Catalyst

Secondary Science Review

Volume 25
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December 2014

Grey matter, white matter

The changing teenage brain

SEP
Science Enhancement Programme

Catalyst

Volume 25 Number 2 December 2014

The cover image highlights the structure of the brain within a human head (Bigstock/decade3d)

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All in your mind

On pages 8-12 of this issue of Catalyst, Ashok Sakhardande describes how we are becoming increasingly knowledgeable about the structure of the human brain and how it functions. In particular, he is interested in how brains change during adolescence, a time when many new skills must be developed. Much of what we know about how brains work come from studies using magnetic resonance imaging (mri scans), but it is difficult to know how to match up brain activity to the thoughts and actions which make us who we are.

Another way to reveal what's going on in our brains is to use X-rays. On pages 19-21, Silvia Pani describes some of the latest uses of X-rays, from security scanning to scans of the human body. These techniques are always being improved so that their original inventors might be surprised by all that is possible today.

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www.catalyststudent.org.uk

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Jennie Hargreaves

Crash investigators

Understanding road traffic accidents

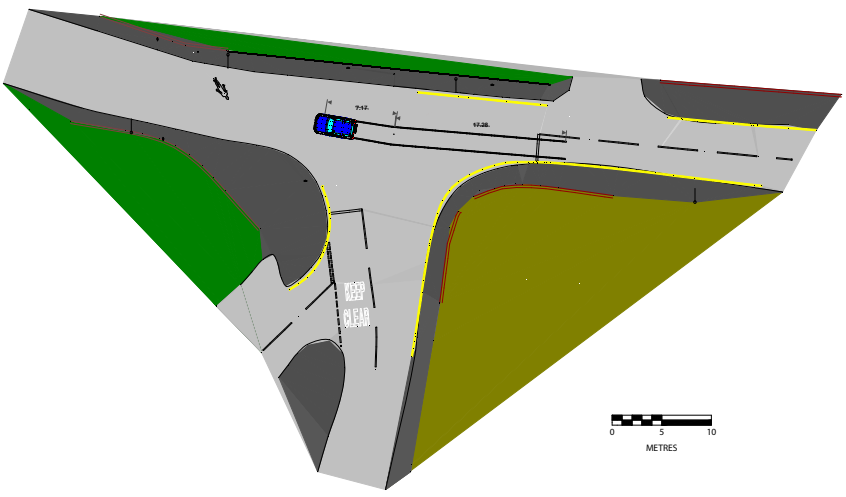
Key words
acceleration
collision
rationalisation
road safety

*Students from Lockerbie Academy have been working with **Inspector Neil Hewitson**, a Road Crash investigator from Police Scotland's Roads Policing Department, to use science to interpret evidence from real car crashes. The Police Accident Investigators provided data from a serious accident that occurred in the region. Their science teacher, **Jennie Hargreaves**, describes how they tackled the problem.*

The accident

The scenario we were faced with was: A man was hit on a quiet, urban road (with a 30 mph speed limit) near a pub at about 10.20 pm on a dark, rainy night. There were street lights. The driver fled the scene. The pedestrian ended up unconscious in hospital. There were witnesses but their reports were contradictory. One thought the pedestrian might have been drunk, the other thought the driver was exceeding the speed limit.

The crash was laid out to 1/3 scale in the Assembly Hall using standard toys. The diagram shows the scene. Our task was to use science techniques to find out the cause of the accident, who was responsible and if any traffic offences were committed. This involved students in observing, hypothesising, recording and noting, measuring, calculating, drawing conclusions and evaluating our work.



Plan of the crash scene

Before we started we secured the scene with police tape and took photos of any evidence that we thought was relevant.

Investigations start at the mock-up of the crash scene.

Interpreting the evidence

Tyre marks: Crash investigators measure tyre marks to determine the speed of the vehicle prior to impact and when the car started to skid. The tyre marks can indicate whether a car was accelerating, decelerating or sliding sideways.

A student measures the skid marks

The lengths of the tyre marks (displacement) were measured and scaled up to find the length of the real skid marks. It was found that the car skidded for 17.28 m before impact and a further 7.17 m before finally coming to a halt, giving a total of 24.45 m.

We were surprised to discover from the police that the tyre marks are not produced from the melting rubber but by melting of the bitumen road surface.

When the brakes go on

It helps to think of four stages when a driver starts braking in an emergency.

1. The driver's foot strikes the brake pedal and pressurises the braking system causing maximum braking effort to the rotating wheels. The speed of the vehicle begins to reduce without tyre marks being left on the road surface.
2. The braking system is still pressurised and the vehicle continues to reduce speed. There is still maximum braking effort but the friction material in the brake linings begins to cause the wheels to 'lock-up'. Still no visible tyre marks.
3. Now the brake linings prevent the wheel from revolving. It is locked and the tyre is sliding over the road surface. Heat is generated due to the friction between the tyre and road. This melts the surface of the road resulting in 'shadow' marks being left on the road surface.
4. The wheel continues to be locked, sliding over the road surface.

Dark tyre marks are left on the road surface once the frictional temperature increases to a point where the surface melts. As the vehicle continues to slide its speed will decrease and tyre marks will continue to be left until either the vehicle slides to a stop or the driver reduces the pressure on the brake pedal.

Pedestrian collision: The body of the pedestrian and the car bear different marks depending on where and how they hit each other. If the pedestrian is hit below the waist, the body is thrown upwards and the vehicle passes under the pedestrian, so the pedestrian is 'run under'. If the pedestrian is hit above the waist, they are knocked down and 'run over'.

The tags on the victim's body shows where he was hit during the collision.

In our accident the pedestrian was run under so his initial velocity was the instantaneous velocity of the vehicle. He travelled through the air straight ahead of the vehicle until hitting the ground and was found a long way in front of the car which had decelerated to a halt. He had marks on his upper right leg, right abdomen, right shoulder and on the right side of his head. The car had marks on its bumper, the top of its bonnet and the windscreen.

The car was damaged where it was struck by the victim during the collision.

Witness statements: Further evidence about the collision comes from two fairly contradictory witness statements. The police had to determine if their accounts were true, or whether the witness got confused in some of the detail. It is an offence to give wrong information to the police, but people are bad at recalling events accurately. This is called 'rationalisation' and happens when you don't quite know what has happened so you unintentionally and subconsciously fill in any gaps in what you observe.

We had a flipchart page with six small sketches. When a whistle was blown we were given a few seconds to take in the pictures before they were covered over again. Not one student or adult correctly identified even five of the shapes and most of us made up items that were not present. We were all shocked at how badly we performed as witnesses.

Calculations

To calculate the speed of the vehicle at impact we needed an estimate of its deceleration as it skidded along the road. Crash investigators do a skid test to establish this value. Where possible they use the actual vehicle involved in the collision; otherwise they use a car of the same make and model loaded to the same extent. This is fitted with an accelerometer and is driven on the same road in the same weather conditions. The driver applies the brakes fully to lock all four wheels and stop the vehicle. The accelerometer shows the car's deceleration (its negative acceleration) in m s^{-2}. Two of these tests are carried out; if the results are within 10% of each other then the lower value is selected to use in the calculations.

Calculating initial speed

For our scenario, the crash investigators found values for the deceleration of -6.80 m s^{-2} and -7.01 m s^{-2}. The smaller result is used as it gives the lowest speed for any calculations made, giving the benefit of the doubt to the driver.

To calculate the car's speed when the driver braked, we used the formula $v^2 = u^2 + 2as$: The list in the margin shows the values:

$0 = u^2 + (2 - 6.8 \times 24.45)$

so $u^2 = 332.52$ and $u = 18.23$ m s^{-1} or 41 mph.

The driver was clearly exceeding the 30 mph speed limit.

Calculating impact speed

initial velocity u = ?
final velocity v = 0 m s^{-1}
acceleration a = -6.80 m s^{-2}
displacement s = 24.45 m

We measured from the centre of the front wheels back to where the skid mark deviated slightly indicating where the impact occurred. This was 7.17 m. Using the equation above we found the speed at impact to be 9.87 m s^{-1} or 22 mph.

We then asked ourselves: if the car had been travelling at the speed limit of 30 mph would the collision have happened? Using the same equation with an initial velocity of 13.4 m s^{-1} (30 mph) gives a stopping distance of 13.22 m.

Therefore had the car been traveling at 30mph it would have stopped approximately 4 m short of the pedestrian's position, and would not have hit him.

Our conclusion

The results clearly demonstrated that the driver was to blame as he was exceeding the speed limit. Had he obeyed the speed limit no collision would have occurred and the pedestrian would not have incurred life-limiting injuries.

The driver was banned from driving and spent 8 months in jail. Don't let something like this happen to you!

The work described in this article was supported thanks to a Partnership Grant from the Royal Society. In July 2014, students from Lockerbie Academy spent a week in London demonstrating their work at the Royal Society's Summer Science Exhibition.

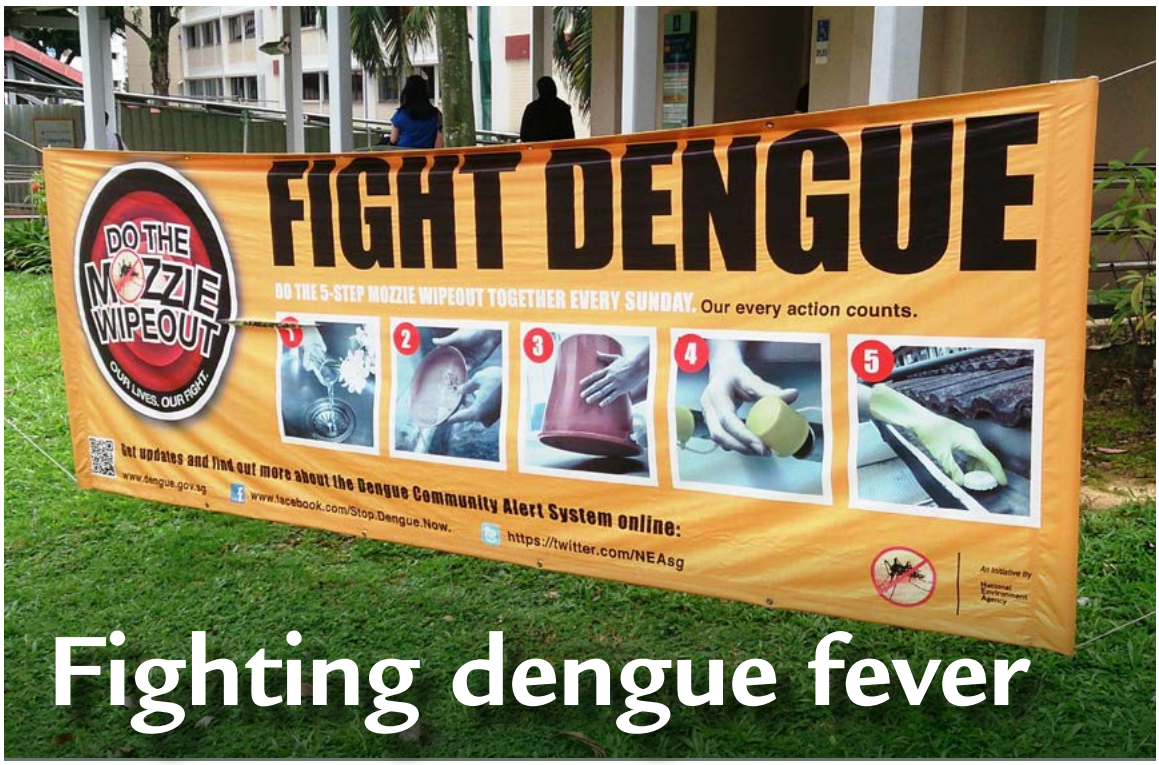
Jennie Hargreaves teaches science at Lockerbie Academy (www.lockerbieacademy.com). *We acknowledge the assistance of officers Neil Hewitson, Peter Monteith, Chris Parker, Alan Hope and Ewan Cannon from Police Scotland without whose help this project could not have happened.*

Look here!

Test your own ability as a witness.
http://www.youtube.com/watch?v=vJG698U2Mvo

Investigating the scene at Lockerbie Academy July 2013:
http://www.youtube.com/watch?v=MJbjKqPxUkY
http://www.youtube.com/watch?v=RY_GRIFcpeU

Stefania Hartley



Fighting dengue fever

Key words
virus
dengue fever
mosquito
bacteria

Stefania Hartley is a science teacher who grew up in Sicily. She now lives in Singapore where she recently contracted dengue fever. She decided to take a closer look at this disease which, according to the World Health Organisation, is the fastest-growing mosquito-borne disease in the world.

