

# The Brain in the new Millennium

*by Andrew Matus<sup>§</sup>*

The century that is now coming to a close has seen a revolution in the way that human beings think about their own nature. Gradually, the ancient concept of a material body brought to life by an immaterial spirit has lost its grip on human belief as the results of biological research have insistently pointed to gene-based mechanisms as being responsible for driving and controlling living processes. These new insights from biology have had a particularly dramatic impact on our concept of the relationship between the mind and the brain as new techniques such as computerized brain scanning have revealed that even our most abstract thoughts are supported by organized activity in the brain. Many of the most fascinating discoveries are extremely recent and the pace of progress shows no sign of slowing, on the contrary it seems to accelerate relentlessly making life both exciting and challenging for neuroscientists. What are the implications of this revolution in the brain sciences? As we stand on the threshold of a new millennium the

greatest and certainly the most emotionally charged question we face is whether neuronal mechanisms in the brain can explain all of our mental life, even our own consciousness. This is a unique moment in human history as the organ that does our thinking tries to fathom the depths of its own function. Can the brain explain itself? A miniature academic industry of books and conferences has sprung up in the wake of this question, but much of the often feverish debate is futile because we simply do not yet have enough data to formulate a satisfactory answer, and impatient speculation is no substitute for knowledge. Nevertheless, through the fog of incomplete data the vague outlines of a new synthesis of ideas is beginning to emerge. Here is a sketch of some of its major features.

## **Information about sensations and actions is represented in the activity of individual nerve cells**

One of the truly great discoveries of this century has been that in the brain complex data is represented in by the

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electrical activity of individual nerve cells. Neurophysiologists can listen in on this activity by placing a microscopic electrode on an individual nerve cell and recording the rate at which it "fires" electrical signals as the animal receives information from its sense organs or makes behavioural movements. Most of these investigations have been focussed on the cerebral cortex, the great sheet of nervous tissue that almost envelops the human brain and which is responsible for its most complex and sophisticated operations. One basic principle of cortical organization is that different functions are located in different places, for example nerve cells at the side of the cortex receive signals from the inner ear and respond to the sounds that we hear whereas nerve cells at the very back receive signals from the eyes and respond to things we see. The cortex is not just responsible for receiving signals but also sends them out, and other nerve cells further to the front are active when we plan and carry out movements. An important insight that has emerged from these electrophysiological studies is that throughout the cortex individual nerve cells are "tuned" to respond to particular events. The easiest place to see how this works is the auditory area of the cortex where individual nerve cells are tuned to respond to sounds of different pitch. Many thousands of differently tuned cells are involved in this function so that together they cover the entire spectrum of frequencies we are able to hear. In this way a complex sound, such as a

baby crying, is represented in the brain by a combination of nerve cells each of which responds to a different frequency in the baby's howls by increasing its electrical activity. This same principle is used throughout the cortex so that in each area there are nerve cells "tuned" to respond in different circumstances. For example, some of the cells in the visual area of the cortex are tuned to respond selectively to objects that move across our field of vision in a particular direction while other cells are tuned to recognize the apparent distance away of an object while still others respond to its colour. A further important aspect of this discovery is that as the signals from the outside world travel through the circuits of the cortex the tuning of individual nerve cells becomes increasingly more refined so that eventually the neurophysiologist's electrode encounters cells that respond preferentially not to colours or directions of movement but to entire complex objects, such as a hand or a face. Whether these cells are really responding to a face or whether they are tuned to the particular blend of characteristics such as shape, pattern, texture and colour that happen to be combined in the features of a face, is still a matter of debate, but the importance of the scientific observation lies in the principle that it reveals; that within the brain even complex information is represented in the activities of individual nerve cells.

This is only part of the story, a nerve cell does not exist in isolation, and the purpose of its complex pattern of electrical activity is not to tell a curious physiologist that it has "seen" a face but to regulate the transmission of information in a neuronal circuit. It is the combined action of these circuits that turns data from the sense organs into the programs of movement we need for behaviour. This explains why the primary objective of contemporary neuroscience is to find out how the brain's circuitry is formed during early development and how its connections can be modified by experience in childhood and adult life. This is a sensible priority because until we understand the circuit properties of the brain we shall never be able to give a satisfactory account of its role in producing the mental phenomena with which we are so personally impressed. This is the key respect in which neuroscience differs from the traditional approach of philosophy – the primary objective of neuroscience is to understand the circuit properties of the brain whereas the primary objective of philosophy is to find an explanation for the mechanism of thought. It is because philosophers are not committed to the brain as a reference point that many of them still discuss mental phenomena as if they were independent of the brain and why others, such as the British mathematician Roger Penrose, speculate that mental events may involve mechanisms such as quantum mechanics

that are divorced from the pattern of connections in the brain's circuitry. I am personally suspicious of such proposals because they follow the well-established human habit of filling in gaps in our knowledge of natural world with speculative explanations. There are many examples of this misleading tendency, ranging from ancient creation myths to the 19th century belief that the cosmos was filled with an invisible medium, the ether, which was invented because the light waves from distant stars can travel across empty space and it was "obvious" that waves require a flexible medium to carry them. Eventually scientific investigation revealed that light is composed of particles, photons, which can travel across the void of interstellar space using their own intrinsic energy. The "ether" that had been supposed to fill the cosmos then promptly did what in reality it had always been doing, which was not to exist. For neurobiologists the "mind" is the "ether" of the brain and they expect that it too will suffer a similar fate once the cellular mechanisms that underlie brain function are sufficiently understood.

