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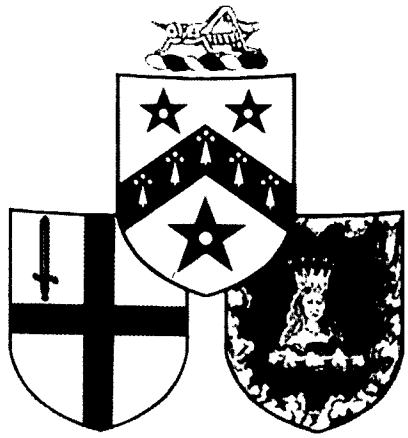

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EXPLORING THE BRAIN

Lecture 4

GROWING A BRAIN

by

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SUSAN GREENFIELD: *GRESHAM LECTURE 4*

Growing a Brain

Life, as we all know, starts with the fertilisation of the mother's egg, when a single sperm from the father becomes embedded in it. But it is a long way from an egg with a diameter of about 0.005 inches, to a brain. The first step towards building a brain, and indeed the rest of a body, is to form a single cell from the egg and the sperm, a 'zygote'. After just over a day, some thirty hours, this zygote divides into two cells and repeats the process again and again so that within three days it has formed into a ball of cells resembling a mulberry, hence it's name morula (Latin for mulberry).

Five days following fertilisation, these cells start to diversify both in the position they take up and hence in the roles that they start to perform. Some cells form an outer wall, creating a hollow sphere, leaving the remaining cells to congregate into a tight mass inside the sphere at one end, so forming an inner cell mass. This sphere is referred to as a 'blastocyst': the cells making up its outer wall will provide food for the developing embryo, which will develop from the inner cell mass.

At about six days after conception, the surface of the blastocyst closest to the inner cell mass adheres to the lining of the womb and becomes implanted. Within just a day or so the cells that had formed the

inner mass have separated away from the cell wall fusing with the womb and have started to form an oval sheet that is two cell layers thick, the 'embryonic disc'.

At around twelve days, the embryonic disk becomes three layers thick. It is the upper layer of cells that will become the nervous system, and which is now referred to as the 'neural plate'. By about eighteen to twenty days, the neural plate has thickened in the middle, so that the centre sinks inwards and the edges move upwards and out. After some three weeks, these edges will start to rise up, creating a 'neural groove'. The edges of the groove then fold inwards and fuse so that they form a kind of cylinder, a 'neural tube'.

And so, by the end of the first month in the womb, a primitive brain has already been formed: indeed, even at the stage of the neural plate, certain segments were already destined to form specific brain regions: indeed, even before the neural tube has been formed, the young brain has started to manifest itself. The neurons-to-be will divide several times each, so that there is a massive proliferation in cell number: at maximum rates cells will be dividing to give 250,000 new neurons per minute!

By the start of the second month, there are recognisable brain regions in place. The primitive brain continues its development as the top of the neural tube thickens into three swellings. The front stump of the neural tube initially bends in two places set almost at right angles

with the developing spinal cord, as parts of the brain grow faster than others. The very front part swells out into two hemispheres, whilst eventually at around eleven weeks, the back part sprouts an outgrowth that becomes the easily recognised little brain, the 'cerebellum'.

As the brain develops, the neurons-to-be first proliferate. In order to divide, a neuron will embark on a short journey that can be repeated several times. By putting out a tentacle like extension, a neuron slithers from the outer region of the neural tube towards the centre. Once at the centre, it will divide so that the two new cells then journey back to the outer edge of the neural tube to start the cycle again, or they will move on to the next stage that enables the brain to grow. It is important to remember that the brain is not just a homogenous mass, but is composed of highly specialised regions that can be distinguished by shape and by the roles they perform in overall brain function. It is not only important for a growing brain to have more cells, but to have them in the right regions. The new neuron then, once it has divided, must 'migrate' to its correct location in the new brain.

Initially, neurons will simply migrate to the middle region of the neural tube, but as this zone becomes thick with cells and well established, then cells will move on in different directions according to their different destinies. Some of the cells will not end up as neurons at all, but as a very valuable type of cell in the brain nonetheless: a 'glial cell'.

Glial cells are not neurons but abound in the brain where they outnumber neurons ten to one. Although the process of neuronal migration is a long way from being well understood, it is known that one particularly important job that glial cells do in the development of the brain, is to act as a kind of temporary scaffolding. Glial cells set off from their point of origin ahead of neurons, as though laying a track. In their wake the neurons then slither along the glial cells as though on a kind of monorail. If the glia are absent, then certain neurons will not be able to migrate, with dire consequences.