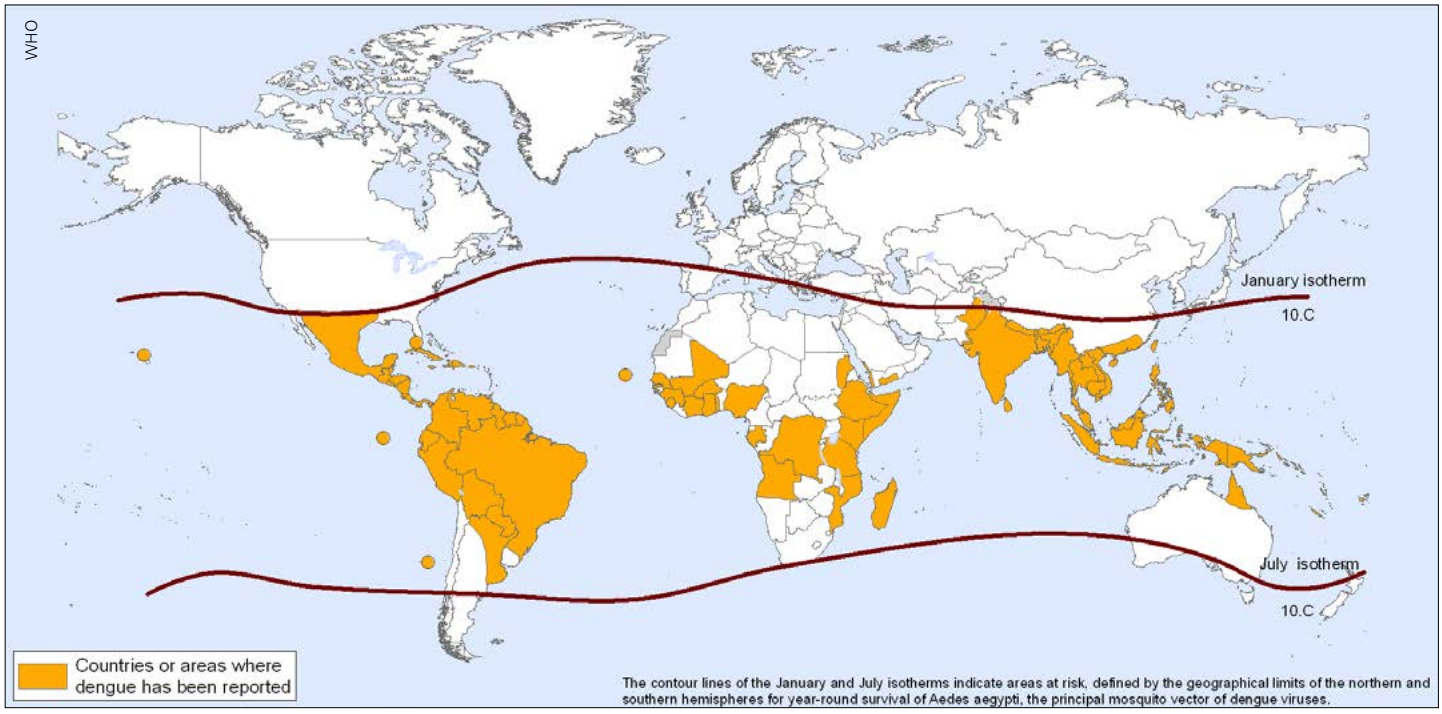
A growing concern

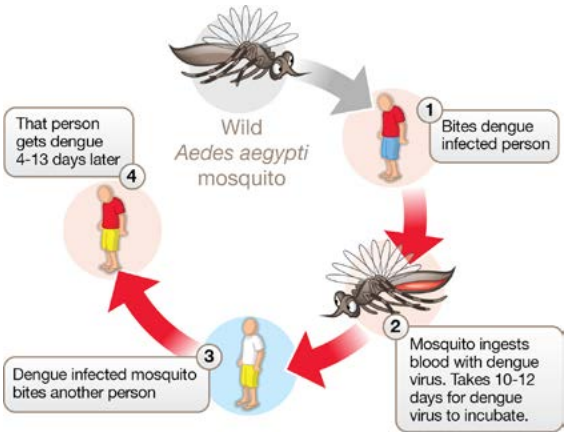
Rates of dengue infection increased thirty-fold between 1960 and 2010, with the disease spreading to countries that had never seen it before (from 9 countries in 1970s to over 100 now). More than 2.5 billion people – about 40% of the world's population – are currently at risk and more than 50 million people contract the disease every year – I was part of the 2014 batch!

Historically affecting only tropical climates, the adaptation of the vector (all the technical terms are explained in the glossary) mosquito to cooler climates is causing the disease to spread to new areas outside tropical regions. In 2010 some local cases of dengue were reported in France and Croatia and in 2012 an outbreak of dengue in the Portuguese island of Madeira caused 2000 infections.

Dengue virus

The dengue virus belongs to the family *Flaviviridae* and is passed from one human host to another through the bite of the mosquito *Aedes aegypti*, the main vector.





The Aedes aegypti*-dengue lifecycle*

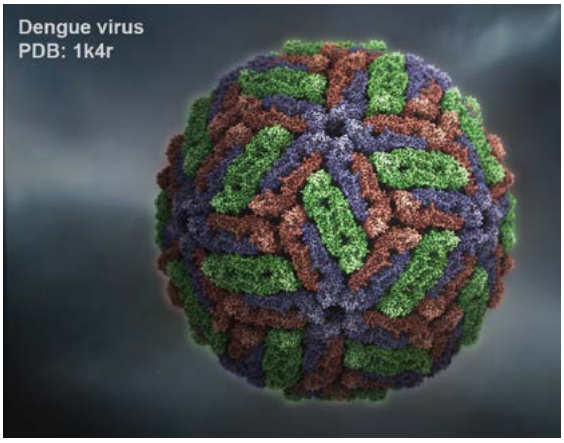
Unlike other mosquitoes, *Aedes aegypti* bites during the day. It thrives in urban habitats, where it breeds in stagnant water found in man-made containers. *Aedes albopictus*, a less common dengue vector, is further cause for concern because, being able to tolerate cooler temperatures, it is spreading to North America and Europe, mostly through the import of goods like used tyres and lucky bamboos (which are mosquito breeding habitats).

'Lucky bamboo' (actually not bamboo but Dracaena braunii*) is often imported in water to keep the plants green. The water can harbour* Aedes albopictus*, a vector of the dengue fever virus.*

Pathogenesis

After a female *Aedes* mosquito takes a blood meal from an infected person, the virus gradually spreads through the body of the mosquito until it reaches the salivary glands. It takes 8-10 days for this to happen (extrinsic incubation) and, from then on, the mosquito will transmit the virus through its saliva at every bite, for the remaining 2-4 weeks of its life.

The dengue virus (a lipid-enveloped positive-strand RNA virus) binds to and enters white blood cells, causing symptoms ranging from mild to severe (in 6% of cases), resulting in death in about 2.5 % of cases.



A model of the dengue virus – the different colours represent different regions of its surface; image from PDB 1k4r by J.Y.Sgro, UW Madison

Initial symptoms are non-specific: fever, severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands, gum bleeding and rash. If the disease progresses into severe dengue, the liver and the bone marrow can also be affected, causing a drop in blood pressure, platelet and white blood cell counts. Liver enlargement, respiratory distress and damage to various organs with spontaneous internal haemorrhages can also occur. There is no cure for dengue fever so patients are given palliative care and hydration to counteract the leakage of plasma out of the blood vessels. In some cases, blood transfusions are necessary.

How the viruses cause all of this (the pathogenesis) is not entirely known. The intriguing fact is that the highest risk of developing severe dengue doesn't occur during the peak of fever and virus count, but only afterwards, when the patient seems to be recovering. This suggests that the body's immune response might be the cause for the increased severity of the symptoms. The discovery of antibodies against the patients' own platelets, endothelial cells and coagulatory molecules in the blood of patients with severe dengue, support this hypothesis.

Vaccine development

There isn't yet an effective and safe vaccine against the dengue virus, although there are a few at various stages of trial. Developing a vaccine is proving difficult for several reasons:

Our knowledge of the pathogenesis of the disease is incomplete.

There are five types (serotypes) of the virus (the fifth one only discovered in 2013).

There is a danger of Antibody-Dependent Enhancement (ADE), which make it paramount that the vaccine should be equally effective against all serotypes (see Box).

There are no suitable animal models for trials: the dengue virus replicates poorly in mice.

There is a need to keep the cost of the vaccine affordable to those who most need it.

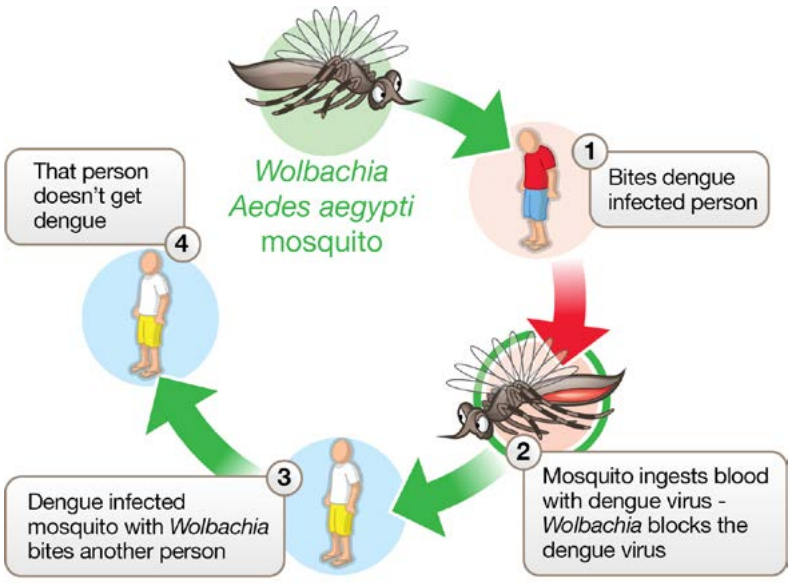
Immunity and reinfection

Once infected with one serotype, patients have lifelong immunity to that serotype but cross-immunity to the other serotypes is partial and short-lived. To make matters worse, patients are at increased risk of developing severe dengue if subsequently infected with one of the other serotypes. The explanation for this is a mechanism called Antibody-Dependent Enhancement (ADE). Some of the antibodies in an ex-dengue patient will partly recognise the new infecting serotype but will be unable to neutralise it. The virus-antibody complex will gain entry into the white blood cells (even those white cells which do not have the usual surface receptors to which the virus binds) through their Fc receptors – those which bind to the Fc region of the antibody.

Vector control

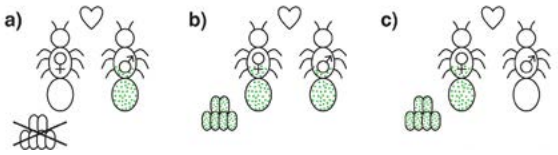
Without a vaccine and without a cure, it's not surprising that vector control is currently the method of choice in the fight against dengue. The firm Oxitec has produced genetically modified *Aedes* mosquitoes which, released into the wild, will mate with their wild counterparts and pass on their lethal traits (features) to their offspring. This method requires periodic releases of GM mosquitoes, as the lethal traits cannot perpetuate themselves.

Another approach, using the *Wolbachia* bacteria, has been developed and tested by a research group at Monash University, Melbourne, led by Prof Scott O'Neill. *Wolbachia* bacteria are naturally found in about 60% of all insect species – not including *Aedes aegypti*. The research group has infected *Aedes aegypti* mosquitoes with *Wolbachia* bacteria and discovered that the presence of *Wolbachia* reduces the mosquito's ability to transmit dengue viruses.



The Wolbachia*-mosquito lifecycle*

Furthermore, once *Wolbachia*-infected mosquitoes are released into the wild, the *Wolbachia* infection spreads through the wild population, so that after only about 17 weeks all the mosquitoes in area will carry *Wolbachia*. This method is thus low-cost and self-sustaining.



How Wolbachia *spreads:* **a** *When a non-*Wolbachia *female mates with a* Wolbachia*-infected male, the eggs do not hatch;* **b** *and* **c** *The eggs of a* Wolbachia *female are infected whether or not the male is also infected.*

Dengue is very common in Brazil. Here the first release of Wolbachia *mosquitos occurs in Tubiacanga near Rio De Janeiro.*

The *Wolbachia* method has also been proven to reduce the *Aedes* mosquito's ability to transmit other viruses for which it is a vector (Chikungunya and yellow fever) and there is hope that this approach will also work on the mosquitoes that transmit malaria and other diseases.

Stefania Hartley lives in Singapore.

Glossary

Extrinsic incubation: the period between when a vector acquires the infectious agent and when it starts being able to transmit the agent to the host.

Pathogenesis: the mechanism that causes the development of a disease, including cellular events and reactions.

Palliative care: care that relieves the symptoms rather than eliminating the causes.

Serotype: within a species, a group distinguished by different antigens.

Vector: an insect or animal that transmits a disease or parasite from one animal or plant to another.

Look here!

