In 1944, during the second world war, Erwin Schrodinger working in Dublin published a book which had an enormous influence on the history of biological science in the second half of the twentieth century (figure 1). Schrodinger, together with Heisenberg, had created in 1925 the theory of quantum mechanics which was the most revolutionary concept in the history of the physical sciences. Towards the end of the thirties Schrodinger turned his mind to the question of what are our physical origins. He therefore started to consider the structure of genes and the extent to which our development occurs as a consequence of the unfolding of the information in genes. It was not known what the genetic material was made of at the time that Schrodinger wrote his book "What is Life". The guess at that stage was that it was made of protein and it was only shortly after the appearance of Schrodinger's book that it was discovered by an elderly gentleman working in the Rockefeller Institute in New York, Oswald Avery, that the genetic material was made of deoxyribonucleic acid (DNA). What Schrodinger's little book did was to bridge the revolution in physics that occurred in the first half of the century to the new revolution that was to dominate the second part of the century, namely molecular biology. Schrodinger conjectured in his book that there must be a code in the genes which is read out by the cell as a set of instructions that guide its differentiation so as to give rise to the structure of the human embryo and therefore to our further development. In this way Schrodinger developed the concept of a genetic code, one of the most fruitful ideas in biology. Furthermore he speculated that the structure of the genetic code should be susceptible to physical analysis by means of such new techniques as crystallography. Crystallography had been developed as a science in the United Kingdom by the Braggs, father and son; they were from Adelaide and had won the Noble Prize together in 1915.

After the second World War some of the brightest physicists decided not to go into Theoretical Physics but instead to try their hand at Biology. The end of the heroic period in Physics, which had been dominated by quantum mechanics, occurred about 1948 when Richard Feynman working at Cornell developed the theory which is referred to as Quantum Electrodynamics; this provides a description of how light interacts with matter. It is somewhat fortuitous that only a year after Richard Feynman had developed his theory, bringing quantum mechanics to its highest point of development, that a physicist named Frances Crick began working in the laboratory of the Braggs in Cambridge in 1949 (figure 2). Schrodinger's book had a major influence in Crick making this move. Together with a young and somewhat eccentric American called James Watson he applied the concepts of crystallography to the task of unravelling the detailed structure of DNA itself in 1951. In this way he furthered the research programme in the laboratory of the Braggs laid down by Schrodinger some five years earlier. To some extent the famous paper by Watson and Crick, published in Nature in 1953, completed the research aims of Schrodinger's book by indicating that the structure of the DNA molecule held within it the clues to its own replication. The last forty years of science have been dominated by molecular biology which has as part of its foundations these observations by Watson and Crick made in the Cavendish Laboratory at Cambridge run by Sir Lawrence Bragg from Adelaide.

In 1988 Crick, like Schrodinger before
him, published a book that is likely to have far reaching effects on the future of research as young scientists see it. Crick suggests in "What Mad Pursuit" that the great challenge for science in the next century is not to be found in quantum mechanics, nor in molecular biology, but in the understanding of what it is that develops in the brain of human embryos that gives rise to consciousness (figure 3).

What is this phenomenon of consciousness? In order to tackle consciousness we have to look at the human brain, at its structure and function. There is general agreement that the best path to follow in our quest to understand consciousness is offered by the problem of visual perception. This is because man like other primates receives most of his sensory information via the visual system and our consciousness is closely linked with visual perception. This is because man like other primates receives most of his sensory information via the visual system and our consciousness is closely linked with visual perception. Figure 4 delineates the principal pathways in the higher levels of the visual pathway, those concerned with the identity of objects and their movement in space. The identity of objects and their colour is taken up by a set of retinal ganglion cells and conveyed via the structure called the thalamus, which acts as an interface between the external world and the neocortex, to the visual cortex at the back of the head. From there it is projected down into the temporal lobe and it is here, as is explained in more detail below, that the identification of something as sophisticated as your mother's face is actually carried out. There are also other main pathways of the brain concerned with determining where an object is located in visual space. This is to a large extent dependent on information concerning the motion of objects in space. Such information is conveyed from the retina through the thalamus up to the visual cortex within the occipital lobe and into the parietal cortex. These two pathways going either to the temporal lobe or to the parietal cortex give us the holistic experience of seeing an object which moves.

To what level of sophistication can the temporal lobe identify an object? In order to determine that Gross and others have put electrodes into the temporal lobe of primates other than man and determined whether there are neurones which fire maximally when the primate is viewing a specific object. Figure 5 illustrates the main results of this kind of experiment. It turns out that there are in the monkey temporal lobes neurones which respond specifically to the presentation of human faces; indeed these neurones discharge specifically when the faces are presented in profile or face on. The firing rate of neurones is given in the upper part of each panel in the figure as the primate looks at the images given in the lower part of each panel. You can see in this set of images that when the primate is looking directly at the image of another primate face on we get maximal firing but when the image of the head gradually turns around so that it only appears in profile then the firing occurs at a much lower rate. Now you cannot fool this neurones into firing at a high rate by presentation of an image consisting of bits and pieces of a head. If the picture of a brush of the kind used to clean the toilet is presented then the rate of firing of the neurone is much less than that when the image of another primate face on is presented (figure 5). Also if we present an image consisting of the juxtaposition of different elements of the face in a bizarre geometry again the firing rate is not nearly as high as it is when we put those elements together to make up a proper primate face (figure 5). Furthermore, if it is shown us if the particular neurones in your visual world, which is specific in the sense that they will fire vigorously only when a particular kind of object, in this case a particular face, is presented.