### **There is no executive office in the brain**

In the same way that the activity of individual nerve cells in sensory areas of the cortex represent complex perceptions, the activities of cells in other cortical regions represent the complex patterns of muscular activity

that make up behaviour. The existence of these separate areas devoted to sensation and action raises the important question of how the sensory signals that represent the identity and location of an object are used to initiate appropriate behavioural actions for dealing with it. It is one thing for my brain to form a representation of a pencil lying on the table in front of me but how does this knowledge get translated into the decision to pick it up and use it to write? Originally it was thought that there must be a separate "executive" area of the brain that assembled all the relevant sensory information and issued commands about which programs of action should be carried out, but recently it has begun to seem more likely that the same circuits which carry the information also manage the transition from sensation into action. If this scheme is true then we should expect to find that as we follow signals through the brain's circuitry we should eventually encounter an interface area where the activities of individual nerve cells stop depending on signals coming in from the sense organs and instead begin to reflect potential patterns of behavioural action. Nerve cells with exactly these properties have been discovered in parts of the cortex that lie between the purely sensory and the purely motor areas. These cells increase their activity when a monkey is waiting to perform an action, such as pointing at a spot of light that has been shown to it on a television screen, but they do not

respond if the animal is merely looking at the screen without being required to do anything. In some of these tests the colour of the target spot tells the monkey that its correct response is *not* to point at the spot. Interestingly these "decision" cells increase their activity both when the signal tells the monkey that it should make the movement and when the signal tells it not to make the movement, showing that the circuits containing these nerve cells are involved in planning behavioural movements rather than in carrying them out. The actual execution of the behaviour is organized by circuits further along the pathway and in these areas the nerve cells only increase their activity in circumstances where the monkey knows that it will be required to carry out the behaviour.

Can the brain contain sufficient circuitry to manage all the possible transitions from sensory input to behavioural output that an animal might ever need? Several lines of evidence suggest that it can. One of the most convincing is what happens when the brain is injured by an accident or stroke. The neurological symptoms that bring the patient to the clinic vary widely depending on which part of the brain has been damaged, for example if the damage involves the visual area of the cortex the patient will probably suffer from some degree of blindness but the effects can sometimes be strange and revealing as in the condition known as blind sight, where patients deny that they can see anything but can nevertheless

perform actions, such as catching a ball, that require vision. Even stranger is the opposite condition where patients claim that they can see even though their behaviour shows clearly that they are in fact blind. Brain damage in other areas of the cortex produce deficits that are more conceptual in character such as the condition known as visual neglect, in which patients lose awareness of entire areas of visual space. One textbook case concerns a retired American army major who after suffering a stroke denied all knowledge of his own left leg and repeatedly tried to throw the "foreign" object out of his hospital bed. Another case involved a patient from Milan who when asked to describe from memory the Piazza del Duomo mentioned only the buildings on the right hand side – both when imagining the scene looking towards the cathedral and when imagining it looking in the opposite direction so that the second description included the buildings that had been ignored the first time and left out those that had been described previously.

**It all depends on the arrangement of the connections**

The complexity of these damage-induced defects underlines how important a thorough understanding of the brain's circuitry is for a satisfactory explanation of its function. One significant recently introduced concept is that processing of information in the brain takes place in a vast number of local "microcircuits". Although this idea

seems obvious once stated, it is an important advance over older descriptions of the brain's anatomy that gave a reasonably good account of the "long lines" that carry information from place to place but provided little idea of how it was processed along the way. The real breakthrough came in the 1960's with the discovery that nerve cells in the cortex are arranged in columns, each about one twentieth of a millimetre across. These column modules make up the functional units that carry out the "elements" of signal processing so that, for example, in the visual area of the cortex there are "orientation" columns whose cells are all "tuned" to respond to objects moving in one particular direction which is slightly different for each neighbouring column. Initially these studies were performed using microelectrodes to record the electrical activity of individual nerve cells but more recently methods have been developed for making optical recordings directly from the surface of the cortex so that the pattern of responses over a wide area can be established rapidly. This has confirmed that neighbouring columns of cells respond to objects moving across the visual field at slightly different angles so that the entire 360 degrees of possible directions of movement are laid out in a series of repeated circular arrays. These are known as "pinwheels" because when they are mapped out, the pattern of each of them resembles a child's windmill. This pattern, in which the same data is represented with small

transformations in neighbouring columns, is a feature of functional organization throughout the cortex, for example in the area containing the face-sensitive cells neighbouring columns are "tuned" to different orientations of the head ranging from profile through three-quarter view to full face.