More about the fight to eliminate dengue fever: *www.eliminatedengue.com*

Make a model of the dengue virus: *http://bit.ly/1oQ2YXK*

MeiTeng

Try This

Banana blues

As a banana ages, black spots appear on the ripening skin. Shine ultraviolet light on them and you will see an amazing blue, fluorescent ring around each black spot.

You will need

- a banana that is just ripe and beginning to get a few black spots on its skin
- an ultraviolet torch – I bought myself a cheap UV keyring torch

Bananas that look like this are perfect for this experiment; avoid bananas that are brown and mushy.

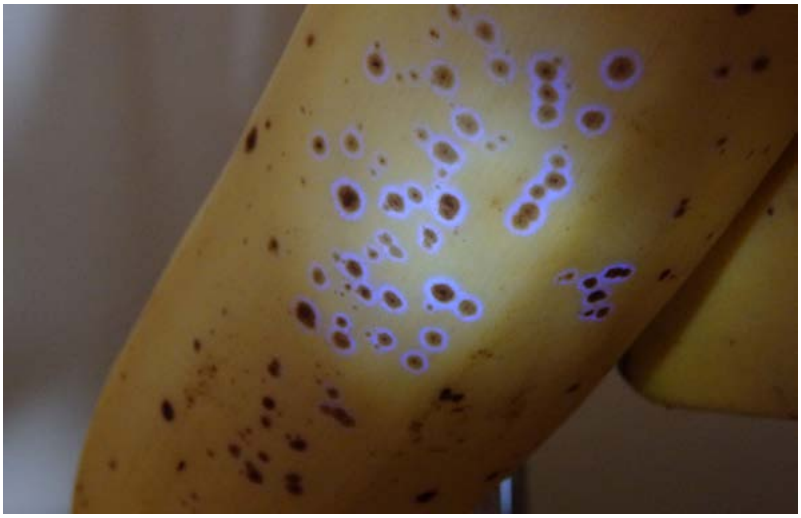
What you do

Place the banana in a darkened place (e.g. a cupboard or cardboard box). Shine your torch on the banana and observe the fluorescent ring around each spot. You may also notice that the yellow skin is giving off a less intense blue fluorescence too.

What's going on?

As a banana ripens, its skin changes colour from green to yellow. Research carried out in the last twenty years has shown that, during ripening, chlorophyll molecules in the skin of the unripe banana are broken down to into smaller, colourless molecules. With the loss of the green chlorophyll, the yellow pigments in the banana skin can be seen. In ultraviolet light, the small, colourless molecules produce the less intense blue fluorescence in the yellow banana skin.

The black spots that form on the skin of a banana as it ripens are the result of a process called apoptosis, or programmed cell death. These black spots begin to from around stomata in the banana skin and consist of dead cells. Scientists have discovered that it is the dying cells at the edge of each spot that emit the very intense blue fluorescence.



Fluorescing banana spots observed in a darkened room

Fluorescence and ultraviolet light

A UV torch emits light of wavelength between 380–420nm, at the boundary of the UV-A and visible spectrum. Light of this wavelength is not hazardous and these sorts of lights are often used to test banknotes. **Take care!** You must avoid looking directly at the UV LEDs when they are illuminated and must not shine their light directly into the eyes.

Fluorescent substances absorb light of one wavelength and re-emit the energy as light of a longer wavelength. UV is invisible to our eyes but the blue light emitted by the banana's spots has a wavelength in the visible part of the spectrum.

Gary Skinner is Biology editor of Catalyst.

Look here!

Read a scientific review of this topic, by Thomas Müller Bernhard Kräutler from the University of Innsbruck, Austria: *www.karger.com/Article/Pdf/321877*

Ashok Sakhardande

Inside the teenage brain

Key words
brain
neurons
adolescence
MRI scan

What differentiates a 14-year-old from their 40-year-old parent? Some people may say it's their taste in music, food and clothes. Other people may say it's the way they talk, what they do for fun and whether they watch the news. Neuroscientists think the answer, at least partially, lies in their brains. To explain why, we first need to understand what the brain is made of.

What is the brain made of?

The human brain is made of 86 billion (86 000 000 000) brain cells known as neurons that work a little bit like the crocodile clips and wires used in science lessons. Just as crocodile clips can connect to other crocodile clips, neurons connect up to other neurons. We can call the two ends of a neuron end A and end B (see Figure 1). End A, the axon terminals, connect up to end B, the dendrites in another neuron. This connection is called a synapse.

When a neuron 'fires', an electrical signal runs from the dendrites, along the axon, to the axon terminal. This causes a tiny chemical signal (a neurotransmitter) to be released, from the axon terminal of the first neuron, across the synapse, into the dendrite of the second neuron, causing that neuron to 'fire'. This is very similar to electrons passing between the crocodile clips in electrical circuits. Additionally, whereas crocodile clips are covered with rubber to insulate the wires underneath, neurons are covered with an insulating layer of fatty cells called the myelin sheath. This layer of insulation helps to make the signal faster and more efficient, preventing it from being lost or weakened as it passes down the axon.

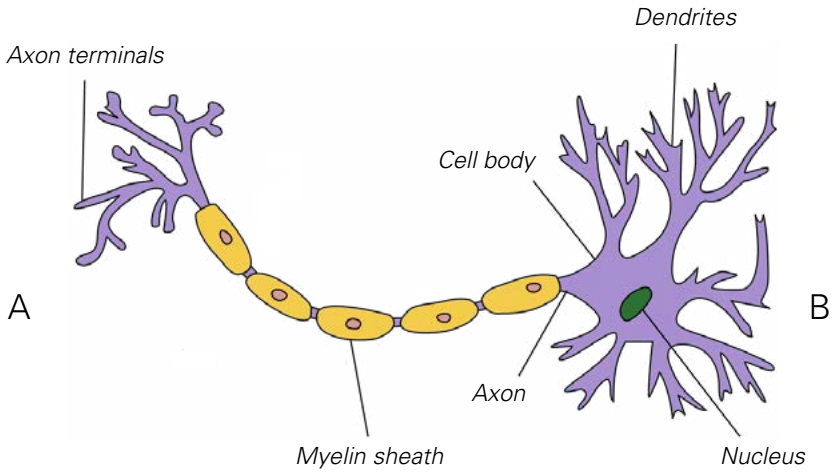


Figure 1 *A typical neuron or brain cell*

Within the brain a single neuron can connect up to thousands of other neurons, forming a vast, complex network of dendrites, axons and axon terminals. As can been seen in Figure 2, this network can be classified as two different types of matter; grey matter, containing the nucleus, dendrites and axon terminals (i.e. the connections); and white matter, containing the axons and myelin (i.e. the wires).

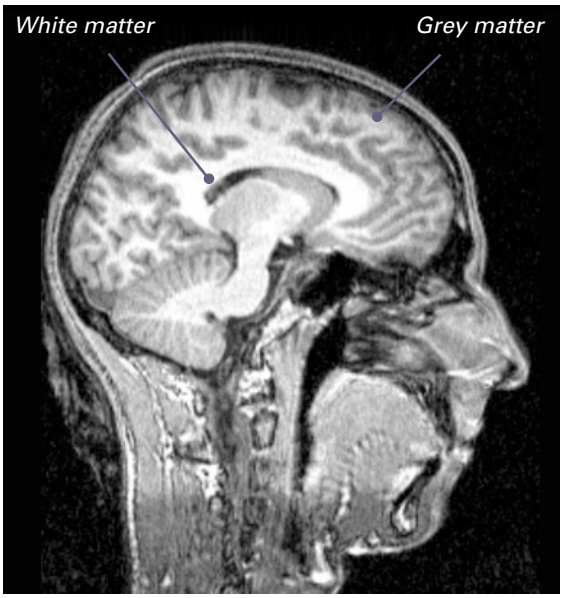


Figure 2 *A structural MRI scan of the author's brain showing white and grey matter*

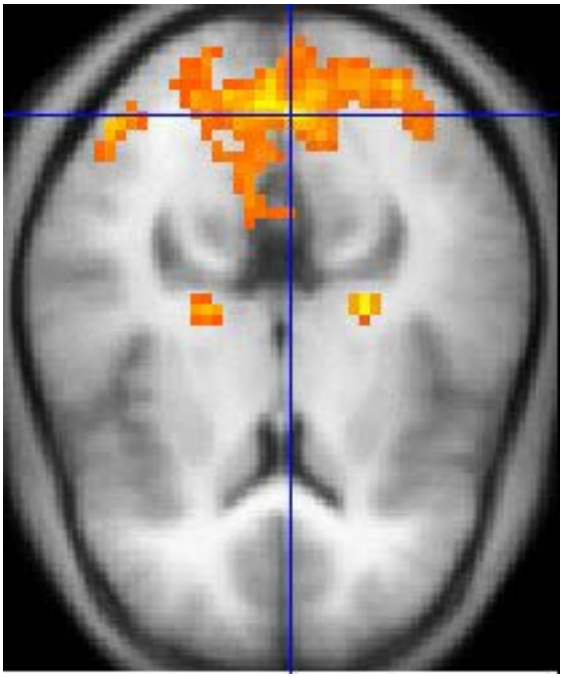


Figure 3 *A functional MRI image showing brain activity. The warmer colours (yellow and orange) indicate an increase in blood flow. This image shows activation in the area of the brain responsible for vision.*

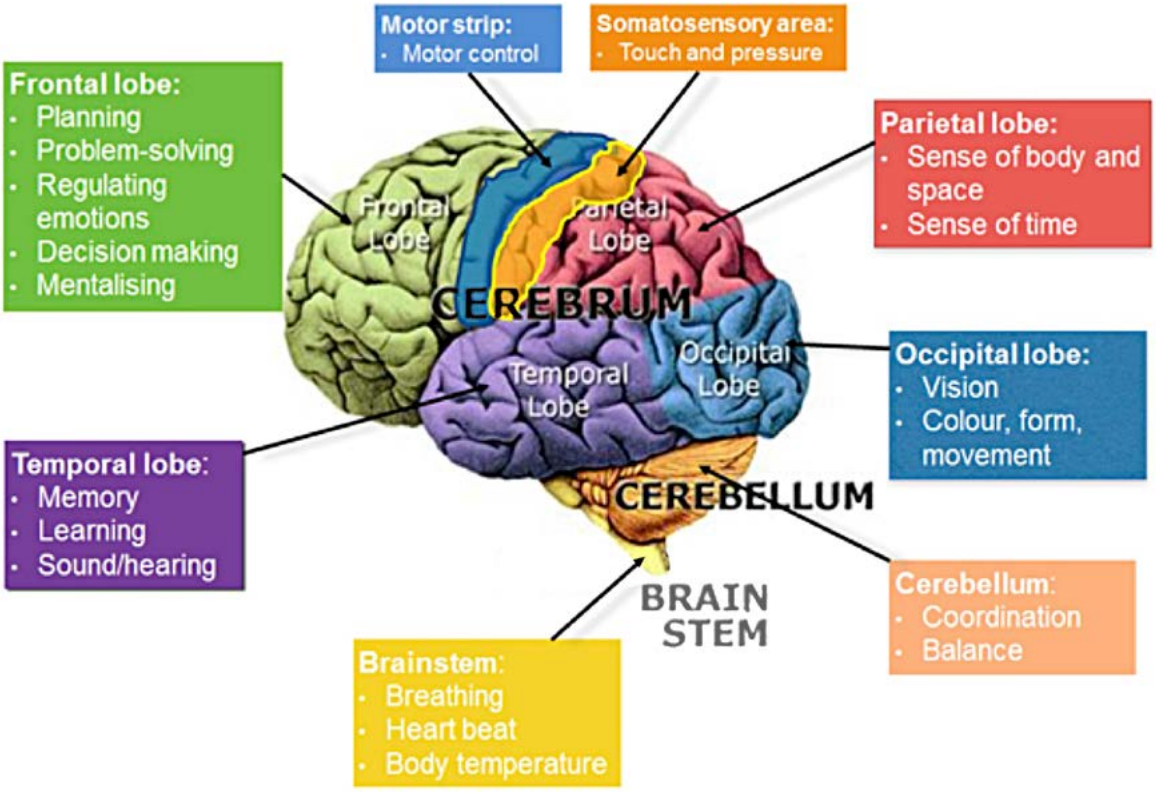


Figure 4 *A map of the human brain showing the areas of different brain function*

How do you study the brain?

In the past we could only learn about the brain through studying patients who had sustained head injuries, dissecting their brains after they had died. Now, new technologies such as magnetic resonance imaging (MRI) allow us to look inside the living human brain. MRI scanners are giant ring shaped magnets that are hooked up to a computer. These magnets can be anything between 50 000 and 100 000 times the strength of the Earth's magnetic field. In the scanner, pulses of radio waves are sent into the brain where they are absorbed by the brain tissues. The energy of the absorbed waves is gradually re-radiated and this tiny signal is detected and fed into a computer to generate an image of either brain structure or brain function.