The problem though that we now face is that we might have in temporal lobe neurones for identifying the experience of whether this face is moving across our visual field is not in the temporal lobe but in parietal cortex. As I indicated in figure 4 the problem now is how do we have an holistic experience in our consciousness when the face is moving past us. We have obtained very recently some insight concerning this problem from the work primarily of Wolf Singer working at a Max Planck Institute for Brain Research in Frankfurt. Singer and his colleagues have shown that neurones firing in one part of the brain, concerned for example with the movement of an object such as in parietal cortex, and neurones firing in a different part of the brain, such as in temporal cortex concerned with the fact that the thing that is moving is a face, are both firing at a rate modulated at a frequency of about 40 to 50Hz. Furthermore they fire in phase together synchronously (figure 6). There is then a binding together of the firing pattern of those neurones which are activated by the same visual object even though the neurones are
located in different parts of the cortex. This discovery is causing a lot of excitement in neurophysiology because it is only those neurones which are firing in phase with this 40 to 50Hz frequency that are giving us the experience of attending to a different part of our visual field. The rest of the visual scene projects from our retina onto the visual cortex at the back of our skulls. The neurones in our brains suberving those parts of the image on our cortexes that is currently being attended to are not firing with a modulation of 40 to 50Hz and air not firing in phase.

To some extent it can be claimed that this is all very interesting but that the problem has merely been pushed back one step. You consciousness of phenomena around you might be associated with sets of particular neurones in your brain firing in phase at 40 to 50Hz but how is it that neurones firing off in this pattern give rise to you attending or experiencing a particular facet of your visual world? Only a particular facet of your visual world is entering consciousness. What is there particular about the neurones firing at 40 to 50Hz and in phase which allows you to experience at the conscious level those events which are coded for by these particular neurones? A senior colleague of mine recently commented that this is as far as neurophysiology is going to take us. All that science will illuminate in relationship to your consciousness of the world around you may be that sets of neurones suberving certain specific kinds of functions fire in a certain way. The question of what it is that links consciousness to these sets of neurones is not one which science can answer. If there is any interference with normal brain function at all, for example through disease or injury to the inferior temporal lobe, or through inappropriate development, then we are not capable of consciousness in those areas of experience normally suberved by the injured neurones.

There is another exiting component to the claim that neuroscience is going to dominate research in the 21st Century. It is that a deeper knowledge of the nervous system will lead to the alleviation of neurological diseases whether this occurs through developmental malfunction, through injury, or through for example the invasion of our brains by a particular virus as probably occurs in multiple sclerosis. The inferior temporal lobe which we are emphasising in this essay is involved in the identification of objects. A vascular stroke results in the destruction of certain parts of our brains. Hypertension leads to a breakdown of the vasculature most commonly in certain areas of our brain. One area in which hypertension most commonly leads to stroke is in the temporal lobe where we have seen, information is gathered about the identification of objects and our consciousness of them. Figure 7 shows a self portrait of a painter that suffered a stroke. The stroke occurred in the parietal cortex concerned with the location of an object in space. However the parietal cortex is not only concerned with the location of movement it also subserves the process of attention. There is a mechanism in the parietal cortex which determines which sets of neurones will fire off in phase at 40 to 50Hz throughout the rest of the cortex. The stroke had the effect of blocking the attentional mechanisms in the inferior temporal cortex on one side of his brain so that the painter was not able to recognize one side of his face when he looked in the mirror. This did not occur because there had been a direct injury to the temporal lobe. Rather it occurred because the attentional mechanism in the parietal cortex on one side of his brain could not determine that the temporal lobe on that side should contain neurones that fired in phase at 40 to 50Hz. As a consequence when he was asked to paint a portrait of himself the painter ignored that side of his body which was no longer attended to because of the stroke. He then only painted one side of his body (figure 7). But over a period of about 12 months successive self portraits gradually reconstituted the entire image until finally, after a year, he was able to attend to the entire aspect of his face (figure 7), although recovery is not complete even then.

I emphasise the fact that the reason our painter was unable to see, as it were, one side of his face and body when he did a self portrait was only weeks after the stroke was not due to any injury to the visual pathway. What had been injured was the mechanism in parietal cortex which determine the setting up of 40 to 50Hz in phase firing of neurones which then allows consciousness to be expressed. An easy experiment could be carried out to show that he could see the other side of his body. All that had to be done was to block off that side of the painter's visual field which allowed him to see the side of his body which he could normally paint. When that occurs he will be painting the side of his body and face that he normally doesn't attend to at all.

In other words it is the attentional mechanism that has been injured. In fact when some experience a lesion of this kind they don't want to know about the side of their body to which they are not attending. When you carry out this experiment with some people who have had a stroke affecting the parietal cortex they...
get emotionally upset when they are forced to attend to that part of their body that they don't normally recognize as being there. In fact they regard that part of their body as foreign. It is as if they had a Siamese twin attached to them which they did not want to know about.