A significant feature of this columnar organization is that it is inherently flexible and this has allowed for the rearrangement of columns during evolution to fit the special behavioural needs of different animals. This evolutionary "plasticity" has given the human cortex a particularly large number of columns that are connected to receive signals from the thumb and forefinger to support our highly developed sense of touch. By contrast in the mouse a large area of the sensory cortex is devoted to the whiskers and in the mustache bat there is an expanded area in its auditory cortex that contains nerve cells responding exclusively to sounds of 61 kilohertz, the frequency of the echoes it uses to locate objects in the dark. The most important aspect of the flexibility of this modular structure is the relative ease with which columns can be added during evolution to increase the amount of circuitry available for new functions. The expansion of the cortex has been especially great in humans where the cortex and its connections make up around 80% of the volume of the brain. The scale of this evolutionary development can be appreciated by comparing the cortex of a cat which has

an area of about 100 square centimetres to that of a human which is around 2400 square centimetres. The significance of this huge increase lies in the opportunity it offers for forging new connections between pre-existing areas and during evolution this capacity has been used to develop additional circuits with radically new functions. Comparing functional maps of the cortex through a series of from mammals, from relatively primitive animals such as the hedgehog through to humans, shows a progressive increase in the size of the so-called "association areas", where interactions between data from different primary sources can occur. The positioning of these association areas often gives a good indication of how they arisen from the merging of less complex circuits. For example, the areas that are required for representing our image of the external world lie at the end of an upper branch of the visual pathway that extracts information about the location of objects in space. A separate lower branch focuses on the identity of objects and it is intriguing that the area of the human brain that holds the lexicon of words we use in language is situated just beyond this object recognition area of the visual system in a new area that is not present in even our closest evolutionary relative, the chimpanzee.

The shear density of information processing that happens in local column circuits of the cortex can be appreciated by considering the numbers of functional

elements they contain. Based on studies using electron microscopy it has been estimated that one cubic millimetre of tissue in the visual area of cortex contains around 50,000 nerve cells each making an average of 6,000 connections with its neighbours so that there are a total of around 300 million connections in this tiny fragment of brain tissue. In total the human cortex contains in the order of 10 billion nerve cells with some 60 trillion, that is 60 million million, connections between them. To put these figures into the perspective of the everyday world consider that each cubic millimetre of cortex contains around 3 km of axons, the fibres that carry signals between nerve cells. These vast numbers are possible because the individual components themselves are so small; each axon is only about a micron, that is one thousandth of a millimetre, in diameter. Our concept of how these circuits operate has recently undergone a revolution as it has been established that the vast majority of connections between nerve cells in the cortex are made with close neighbours, emphasizing that principles of feedback and recurrent processing that have long been discussed in the literature of cybernetics are key features of information processing in the brain.

#### **Connections between neurons in the brain are plastic**

Even this is far from the whole story because the most important feature of the circuits in the brain is that their

connections can change, a property known as plasticity. One particularly striking example of this occurs when an animal loses a limb. Within a short time after this happens the cells in the part of the cortex that used to receive signals from the lost limb begin to respond to signals arising from neighbouring structures so that after the loss of the middle finger the corresponding nerve cells in the sensory cortex begin to respond to touch signals from the second and fourth fingers. These changes can be extremely rapid and some alteration in the response of nerve cells can be detected in minutes although it takes weeks for the full rearrangement of connections to occur. It has become increasingly clear that these functional rearrangements do not only happen when connections are cut but are also produced by changes in the use of circuits. This occurs in blind people learning to read Braille, which demands extreme skill in using the pads of the fingers to discriminate the fine patterns of raised dots that make up the characters. Brain scanning studies have shown that the area of the cortex corresponding to the fingers that are used for Braille reading undergoes a large increase over a period of a year as the subject learns the new skill. Corresponding studies on monkeys have shown that the response properties of individual nerve cells in the cortex change when the animal learns a task that involves discriminating between objects by touch. There is no reason to

believe that this plasticity in the brain's connections is limited to the few particular cases that neuroscientists have studied and so it is generally believed that changes of this kind are constantly occurring throughout the brain, and particularly in the cortex, as we learn to adapt to the changing conditions in the world around us. Perhaps this is why it is such a sobering experience to re-read what we have written in an old diary and discover that our present memory of our past thoughts and actions are so different from what we recorded at the time. Could it be that our entire brain is in a constant state of flux, altering its connections so that the functions it performs in determining our behaviour and even the memories that we thought were fixed are also constantly changing?

