my lovely wife Fiona mopping my brow saying “don’t worry dear, it was only a nightmare”. This caused me to think, how do we know that what we are experiencing is reality rather than a dream? This is not an original thought. Three hundred years ago it occurred to René Decartes, the father of modern philosophy (fig 1). As we will see later in this talk, neuroscientists and philosophers are still struggling with the concepts of consciousness.

It is my impression that most people take their brains for granted. Having taught every Belfast medical graduate for the last 26 years, I am familiar with a sense of mental blankness in our students after the long summer break. Occasionally we

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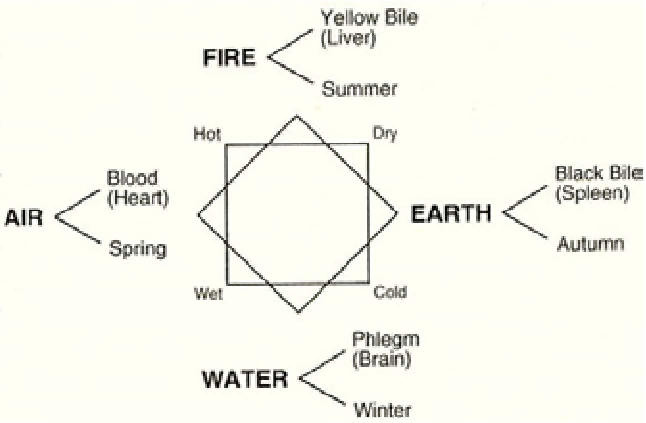

Fig 3. Schema of ancient Greeks' concepts of the balance of humours

see the brain referred to the in the news media, for example "Time Magazine" from February 2007 (fig 2), also from the same month the front page of the "Guardian" featured a story about modern brain imaging.

I would like you to ponder this quotation: "*Men ought to know that from the brain and from the brain only arise our pleasures and joys, laughter and jests, as well as our sorrows, pains, griefs and tears, through it in particular we see, hear and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant, it is the same thing that makes us mad or delirious and inspires us with dread or fear*".

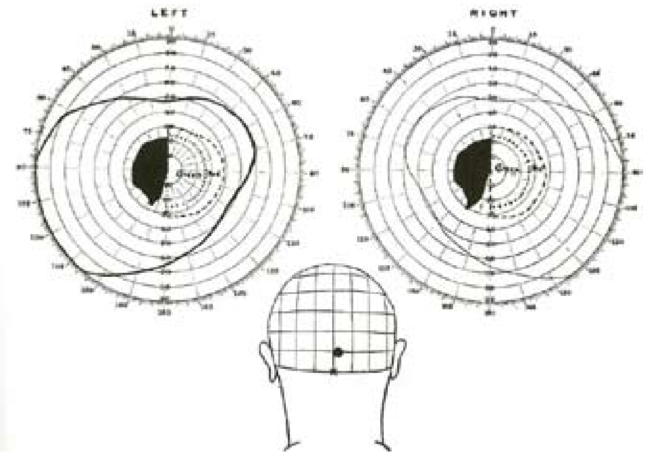

Fig 4. Illustration from a paper by Dr Gordon Holmes. In *Br J Ophthalmology* 1915

This was not written last year, but around 400 BC by Hippocrates[4]. His thoughts on the brain sound surprisingly modern but should be put in the context of how the ancient Greeks thought of human physiology. They thought there were four fluids in the body, and they felt that madness came from excess moisture in the brain. The four fluids were: blood, yellow bile, phlegm and black bile (fig 3). Blood, phlegm and yellow bile are familiar to us. Phlegm was thought to emanate from the brain via the pituitary gland and thence into the nasal passages. Black bile is the only fluid that does not exist but its translation into Latin "melancholia" still exists in modern language.