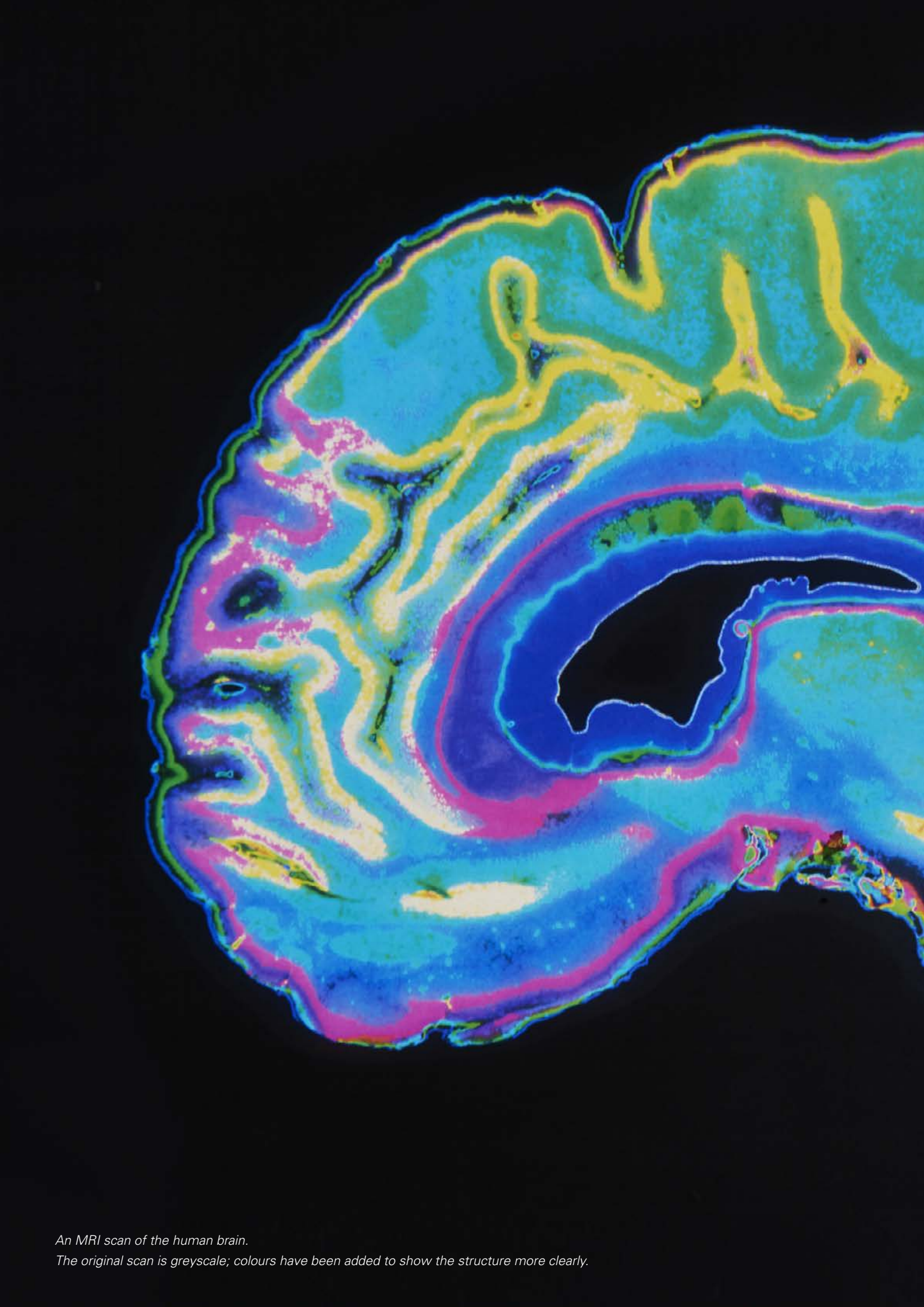
Different parts of the brain contain different concentrations of water (H_2O). MRI scanners can detect the signal given off by the hydrogen (H) atoms; the signal differs slightly depending on the concentration of water in a given brain region. These signals are then used to produce an image of brain structure (Figure 2 opposite).

Like the muscles in your body, the brain needs blood to work properly. When neurons in one part of the brain start to fire, blood flows to that region of the brain to provide it with oxygen. MRI can be used to study where in the brain blood is flowing to and this can be correlated with the task a person is performing (Figure 3). This process is known as functional MRI and scientists have used it to find out what bits of the brain 'light up' when we perform a range of tasks. This has given us a map of brain regions and the functions they are involved in (Figure 4).

Brain changes during adolescence

Prior to the invention of MRI scanners, little was known about how the brain changed during the teenage years but now a number of studies have been conducted that shed light upon this issue. By scanning volunteers aged 5-20 researchers have found that white matter increases and grey matter decreases (Figure 5) during this time. The increase in white matter suggests that, throughout the teenage years, axons get covered in more and more myelin. The decrease in grey matter suggests that neurons lose connections with other neurons.

Lastly, researchers have found that different regions of the brain develop at different times (Figure 6). Notice in the figure how the yellow colour (indicating loss of grey matter) moves from the back of the brain to the front of the brain as we move through our teenage years. Regions of the brain involved in simpler processes, like vision and hearing in the occipital lobe, develop earlier than regions of the brain involved in more complex operations like thinking about the future and other people, in the frontal lobe. Together these factors result in efficient and specific brain networks that develop at different ages.



An MRI scan of the human brain.
The original scan is greyscale; colours have been added to show the structure more clearly.

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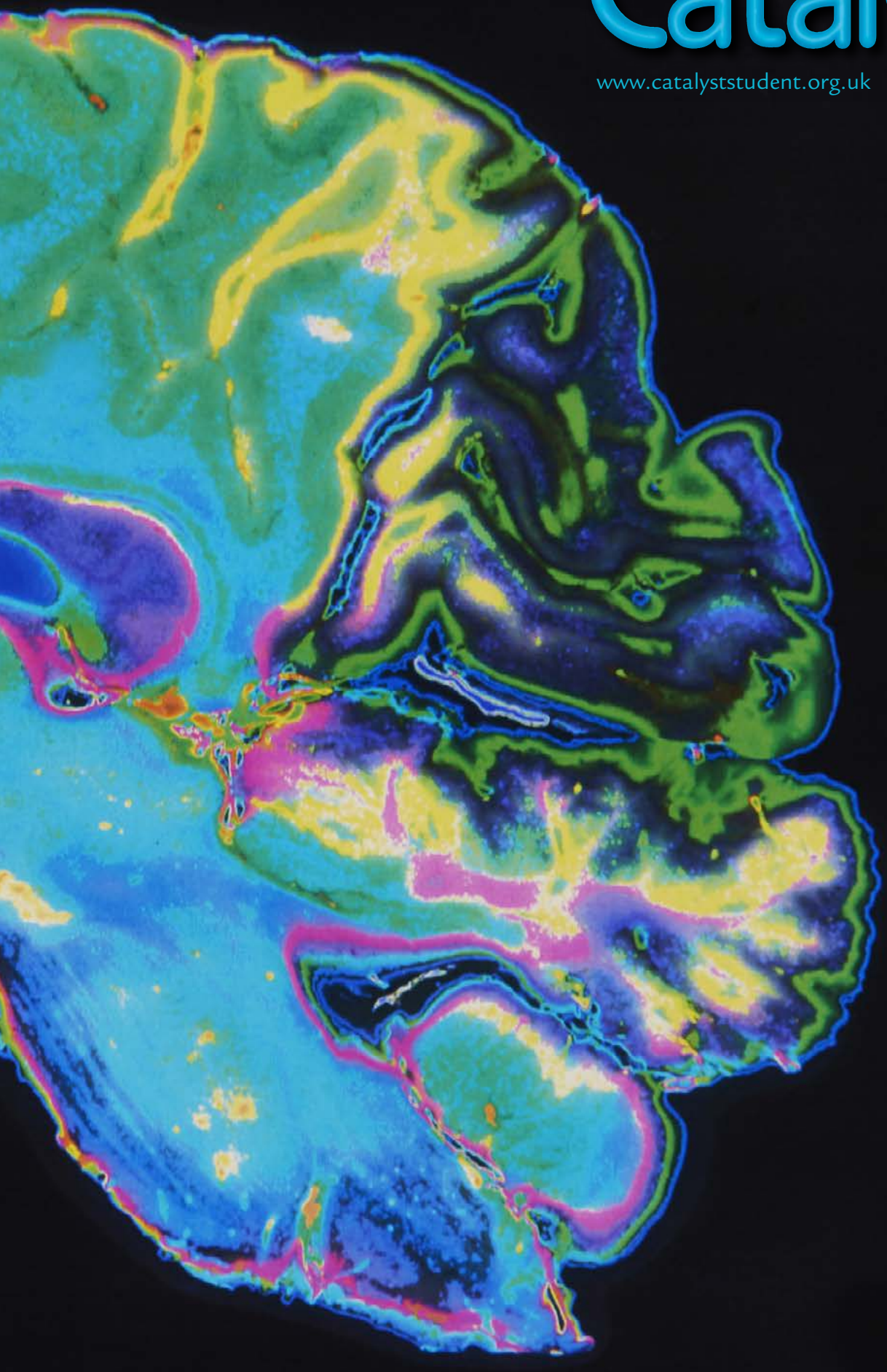

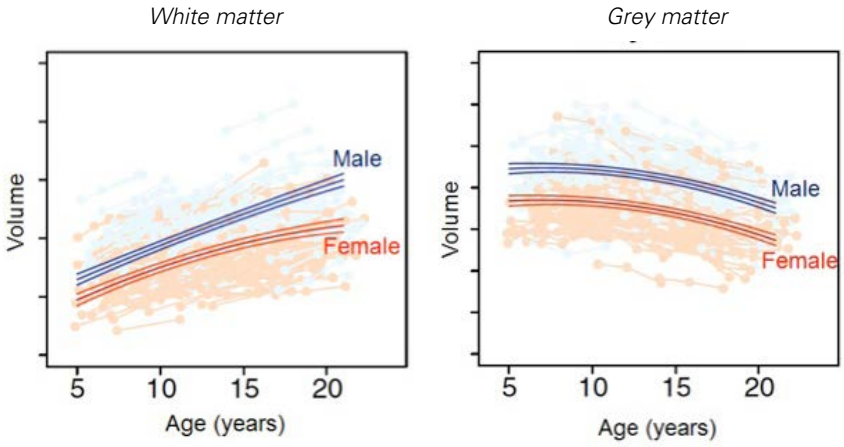

Figure 5 *Graphs showing* ***a*** *white matter increase and* ***b*** *grey matter decrease during the teenage years.*

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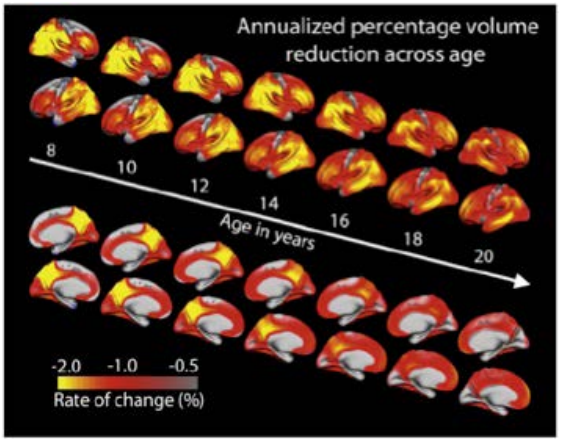

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Figure 6 *A heat map showing brain change during the teenage years. The top two rows show the outer surface of the brain (with the brain facing right then left); the bottom two rows show the inside surface (brain facing left then right). Yellow indicates a large change, red indicates a smaller decrease, grey indicates little change.*

How do brain changes affect behaviour during adolescence?

As we've seen, during adolescence the changes occur in the brain in regions responsible for planning, emotion regulation, understanding other people and a variety of other functions. What behaviours do you therefore predict may change during your teenage years? Researchers asked themselves this question and came up with a number of ideas. One group thought that teenagers may respond differently to social exclusion ('being left out of a group') as this uses both emotion regulation and our ability to understand other people.

To investigate the effect of social exclusion the group asked teenage and adult volunteers to play a game of catch on a computer with two other players who were not in the room and that they had not met (Figure 7). In one version of the game volunteers were thrown the ball regularly (i.e. they were included) and in the other they were only thrown the ball once (i.e. they were excluded). Before and after playing the game volunteers were asked to answer some questions about their mood, this allowed the researchers to study how the game affected the volunteers.