Strokes which affect the temporal cortex subserving the actual mechanisms by which you recognize yourself and others is usually accompanied by different kinds of psychological disturbances. Injuries to temporal cortex give rise to epileptic seizures (figure 8). This is because temporal cortex is very closely associated with the hippocampus which is the area of your brain concerned with laying down memory. For example injury to temporal cortex may lead to hallucinations that can involve you seeing people or objects that aren't present in the room (figure 8). This is due to epileptic discharges in the neurones of the temporal cortex which, for example, are normally activated by the image of your mother's face but start to fire despite the fact that your mother is not passing through the room at all. Hallucinations are associated with injuries to temporal cortex and of course hallucinations are also associated with schizophrenia (figure 8). In this case subjective phenomena apparently occur in the room that are more real to a person than sets of phenomena which are really occurring in the room. Other forms of temporal lobe epileptic activity occurring as a consequence of stroke in the temporal lobe area are seizures which give rise to the sudden enlargement of the face of someone that you are looking at (figure 8). You may be looking at your mother in the room and then suddenly her face will start to increase in size, become distorted and fill the entire room (figure 8). So there are not just perceptions of events occurring in the room which are not occurring at all but real events in the room may trigger hallucinogenic kinds of phenomena in the way I have just indicated, that is they will distort phenomena in the room as well.

To what extent will we be able in the 21st Century to bring some kind of alleviation of the symptoms resulting from stroke and the diseases of different kinds which affect the inferior temporal lobes? This really requires us to focus on a number of different technologies and approaches to understanding the diseases of the brain which have been initiated in the last few years. These are concerned with being able to introduce neuronal tissue into the brain that can replace neuronal tissue which has been diseased or destroyed. When this is achieved it is then necessary to get these new neurones that have been introduced into the brain to form functional connections with the rest of the brain. These must be of an appropriate kind to reconstitute the normal circuitry of the brain. In addition there are now known to be growth factors, referred to as neurotrophic growth factors, which are required in normal health. These provide substrates for the neurones in your brain and may be introduced exogenously into the brain from outside. They can allow for the survival of neurones which would otherwise degenerate and they can also allow for neurones which have been injured or neurones which have been introduced into the brain to form appropriate synaptic connections.

Rita Levi-Montalcini was able to show something extraordinary in a series of experiments, some of them conducted during hiding from the Nazis in Italy during the last world war. She was able to obtain growth factors that allowed neurones which would otherwise degenerate to survive. Levi-Montalcini won the Nobel prize a few years ago for her discoveries of neurotrophic factors. This work was begun as she hid from the Nazis in a house in Turin. Montalcini had microtomed an attic room which was used for cutting thin sections through the fixed embryos of birds. This, together with a microscope, enabled her to make fundamental discoveries concerning the development of neurones belonging to that part of your nervous system concerned with the control of your internal organs, such as your heart. Montalcini showed that in this part of your nervous system, called the autonomic nervous system, neurones die normally during development so that you have more neurones very early in your life than when you are an adult. She went on to show that if neurones were removed from birth if they were provided with growth factors which can be supplied by the targets with which these neurones normally make junctional connections. Ten years ago my colleague Bogdan Dreher and I set out to see if what Levi-Montalcini had discovered for the peripheral nervous system, namely that autonomic neurones could be induced to survive if provided with the material from their normal targets such as cardiac muscle or smooth muscle, might also apply for neurones in the central nervous system. We first showed that retinal ganglion cell neurones that connect the retina to the rest of the brain, and are shown in figure 9, normally die during development. Furthermore these retinal ganglion cells could be induced to survive when provided with a nutrient neurotrophic molecule from their targets in the brain. Those areas of the brain which are called the superior colliculus and the lateral geniculate nucleus. The neurones survived and sprouted nerve processes profusely in a
tissue culture plate if provided with the neurotrophic factor, just as Montalcini had described for embryonic neurones (figure 10). The difference was that in this case the retinal neurones were supplied with a factor from the brain and not from muscle. This was probably the first indication that neurotrophic growth factors exist in the brain not just in the peripheral nervous system and these growth factors can allow for the survival and profuse axon sprouting of a central neurone such as a retinal ganglion neurone.

The question then arises as to whether neurones lying deeper in the brain such as those belonging to the temporal lobe and to the hippocampus also have growth factors which will allow for their survival. The neurotrophic factor which keeps retinal ganglion cells alive is not the growth factor that Levi-Montalcini discovered in smooth and cardiac muscle that keeps autonomic neurones alive. The question then is to what extent can we reconstitute an injured temporal lobe or hippocampus by adding in a neurotrophic factor. The hippocampus, a relatively old and primitive type of cortex, abuts onto the temporal lobe (see figure 11). Despite its relative simplicity, the hippocampus is crucially involved in the formation of memories. If a transverse section is cut through this region of the brain many different classes of neurones can be identified (see figures 12 and 13). Some of these are the first neurones to degenerate anywhere in your brain if you have Alzheimer's Disease, particularly those neurones which project into the hippocampus from the part of brain called the septum. Surprisingly, these septal neurones are kept alive by Levi-Montalcini's growth factor, first found to keep autonomic neurones alive in the peripheral nervous system. So if a neurotrophic factor is discovered that saves a certain class of neurones in the periphery it may well work on a class of neurones in the brain.