### **The secret lies in the synapse**

Conclusive answers to these questions will only be possible when we know the mechanisms that determine how the connections between nerve cells are made and modified. This ultimate challenge for neuroscience is being pursued by studying the structure of the connections themselves, the synapses. Synapses were first seen when electron microscopes became available in the late 1950's although their existence had been predicted early in the present century on the basis of electrophysiological studies. Their appearance in the electron microscope is extremely revealing because it shows that many of the things we know about the function of

synapses arise as a direct consequence of their structure. For example, electrical signals only cross synaptic connections in one direction, from one nerve cell to the next in a series, which is why electrical signals in the nervous system travel from the sense organs to the muscles and not back the other way. Once the structure of the synapse was visualized the reason for this unidirectional transmission became obvious; each synapse consists of a component from the first nerve cell that is specialized for sending the signal and a component from the second cell that is specialized for receiving it. The component of the cell that is sending the signal is an expanded bulge in its axon containing hundreds of tiny sacs filled with a special chemical, the transmitter substance, that carries the signal to the receiving cell. These chemical signals can be modified by exposing nerve cells to substances that through their resemblance to the transmitter substance inhibit or promote its action. Such substances are commonly known as drugs and their use in medicine, and as the basis of the pharmaceutical industry, is a direct consequence of the structure of the synaptic connections in the nervous system.

Much of the effort in neuroscience at the present time is devoted to exploring in great detail how synapses work. Many projects are concerned with defining the function of genes that guide the formation of synaptic connections during

brain development while others are focussed on the genes that are involved in the transmission of signals at the synapse. All of these studies use the increasingly powerful methods of molecular genetics which over the past two decades have immeasurably improved the speed, depth, and precision of experimental work. However, the greatest value of these new techniques has been in making possible scientific observations that were previously impossible or were not even dreamed of. A good example of this that has been particularly useful in the work of my own group is the use of a gene from a jellyfish that produces a molecule called green fluorescent protein or GFP. As its name implies, if you illuminate some GFP with light of the right wavelength it responds by producing light of a brilliant green colour. What makes GFP particularly useful is that it remains fluorescent even when you join its gene to the gene for another protein so that you can choose a normal non-fluorescent protein that you want to investigate and make it visible by doing a bit a relatively simple gene cloning. This technique was described for the first time only in 1994 but in the few years since it has been used to watch and record the function of dozens of different kinds of proteins inside living cells with often spectacular and surprising results. We have used GFP to make visible the internal structure of brain synapses by attaching it to a actin, a protein that is involved in many of the different kinds of cell

movements in the body like the crawling of cells into the damaged area when a wound is being repaired. In the brain actin is associated with a particular kind of synapse that is made onto a tiny protrusion from the surface of the nerve cell called a spine. This can be seen in the illustration where the spines appear green against the background of the dendritic process of a nerve cell growing in cell culture which is coloured red using a different stain. Each of these spines marks the site of one of the thousands of synapses on these cells and the obviously high concentration of actin in the spines gave us an initial clue that they might be able to move. This was confirmed when we made recordings from living cells and discovered that these spines are rapidly changing shape on a time-scale of seconds. This is significant because previous studies from many different laboratories had suggested that changes in the shape of spines might alter the efficiency with which electrical signals are transmitted at individual synapses and it was widely speculated that this might contribute to the storage of memory traces in the brain. What no one, ourselves included, had suspected was that these movements at synapses could be so fast – they suggest that in our brains synaptic connections can alter their state of connectivity very rapidly. Exactly what means for brain function is still a matter of speculation but these results show at least that brain circuitry is far less fixed

than most people had assumed in the past.

**From brain to mind – a means but not an end**

This work is only one among many rapid developments that are taking place in the neuroscience today. Whatever the outcome of this ferment of activity in the brain sciences proves to be, we can be sure that there will be many more surprises that will alter our concept of how the brain works. Every neuroscientist is aware that many people are uneasy about these advances in our knowledge perhaps fearing that they will be used as an excuse to devalue the status of our mental life. It is possible that such opinions will be voiced but there in fact is no more reason to assume that discovering how the brain produces mental phenomena will devalue the content of our thoughts any more than knowing that light consist of photons devalues our appreciation of the wave-like properties that convert sunlight into a rainbow. Indeed it may well be a relief to end the whole tedious and confusing debate over the relationship between the mind and the brain so that we can put the content of human thought back where it belongs in the realms of art, logic and moral responsibility. By the same token it would be an act of dreadful cowardice to abandon our enquiry into the workings of the brain for the ultimate step in the human investigation of the natural world will be when the organ that does the investigating faces the

challenge of understanding its own nature. As we face the new millennium we are better prepared for this task than ever before.