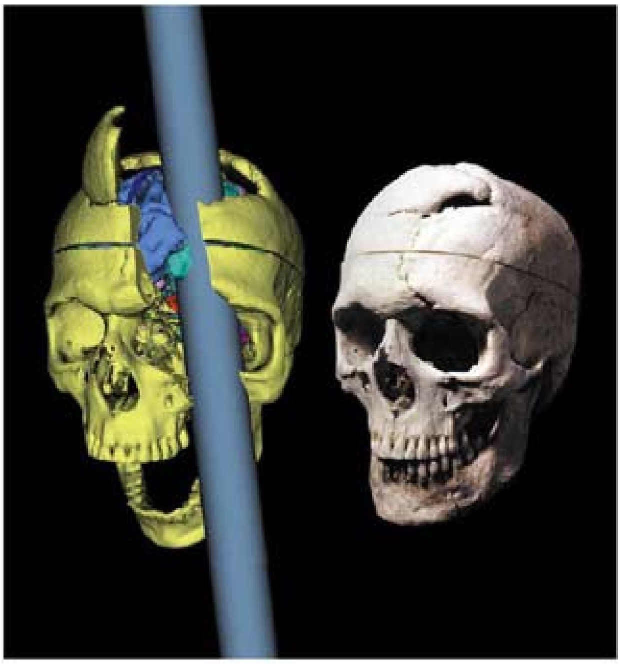

Fig 5. Reconstruction of the track of the tamping iron through the head of Phineas Gage. From Ratiu P, Talos IF *New England J Med* 2004;**351:**e21.

The ancient Greeks had taboos about human dissection. Around 160 AD the Greek, Galen dissected many animal species, but not humans. Treating surviving gladiators in Greece and Rome after their contests was the basis of his knowledge of human anatomy. René Descartes lived from 1596 to 1650; he was the most distinguished philosopher of his day and the father of modern scientific method[5]. Following the example of Andreas Vesalius (1514-1564), Professor of Anatomy at Padua, Descartes dissected the brain. He was puzzled that most of the brain existed in two mirrored halves, apart from certain mid-line structures like the pineal gland. From his musings he concluded that the pineal gland was the seat of the soul and the centre of consciousness. Descartes felt that as conscious individuals, we must feel pain. The saying "Cogito ergo sum" was his most memorable quotation. Thomas Willis (1621-1675) in Oxford took the study of the anatomy of the human brain to a higher level. His friend Christopher Wren drafted some of the illustrations of dissections of the brain.

When I started my preclinical studies of anatomy in 1966, 41 years ago, I was inspired by Professor Thomas (Thos) Harrison and I read the anatomy of the nervous system by Ranson and Clarke[6] in great detail. This book drew on the researches of Ramón y Cajal on the cellular anatomy of the brain. Brodmann discovered that the cytoarchitecture of the cortex varies from place to place, and as a result he inferred that the function of the cortex must vary from place to place. As a student of physiology, in 1968-9, I studied the papers of Hodgkin and Huxley based on the giant axon of squid caught off Plymouth. They worked out the basis of the action potential, and as a result won the Nobel Prize for medicine and physiology in 1963. When I entered clinical studies, I was enthused by the neurologist Dr Louis Hurwitz. He was an inspirational teacher, who died in 1971, during my final year. I have already paid tribute to him and my predecessors in Belfast neurology in the presidential address to the Ulster Medical Society[7]. Having been trained in London, Paris and New York, Louis Hurwitz followed the best traditions of British and French neurologists.

The pre-eminent British neurologist of the last century was Sir Gordon Holmes, a man born Castlebellingham, County Louth into a family of Yorkshire ancestry. Following Trinity College Dublin he went on to study in Frankfurt and London. During the First World War he served in the RAMC in France. He made his mark by studying the effects of brain damage in the victims of head injuries (fig 4) sustained during trench warfare[8]. The study of individuals who had survived brain injuries, strokes and tumours was how clinical neurology was first developed.

Fig 6. Department of Neuroradiology, RVH, circa 1974, showing Dr Harry Shepherd and Mr Tom Fannin looking at cerebral angiograms

The story of Phineas Gage (1823-1860) is a wonderful example of an early study of a damaged brain[9]. In 1848, when he was working on the construction of the railways in Vermont, North America a premature explosion caused a metal tamping iron 109cm long and 3cm wide to be projected through his head, landing more than thirty metres away (fig 5). Quite fortuitously he survived without losing consciousness. His lucidity was short lived and he entered coma for several weeks. Eventually he recovered from cerebral abcesses and meningitis, but his personality had changed. Prior to the accident he was conscientious and diligent. Following the injury he became foul-mouthed and erratic. Despite living for another 11 years, he was never his former self. We now know that the change in his pattern of behaviour is typical of frontal lobe damage - the first clear example to be described.