As already mentioned, rather than introducing growth factors into the brain in the hope of saving a certain class of neurones that are degenerating because of a neurological disease, it is possible to introduce embryonic neurones of the same class that have been destroyed by the disease (figure 14). These can be obtained from a set of neurones that have been genetically manipulated to be of a similar kind to those that have degenerated. If you introduce these neurones into the brain (see figure 14), they reconstitute the normal circuitry, making the correct functional connections. In this way they restore the normal function, or at least almost the normal function, of that part of the brain which had degenerated.

There are now standard techniques for introducing neurones into the brains of animals. Neurones are taken from an early embryonic rat brain, for example from that part of the brain that degenerates in Alzheimer's Disease. Further purification of these then occurs using various cell sorting techniques. Finally just the specific class of neurones required are placed in a tube from where they are sucked up into an pipette (see figure 14). This pipette is then used to inject the neurones into just that part of the brain which has degenerated or been injured (figure 14).

How do we test out if we have reconstituted normal function after say a transplant into the hippocampus of a set of neurones to replace those that have degenerated? Figure 15 shows one procedure that is used to determine this. It is called the alternating T-maze test. A rat is put at the end of one arm of the T-maze and is allowed to run to the other end where a choice is made of either turning left or right. In the first trial food is placed on the right arm and the rat is forced to turn right because a trapdoor prevents it from turning left. On the second trial there is no trapdoor to force the rat to turn a particular way so tha it may now turn either left or right. However a nasty trick is carried out before this second trial. Before the rat is allowed to run the second trial food is placed on the left arm of the maze, opposite its original position. After this trial the rat is taken out of the maze and allowed to rest for a while before another alternating trial is attempted. Altogether this is repeated about six times a day. It doesn't take very long before the rat appears to figure out what is going on. It turns right on the first trial and gets the food; on the second trial, when you put the food on the opposite arm, the rat immediately turns left and doesn't make the mistake of turning right. The graph in figure 15 shows the rate at which the rat learns to make the correct choice on the second trial, namely to turn left. In a sham trial the neocortex is exposed without any experimentation, and then closed; over a period of about one and a half weeks the rat learns on 100% of occasions to always turn left to get the food on the second trial. If however there has been an injury to the septum, then the rat turns left on the second occasion at random frequency (namely on 50% of the occasions). It hasn't learnt at all: it cannot lay down the memory that it should turn left always on the second trial. But if we do a transplant of healthy septal neurones from an embryonic rat into the hippocampus of this injured adult rat or of a rat whose septal neurones have degenerated because it has a
form of senile dementia, then it only takes a matter of about two months before we find that the rats can learn at the 90% level to turn left (figure 15). The rats that received the transplant have learnt to nearly always turn left on the alternate T-maze performance because normal hippocampal functioning has been reconstituted by this septal transplant.

You might well ask how is it that the rat can tell where it is in the T-maze because the maze is symmetrical; how can the rat tell its left from its right despite the fact that it has no visual clues to orientate itself. Well the trick here is that the T-maze is set in a room which has lots of interesting objects in it and these allow the rat to work out exactly where it is. These interesting objects may include curtains, clocks, and pictures of female rats as shown in figure 16. This allows the rat to determine, when it is sitting at the start position in the T-maze, the geometry of the situation around it. The hippocampus calculates the spatial layout of the room from this information allowing the rat to determine what is its left and its right. These spatial clues are very necessary for it to be always able to distinguish left from right in the alternating T-maze performance.

In the above experiment an attempt was made to mimic the effects of senile dementia or stroke that lead to degeneration of the septal neurones innervating the hippocampus by introducing a lesion into the hippocampus. However it is now possible to distinguish aged rats that suffer from a form of senile dementia from those that do not suffer from this complaint involves placing rats in a water tank of the kind shown in figure 16. Rats don’t like being forced to swim around in a tank any more than we do so a little stand is placed about an inch under the water, which is opaque so that the rat cannot see the stand; as the rat swims around its feet sometimes bump into this little stand and not being stupid it sits on the stand, rests and looks around the room to trace the movements of the rat in the water before it finds the stand using a TV camera elevated above the trough which is shown in figure 16. In this way the actual locus of movement of the rat in the water before it sits on the stand can be from lower left to upper left. The rat knows its position in the water because it can trace the interesting objects in the room, such as the clock etc, so that it can form a spatial map of the room in its hippocampus as was described above in relation to the T-maze. When the rat forms this map it has the coordinates of the stand with respect to the spatial layout of the objects in the room.

If we take a young rat about 6 months old and put it into the water for a few minutes, then the locus of its movements on this first trial on the first day is given in the first row and column of figure 17: in this particular trial the rat’s legs didn’t hit the stand beneath the water; the rat just swam around for a couple of minutes. But a few trials later, namely the fifth trial on this first day (see figure 17), the rat has learnt in the intermediate trials the position of the stand and so it swims immediately to it and sits down. Presumably this rat has formed a spatial memory of the position of the stand as a consequence of the normal functioning of its septo-hippocampal circuits. Of course by the fourth trial on the fifth day the rat has no trouble at all, no matter where it enters the water, it immediately locates where the stand and is (see figure 17). On the fifth trial of the fifth day a nasty trick is carried out: the stand is removed and the rat is entering the water tank at a random position swims around frantically trying to find the stand; the locus of its movements are then centred on the position where the stand was, as shown in figure 17. We can use this technique to pick out those rats which are suffering senile dementia from those that are not. In the second row of figure 16 the results are shown for a three and a half year old rat, about the equivalent of a human at eighty: it is apparent that even by the fifth trial on the fourth day after the rat had bumped into the stand many times during the preceding days, it could still not locate the stand using spatial clues. This was an aged impaired rat, that is it had senile dementia. All old rats do not get senile dementia any more than all old humans do: in the fourth row of figure 17 the results are shown for another three and a half year old rat: by the fifth trial on the first day it had evidently formed a good spatial map of the whereabouts of the stand. On succeeding days it did as well as the young rat whose performance is shown in the first row.