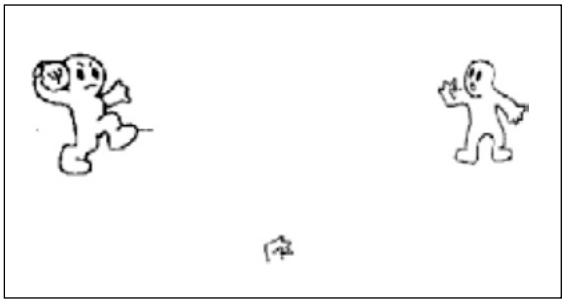


Figure 7 *A virtual, on-screen game of catch. You are represented by the hand at the bottom of the screen, the other two players are shown above.*

The researchers found that when volunteers, of any age, were not thrown the ball they reported feeling excluded. This suggests that the online game used in the study produced similar feelings to being left out of a game of catch in the real world.

Interestingly, only the teenage volunteers reported having a worse mood and greater anxiety after playing. This result suggests that teenagers are particularly vulnerable to the effects of social exclusion, as you might predict given that the frontal region of the brain responsible for mood regulation and understanding other people is still developing.

Another study used the same method except volunteers had their brains scanned whilst playing the task. This study reported that teenagers showed less activity in a region of the frontal lobe responsible for mood regulation, supporting the theory that differences in brain development may be responsible for differences in behaviour between teenagers and adults.

What does this all mean?

As more and more studies report changes in the frontal cortices during the teenage years, researchers are asking more and more questions about how these changes affect teenagers' behaviour. Some of the main questions being asked relate to how other people affect the way we think and act, why teenagers take more risks than people of other ages and whether changes in our brain affect how we think and learn.

The field is still relatively young with new questions being asked all the time. Although this article has focused on the frontal lobes, large questions still remain about what effect changes in the parietal and temporal cortices have during the teenage years. What effect do you think brain changes have had on your behaviour?

Ashok Sakhardande works in the Institute Of Cognitive Neuroscience, University College London

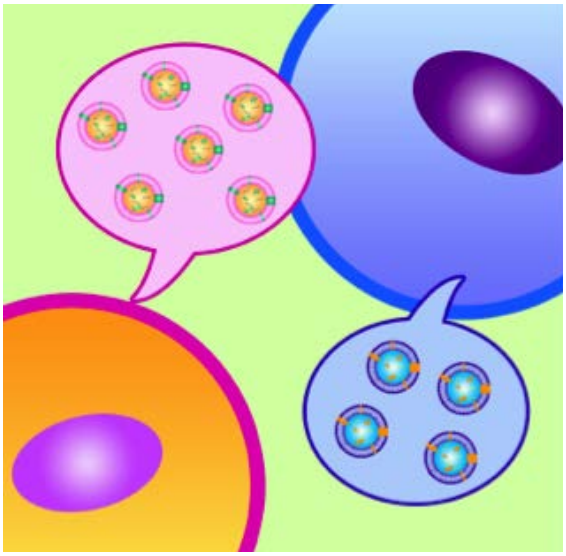
Express delivery

Good things come in small packages!

Laura Mulcahy

Key words
cells
communication
communication
microscopy

Have you ever waited all day for a parcel to arrive? Looking out of the window every five minutes in hope of a glimpse of the postman, you refuse to leave the house and watch the clock as the minutes slowly tick by. Parcels are also delivered to cells inside the body, but your cells do not wait all day; little packages, scientifically referred to as exosomes, are constantly being delivered to cells. The time between release of exosomes from the cells where they are produced to their delivery to recipient cells can be as short as 30 minutes. Exosomes are carried in biological fluids, most commonly in the blood.



Different types of cell produce different types of exosome.

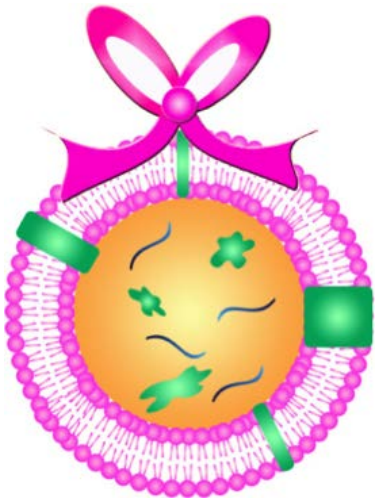
Small packages

In order to maintain life it is vital that all 37 000 000 000 000 (37 trillion) of our cells communicate with each other. There are many processes through which this occurs. Hormones and neurotransmitters are the best described forms of intercellular communication; however exosomes also participate substantially in cell-to-cell signalling. Unfortunately, due to their excellent communication ability, exosomes also support disease development.

Exosomes are approximately 30-120 nm in diameter; this is 20 times smaller than bacteria, about the same size as a virus. In order to examine exosomes they are extracted from biological fluids by ultracentrifugation for at least 60 minutes at 100 000 *g* (*g* = acceleration due to gravity).

Wrapping paper

Exosomes are delivered to neighbouring cells or distant organs in the same way that packages can be distributed both nationally and internationally. In same way that we might wrap a parcel with packaging suitable for the recipient – for example, (excuse the stereotypes!) pink wrapping paper for girls and blue wrapping paper for boys – exosomes do the same. They encase their cargo in a lipid shell which displays different proteins on the surface to ensure interaction with the correct recipient cell.



An exosome is a package delivering material from one cell to another. Its outer membrane is a double layer of lipid molecules.

Unlike most good delivery services though, it is likely that only a small percentage of exosomes reach their target cell. For this reason excessive numbers of exosomes are released to maximise the chance of signal transfer. Some exosomes may carry messages suitable for receipt by more than

one cell type so their surface may be less specific; comparable to Christmas wrapping paper – suitable for all.

It is also important that the contents of the parcel are protected. The exosomal membrane is less fluid and more stable than the cell membrane despite being made of the same components. This is due to the rigidity of the exosomal membrane caused by enrichment in cholesterol and lipid raft domains which are compact structures made of densely packed lipids and proteins; they reside on the plasma membrane (which is much more fluid structure) much like boats (or rafts, hence the name) out at sea. This is thought to help exosomes stay intact and maintain their spherical structure, even in harsh conditions, such as high or low *p*H, that they often become exposed to during transit.

Packing a parcel

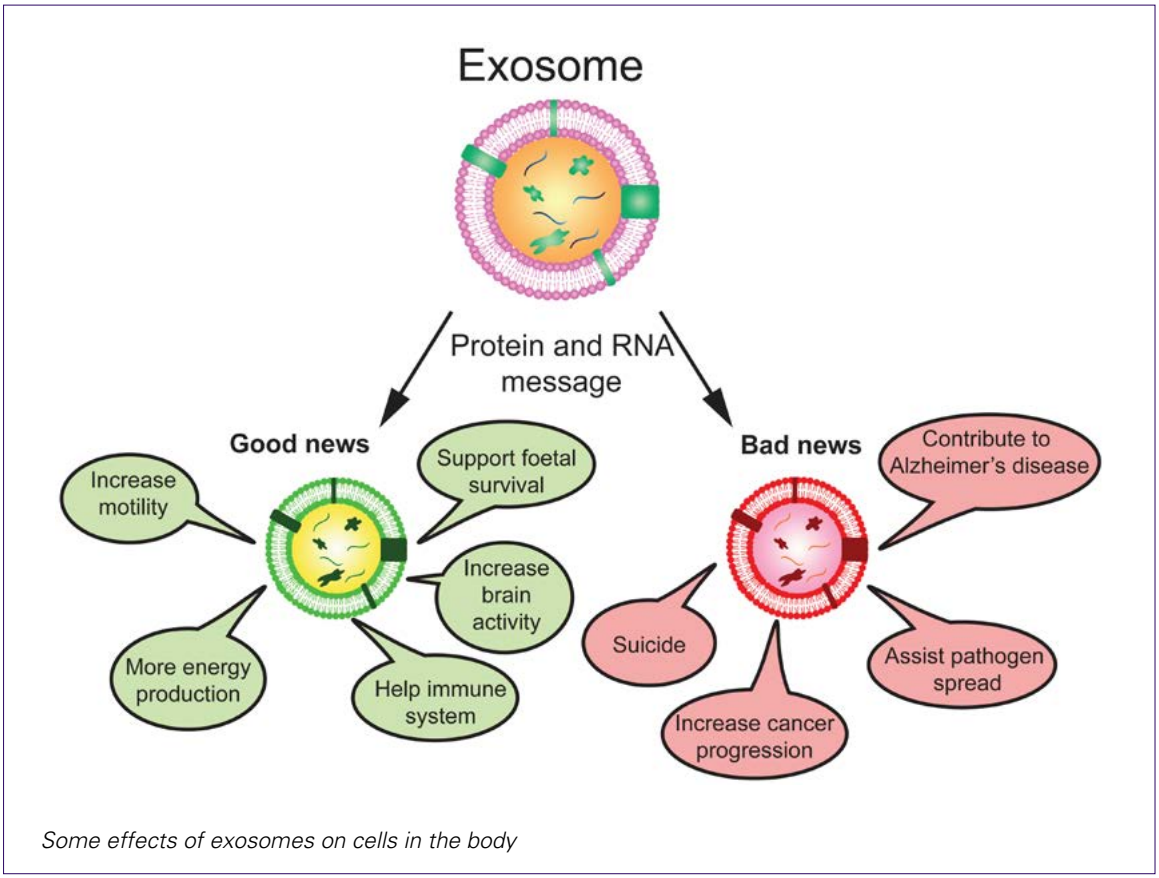
Exosome assembly is not a process that occurs at random. Exosome cargo is carefully selected during biosynthesis. Proteins including Alix and heat-shock protein 70 (HSP70) are exosomal markers. Markers are proteins that are used to identify biological structures because they are known to be associated with that structure. The contents are often representative of the cell of origin, but are also tailored to the recipient cell.

Once the exosome content has been selected, the endosomal sorting complex required for transport (ESCRT) machinery and associated proteins begin to fold the endosomal membrane inwards, encasing the selected cargo. This process forms intraluminal vesicles (immature exosomes) that remain held inside the endosome (a component of the cell responsible for transportation of molecules). When the endosomal membrane fuses with the plasma membrane, exosomes are released into the external environment, ready to interact with target cells.

Good news, bad news?

Our actions, as a result of receiving a parcel or letter, differ, depending upon its contents. In the same way, a cell changes its activity depending upon the exosome message it receives. Exosomes carry messages in the form of proteins and ribonucleic acids (RNA). These molecules have the potential to alter gene expression, and hence protein synthesis, in the recipient cell which can dramatically change its characteristics. For example, the cell may decide to move or make more energy or even commit suicide in response to an exosomal message.

Exosomes deliver good news in many situations. For example, they assist with identification of invading microbes in the immune response, contribute to brain development, and support foetus survival in pregnancy. However exosomes can also deliver bad news. They facilitate development of numerous diseases. Exosomes encourage cancer progression by promoting tumour development growth. They also assist pathogen spread during infection and contribute to the development of Alzheimer's disease. Additionally, exosome concentration in the biological fluids of disease sufferers is elevated. This increase in exosome numbers also contributes to development of disease and hence may one day assist with disease diagnosis.

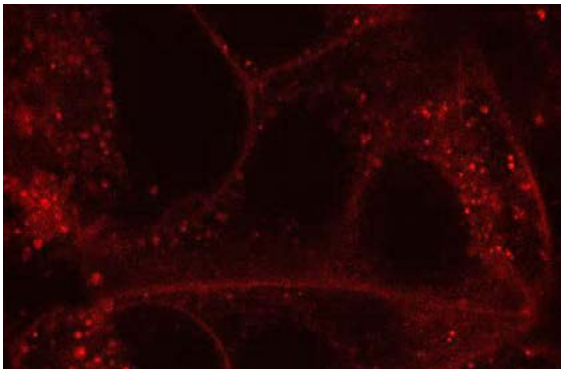


Some effects of exosomes on cells in the body

Despite significantly contributing to disease development it is important to note that no diseases to date have been found to be caused by 'bad' exosomes. It rather appears that 'bad' exosomes are a consequence of disease. Because of their unique durability and transport capabilities, exosomes show great potential as future therapeutic drug vehicles. I sincerely hope that one day it will be possible to isolate exosomes from a patient, manipulate their external appearance (to ensure they target specific tissues), and load them with relevant therapeutics that will fight disease upon re-administration to the patient.

What next?

In my current research, I am using fluorescent lipid stains to label the lipid-rich membranes of exosomes. Using a confocal microscope at ×630 magnification, I am able to watch exosomes enter cells (see Box). I plan to test a range of chemicals to see which ones are able to enhance or prevent exosomes from communicating with cells. Recently, for example, it was shown that heparan sulphate proteoglycans may help exosomes to enter mammalian cells.



Fluorescent exosomes inside cells, magnification ×630.