One of the best known illustrations of the type of problems that ensue when neurons in the brain are unable to migrate along their glial monorail, occurs in a certain strain of mutant mouse, the 'weaver', so named because of the severe disorder of movement displayed. Instead of walking in straight lines, these particular mice will suddenly turn off in random directions, and are generally weak and subject to incessant trembling. The problem for the weaver mouse lies in the 'little brain' at the back of its head, the cerebellum. Due to a mutation in the genes, the glial cells in this region do not develop as they should, with the result that a class of cerebellar neurons do not migrate to their rightful place. In turn, further neurons end up misalligned and the whole cerebellum remains abnormally small. Since the cerebellum is important in coordinating movement and senses, it is hardly surprising that animals with such a compromised cerebellum exhibit disorders of movement.

Normally however, as more and more neurons proliferate, migrate along the glial monorail and then alight, so gradually the brain grows, accumulating cell layers like the layers of an onion. The commitment of any neuron to a particular size, shape, location and connectivity will all be occurring at different times. But changes are still possible in very young systems, according to the influence of the local environment, as we shall see in a moment.

It is time now to pause however, in the narrative of the developing brain, because a seemingly chance event occurs: we are born. Birth allows the brain to go on growing since otherwise the head would soon become too big for the birth canal of the mother. At birth, the human head is roughly the same size as a chimpanzee, some 350 cubic centimetres. However by six months, it will be half its eventual size and by two years it is already three quarters the size of the adult head and at four years old it is four times the size it was at birth, some 1400 cubic centimetres.

Once born then, what is happening within the brain during the early stages of life? As soon as the neurons have proliferated, migrated to the appropriate brain region, they effectively set down roots, initiate communications with neighbouring neurons by establishing a synaptic circuitry. Much of the increase in brain size see after birth is actually due to the development of these connections, rather than simply to the addition of more neurons.

How do these young neurons know where to go? It is thought that their primary orientation is probably genetic, but that any final routing will be fine-tuned later by local factors. Another idea is that the direction of growth is determined by the gradient of chemical concentration emanating from the target cells. On the other hand, it is hard to imagine how this process would work for some of the very long distances that axons are known to travel. A further possibility, during early development when the brain structures are still close, is that there are a few 'pioneer fibres' that then become stretched out like melting toffee, but along which other neurons will be able follow.

Another important factor in the growth of neurons and the subsequent establishment of individual neuronal circuits, are chemicals which act as chemical guides, so called 'tropic factors'. It is thought that these chemicals, of which the prototype is 'Nerve growth factor' (NGF), provide a trail along which neurons will grow. Although certain neurons will grow unconditionally along a trail of NGF laid down for them, it is also thought that NGF works by being carried back inside a cell, once contact between neurons has been established. It is possible that the way NGF works, once transported back in this way, is to invade the nucleus and actually to interfere with the expression of genes, in that it switches off a genetically programmed self-destruct mechanism. Conversely, if antibodies to NGF are given, then the neurons in which it normally operates, will die. We must remember however that, whilst NGF is used

in neurons outside of the brain and on certain neurons within the brain, it is only one example of probably many such guiding chemicals.

As our development continues after birth, the jostling, restless neurons in the brain are very sensitive as they form circuits, to whatever changes, or simply signals are imposed from the outside world. Inside the brain, right up to sixteen years of age, a bloody battle is being raged between our neurons. It is a battle for establishing connections. If a new neuron does not make contact with a target neuron, then it dies.

Another related and very important factor in determining cell survival, once contact is established between neurons, is activity, the sending and receiving of electrical signals. This point is tragically illustrated by the recent example of a six year old Italian boy. This boy was blind in one eye. Yet the cause of his blindness was a medical mystery. As far as the ophthalmologists could tell, his eye was totally normal. Eventually, the enigma was solved. It finally emerged that when he was a baby, the boy's eye was bandaged for two weeks as part of the treatment for a minor infection. Such treatment would have made no difference to our older brains with their more established connections. But two weeks after birth the connections of the eye were at a critical period for the establishment of eye to brain circuits.

Since neurons serving the bandaged eye were not working, their normal target became taken over by nerves from the normal, working eye. In this case the neurons that were not signalling were treated as

though they were not there at all: the target of these inactive, functionally non-existent neurons was readily invaded by the active brain cells. Normally, this rule would be beneficial as it would mean that neuronal circuits were being established according to the working cells which reflected in turn the environmental requirements in which the person had to live. Sadly, the bandaging of the eye was misinterpreted by the brain as a clear indication that the boy would not be using that eye for the rest of his life.