Using this water tank technique, invented by Morris, we are able to sort out rats suffering from senile dementia from those that are not suffering from senile dementia. This is we can separate out those whose septo-hippocampal circuits are functioning from those in which these circuits are in bad shape. If we take an aged rat suffering from senile dementia now and operate on it in the way I previously described, that is introducing...
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Further Reading


Figure 1.

Erwin Schrodinger (1887-1961), the co-founder with Werner Heisenberg of quantum mechanics, and the author of the small book "What is life" in 1944. Schrodinger was in his thirties when he formulated one of the most revolutionary theories of matter in the history of physics. Many, such as the English mathematician Roger Penrose, believe that quantum mechanics holds the answer to the question of what is consciousness, an issue which Schrodinger wrote on extensively himself, especially in his small book "Mind and Matter". The theory of quantum mechanics was brought to a high degree of development by the American physicist Richard Feynman in 1952, with his ideas on how light and matter interact. In his late fifties Schrodinger, inspired by the youthful theoretical physicist who had come over to biology, Max Delbruck, penned "What is life". This speculated on the basis of heredity and included the revolutionary ideas that the chromosome contained a "genetic code" laid out along its length which constitutes an imprint of the information needed to be read for the formation and functioning of the species. Schrodinger also suggested that the code could be understood at the atomic level providing the chromosomal material can be crystallized as an aperiodic crystal, capable of being subjected to the techniques of X-ray crystallography. These prescient suggestions were to bring some brilliant young physicists into biology, such as Crick and Randall.
Francis Crick (born in 1916) was a young physicist who came into biology shortly after the publication of Schrödinger's book "What is life" in 1944. He became the leading intellectual force in interpreting the crystallographic data on the chromosomal material, Deoxyribonucleic acid (DNA), that lead to its known atomic structure in 1952; secondly he designed experiments that solved the genetic code by which DNA gives rise to specific proteins. These ideas helped lay the foundations of Molecular Biology, the dominant area of science in the second half of the twentieth century. In this way Crick brought to fruition the research plan of Schrödinger. Crick now works in Brain Research and in his recent autobiography (1988) "What Mad Pursuit" speculates on how we are going to understand the origins of consciousness. Crick suggests that the clues to understanding this phenomena, so dear to us all, are to be found in the attentional mechanisms of the brain by which we concentrate our sensory and motor systems on some element of our environment, to the exclusion of all else in the environment. He also believes that as the memory of some thing attended to lasts for only about 60 seconds or so, then the molecular and atomic mechanisms involved should have only this time scale of change.
Figure 3. A human embryo at 5 weeks after conception (11mm long). The hands and legs are already formed but there is only a hint of the digits. The body is clearly connected to an umbilical cord. The brain is developing above the eyes (to their left). The spinal cord is also clearly delineated. The adult brain has some 100,000,000,000 neurons, many of which have about 10,000 connections (or synapses) on them from other neurons. This results in some 100 million million synapses in the brain. As these synapses are capable of modifying their properties according to experience there is a truly wondrous range of possibilities in the wiring of the brain.

Fig2

Figure 2. Francis Crick (born in 1916) was a young physicist who came into biology shortly after the publication of Schrödinger's book "What is life" in 1944. He became the leading intellectual force in interpreting the crystallographic data on the chromosomal material, Deoxyribonucleic acid (DNA), that lead to its known atomic structure in 1952; secondly he designed experiments that solved the genetic code by which DNA gives rise to specific proteins. These ideas helped lay the foundations of Molecular Biology, the dominant area of science in the second half of the twentieth century. In this way Crick brought to fruition the research plan of Schrödinger. Crick now works in Brain Research and in his recent autobiography (1988) "What Mad Pursuit" speculates on how we are going to understand the origins of consciousness. Crick suggests that the clues to understanding this phenomena, so dear to us all, are to be found in the attentional mechanisms of the brain by which we concentrate our sensory and motor systems on some element of our environment, to the exclusion of all else in the environment. He also believes that as the memory of some thing attended to lasts for only about 60 seconds or so, then the molecular and atomic mechanisms involved should have only this time scale of change.
The main pathways in the brain concerned with the visual identification of objects and their location and movement in space. A coloured triangular form is observed moving in the visual field. The information about colour and form of an object on the one hand and about the movement of the object on the other are coded for separately within the retina of the eye. This coded information is then sent in parallel pathways along separate sets of axons, first to a part of the brain called the dorsal lateral geniculate nucleus and from there to the primary visual (striate) cortex in the occipital lobe at the back of the head. Here the coded information undergoes a transformation into the elements that recognisably belong to the object in the medial temporal area (MT) just in front of the striate visual cortex; at this site neurones fire in relation to seeing each of these elements. The other parallel line of coded information is sent to the posterior parietal cortex, also in front of the striate cortex, where neurons fire in relation to the movement of the object. The final pathway for the identification of an object is in the inferior temporal cortex, where reconstruction of the complete object and its colour is carried out. Here specific neurones fire when the object is viewed.
Figure 5.
A neurone that fires action potentials at a maximum rate when a particular face is observed. These face neurones are found in the inferior temporal lobe. Note that for this primate temporal lobe neurone, recorded from an awake monkey, the maximum firing of impulses (given by the black vertical bars) occurs for the frontal view of the face of another primate, as shown by the top row of different face orientations. The bottom row shows that masking out the eyes or substituting a human face for a monkey face results in reduced responses. Very low rates of action potential firing were recorded from this neurone when a scrambled face was presented or a hand or a brush.