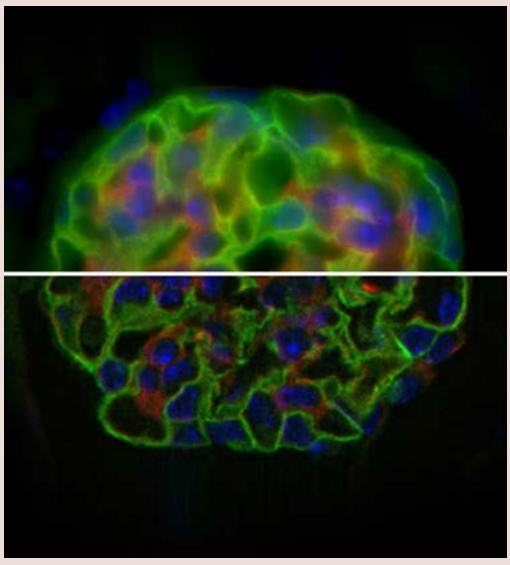
Summing up

Exosomes provide an 'express' delivery service from one cell to another; they can transport messages in just 30 minutes. They help regulate homeostasis which controls vital biological processes; in fact, it is highly likely that without exosomes human beings would not be able to maintain life, so we really have a lot to thank them for.

Laura Mulcahy is a PhD student researching the role of exosomes in cellular communication at Oxford Brookes University

Confocal microscopy

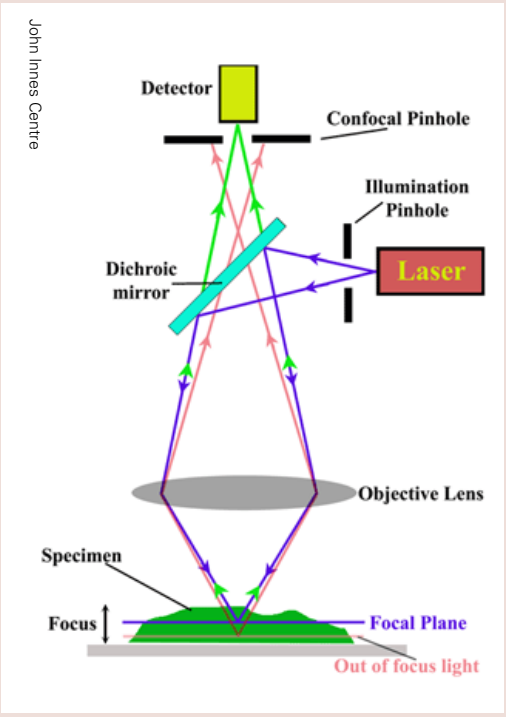
Conventional microscopy often gives rise to blurred images due to light from regions outside the focal plane of the microscope. In fluorescence microscopy, where molecules are labelled in order to see where they end up, as here on a cell, it is important that the image shows only a restricted region. Conventional microscopy gives a haze around the image, whereas with confocal microscopy, this is largely removed, giving a much clearer image.



AOMF,University Health Network, Toronto, Canada

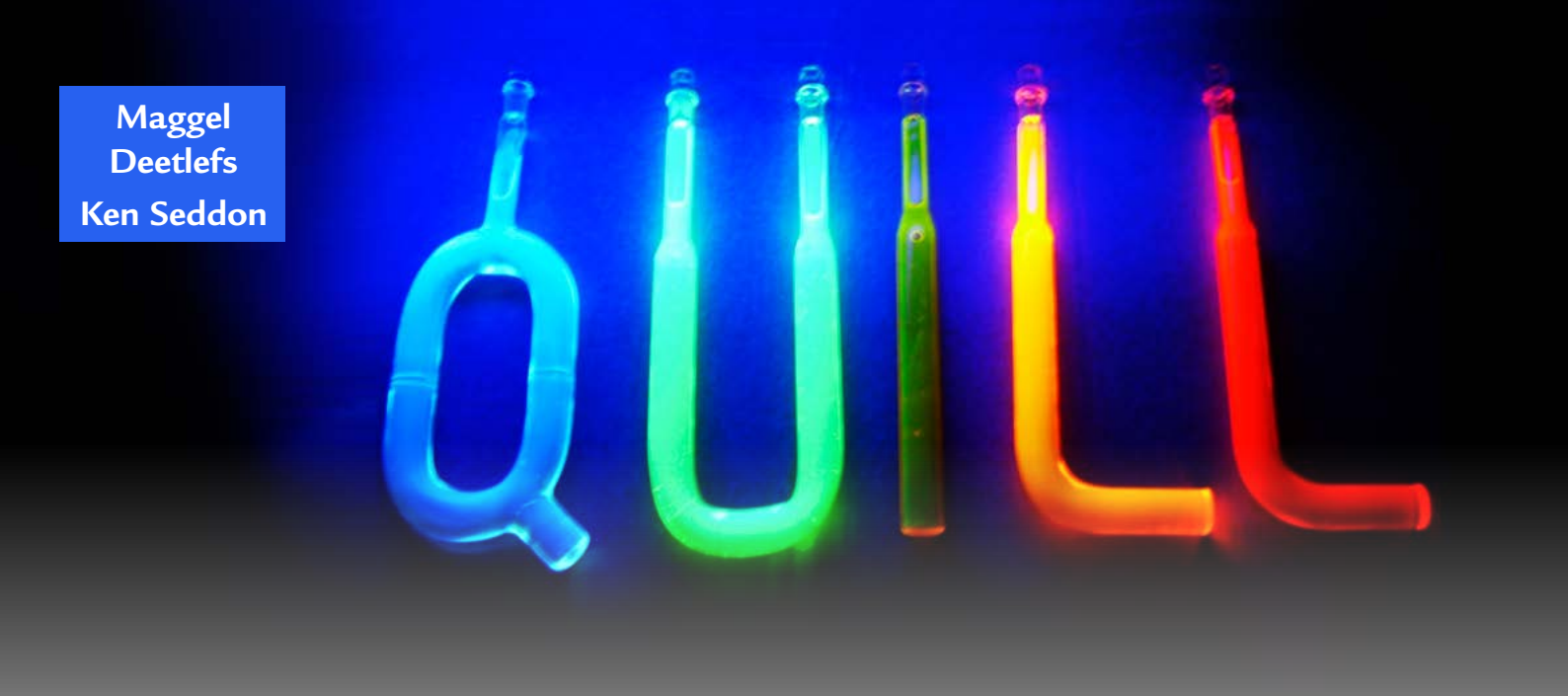
Mouse kidney section seen with a conventional light microscope (top half) and with a confocal microscope (bottom half). In this image, cell nuclei are blue.

How does a confocal microscope work? The object is viewed through a pinhole so that only a tiny area, at the focal point, is seen at any instant. Light coming from other areas of the object is blocked. The microscope scans across the object and gradually builds up a clear image on a screen.



How a confocal microscope works: only light coming from one point on the specimen (green rays) reach the detector. The confocal pinhole blocks light from out-of-focus points (brown rays).

Maggel Deetlefs
Ken Seddon



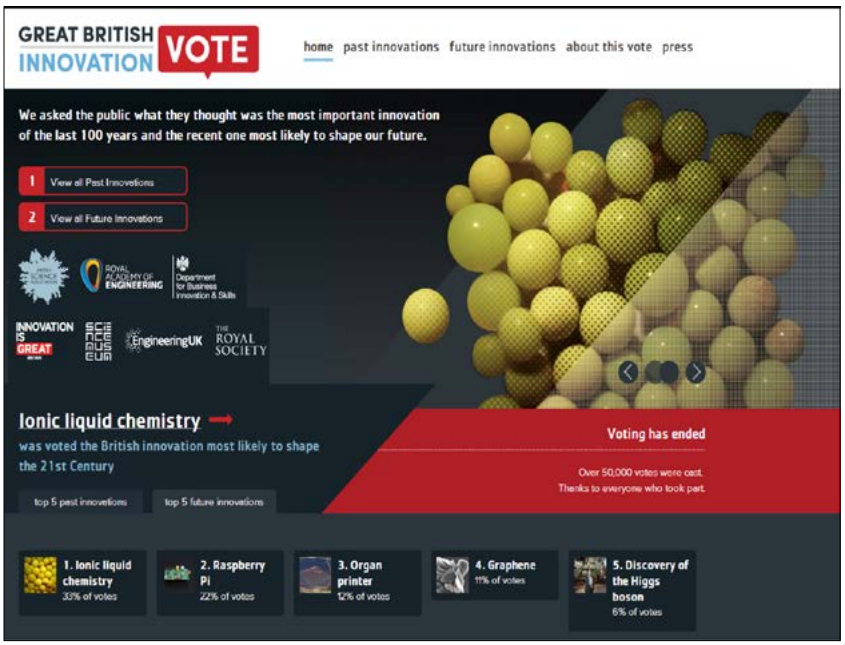
Ionic liquids can be made in a range of colours. QUILL is the Queen's University Ionic Liquid Laboratories in Belfast.

IONIC LIQUIDS

The discovery most likely to shape the 21st century

Key words
liquids
ions
solvents
green chemistry

A new class of fluids, called ionic liquids, are revolutionising the world of chemistry. In 2013, they were voted as the British innovation most likely to shape the 21st century, in a nationwide poll organised by the Science Museum (image 1). In 2014, they were also featured in the prestigious Royal Society Summer Science Exhibition. Ionic liquids are currently being used in industry and in our homes, and they have also won many awards for their pollution-fighting abilities. But what exactly are these liquids, and why are they taking the world by storm?

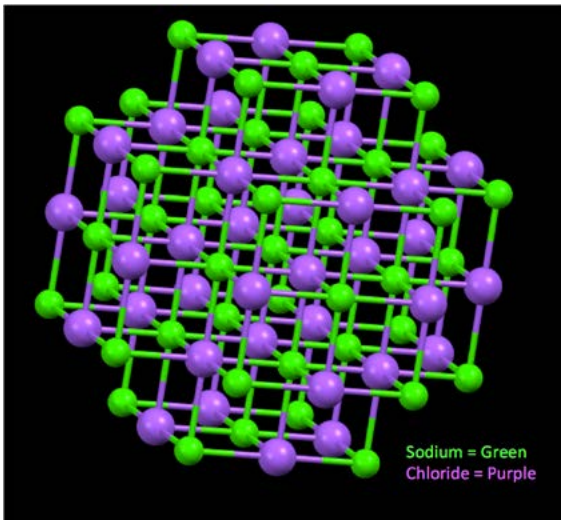


Great British Innovation Vote website showing ionic liquids selected as the winner

What are ionic liquids?

Ionic liquids are, quite simply, salts that are liquid at, or near to, room temperature. Just like table salt, that consists only of ions (sodium cations, Na^+, and chloride anions, Cl^-), ionic liquids also consist only of ions (positively charged cations and negatively charged anions). In table salt, the sodium cations and chloride anions pack together tightly because they are small, 'beautiful' and symmetrical, which is why table salt must be heated to 801 °C (similar to the temperature of volcanic lava) before it will melt. In ionic liquids, the cations and anions are typically big, 'ugly' and unsymmetrical, and cannot get close enough together to crystallise. This inability to form a solid is known as frustrated crystallisation and, as a result, many ionic liquids are fluid at room temperature.

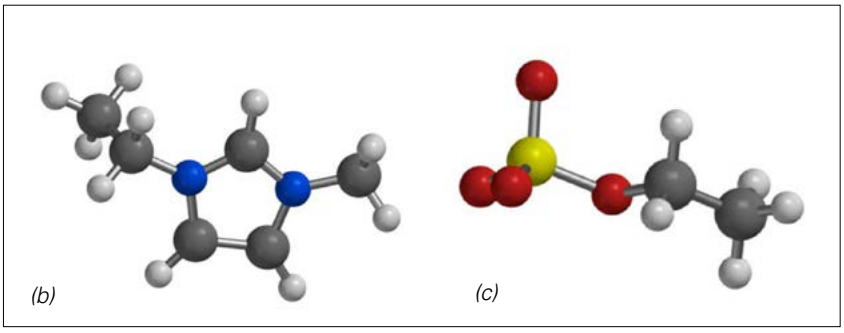
Sodium chloride (table salt)



Sodium chloride crystal lattice

An ionic liquid (1-ethyl-3-methylimidazolium ethylsulfate; melting point < -20 ˚C)

Ionic liquids turn our understanding of the nature of liquids on its head. Most liquids we are familiar with, such as water and alcohol, are molecular, meaning they are composed of neutral molecules. When molecular liquids are heated, the molecules at the surface gain enough energy to enter the gas phase and they evaporate into the atmosphere. In contrast, ionic liquids, which are composed only of ions, cannot pollute the atmosphere because they do not evaporate under normal conditions when they are heated – this fundamental, ever-present, characteristic of ionic liquids is one of the reasons why they are called 'green' solvents. An added bonus of not being able to evaporate is that ionic liquids cannot burn, and they are thus much safer to use in industrial plants which need large quantities of solvents.



(a) Ionic liquids cannot burn because they do not release vapours. Here, a phosphonium ionic liquid will not ignite while ethylbenzene, found in petrol, burns. Below, the molecular structures of two ionic liquids: (b) ethylmethylimidazolium ethylsulfate and (c) a phosphonium liquid.