In 1974 I entered my clinical training as a registrar in neurology, my teachers were Jo Lyttle, Michael Swallow and Harold Millar, all gifted men who brought their very remarkable talents to the practice and teaching of clinical neurology. I worked in Quin House and Claremont Street Hospital. Professor Frank Pantridge when he heard that I was interested in neurology, encouraged me to think of cardiology instead. He said: "*Hawkins, when your heart stops you are dead. I know people walking around Belfast who have shown no sign of cerebral activity for years*". I was aware of the distinguished work of my predecessors Harold Millar and Sydney Allison in the field of multiple sclerosis. Dr Orla Gray, in our department has recently found that the risk of developing MS in women in N. Ireland is 1 in 130.

Since the techniques for imaging the brain and spinal cord were very rudimentary in 1974-5, the emphasis was on the clinical history and examination. We had isotope brain scans that to our eyes appear primitive. We had a good neuro-radiology department (fig 6). Cerebral angiograms were performed by direct stab into the common carotid artery. This allowed us to demonstrate the swelling caused by malignant brain tumours and arterial venous malformations. Occasionally we would perform lumbar air encephalograms. This procedure involved removing 30mls of CSF and injecting 30mls of air, somersaulting the patient on a special chair and taking X-rays of the brain (fig 7). Another technique was myelography where we injected oil-soluble dye, into the spinal fluid and took pictures of the spinal cord by negative contrast. Occasionally the dye was run up into the head and we took X-rays of the cerebral ventricles.

In 1975 the first CT scanner was installed in Belfast. We were astonished at the quality of the results that now to our modern eyes look very fuzzy. Modern CT scanners produce images that can show abnormalities the size of a grain of rice within the brain. I had a patient who we felt had a spinal tumour. She had to travel to England for MRI imaging prior to planned surgery. She worked as a primary school teacher in Carrickmannon, Co Down. Her headmistress, Mrs Montgomery was instrumental in setting up a charity to assist in the provision of the first MRI scanner in Northern Ireland. In 1993 the scanner was installed. The diagnosis of multiple sclerosis was made more accurate and reliable (fig 8). Some cynics said that clinical neurology would be dead following the introduction of these imaging techniques. MRI scans did not provide us with the diagnosis in every case. In 1995 a patient who had an entirely normal MRI scan of the brain reported at the time, was dead within six months with an irreversible neurological illness which was subsequently found to be variant CJD - the first case in Ireland.

Fig 7. Lumbar air encephalogram

During the last 30 years there have been very substantial advances in clinical neurosciences. Can there ever have been a more interesting era to practice clinical neurology? Our understanding of how the brain interprets visual images, smell, hearing, touch and taste has been revolutionised e.g. the Nobel Prize for Medicine and Physiology in 2004 was awarded to Axel and Buck for their studies on odorant receptors. Our