Figure 4.
The main pathways in the brain concerned with the visual identification of objects and their location and movement in space. A coloured triangular form is observed moving in the visual field. The information about colour and form of an object on the one hand and about the movement of the object on the other are coded for separately within the retina of the eye. This coded information is then sent in parallel pathways along separate sets of axons, first to a part of the brain called the dorsal lateral geniculate nucleus and from there to the primary visual (striate) cortex in the occipital lobe at the back of the head. Here the coded information undergoes a transformation into the elements that recognisably belong to the object in the medial temporal area (MT) just in front of the striate visual cortex; at this site neurones fire in relation to seeing each of these elements. The other parallel line of coded information is sent to the posterior parietal cortex, also in front of the striate cortex, where neurons fire in relation to the movement of the object. The final pathway for the identification of an object is in the inferior temporal cortex, where reconstruction of the complete object and its colour is carried out. Here specific neurones fire when the object is viewed.
A neurone that fires action potentials at a maximum rate when a particular face is observed. These face neurones are found in the inferior temporal lobe. Note that for this primate temporal lobe neurone, recorded from an awake monkey, the maximum firing of impulses (given by the black vertical bars) occurs for the frontal view of the face of another primate, as shown by the top row of different face orientations. The bottom row shows that masking out the eyes or substituting a human face for a monkey face results in reduced responses. Very low rates of action potential firing were recorded from this neurone when a scrambled face was presented or a hand or a brush.
The main difficulty in trying to understand how we see an object amongst the many different complex impressions that impinge on our retinas involves the linking together of related features that constitute the object. This is referred to as the "binding problem" in which the constituent visual elements of the object must be bound together in the visual cortex so that we identify the object as separate from the other components in the visual image on our retinas. A very important discovery concerning this problem was recently made by two groups in Germany: Wolf Singer and his colleagues as well as R. Eckhorn and his colleagues. They found oscillatory firing of neurones at about 40Hz that were phase-locked between assemblies that represent the linking features of the visual scene; this phase-locked oscillatory firing occurred even for neurones that were found in different cortical areas that coded for different aspects of the object. Visually related activities constituting an object are by this means transiently labelled by a temporal code that signals their momentary association. In the diagram are shown the two main visual areas at the back of the brain called the occipital cortex (area 17 and 18). Highly correlated stimulus evoked resonances were found between neurones in the two tracts through this area of the brain indicated by the two electrodes pictured at the top. The numbers 1 to 8 and 10 to 14 on these two tracts through the brain show correlograms of the impulse firings that are mostly in phase. These coherent-evoked 40Hz resonances were found at distal cortical locations when at least one of the primary coding properties of the object (namely its orientation, position, movement of direction or velocity) was present.
Common seizure patterns

Clinical type

Localization

1 Somatic motor:
- Jacksonian (local motor)
- Masticatory
- Simple contraversive

2 Somatic and special sensory (auras):
- Somatosensory
- Visual
- Auditory
- Vertiginous
- Olfactory
- Gustatory

3 Visceral:
- Autonomic

4 Complex partial seizures:
- Formed hallucinations
- Illusions
- Dyscognitive experiences (deja vu, dreamy states, depersonalization)
- Affective states (fear, depression, or elation)
- Automatism (ictal and postictal)

5 Absence
- Bilateral epileptic myoclonus


Figure 7
Defects in the ability to attend to parts of one's own body following a stroke. This person was an artist, Anton Raderscheidt, who suffered a vascular stroke affecting the right hemisphere of the brain. Shown here are four self-portraits that he painted at different stages of recovery from the stroke. A specific part of the brain, called the parietal cortex, an area of the brain involved in visual attention, was damaged during this stroke. Note that in the earliest painting (upper left) the artist completely ignored the side of his face opposite to the damaged parietal cortex. He then gradually improved over the next few months (upper right and lower left) until in the end (lower right) most spatial relations for his face were reconstituted, although still remaining somewhat distorted. The artist never really recovered. He died several years after the stroke which affected his right parietal cortex.