Super solvents

So, ionic liquids do not evaporate and have far lower melting points than traditional salts, but so what? The answer is that they are extremely good at dissolving things – they are excellent solvents. The vast majority of solvents in use today are molecular and their biggest weaknesses are that they release vapours into the atmosphere, known as VOCs, they can burn, and they cannot dissolve many substances. For example, only ionic liquids can dissolve coal. It is not possible to use high melting salts to dissolve coal (and most other substances for that matter) because working at molten lava-type temperatures would simply incinerate most compounds of interest.

VOCs are Volatile Organic Compounds

With ionic liquids, we can work close to room temperature, which has opened up a treasure chest of opportunities to dissolve many substances that are traditionally considered insoluble. We can also access chemistry that wasn't possible before, simply because we couldn't dissolve the reactants. It is very fortunate that ionic liquids do not dissolve glass or stainless steel, otherwise we would not have any reaction vessels in which to use them! In addition to their 'green', super-solvent abilities, there is yet another reason why ionic liquids are such extraordinary materials.

Designer, green solvents

Ionic liquids can be tailor-made to exactly meet the needs of virtually any application! By carefully manipulating their cations, anions, or both, ionic liquids can be designed to possess specific properties e.g. they can be magnetic or luminescent. It is not possible to tailor-make molecular solvents since their properties cannot be easily tuned, and so their applications range is limited too. In addition, there are only about 300 conventional, molecular solvents used in industry today, while there are at least a million (1 000 000) possible simple ionic liquids!

There are so many ionic liquids available because of the ability to combine various different cations with various different anions. If we mix two ionic liquids, there are at least a billion (1 000 000 000 000) options, and if we mix three, at least 10^{18} possible choices! Making ionic liquids in the laboratory is also quite easy - some of them are simply made by mixing two solids. There are now many companies throughout the world that are manufacturing and selling ionic liquids on very large scales.

Preparing the ionic liquid, cholinium tetrachlorocobaltate(II), $[NMe_3(CH^2)_2OH]_2[CoCl_4]$, in the laboratory. ***a*** *Combine two solids, cholinium chloride and cobalt(II) chloride.* ***b*** *Mix them for 15 minutes at room temperature.* ***c*** *Pour the ionic liquid product.*

It is important to be aware that, although ionic liquids can be tailor-made to be non-toxic and biodegradable, the flip side of the coin is that we can also design ionic liquids to be toxic. This might seem contradictory to the green aims of ionic liquid science, but actually has important implications for applications such as fighting hospital superbugs like MRSA and *C. difficile*. The key concept to be kept in mind is design - this process is constantly being refined so that we have better control of what properties an ionic liquid will possess, ranging from environmentally-friendly to toxic.

Access to so many ionic liquids, in addition to their green credentials, has caused a major shift in the way we approach chemistry, particularly its green application, but where and how are ionic liquids being used?

Ionic liquid applications

Although you may not realise it, ionic liquids are probably already 'in' or 'on' your home – some fabric softeners and household paints contain them. Industrial applications range from using ionic liquids to capture greenhouse gases such as carbon dioxide, making new products, 'trapping' and transporting hazardous gases, cleaning metal surfaces, using them in safer batteries (which do not catch fire), as well as using them to remove toxic mercury from natural gas (to be discussed in a later issue of Catalyst).

Ionic liquids can also be used on smaller scales as, for example, less volatile and therefore safer fluids for studying gems and minerals, to dissolve biomass in the quest for producing biofuels, and even as replacements for toxic and smelly formaldehyde for embalming corpses! In conjunction with NASA, they are also planned to be used as the basis of a massive Lunar Liquid Mirror Telescope, which would enable us to see much, much further into space and time than is currently possible. The possibilities seem almost endless, and they are - wherever a conventional liquid can be used, an ionic liquid, designed to be better, can replace it.

Lord Browne of Madingley (chief executive of BP from 1995 to 2007) with a collection of luminescent ionic liquids

The ionic liquid bottom line

Since nearly every product in use today has had a molecular solvent of some kind involved in its manufacture, replacing these solvents with ionic liquids would have a massively beneficial effect on lowering atmospheric pollution and, at the same time, would make industrial applications greener, cleaner, more economic, and more efficient.

Dr Maggel Deetlefs is CEO of QUILL and Prof Ken Seddon is co-director. QUILL is the Queen's University Ionic Liquid Laboratories in Belfast, Northern Ireland: quill.qub.ac.uk.

Look here!

For more information about ionic liquids see:
What are ionic liquids? *http://bit.ly/1wqTH79*

Ionic liquids at the 2014 Royal Society Summer Science Exhibition
Video: *http://tinyurl.com/pczn8fl*
Podcast: *http://tinyurl.com/ozur5yh*

Silvia Pani

Superman's not dead

Exploring X-ray vision

If you have gone through airport security you may have taken a peek at the screen next to the baggage scanner. It's interesting to see your bag, with the shapes of your phone and earphones, your wallet, pencil case, and book – perhaps even some lost coins at the bottom. As Silvia Pani explains, this is only one of many things you can do with X-rays.

Baggage scanner

Airport baggage scanners have two aims: finding weapons and finding illegal substances such as drugs or explosives. **Figure 1** shows how a scanner works.X-rays are emitted in a fan-shaped beam by an X-ray source above the luggage conveyor belt; an image is acquired by a detector placed underneath the conveyor belt while the object moves.

The detector works by collecting the X-rays that have not been stopped by the object and converting their intensity into a grey scale: high intensity (no X-rays stopped by the object) appears white, and low intensity (X-rays almost completely blocked) is black. So X-ray imaging is imaging of shadows: the thicker the shadow an object casts for X-rays, the darker it will look.

A gun hidden in a suitcase would look something like **Figure 2**, very dark amidst the grey shapes of other objects.

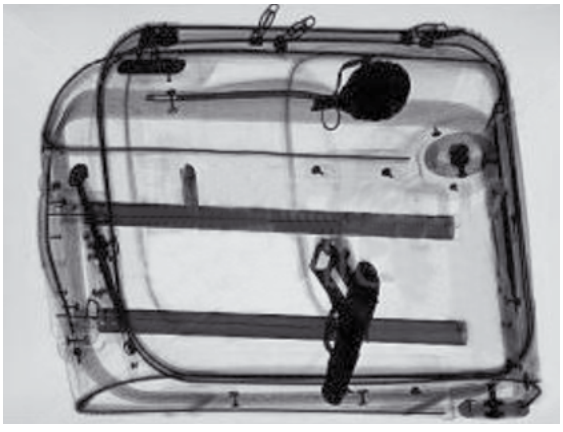


Figure 2 *An X-ray image of a bag with a gun inside it*

Why does a gun appear black whilst a book appears grey? The answer lies in the way X-rays interact with different materials. When an X-ray beam traverses an object, it is partially absorbed; a higher fraction of X-rays is absorbed by a thicker

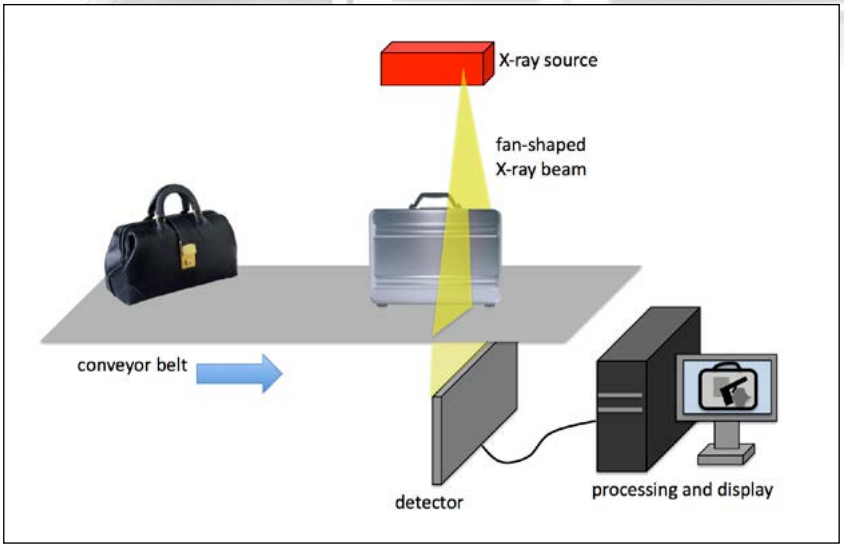


Figure 1 *An airport X-ray scanner*

object. At the same time, a material made of atoms of high atomic number also absorbs more X-rays. A gun is made out of metals, such as iron, with high atomic numbers while paper is a compound of low atomic number elements such as carbon, hydrogen and oxygen. Therefore a greater fraction of X-rays pass through a book than through a gun and the paper appears grey while the gun appears black.

Key words
X-rays
absorption
CT scanning
radiation dose

What are X-rays?

X-rays are electromagnetic waves just like visible light, infrared or radio waves; the difference is their wavelength which, for X-rays, is one of the shortest ones in the electromagnetic spectrum.

X-rays get stopped in materials by various processes, most importantly the photoelectric effect. An X-ray knocks an electron from the inner shells of an atom – the orbits closest to the nucleus – and is removed from the beam. The denser the material and the higher its atomic number, the more the X-rays are absorbed. An atom which loses an electron in this way becomes an ion, and so X-rays are classed as **ionising radiation**.

Seeing things in depth

The image in **Figure 2** is called a projection image; all structures are projected onto a plane, and there is no way of telling the arrangement of two objects that overlap. We would have the same image whether the gun was sitting on top of the suitcase or inside it. To understand how this may prevent the detection of objects, have a look at **Figure 3a**. It's an X-ray image of a plastic pot containing some objects. Can you tell what they are?

Looking at one view only can prove tricky; what if we look at the same object from different angles? The following images show the same object rotated: is it clearer now? (The solution is at the end of this article.)

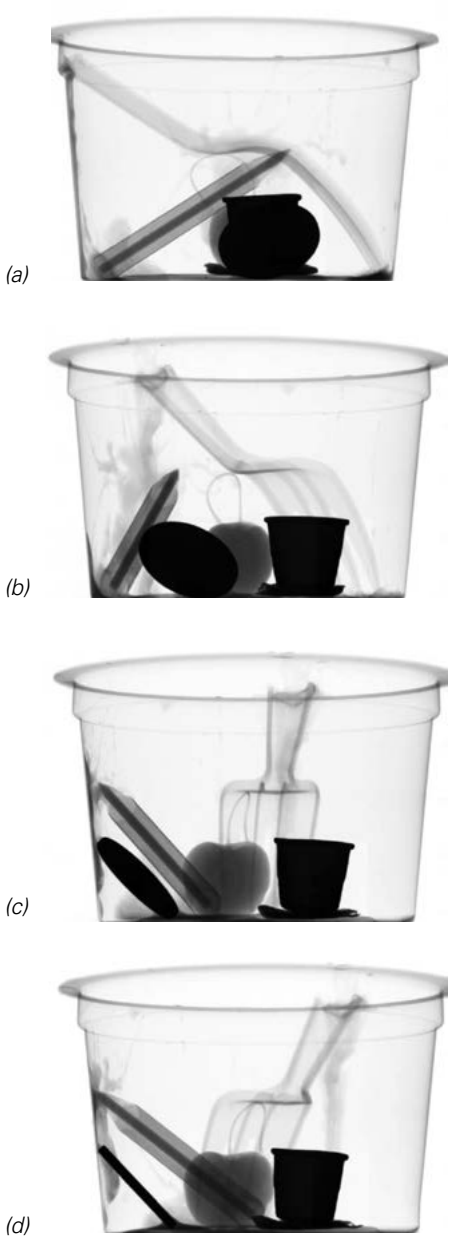


Figure 3 *X-ray images of an object made at different angles*

So looking at an object from different angles helps identifying the structures inside it. This is the principle of Computed Tomography (CT). CT goes further, and uses computer algorithms to combine many views from different angles into a single image, showing a cross-sectional slice of the patient.

Look for instance at **Figure 4**, which shows a plastic spider. **Figure 4a** shows a projection image, and **Figure 4b** shows a cross-section of the spider obtained by combining many single views at different angles (imagine cutting the spider along a horizontal plane, shown by the red line in **Figure 4a**, the way you would cut an orange).

From the CT image you can see that the body of the toy is hollow, which you would hardly have guessed from a single image. Also, it is made of different materials; the feet appear brighter, so must be made of a denser material than the body. By stacking up many slices, a three-dimensional image can be obtained, as shown in **Figure 4c**.