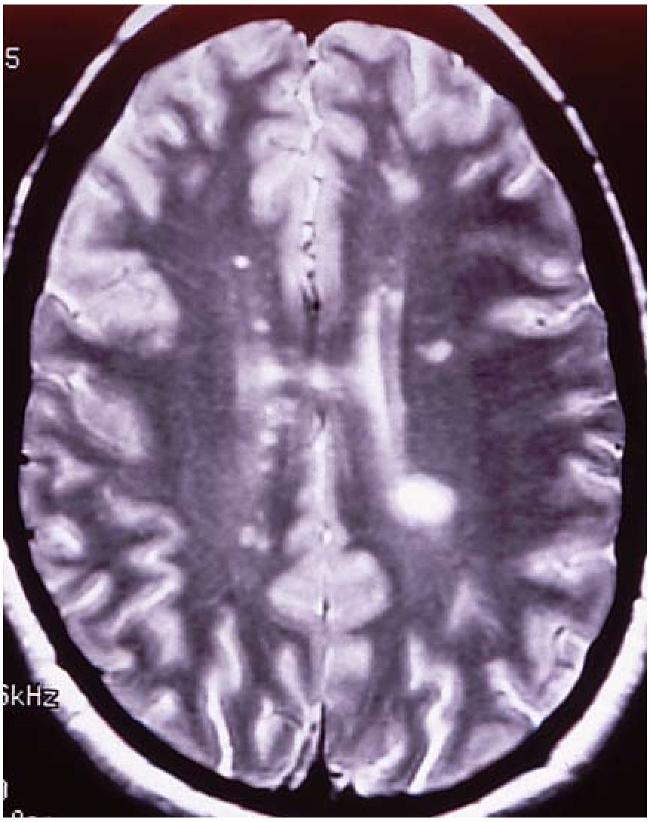

Fig 8. MRI in a case of multiple sclerosis

understanding of the organisation of posture and movement has been clarified. Our understanding of language has been revolutionised. We are starting to understand how memories are processed, stored and retrieved within the brain. For decades the prevailing dogma in neurosciences was that adult human brain had matured and was fixed in form and function. By the time children mature into adulthood it was felt that the brain is rigid and incapable of change. This view held that genes and development dictate that one cluster of neurones will process signals from the eye, another, the fingers of the left hand and they will do nothing else until the individual dies. We now know that the adult brain is capable of learning and making new connections and this is called neuro-plasticity. Also there have been amazing advances in cell biology. It is possible to grow neurones in cell culture and study their physiology in great detail. It is also possible now to transplant neuronal stem cells into the brains of animals and humans in order to ameliorate clinical conditions. Also, studies of neuropathology have been revolutionised by a range of techniques.

The amazing advances in clinical neurosciences have been based on our understanding of imaging of the brain, CT, MRI, and PET scans. Also, we have entered the age of genetic engineering. The structure of DNA was discovered by Watson and Crick, and published in Nature in April 1953[10]. In 1961, Brenner and Crick discovered the genetic code was made up of nucleotide triplets[11]. A rapid method of gene sequencing by Fred Sanger in Cambridge and Walter Gilbert in the United States was discovered in the late 1970's. The Human Genome Project produced results that were published in Nature and in Science in February 2001 (fig 9). We now know that the human genome consists of about 30,000 genes, fewer than was originally thought. 6000 of these are expressed exclusively in the brain.

The brain weighs about 1.4-1.5 kg. Seventy percent of its weight is water. The cerebral cortex is the main computing and storage facility within the brain. If the cerebral cortex were spread out it would be about the same surface area as a large table napkin although somewhat thicker. It contains about 100 billion nerve cells or neurons. When you include the additional supporting tissue the total cell count of the brain is 1 trillion cells. It has been estimated that there are one quadrillion (10^{16}) synaptic transmissions per second[12].

Fig 9. Front cover of Nature Feb 15th 2001

The lobes of the cerebral hemispheres are merely named after the bones that overly them. There is some functional significance to this, but it is rather limited. Modern imaging techniques have enabled us to study functional correlations better, showing that important connections cross the borders of the lobes. Damage around the Sylvian fissure is likely to result in language deficits. The first modern studies of language were performed in France and Germany. Paul Broca and Karl Wernicke found that faulty language was a consequence of damage to the left cerebral hemisphere. Broca lived in France between 1824 and 1880. He discovered that damage in the frontal lobe of the left cerebral hemisphere made it impossible for a man called Leborgne to say anything other than "Tan". Wernicke, from Germany later discovered that damage to the posterior part of the left cerebral hemisphere made it impossible for a person to understand speech, either speech that was spoken to him or his own spoken words.

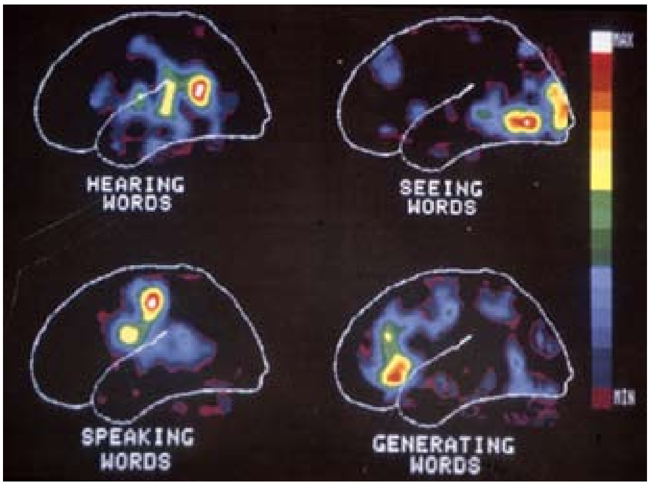

Fig 10. PET scans of cortical anatomy of processing of single words. From Petersen SE *et al. Nature* 1988;**331:**585

There are two steps in language production. First of all hearing is interpreted in the upper part of the temporal lobe, the visual cortex, at the back of the brain is in the occipital lobe. Interpretation of the written word starts there, then words are generated in the frontal lobe. Most of us communicate all the time by speech but we don't really think about how we do it.