It should be emphasized that the parietal stroke did not involve any injury to the purely "visual" mechanisms of the brain. For example the artist could see objects perfectly well on that side of his body opposite to the parietal lesion. However, if a second object was then brought into the visual field on the other unaffected side, then attention to the first object was lost and the artist was "blind" to its presence.
Common seizure patterns

<table>
<thead>
<tr>
<th>Clinical type</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Somatic motor:</td>
<td>Prerolandic gyrus</td>
</tr>
<tr>
<td>Jacksonian (local motor)</td>
<td>Amygdaloid nuclei</td>
</tr>
<tr>
<td>Masticatory</td>
<td>Frontal</td>
</tr>
<tr>
<td>Simple contraversive</td>
<td></td>
</tr>
<tr>
<td>2 Somatic and special sensory (auras):</td>
<td>Postrolandic</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>Occipital or temporal</td>
</tr>
<tr>
<td>Visual</td>
<td>Temporal</td>
</tr>
<tr>
<td>Auditory</td>
<td>Temporal</td>
</tr>
<tr>
<td>Vertiginous</td>
<td>Mesial temporal</td>
</tr>
<tr>
<td>Olfactory</td>
<td>Insula</td>
</tr>
<tr>
<td>Gustatory</td>
<td>Insuloorbit-frontal cortex</td>
</tr>
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<td>3 Visceral: Autonomic</td>
<td></td>
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</tr>
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</tr>
<tr>
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</tr>
</tbody>
</table>


Figure 8

Localization of focal epileptic seizures in the brain. The common form of epileptic fit, as the table shows, occurs as a focal seizure originating in a localized region of the temporal lobe, often referred to as the limbic system. These seizures involving the temporal lobe, are accompanied by visual, auditory and olfactory (smell) hallucinations. They also involve their vivid recall of memories because the limbic system includes the hippocampus, required for the laying down of new memories. The temporal lobe itself includes neurones for the identification of objects, such as faces, as shown in figures 4 and 5. Thus the most common human epileptic condition is not that of generalized seizures, which start out in the entire neocortex of grey matter as in “petit mal” or “grand mal” epilepsy, as commonly thought, but as focal seizures in the limbic system.
Neuronal growth factors for the survival of neurones were first discovered in the peripheral nervous system that controls such organs as blood vessels; these are called sympathetic neurones. Rita Levi-Montalcini and Cohen purified this sympathetic nerve growth factor (NGF) down to a single type of molecule. This figure shows a clump of sympathetic neurone cell bodies in a culture dish in the absence of NGF (upper figure) compared with a clump in the presence of NGF (lower figure). Note that hundreds of axon processes emerge from the clump of neurones in the presence of NGF indicating that these neurones are alive and growing.

The neurones shown are found in the retina and are called retinal ganglion cells. They connect the retina in the eye to the visual centres of the brain. Many of these neurones degenerate during normal development as the retina is making appropriate connections with the visual centres of brain. Present evidence suggest that this naturally occurring cell death occurs as a result of the neurones failing to obtain a growth factor necessary for their survival. This growth factor is synthesized in the visual centres of the brain where the terminals of retinal ganglion cells obtain the factor and transport it along their axons back to the ganglion cell bodies in the retina. There it is utilized to maintain the integrity of the neurone.
Figure 11
The limbic or "border" system of the brain comprises primarily the inferior temporal lobe, hippocampus and amygdala. The hippocampus and amygdala lie on the medial surface of the brain rather than on its lateral aspect. Not only is the system most frequently involved in epileptic fits but it is also one of the first parts of the brain to degenerate in Alzheimer's disease.

Figure 12
A section through the hippocampus, isolated from the rest of the brain. The diagram also shows the layout of the principal neuronal types (indicated as spheres with branching trees of processes called dendrites) together with their interconnections (indicated by the long thin processes, called axons, with arrows attached). The specific input, bringing information about all sensations from the cortex (such as sight, sound or smell), come from the axons arising in entorhinal cortex which synapse on the dendritic processes of granule cell neurones in the so called fascia dentata. These neurones themselves relay this transformed information to the pyramidal neurones in the CA3 region via their axons that form synapses on the CA3 neurones. These neurones are known to code for memories; they connect with each other through processes called recurrent collaterals (only two of which are shown). It is the excitability of these neurones, in part conferred upon them by these recurrent collaterals, that makes this region of the brain the most likely to trigger an epileptic seizure.

The CA3 neurones in turn project to the CA1 pyramidal neurones on which they synapse. These neurones also code for memories and their axons project to the region called the subiculum in the old paleocortex and from there to the neocortex. Thus the trisynaptic pathway is from entorhinal cortex to fascia dentata to CA3 pyramids to CA1 pyramids back to the cortex. There is another, less specific input (on the left) necessary for the normal functioning of the hippocampus and that comes from the subcortical structure called the septum. These axons synapse on all neurones in the hippocampus. They are the first neurones to degenerate in the brain of people suffering from Alzheimer's disease. This leads to the loss of memory formation that characterized this disease.

Figure 10.
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The functional circuit between different types of neurones, shown in figure 12, the synaptic connections within this circuit have the very special property of remembering over very long periods of time if they have been subjected to impulse traffic. "A" shows a transverse section through the hippocampus, like that shown in figure 12, except that stimulating electrodes have been placed on the nerves from the entorhinal cortex (called the perforant pathway axons) and a recording electrode in the dendritic layer of the granule cells, where the

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perforant pathway axons synapse. "B" shows an enlargement of the boxed area in "A", with sample electrical recordings of the compound population spike occurring because many granule cells fire in synchrony due to stimulating the perforant path axons; the population excitatory postsynaptic potential (epsp) is recorded from the synaptic regions between the perforant path axons and the granule cells on stimulation and gives a measure of the efficacy of synaptic transmission. "C" shows the results of stimulating the perforant pathway at a frequency of 15Hz for 10 seconds at the four times indicated in the graph of the relative amplitude of the population epsp against time; if the perforant nerves are stimulated every few minutes with a single impulse before, during and after the 15Hz stimulating periods then the amplitude of the population epsp at each 6 minute period is shown to grow over 3 hours until it settles down to a size 300% that of the control (in which no stimulation occurred at 15Hz); two examples of this long-term potentiation of the population epsp are shown one before and one after the 15Hz conditioning period. This enhanced efficacy of transmission through the synapses of over 300% is shown to last for 3 hours after the 15Hz stimulation but may continue for days or months. The mechanisms responsible for this potentiation are required to retain a memory.