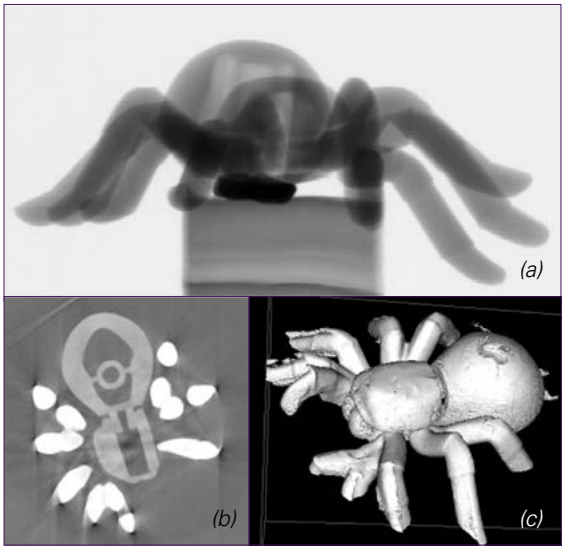


Figure 4 ***(a)*** *Single-view image,* ***(b)*** *CT reconstruction and* ***(c)*** *three-dimensional reconstruction of a plastic toy spider; note that, in CT, the greyscale is inverted: non-absorbing regions such as the air surrounding the object are black, and strongly absorbing regions are white (images by R. Ealden).*

Medical applications

Staff examining baggage scans must assess whether a bag contains a threat or not. They have to make a decision based on their experience so that no weapons or illegal substances get missed, but also to ensure that no false alarms are raised for harmless objects.

This is not too dissimilar from the task faced by doctors examining X-ray images of a patient. They won't know if the patient has a disease, but they aim at getting as many 'true positives' as possible (i.e. identifying a disease that is present) and as few 'false positives' as possible (i.e. thinking that a disease is there when it isn't). If a disease is missed, the patient may not get treatment and their condition may get worse; if a disease is believed to be there when the patient is healthy, the patient will have to undergo costly and stressful extra examinations for no reason.

However, there is a big difference: if your object is a human, one extra factor to take into account is that X-rays are ionising radiation. They knock electrons from atoms and such electrons will ionise other atoms. Removing electrons from the DNA of cells may cause damage to the cell and therefore poses a risk for the patient. Medical X-rays must therefore limit as much as possible the amount of radiation stopped within the patient, or *patient dose*.

Nowadays images with amazing quality can be obtained at low dose. **Figure 5** compares the first image of a human, obtained by Dr Roentgen in 1895, and a modern image of a hand. You can see how much more defined the structures are in the modern image, with subtle variations in density (different grey levels) in different regions of the hand.

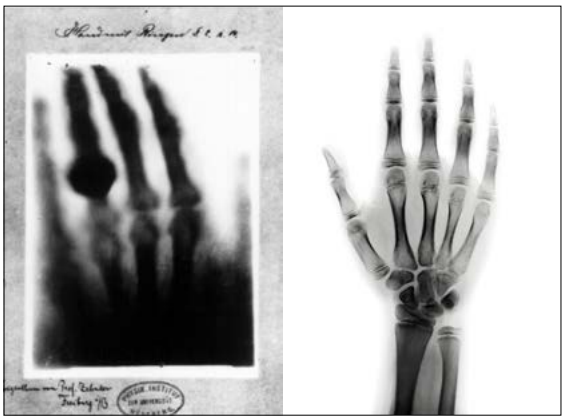


Figure 5 ***(a)*** *The first X-ray image of a human (Mrs Roentgen's hand), and* ***(b)*** *a modern radiograph of a hand*

CT is particularly useful for thicker regions of the body such as the abdomen (**Figure 6**), where the overlap of many structures may prevent detection of illnesses.

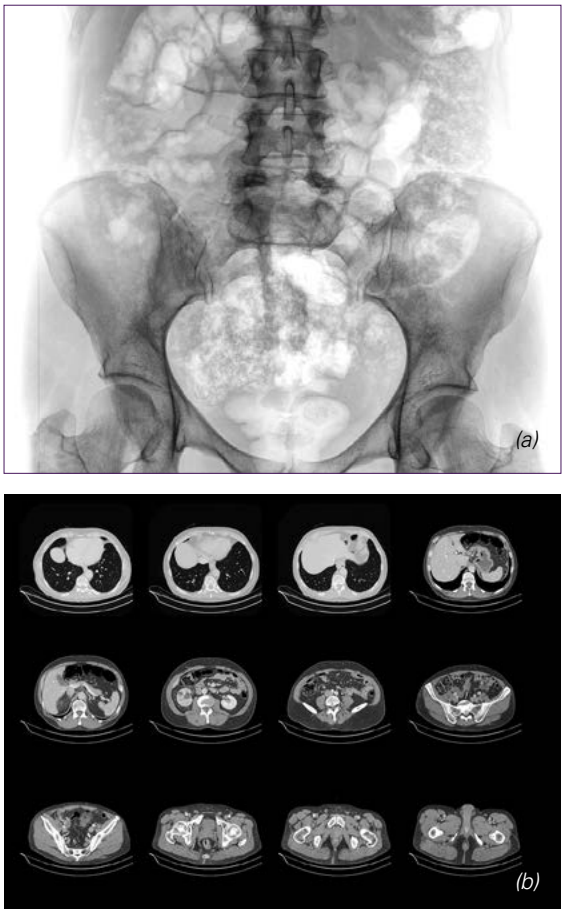


Figure 6 ***(a)*** *In this projection image of the abdominal region you can hardly make out any structures other than the bones;* ***(b)*** *These CT slices show the positions of the organs in different planes without overlap, making diagnosis a lot easier.*

Looking ahead – synchrotron radiation

For very specific applications, a standard X-ray generator is not sufficient, and X-rays from a synchrotron source may be used. In a synchrotron, electrons are accelerated in a circular trajectory; when their trajectory bends, they emit X-rays described as synchrotron radiation.

Synchrotron radiation has many properties that make it the ideal tool for imaging, but one of the most appealing ones is that it can be exploited for *phase contrast imaging* – see **Figure 7**. In phase contrast you exploit the wave nature of X-rays, and you indirectly see details that are too small to be detected with conventional imaging by seeing the distortion they cause to the wave. It's like looking at a pole in the sea; from a distance, you can't see the pole, but you can see that a wave incident upon it gets distorted.

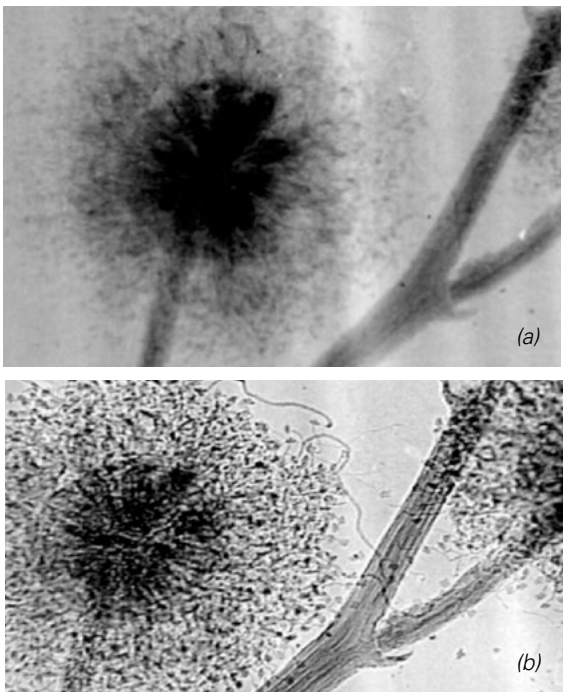


Figure 7 X-ray images of a mimosa flower obtained ***(a)*** *with conventional methods, and* ***(b)*** *with phase contrast imaging to show all the fine structures of the flower (courtesy The SYRMEP Collaboration)*

Phase contrast would be ideal for diagnosing illnesses in their early stages as it allows detection of very fine structures. However, a synchrotron cannot be available in every hospital, and research is going on to develop X-ray sources that reproduce the characteristics of synchrotron radiation.

The main streams of research in X-ray imaging are the development of new X-ray sources and new X-ray detectors, so that the maximum information is obtained at the minimum dose cost for the patients.

X-ray imaging is a truly interdisciplinary field, bringing together the expertise of physicists, engineers and computer scientists for the development of the technology and of the data processing algorithms, and doctors to identify the areas for improvement of the current technologies and provide advice and support for the new developments.

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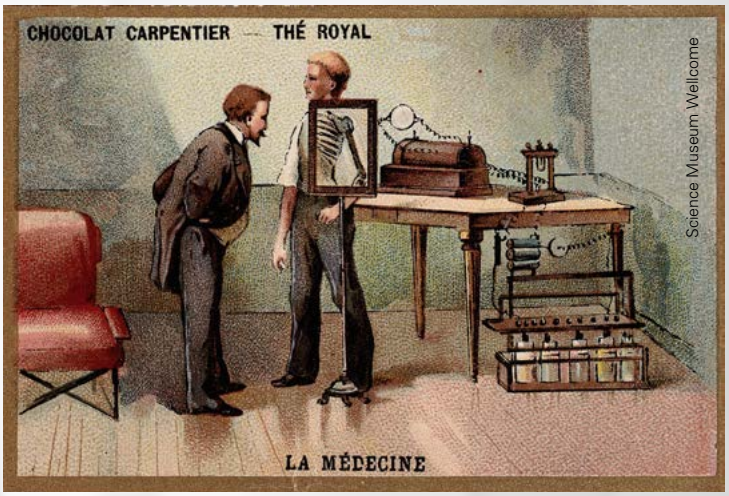
The objects in Figure 3 are a plastic fork, a pencil, a cherry, a thimble and a coin.

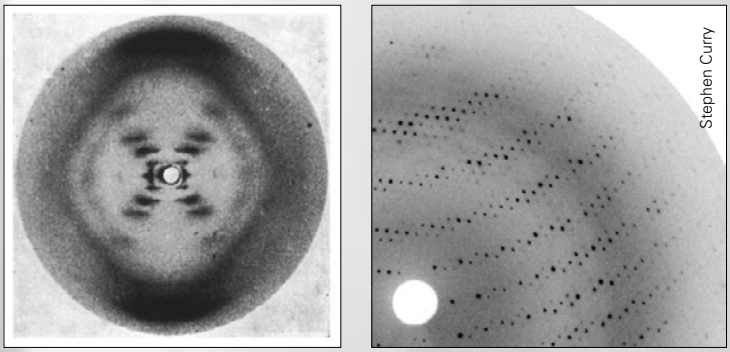
X-rays then and now

X-ray technology has improved greatly over the last century, allowing much greater detail to be observed.

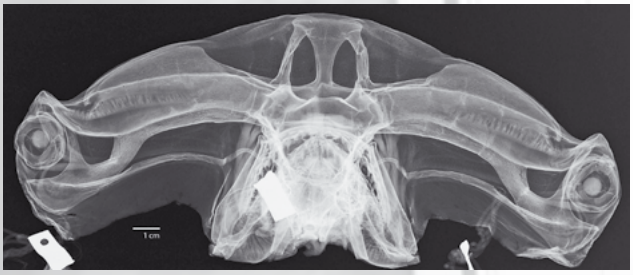


X-rays were discovered by Wilhelm Roentgen in 1895. This image suggests the crude images which could be obtained at that time.

In the 1930s, the Omniskop allowed the doctor to move the X-ray source to shine through different parts of the patient's body.

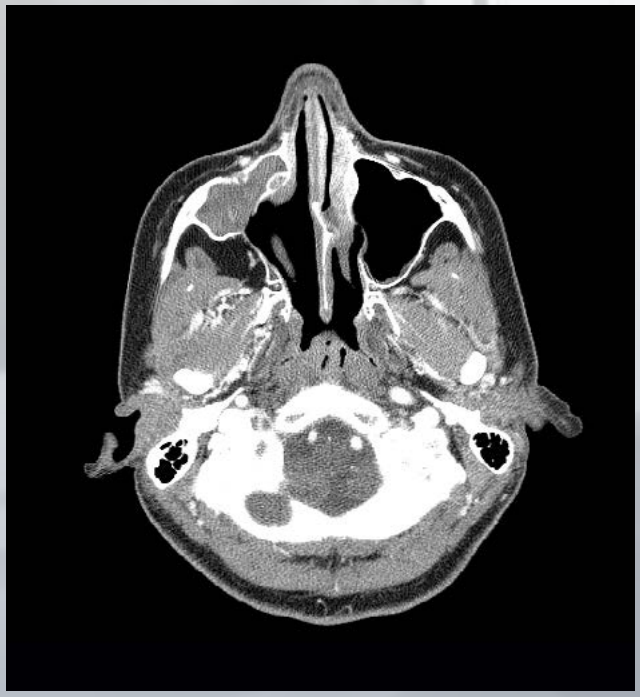


X-rays are used to determine the structures of molecules. The image on the left, made in 1953, was used to deduce the double helix structure of the DNA molecule. The modern image on the right has many spots of varying brightness, allowing the detailed structure of a complex protein molecule to be deduced.



The skull of a hammerhead shark, showing the fine detail which can be achieved today.

A modern CT scanner can produce a 3-dimensional image of the patient's body.



A slice through a human head, obtained using a CT scanner.