In the Boston School in 1960's and 1970's Frank Benson and Norman Geshwind worked out that language understanding and production is modular, different parts of the brain having different functions. They worked this out through the study of damaged brains[13]. In order to study the brains of their patients at autopsy, their strategy was that the researcher had to live longer than his or her patients. This was difficult. A better approach was necessary.

Fig 11. Visual fields. After Frisby 1979

A major advance has been the PET scan. Positrons are positive electrons. They are produced by very unstable nuclei, with short half-lives. Oxygen[15] and Fluorine[18] are very unstable isotopes that degrade, causing positrons to be emitted. When a positron encounters an electron both particles are annihilated producing two gamma rays at 180 degrees to each other. A co-incidence processing unit registers simultaneous detection of these gamma rays and the images are produced in a computer. Differences between the original resting scans and during stimulation show the occipital cortex lighting up when the subject looks at an object.

John Mazziotta in UCLA in the 1980's produced images

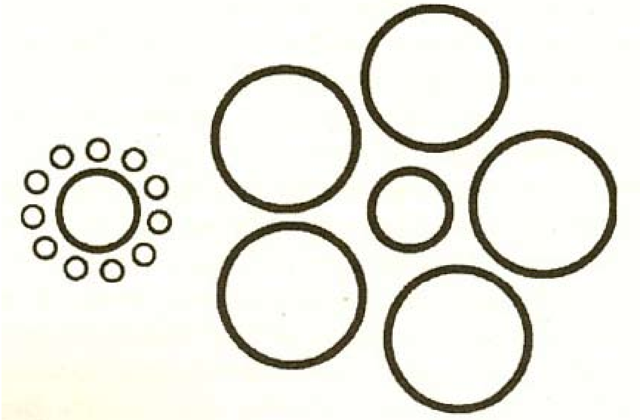

Fig 12. Circles

showing focal changes in metabolism in the occipital lobes where a patient has eyes closed, has eyes open and then is looking at a complex scene. He also produced images of a volunteer listening to music. This showed increased metabolic activity in the right perisylvian region. For some decades before these studies it had been felt that the interpretation of melody was situated in the right "non-dominant" hemisphere in right-handed people. This was the first time that it was demonstrated to be true in living intact individuals. He also produced a scan of someone with a low-grade astrocytoma, a primary brain tumour at the back of the brain. During a focal epileptic seizure there is focal increase in metabolism in the tumour.

Experiments in living volunteers in St Loius during the 1990's showed different parts of the brain lighting up. Hearing words, seeing words, speaking words and generating words (fig 10) showed modular function in discrete locations[14]. This demonstrated how the modular nature of language function, proposed by the Boston school through the study of people with damaged brains had been validated in living normal volunteers.

The linguist Noam Chomsky is interested in our innate ability to learn and produce language[15]. In Chomsky's view all languages share a universal structure or grammar and this universal grammar seems to be pre-programmed into our brains rather than something that is learned through teaching and experience. There are approximately 5000 known human languages. It appears that they all obey certain common rules that are innate. The rapid development of language in children is a wonder to all parents. Typically at about 10 – 12 months babies produce their first recognisable words. New words come slowly at first but then typically at about 15 – 20 months the rate begins to accelerate. Between the ages of 2 and 17 years a typical person learns about 60,000 words, an average of 10 new words per day[16].

Following on from this came functional imaging using MRI. The principle is that where there is increased metabolism in different parts of the brain there is increased blood flow. Modern MRI scanners can measure this. Oxyhaemoglobin is present in increased amounts and this has different MRI decay characteristics. It is possible to show how local changes in brain metabolic activity varies in response to differing stimuli.