**Figure 14.**

Procedure for transplanting embryonic septal neurones from the hippocampal region of a foetus to the hippocampus of a mature animal with a degenerating septum. The septal region (black area) is first removed from the foetal brain and placed in a culture dish with enzymes that loosen the tissue into separate neurones. The partly separated neurones are then placed in a test tube and the isolation process taken further by rapidly shaking the neurones up and down in a pipette in the test tube. The completely dissociated neurones are next taken up into a syringes. The syringe needle is then located with great accuracy in the appropriate part of the hippocampus and the dissociated septal neurones injected into this area of the brain.

**Figure 15.**

Use of the forced alternation T-maze to show that following degeneration of septal neurones transplanted embryonic septal neurones can reconstitute the memory system of the hippocampus. The rat is put in the starting position in the T-maze. In the first trial the door on the right, door 1, is open; the door on the left, door 2, is closed and food is placed at 'a'; the rat runs and is forced to turn to the right where the door is open (it can neither see nor smell the food at the starting
position). In the second trial the door 1 is open and now the door 2 is also open and the food placed at 'b'. A correct response is regarded as one in which the rat turns left on trial 2. The trial- -trial 2 sessions are repeated 5 times per day. The room in which the T-maze is placed contains many items, such as curtains, clocks and computers which despite the rats poor visual acuity appear to allow the rat to orientate itself on the T-maze.

The graph shows the percentage of correct responses performed by the rat on the T-maze alternation task over time. Following lesion or degeneration of the septal region of the hippocampus there is a 50% chance that the rat will turn left on the second trial, so nothing has been remembered and the choice is random. Following a sham operation, in which only a harmless placebo substance is injected into the hippocampus, the rat learns to make 100% left-hand turns on the second trial within 3 weeks of testing so that at this time its' memory for the T-maze performance is perfect.

Following transplantation of embryonic septal neurones into a rat with a lesioned septum the rat learns to perform at the 90% correct level of performance within about 10 weeks after the operation.
The Morris water tank used to determine the spatial memory of rats. The water tank is placed in about the middle of the room. It contains opaque water and a stand (shown in the cut-away of the tank wall) which is about one inch beneath the surface of the water; this is sufficiently deep for the rat not to see it when swimming in the tank so that it only becomes aware of the stand if its' feet come in contact with it. Surrounding the tank are objects on the wall, such as curtains, clocks and potplants (and a large picture of other rats) which allow the swimming rat to determine its' orientation; the spatial location of the rat in the water tank is laid down as a spatial memory in the hippocampus and this allows a healthy rat to determine the position of the unseen stand with respect to the objects in the room, once its' feet have come in contact with the stand. A television camera is placed above the water tank which allows the operator at the television - computer terminal shown to monitor the locus of the swimming pathway of the rat once it has been placed in the tank at an arbitrary position.

The locus of the swimming pathway of rats (determined by the methods given in the legend to figure 16) after they have been placed in the Morris water tank. The view is looking down on the tank, and shows the position of the stand beneath the opaque water in the tank. Each row shows the results for series of trials which determined if a rat found the stand (and then sat on it) during a 5 minute period; there were five trials on each of five successive days and the results are shown for the first trial on the first day (1.1), the fifth trial on the first day (5.1), the fifth trial on the fourth day (5.4) and the fifth trial on the fifth day (5.5). In the first row a young control rat (about 6 months old) was placed at a random site in the tank at 1.1 and left to swim; it will be noted that at 1.1 the rat's feet did not accidently make contact with the stand; by 5.1 this had happened and the spatial memory system of the hippocampus had located the position of the unseen stand with respect to the objects in the room enabling the rat to swim directly to the stand and sit on it, as shown; this also occurred at 5.4; at 5.5 the stand was removed and the rat swam repeatedly over the site where the site had been, seeking a rest. In the second row an Aged Impaired rat (about 3 years old) is shown to be unable to lay down a
spatial memory of the position of the stand, even though its feet accidently come in contact with it several times over the 25 trials. In the third row an Aged Unimpaired rat (again about 3 years old) is shown to be able to lay down a spatial memory as well as the Young Control rat, and performs in a like manner. The final row shows an Aged Impaired rat that had a transplant of embryonic neurones from the septum in its' hippocampus; the locus of the swimming pathway of the rat in each case shows that it has formed a spatial memory of the stand as quickly as the Young Control.

Figure 18.

A human embryo at 5 weeks (15 mm long). The hands are clearly visible with the just clearly delineated fingers. The heart, with liver below, can be seen between the hands; the diaphragm separates the heart and liver. Most striking, are the two halves of the cerebrum which can be seen through the transparent skin of the forehead above the developing eyes.

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