But what is happening in the brain as we interact with the environment in normal circumstances? It seems that brain circuits that grow more than others, within a specific brain region, are also those that are the most active, as measured by their average electrical activity. It is not just a question of 'use it or lose it', as much as 'use it as much as you can'.

An illustration of how precise the change in neuronal circuitry can be comes from a study where kittens were simply trained to lift one particular paw up to show they could discriminate between patterns of horizontal versus vertical lines. Examination of their brains revealed an increase of about thirty percent more connections in the specific part of the cortex relating to sensations in that paw. So, it is connections that are important and the degree of the enrichment of your environment: in turn the degree to which you are active will determine how the connections between neurons are formed, and thus make you finally into the person you are.

It is a popular idea that this selection of connections is taken from a wider pool of existing connections that are then 'lost', rather like one might make a sculpture by removing or 'losing' the extraneous marble. Although some neuronal connections do undoubtedly die off in development, such a loss is more then off-set by the runaway growth of the brain, as it forges the appropriate connections between neurons as a result of how much they are being used and consequently as a result of how active they are. Hence there is no net loss of neurons as the brain develops, no generic brain that gets shaped into an individual one: rather the individual grows as the brain does, over some sixteen years in all.

Finally, we come to the mature brain that, at the age of sixteen, has finally increased in size by a final five percent. However, although the brain is particularly impressionable whilst it has been developing, such adaptability does not cease, but merely lessens somewhat, in maturity. It is actually possible to manipulate the environment and observe long-term changes in the brain. For example, adult rats were exposed to what is referred to as an 'enriched environment' where they had lots of toys, wheels, ladders and so forth to play with. In contrast, other rats were kept in an ordinary cage, where they received as much food and water as they wanted: it was just that they did not have anything to play with.

However when the brains of these two groups of rats were examined, then it was found that the number of connections in the brain

had increased only in the animals in the enriched environment, not in those from the ordinary cages. It appears that sheer numbers of neurons are not so important as the connections between them in the brain, and these connections are not fixed but are highly changeable, not just in development but also in adulthood. Specific experiences will enhance the connectivity in highly specific neuronal circuits.

Our brains continue, on the one hand, to slow down in certain ways, but on the other hand, to adapt and change in others, as we live our lives as consistent yet developing individuals. All the time, most of us nurture the hopes of living a long time, eventually reaching old age. It is now well known that we are living longer. By the year 2020, twenty percent of the population will be over sixty five. More than any other generation, we have a greater chance than our predecessors of being in excellent health due to a good diet, better medical care and increasing interest in physical fitness.

However, it is at this final stage in life that the brain starts to diminish in its mass. There is twenty percent loss in brain weight by the time one is ninety and even by seventy, five percent loss in brain weight. On the other hand, we do know that the remaining neurons can take over certain roles. But why does the brain age? There are various theories such as that there are 'ageing genes' that run out of genetic information, or alternatively, the genetic programme suddenly becomes subject to random damage over time, or again that inactive or harmful proteins are suddenly produced. We still do not know the cause of the devastating

diseases of old age, Alzheimer's disease and Parkinson's disease, where different parts of the brain are subject to massive neuronal loss. However, it is important to realise however that these diseases are actually illnesses; they are not a natural consequence of old age.

The brains of older rats can still form new connections in response to a rich environment, and although older people perform worse on some problem solving task and they process information a little slower, there is no evidence of a general ability for learning which decreases with age. In fact vocabulary, for example, improves. Moreover politicians, heads of business, heads of the church, political leaders, are very often in their sixties and seventies, and all presumably, or at least one hopes, at the peak of their powers. It is perhaps telling that in ancient Rome you could only ever be a judge once you were over sixty years of age.

Even at the physical level there is no reason to assume that we are all definitely destined to become debilitated. There is one lady, Hilda Crooks, who climbed Mount Fuji at the age of ninety one. We only have to think of some very active yet elderly figures for example, Mother Teresa, Nelson Mandella, Pablo Picasso, to realise that old age can be the ultimate expression of you as an individual.

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GRESHAM COLLEGE

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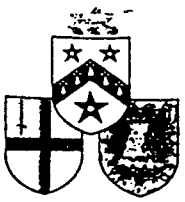
An independently funded educational institution, Gresham College exists

- to continue the free public lectures which have been given for 400 years, and to reinterpret the 'new learning' of Sir Thomas Gresham's day in contemporary terms;

- to engage in study, teaching and research, particularly in those disciplines represented by the Gresham Professors;

- to foster academic consideration of contemporary problems;

- to challenge those who live or work in the City of London to engage in intellectual debate on those subjects in which the City has a proper concern; and to provide a window on the City for learned societies, both national and international.



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