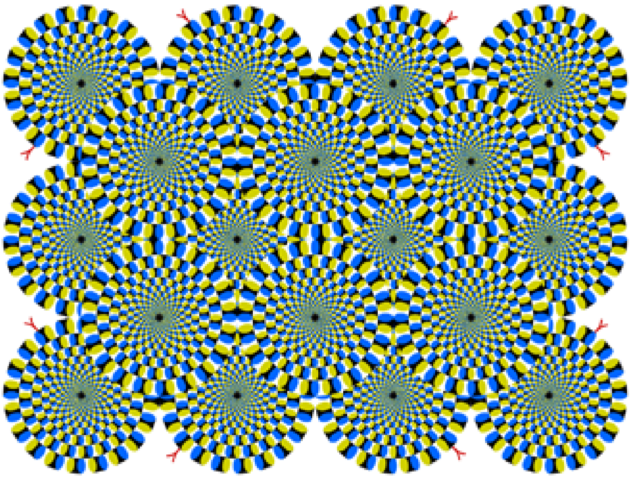

Fig 13. Akiyoshi illusion

Our understanding of the visual system has been transformed over the last century, but especially in the last thirty years. The retinae at the backs of our eyes receive images of our environment in two dimensions, up-side down (fig 11). The brain enables us to perceive our surroundings the right way up and with a perspective of depth and colour. We are conditioned to believe what we think we see. Our perceptions are conditioned by what we expect to see. The mechanisms of visual perception are complex. There are cells in the cortex that respond to stimuli in different orientations and there are other cells the respond to motion only in particular directions. In addition there are cells that respond to faces. In the 1960's researchers tracked how we recognise faces. The eyes dart momentarily from the eyes to the mouth, which are the major points of recognition in peoples' faces.

The distinguished neuroscientist Semir Zeki has spent a lifetime investigating the perception and processing of visual imagery. He reckons that 1/3 of the cerebral cortex is taken up with interpreting and processing visual imagery. He discovered that the primary visual cortex which is at the back of the brain first identified before the days of Gordon Holmes, is a primary staging point for cortical processing. Colour is processed in a separate area called V4 and motion is processed in a site on the lateral surface of the occipital lobe called V5[17]. It is of particular interest that colour perception is perceived before motion perception by a matter of 80 milliseconds. There are perhaps 30 different modules of visual perception. The question of what binds them all together into a consciously recognised whole is imperfectly understood. Colour, faces, language and interpretation of the human body are processed in different parts of the brain[18].

An illusion of two circles surrounded by rings of circles of different sizes confuses the brain to imagine that the inner circles are different sizes, when in fact they are the same size (fig 12). Hermann's grid - shows bouncing grey dots at the intersections of lines. The bouncing dots are generated in our brains. Our perception of colour is changed and altered by the context in which colour is viewed. Also, you can get illusions of movement. This is because when the eyes look at complex images they dart from side to side and this can stimulate the motion centre giving an illusion of movement (fig 13).

The next illusion shows a domino effect. The images are two-dimensional, but because of the way our brains are wired up the dominos appear to have concave and convex additions to the surface. When this is turned upside down the reverse appears (fig 14). Our brains are conditioned to perceive that light comes from on high and it appears as if the additions on the dominos are convex and concave. The famous Thatcher illusion is worthy of mention (fig 15). Margaret Thatcher looks more normal upside down than she does the correct way up. This was first described by Thompson[19]. Illusions arise because the brain interprets the world in relation to stores of memories of perceptions.

In the Guardian newspaper that I quoted earlier, reference is made to a publication by Haynes in Nature Neurosciences showing different parts of the brain lighting up when an individual looks at a place compared to a face[20]. The Guardian was concerned with the effects on civil liberties if such techniques are used as new lie detectors. Using modern MRI imaging it is possible to investigate emotional changes within the brain investigating romantic versus maternal love[21]. The changes fit in with the distribution of neurotransmitters. Variations in brain metabolism generated by our perception of beauty can be detected.

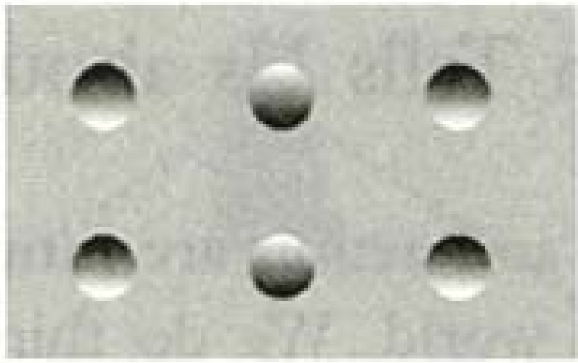

Fig 14. Dominos – from Frith C. Making up the mind. Blackwell, Oxford, 2007. Invert the page and the concave become convex and vice versa.

Earlier I made reference to neuroplasticity. PET scans of the hippocampus of London taxi drivers have shown that the longer people had worked driving taxis in London the greater the metabolism in the hippocampus, indicating that the metabolic activity of the hippocampus and indeed its size was increased by the learning experience of navigating London streets[22]. Implanted dopaminergic neurons in the basal ganglia of patients with Parkinson's disease survive multiply and make new connections[23]. Professor VS Ramachandran has studied the perception of phantom limbs in people who had amputations. Sensation interpreted by the brain as coming from the phantom limb arise when the face or the shoulder are touched with a cotton bud. The hand area of the sensory cortex makes new connections[24].

Women who have had treatment for leukaemia with bone marrow transfusions from their brothers have been found to have male cells incorporating the male Y chromosome in adult neurons, indicating that stem cells coming from males transplanted into female patients are capable of becoming functional mature neurons and glial cells. 1% neurones and 1-2% of glial cells came from the brother's bone marrow stem cells[25]. It is not recorded whether after the transplants, the ladies expressed a greater interest in football.

Fig 15. Margaret Thatcher – head inverted, but mouth and eyes right way up. Invert the page, and she looks very odd!

In my preparation for this talk I read the life history of Eric Kandel who won the Nobel Prize for medicine and physiology in 2000. He became interested in how the brain, behaviour and memory are controlled. Kandel feels that in the last century much was done to work out how the brain works and during the 21st century much work will done on the mechanisms of the mind[26].

Going back to our impressions of the mind, René Descartes said, "Cogito ergo sum", "I think therefore I am". There are more sceptics now and some might say "I think, therefore I am, I think" and our students who use text messages say "I text, th4 I iz".

The debate on consciousness is essentially a division between dualism and materialism. Dualists feel there is a split between mind and brain or body and soul. This thread has been present in philosophy for hundreds of years. Famous dualists were Popper and Eccles, who were friends and collaborators. Karl Popper was a philosopher, and John Eccles was a neurophysiologist who shared in the 1963 Nobel Prize. Materialism and materialists feel that neural activity accounts for everything and when neural activity stops – what?

Much has been written about consciousness. Wittgenstein felt that there was an unbridgeable gulf between the brain and the mind. Bernard Baars, an American cognitive neuroscientist said that "performing research on consciousness and the mind was the last taboo" and neuroscientist Antonio Damasio, an American neurologist said that consciousness is "a story that we tell ourselves". Daniel Dennett, said that "the brain is part of a clever robot" and others such as the columnist, Tom Wolfe, who has promoted an entirely materialistic point of view stated that "the soul has died"[27].

David Chalmers, the Australian philosopher says that there are two steps in trying to understand consciousness - the "easy problem" and the "hard problem". The easy problem is to distinguish conscious to unconscious brain processing, and the hard problem is – how subjective experiences arise from neuronal activity. Does it feel the same for me as for you? Am I dreaming? – and - What is reality?[28]

Fig 16. Portrait of Sir Hans Sloane, Ulster Medical Society Rooms, with permission from the Ulster Medical Society.

This has been my discourse over how the brain and mind works and I want to try and draw my talk to some conclusion for medical students. Thomas Sydenham taught Sir Hans Sloane (Fig 16) who was born in Killyleagh, Co Down and Sydenham said to Sloane when he wanted to study botany – "*You must concentrate on the bed side, it is there alone that you will learn disease*"[29]. At the end of the day clinical medicine involves an interaction between an individual doctor and an individual patient. Listening to a patient's history is absolutely fundamental. That is the story of their life and the account of their symptoms. I tell students that we do not treat diseases; we treat people with diseases. You cannot be a physician unless you enjoy meeting people. While diagnostic techniques have become more humane than injecting air around the brain, and treatments are improving all the time, you must still put your patients first. It is also important to feel that there is a purpose to life.

Finally "More than a Sum of its Parts" the hospital. There are around 350 consultants, 550 junior doctors, 2000 nurses and 2000 administrative and clerical staff. It is possible for sick patients to obtain expert advice from colleagues at any hour of the day or night, whether they are officially on call or not. The reputation of the hospital depends on the excellence of medical and nursing staff. We also depend heavily on the commitment of our unsung heroes, the secretarial and administrative staff. Without them, the hospital could not function. The Royal Victoria Hospital has been in existence since 1797, some 210 years. It has survived many changes with its spirit undiminished. I am confident it will outlast the current fashion in management conglomeration.

Many orations start with a quote from William Osler - I finish with one. In a busy professional life, it is essential to have outside interests. On hobbies he said *"no man is really happy or safe without one, and it makes little difference what the outside interest may be – botany, beetles or butterflies, roses, tulips or irises, fishing, mountaineering or antiquities – anything will do"*[30]. I hope I have convinced you that the brain is greater than the sum of its parts.

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